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Criterion 3

Metric No. 3.3.1

Research Papers Published during the last five years

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3.3.1 Number of research papers published per teacher in the Journals notified on UGC website during the last five years					
Sl.No.	**Title of paper**	**Name of the author/s**	**Department of the teacher**	**Name of journal**	**Year of publication**
2017-18					
1	A Study on RythuBandu Scheme its impact on Agriculture development in Telengana state-issues and chalenges	Dr. Shyamu Ganta	Economics	Education Times	Jan-18
2	A study on the impact of smart cities in Urban Development of India -Issues and Challenges	G. Vijaya	Political Science	Edu World	Apl-2018
3	A Study on Health and Education in socio-economic development of Telangana state -An Overview	Dr. Shyamu Ganta	Economics	Edu World	Apl-2018
4	Managerial Assessment on Tribal Development and Empowerment - An Overview	B. Santhosh Kumar	Political Science	Desh Vikas	Apl-2018
5	Strategies for livelihood promotion of human self help groups in indirakranti patham in Andhrapradesh	Dr. Shyamu Ganta	Economics	Education Times	May-18
6	Provervs of Lambadas (Gwar Matiri Saaki)	B Hathiram	History	Andhra Pradesh History Congress-XLI	Jul-17

2018-19					
7	RURAL INDEBTEDNESS: A STUDY IN MAHABUBABAD DISTRICT OF TELANGANA STATE	Dr. A. Venkataramana	Economics	Journal of Emerging Technologies and Innovative Research (JETIR)	Oct-18
8	E-NAM: A STUDY IN MAHABUBABAD DISTRICT OF TELANGANA STATE	Dr. A. Venkataramana	Economics	International Journal of Research and Analytical Reviews (IJRAR)	Mar, 2019
2019-20					
9	Residues from the proceeding of Amarnath and Quinoa flour cultured shrimp litopenaeus rannamei isolation of carotenoid pigments	T.Sharada	Zoology	Parishodh journal	Feb ,2020
10	Amitav Ghosh's sea of Popies:A Saga of the Marginalized and Subaltern Afflictions	Y. Ramesh	English	Langlit	Feb, 2020
11	Design and synthesis of 4β-Acetamidobenzofuranone-podophyllotoxin hybrids and their anti-cancer evaluation	Dr.N.Srinivas	Chemistry	Bioorganic & Medicinal Chemistry Letters	June, 2019
12	Synthesis of D-ring modified acid hydrazide derivatives of podophyllotoxin and their anticancer studies as Tubulin inhibiting agents	Dr.N.Srinivas	Chemistry	Bioorganic Chemistry	Nov, 2019
13	Synthesis of novel fluorophenylpyrazolepicolinamide derivatives and determination of their anticancer activity	Dr.N.Srinivas	Chemistry	Synthetic Communications	Jan, 2020

2020-21					
14	Call An Essential Approach in the Pandemic Period	Y. Ramesh	English	Langlit	July, 2020
15	Phyto-Pharmacological activity of Tecoma Copensis (Thumb) lind.plant flowers	D. Suneeta	Botany	International Journal of Botany Studies	Aug-20
16	Indigenous People and white Settlers in Kate Grenville's the Secret River	Y. Ramesh	English	Langlit	May, 2021
17	Green Synthesis of Chromene Congeners via Multi-Component Reaction and Their Antimicrobial Studies	Dr.N.Srinivas	Chemistry	ChemistrySelect	2021
18	Synthesis of podophyllotoxin-glycosyl triazoles via click protocol mediated by silver (I)-N-heterocyclic carbenes and their anticancer evaluation as topoisomerase-II inhibitors	Dr.N.Srinivas	Chemistry	Natural Product Research	2021

2021-22

19	Comparitive Analysis on various Natural Polymers	T.Venkanna	Physics	International Journal for research and Development in Technology	Aug, 2021
20	English Language Teaching : Problems and Remedies	Y.Ramesh	English	Langlit	Sep, 2021
21	Isolation and screening of Indigenous Rhizobia from Black gram Cultivated in fallow Rice soils for plant growth promoting traits	D. Suneeta	Botany	Malaysian Journal of Soil Science	Dec, 2021
22	Synthesis and Bioevluation of BIS methane derivatives using copper halide catalyst	Banoth Reddy	Chemistry	Research Journal of Chemistry and Environment	Feb, 2022
23	Impact of COVID-19 Pandemic on indian Economy :An Analysis	Dr. A. Venkataramana	Economics	International Journal of Creative Research Thoughts	Mar, 2022
24	One pot Synthesis characterization and antimicrobial activity of Methyl-6-Methyl-4-Phenyl-2-Thioxo-1,2,3,4-Tetra hydropyrimidene-5-	Banoth Reddy	Chemistry	World Journal of Pharmaceutical research	Jun-22
25	Bronsted Acid Catalyst promoted for Bioactive Synthesis of 2,4,5-Triphenyl Imidazol Derivatives	Banoth Reddy	Chemistry	International Journal of Modern Pharmaceutical Derivatives	Jul-22
26	Review on Alalysis Polymers and its blends and Apllications	T. Venkanna	Physics	Journal for Innovative Development in Pharmaceutical and Technical Science	Apl, 2022

27	Knowledge and Attitude towards COVID-19 among rural people - An empirical study	Dr. A. Venkataramana	Economics	Juni Khyat	June, 2022
28	Diclofenac induced Genotoxicity in the gill tissue of *Channa Punchtatus*	Dr. P. Rohini	Zoology	Biolife	July, 2022
29	IMAGE RECOGNITION USING DEEP NEURAL NETWORK ALGORITHMS	G. Vijay	Computer Science and Application	INTERNATIONAL JOURNAL FOR RESEARCH & DEVELOPMENT IN TECHNOLOGY	July, 2022
30	DEEP RESIDUAL NETWORKS BASED IMAGE RECOGNITION-REVIEW	G. Vijay	Computer Science and Application	Journal For Innovative Development in Pharmaceutical and Technical Science (JIDPTS)	July, 2022
31	Efficient Synthesis and Antybacterial and Anti-Inflammatory properties of 9-Aryl-6-(3-Methyl Phenyl) (1,2,4) Triazole (4,3-A) (1,8) Naphthyridile	Dr.Anjum Aara	Chemistry	High Technology letters	2020
32	Cecl3.7H2O Catalyzed friedlander Synthesis of 1,8-naphthyridenes under solvent free conditions	Dr.Anjum Aara	Chemistry	Infokara research	2020

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A study on Rythu Bandhu Scheme its impact on Agriculture Development in Telangana State – Issues and Challenges

Dr. Shyamu Ganta*

Abstract

Indian agriculture is a critical area not just for the policy makers but also for the producers who are engaged in this business. Even today, Indian economy is vastly dependent on its agricultural needs and therefore, telangana is the 12th largest state in terms of geographical area and in terms population, with the problems that persist in the domain of the agriculture, reflecting upon the situations and conditions in the state of Telangana in particular. It deals with the need of an Agricultural Investment Scheme like Rythu Bandhu Scheme that was implemented by the Telangana state. Particularly the vision of the state to break and stop the vicious cycle of the 'debt trap', which is the biggest concern for any farmer suicides. Thus in totality, it presents a holistic viewpoint regarding the agricultural investment scheme. Cash transfers have been described as a class of instruments through which beneficiaries are endowed with purchasing power to acquire certain goods rather than the goods themselves. There are different types of cash transfers. An unconditional cash transfer entails no restriction on use; there are no strings attached and beneficiaries are free to decide how they wish to spend it. Conditional cash transfer schemes, (CCTs), unconditional cash transfers can be further divided into restricted (targeted) transfers- targeted to a specific sub-population such as the poor, elderly, lactating mothers etc, main objective of the scheme as relieving the farmers from debt burden and not allowing them to fall in the debt trap again. It further states, This new scheme is proposed to provide support to Agriculture and Horticulture crops by way of a grant of Rs. 4000/- per acre per farmer each season now Rs. 5000/ for purchase of inputs like Seeds, Fertilizers, Pesticides, towards Labour and other Investments in the field operations of farmers' choice for the crop season thus, at the outset, the scheme had two primary objectives- the first intended to provide an initial income support to farmers- right in the beginning of the sowing season to aid the purchase of agricultural inputs and facilitate agricultural investment.

INTRODUCTION:

This dissertation is an attempt to evaluate the Rythu Bandhu Scheme first cash transfer scheme for farmers which started in May 2018 in Telangana. Cash Transfers as a policy instrument have been debated, discussed and implemented in various forms, in various parts of the world and at various points of time in history. It was in this context, that Telangana launched Rythu Bandhu- what it called a 'farmers investment support scheme' in May 10th 2018- disbursing to all land-owning famers in the state, a cash transfer of Rs 4,000 per acre per season (which later increased in 2019-20 to Rs 5,000 per acre) to help support investment in agriculture in the initial sowing season. The scheme

was novel in more ways than one- not only was it the first of its kind for farmers, but more importantly the scheme required a definition of cultivators based on land-ownership. In less than a year of the scheme's launch, other states- namely Odisha, West Bengal, Andhra Pradesh started supporting farmers through cash transfers and the scheme went on to inspire the flagship PM-KISAN (Pradhan Mantri Kisan Saman Nidhi) at the central level. While other states had different mechanisms of identifying beneficiaries for the cash-transfer, both Rythu Bandhu and PM-Kisan were unique in that they relied completely on land-records for the identification. But in a country where land titling is hardly conclusive, errors and disputes are likely inevitable. Rythu Bima Scheme is an extension to the Rythu Bandhu Scheme. It was launched on 15th August 2018. The idea behind the launch of the scheme is to provide an insurance cover to farmers of Rs. 5 lakh during the emergency crisis to their family members. In case of a death of the farmer, the family would receive the amount within 10 days. To make the implementation effective, the state had joined hands with the Life Insurance Company (LIC) of India. A farmer who is eligible for the Rythu Bandhu Scheme is automatically eligible for the Rythu Bima Scheme and vice versa. Both these schemes working in collaboration with each other, provides a social security to the farmers and their families because mostly these schemes will cover those farmers that are the worst sufferers in the society.

Agriculture in Telangana State is characterized by poor productivity and production owing to frequent occurrence of droughts, lesser technological penetration and poor investment capacity of the famers, resulting in lower levels of income and social security to the farmers. The majority of the farmers are small, marginal and resource poor, dependent solely on farming for their livelihood. Keeping this in view, in order to ensure the economic and social security to the farmers, the Government of Telangana has conceptualized and implementing an innovative scheme named as Farmers Group Life Insurance Scheme (Rythu Bima) in addition to other initiatives in agriculture sector. This scheme is first of its kind and unique in the country as it is implemented based on farmer-wise online land data base through Information Technology and Online Portals and MIS that are being used by all the outreach officers for effective and efficient implementation. The main objective of the Farmers Group Life Insurance Scheme (Rythu Bima), is to provide financial relief and social security to the family members/ dependents, in case of loss of farmer's life due to any reason. In the event of the loss of the farmer life, their families are facing severe financial problems even for their day-to-day needs. The farmers Group Life Insurance Scheme ensures financial security and relief to the bereaved members of the farmer's family. Farmers in the age group of 18 to 59 years are eligible for enroll under the scheme. The entire premium is paid by the government to the Life Insurance Corporation of India (Largest public sector PSU for Insurance in India).In the event of the death of the enrolled farmer due to any cause including natural death, the insured amount of 5.00 Lakhs INR (Approx. USD 6928) is deposited into the designated nominee account within (10) days. This scheme has a tremendous impact on the lives of the bereaved families and helping their livelihoods, since most of them are resource poor small farmers and belong to weaker sections of the society. This scheme has been implemented through the Information Technology with development of Online Portals and MIS developed by National Informatics Centre (NIC). The uniqueness of this scheme is that, the nominee is not required to approach any office for the settlement of claim amount. The outreach officers at village level collects data from revenue department in the event of loss of life of any farmer and submitted to the LIC on behalf of designated nominee of the farmer. The claimed amount would be transferred through RTGS into nominees account. According to the Telangana Government, the scheme had been implemented in 30 districts with 108 divisions and 568 Mandals. Within this, the scheme covers 2,245 clusters and the total of 10,874 villages of the state. To make farmers rely on the formal institutions for their credit needs, government is working in collaboration with the banks such as State Bank of India, Andhra Bank, Syndicate Bank, Indian Overseas Bank, Canara Bank.

To inculcate the participation of banks at the ground level banks such as Telangana Grameen Bank and AP Grameen bank will also providing financial assistance to the farmers. This will directly reduce the role of moneylenders in village areas where they provide loans at the high interest rate to the farmers. Thus, the farmers decreased dependence on the informal credit institutions and the increased dependence on the formal institutions will result in to breakdown of the cycle of debt. Agriculture provides a livelihood as we said, to more than 55.5 percent of the state's population. But four-and-a-half years since it won statehood, Telangana faces acute farm distress, with 2,190 farmers having committed suicide--more than one every day--according to data from the state government's police department. the National Crime Records Bureau has not published data on farm suicides since 2015, of these, 124 suicides took place in Siddipet district, Gajwel. Telangana had the third highest farmer suicides in the country after Maharashtra and Karnataka in 2015 due to initiate to this one.

The Rythu Bandhu Scheme provides the financial assistance to the farmers for two seasons of the year, that are kharif season (which include the summer crops) and the rabi season (which include the winter crops). But, the land cultivated during the rabi reason is 70 per cent less than the land cultivated during the kharif season. With this the problem arises as majority of the land owners would still receive the same benefit. Farmers of Peesara village in Warangal district had not received the financial assistance. They blame the administrators for not carrying out the proper task of upgradation of the land records. Therefore, there are various issues regarding updating and digitisation of the land records undertaken by the state government (Venkatesh, 2018). Some cultivators believe that the amount or the assistance is too low which adds nothing to their incomes. They believe that government could have increased the amount which they had sanctioned for the scheme, because Rythu Bandhu Scheme is covering only small part of the input cost of an agricultural field. This, negligence on the part of the state government could lead the farmers to turn towards the traditional or informal way of receiving credit from the moneylenders. Therefore, the cash support can cover an input cost, but cannot ensure the returns of the demand in the economy (Jitendra, Pandey, Mishra, Brahma and Nagaraju, 2019). Arvind Subramanium, former Chief Economic Advisor had criticized the scheme on the basis that it left out the two vulnerable agricultural groups that are agricultural workers and landless labourers. While on the other hand, the scheme is regressive since small landlords will receive small payments and big landlords will receive larger payments because the payments will be released according to the size of the land holding.

REVIEW OF LITERATURE

1. **Theodore W. Schultz (1953):** had expressed his views regarding the need for income payments to farmers. When there is a failure on the part of fiscal and monetary policy to keep the agriculture sector stable, then it is necessary to emphasis on income payments to farmers directly. This direct support to the farmers keep up with the aggregate income of the agriculture and thus the falling demand of this sector can be curtailed. This method, in addition can also increase the demand for agricultural inputs which are used by the farmers which would open the channels for trade.
2. **Swerling (1959)**: is of the view that direct investment in agriculture through cash would not be a permanently supported but rather is a temporary act. The benefits would not be attached to the farm land but it would be attached to the person (farmer) and therefore it would not be transferable. The benefits enjoyed out of it can comply with the non-farm income as well. He advocates the idea that the main purpose of an income support scheme or an approach is to protect commercial farmers against unstable incomes and to raise farm income levels according to justifiable standard.

3. **Bhaumik (2008):** highlights the direct support scheme or an investment scheme is an alternative to MSP (Minimum Support Price). The scheme involves direct transaction of money through which the farmers will be compensated for the income that had been lost to them due to price or yield collapse at the pre-decided price or market price during that year.
4. **Soni and Malhotra (2015):** mentions in their book that it is better to have income transfers to the farmers that are direct rather than indirectly through market price measures. The compensation to the farmers in this way can be based on the prices or the incomes. This will help in allocation of resources and thus income will be generated to all the factors of the production.
5. **Ashok Gulati (2018):** is an agricultural economist who holds the view that loan waivers are nothing but the "Poll Bait". The need of an hour is to have a stable income support scheme. Towards this direction Rythu Bandhu Scheme is an alternative to the loan waivers to the farm sector. The beneficiaries of the scheme are farmers having small land holdings. The scheme by Telangana strikes the right balance between the consumers and the farmers.

Agricultural economist who holds the view that loan waivers are nothing but the Poll Bait. The need of an hour is to have a stable income support scheme. Towards this direction Rythu Bandhu Scheme is an alternative to the loan waivers to the farm sector. The beneficiaries of the scheme are farmers having small land holdings. will provide the farmers with an income of Rs. 8000/- per acre annually (Government of Telangana, 2018, in 2019 Rs 10,000). From this income farmers can purchase or upgrade their existing factors of production like seeds and machine equipments, to increase the production in the agriculture. This would also provide them a base to have a good start for the following season. A scheme is null and void without its proper implementation. To implement it properly the government had updated and digitized paper based land records between September 2017 and March 2018. Along with it, to over 50 lakh farmers, it distributed cheques and patta passbooks. There is no application process involved. The farmers that are not included are those whose lands are disputed and these farmers comprise around 3% of the state

FINDINGS OF THE STUDY

1. Telangana is a agrarian state misery of farmers is not narrow in its nature, it implies various problems that persist in the domain of agriculture. Its seriousness increases when
2. In the discussion regarding the farmer"s suicide comes into light, which itself is due various reasons like lack of credit, droughts, the never ending role of middlemen, the small landholdings that are leading to poor incomes.
3. Rythu Bandhu Scheme is an alternative to the age old government policies like Minimum Support Price (MSP), subsidies and loan waivers. Henceforth, it tries to fill in the gaps that were left by these earlier schemes.

CONCLUSION

The tenant farmers should be the part of the scheme, here should be a proper monitoring system to analyses all kind of difficulties that are faced by the farmers under this scheme and provides need of the farmers below 15 acre of land margin is necessary for successful implementation. The government should organize workshops and awareness programs regarding the benefits of formal institutions of credit like banks, the prediction for the sudden natural disasters should be communicated to the farmers in advances so that they can make alternative arrangements. After formation of Telangana majority farmers committed suicides for financial crises and marketing prices.

The continuous farmer suicide due to the drought have had negative impact on the income generation of the farmers. This programme direct support to the small and marginal farmers in the state. It has come up with an agricultural investment scheme like Rythu Bandhu scheme. The idea and its approach in the state had led the other states of India to adopt the similar measures to address the concern of their farmers. Recently, Odisha, have announced the Krushak Assistance for Livelihood and Income Augmentation (KALIA) scheme. With the success of these schemes at the state level, the central government has also announced a scheme on similar line, which is Pradhan Mantri Kisan Samman Nidhi (PM-KISAN) for small and marginal farmers. Rythu Bandhu and Rythu Bima mostly help to the rural farmers. The schemes like these are also supporting the initiative of doubling up of the farmer's income by 2022. They, if are implemented properly, can replace the Subsidy model by an Investment model, in spite of various challenges that are seen and faced by the beneficiaries the telangana government taken dictions to limit of 10 to 15 acres land margin it is mostly useful to them and farmers also happy in the same way there is no misuse of public interest and finance

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A Study on the Impact of Smart Cities in Urban Development of India – Issues and Challenges

G. Vijaya*

ABSTRACT

India is fastest developing economy in the world, with the complexity is like infrastructure networks which are changing drastically. People are trying to change their life and the shifting from rural areas to urban areas. I will discuss in my paper Modi stared as smart cities mission flagship programme in the 2014 by the BJP Government. The idea of this mission is to develop technology driven cities in india due to fast urban growth citizens suffer from problems like heavy traffic jams, poor waste managemebnt, inaduequate water supply management, many more to over come these issues smart cities terminology come existence. It provides the inclusive improvement of smart cities and its challenges while making the smart cities are also discussed. The main themes constitutions of the smart cities like smart governance, smart education, smart living, and smart health care, smart citizens. Initially, the Mission aims to cover 100 cities across the India. The smart solutions and strategies creation good infrastructure and transformation for making a city smart. The Mission may be continued thereafter in the light of an evaluation to be done by the Ministry of Urban Development (MoUD). It aims to focus on area-based development in the form of redevelopment of existing spaces, (Greenfield) to accommodate the growing urban population and ensure comprehensive planning to improve quality of life, create employment and enhance incomes for all-especially the poor and the disadvantaged. On 27th August 2015 the centre unveiled 98 smart cities across India which was selected for this Project. 13 crores population 35 percent of the urban population will be included in the development plans. The Smart City Mission (SCM) operated as a Centrally Sponsored Scheme (CSS).

Keywords: smart cities impact and development, social issues and challanges, smart solutions, technology, urban development.

INTRODUCTION

India is one of the fastest growing economies in the world after recording a growth of 5.5 percent annuam during 1981-2001. There was further acceleration in GDP growth to 7.7 percent per annuam during 2001-2011. The economy has weathered the impact of the global slowdown 2008 much better than most and is well on its way to resuming its journey to 8-9 percent per annual GDP and urban population is 27.8 percent in 2001 31.2 percent in 2011 is estimated to grow 40 percent by 2030 and more than 50 percent by 2050. The population growth in cities is accompanied by infrastructure management and service delivery challenges. The development of smart cities is one strategy being deployed to efficiently and effectively cope with these challenges. urban infrastructure consists of smart governance, smart education, smart living, smart mobility, smart energy, and smart environment, health care. The 21st Century is facing major challenges for humanity, due to population growth the resources are under constant threats and always falling short of needs and demands.

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Hence now cities have to address various issues such as ICT, urban planning, climate change, environmental matters, non-renewable resources, social and economic development, increasing populations, city infrastructures, Governance & Funding etc. Greater emphasis on cities needs cities to think independently for economic growth and sustainability of various infrastructures, where resources can be effectively shared and good governance achieved for smooth citizen empowerments. Thus in a determined bid to recast the urban landscape of the country to make urban areas more livable and inclusive besides driving the economic growth.

Constitution (74th Amendment in India–1992) Act has introduced a new part IXA in the Constitution, which deals with Municipalities in an article 243 P to 243 ZG. It is also known as Nagarpalika Act, came into force on June 1st 1993. It has given constitutional status to the municipalities and brought them under the justifiable part of the constitution. States were put under constitutional obligation to adopt municipalities as per system enshrined in the constitution. 243Q provides for establishment of 3 kinds of Municipalities of every state. Nagar Panchayat, Metropolitan area in the country is an area where population is above 10 Lakh (Article 243P). Article A Nagar Panchayat is for those areas which are transitional areas i.e. transiting from rural area to urban areas. "Governor" will by public notice, will define these three areas based upon the population, density of population, revenue generated for local administration, percent of employment in Non-agricultural activities and other factors. 12th schedule of the constitution of India–urban planning including town planning, regulation of land-use and construction of buildings, planning for economic and social development, roads and bridges, water supply for domestic, industrial and commercial purposes, public health, sanitation conservancy and solid waste management, fire services, fire services, safeguarding the interests of weaker sections of society, including the handicapped and mentally retarded, slum improvement and up gradation, urban poverty alleviation, provision of urban amenities and facilities such as parks, gardens, playgrounds, promotion of cultural, educational and aesthetic aspects.

Urbanization is a part of the development process in backward stagnant societies the process of urbanization is rather slow. Because cities fail to offer employment opportunities to people living in the countryside. It is fast rapidly growing economies where newly established industries and ancillary activities continuously provide jobs to people who wish to migrate to cities. It is not a new concept for rapid urbanisation, under this programme creation of economic infrastructure and digitalisation in 100 cities in many fields for the smart India. The vision of the smart city concept is to improve the capabilities and simplify numerous problems of the city through optimized energy consumption, carbon emission, mitigation, maximum recycling, smart transportation, Closed Circuit Television (CCTV) installation, internet things, urban informatics, traffic management, Health care, e–governance, e–participation, and built environment, 24×7 services for inhabitants and intelligent security and development of urban regional forces. The characteristics of smart cities vary from city to city. Smart Cities can be identified in six main dimensions. These are 1.Smart economy, 2. Smart mobility, 3. Smart environment, 4.Smart people, 5.Smart living, 6.Smart governance. And these six axes are based on traditional regional and neoclassical theories of urban growth and development. As a great first step, 100 smart cities have been identified. For the number enthusiasts, the five states with the largest number of future smart cities could be Uttar Pradesh -13,Tamil Nadu -12, Maharashtra -10, Madhya Pradesh -7, Karnataka -6, and Gujarat – 6, each state and union territory would get at least one each the total 100 smart cities finalised by the Government of India. Attention is being paid to make use of technology to improve water management processes, apart from ensuring that cleanliness of public places is duly maintained. And of course, digitalisation of the law and order functions is very much in area of focus.

OBJECTIVES OF THE STUDY

1. To study improve and performance of the administration, planning and decision ma transparency, with less cost and time maximise benefits of smart cities.
2. To study enhance accountability and, successful implementation of the public sector private sector issues and challenges.
3. To find out the creation socio–economic infrastructure in the selected cities throughou country.
4. To know the need of smart cities and analyze factors influencing and indicates the ur development.

METHODOLOGY

This research paper seeks to explore these potential differences. The Indian perspectives smart city was obtained by analyzing tree defferent data sources they are a citizen survey a list planned smart city projects and smart ciy vision the cities considered in this study were grouped int various clusters based on their population. The impact of population size on citizen's priority ar focus areas expressed in the vision statements. It is exclusively based on secondary data, which is collected from various books, journals, publications, articles, Indian economic survey, economic and political weekly, economic times, Indian economic journal, government website etc. The role and importance of smart cities in urban development in India and which is focus on the urbanisation modernisation, and digitalisation.

SCOPE OF THE STUDY

This study covers the issues and challenges of under the smart cities in India and urba development. And performance of the admistration, planning, decision, and creation of socio and economic infrastructure in the selected smart cities and various fields.

NEED OF THE STUDY

Two and a half years after announcement of the smart city mission 6.4 percent of the total identified projects have been completed with utilisation of just 1.6 percent of the total envisaged investment of Rs 1,38,730 crore (17.36 billion euro). Many projects are stuck as local governing bodies are unable to raise money using their own resources many cities are also facing resistance in execution of projects as citizens have opposed user charges for services provided under the smart city mission.

IMPORTANCE OF THE STUDY

India has bright prospects of smart cities with the support of the government of India the foundation year efficient planning for designing smart cities in whereas cities and well defined policies give support for the successful execution of smart cities mission smart cities projects can have good impact on the quality of life of the citizens some of the major challenges towards completion of smart city mission are discussing the accurate background model for smart city, societal adequacy and lack of awareness about ICT, difficulty in upgrading the old cities has smart cities has smart cities, a requirement of efficient coordination, efficient governance, the requirement of funds. Along with the urbanization the people of the rural areas have a tendency to migrate towards the urban areas. The union cabinet on 29th April 2015 cleared a project to develop smart cities. Rs. 48,000 crore

of Rs 50,000 crore has been approved by the Cabinet. Most of the smart cities will be brown (old) ventures and will be implemented through an 'area-based' approach including retrofitting redevelopment. There will be green field (new) projects, too, that will Leeds in development cities. Focus will be on core infrastructure services like adequate and clean water supply, sani and solid waste management, efficient urban mobility and public transport, affordable housing the poor, power supply, robust information technology connectivity governance, safety and se of citizens, health and education, and sustainable urban environment.

It is set to take steps within the current financial year, there were already smart city constru projects in India including Lavasa (Maharashtra), GIFT (Gujarat), Smart Kochi (Kerala), Mahi World City Chennai (Tamilnadu) and Jaipur (Rajasthan) in different operational modes inclu Public Private People Partnerships (PPPP). It is a good sign for the government of India to constructing 100 Smart Cities across the India by in collaboration with multinational companies un PPPP model, which will really increase our national economy. As smart city is a system complica and completive so, at a time we cannot construct entire 100 smart cities in India which is ve expensive and very tedious job. It can be explained in two ways, the first one is converting bro field cities (the existing cities) into smart cities by deploying technology in all the pillars of the ci

ISSUES AND CHALLANGES OF SMART CITIES IN INDIA

Financing to smart cities–The High Power Expert Committee (HPEC) on investment estima in urban infrastructure has assessed a per-capita investment cost (PCIC) of Rs 43,386 for a 2 years period. Using an average figure of 1 million people in each of the 100 smart cities, the to estimate of investment requirements for the smart city comes to Rs 7 lakh crore over 20 years. Th translates into an annual requirement of Rs 35,000 crore, one need to see how these projects w be financed as the majority of project need would move through complete private investment o through PPPs (public-private partnership). Smart cities project is not smartly privileged, unfortunate when it comes to funding. Financing is said to be one of the biggest challenges when it comes t the smart city challenge. The total investment approved under the smart city plans of 90 cities ha gone up to Rs 1, 91,155 crore.

Availability of master plan- Most of our cities don't have master plans or a city developme plan, which is the key to smart city planning and implementation and encapsulates all a city needs to improve and provide better opportunities to its citizens. Unfortunately 70-80 percent of Indi cities don't have one. Fruitful implementation of a project can be done only if there is a co-ordinatio between various government bodies. There is a need of proper regulation when it comes to planning for the development of smart cities. Both horizontal and vertical co-ordination is the requisite right now

Financial sustainability of ULBs- Most ULBs are not financially self-sustainable and tariff leve fixed by the ULBs for providing services often do not mirror the cost of supplying the same. inadequate cost recovery will lead to continued financial losses, most cities in India do not have their master plans and development plans in place. This is a tragic situation if we talk about developing them int smart cities. The presence of both the requisites is the key to the implementation and encapsulation of the smart city project as that is where the changes would be monitored and there is no other way to make it simple, better and efficient, unfortunately most cities in India lack the presence of it

Technical constraints of ULBs- Most ULBs have limited technical capacity to ensure timely and cost-effective implementation and subsequent operations and maintenance owing to limited recruitment over a number of years along with inability of the ULBs to attract best of talent at market competitive compensation rates. The entire smart city plan is a one big plan which should get all the clearances if not before time then on time, everything should be online and timely which unfortunately

is not happening in this case. The most important step to be taken in this context would be setting up a single regulatory body which monitors all the requisite approvals for the project, doing this will address two major issues one of co-ordination and one would be the timely execution, also the body should be solely responsible to cater to the financial requirements.

Retrofitting existing legacy city infrastructure to make it smart- There are a number of latent issues to consider when reviewing a smart city strategy. The most important is to determine the existing city's weak areas that need utmost consideration, e.g. 100 percent distribution of water supply and sanitation. The integration of formerly isolated legacy systems to achieve citywide efficiencies can be a significant challenge.

Three tier Governance- Successful implementation of smart city solutions needs effective horizontal and vertical coordination between various institutions providing various municipal amenities as well as effective coordination between central government (MoUD), We are very much aware of the unfortunate fact that India as of now is not that equipped when it comes to skilled manpower and advanced technology requirements for developing 100 smart cities. That is a huge number and requires lot of skilled efforts. If we talk about creating skilled labour and capacity building, not much funds have been allocated by the centre and state in such initiatives. Providing clearances in a timely manner- For timely completion of the project, all clearances should use online processes and be cleared in a time-bound manner, a regulatory body should be set up for all utility services so that a level playing field is made available to the private sector and tariffs are set in a manner that balances financial sustainability with quality. This point probably was meant to be from the first as this is the root cause for all above challenges. But if we talk about it solely this is also a major challenge. Corruption is responsible for all the co-ordination mismatch and time lag happening. The financial constraint also somehow creeps in because of this issue. It is a challenge which has always been a reason for non-execution or ineffective execution of most big projects in the country.

Dealing with a multivendor environment- Another major challenge in the Indian smart city space is that (usually) software infrastructure in cities contains components supplied by different vendors. Hence, the ability to handle complex combinations of smart city solutions developed by multiple technology vendors becomes very significant.

Reliability of utility services- the focus is on reliability of utility services, whether it is electricity, water, telephone or broadband services. Smart cities should have universal access to electricity 24×7 this is not possible with the existing supply and distribution system. Cities need to shift towards renewable sources and focus on green buildings and green transport to reduce the need for electricity.

Capacity building programme- 100 smart cities is not an easy task and most ambitious projects are delayed owing to lack of quality manpower, both at the centre and state levels. In terms of funds, only around 5 percent of the central allocation may be allocated for capacity building programs that focus on training, contextual research, knowledge exchange and a rich database. Investments in capacity building programs have a multiplier effect as they help in time-bound completion of projects and in designing programs, developing faculty, building databases as well as designing tool kits and decision support systems. All the above points are exemplary of the fact that the smart city project although being a dream project has many implementation challenges. The project had been launched with different names many times but the final outcome is still awaited.

India's SCM hopes to revolutionize city life and improve the quality of life for India's urban population. It would require smart economy, bright people, smart organization, smart communication, smart engineering, smart transit, fresh environment and bright living. Nevertheless, with mass migration leading to basic publications, like water shortages and overcrowding, the rate at which these cities will be developed will be the key. Several initiatives are being led by the Government of India to convert 100 cities into smart cities. The government is concentrating on encouraging Public Private

Partnership (PPP) for successful implementation of the smart city project in India. Financial ar services sectors are on the priority list of the government to garner investments from leading compa such as Cisco, Synoate, Knight Frank and AECOM India. The real challenge before the Governm is to build inclusive smart cities for all its residents, regardless of whether they are rich or poor. The smart cities would concretize the dream of every Indian to live in an urban city. Not only there wi cleaner streets but also advanced public transport and other well managed infrastructural facili The big challenge will be to create self-sustaining cities, which create jobs, use resources wis and also train people. Even though it is Rs. 7060 Crores for the initial investment for set out Sm Cities, let we put hands together to make India more economically brighter. In addition, to this gl warming can be reduced in constituent of this Smart Cities. Let us hope that soon India will prov Quality of Life, better life to its citizens on par with other Smart Cities like Barcelona, Helsinki, a San Fransco, New York, Singapore. Smart cities are equitably distributed across all the states

SUGGESTIONS

1. The first priority should be given to 100 smart cities for the rapid development The prop utilisation of resources and budget to aware the society for way of clean and green a swatch cities.
2. The only way out is planned urbanization. Public and private bodies must join hands a come up with smart, sustainable and long-term solutions.
3. Creating thriving and self-sufficient urban spaces will not only ensure inclusive growth b also contribute to overall economic advancement. The future of India lies in cities and w must fortify the mif the country has to prosper.
4. It is extended 100 cities to 1000 cities throughout the country increase financial source constitute a special body for inclusive and sustainable development in India.

CONCLUSIONS

Smart solutions for smart cities the government is taking initiatives to provide smart solution in the major components of smart cities. It will help to drive the various innovative solutions tha incorporated to make cities smart. The government is playing a vital role during progress of a smar city the growth of smart cities is good in later years compare to earlier years the current growth o smart cities will strengthen the assimilation of resources in India. To make existing cities as smar cities or quite challenging the challenges faced during the constructions of smart cities can be overcome by providing a good economic structure and with good governance smart cities can provid a sustainable environment with innovations using information communication technology such as bi data plot forms, artificial intelligence and the internet of things IOT make smarter in a much bette way. Introducing the concept of smart cities in India is a great idea but due to increasing power rate, lack of infrastructure and basic amenities, the cities might have to face a lot of challenges Before initiating the project, the government should try to attend to the basic issues of the nation such as implementing a proper drainage system, providing good water, sanitation and health care facilities etc. Smart cities could thus be the catalysts for digitalisation of surveillance systems tha can be automated to generate near – real time triggers and alerts while also respond to advance queries and searches seamlessly. At the same digitalised surveillance could help smart city projects get to speed quicker with regard to their economic, environmental, as well as citizen – centric goals After all cities that are safe to live, communicative, and do business in a sustainable manner only can be truly SMART. We welcome to the future of 100 Smart Cities in India, with a positive way collectively and cheerfully.

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CONTENTS

A Study on Health and Education in Socio–Economic Development of Telangana State–An Overview

Dr. Shyamu Ganta*

ABSTRACT

The present paper focused on the role of health and education in socio-economic development of Telangana state. Telangana is the 29th state of south India it is agrarian state results majority population lives in rural areas. The social economic development equity is the most important dimension it is directly influenced by the quality of health and education sectors but both sectors are poor stage in rural and semi urban in Telangana. The separate roles of education and health in promoting human development have been extensively studied and discussed. As the impressive social and economic performance of Telangana seems to show, strong education and health systems are vital to economic growth and prosperity. In addition to health and education the most important drivers of development include governance and other political factors, geography and climate, cultural and historical legacies, The interactions among these factors carry important implications for our understanding of the development process as well as for policy. It is now clear that increased access to education, although of great importance, is by itself no magic bullet. Its positive effects on development may b these connections and briefly outlines some central issues. Education is fundamental to development and growth, the human mind makes possible all development achievements, from health advances and agricultural and industrial innovations to efficient public administration and private sector growth for countries to reap these benefits fully, they need to unleash the potential of the human mind and there is no better tool for doing so than education. Government officials and development partners met to affirm the importance of education in economic development and broadly on improving people's lives and together declared education for all as a goal. While enrolments have risen in promising fashion around the world, learning levels have remained disappointingly and many remain left behind. Because growth and development and poverty reduction depend on the knowledge and skills that people acquire, not the number of years that they sit in a classroom, we must transform our call to action from education for all to learning for all. Key wards: importance of health and education sector, role government, and its influenced factors.

INTRODUCTION

The present paper is concentrated on the role and importance of quality of health and education in economic development of Telangana state. Telangana is the 29th state of India it is in June 2nd 2014, the birth pangs of the new state, pertaining to bifurcation of staff, institutions and assets, within the framework of the Andhra Pradesh State Reorganisation Act, 2014. While many of these disputes remain unresolved even after seven years, the determination of the state of Telangana to overcome these challenges and to prove the prophets of doom wrong came out loud and clear in

the first few months of the formation of the state. Telangana crucial role plays for reduce poverty and unemployment in the state the government initiates to provide socio economic infrastructure, the socio and economic equity is the most important dimension it is directly influenced by the health and education factors. The availability of health and education facilities in public sector economic development is growing rapidly. The separate roles of education and health in promoting human development have been extensively studied and discussed, as the impressive social and economic performance of India and Telangana seems to show, strong education and health systems are vital role in economic growth and prosperity. Moreover, the Millennium Development Goals adopted by member states of the United Nations in September 2000 are evidence of an international consensus regarding human development: five of the eight goals relate to education or health. Recent research that links education and health suggests novel ways to enhance development policy by taking advantage of the ways in which the two interact. Development is a complex process involving multiple interactions among different components. In addition to health and education, the most important drivers of development include governance and other political factors, geography and climate, cultural and historical legacies, a careful openness to trade and foreign investment, labour policies that promote productive employment, good macroeconomic management, some protection against the effects of environmental shocks, overall economic orientation, and the actions of other countries and international organizations. The interactions among these factors carry important implications for our understanding of the development process as well as for policy, the first part of the paper discusses why interactions between health and education are important. Education is fundamental to development and growth. The human mind makes possible all development achievements, from health advances and agricultural innovations to efficient public administration and private sector growth. For countries to reap these benefits fully, they need to unleash the potential of the human mind. And there is no better tool for doing so than education, twenty years ago, government officials and development partners met to affirm the importance of education in development on economic development and broadly on improving people's lives and together declared education for all as a goal, while enrolments have risen in promising fashion around the world, learning levels have remained disappointingly and many remain left behind, because growth development, and poverty reduction depend on the knowledge and skills that people acquire.

The first step taken towards the formation of a state educational system was opening of Oriental college as Dar-ul-Ulum by Salar Jung at Hyderabad in 1853-54 with 130-160 pupils on roll. This college imparted knowledge of oriental lore in the Deccan and taste of learning through two classical languages, viz., Arabic and Persian. Provision was also made for instruction in four modern languages urdu, telugu, english, and Marathi. Subjects like Physics, Chemistry, Mathematics and Astronomy formed part of the curriculum. In 1860, a school was opened in each district headquarters and Taluk headquarters. A school of engineering was established in 1870 to produce the required technical staff to public work department. In the year 1876, students were awarded foreign scholarships to go abroad for advanced study. They were also promised employment in government services on completion of their studies in such advance courses, in the first phase of reforms from 1853 to 1883 the efforts of Salar Jung to modernize the administration required officials trained in British India. There are certain private institutions known for their outstanding standards, but, they remain islands of excellence in an ocean of ignominy. For instance in 2011-12, GER in higher education ranged between 8.4 percent in Jharkhand and 53 percent in Chandigarh. The GER in higher education is 24.5 percent for boys, 22.7 percent for girls, 18.5 per cent for SCs and 13.3 per cent for STs in 2014-15. Data for enrolment by category showed that those not belonging to the Scheduled Castes (SCs), the Scheduled Tribes (STs) or the other Backward Classes (OBCs) dominated higher education in the country, occupying 60 percent of seats in all universities, 72 percent in Central universities and

58 percent in State public universities. Members of the SC communities accounted for just 10 percent of all university seats nationwide, STs 4 percent and OBCs 26 percent within central universities, their representation was 11 percent, 4 percent and 13 percent respectively.

NEED OF THE STUDY

Telangana state 29th rank in education in the country it has a literacy rate of 66.54, as against All India literacy rate of 74.2 percent. In India, Kerala has a highest literacy rate of 94 percent, Bihar with a lowest rate of 61.8 percent. For Human Development, it is important to see the differences in urban-rural literacy gaps as well as male-female literacy gaps in 2011. urban-rural gap rural Telangana literacy rate was 57.3 percent and urban literacy rate was 81.1 percent of literacy rate. The gap in the literacy rate between urban–rural is 23.84 percent, whereas at all India level urban-rural literacy gap is 16.3 percent. male-female literacy gap male literacy rate in the state was 75.04 and female literacy rate was 57.99. male-female literacy gap was 17.05 percent which was higher than the all India male-female literacy gap of 16.68 percent, caste and literacy rates were lower among SC and ST communities as compared to other communities. While overall literacy rate was 66.5 percent, corresponding rates among SC and ST communities were 58.9 percent and 49.5 percent respectively in the year 2011.

OBJECTIVES OF THE STUDY

1. To study the role and importance of health and education in socio economic development of the state.
2. To understand the concept of health and education infrastructure in the study area and monitoring the private sector issues.

HYPOTHESIS

1. To study the current scenario of health and education facilities, to examine the role government in health and education under the public sector.
2. To evaluate the present and combined state in same factors.

METHODOLOGY

The present study completely based on secondary data the data collected from the various journals, books, publications, news papers, magazines, research papers, government web site, etc. the present paper is focused on the importance of health and education in socio economic development of Telangana and its influenced factors public private sector role in the state.

IMPORTANCE OF THE STUDY

The government of telanagana introduced kanti velugu, basti dawakhana, health and wellness centers, ayurvda yoga naturopathy unanai and homeopathy AYUSH arogya sri health centers provides healh facilitites but it has not achieved. The central National rural health missions, Naional Urban Health Mission, Urban Slum Health Services, Birth Waiting Homes, Residential Gurukul schools for girls and boys, Telangana Vaidya vidhana Parishad, Ashram Schools and Hostels, Sanna Biyyam Pathakam, Anganwadi Schools, Good health can also alter the population growth rate in ways that promote development. Health improvements often have the greatest effect on those who are most vulnerable, children in particular. Advances in medicine and nutrition increase the likelihood

that a child will survive into adulthood, and parents therefore need to bear fewer children to attain their ideal family size high fertility, still prevalent in much of the developing world, tends to decline when child survival improves (Stark and Rosenzweig, 2006). Reduced fertility means parents can concentrate investments of time and money on a few children rather than spreading these resources across many, thus enhancing their children's prospects of leading healthier and better-educated lives. Reduced infant and child mortality lessens emotional stress on families, potentially increasing family cohesion, and gives parents more time to devote to productive activities as the need to care for sick infants decreases.

The literacy rate in the two states is second lowest in the country next to Bihar and lower than all India average of 69 percent. In Andhra Pradesh the percentage of dropped out school students is 58.9 while 67.2 in Telengana. Most of the dropped out students are from farmers' families/families involved in agriculture, the computer knowing students in the age group of 14-29 is the lowest in Telangana compared to other Indian states. The students pursuing professional/technical courses per thousand are lowest in Telengana compared to other states. However, the number of students per thousand studying engineering is highest in Telengana. Moreover, the report suggests the states to promote medical education. As per the report, the figure for the number of students per thousand who are pursuing professional/technical courses, is among the lowest in AP 34 and Telangana 30, compared to states like Maharashtra 86, Kerala 156 and Punjab 100. However, number of students per thousand studying engineering is the highest in AP 579 and Telangana 599. The survey report shows students taking admission in the government institutions which is among the lowest in the country. However, there were also some parameters both the states have performed well. AP is among the top five states with 335 out of thousand students have internet connections, with Telenagana (185) standing at fourth position.

Education plays a key role in determining the increase in work participation rate and productivity. However, education levels in the working population in Telangana leave much to be desired. Telangana State, ranging from up to primary to secondary, intermediate, graduation, post-graduation and above, and also diploma/polytechnic/ITI. Of the state's 2.39 crore working age population, about 34 percent are illiterate. Of the educated working age population, 7 percent are educated up to primary level, about 29 percent have completed secondary school and 10 percent have studied upto intermediate level. The working age population that has studied or are pursuing higher levels of education is about 20 percent (graduation 14 percent and post-graduation 4 percent or above). Only 1 percent of the working age population in the state are having polytechnic/ industrial training institute diploma. Thirty-seven per cent of students in Telangana are in primary level, 20 percent in middle level, 13 percent at collegiate level, 2 percent each in PG level and diploma courses. The proportion of ST students pursuing collegiate education is the lowest. The OBCs have the highest proportion of students in graduate and PG level. Among socio-religious groups, Hindus have the highest proportion of students in PG while Muslim students are highest in primary school 43.4 percent, with attendance dropping sharply in higher secondary 7.6 percent. 94 percent of students are in the general stream whereas only 6 percent are in the professional/technical stream. Proportion of students attending government institutions is the highest among ST students and it progressively declines as it moves up the social hierarchy. Forty percent of students attend government institutions. Among rural students, 54 percent attend government institutions whereas 44 percent attend private unaided institutions. In contrast among urban students, nearly four-fifths attend private unaided institutions. Among social groups, more ST students attend government institutions 65 percent rather than private. Half of the SC students attend government institutions. In contrast other students predominantly attend private unaided institutions 72.6 percent. 41 percent of ST students claimed better environment of learning in private schools and another 33 percent complained about poor quality of education in

government institutions; 30 percent of SC students who are in private stream are in it for the sake of English medium education and 10 percent of them did not get admission in government institutions; poor quality of education in government schools is most important reason for the OBCs and others for choosing private institutions. Thirty-eight percent of students in the state get free education. The proportion of students who get free education is the highest among STs and it declines with the higher social groups, one fifth of the students in the state get scholarships, the highest proportions of students who get scholarships are SC students and the next highest proportions of students who get scholarships are OBC students.

In Telangana, the percentage of women married before the age of 18 years (who belonged to the age group of 20–24 during the time of survey) is much higher in rural areas (about 35 percent). In urban areas, the corresponding percentage is 15.7. This indicates the prevalence of early marriage system in Telangana especially in rural. The IMR is also not showing a good sign of health for society, rural IMR is 35 and urban IMR is 20, the situation of under-fi ve mortality rate is also a concern in Telangana with 38 in rural and 25 in urban (NFHS-4, 2015-16). The use of family planning methods is about 59 and 56 per cent in urban and rural areas respectively among the women of age group 15-49. The role of health workers in spreading this is also to be improved a lot. According to NFHS-4 (2015-16), even though the antenatal care is good among the women in terms of their fi rst visit, it is only 47 and 37 per cent respectively for urban and rural areas who got full antenatal care, around half of the pregnant women had consumed iron folic acid for than 100 days. Although institutional births in Telangana are higher 96 percent in urban and 87 percent in rural, the institutional births in public facilities are too low at about only 27 and 34 percent for urban and rural areas. According to the NSSO 2014 71st Round survey, the percentage distribution of women (aged 15–49 who gave birth in private hospitals is higher in Telangana both in rural 59.3 percent and urban area 74.3 percent when compared to all India 22.5 percent and 45.8 percent respectively the rate of utilisation of public hospital for this purpose is very low in Telangana 29.4 percent in rural and 22.5 percent in urban when compared to all India 41.4 percent and 38.4 percent respectively, it is to be noted that the rate of deliveries at home is very low in Telangana 2.2 percent in rural and 1.6 percent in urban when compared to all India 19.9 percent and 10.5 percent respectively. This necessitates state policy orientation towards ensuring mother and child care through public institutions. The SDGs is that health is a major contributor and beneficiary of sustainable development policies. It is believed that health affects, and is in turn affected, by many socio-economic and environmental determinants. Although health for all is one of the 17 goals in SDGs, it emphasises that policies made in all sectors can have a profound effect on population health and health equity. To address the multi sect oral nature of health determinants requires the political will to engage the whole of government in health. The health sector should promote Health in All Policies, an approach to public policies across sectors that systematically takes into account the health implications of decisions, seeks synergies and avoids harmful health impacts in order to improve population health and health equity and address the social determinants of health. Within the health sector, India's priority concerns are maternal, newborn and child health related issues. Maternal and infant deaths are still critical concerns. Undernourishment among children is another major issue across all the states in the country.

The high birth rate and low death rate indicate the demographic transition India is going through. In India the demographic transition is being accompanied by an epidemiological transition where Non Communicable Diseases (NCDs), mental health disorders and injuries become much more prominent as a cause of death and disability. Major health statistics on Maternal Mortality Ratio (MMR), Infant Mortality Rate (IMR), sex ratio, birth rate and death rates of Telangana. MMR is considered to be low if it is less than 100, moderate if it is 100–299, high if it is 300–499, very high if it is 500–999 and extremely high if it is equal to or higher than 1,000 maternal deaths per 1,00,000 live births,

to promote institutional deliveries at public health facilities and to bring down the MMR, the state government is strengthening Comprehensive Emergency Obstetric and Neonatal Care (CEMONC) services at various places in the state. Presently there are 66 CEMONC centres in the state to promote institutional deliveries and attend to pregnancy related emergencies. The CEMONC centres provide the services of obstetricians and anaesthetists, and emergency blood transfusion services round the clock. Provision of public health services is vital. A few important reasons are high rural population, low literacy rates, low incomes in rural areas. Only people whose motto is welfare can operate in such conditions. Obviously, it is only the public health system which can operate effectively and efficiently. With this backdrop, public health infrastructure needs greater attention in the state. In existing facilities are compared with the norms set by the Indian Public Health Standards (IPHS). The IPHS has set the requirements for public facilities in a state based on the population of the state. Compared to the required numbers, Telangana State has 69 percent of Sub centres, 74 percent of PHCs, 37 percent of CHCs and 53 percent of area hospitals. Apart from seven district hospitals, there are five mother and child care hospitals (MCH) and 18 teaching and specialty hospitals operating in the state, KCR kit to after deliver, the mother is provided with the KCR kit. The kit consists of 16 items that are essential to keep the new born clean and hygienic. The kit supplies would suffice the needs of the baby for three months, it has diapers, napkins, toys, mosquito nets, baby powder, baby oil, baby soaps, and clothes. It was launched in 2017, allocated Rs 605 crores for the scheme, compared to the adult literacy rate in India, the youth literacy rate is about 9 percent higher, despite this, it is matters of concern that yet so many people in India cannot even read and write, despite several initiatives by the government, the numbers of children who do not get education, especially in the rural areas, are still a concern. Nevertheless, the analysis on gender and age-wise literacy rates for Telangana revealed a higher literacy rate for the age group of 7–24 years 88.56 percent than the all-India literacy rate of 86.98. The data also shows a better situation in the state for males and females in the age group of 18–24 years at 90 percent and 79.5 percent respectively. And these figures are higher than the national average of 89.3 percent and 79.1 percent respectively, for the corresponding age group and gender. Hence, there is a need for focusing on adult education in the state. As per census 2011, among the literate population, 48.6 percent have studied up to middle school, 17.9 percent did pre-university, 1.6 percent did technical diploma, 0.3 percent completed non-technical diploma, 21.9 percent have graduation and above level of education, 0.9 percent completed un-classified courses and 8.8 percent are literates without education.

SUGGESTIONS

1. Government must provide quality of health and education facilities in the public sector free and compulsory.
2. Government must and should control and monitoring private/corporate schools colleges, institutions, and medical field, labs and hospitals.
3. Government must provide free and compulsory education through improve enrolment in primary level education in rural and semi urban areas.

CONCLUSION

It concludes this paper the health and education important role plays in socio economic development the state and as well as nation both, The national averages are high for those in the age group above 24 years, while averages for the same age groups in the state show low literacy rates in Telangana, the younger generation is going to school or able to access education than their elders, The quality health and education is a fundamental right, which leads to achieving the goal of

education for all over the years, efforts have been made at the state and national level to achieve this goal as per article 45 of the constitution of India, universalization of elementary education is a directive principle of state policy that underlines the need to provide free and compulsory education for all children up to the age of 14 years as per article, 21A and 93rd constitutional amendment 2009, education has become a fundamental right, this article spells out the responsibility of the state for providing free and compulsory education to all children from the age of 6 to 14 years this article has stated the constitutional position of right to education in our country.

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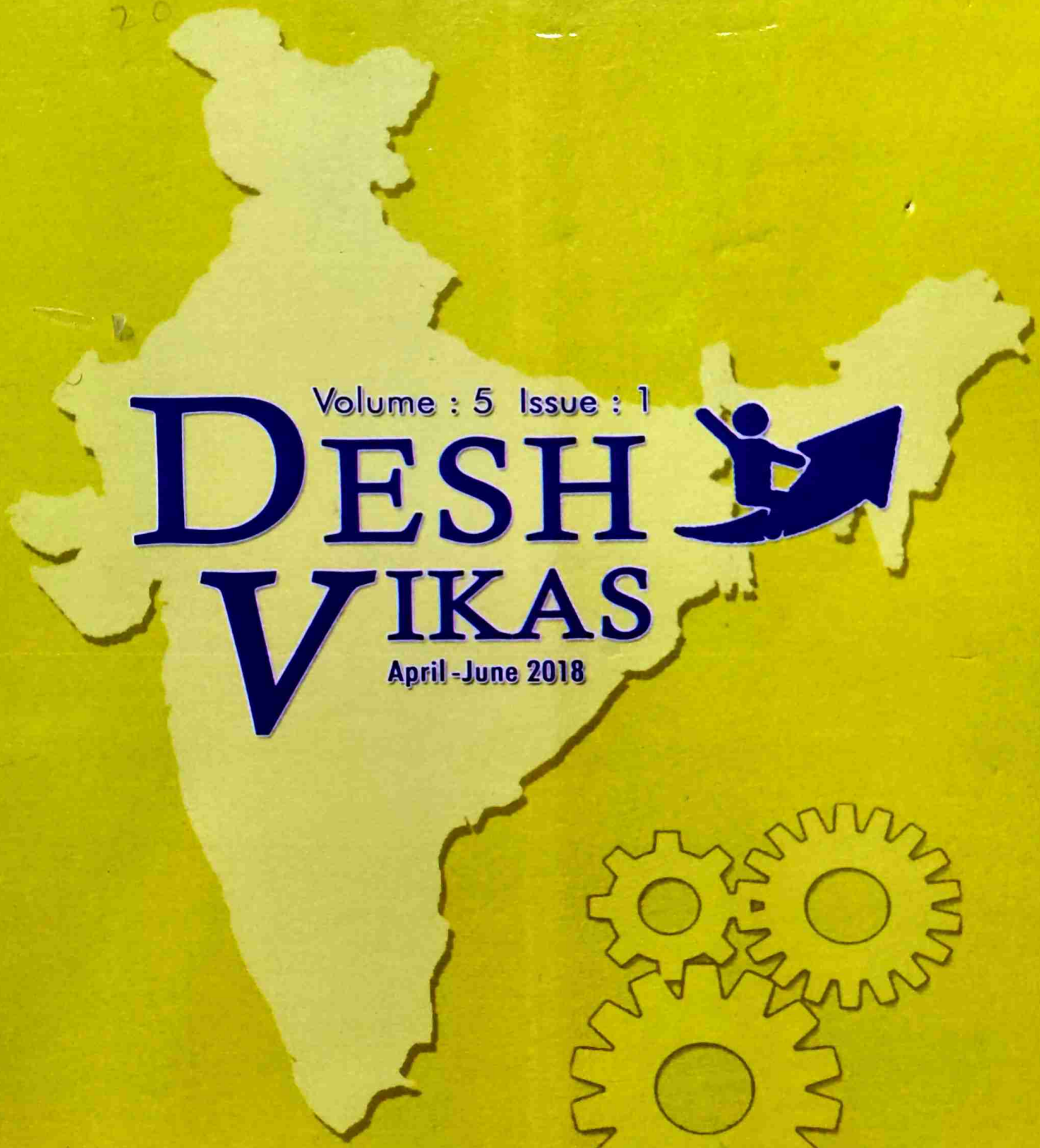

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Managerial Assessment on Tribal Development and Empowerment - An Overview

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ABSTRACT

The tribal and indigenous peoples of India constitute an important segment of the Indian population. The Constitution accords them special rights and privileges. Both the Government and the Non-Government Organizations (NGOs) have been engaged in their socio-economic development ever since Independence. But the question is whether the tribals have benefited from the various development interventions and been empowered in the country's federal structure in terms of governance and political participation. It first examines the tribal situation in the country and gives a critical appraisal of tribal development both by the government and the NGOs. It also analyses the process of tribal empowerment, particularly through the 73rd Constitutional Amendment and the consequent legislations for tribal self-rule. the discusses the indigenous question at the national and the international levels. Finally, based on the past and present scenarios, it tries to spell out the future trends of tribal development and empowerment in India.

Introduction

One way to examine the tribal development situation is to browse through the Report of the Working Group for Empowering the STs during the Tenth Five-Year Plan (2002-2007), under the Chairmanship of Dr. Ram Dayal Munda.which also reflects the framework of the Fifth and Sixth Schedules of the Constitution. But the report finds a reversal of this philosophy on three grounds.

1) The New Economic Policy and Scheduled Areas. There has been a clear shift from the strong protective role of the state towards the disadvantaged communities like tribals, to one of justification for their exploitation in the name of economic development.

2) Alienation of Tribal Lands to Non-Tribals. The case of Samatha against the State of Andhra Pradesh is a classic example of how the state has been violating its own constitutional duty in the Fifth Schedule Areas. In the name of economic development through industrialization, the state has been alienating tribal lands to private industries and development projects like mining, hydro-electric projects, industries and tourism. Between 1951 and 1995 about 35 million people have moreover been displaced on account of various development projects, 40% of them tribals. And only ¼ of the displaced persons have been rehabilitated.

3) Law and Order in the Scheduled Areas.

Extremism, political disturbances in the tribal areas are a result of exploitation or neglect, which is used by militant groups. Hence, it is the duty of the state to address the actual socio-economic problems of the tribal people and not to deal with the situation as an ad hoc law and order problem. Ruling the areas with armed forces or police battalions cannot solve the problem of violence or unrest.5 Similarly, the misuse of POTA by the police shows the state's high-handedness in containing naxalism in tribal areas. Today's tribal situation is distressing to say the least. About 1/3 of the Indian tribals still subsist through hunting and gathering or slash and burn cultivation, and there are tribal bonded labourers in the coffee plantations of Tamil Nadu and in the villages of Daltonganj and Giridih in Andhra Pradesh, not to mention those who work in the stone quarries in Uttar Pradesh and Madhya Pradesh. Considerable disparities also persist, although they are narrowing, in literacy and educational development.

As against the national average of 52.2%, the literacy rate of the Scheduled Tribes (STs) was around 29.6% in 1991. The ST women were illiterate. These disparities are compounded by higher dropout rates in formal education, resulting in the ST representation in higher education being disproportionately low. Not surprisingly, the cumulative effect has been that the proportion of the STs below the poverty line is substantially higher than the national average. As per the estimates of the Planning Commission, 51.92% of the rural and 41.14% of the urban ST population was still living below the poverty line in 1993-94, compared to 32.36% and 37.27% respectively of the total population. (The corresponding data for the SCs were 48.11% and 49.48%.).

Constitutional Privileges for Tribals

The Constitution of India has provided many safeguards for the welfare and development of the tribals. The relevant articles can be classified under four major heads: (A) protective provisions (Arts. 15, 16, 19, 46, 146, 342, etc.); (B)

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developmental provisions (Arts. 46, 275, etc.); (C) administrative provisions (Arts. 244 & 275) and (D) reservational provisions (Arts. 330, 332, 334, 335, 340, etc.) The protective provisions safeguard tribal people from social injustices and all forms of exploitation, while the developmental provisions promote with special care the educational and economic interests of the weaker sections like the STs & SCs. The administrative provisions under the Fifth and Sixth Schedules give special powers to the state for the protection and governance of tribal areas and the reservation provisions ensure due representation of the STs and SCs in legislative bodies and government jobs.

Whither tribal welfare Implementation?

Crores of rupees for dozens of Central or State programmes for tribal welfare and development are allocated every year, but the utilization of the funds falls short of the outlays, not to mention the impact of such schemes. Looking at the rural scenario in Andhra Pradesh, Chhattisgarh and Orissa where there is a substantial tribal population, one is dismayed to find that, even after more than 50 years of government's interventions, the majority of the people still live in stark poverty, malnutrition and illiteracy, prone to hunger, sickness, high morbidity and mortality, and exploitation. The buildings for schools, health centers and Panchayat Bhawans and the infrastructure like roads, bridges, wells and hand pumps are either dilapidated, poorly maintained or simply non-existent. The key problem is not a dearth of money, but the lack of political will and implementation capacity by the various departments and officials. The lack of responsibility, accountability and transparency has also led to the misuse of funds by government officials and ministers. Clearly, government inefficiency, bureaucratic lethargy and political apathy have all but kept the tribal people undeveloped and open to all sorts of exploitation.

The Govt.'s Anti-People Policies

The fact that the state has gradually abdicated its welfare responsibility, particularly towards the weaker sections, is demonstrated by a series of anti-people policies. It is ironical that, while India is emerging as an Asian economic miracle, most people from the weaker sections are adversely affected by major policy decisions. Let us mention a few of them.

(1) The Land Acquisition Amendment Bill, 1998. This bill further strengthens the hand of the government, when the Land Acquisition Act of 1894 as amended in 1984 was already bad enough, as it supported the principle of 'eminent domain' and empowered the Govt. to acquire any land for public purposes.

(2) The National Policy, Packages and Guidelines for Resettlement &

Rehabilitation, 1998. While the land acquisition part of the bill was debated in the Parliament, the second part on resettlement and rehabilitation did not even merit a debate by the political establishment!

(3) The Draft National Policy on Tribals.Though the first of its kind, the policy is fraught with misgivings on tribal identity, the tribals' rights and control over resources, and the significance of their traditional system of self-governance. The draft moreover undermines the significance of the Fifth Schedule, which prohibits tribal land alienation to non-tribals. A brief examination of government interventions thus reveals that, though the schemes promise a lot, little practically materialises for the welfare of the tribals and the enhancement of their quality of life. The government's anti-people policies even indicate that it is not truly interested in the development and empowerment of the tribal people.

The SWOT Analysis of NGOs/VOs

A few words need to be said about the strengths, weaknesses; opportunities and threats (SWOT) of the NGOs/VOs, to ascertain their place in society. The strengths of the NGOs are that they are closer to the people – the poor, marginalised and exploited. In each sphere, they have accumulated a significant body of experience and knowledge which can serve as resource for new models, policies and practices. One of the weaknesses of the NGOs is that they are too dependent on external funding, which has often its own agenda. There is also a rat race to start NGOs without making them instruments of social change. Many of them primarily serve their own interests rather than people's interests; they are like shops doing business with the funding agencies. As for opportunities, the NGOs have them in abundance, depending upon their initiative, commitment and action in today's heavily polarised, exploited and dehumanised world. Finally, their threats lie in being co-opted by the forces of globalisation and liberalisation and the policies of the rich and powerful.

Assessment of the Christian missionaries Role

In the eyes of the general public, the Church's role in development including tribal development is known as that of the Christian missionaries. Both the Government and the NGOs recognise the pioneering role played by the Church in education, health care and the welfare and development of marginalised societies. Looking at tribal development from within the Church, we can say that it was done according to her own social teaching but also in line with the country's development framework and ideology, which is stated in the Directive Principles of State Policy. The Church's involvement in tribal development is very varied and covers practically every aspect of tribal wellbeing: be it in education, health, agriculture, technical development, cooperatives, self-help groups (SHGs), people's empowerment and human rights issues.

What is important is to get an overall assessment of the Church's role in tribal development. Instead of making a theoretical evaluation, let us give an example of the Church's role from a study recently conducted in Chhattisgarh.The five major areas considered were primary, non-formal and vocational education, health care especially for mother and child, income generation, women's development and human rights issues. The main assessments of the Church's role by the 400 respondents from all over the State are worth noting. (1) Govt. facilities are generally preferred in many fields. Most respondents felt that they benefited more from government schools than Church schools, not only in terms of jobs but also with regard to the awareness of human rights issues and the promotion of tribal culture and identity. The main reason for the people's preference for govt. schools is their proximity and affordability. The inference is that the mission schools have not reached as widely and are costlier. Nevertheless, the mission schools are always preferred regarding quality education.

The people similarly assess the respective contributions of the Government and the Church in health matters, income generation and women development: the govt. facilities have benefited the people more, but the quality services of the mission are preferred. (2) The NGOs fare better than Church organisations in nonformal education and justice issues. (3) The Church's pre-primary and primary schools are more effective for children's capacitybuilding. (4) The RAHA module of health services is unique. The Raigarh Ambikapur Health Association (RAHA) envisions a wholesome, sustainable, caring and transformed community of people. It is greatly appreciated. (5) The CRS programmes for sustainable agriculture are quite effective. In the Ambikapur and Raigarh dioceses, the resource mobilisation for sustainable agriculture has paid rich dividends to the people through agro-based income-generation programmes based on vegetable cultivation and tree plantation. The CRS has also shown the way through watershed management. (6) The Church-run SHGs and women's groups are equally effective. The formation of dozens of women's SHGs and cooperatives in the villages of Raipur diocese is exemplary. It is quite effective as a socioeconomic intervention for self-reliance and social action.

Tribal Empowerment

A process of tribal empowerment was initiated in India through the landmark 73rd Constitutional Amendment in 1993. The reasons for this amendment were the largely Panchayati Raj system in the country and the need for adapting to the tribal system of local self-governance. The Provisions of the Panchayat (Extension to the Scheduled Areas Act), 1996 (PESA) was thus legislated and the States having Fifth Schedule Areas were required to enact conformity laws within a year. The distinguishing feature of these legal instruments is to recognise the traditional structures of self-governance in the tribal areas and to transform them into units of

local self-government, particularly through the Gram Sabha. Salient features of this Act. (1) The state legislation on the Panchayats has to be in consonance with the customary laws, social and religious practices and the traditional management practices of community resources and dispute resolution. (2) The community is the centre of the Gram Sabha. (3) The Gram Sabha has wideranging powers and functions: approval of the plans, programmes and projects for social and economic development; selection of beneficiaries for poverty alleviation; (4) being consulted for land acquisition for projects; control over minor water bodies, minerals and forest produce; enforcing prohibition; management of local markets and check on moneylenders, etc. As far as the praxis of tribal self-rule is concerned, many state laws, particularly in Andhra Pradesh, are not in conformity with the Central PESA Act.

The Indigenous Question

The tribals of India are also called Adivasis. In Hindi, the term means original settlers and adequately expresses the indigenous character of the tribals. But the Government of India does not accept the term 'indigenous'. This has put the very identity of the tribal people in question, for they assert that they are the original settlers of the country and are entitled to enjoy this status. The Government of India has consistently denied that there are any indigenous population in the country. At least on two occasions, the Indian delegates reiterated this position at the UN Working Group on Indigenous Populations at Geneva, mainly on the ground that the tribal communities of India do not retain their pristine tribal character. There are two obvious problems with these statements, according to Sanders who was present at the 1992 UN Conference.13 On one hand, the Indian representative claimed that the tribals had all been absorbed, but on the other he mentioned the special programmes for tribals and noted the existence of the tribal majority States in the Northeast. Either tribals survive or they do not survive! The second problem is the preoccupation with racial and cultural purity. The statements suggest that only tribals who retain their "pristine" tribal culture are real tribals. If such racial and cultural criteria were universally applied to indigenous peoples, there would be almost no "indigenous people" anywhere. Indigenous or tribal peoples do, not forfeit their character as distinct peoples by adaptation! All the same, the debate continues on the indigenous question, which is primarily a political question to firmly establish the tribal quest for social justice. One of the reasons why the indigenous status is not granted to the tribals, comments Fernandes, is that a clause in the ILO Convention can be interpreted to mean that indigeneous peoples have a right to demand secession. It should however be clear, for example from the ICITP Charter, that what the tribals are demanding is self-reliance

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Conclusion

The tribal development and empowerment as carried out in India by both the Government and the NGOs presents a mixed scenario. The Government gives constitutional guarantees to the tribals, but fails to implement them adequately. Over the years it has also made various policies which are against the poor and the marginalized like the tribal. The NGOs have fared a little better, but need to address the tribal problems and issues more consistently and adequately. Except for a few NGOs/VOs known for their wider mass base and capacity to bring about socio-economic change, many or most of them are complacent and just do the routine work, primarily serving their own interests.

The Church institutions have contributed their own share to tribal development, and are often lauded in the areas of education, health services and other works of charity, welfare and development. But they too need to broaden their base and reach out to the disadvantaged tribal groups in the remotest areas. Moreover they need to adopt the social action approach of people's empowerment and not be confined to the safe and secure approaches of charity, welfare and economic development. In this regard they must join hands with secular civil society groups and work for greater tribal development and empowerment. The three institutions of the Government, the NGOs and the Church can play complementary roles in tribal development and empowerment. While the Government has constitutional provisions and resources, its delivery mechanism needs to be strengthened in collaboration with the NGOs and Church institutions. But it is ultimately the people who must demand their rights and privileges.

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Strategies for Livelihood Promotion of Women Self Help Groups in Indira Kranthi Patham in Andhra Pradesh

Dr. Shyamu Ganta*

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ABSTRACT

Achieving the Millennium Development Goal (MDG) of having the proportion of people living in absolute poverty by 2015 will require agriculture to play a major role. Increasing agricultural productivity remains perhaps the single most important determinant of economic and poverty reduction and hence provides the key to achieve the MDG. The goal of the Indira Kran-thi Patham project is to reduce poverty of below poverty line households through sustainable community based women organizations by introducing livelihood interventions through institution building, human resource capacity building and community managed sustainable agriculture. A study was conducted to understand these aspects of Indira Kranthi Patham (IKP) along with the problems encountered by the members of women self help groups for livelihood promotion.Based on these results,strategies were suggested for effective implementation of IKP for livelihood promotion. Various organizational, technical and extension strategies for livelihood promotion of self help groups through IKP were proposed after a thorough study of the programme. There is no assured water supply because of the vagaries of nature, often crops dry up. It has therefore, become imperative to protect farmers against such losses. If such assurances are not given to farmers, they may give up farming and turn to some other vocation or employment. Andhra Pradesh has used Self Help Groups (SHGs) extensively as a primary tool for poverty alleviation and empowerment. The basic principle behind SHG functioning is collective action with suitable support, self help groups can move on to collective action at the community level but more remains to be done for sustained poverty alleviation.

Keywords: Self Help Group, Indira Kranthi, SERP, DRDA etc.

INTRODUCTION

The largest poverty alleviation project being implemented by SERP and funded by DRDA in Andhra Pradesh is Indira Kranthi Patham (IKP). The goal of the Indira Kranthi Patham project is to reduce poverty of below poverty line households through sustainable community based women organizations by introducing livelihood interventions through institution building, human resource capacity building and community managed sustainable agriculture. With this background, a study was conducted to examine the progress of programme in the BPL self help groups.

METHODOLOGY

Exploratory research design was followed for the study. Mahaboobnagar district was selected as it is one of the largest districts in Telangana region with highest number of mandals under Indira

Kranthi Patham. Out of sixty four mandals, two mandals *viz*., Kolhapur, Achampet were selected by random sampling on discussion with IKP staff.

Two villages *viz*., Chukkayapalli and Yenamalametla from Kolhapur mandal, Uppunutala and Gattuthumen from Achampet mandal were selected at random from each of these mandals and thus, a total of four villages were selected for the study. Thirty women belonging to two groups were selected at ran dom from each village. A total of one hundred and twenty (120) respondents of eight groups were selected from the above selected villages for the study. The problems perceived in lively hood promotion and suggestions thereof were expressed by the women and recorded in terms of frequencies and percentages.A study was conducted to understand various aspects of Indira Kranthi Patham (IKP) based on which strategies were suggested for effective implementation of IKP for livelihood promotions. The study shows a path of movement to make groups self sustainable and self reliant.

RESULTS AND DISCUSSION

Table-1: Distribution of respondents based on problems perceived and suggestions given for livelihood promotion n=120

S. No.	Problems	F	Rank	Suggestions	F	Rank
1.	Diverse interest in groups	103 (85.83)	I	Formation of homogeneous groups with common interest	101 (84.16)	I
2.	lack of encouragement to each and every group member to	100 (83.33)	II	Encouragement should be given to every member in the group to	98 (81.66)	II
3.	Lack of capacity to formulate plans for group development	87 (72.50)	III	Capacity building of groups for formulation of plans	86 (71.67)	III
4.	Lack of a rider before & during loan utilization	79 (65.83)	IV	Provision of a rider before & during loan utilization	76 (63.33)	IV
5.	Less farming activity in the	66	V	Increase of farming activity in the area	61	V
6.	Lack of resource persons at village level	60 (50.00)	VI	Creation of of resource persons at village level	57 (47.50)	VI
8.	High cost of cultivation	36	VIII	Decrease of cost of cultivation	33	VIII
9	Lack of remunerative price for produce at IKP marketing centres)	31	IX	Provision of remunerative prices	30	IX

Figures in parentheses indicates percentages Organizational strategies

1. Group formation at grass root level needs to be done by employing participatory techniques like social mapping, wealth ranking and preference ranking. This enables to form homogeneous and common interest groups in a participatory mode.
2. Rotational leadership in a democratic way in a group empowers each and every person in the group. Through experiential learning each member acquires the skills. Practical oriented self help group visits to self reliant and successful groups enables them to understand

group dynamics, team building, acquire entrepreneurship orientation and thus individual capacities of self help group members can be developed.

Creation of role self help group model after a thorough participatory training need assessment enables in showcasing the different technologies through demonstrations based on principle of 'seeing is believing & learning by doing'. This also facilitates in producing, sharing and saving of resources at village level there by external input dependence in agriculture can be reduced besides securing livelihoods

Technical Strategies

1. As agriculture was not sustainable in the studied area, in-crease in farming activity was suggested. This can be done through introduction of participatory watershed programmes. This enables pooling small farms of common interest groups which facilitates technology adoption with reduced cost and assured income. The soil productivity and fertility enhancement activities, introduction of farm-ing systems approach on a watershed basis with inclusion of dairy, agroforestry is possible in the area to provide employment to the people. Through proper utilization of CIF and abhayahastam there is also scope for promotion of fisheries, poultry, sheep and goat rearing besides intro-duction of second crop in the area.
2. Cost of cultivation in agriculture can be reduced due to recy-cling of bi-products of various enterprises taken up on farm and through popularization of integrated crop management practices.
3. IKP staff needs to orient women to various sustainable ways and means of utilization of funds provided under the pro-gramme as it serves as a rider to them before & after loan utilization & results in purposeful utilization.

   Eg: 1. Purchase of assets like agricultural implements/ soil te ing kit and custom hiring of the same.

   2. Establishment of bioenterprise / agro processing units.

Extension Strategies

1. IKP needs to introduce minimum support price for various crops at IKP marketing centre in an effort to provide remunerative prices to the farm produce.
2. Identification of educated person with good communication skills as resource person in the village and training them in various farming techniques like soil & fertilizer testing, vaccination enables him to gain proficiency. He in turn helps in social mobilization process and the technology will be learnt effectively through social learning. They also serves as a practical evidence for technologies at village level & enables effective delivery of extension services.

CONCLUSION

The findings of the study are expected to be useful in future empowerment policies and programmes for women. Community organizations built up through this programme are seen as use-ful organizing mechanisms for mobilizing peoples collective self help action aimed at improving their own economic and social situation and that of their communities. The study shows a path of movement to make groups self sustainable and self reliant.

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Proverbs of Lambadas (Gwar Matiri Saaki)

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Proverb is a word derisive from Latin proverbium. Proverbs are some sentences that come with a long period of human life. Those sayings are normally look as simple and concert sentences, popularly known and repeated, that expresses a truth based on common sense or the practical experience of humanity. They are often metaphorical.

Proverbs are often borrowed from similar languages and cultures, and sometimes come down to the present through more than one language. In lambada this is one of the oldest practices known as "GWAR MATIRI SAAKI". From these proverbs we can understand lambada language is the old language.

These proverbs of lambada's show their accuracy and fluency towards the language. Life of lambadas not only depends on their routine speeches but also proverbs. Lambada proverbs can have huge impact of their own experiences, while roaming towards one end to the other end of the earth on their duties and business. As per their experience they gained knowledge and put that in to as proverbs. Proverbs explains real life incidents of lambadas and they formed those words as universal truth.

In community of the lambadas proverb can represent perfect and reality of life as a part. As a human being man can get sorrows and joys in the same manner. So he who gets the knowledge about personal experience can be a creation of words as proverb. In one note we can say the proverb can be framed through a single person experience but creation of proverb can be one single persons but it can have universal appeal.

A saying cannot be a sentence because it has to be accepted by the people and used in general speeches. Proverb represents entire meaning of human life in one word. According Sundaram "In generally a proverb consist a sentence or two but it has uniformity of words at the end of sentence, as a proverb can be divided as two parts consisting same number of words in each part like.

Chesindhipodhu – cheyandhiradhu
Cheseutlopalu – chebithekopalu
Nelugurunadichindhebaata – palururupalikindhemaata

In this proverbs cannot be consist equal parts of proverbs but it can followed rhyme scheme and rhythm. Thomas Fuller says proverb means "much matter in decocted in decoted in a few words".

Characteristics of Proverb

1. Simplicity of words.
2. Must be a sentence.

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RURAL INDEBTEDNESS: A STUDY IN MAHABUBABAD DISTRICT OF TELANGANA STATE

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Abstract: Indebtedness is one of the major problems concerning to the rural society. Taking debt for the purpose of agricultural activities is indeed necessary. However, the rural people take mostly debts for non-productive purposes i.e. to meet the family needs, perform social functions like marriages, birth, death, and litigation, etc. Since money taken does not contribute to production but instead to consumption, it drags the rural people into indebtedness web. For many small farmers, the agricultural production is so less that they are unable to provide for such unproductive expenditure which drives them to take loans. The main objectives of the present study are: To study the socio economic conditions of rural indebted people, to study the causes of indebtedness among the rural households with special reference to their needs and to analyse the borrowing and repayment behaviour among the rural households. Indebtedness is found to be high among farmers when compared to that of non-farmers. The main causes of indebtedness are poverty, ancestral debt, illiteracy and ignorance, defective agricultural structure, low savings, unproductive expenditure, uncertain monsoons, moneylenders, fragmentation, litigation, defective marketing system, natural calamities. The consequences of indebtedness are low standard of living, health problem, low productivity, suicides etc. It is known that rural indebtedness is an indicator of the weak financial infrastructure of our country. The measures can tackle the problem of rural indebtedness in India in an effective manner are reducing dependence on moneylenders and control over them, control of new loans for non-productive purpose, encouraging the saving habit among the rural etc. The heartfelt measurements only needed in this hour to make the rural people to get rid of indebtedness.

(Key words: Indebtedness, Rural, Farmers, Credit, Institutional, Non-institutional)

1. INTRODUCTION: Indebtedness is one of the major problems concerning to the rural society. Taking debt for the purpose of agricultural activities is indeed necessary. However, the rural people take mostly debts for non-productive purposes i.e. to meet the family needs, perform social functions like marriages, birth, death, and litigation, etc. Since money taken does not contribute to production but instead to consumption, it drags the rural people into indebtedness vicious circle and it becomes impossible to repay these loans. To clear these loans, the rural people bring debts again and again. In this way, they are stuck in the clutches of indebtedness vicious circle, which passes on from one generation to another. For many small farmers, the agricultural production is so less that they are unable to provide for such unproductive expenditure which drives them to take loans.

a. Meaning of Indebtedness: The term 'indebtedness' may be understood as, 'the state of being under obligation,' which is financial in nature. Indebtedness may be extended to an individual, to a household and to an organization. Indebtedness of an Indian rural household often caused to take the borrowing for certain needs like accident or illness of a family member or for certain social occasions like marriage, birthday, death, etc. Because of hardly enough savings and no provision for institutional credit for above needs, the rural people are approaching local money lenders though the rate of interest highly charged. Now the borrower does not have enough resources or income to repay the debt which sets off a series of miseries for the household propelling it in the vicious cycle of indebtedness.

b. Credit Sources: The sources for rural credit in India can be classified in to two types. One is institutional credit sources which comprise commercial banks, RRBs, SHGs, Cooperative Societies, Finance companies etc. Another one is non-institutional sources which comprise friends, relatives, landlords, money lenders, input suppliers, traders etc. Earlier in 1950s, the non-institutional credit sources played a crucial role in providing rural credit especially by money lenders which forced the rural poor in to poverty vicious circle. Later, the government encouraged various institutional sources to provide loans to agricultural sector as priority sector by nationalising the commercial banks in 1969 and 1980. Nowadays the institutional sources have major share

in extending the credit to the rural poor. The following table gives the details of loans taken by agricultural and non-agricultural households from different sources of credit.

Table 1. Source wise Distribution of Loans for households
(loan taken between July 2015 to June 2016)

(In Percentage)

Agency	Agricultural Households	Non-agricultural households	All households
A. Institutional Sources			
1.Commercial Banks/RRB	46.2	26.4	36.6
2.SHG Bank Linked	10.6	14.4	12.4
3. SHG-NBFC/MFI	9.2	13.5	11.3
4. Coop Society/Bank	6.0	5.3	5.7
5.Financial Company	1.0	1.7	1.3
6.Finance Corporation	0.7	2.1	1.3
7.Provident Fund	0.5	0.2	0.3
8. Insurance	0.3	0.2	0.2
B. Non-institutional Sources			
1.Relatives & Friends	22.7	26.8	24.7
2. Money lenders	10.8	12.3	11.5
3.Landlord	6.1	4.3	5.2
4.Doctors, Lawyers etc.	0.1	0.1	0.1
5.Input supplier	0.1	0.1	0.1

Source: NABARD All India Rural Financial Inclusion Survey 2016-17, pp.68
Note: Totals exceed 100% as a household may have taken loan from more than one source.

The most available source for all households is Commercial Banks/RRBs with 37% loans. Agricultural households depends more on this source with 46% whereas it is 26% in case of non-agricultural households. The second most source for loans is Relatives & Friends with 24.7% share of total households. The non- agricultural households are depending more (26.8%) on this source whereas agricultural households with 22.7%. The Self Help movement shows a fruitful result in India. The SHG sources (SHG Bank Linked and SHG-NBFC/MFI) evidences with a 33.7 % loans to all households. The Non-agricultural households are more depending on SHGs with 27.9% (SHG Bank Linked and SHG-NBFC/MFI) whereas agricultural households with 19.8%. The moneylenders are still playing a significant role a source of rural credit with 11.5% to all households. Non-agricultural households more depending on Moneylenders with 12.3% as the institutional credit is not available for non-productive needs such as socio-religious-cultural needs which forced them to approach money lenders. The agricultural households are also taking significant loans from money lenders with 10.8%.

In the Institutional sources, Commercial Banks/RRB is the major source with 36.6% whereas SHG Bank Linked and SHG-NBFC/MFI are occupied second and third places with 12.4% and 11.3% respectively. Coop Society/Bank has share of 5.7% in all households whereas other 3.1% distributed among Financial Company, Finance Corporation, Provident Fund and Insurance etc.
The Relatives & Friends occupy first place with 24.7% in all households in Non- institutional sources. Moneylenders and landlords plays significant role in acting as credit source for all households with 11.5% and 5.2% respectively. Doctors, Lawyers and Input Suppliers are also sources of credit for households but meager.

c. Incidence of Indebtedness: As per the NSSO Report, the Incidence of Indebtedness (IOI) was about 31.4 % among the rural households and 22.4% among the urban households. The NSSO report is prepared on the information collected through NSS - Debt and Investment during the period of January-December, 2013 from 110,800 households in 4,529 villages and 3,507 urban areas throughout the country. According to the report, the average Amount of Debt (AOD) per indebted household was Rs. 1,03,457 in rural areas and Rs 3,78,238 in urban areas.

Land and building together accounted for around 90% of total value of assets at the national level for indebted households and as well as for all households. Non-institutional agencies are source of credit to 19% of rural households, while institutional agencies are 17% households. In urban areas, institutional agencies played a greater role, providing credit to 15% of households against 10% by non-institutional agencies.
In rural areas, the institutional credit agencies were providing 56% share of debt against 44% from non-institutional credit agencies. In Urban areas, the share of debt from non-institutional credit agencies was 15% only compared to 85% from institutional credit agencies. Cooperative societies and commercial banks, together accounted for half of the outstanding cash debt in rural areas, whereas cooperative societies (24.8%) accounting for a little lower share than the Banks (25.1%). Moneylenders were found to be the key source of finance (28.2%) among non-institutional credit agencies in rural areas. However, about 75% of the total cash debt was from cooperative societies and commercial banks, their respective shares being 18% and 57% in urban areas.

d. Consequences of Indebtedness: A number of economic and non-economic consequences are caused by rural indebtedness. The farmer has to use major part of production to pay for clearing debts, interest and principal amount which may lead to loses interest on agriculture consequentially low production and low income level. The farmers are forced to sell their produce to moneylenders lower than the rate obtaining in open market. This makes benefit to moneylender and loss of a substantial income of farmers. In turn, farmer was trapped in poverty web and loses or sell his land and become landless labour.

2. REVIEW LITERATURE: The people of rural India are suffering from many problems; rural indebtedness is serious among them. Even though there is a large network of formal financial institutions in our country but still farmers in rural area are dependent on informal sources of finance for their credit needs. They find it easier to get loans from local money lenders and commission agents as compare to formal institutions because the latter requires a collateral and proper documentation which is a lengthy process. The over dependence of farmers on informal sources of finance is a major cause of rural indebtedness. A high rate of interest is charged by informal sources as compare to formal institutions. The banks should devise a system that can monitor the requirement of the loan before sanctioning the loan and the loans for unproductive purposes should be curtailed as they does not yield any production. There is a dire need of government policies and programmes that aimed to enhance the borrowing and repaying capacity of the rural poor so they can live with dignity (Dharminder Singh,2018).

Sometimes, indebtedness originates in the loan incurred for productive activities also. The farmer who has taken loan for cultivation is forced to dispose the produce to the lender. If prices of the agricultural produce increases by a growth rate (r1) and the principal of debt multiplies itself by a growth rate (r2) such that r1 is less than r2. The current value of the output X as a means to optimize the debtor's gain is optimal only if X is sold at the current prices. Hence the farmer sells his produce at the harvest prices and pays his debt off (Mithra MK *et al*, 1986).

3. STATEMENT OF THE PROBLEM: Agricultural returns are always fluctuating due to diverse natural causes and market causes but interest payments continue as fixed charges on land income. Agriculture in India has been rightly described as a deficit economy. The small land holdings, over-strained soil, untimed monsoons and insecurity of harvests have made the majority of farmers to be below the subsistence line. For the characteristic trait of the Indian farmer is his unappeasable land hunger, a considerable amount of savings has flowed into the field of land purchase. The marketing deficiencies, lack of support prices, duplicate seeds etc caused the famers to fell in to the indebtedness vicious circle. In this backdrop, it is opt to study the causes and severity of the rural indebtedness with the following objectives.

4. OBJECTIVES: The main objectives of the present study are:-

- To study the socio economic conditions of rural indebted people.
- To study the causes of indebtedness among the rural households with special reference to their needs.
- To analyse the borrowing and repayment behaviour among the rural households.

5. METHODOLOGY: The present study based on both primary data and secondary data. The Primary data is collected using structured questionnaire. For this, 50 sample respondents have been randomly selected from Five villages namely Danthalapally, Ammapuram, Gurthur, Chinthalapally and Matedu (10 respondents from each village) which purposefully selected from Thorrur Division of Mahabubabad District of Telangana State. The secondary data is collected from various reports of NSSO, Journals, Books and Magazines etc.

6. DATA ANALYSIS: Indebtedness is found to be high among cultivators group when compared to that of non-cultivators. So that, the Indebtedness became a serious problem of Indian farmers. The saying given by the then Royal commission, 1927, "The Indian Farmer is born in debt, lives in debt and dies in debt" is applicable even now. The rural people suffer a lot for the credit needs, especially for non-productive, and trapped in indebtedness web.

a. **Socio-economic conditions:** The socio-economic conditions respondents reveal the information and helpful to understand the nature and causes for indebtedness.

Table 2: Socio-economic conditions of sample respondents

Item	Description	No. of Respondents (Percentage)
Sex	Male	44 (88)
	Female	06 (12)
Age	<35	04 (08)
	36-59	38 (76)
	60>	08 (16)
Caste	BC	33 (66)
	SC	08 (16)
	ST	06 (12)
	Others	03 (06)

Education Status	Illiterate	14 (28)
	Primary	18 (36)
	Secondary	16 (32)
	Higher	02 (04)
Family size	<3	08 (16)
	4-5	41 (82)
	6>	01 (02)
Housing	Pucca	37 (74)
	Kacha	11 (22)
	No own house	02 (04)
Occupation	Agriculture	37 (74)
	Non-Agriculture	13 (26)
Agricultural Land	No Land	09 (18)
	<2.5 acres	21 (42)
	2.5 – 5 acres	18 (36)
	5 acres>	02 (04)
Income Source	1. Agriculture	37 (74)
	2. Agriculture Labour	10 (20)
	3. Business	2 (04)
	4. Other source	01 (02)

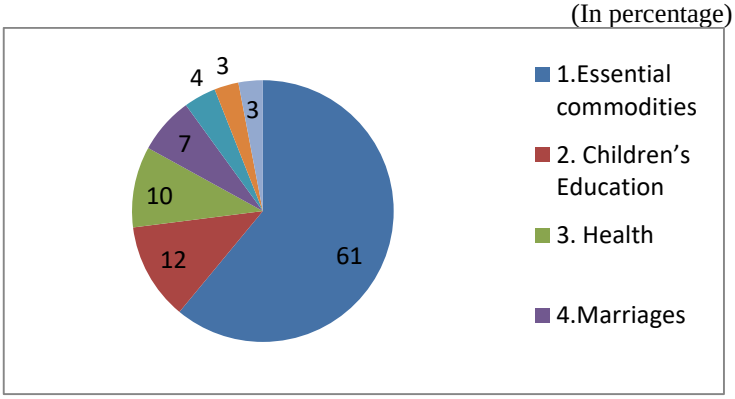
Source: Field Data collected.

The table 2 reveals the socio-economic conditions of sample respondents. The total respondents are rural people. Most of the respondents are male (88 percent). 76 percentage of respondents are middle aged i.e. between 36-59 years while 16 percent are above 60 years and 8 percent are below 35 years. All the respondents are Hindu religion people. There are 66 percent, 16 percent, 12 percent and 6 percent respondents belong to BC, SC, ST and others respectively. Most of the respondents are BCs. The Educational status reveals that 28 percent of respondents are still illiterate despite various literacy programmes taken up by the government. 36 percent respondents are with primary education while 32 percent are with secondary education. Only 4 percent respondents are with higher education status. All the respondent family are nuclear families. The family size is 4-5 persons for most of respondent families with 82 percent. 16 percent families are having below 3 persons and only 2 percent with more than 6 persons as family size. Most of the respondents (74 percent) are residing in pucca houses while 22 percent in kacha houses. Still 4 percent of respondents are not having own house. Majority (74 percent) respondents are engaging with agriculture activities while other 26 percent in non-agricultural activities. Most of the respondents (42 percent) are marginal farmers having below 2.5 acres of land. 36 percent respondents are small farmers having land between 2.5 to 5.0 acres of land. Only 4 percent respondents are having more than 5 acres of land. And, 18 percent respondents are having no land. The main income source is agriculture for 74 percent respondents. 20 percent respondents earns as agricultural labour. Four percent are getting money from business while two percent are other source which is reported as private sector job. The average income of respondent family is Rs.1, 14,960 per annum.

b. Expenditure details: All the income is for the expenditure. The expenditure pattern shows the nature and priority of needs of the respondents. The pie chart shows the main expenditure items incurred by respondents. Most of the expenditure (61 percent) goes to essential commodities. Next to it, the most expenditure one is children's education (12 percent). The healthcare occupies third position with 10 percent expenditure. Performing marriages also occupied share with 7 percent. Festivals, Deaths and others occupy 4 percent, 3 percent and 3 percent respectively in total expenditure incurred by respondents. The average expenditure of respondent family is Rs. 1, 32,640. The total income of respondents incurred on various expenditure items so that there is hardly scope of savings. And also the income of respondent family is lower than the expenditure. As there is low level of savings and still having the needs to fulfil, the respondents incurring debts and unable to repay and become prey in to the indebtedness web.

Chart 1: Pie chart showing the expenditure details of respondents

(In percentage)



Source: Field Data

c. Debt particulars: As the income is lower than the expenditure, the respondents are forced to take debts. The details regarding the reasons for debts, sources of debts, rate of interest, repay sources have been collected and analysed below. Table 3 reveals the debt particulars of sample respondents. The details reasons for taking loan have been collected. It is found that most of respondents (72 percent) taking loan to meet the expenditure towards quality education for their children. It is due to the attitude of parents that quality education may be available at corporate/private educational institutions only so that they are no hesitating to pay huge amounts in the name of fees even bringing the amount from various loans. Another need for which respondents take loan next to education is healthcare. 66 percent respondents said that they are in debt trap due to high cost healthcare in corporate/private hospitals. The same attitude of people that they can find good health services at corporate/private hospitals is the main reason for their indebtedness. On the other hand the public sector education and health is given less priority by the government by allocating meagre funds hence these sectors lost the people's confidence. The third net for respondents become indebtedness is marriages. Marriage is a social obligation and involved dowry and other expensive activities. So that the people are even ready to take huge amount of loans to perform children's marriages especially girl child's by giving dowry. 56 percent of respondents send their loans on purchasing consumer goods which shows the consumerism to buy the goods on Loan/EMI due to advertisements and easy availability of loans. It is also worthy to note that 46 percent respondents are taking new loans to repay the old ones which shows the debt trap. The social obligations like festivals, customs etc also are caused for bringing loan as reported by 42 respondents. 22 respondents are in clutch of debts due to performing family members' death and post death ceremonies. 16 percent respondents conveyed other reasons of purchasing assets like house, land etc. These borrowings are mostly used for non-productive activities only as reported by 82 percent respondents but only 28 percent respondents are using the loans for productive purpose.

Table 3: Debt particulars of sample respondents

Item	Description	No. of Respondents (Percentage)
Reasons for Debts	1.Education	36 (72)
	2.Health care	33 (66)
	3.Marriage	32 (64)
	4.Consumer goods	28 (56)
	5. To repay old debts	23 (46)
	6. Festivals etc.	21 (42)
	7. Death	11 (22)
	8. Others	08 (16)
Debt used for	1. Productive	14 (28)
	2. Non-productive	41 (82)
Source of Debts	1. Friends & Relatives	34 (68)
	2. Money Lenders	28 (56)
	3. Landlords & Traders	11 (22)
	4. Commercial Banks	20 (40)
	5. Cooperatives	12 (24)
	6. SHGs	31 (62)
	7. Finance companies	26 (52)
	8. Other	08(16)
Rate of Interest	Below 12 % p.a.	14 (28)
	12 – 24 % p.a.	16 (32)
	24-36 % p.a.	18 (36)
	36 % above	04 (08)

Source: Field Data collected.

Note: Totals exceed 100% as respondents may have taken loan for more than one reason/from multiple sources

The relatives and friends are still main source for credit as 68 percent of respondents depending on it. It is due to the non-productive credit nature and institutional sources will not give loans for that purpose. The Self Help Groups are playing crucial role in providing micro credit as 62 percent respondents depend on them for their needs. Money lenders in villages still have their grip by easily access providing loans to 56 percent respondents particularly for non-productive needs. Finance companies also are easily accessible for loans as reported by 52 respondents. Commercial banks are providing loans to 40 percent respondents only as they only give loans to productive activities. 22 percent and 16 percent respondents are taking loans from landlords & traders and other sources respectively. Most of the respondents (36 percent) are taking loans for high rate of interest i.e.24-36 % per annum. It shows the burden of loans up on them and leads to debt trap. They are unable to pay accumulated loan with high rate of interest and further taking loans to repay the old loans. 32 respondents are taking loans for rate of interest 12-24% per annum which is also burdensome. Only 28 respondents are getting loans on low rate of interest i.e. below 12 percent. The 8 percent respondents are going for loans even for high rate of interest (above 36%) for emergency needs.

7. FINDINGS: Some of major findings of the study are as follows.

1. Most of the respondents are male and middle aged.
2. All the respondents are Hindu religion people and most of the respondents are BCs.
3. Most respondents are with primary education.
4. All the respondent family are nuclear families and the average family size is 4-5 persons per family.
5. Majority respondents are engaging with agriculture activities.
6. Most of the respondents are marginal and small farmers.
7. The main income source is agriculture for most respondents.
8. Most of the expenditure spent on essential commodities. children's education and healthcare are stood next.
9. The expenditure of respondent family is more than the income which forced them to take debts.

10. Most of respondents taking loan to meet the expenditure towards quality education for their children. It is due to the attitude of parents that quality education may be available at corporate/private educational institutions only so that they are no hesitating to pay huge amounts in the name of fees even bringing the amount from various loans.
11. The item for which respondents bringing loan next to education is healthcare. The attitude of people that they can find good health services at corporate/private hospitals is the main reason for their indebtedness.
12. Marriage is became social obligation and involved dowry and other expensive activities. So that the people are even ready to take huge amount of loans to perform children's marriages especially girl child's by giving dowry.
13. Loans for purchasing consumer goods show the consumerism to buy the goods on Loan/EMI due to advertisements and easy availability of loans.
14. It is also worthy to note that new loans are being taken to repay the old ones which shows the debt trap.
15. The social obligations like festivals, customs, deaths etc also are caused for bringing loan.
16. Only few are taking loans for purchasing assets.
17. The borrowings are mostly used for non-productive activities.
18. The relatives and friends are still main source for credit. It is due to the non-productive credit nature and institutional sources will not give loans for that purpose.
19. The Self Help Groups are playing crucial role in providing micro credit.
20. Money lenders in villages still have their grip by easily access providing loans particularly for non-productive needs.
21. Commercial banks are providing loans to 40 percent respondents only as they only give loans to productive activities.
22. Most of the respondents are taking loans for high rate of interest i.e.24-36 % per annum. It shows the burden of loans up on them and leads to debt trap. They are unable to pay accumulated loan with high rate of interest and further taking loans to repay the old loans.

The main causes of indebtedness are poverty, ancestral debt, illiteracy and ignorance, defective agricultural structure, low savings, unproductive expenditure, uncertain monsoons, moneylenders, fragmentation, litigation, defective marketing system, natural calamities. The harmful consequences of indebtedness are low standard of living, health problem, low productivity, suicides etc.

8. SUGGESTIONS: There are different suggestions given by respondents to come out of indebtedness. It is shown in the following Table 4 that the suggestions given.

Table 4: The remedies suggested by respondents to curb the indebtedness

Description	No. of Respondents (Percentage)
1. Economic support by Government	37 (74)
2. Strict implementation of anti dowry act	38 (76)
3. Support prices	34 (68)
4. Encourage the small, cottage industries	28 (56)
5. Employment schemes	23 (46)
6. Crop Insurance	41 (82)
7. Distribution of surplus land	14 (28)
8. Settlement of old loan	15 (30)
9. Others	09 (18)

Source: Field Data collected.

Crop failure is the main reason for not getting money so that 82 percent respondents suggested for a scheme of crop insurance. 76 percent respondents strongly opined to strictly implement the anti dowry act as the dowry became a main cause for indebtedness. But it is socio-economic issue and unofficially dowry is key part of marriage and only government cannot curb it without the cooperation of public. 74 percent respondents said that they required financial support. It is the time to think of Direct Cash Transfer to public instead of numerous social security schemes which functionally not reached the last poor.

Reasonable Support prices for agricultural products is better way to come out of debt trap as reported by 68 percent respondents. 56 respondents supported the idea of encouraging more the small scale and cottage industries and 46 percent respondents opined to review the employment schemes in order to beneficiaries get more income. One time settlement of old loans of rural people especially ancestral also helpful to get rid of debts as put forwarded by 30 percent respondents. Distribution of surplus land is desired by 28 percent respondents which enabled them to get more money. 18 percent respondents are suggested other solutions like more institutional credit facilities.

9. CONCLUSION: In India nearly 72 percent of population lives in rural areas and is mostly dependent for their livelihood on agriculture and allied activities. Many policy changes have taken place since I960, when the agricultural credit scenario was largely dominated by private informal sources of credit, to increase the flow of institutional credit to the agricultural sector. It is known that rural indebtedness is an indicator of the weak financial infrastructure of our country. The some other measures can tackle the problem of rural indebtedness in India in an effective manner are reducing dependence on moneylenders and control over them, control of new loans for non-productive purpose, encouraging the saving habit among the rural etc. The heartfelt measurements only needed in this hour to make the rural people to get rid of indebtedness.

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E-NAM: A STUDY IN MAHABUBABAD DISTRICT OF TELANGANA STATE

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Abstract :Agriculture plays a vital role in Indian economy. As per census 2011, 54.6 percent of the total population is engaged in agriculture and allied activities. This sector contributes 17.4 percent to the country's Gross Value Added. Government of India took several steps for its sustainable development by giving the importance of agriculture sector. Marketing of agricultural commodities in India is carried out through the regional Agricultural Produce Marketing Committees. A vast network of regulated markets has been established under this system. Government of India launched the National Agriculture Market (e-NAM) scheme on 14 April, 2017. The main purpose of this is to increase transparency in transactions, price lists and availability of larger number of markets for farmers to sell their produce to buyers of their choice and at their convenience. The scheme provides a National internet based unified Agri-marketing portal for inter market and inter-state trading of Agri-produce. The farmers can get better prices for their produce by transparency and competition and e-NAM ensure cashless payments directly to farmers' bank accounts. The 585 wholesale regulated markets are intended to be integrated with e-NAM by March, 2018. The main objectives of the present study are: To know the e-NAM and its objectives, to study the e-NAM related issues and to understand the e-NAM activities at AMC Kesamudram. e-NAM is a good facility for farmers and traders in India. The entire farmers of country are consolidated in single stage on web. It is totally modernized web in single programming. It curbs the various malpractices generally prevailed in agricultural markets. e-NAM avoids the uncertainty in selling the produce, payments, quality determination of produce etc.

Key words: Agriculture, Marketing, Farmers, Traders, Produce, Price

1. Introduction: Agriculture plays a vital role in Indian economy. As per census 2011, 54.6 percent of the total population is engaged in agriculture and allied activities. This sector contributes 17.4 percent to the country's Gross Value Added (GVA) (current price 2014-15, 2011-12 series). Government of India took several steps for its sustainable development by giving the importance of agriculture sector. Many steps have been taken to improve the agricultural aspects. The soil health card scheme for soil fertility on a sustainable basis, Pradhanmantri Gram Sinchai Yojana is to provide improved access to irrigation and enhanced water efficiency, Paramparagat Krishi Vikas Yojana (PKVY) to support organic farming and e-NAM to support for creation of a unified national agriculture market to boost the incomes of farmers.

India's total geographical area is 328.7 million hectares. The reported net sown area is 139.9 million hectares and the gross cropped area is 194.4 million hectares with 138.9% cropping intensity. In India, the net irrigated area is 66.1 million hectares.

On 30 January, 2015, the Central Statistics Office (CSO) has released the New Series of National Accounts revising the base year from 2004-05 to 2011-12. As per the revised estimates released by CSO on 29 January, 2016, the Agriculture and its Allied Sector contributed approximately 17.0% of Gross Value Added (GVA) in India during 2014-15 (Current Prices).

There has been a constant decline in the share of agriculture and allied sector in the Gross Value Added (GVA) from 18.5% in 2011-12 to 17.4% in 2014-15 in view of the structural change in the economy. The decreasing trend in the share of the agriculture and allied sector in GVA is outcome of structurally changing economy. The details of Growth in the Total GVA and that in the GVA of Agriculture and Allied Sector at 2011-12 basic prices is given below:

Table 1: Details of Growth in the GVA of Agriculture and Allied Sector(at 2011-12 basic prices)

Period	Expenditure (In Rs.)	Percent to Total GVA
2011-12	15,01,816	18.5
2012-13	16,80,797	18.2
2013-14	19,02,452	18.3
2014-15	19,95,251	17.4

Source: Central Statistics Office, MOSPI, Govt. of India

Table 2: Percentage of Total GVA and GVA of Agriculture and Allied Sector

Period	Total GVA (in percent)	Agriculture & Allied Sector GVA(in percent)
2012-13	5.4	1.5
2013-14	6.3	4.2
2014-15	7.1	-0.2

Source: Central Statistics Office, MOSPI, Govt. of India

2. Review Literature: India has always been an Agrarian economy, which means it is also a huge employer. Agriculture is the primary source of livelihood for about 58% of India's population and contributes to around 18% to overall GDP.
Kushankur Dey (2016), in his article entitled "National Agricultural Market" revealed that Electronic trading portal of NAM (e-NAM) was newly officiated with a national awareness to connect more than 580 APMCs throughout the country. The benefits of negotiated dealing system in trading and other services in terms of price and proper information of trading commodities might not accrue to small and minor farmers.

Roshini, S *et al* (2018) describes the implementation of e- NAM and its progress in India. e - NAM is India wide electronic trading portal which provides a unified national market for agricultural commodities and creates single window service by networking existing APMCs (Agriculture Produce Marketing Committees). For trading on e –NAM platform, about 90 commodities are notified. 13 states were, till now, covered under this scheme. Uttar Pradesh stands top the list with 100 markets and Uttarkhand is at the bottom line with 5 markets only. Gujarat tops with 7441.7 tons of quantity traded for a total trade value of Rs.14117.05 Crore while Odisha is lagging with 0.63 tons of quantity traded for a meager Rs. 1.11 Crore of trade value. e-NAM enhances the quality of agricultural marketing by reducing the regional barriers throughout the country to achieve the "one nation one market" goal.

Nedumaran G and Manida M (2019) revealed that Agribusiness exhibiting is constrained by the States as indicated by their agri-advancing bearings. The State is divided into a couple of market zones, all of which is regulated by Agricultural Produce Marketing Committee (APMC). e-NAM addresses various challenges by making a unified market through internet trading and advances consistency, streamlining the planned markets, removes information asymmetry among buyers and sellers.

3. Statement of the Problem: In agricultural sector, India is one among the 15 leading exporters globally and its contribution to total export is 12.26 per cent in fiscal year 2017. Agricultural marketing contributes around 25 per cent of the GDP and provides employment to 65 per cent of the workforce. In order to monitor and boost agricultural marketing, under the ministry of agriculture the Government of India has set up specific commodity boards and export promotion councils like coffee board, Cotton Corporation of India (CCI), Agricultural Products Export Development Authority (APEDA). It fixes Minimum Support Price (MSP) to remove the elements of uncertainty and ensure remunerative prices to growers based on recommendation made by Commission for Agric and Prices (CACP). To reduce the malpractices in marketing of agricultural commodities, the regulated markets have been increased from about 200 in 1950-51 to 7,114 in 2013-14. Marketing of agricultural commodities in India is carried out through the regional Agricultural Produce Marketing (Regulation) Acts in various the States and UTs. A vast network of regulated markets has been established under this system.

The basic objective of the APMC Act is to ensure an effective price discovery through interplay of supply and demand forces. Over time, however, these markets have become restrictive and monopolistic and have, therefore, failed not only to achieve their basic objectives but owing to restrictive provisions of States' APMC Acts prevented a seamless integration of farmers and buyers and evolution of an efficient supply chain. Some of the major problems with the current system are the insufficient number of APMC markets and their inadequate Infrastructure, limited access to market for small farmers, less remuneration to the farmers and high intermediation cost, lack of market information / Information asymmetry, need to physically bring the produce to mandi, high incidence of market fee/ charges, fragmentation of markets, requirement of multiple licenses for trading, multiple point levy of market fee, existence of opaque/ semi-transparent processes of bidding and lack of emergence of alternative channels of marketing.

4. Objectives: The main objectives of the present study are:-

- To know the e-NAM and its objectives
- To study the e-NAM related issues
- To understand the e-NAM activities at AMC Kesamudram.

5. Methodology: The present study based on both primary data and secondary data. The Primary data is collected by observing the activities taken place at AMC Kesamudram and interacted with the farmers and traders and officials at AMC Kesamudram, District Mahabubabad of Telangana State. The secondary data is collected from various reports of NSSO, Journals, Books and Magazines, Marketing Department etc.

6. Data Analysis: Agriculture sector needs structured and functional markets to steer growth, employment, remunerative prices and economic development in rural areas of the country. A systematic mechanism is required for procurement of agricultural commodities from farmers' field and to establish helpful linkage between the farm production, the retail chain and food processing industries. Department of Agriculture, Cooperation & Farmers' Welfare has prepared policy in the shape of a new Model Agricultural Produce and Livestock Marketing (Promotion and Facilitation) Act 2017. The new Act provides the market options for farmers in addition to the APMC regulated market yards. The provisions are included for private markets, direct marketing, farmer-consumer markets, special commodity market yards, declaring warehouses/cold storages as market sub yards so as to reduce the number of intermediaries between producers and buyers to increase the share of the farmer in consumer's price.

6.1. Launching of e-NAM: National Agriculture Market (eNAM) is a India wide electronic trading portal. It networks the existing APMC/mandis to provide a unified national market for agricultural produce. Small Farmers Agribusiness Consortium (SFAC) is the nodal agency for implementing eNAM scheme. Government of India launched the National Agriculture Market (e-NAM) scheme on 14 April, 2017. The main purpose of this is to increase transparency in transactions, price lists and availability of larger number of markets for farmers to sell their produce to buyers of their choice and at their convenience. The scheme

provides a National internet based unified Agri-marketing portal for inter market and inter-state trading of Agri-produce. The farmers can get better prices for their produce by transparency and competition and e-NAM ensure cashless payments directly to farmers' bank accounts. The 585 wholesale regulated markets are intended to be integrated with e-NAM by March, 2018.

6.2. Telangana Agricultural Department: The Departmental of Agricultural Marketing was established with an objective to regulate, control and supervise the marketing network of sale, purchase, storage of Agricultural Produce, notified in Schedule- II of Telangana (Agricultural Produce and Live stock) Markets Act, 1966. The state at present is serving through the Network of 192 Market Committees. Apart from the main Market Yards, there are 87 Sub Market Yards. These AMCs are classified in terms of Market Fee Collected.

The Telangana State Agriculture Produce is being regulated under the Telangana State (Agricultural produce and Live stock) Markets Act, 1966. It is intended to consolidate and amend the laws related to the regulation of purchase and sale of Agricultural produce, Live stock and the establishment of new Markets. The Primary objective of the Telangana Agricultural Department and AMCs are to establish modern Markets for well-organized Marketing of agricultural commodities by providing various facilities in the markets and to implement Act, Rules, Bye-laws framed there under. The following Table shows the details of commodities traded in e-NAM.

Table 3: details of commodities traded in e-NAM

Commodity Category	No. of Commodities
Food Grains/ Cereals	26
Oilseeds	14
Fruits	31
Vegetables	50
Spices	16
miscellaneous	38

Source: https://www.enam.gov.in

6.3. Standard quality parameters: The Department of Marketing and Inspection (DMI) clearly defined the standard quality specifications for all the 175 commodities listed on e-NAM platform which are to be determined for certification. The major tradable parameters are to be tested in physical nature.There are no penalties for the shortcomings in the quality of the produce. The different quality produce will be put in its respective testing range i.e. range 1 or 2 or 3.

6.4. Assaying: An established Quality Assaying lab is a requisite for APMC that assesses and certify the quality of produce. The number of parameters varies for various commodities. Oil content or chemical testing is also performed for some commodities and then certification result is published on e-NAM website. Presently the assaying is conducted by the APMCs. They do not charge any fee from the farmers. The Farmers may sell their produce on e-NAM without assaying. In such cases, he may or may not get the better price on e-NAM. The following table shows the number of Mandis which are doing online trading.

Table 4: Details of No. of Mandis doing online trading.

State	No. of APMC	Mandis doing Online Trade
Andhra Pradesh	33	16
Chandigarh	1	1
Chhattisgarh	14	7
Gujarat	122	17
Haryana	81	61
Himachal Pradesh	19	10
Jammu and Kashmir	2	0
Jharkhand	19	1
Karnataka	2	1
Kerala	6	0
Madhya Pradesh	80	26
Maharashtra	118	60
Odisha	41	21
Puducherry	2	1
Punjab	37	16
Rajasthan	144	138
Tamil Nadu	63	17
Telangana	57	30
Uttar Pradesh	125	47

State	No. of APMC	Mandis doing Online Trade
Uttarakhand	16	7
West Bengal	18	12
Total	1000	489

Source: https://www.enam.gov.in

The payment related incentives are varied from state to state. The following table shows the different payment incentives of different states.

Table 5: Details of different payment incentives of different states.

States	**Payment Incentives**
Chattisgarh	Rebate on Mandi Fee for the Trader of 25 paisa on every purchase of Rs. 100 of notified agricultural product and payment to the seller through e-NAM
Gujrat	In Sidhpur APMC, For Traders 33% Mandi fees reduced while e-payment through e-NAM. An incentive of 1.60 Paisa instead of 1.50 Paisa for CA, Attractive Gifts for Farmers
Rajasthan	State Level: Annual cash Prize of One Lakh each to best1 farmer & best 1 trader State Level: Rs.50,000/- (Two Prizes – 2 farmers & 2 traders) Division Level: Annual cash Prize of Rs.50,000/- each to best1 farmer & best 1 trader Division Level: Rs.25,000/- (Two Prizes – 2 farmers & 2 traders) APMC Level: Annual cash Prize of Rs.30,000/- each to best1 farmer & best 1 trader APMC Level: Rs.15,000/- (Two Prizes – 2 farmers & 2 traders) For Farmers, Mandi Level: 25% of market fee of the traded amount to the farmer for taking e payment on e-NAM
Uttarakhand	10% reduction in mandi fees for each trader transacting business under e-Nam scheme for 6 months with effect from 09-10-2018.
Andhra Pradesh	Rebate of 0.25% on Mandi Fees if payments are made online

Source:https://www.enam.gov.in

The trade related incentives are varied from state to state. The following table shows the different trade incentives of different states.

Table 6: Details of different trade incentives of different states

States	**State Incentives**
Haryana	State Level - Prize "Rotavator" to best participating Farmer Mandi Level - Rewari Mandi “Milton tiffin” to the top 10 best participating farmers.
Uttar Pradesh	State Declared 14th of every month as e-NAM Day and Awarded certificates to top three Traders for best participation at Mandi Level Top three Farmers for selling commodity on the eNAM Platform.
Telengana	Exemption of Market Fee @ 0.25 % and collecting only 0.75% if trader/CAs undertake market transactions from end to end trading process in eNam programs for a period of 1 year starting Dec 12, 2018
Tamil Nadu	Commodity wise Annual Cash Prize for 1 Farmer and 1 Trader in each commodity category (Cereals, Pulses, Oilseeds, and others) for each Regulated Market, Cash Prize of Rs.25,000/- where arrival is greater than 5000MT and Cash Prize of Rs.15,000/- where arrival is less than 5000MT. Annual Cash prize incentive of Rs.1,00,000/- along with the best performance award will be given to the market committee based on the highest quantity of the transaction, digital transaction through e-National Agriculture Market Portal.

Source:https://www.enam.gov.in

6.5. Registration of Farmers on e-NAM: The Registration on e-NAM can be done through three ways viz.
- Via e-NAM Portal- http://www.enam.gov.in
- Through Mobile Application
- Through Mandi Registration (At Gate Entry)

After the online registration, farmer has to visit the nearest e-NAM market with proper required documents.

6.5.1. Benefits for Farmers: The following benefits are there from e-NAM for a Seller/ Farmer:
- Transparency in Trade transactions and better price discovery
- Access to more markets and buyers
- Real time information on prices and arrival in nearby markets
- Quick payments for their transactions

The e-NAM facilitates better prices for farmers through transparent bidding and increased number of buyers from different markets will lead to greater negotiation power. Price commensurate to the quality of produce is obtained by the seller by assaying.

e-NAM facilitates e-payments using various online modes such as NEFT, RTGS and BHIM UPI. The payments are made to sellers instantly in their respective bank accounts.

e-NAM maintain record of all arrivals digitally and assigns unique LOT identification numbers that could be tracked from the mobile until it is sold. This digitization is aimed to reduce the time of transaction in an e-NAM market. However, the time of completion of transaction may depend on other factors such as the quantity of produce arrived to that market and season.

6.6. Registration of Traders on e-NAM: The Buyers or Trader can also register in e-NAM through following ways viz.
- Through e-NAM Portal- http://www.enam.gov.in
- Through Mobile Application
- Through Mandi Registration (by physically visiting a mandi)

There is no registration fee on e-NAM.

6.6.1. Benefits for Traders: The following are the benefits from e-NAM for Buyers/ Traders:
- Extended reach to other markets and access to more sellers
- Access to a larger number and integrated markets
- Access to real time information on arrival, quality and price of agricultural commodities
- Ease of doing the transactions through Mobile-App
- Access to online banking and payments through e-payments

6.7. APMC's:
The Agricultural Produce & Livestock Market Committees (APMC) are established under the provisions of APLM Act. There are 1000 markets are presently linked to the e-NAM network from 18 states and 3 UT's.

6.8. Farmer Producer Organizations (FPOs): The Farmer Producer Organisations are formed on the basis of mutual cooperation of small farmers.The Small Farmers' Agribusiness Consortium (SFAC) was mandated to support the State Governments in the formation of Farmer Producer Organizations (FPOs). Presently, there are 2009 FPO's on boarded on e-NAM platform. FPOs act as aggregators for member farmers from inputs to output which will enhance the economy of scale and increase the bargaining power of members. Logisitics arrangement also be made by FPO/FPC in case of unsold Lots.

6.9. Kesamudram Agriculture Market under e-NAM: Various transactions are taken place under Kesamudram AMC. The farmers, Traders felt that it is easy and useful for them to take the selling and buying activities under e-NAM. The following table shows various prices for different commodities in AMC Kesamudram.

7. Suggestions: Since the transaction of agricultural commodities has been started, marketing of the produce have always been a problem faced by the producers specially the small farmers. The govt. has tried to overcome all the problems related to marketing by introducing e-NAM in collaboration with APMC.

- For efficient work of e-NAM the farmers should be well informed about the availability of the facilities of e-NAM in order to avail them. Creation of awareness among the producers through various communication channels can be done to add to the quality of functioning of e-NAM.
- Provision of transport facilities can be encouraged to reduce the problem of rural farmers along with maintenance of the quality of produce by reducing physical damages.

8. Conclusion: Electronic National Agriculture Market (e-NAM) is extraordinary facility for farmers and traders in India. The entire farmers of country are consolidated in single stage on web. It is totally modernized web in single programming. In India, Markets are wide and has to be interfaced. It curbs the various malpractices generally prevailed in agricultural markets. e-NAM avoids the uncertainty in selling the produce, payments, quality determination of produce etc. There are certain issues lagging behind the e-NAM success viz. illiteracy of farmers, lack of technological skills to operate mobiles/computers, low internet connectivity, non availability of logistics, lack of infrastructure facilities. e-NAM is a continuous process on the marketing in nationally connected the whole market on web in India.

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Residues from the processing of Amaranth and Quinoa Flour cultured shrimp *Litopenaeus vannamei*: Isolation of carotenoid pigments

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Abstract

Carotenoids extracted from the head of the shrimp *Litopenaeus vannamei* could be a useful alternative to the current method of use. Five experimental diets (Amaranth and Quinoa flour in diets) (0 %, 15%, 25%, 35 %, and 45 %) were found to be isoproteic and isoenergetic using a randomised design (3400kcal). After extracting the carotenoids with cooled acetone and then hexane, a raw pigment paste was made by extracting the carotenoids from the residues at 100 °C for 15 minutes in a 1:2 ratio of shrimp head to water and n-hexane. An acidified fraction was obtained after partitioning the material with dimethylsulfoxide (DMSO). The carotenoids in an open column were identified using the fraction elution parameter, the visible absorption spectrum, and the R_f value in a thin layer of silica gel. The absorption spectra of each fraction, which ranged in wavelength from 350 to 550 nm, were quantified using thin-layer chromatography. The total carotenoids (37.62 g/g of the pigment paste) were calculated using the sum of the hexane, DMSO, and acidified fractions, with extinction coefficients of 2592, 2100, and 1690, respectively, for beta-carotene, astaxanthin, and astacene. The most common pigments were beta-carotene-5, 6-epoxide (33.5 %) Astaxanthin (45.5%) and astacene and (21.0 %).

Keywords: *Litopenaeus vannamei*, Amaranth and Quinoa flour in diets, waste materials; Extraction, carotenoid pigments

1.0 Introduction

Litopenaeus vannamei is an important commercial species, accounting for 90% of global farmed shrimp production (Liao, 2011). In India, favourable climatic conditions and the mastery of production technologies have made the country the leading shrimp producer in India. (Maity, et al., 2021). Part of the shrimp produced is sold frozen, without the cephalothorax, or in the form of fillet, generating a large amount of waste, often discarded incorrectly, which can cause environmental problems. Considering that shrimp processing residues consist of proteins, lipids, minerals, chitin, in addition to being sources of carotenoids (Zelaya,et al 2007), their reuse would provide an alternative source of nutrients for animal or even human food, increasing the productivity of the sector, in addition to contributing to the reduction of clandestine disposal in the environment. Astaxanthin is the primary carotenoid found in crustaceans. Sowmya & Sachindra (2012) results demonstrated the high antioxidant activity of astaxanthin extract from shrimp residues. This high

antioxidant power has shown beneficial effects in patients with cancer and hypertension, thus increasing the interest in sources of astaxanthin. Due to the high cost of synthetic pigments and the valorisation of natural products, the residues produced during the processing of shrimp could be used as sources of carotenoid dyes in food products or in diets used in aquaculture. Many studies (Verma, et al., 2019) have been carried out regarding the use of these residues in different ways: shrimp flour; elaboration of flavouring products, and chitin and chitosan. A possible alternative of significant value aggregation for this material is its use to extract carotenoid pigments, as there is potential and demand by the food, pharmaceutical and feed industries. Thus, the present work aims to investigate the presence of the primary carotenoid pigments found in the cephalothorax of cultured shrimp *L. vannamei*. Data regarding the concentration of carotenoids in shrimp residues cultivated in India are still scarce (Sachindra, 2006). Thus, the objective of this work was to determine the concentration of total carotenoids in residues and the *L. vannamei* shrimp meal during frozen storage.

2.0 Material and Methods

Location of the study: The design was completely randomised, consisting of five treatments with three replications. *Litopenaeus vannamei* juveniles were acquired from a farm in Ramayapatnam, Andhra Pradesh, with an average weight of 1.42±0.23g, being acclimatised for two days, gradually decreasing the salinity to 2.5%, being distributed in their respective treatments in the density of 10 shrimp/treatment.

Formulation and preparation of diets: Five isoproteic (35% crude protein) and isoenergetic (3,400kcal of ED kg-1) diets were formulated with different percentages of lyophilised Amaranth. Quinoa flour diet: 0%, 15%,25%,35% and 45% submitted to the pelleting process, where the dry ingredients were crushed, weighed and mixed in an industrial planetary mixer with the vitamin supplement (premix) and soybean oil, adding water at 60ºC until a consistent wet mass is formed. The mixture was introduced into a manual meat grinder to form pellets with a diameter of 2 mm and then dried in an oven with forced air circulation at 80°C for 24 hours and stored in paper bags at room temperature.

Fish Meal: The experimental diets were offered three times a day ad libitum until the shrimp satiety, and for comparative effect, a commercial diet containing 35% crude protein was used. The symphony was performed every two days to remove the remains of feed and faeces, and then water samples were taken to measure the physical and chemical parameters of the water. Ingredients are Fish meal; Squid flour; Amaranth flour; Quinoa flour; Fish oil; Liquid lecithin; Cholesterol; Vitamin blend; Mineral mix; Carboxymethyl, cellulose; Chromium oxide and Corn starch.

Extraction by the cooking of pigments from shrimp heads: The shrimp heads, *Litopenaeus vannamei*, were obtained in fresh state crustacean processing plants in Bhimavaram, India and were immediately taken to the laboratory location. Through a cooking process at 100 °C for 15 minutes (ratio 1:2 shrimp and water), a reddish paste was obtained containing the crude carotenoid pigments, which, after packaging in glass coated with aluminium foil, was stored in a freezer until the start of the analyses.

Analysis of carotenoid pigments: The procedure used for the study of carotenoid pigments was performed according to the recommendations of Ponce et al (2006), involving the steps of extraction, saponification, separation and quantification of carotenoids, as described below:

Extraction of Pigments: The carotenoid pigments were extracted from 30 g of paste, through a blender homogenisation with cooled acetone (60 mL). The mixture was filtered under a water pipe vacuum using a kitasate and a Büchner funnel, equipped with commercial, fast-filtering filter paper. The residue was washed with acetone until the filtrate was colourless.

The aceto-pigmented solution was transferred to a separatory funnel, where 150 mL of hexane was added. After separating the two phases, the lower layer containing acetone was discarded. The hexane phase, including the pigments, was kept in the funnel and repeatedly washed with distilled water to remove the acetone altogether. Residual water was removed by filtration with anhydrous sodium sulphate. The final volume of the total pigment extract in hexane was made up to 350 mL by the addition of solvent.

Hexane/DMSO partition: The crude pigments present in the hexane extract were partitioned in a separatory funnel, using 350 mL of DMSO and obtaining the epiphanic (pigments in hexane) and hypophysis (pigments in DMSO) phases. After separation, the hexane phase was washed with distilled water until reaching a light orange colour, always adding small portions of ethanol to avoid its emulsification. The solution was filtered through anhydrous sodium sulfate to altogether remove the water, concentrated in a rotary evaporator under vacuum at 35 °C and stored in a freezer. The carotenoids present in the DMSO phase were purified by adding distilled water (150 mL), saturated NaCl (70 mL) and ethanol (225 mL). The solution was stirred, cooled in an ice bath and extracted with a mixture of ethyl ether and hexane (1:1) until colourless. The DMSO fraction was washed with distilled water and filtered over anhydrous sodium sulfate, then evaporated in a rotary evaporator under reduced pressure and stored in a freezer.

Saponification of the hexane fraction and obtaining the acidified fraction: The hexane fraction was dissolved in 150 mL of ethyl ether and 250 mL of 5% KOH in 90% ethanol, then left to stand for two hours at room temperature and in the absence of light. Then, distilled water (375 mL) was added and extracted with 200 mL of ethyl ether and hexane (1:1) mixture, resulting in hexane and aqueous phases. The hexane phase was then washed to slightly acidic pH (pH ± 5), filtered over anhydrous sodium sulfate, evaporated under vacuum on a rotary evaporator (35 °C) and stored in a freezer. The aqueous layer was acidified with acetic acid (pH:4) and subjected to further extraction with ethyl ether and hexane mixture. It was rewashed in distilled water, filtered on anhydrous sodium sulfate, evaporated under vacuum in a rotary evaporator at 35 °C and stored in a freezer.

Open column chromatography: The separation of pigments from the hexane and DMSO fractions was carried out in glass columns with a diameter of 2 cm, containing a small amount of cotton fibre at the bottom, followed by silica gel 60 up to a height of 11 cm and anhydrous sodium sulfate at the bottom. The upper part of the column absorbs possible water

residues in the sample. Chromatography was initially carried out with hexane and 20% ethyl ether, with a gradual increase in ethyl ether concentrations, maintaining a polarity gradient. Elution was completed using pure methanol.

Identification of carotenoids: Carotenoids were identified by the elution behaviour of the fractions in the column, the visible absorption spectrum and the R_f value in a thin layer of silica gel. The absorption spectra of the pigments in hexane were obtained in the wavelength range from 350 to 550 nm in a spectrophotometer (UV-Visible Spectrophotometer –Elico Model SL 159). The silica gel plate was developed in saturated fat, with a mobile phase consisting of benzene, ether and acetone, in the proportion of 10:2, 5:2, respectively. After development, the R_f values were calculated, and then the plate was subjected to HCl vapours in saturated fat to detect the presence of epoxide groups.

Quantification of carotenoids: Pigments were quantified using the formula shown below:

$$\frac{\mu g \text{ of Carotinoids}}{\text{Weight of the sample (g)}} = \frac{\text{absorbance} \times \text{vol. of the solution} \times 10^6}{100 \times E^{1\%} \times \text{sample weight}}$$

The values of extinction coefficients $E^{1\%}$ 1cm used for quantification of carotenoids were described by Ponce et al (2006), being 2592 (hexane), 2100 (hexane) and 1690 (pyridine), respectively, for β-carotene-5,6-epoxide, astaxanthin and Astacene.

3 Results and discussion

3.1 Identification of carotenoid pigments

Column chromatography of the hexane fraction revealed the presence of five bands, all ranging from weak to solid yellow. The primary pigment (intense yellow colour) was eluted with the initial gradient of solvents (20% ethyl ether in hexane). Similarly, the primary pigment of the DMSO fraction (five bands with colours ranging from light yellow to solid orange) was that of the third fraction (solid orange colour) eluted from the column with 50% ethyl ether hexane.

The results on the spectrophotometric analysis and thin-layer chromatography of the primary pigments of the hexane and DMSO fractions, as well as the acidified fraction of *L. vannamei* shrimp head, are shown in Table 1.

Table 1. Characterisation of hexane, DMSO and acidified fractions.

Pigment Fraction/color	Rf*	Maximum absorption in hexane (nm)	Semi-systematic name	Trivial name
Hexane / Strong Yellow	0.93	448.9; 474	5,6-epoxide-5,6-dihydro- β, β -carotene	β -carotene-epoxide
DMSO/Orange Red	0.73	470	3,3'-dihydroxy- β, β -carotene-4,4 'dione	Astaxanthin diester
Acid / Strong Red	0.64	468.5	β, β -carotene-4,4'-	Astaceno

			dione	

The data presented for the hexane fraction allow, experimentally, to identify the pigment as β-carotene-5,6-epoxide. According to Maoka, et al (2020), this compound must have an absorbance spectrum slightly lower than β-carotene, elute in the open column after β -carotene and a colour change from yellow to yellow blue-green occurs when subjected to HCl vapours, meaning that the pigment presents in its epoxide radical structure.

The DMSO phase retains polar pigments in the partitioning technique, such as free or esterified xanthophylls. The fraction eluted from the column is possibly astaxanthin (Figure 1), a keto-carotenoid commonly identified in fish and crustaceans, considering the presence of a single absorption maximum at 470 nm. The intermediate value of R_f is probably related to the diester form and the red-orange colour of the pigment. The pigment showed no colour change when subjected to HCl vapours. The pigment contained in the acidified fraction resulting from the saponification of the hexane fraction was tentatively identified as astacene, taking into account the data in Table 1, compared to those recorded in the literature (Su et ., 2018) that record a single maximum peak in the range of 465 to 477 nm, similar values of R_f and pigments of colours.

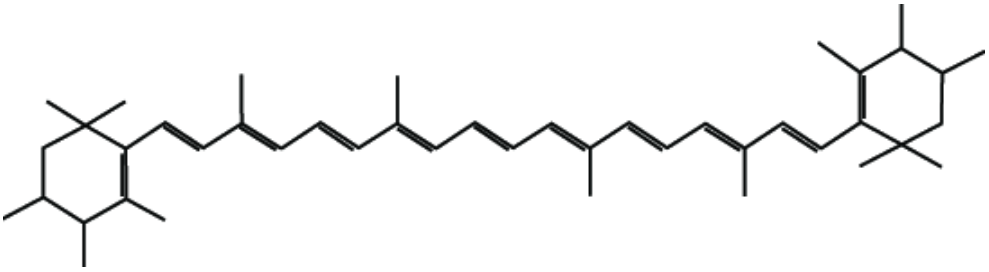

Figure 2. Free astaxanthin. In diester astaxanthin, hydroxyl groups are linked to fatty acids.

Astaxanthin can be converted to astacene (Figure 2) during fish processing and during the extraction, saponification and pigment separation steps. Astacene was the carotenoid present in the acidified fraction of the carapace meal of the aratu crab, Goniopsis cruentata18.

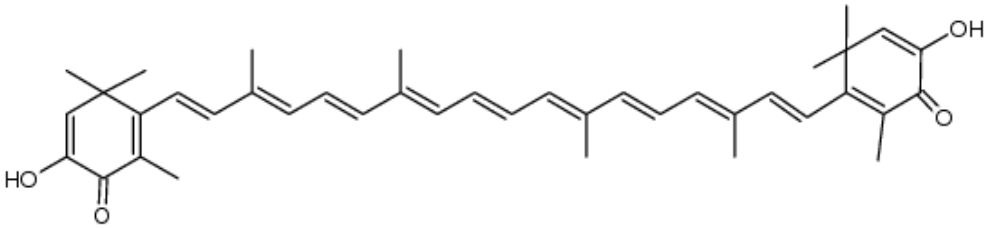

Figure 2. Astacene (3,3',4,4'-tetraacet-β-β-carotene)

According to Takeungwongtrakul et al. (2013), saponification of pigments in goldfish, Carassius auratus resulted in the separation of astacene and canthaxanthin in a Microcell C column.

Confirming the polarity characteristics of the pigments described in Table 1, Su, et al (2018b) showed that under HPLC analysis, the pigments were separated in increasing order of retention time into carotene, astaxanthin ester, canthaxanthin, and semiastacene (an epimeric form of astacene).

3.2 Quantitative composition

The concentrations of the identified carotenoid pigments, present in the hexane, DMSO and acidified fractions, are shown in Table 2.

Table 2. Quantitative composition of total carotenoids present in the hexane, DMSO and acidified fractions.

	Concentration		
Pigment	100mg. g-1 of paste	100mg. g-1 of lipid	100mg. g-1 of dry head
β-carotene-epoxide	1.26	10.8	15.8
Astaxanthin	1.71	14.6	21.4
Astacene	0.79	6.7	9.9
Total carotenoid	3.76	32.1	47.1

It is estimated that the content of total carotenoid pigments, present in the hexane, DMSO and acidified fractions, is around 3.76 mg.100 g-1 of the pigment paste. According to Su, et al (2018b), the head of *L. vannamei* shrimp contains 74.5% of moisture and 3.7% of lipids. The moisture and lipid contents were 72.6 and 11.7% in the paste, respectively. These values seem to indicate that the paste is a water-oil emulsion. The paste yield was meagre, corresponding to 1.2% about the wet shrimp head. Su, et al. (2018) reported astaxanthin contents in white shrimp, pink shrimp and aratu crab of 12.66, 9.93 and 17.7 mg.100 g-1 in pigmented oil, respectively. For the guaiamum crab, the astaxanthin content was only 2.11 mg.100 g-1 of oil. The per cent concentration of astaxanthin in the product was greater than 45%. However, comparing its concentration (14.6 mg.100 g-1 of lipids), it is observed a content slightly lower than that extracted from the whole shrimp head (21.2 mg.100 g-1 of pigmented oil), reported by Radzali, et al.(2017)

The review carried out by Seabra, (2013)reveals that in the ovaries of crustaceans (shrimps and crabs), the content of total carotenoids varies from 0.7 to 3.6 mg.100 g-1 of the wet sample, values in agreement with those presented in Table 2. However, extremely high values were reported by Radzali, et al.(2014) in the abdominal muscle (0.82%) and the exoskeleton (4.1%) of *L. vannamei*.

The total carotenoid content, expressed about dry head weight, is close to that reported by Arredondo et al (2003) for dehydrated snow Crab residues, which was 53.1 mg.kg-1 of whole crab and variable with the type of tissue analysed (16.4 to 139.9 mg.kg-1).

4. Conclusions

A growing interest in the use of astaxanthin in poultry and fish farming has developed since this pigment is not synthesised by animals and must be added to rations to obtain an attractive

colour for consumers. In addition, astaxanthin is a powerful antioxidant and has antitumor properties, which increases its potential for use in health. Commercial astaxanthin is produced by chemical synthesis, and natural alternatives are being sought in the face of growing concerns about food safety and negative aspects of synthetic pigments. Considering the results of the quantitative analysis and the volume of paste obtained in the experiment, it can be estimated that astaxanthin is the most abundant suggested pigment, followed by β-carotene-5,6-epoxide and astacene. Each kilo of shrimp head provided 21.4 mg of astaxanthin, 15.8 mg of β-carotene-5,6-epoxide and 9.9 mg of astacene. It is possible that higher yields can be observed, provided that techniques adopted and equipment on an industrial scale.

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AMITAV GHOSH'S *SEA OF POPPIES*: A SAGA OF THE MARGINALIZED AND SUBALTERN AFFLICTIONS

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ABSTRACT

Amitav Ghosh is one of the most significant writers crafting fiction in English today. He has written thought provoking creative novels which have won great acclaim across the world. He used historical perspective besides creative themes focusing on the lives of downtrodden and subaltern concept in his works. Sea of Poppies, the first in a trilogy, deals with a world made of a few privileged ones and masses of oppressed, exploited subjects. The novel explains how colonial history in Asia, affects lives today, how the modern days are shaped by that era. The paper presents the saga of post-colonial subalterns and historical perspectives in the present time.

Key words: Subaltern, Historical, Ibis

Amitav Ghosh is the most popular Indian writer. His works generally deals with history, the life of subalterns, partition, and politics. His success as historical novelist owes much to the uniqueness of each of his characters. His well known works are: *The Circle of Reason* (1986), *The Shadow Lines* (1988), *In an Antique Land* (1992), *Calcutta Chromosome* (1996), *The Glass Palace* (2000), *The Hungry Tide* (2004) and *Sea of Poppies* (2008). The first part of *The Ibis* trilogy is *Sea of Poppies* and it dramatizes two great economic themes of the 19th century. The first one is about the farming of opium as a cash crop in Bengal and Bihar for the Chinese market and the second one is about the carry of Indian indentured workers to cut sugar canes for the British on some islands as Mauritius, Fiji and Trinidad. It also gives about the life of Deeti, who is marginalized under neo-colonial mindset of people.

Amitav Ghosh's *Sea of Poppies* (2008), the first book of a proposed Ibis trilogy, was received with both critical and popular acclaim, and was a nominee for the Man Booker prize the same year. *The New York Review of Books* describes it as "a rollicking tale, or rather collection of tales—politically forceful, historically fascinating, and rarely subtle" (Schine, 2). The novel tells the story of how it is that in the ship *Ibis*, headed to Caribbean sugar plantations. It is the tale of a British captain, an American, second mate, Indian troops to maintain order, Bengali Zamindars, black men, rural labourers, Chinese seamen, and a crew of lascars. Ghosh has merged history and creative writing in this novel. Michael Binyon says about the novel that "India in the 1830s is wonderfully evoked—the smells, rituals and squalor...Coarseness and violence, cruelty and fatalism, are relieved with flashes of emotion and kindness. This is no anti-colonial rant or didactic tableau but the story of men and women of all races and castes, cooped up on a voyage across the 'Black Water' that strips them of dignity and ends in storm, neither in despair nor resolution. It is profoundly moving" (1). Ghosh provides the reader with all manner of stories, and equips himself with the personnel to man and navigate an old-

fashioned literary three-decker…Yet for all its research, Buchan says that *Sea of Poppies* is full of the open air. It never, as the eighteenth century used to say, 'smells of the lamp" (1). Ghosh has given post-colonial mindset in the novel. Jain Shalini "Ghosh's narrative, while exposing various colonial methods of subjectivations and demonstrating the spirited instances of resistance, also equally importantly takes on the task of critiquing extant Indian social and traditional powers, which were often blatantly patriarchal, feudal and anti-feminist in nature" (67). *Sea of Poppies* is laced with political overtones, revealing the hypocritical and dangerous mindset of the then Englishmen, who compelled the natives to the level of subaltern in their own land. He incorporated about the political and socio-economic conditions that led to the mass migration of impoverished Indian peasants as indentured laborers to the Mauritius islands. Indeed, this work is bitter satire on migration and colonization. Employing many of the conventions of the historic novel, which Georg Lukacs describes as invoking "certain crises in the personal destinies of a number of human beings that coincide and interweave within the determining context of an historic crisis" (Cooppan, 41).

Set in India in 1838, at the beginning of the three-year Opium War between the British and the Chinese, this epic novel follows a few characters from various levels of society, who become united through their personal lives aboard the boat and, all the more by and large, through their connections with the opium and slave trades. Deeti is the protagonist of the novel. She was married to Hukam Singh who is an opium addict. She was drugged with opium by her aunt and brother-in-law, Chandan Singh on the marriage day. Chandan Singh rapes her. He is the real father of Deeti's daughter Kabutri. Hukam Singh who works in an opium factory is also victim of the British two times over: 'a sepoy who served them in campaigns overseas, crippled by his battle wounds, he has turned to opium for the pain, which has crippled him further. You should know, he tells Deeti of his cherished opium pipe, that this is my first wife. She's kept me alive since I was wounded: if it weren't for her I would not be here today. I would have died of pain, long ago' (97).

A description of the conditions prevalent in the Ghazipur Opium factory gives us cruel and heinous conditions of its employees as witnessed by Deeti, who is summoned to take her sick husband home from work: "Her eyes were met by a starting sight – a host of dark, legless torsos was circling around and around, like some enslaved tribe of demons… they were bare-bodied men, sunk waist-deep in tanks of opium, tramping round and round to soften the sludge. Their eyes were vacant, glazed and yet somehow they managed to keep moving, as slow as ants in honey, tramping treading…these seated men had more the look of ghouls than any living thing she has ever seen: their eyes glowed in the dark, and they appeared completely naked" (95). Even after seven years, Chandan Singh wants Deeti for his bed and expects that Deeti would come to him. He tells her that:

> If you conceive a son while he is still living, he will be his father's rightful heir. Hukum Singh's land will pass to him and no one will have the right to dispute it. My brother's land and his house will become mine on his death. Jekhar khet, tekar dhan – he who owns the land, owns the rice. When I became master of this house, how will you get by except at my pleasure? (157)

When her husband dies, Deeti sends her daughter Kabutri to stay with relatives. Kalua, who is an ox man from the neighboring village, saves her from Sati ritual. He is a man who is marginalized as he is an untouchable and chamar by caste. He expressed his true feelings, when Deeti asked her about saving her, "It was myself I saved today, he said in a whisper. Because if you had died, I couldn't have lived; jinda na rah sakela" (179). Both Kalua and Deeti escape from the villagers. They secretly marry in a simple ceremony to commemorate the sacredness of their union. Their marriage represents as a revolutionary step. It is not acceptable to the high class villagers. In order to escape Deeti's in-laws and there is no alternatives left that sound good to her, she get away, in the long run joining the vagrants on board the Ibis which is a former slave ship. She changes her name Aditi. "Did not feel herself to be living in the same sense as before: a curious feeling, of joy mixed with resignation, crept into her heart, for it was as if she really had died and been delivered betimes in rebirth, to her next life: she had shed the body of the old Deeti…and was free now to create a new destiny as she willed, with whom she chose" (178). They hide their actual names. The writer has given: "It was on her lips to identify herself as Kabutari-ki-ma, the name by which she had been known ever since her daughter's birth... her proper, given name was the first to come to mind and since it had never been used by anyone, it was as good as any. Aditi, she said softly, I am Aditi" (233).

Kalua is a giant of a man but he "made no move to help his passenger and was careful to keep his face hidden from him: he was of the leather workers' caste and Hukum Singh, as a high-caste Rajput, believed that the sight of his face would bode ill for the day ahead" (4). His caste made him bear the burden of being lowest in the caste hierarchy. He became the victim of British colonial rule. Ghosh states that "he was of the leather workers' caste and Hukum Singh, as a high-caste Rajput, believed that the sight of his face would bode ill for the day ahead" (4). Kalua's character represents the downtrodden and marginalized. He is the victim of cultural constructs of caste. He like other low caste people lives at the outskirts of the village away from the village.

The illegal opium exchange among India and China is going on and one of the enormous exporters is Mr Burnham, of Burnham Bros in Calcutta, and he purchases the Ibis in 1837 to refit it for pulling opium. Both Calcutta and Ibis are polyglot communities; the people on this ship speak everything from pidgin and Bhojpuri to the comically mangled English of a Bengali Babu and a young Frenchwoman called Paulette. She has been grown up in India. Since Mr. Burnham desires her in private, she has decided to run away. Paulette meets Zachary Reid, the American sailor. She has resolved to travel to Mauritius. Along with Jodu, she boards the Ibis. As she has already learnt Bengali in her childhood, she is good at Bengali. She easily disguised herself as an Indian woman. The members of *Ibis* as Deeti, Kalua, Paulette, Neel, Ah Fatt and other passengers share a common past on Ibis. The main character of the novel Deeti represents high class Rajput woman, Kalua is a dalit subaltern, Paulette is an orphan. The novel is about seeking freedom. A galaxy of characters like poppy seeds emerges in the unique situation and a large portion of the characters are violators and of course they experience class or race discrimination. It is fitting to summarize by expressing that the novel is a mix of issues identified with the people who flourish with the margins. Ghosh presents office to the silenced, an opportunity to highlight the forgotten and disregarded stories keeping the point of marginalization in his mind.

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Design and synthesis of 4β-Acetamidobenzofuranone-podophyllotoxin hybrids and their anti-cancer evaluation

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ABSTRACT

A new series of amide derivatives of 4β-Acetamidobenzofuranone-podophyllotoxin hybrids (**14a–g**) were synthesized and their chemical structures were confirmed by ^{1}H, ^{13}C NMR and mass spectral data. Further, all the synthesized Acetamidobenzofuranone-podophyllotoxin hybrids were evaluated for *in vitro* cytotoxic activity against a panel of four human cancer cell lines i.e., human breast (MCF-7, MDA MB-231), lung (A549), and prostrate (DU-145). Among benzofuranone-podophyllotoxin hybrid compounds, **14b** and **14e** were exhibited more potent activity than standard drug and **14c** and **14f** were showed anticancer activity equivalent to etoposide.

Cancer is a very harmful disease and leading cause of death all over the world.[1] It occurred by the abnormal cell division without manage and are capable to occupy other tissues.[2] There are three major types of treatments are available in the field such as radiation, surgery and chemotherapy. Among them, chemotherapy is the most efficient treatment to devastate the cancer cells without any damaging upshot on the normal cells for various cancers, in which several types of chemotherapeutic agents are used.[3] The human DNA topoisomerse inhibitors are frequently used chemotherapeutic agents.

Podophyllotoxin (**1**) is an antitumor lignan mainly found in the plants *Podophyllum peltatum* and *P. emodi*.[4] It inhibits the microtubule assembly through binding to tubulin (Fig. 1).[5] The biological activity of podophyllotoxin has led to extensive structure modifications resulting in several clinically useful compounds such as etoposide (**2**) and teniposide (**3**) (Fig.1). These are used as DNA topoisomerase II inhibitors in chemotherapy for various types of cancer.[6] However, their acquired drug resistance and poor water solubility hampered their clinical use. To overcome such problems, extensive synthesis efforts have been carried out by research groups to develop NK-611 (**4**)[7] and GL-331 (**5**).[8] Furthermore, these exhibited improved cytotoxicity and topo-II inhibition.[9]

GL-331 induces the apoptotic cell death through independent mechanism and that would also contribute to their cytotoxicity, which was undergone a phase II clinical trials for the treatment of various cancers,[10] and trials are stopped in 2001. In addition, previous reports reveal that GL-331 analogues having electron withdrawing groups on 4β-carbon position is more active.

On the other hand, aurone (**6**) is one of most privileged fused bicyclic heterocyclic scaffolds and is isolated from *Uraria hamiltonii*.[11] Aurones, are secondary metabolite belong to the flavonoids family and are structural isomers of flavones.[12] Several synthesized aurone derivatives are possessed a wide range of biological activities including anticancer,[13,14] tubulin agent,[15] CDK inhibitor,[16] anti-malarial,[17] and acetylcholinesterase inhibitors.[18] Besides, the main reason for the anticancer activity of aurone derivatives was due to the position and the number of hydroxyl groups present on phenyl ring attached to carbon skeleton. In general, aurone derivatives containing the hydroxyl group in *para* position are more potent than that of *ortho* and *meta* positions.

In view of the above impressive biological properties of both podophyllotoxin and aurone scaffolds, we are interested to know the combined effect of both these moieties in a single molecular framework. Hence we would like to synthesize these hybrid molecules to evaluate their anticancer effect.

In furtherance of our research work in the fields of (i) natural product based hybrid molecules,[19–21] NHCs,[22–25] and anti-cancer hybrid molecules,[26–28] herein we report for the first time in this manuscript a facile and new series of aurone-podophyllotoxin hybrids. In the present work, we have synthesized a series of 4β-Acetamidobenzofuranone-

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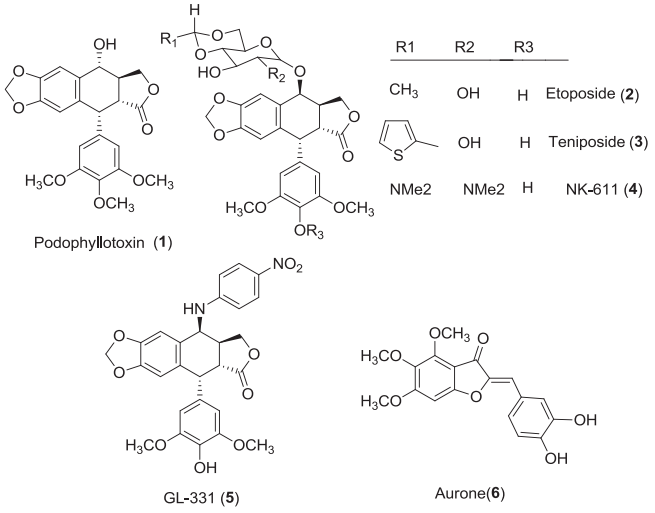
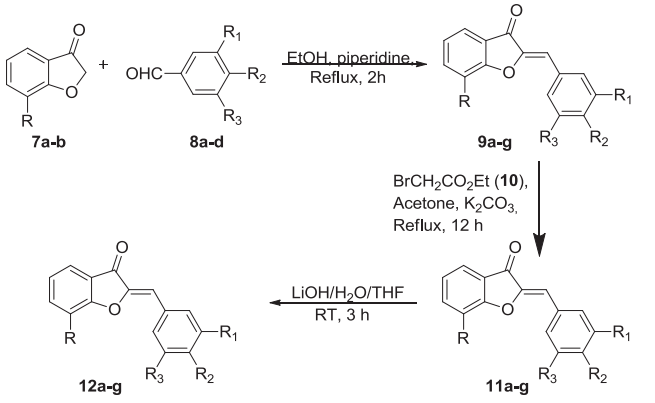


Fig. 1. Semi-synthetic derivatives of podophyllotoxin and aurone.



R = H (**7a**), OCH_3, (**7b**)
R_1 = OCH3, R_2 = OH, R_3 = H (**8a**)
R_1 = OH, R_2 = OCH_3, R_3 = H (**8b**)
R_1,R_3 = OCH_3, R_2 = OH (**8c**)
R_1,R_3 = H, R_2 = OH (**8d**)
R, R_1 = OCH_3, R_2 = OH, R_3 = H (**9a**)
R,R_2 = OCH_3, R_1 = OH, R_3 = H (**9b**)
R,R_1,R_3 = OCH_3, R_2 = OH (**9c**)
R = OCH_3, R_1,R_3 = H, R_2 = OH (**9d**)
R,R_3 = H, R_1 = OCH_3, R_2 = OH (**9e**)
R,R_3 = H, R_1 = OH, R_2 = OCH_3 (**9f**)
R,R_1,R_3 = H, R_2 = OH (**9g**)

R, R_1 = OCH_3, R_2 = -OCH_2CO_2Et, R_3 = H (**11a**)
R,R_2 = OCH_3, R_1 = -OCH_2CO_2Et, R_3 = H (**11b**)
R,R_1,R_3 = OCH_3, R_2 = -OCH_2CO_2Et (**11c**)
R = OCH_3, R_1,R_3 = H, R_2 = -OCH_2CO_2Et (**11d**)
R,R_3 = H, R_1 = OCH_3, R_2 = -OCH_2CO_2Et (**11e**)
R,R_3 = H, R_1 = -OCH_2CO_2Et, R_2 = OCH_3 (**11f**)
R,R_1,R_3 = H, R_2 = -OCH_2CO_2Et (**11g**)
R, R_1 = OCH_3, R_2 = -OCH_2CO_2H, R_3 = H (**12a**)
R,R_2 = OCH_3, R_1 = -OCH_2CO_2H, R_3 = H (**12b**)
R,R_1,R_3 = OCH_3, R_2 = -OCH_2CO_2H (**12c**)
R = OCH_3, R_1,R_3 = H, R_2 = -OCH_2CO_2H (**12d**)
R,R_3 = H, R_1 = OCH_3, R_2 = -OCH_2CO_2H (**12e**)
R,R_3 = H, R_1 = -OCH_2CO_2H, R_2 = OCH_3 (**12f**)
R,R_1,R_3 = H, R_2 = -OCH_2CO_2H (**12g**)

Scheme 1. Synthesis of (Z)-2-benzylidenebenzofuran-3(2H)-one acid (**12a–g**).

podophyllotoxin hybrids (**14a–g**) from 4*β*-aminopodophyllotoxin (**13**) and 7-substituted (*Z*)-2-benzylidenebenzofuran-3(2*H*)-one acid linkers (**12a–g**) (Scheme 2). The main chemical differences are the different substituted aurones and substituted aromatic aldehydes with constant two carbons chain acid linker. Further, anti-cancer activity of these derivatives (**14a–g**) were examined towards four human cancer cell lines i.e., human breast (MCF-7, MDA MB-231), lung (A549), and prostrate (DU-145).

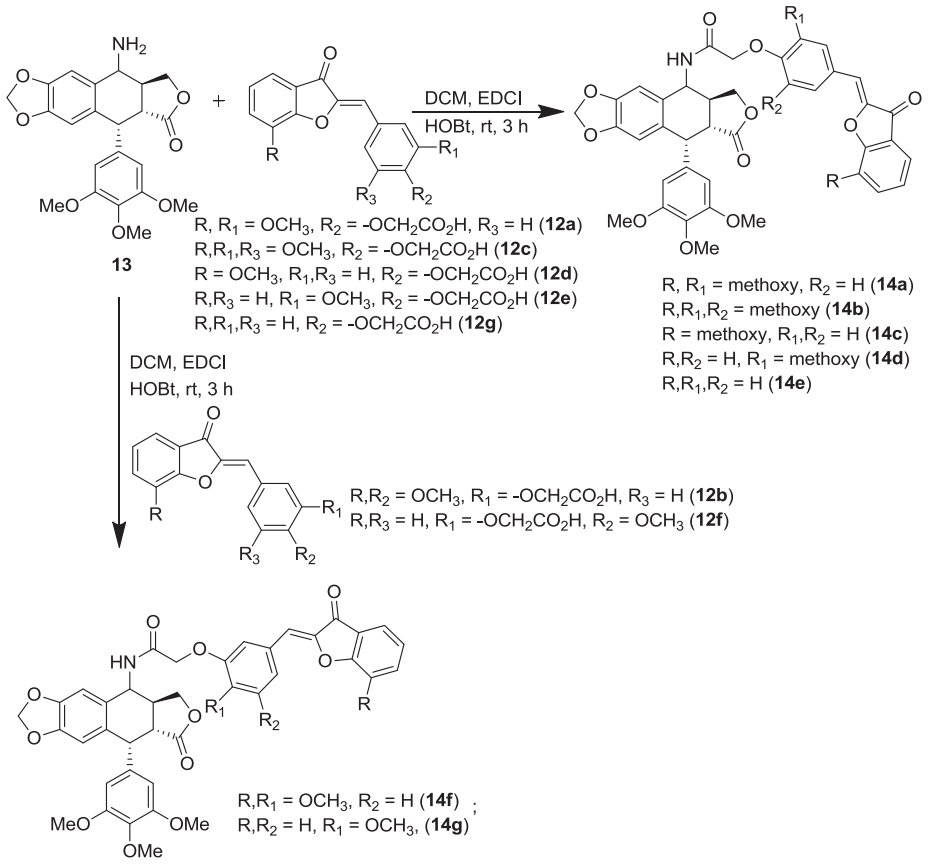
The synthesis of the (*Z*)-2-benzylidenebenzofuran-3(2*H*)-one acid linker derivatives (**12a–g**) is outlined in Scheme 1. Benzofuran-3(2*H*)-one (**7a**) and 7-methoxybenzofuran-3(2*H*)-one (**7b**) are key intermediates for the preparation of the desired compounds (**9a–g**). The compounds **7a** and **7b** were taken separately and treated with different substituted aromatic aldehydes (**8a–d**) in ethanol and 3 drops of piperidine was added then the mixture was refluxed for 2 h to afford pure compounds (**9a-g**). The intermediates **9a–g** was reacted with ethyl bromoacetate (**10**) in presence of K_2CO_3 in anhydrous acetone and reaction mixture was stirred at reflux for 12 h to obtain compounds (**11a–g**). Further, these compounds (**11a–g**) were hydrolyzed under basic condition to afford pure compounds (**12a–g**). Finally, these acid intermediates were subjected to coupling reaction with 4*β*-aminopodophyllotoxin (**13**) in presence of EDCI, HOBt as coupling reagents and stirred at room temperature for 3 h in anhydrous DCM as a solvent to afford pure corresponding products **14a–g** as shown in Scheme 2.

The synthesized (*Z*)-2-benzylidenebenzofuran-3(2*H*)-one acid linker derivatives (**12a–g**) and 4β-Acetamidobenzofuranone-podophyllotoxin hybrids (**14a–g**) were characterized by $^1H/^{13}C$ NMR and mass spectral analysis (ESI). The absence of ^1H NMR signals of acid functional group, and emerging of a new signal corresponds to N—H proton of amide provides a good support for the amide coupling to form aurone-podophyllotoxin hybrids. The same features were reflected in ^{13}C NMR spectra, where the signal belongs to acid carbon was disappeared and a new signal belongs to amide carbon, was appeared after amide coupling.

In vitro cytotoxic activity: All the compounds prepared herein (**14a–g**) were screened for their anti-cancer activity towards four human cancer cell lines including MCF-7 (human breast), A549 (human lung), DU-145 (human prostrate) and MDA MB-231 (human breast) by using MTT assay method and the results acquired were incorporated in Table 1. Etoposide used as standard reference drug and most of tested compound were displayed good to moderate activity with respect to all cell lines. The IC_{50} values of synthesized compounds range from 0.10 ± 0.072 to 8.23 ± 3.61 μM and standard drug showed from 1.91 ± 0.84 to 3.08 ± 0.135 μM. Among them, two compounds, **14b** and **14e** were exhibited excellent activity than etoposide. The other compounds **14c** and **14f** were showed anticancer activity equivalent to etoposide. Further, structure-activity relationship (SAR) studies of these compounds revealed that the compound **14e** with (R,R_1,R_2 = H) substituent on the furan ring and phenyl ring has showed most promising activity (MCF-7 = 0.13 ± 0.087 μM, A549 = 0.10 ± 0.072 μM, DU-145 = 0.97 ± 0.068 μM and MDA MB-231 = 0.45 ± 0.029 μM) than etoposide. The replacement of (R = H) with (R = methoxy) and R_1,R_2 = methoxy groups resulted compound **14b** has exhibited lower activity on all cell lines (MCF-7 = 0.23 ± 0.081 μM, A549 = 1.45 ± 0.77 μM, DU-145 = 1.22 ± 0.69 μM and MDA MB-231 = 0.87 ± 0.052 μM) when compared with compound **14e**. Where compound **14c** having (R = methoxy, R_1,R_2 = H) groups has displayed good activity on three cell lines (MCF-7 = 1.98 ± 0.87 μM, A549 = 1.56 ± 0.65 μM, DU-145 = 2.09 ± 1.59 μM and MDA MB-231 = 1.68 ± 0.34 μM) when compared with compound **14b**. Whereas, compound **14f** with (R,R_1 = methoxy, R_2 = H) groups has exhibited comparable activity on three cell lines (MCF-7 = 1.87 ± 0.38 μM, DU-145 = 2.33 ± 1.76 μM and MDA MB-231 = 2.18 ± 1.98 μM), respectively. The rest of the compounds **14a, 14d** and **14g** were showed moderate activity on all the cell lines.

MTT assay: Individual wells of a 96-well tissue culture micro titer plate were inoculated with 100 μL of complete medium containing 1×10^4 cells. The plates were incubated at 37 °C in a humidified 5% CO_2 incubator for 18 h prior to the experiment. After medium removal, 100 μL of fresh medium containing the test compounds and etoposide at different concentrations such as 0.5, 1, and 2 μM were added to each well and incubated at 37 °C for 24 h. Then the medium was discarded and replaced with 10 μL MTT dye. Plates were incubated at 37 °C for 2 h. The resulting formazan crystals were solubilized in 100 μL extraction buffer. The optical density (O.D) was read at 570 nm with micro plate reader (Multi-mode Varioskan Instrument-Themo Scientific). The percentage of DMSO in the medium never exceeded 0.25%.

In conclusion, we have synthesized a new series of amide derivatives of aurone-podophyllotoxin hybrid molecules (**14a–g**) through a facile route and their anticancer activity was demonstrated. These hybrid compounds were tested for their preliminary anticancer activity towards four human cancer cell lines MCF-7 (human breast), A549



Scheme 2. Synthesis of 4β-Acetamidobenzofuranone-podophyllotoxin hybrids (**14a–g**).

Table 1
In vitro cytotoxicity of 4β-Acetamidobenzofuranone-podophyllotoxin hybrids (**14a–g**) on human cancer cell lines[a] (IC_{50} μM).[b]

Entry	Compound	MCF-7[c]	A549[d]	DU-145[e]	MDA MB-231[f]
1	14a	2.35 ± 1.60	2.99 ± 2.09	3.98 ± 1.93	2.60 ± 1.75
2[g]	**14b**	**0.23 ± 0.081**	**1.45 ± 0.77**	**1.22 ± 0.69**	**0.87 ± 0.052**
3	14c	1.98 ± 0.87	1.56 ± 0.65	2.09 ± 1.59	1.68 ± 0.34
4	14d	4.51 ± 2.18	2.75 ± 1.85	3.82 ± 2.16	ND
5[g]	**14e**	**0.13 ± 0.087**	**0.10 ± 0.072**	**0.97 ± 0.068**	**0.45 ± 0.029**
6	14f	1.87 ± 0.38	ND	2.33 ± 1.76	2.18 ± 1.98
7	14g	6.23 ± 3.29	7.23 ± 3.41	2.55 ± 0.45	8.23 ± 3.61
8	**Etoposide**	2.11 ± 0.024	3.08 ± 0.135	1.97 ± 0.45	1.91 ± 0.84

"ND" = Not determined.
[a] Each data represents as mean values ± SD (standard deviation).
[b] From three different experiments performed in triplicates.
[c] MCF-7: human breast cancer cell line.
[d] A549: human lung cancer cell line.
[e] DU-145: human prostate cancer cell line.
[f] MDA MB-231: human breast cancer cell line.
[g] Compounds with Significant activity.

(human lung), DU-145 (human prostrate) and MDA MB-231 (human breast) by using MTT assay and etoposide used as standard reference drug. All these hybrid molecules showed good to moderate activity. Among all the synthesized compounds, **14b,** and **14e** were exhibited more potent activity than standard drug. The other compounds **14c** and **14f** were equipotent to etoposide.

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Appendix A. Supplementary data

Supplementary data (experimental procedures and spectral data of compounds for **9a–g**, **11a–g**, **12a–g** and **14a–g**) to this article can be found online at https://doi.org/10.1016/j.bmcl.2019.06.060.

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Synthesis of D-ring modified acid hydrazide derivatives of podophyllotoxin and their anticancer studies as Tubulin inhibiting agents

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ABSTRACT

A new series (except compound 3a) of D-ring modified acid hydrazides of podophyllotoxin were synthesized by cleaving of its D-ring with various hydrazines. Furthermore, the synthesized compounds were screened for their anticancer activity against human tumor cell lines i.e., MCF-7, HeLa and A-549 and among the synthesized compounds **3c** and **3f** have shown significant anticancer activity almost similar to that of standard drug etoposide. Molecular modelling studies were also conducted for active compounds and found that the free energies obtained were in good agreement with the observed IC_{50} values.

1. Introduction

The crude extract isolated from the roots and rhizomes of the plants of podophyllum species is called Podophyllum resin and it has been used as a cathartic, antihelminthic agent and a remedy for condyloma acuminatum for several years [1,2]. The active component of this resin is an aryltetralin lignan named podophyllotoxin **(1)**, a promising anticancer molecule. Its analogues Etoposide **(2)** and Teneposide **(3)** were proved to be potential antitumor drugs for various types of cancer ailments [3]. Currently some of its structural analogues such as GP-11 **(4)**, GL-331 **(5)** and TOP-53 **(6)** are drug leads for cancer treatment (Fig. 1) [4]. GL-331 is currently in phase-II clinical trials against gastric carcinoma, colon cancer, non-small cell carcinoma and etoposide resistant malignancies [5]. However, their clinical use has encountered certain problems, such as poor water solubility, drug resistance, metabolic inactivation and certain toxic effects [6,7].

Antitumor property of podophyllotoxin and its analogues was mainly due to its mechanism of action which involves inhibition of Tubulin polymerization [8]. Tubulin inhibiting agents interfere with microtubule dynamics and hinder the assembly of Tubulin into microtubules. Microtubules are vital cytoskeletal filaments that found in eukaryotes and play key role in numerous cellular functions, such as cell motility, vesicle transport and cell division. Disruption of this equilibrium will lead to cell cycle arrest or cell apoptosis. Given their significant role in the growth and function of cells, microtubules are among the most important molecular targets for cancer chemotherapeutic agents. Colchicine is the first drug that is well known to bind Tubulin, and its binding site has been characterized recently. In the past, number of small molecules were discovered which bind to Tubulin, interfering with the polymerization or depolymerization of microtubules and then inducing cell cycle arrest, resulting in cell death [9,10].

On the other hand, acid hydrazides have wide applications as drugs, chemical preservers for plants, for manufacturing polymers, glues, etc., in industry and for many other purposes [11]. A wide variety of heterocyclic compounds like pyrroles, pyrazoles, pyrazolines, oxadiazolethiones, thiazoles, oxadiazoles, triazoles, thiadiazoles and tetrazines can be synthesized starting from acid hydrazides using Gewald reaction, Curtius rearrangement, Dimroth rearrangement, Horner-Emmons reaction and Reid-Heindel reaction.

Based on the SAR studies, initially it was presumed that intact translactone ring of Podophyllotoxin i.e., D-ring was responsible for its anticancer property. But reports thereafter revealed that it may not be the case. For example **GP-11(4)** and other D-ring modified derivatives have disproved it and moreover the former is equipotent to a well-known cancer drug, etoposide [12]. In addition, the clinical success of GP-11, a derivative of Podophyllic acidhydrazide, encouraged us to take up synthesis and anticancer screening of similar derivatives of podophyllotoxin.

To overcome the toxic effects, poor water solubility and other issues associated with the earlier reported podophyllotoxin derivatives, Herein we have shown some necessary modifications to Lactone ring (D-ring) of podophyllotoxin to synthesize podophyllic acid hydrazides. The synthesized compounds were also tested for their efficacy in inhibiting

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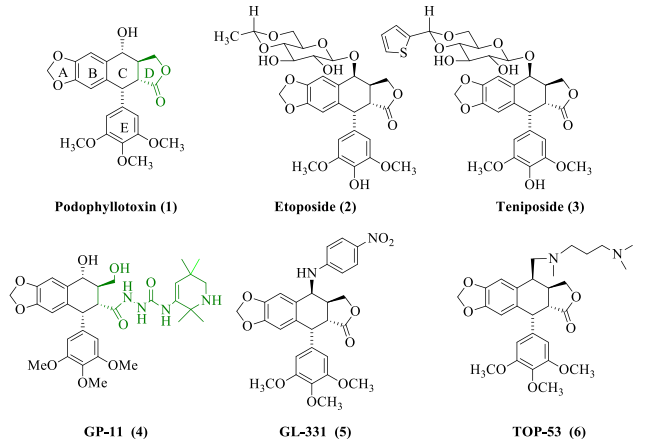
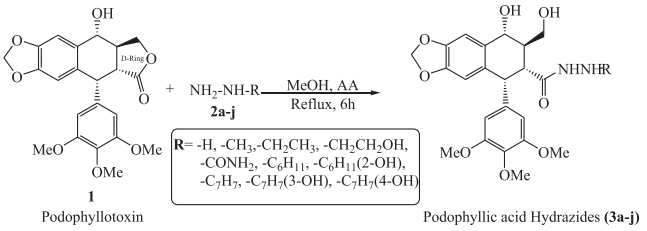


Fig. 1. Podophyllotoxin, its anticancer drugs and drug lead compounds.



Scheme 1. Synthesis of podophyllic acid hydrazides.

tumor growth of three human tumor cell lines (MCF-7, HeLa and A-549).

Initially Podophyllotoxin (**1**) was dissolved in methanol, and then, acetic acid (AA) and corresponding anhydrous hydrazines (**2a-j**) were added with stirring [13]. The reaction mixture was refluxed for about 6–10 h to afford podophyllic acid hydrazides (**3a-j**) in good to excellent yields (Scheme 1).

Podophyllotoxin was made to react with structurally different hydrazine derivatives and the results obtained were summarized in Table 1. It was clear from the table that among various hydrazines, aliphatic hydrazines (Table 1, Entries 1–4) performed well by giving good yields in short reaction times. Semicarbazide and alicyclic hydrazines (Entries 5–7) were took longer times to cleave the ring and gave lower yields than that of aliphatic hydrazines. Even benzylic hydrazines (Entries 8–10) were also equally good at cleaving D-ring of podophyllotoxin to give corresponding acid hydrazides. However, aromatic hydrazines (Entries 11 and 12) were unable to cleave the D-ring of podophyllotoxin and there were no products formed even after refluxing for 24 h. This inability of aromatic hydrazines to cleave D-ring may be attributed their lower basicity than the corresponding aliphatic and other hydrazines of present study.

Table 2
in vitro cytotoxic activity of podophyllic acidhydrazides (**3a-j**) on human cancer cell lines[a] (IC_{50} μM).[b]

Entry	Compound	MCF-7(Breast)	HeLa (Cervical)	A-549 (Lung)
1	3a	30 ± 0.03	35 ± 0.01	30 ± 0.02
2	3b	35 ± 0.05	40 ± 0.13	32 ± 0.14
3	**3c**	**15 ± 0.04**	**18 ± 0.18**	**16 ± 0.02**
4	3d	37 ± 0.01	45 ± 0.24	40 ± 0.01
5	3e	45 ± 0.01	43 ± 0.04	38 ± 0.45
6	**3f**	**12 ± 0.06**	**20 ± 0.07**	**15 ± 0.12**
7	3 g	42 ± 0.05	45 ± 0.25	38 ± 0.01
8	3 h	40 ± 0.02	35 ± 0.06	42 ± 0.01
9	3i	30 ± 0.02	35 ± 0.11	45 ± 0.05
10	3j	34 ± 0.02	35 ± 0.01	38 ± 0.10
11	Etoposide	10 ± 0.32	15 ± 0.37	12 ± 0.12

[a] Data represent as mean ± SEM values. Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cell with respect to untreated cells using the MTT assay.
[b] Data represent as mean ± SEM values of these independent determinations.

The NMR and HRMS techniques were used to elucidate the structures of the synthesized acid hydrazides. The formation of acid hydrazides from podophyllotoxin can be realised by comparing the ^{1}H NMR & ^{13}C NMR spectra of parent compound and formed acid hydrazides. The appearance of new peak in ^{1}H NMR spectrum of acid hydrazides at around 9.16δ (corresponds to CO-NH proton) clearly indicates the formation of acid hydrazides from the parent compound. This peak was not there in the ^{1}H NMR spectrum of parent compound. In ^{13}C NMR spectrum, the peak corresponding to carbonyl carbon of lactone ring was experienced a downfield shift due to deshielding effect with D-ring opening and thus moved from ~175 to ~172 δ. The same downfield shift was also seen in the case of methylene carbon of lactone ring i.e., from ~72 to 68.7 δ. Further confirmation of acid hydrazide formation was also done by HRMS spectra.

In vitro cytotoxicity assay: The synthesized podophyllic acid hydrazides (**3a-j**) were evaluated for *in vitro* cytotoxic ability against a panel of human cancer cell lines, including MCF-7, HeLa and A549 using a MTT assay [14]. The results were summarized in Table 2 and well-known standard drug etoposide was used as a reference. The newly synthesized podophyllic acid hydrazides have shown moderate to good anticancer activity against most of the cell lines in this investigation. Among them, compounds **3c** and **3f** were exhibited significant anticancer activity with IC_{50} values ranging from 12 to 20 μM and the observed activity of these compounds was almost similar to that of standard drug etoposide. As far as structure activity relationship is

Table 1
Showing the results for the synthesis of podophyllic acid hydrazides from structurally diverse hydrazines.

Entry	Hydrazine	Product[a]	Reaction time (hour), (yield, %)[b]	Entry	Hydrazine	Product[a]	Reaction time (hour), (yield, %)[b]
1		3a	6(94)	7		3g	10(75)
2		3b	6(92)	8		3h	7(90)
3		3c	6(94)	9		3i	8(88)
4		3d	6.5(90)	10		3j	8(85)
5		3e	8(65)	11[c]		3k	No reaction
6		3f	10(72)	12[c]		3l	No reaction

[a] All products were characterized by ^{1}H/^{13}C NMR and Mass spectral analysis.
[b] Isolated yields after column chromatography.
[c] 24 h, reflux.

Table 3
Binding energies for active molecules **3c** and **3f.**

Sl.No.	Compound	Binding Energy (PBD ID 1ZXN)	Residues
1	3c	−7.8	ASP A60, GLY A129, GLY A130, THR A131, ASN A88, VAL A164
2	3f	−7.6	GLN A11, CYS A12, GLN A15, PHE A208, SER A126, VAL A164

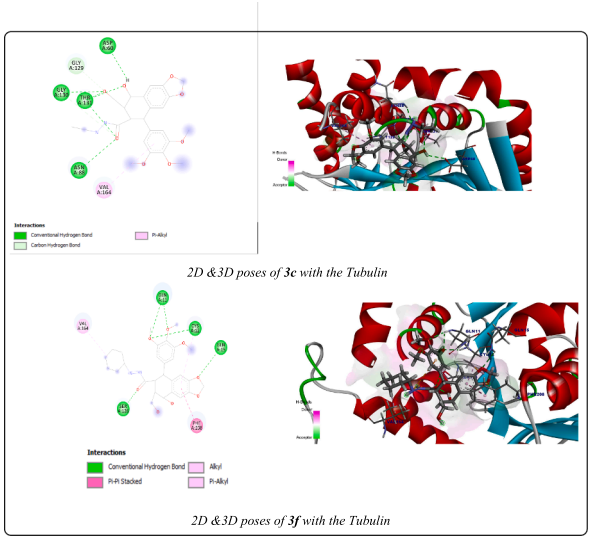


Fig. 2. The docking poses of **3c** & **3f** with Human γ-Tubulin.

concerned, the compounds having ethyl and cyclohexyl substituents on hydrazine i.e., the compounds **3c** and **3f** have shown the most promising apoptotic activity than the other substituents (for 3c, 15 ± 0.04 μM against MCF-7, 18 ± 0.18 μM against HeLa and 16 ± 0.02 μM against A-549; for 3f, 12 ± 0.06 μM against MCF-7, 20 ± 0.07 μM against HeLa and 15 ± 0.12 μM against A-549). In the case of compound **3g,** introduction of hydroxyl group next to the hydrazine of cyclohyxyl ring significantly reduced the activity (38 ± 0.01 μM to 45 ± 0.25 μM). Particularly, the compounds having benzyl moiety on hydrazine i.e., **3h, 3i** and **3j** have shown very moderate activity ranging from 30 ± 0.02 μM to 45 ± 0.05 μM.

Molecular docking studies: Docking studies of the active compounds **3c** and **3f** were performed with Auto Dock software to reveal the interactions of these compounds with the active sites of Human γ-Tubulin with PBD ID 1Z5V. The results were impressive showing high binding affinity of 3c and 3f with the enzyme and free energies of −7.8 & −7.6 kcal/mole were observed for the compounds respectively (Table 3).

Docking studies of **3c** revealed that the compound docked well with enzyme through various types of interactions such as Hydrogen bonding, pi-alkyl and carbon hydrogen interactions (Fig. 2). The cleaved D-ring was actively involved in bonding with GLY A130, THR A131 and ASN A88 through H-bonding. Other notable interactions of 3c include H-bonding between carbonyl oxygen of Asparagine and Hydrogen of C-ring OH.

On the other hand, compound **3f** also interacted well with amino acid residues of the enzyme through various connections which include pi-pi stacked, pi-alkyl and hydrogen bonding. In the case of **3f**, the E-ring efficiently binds with the amino acid residues like GLN A11 and CYS A12 through hydrogen bonding involving oxygens of methoxy groups and hydrogens of amino groups of respective amino acids. The other prominent interactions include hydrogen bonds between etheric oxygen of A-ring and GLN A 15 and between SER A 126 and carbonyl oxygen of cleaved D-ring.

In conclusion, we synthesized Podophyllic acid hydrazides in good yields and estimated the relative basicities of diverse hydrazines in cleaving lactone ring of podophyllotoxin. In future, this chemistry would eventually lead to synthesis of pharmacologically novel heterocyclic analogues of podophyllotoxin as acid hydrazides are important synthetic precursors. Among the synthesized compounds **3c** and **3f** have shown impressive *in vitro* anticancer activity and thus they are identified as promising lead compounds. Molecular docking studies of synthesized compounds as Tubulin inhibiting agents have also supported the observed cytotoxicity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103384.

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Synthesis of novel fluorophenylpyrazole-picolinamide derivatives and determination of their anticancer activity

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Synthesis of novel fluorophenylpyrazole-picolinamide derivatives and determination of their anticancer activity

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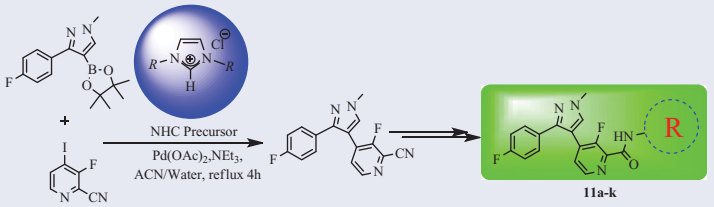
ABSTRACT

A series of fluorophenylpyrazole-picolinamide derivatives were synthesized in high yields using a cross-coupling reaction catalyzed by *in situ* formed palladium-N-heterocyclic carbenes (Pd-NHCs). The synthesized novel derivatives were evaluated for *in vitro* anticancer activity against a panel of four human tumor cell lines, HeLa (cervical), A-549 (lung), MCF-7 (breast), and IMR-32 (neuroblastoma). Four compounds, **11c**, **11e**, **11j**, and **11k**, showed growth inhibition (low μM) comparable with the standard drug cisplatin, providing a preliminary structure–activity relationship for the series. The present procedure is operationally simple and works with a wide range of substrates and may thus be useful in further compound optimization.

GRAPHICAL ABSTRACT



11 examples including aliphatic and aromatic amines with good to excellent yields.

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Fluorophenylpyrazole-picolinamide; cross-coupling; palladium-N-heterocyclic carbenes; anticancer activity

Introduction

Cancer is among the leading causes of human deaths worldwide, with ~9.5 million deaths in 2018. This very serious and potentially life-threatening illness is a heavy burden for the individual patients but also for the health care system and society as a whole. Thus, a constant search for new drugs and improved treatment modalities are needed. Cancer is a highly complex set of diseases; some forms are today efficiently

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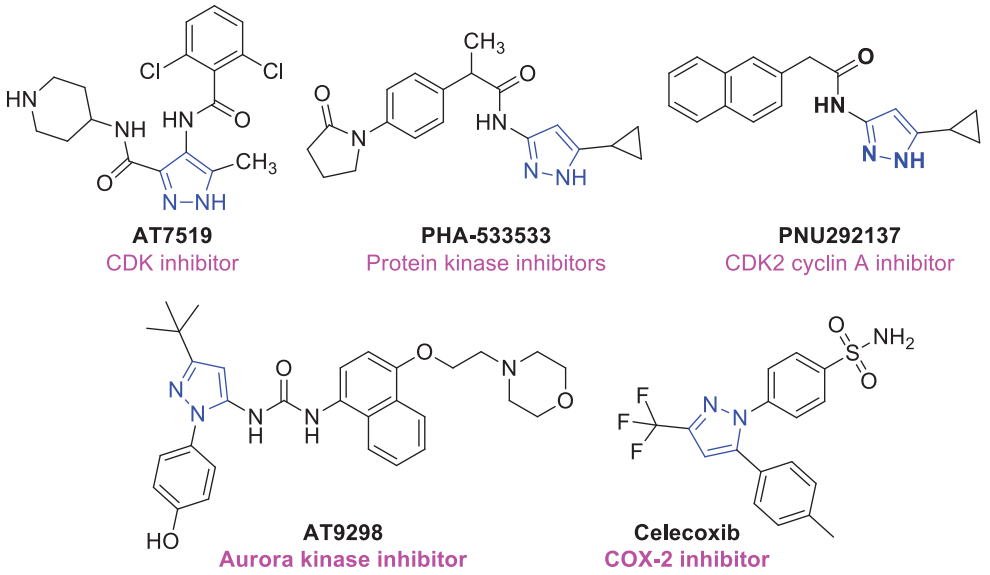


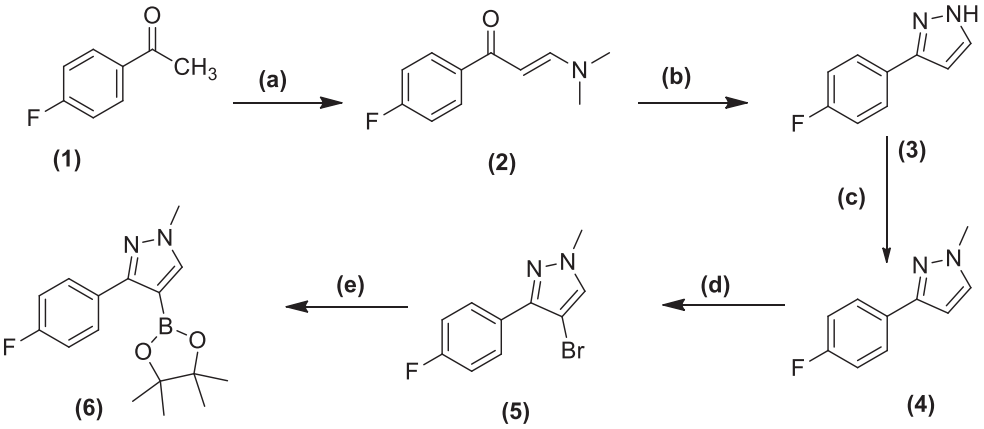
Figure 1. Some representative examples of active pharmaceutical ingredients containing a pyrazole group.

treated, such as testicular cancer, while others only have very limited treatment options, in particular in their advanced stages. There are several common hallmarks of cancer including sustained proliferative signaling, unlimited replicative potential, and activation of invasion and metastasis some of which may serve as therapeutic targets.[1]

In this article, we describe the synthesis and assessment of anticancer activity of a novel series of fluorophenylpyrazole-picolinamide derivatives. N, O, and S-heterocycles are structural units present in many drugs covering most therapeutic areas.[2] Among them the pyrazole group have been extensively used as scaffold for drug compounds (Figure 1).[3] For example, pyrazole containing derivatives have been found to posess potent anticancer activity by the inhibition of the cyclin-dependent kinases (CDKs).[4] Thus, an efficient synthesis of these is most desired. Previously we have reported the synthesis of isoxazole-indole,[5] and isoxazole-mercaptobenzimidazole,[6] derivatives, providing compounds with a combined anti-inflammatory and analgesic activity.

The combination of pyridine amides and pyrazole unit in one structure have been shown to provide synergistic effect in drug action and tunable structure–activity relationship (SAR). Recenlty researchers from Pfizer Inc, USA reported that pyrazole-pyridine derivatives provide potent inhibitors of Casein kinase 1 (CK1).[7] Inspired by this and in continuation of our research work in the fields of (i) N-heterocyclic carbene complexes (NHCs),[5,8] (ii) natural product based hybrid compounds,[9–11] and (iii) anticancer hybrid compounds[12–14] herein we report, a facile synthesis of new series of pyrazole-picolinamide derivatives, which to our knowledge have not previously been synthesized.

Compounds were designed and prepared through the combination of primary amines (aliphatic and aromatic), and fluorophenylpyrazole-picolinic acid. The straight forward



Scheme 1. Synthesis of Pyrazole-boran ester **6**. Reagents and conditions: (a) DMFDMA, DMF, 100 °C, 22 h, yield (87%); (b) Hydrazine, aq. EtOH, 12 h, RT, yield (64%); (c) CH_3I, Cs_2CO_3, DMF, 4 h, RT, yield (82%); (d) NBS, DCM, 4 h, RT, yield (85%); (e) Isopropoxyboronic acid pinacol ester, n-BuLi, THF, −78 °C, 1 h, yield (60%).

synthesis was accomplished by Suziki cross-coupling of readily obtained starting materials using *in situ* formed palladium-*N*-heterocyclic carbenes (Pd-NHCs). The prepared compounds were assessed *in vitro* for anticancer activity.

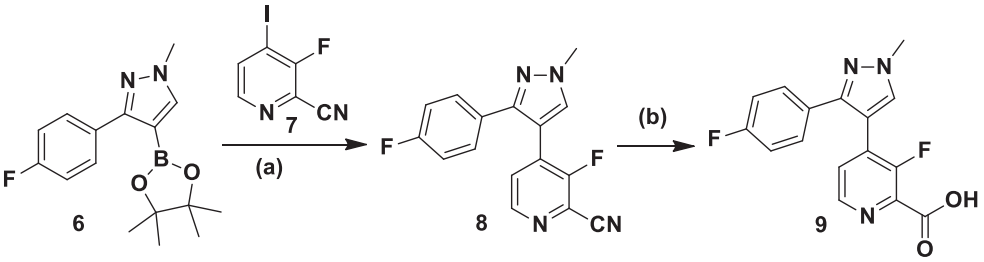
Results and discussion

The fluorophenylpyrazole-boran ester **6** and 3-fluoro-4-iodopicolinonitrile (**7**) are key intermediates for the preparation of fluorophenylpyrazole-picolinic acid **9**. The synthesis of target intermediate pyrazole-boran ester **6** was prepared in five-steps in good yields (Scheme 1).[15,16] Synthesis started with the condensation of 4-fluoroacetopheneone (**1**) with N,N-dimethylformamide dimethyl acetal (DMF-DMA) to afford corresponding enaminone **2**. Further, enaminone **2** was treated with hydrazine to yield 4-fluorophenylpyrazole (**3**). Then, the pyrazole compound **3** was N-alkylated using methyl iodide in the presence of cesium carbonate to furnish compound **4** followed by aromatic bromination using NBS in DCM to afford the brominated compound **5**. In the last step the Pyrazole-boran ester **6** was formed from **5** using isopropoxyboronic acid pinacol ester in the presence of butyllithium.

4-Fluorophenylpyrazole-picolinic acid (**9**) was coupled to primary amines (**10a–k**) to obtain fluorophenylpyrazole-picolinamide compounds (**11a–k**). The carboxylic acid fluorophenylpyrazole-picolinic acid (**9**) was obtained in a two-step synthesis (Scheme 2).

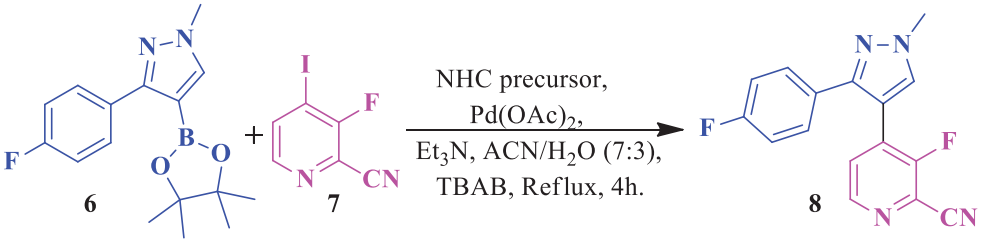
In the first step, the fluorophenylpyrazole-cyanopyridine (**8**) was obtained by Suziki cross-coupling of fluorophenylpyazole-boran ester (**6**) with 3-fluoro-4-iodo-cyanopyridine (**7**) using a catalytic system consisting of 1:2 $Pd(OAc)_2$ + Im-Cl, and slightly excess of base (Et_3N).

Initially the homogeneous Pd(II)-catalyzed Suziki-coupling between fluorophenylpyazole-boran ester (**6**) and 3-fluoro-4-iodo-cyanopyridine (**7**) was investigated as a model reaction using four different sets of catalytic conditions (Table 1, entries 1–4). These experiments were set to assess the influence of *N*-heterocyclic carbene (NHC) ligand



Scheme 2. Synthesis of fluorophenylpyrazole-picolinic acid **9**. Reagents and conditions: (a) 1,3-Bis(2,4,6-trimesitylphenyl)imidazolium chloride, $Pd(OAc)_2$, Triethylamine, ACN/H_2O (7:3), TBAB, Reflux, 4 h yield (96%); (b) aq.KOH, Reflux, 16 h yield (85%).

Table 1. Optimization of reaction condition for the Pd-NHC-catalyzed suziki cross coupling[a].



Entry	Catalyst	Base	Reaction time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	Et_3N	14	43
2	$PdCl_2$	Et_3N	16	52
3	$Pd(OAc)_2$/Im-Cl	Et_3N	6	82
4	$PdCl_2$/Im-Cl	Et_3N	6	79
5	$Pd(OAc)_2$/Im-Cl/TBAB	Et_3N	4	96
6	$PdCl_2$/Im-Cl/TBAB	Et_3N	4	88
7	$PdCl_2$/TBAB	Et_3N	12	40
8	$Pd(OAc)_2$/Im-Cl/TBAB	Cs_2CO_3	5	90
9	$Pd(OAc)_2$/Im-Cl/TBAB	NaOAc	4	92
10	$Pd(OAc)_2$/Im-Cl/TBAB	K_2CO_3	4	88

[a]All products were characterized $^1H/^{13}C$ NMR and mass spectral analysis.
[b]GC yields.

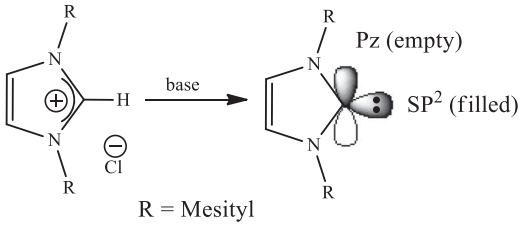
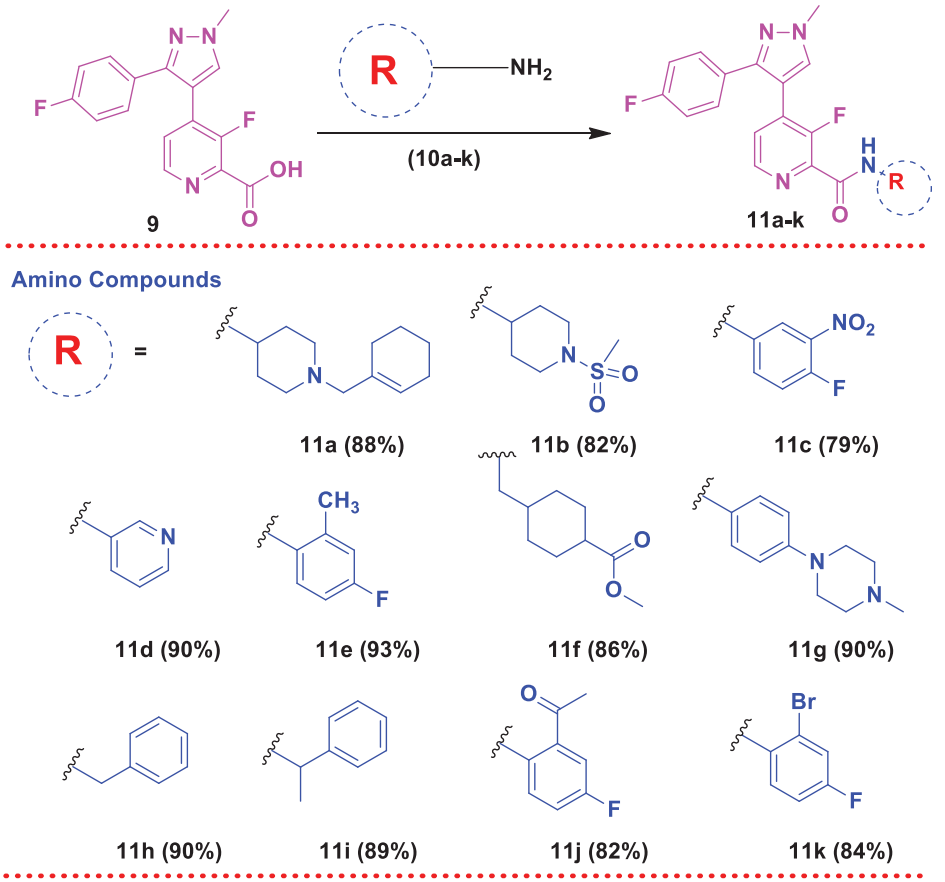


Figure 2. NHC precursor investigated in this work.

(Figure 2), phase transfer catalyst (PTC (TBAB = Tetra-n-butylammonium bromide)) and the influence of the base in accelerating the Suziki coupling reaction. For preparation of compound **8** (Table 1).

As a further improvement, addition of a TBAB produced a maximum 96% yield in short reaction time of ~4 h with the combination of $Pd(OAc)_2$ + NHC ligand precursor



Scheme 3. Synthesis of pyrazole-picolinamides **11a–k**. Reagents and conditions: (a) EDCl, HOBt, DIPEA, DMF, 6 h, RT.

(1,3-Bis(2,4,6-trimesitylphenyl)imidazolium chloride) + Et_3N (Table 1, entry 5). Replacement of $Pd(OAc)_2$ by $PdCl_2$, did not improve the yield of **8** (Table 1, entry 6). In this transformation, no Pd-black was observed. The role of a PTC to form and stabilize the metal nanoparticles including PdNPs is previously described.[17,18]

Overall the Pd(II)/NHC/PTC/Et_3N catalytic system provided better yields (Table 1, entry 5) than those without NHC ligand. The effect of PTC was by self, not significant (Table 1, entry 7). Furthermore, an exchange of base to Cs_2CO_3, NaOAc, or K_2CO_3 from Et_3N did not improve the yield of **8** (Table 1, entries 8–10). This system proved to be more efficient for the Suziki coupling of **6** with **7** than ligand-free Pd(II).

Compound **8** was then converted into the fluorophenylpyrazole-picolinic acid (**9**) intermediate by alkali hydrolysis (aq. KOH) (Scheme 2). Thereafter, compound **9** was subjected to amide coupling with primary amines **10a–k** in the presence of ehtyl(dimethylaminopropyl)carbodiimide (EDCl), hydroxybenzatriazole (HOBt) and diisopropylethylamine (DIPEA) as coupling reagents to afford pure pyrazole-picolinamide **11a-k** in high yields (Scheme 3).

The synthesized fluorophenylpyrazole-picolinamide (**11a–k**) compounds were characterized by $^1H/^{13}C$ NMR, mass spectroscopy and elemental analysis.

Table 2. *In vitro* cytotoxic activity of Pyrazole-picolinamide hybrids (**11a–k**) on human cancer cell lines[a] (IC_{50} μM/mL)[b].

Entry	Compound	HeLa	A549	MCF-7	IMR-32
1	11a	10.43 ± 0.21	11.22 ± 0.04	1.72 ± 0.04	20.56 ± 0.01
2	11b	8.62 ± 0.021	10.04 ± 0.02	1.35 ± 0.002	18.58 ± 0.19
3	**11c**	**4.25 ± 0.55**	**3.44 ± 0.01**	**2.63 ± 0.016**	**8.99 ± 0.38**
4	11d	10.74 ± 0.41	10.21 ± 0.07	1.88 ± 0.004	20.68 ± 0.26
5	**11e**	**4.88 ± 0.01**	**4.01 ± 0.26**	**2.89 ± 0.002**	**13.22 ± 0.21**
6	11f	22.42 ± 0.12	24.31 ± 0.06	4.10 ± 0.018	56.24 ± 0.65
7	11g	8.92 ± 0.01	12.38 ± 0.22	1.55 ± 0.003	20.74 ± 0.71
8	11h	22.58 ± 0.24	24.82 ± 0.22	3.82 ± 0.022	52.17 ± 0.12
9	11i	18.59 ± 0.11	26.01 ± 0.14	5.42 ± 0.001	54.01 ± 0.22
10	**11j**	**5.60 ± 0.07**	**3.89 ± 0.24**	**3.43 ± 0.07**	**11.87 ± 0.10**
11	**11k**	**4.62 ± 0.18**	**3.62 ± 0.12**	**2.06 ± 0.04**	**9.26 ± 0.05**
12	9	25.15 ± 0.22	28.04 ± 0.001	15.26 ± 0.12	66.41 ± 0.11
13	Cisplatin	4.98 ± 0.21	3.55 ± 0.007	1.56 ± 0.005	9.23 ± 1.21

[a]Data represent mean values ± SEM. Cytotoxicity as IC50 for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cell with respect to untreated cells using the MTT assay.
[b]Data represent as mean ± SEM values of these independent determinations.

Biological studies: antiproliferative activity

Many pyrazole containing molecules have shown biological activity toward several drug targets in the past (Figure 1). However, pyrazole-picolinamides have not been synthesized and studied. The new compounds **11a–k** were investigated for their anticancer activity in human cancer cell lines in comparison with the standard drug cisplatin. The cell lines used were (i) HeLa (cervical), (ii) A-549 (Lung), (iii) MCF-7 (Breast) and (iv) IMR-32 (neuroblastoma). The cytotoxic activity (IC_{50}) were determined *in vitro* using a MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as previously reported.[19]

The IC_{50} values presented in Table 2 indicate that all the 11 fluorophenylpyrazole-picolinamide hybrids (**11a–k**) possess growth inhibitory activity against all the four human cancer cell lines tested with activities comparable to cisplatin. In particular, some of the compounds (**11c, 11e, 11j**, and **11k**) were slightly more potent than cisplatin against the HeLa (cervical), A-549 (Lung) and IMR-32 (neuroblastoma) cell lines. In respect to the structure–activity relationship, for this set of compounds only limited conclusions can be made. In comparison with starting compound **9** all new derivatives showed a increased antiproliferative activity. This suggests an improved drug–target interaction. Since the drug target is not known, further conclusions regarding stereochemical or electronic properties needed to obtain improved activity will only be speculative.

However, the synthetic options for modification of the most potent compounds are vast, which could lead to further amplification of the cytotoxic activity. As discussed above, compounds **11c, 11e, 11j, and 11k** with F-aryl substituent on amide linker showed the highest antiproliferative activity (Table 2, entries 3, 5, 10, and 11) particularly against the four cancer cell lines (HeLa, A-549, MCF-7, and IMR-32). However, in the case of breast cancer cell line MCF-7 the cytotoxic activity of **11c** was less than cisplatin (Entry 3). Compound **11k**, with a $-$2-Br-4-F-C_6H_4 substituent (Entry 11), was also more active than cisplatin in all the cell lines except the MCF-7.

Compounds **11f**, **11h**, and **11i** (entries 6, 8, and 9) with a simple cyclohexyl/phenyl substituent (i.e. without heteroatom substituent) on amide linkers showed moderate

inhibitory activity against all the cell lines. These findings may guide further modifications with respect to cancer cell selectivety and potency.

Experimental

General

All chemicals or reagents were purchased from standard commercial suppliers and treated with standard methods before use. Solvents were dried and deoxygenated by heating at reflux and storing over sodium. The reactions were monitored by thin layer chromatography (TLC) on pre-coated silica GF254 plates. Melting points were determined on a XT4MP apparatus (Taike Corp., Beijing, China), and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker MHz spectra were recorded on a Brucker 400 NMR (for ^{1}H), 100 NMR (for ^{13}C) spectrometer with DMSO-d_6 and $CDCl_3$ as the solvent.

General procedure for the synthesis of compound (9)

4-Fluorophenylpyazole-boran ester (**6**) (1 mmol), 3-fluoro-4-iodopicolinonitrile (**7**) (1 mmol), $Pd(OAc)_2$ (0.25 mmol%), NHC-precursor (0.5 mmol%), Triethylamine (2 mmol) and TBAB were suspended in acetonitrile and water (7:3). The mixture was stirred at 80 °C for 4 h under inert atmosphere. After the reaction, aqueous-ACN was removed in a rotavapor and the residue was extracted with cold ether (5 × 15 ml). The combined ether layers were washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to column chromatography (silica gel, 60–120 mesh, eluent; n-hexane/EtOAc, 8:2 gradient) to afford pure nitrile compound (**8**). Further subjected to hydrolysis by using 10% KOH solution and then refluxed for 16 h, at which point it cleared and TLC analysis indicated complete consumption of the compound **8**. The reaction mixture was neutralized with acetic acid and cooled in ice, and the precipitate was collected by filtration. After being washed with cold water (2 × 25 mL), the precipitate was dried under vacuum to afford a pure product (**9**).

General procedure for the synthesis of title compounds (11a–k)

4-fluorophenylpyrazole-picolinic acid (**9**), amine (10a–k) (1 eq), EDCl (1.1 eq), HOBt (1.1 eq) and DIPEA (2.5 eq) were suspended in DMF. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction added water and extracted with ethylacetate. The combined organic layers were washed with brine, dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford a crude product which was subjected to column chromatography (silica gel, 60–120 mesh, eluent; *n*-hexane/EtOAc, 8:2 gradient) to afford pure title compounds (**11a–k**).

Spectral data of the compounds 8, 9, and 11a

3-Fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinonitrile (8)

Tan yellow solid: mp 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (s, 3H), 7.06–7.10 (t, 2H), 7.26–7.29 (t, 1H), 7.38–7.42 (m, 2H), 7.85–7.86 (d, 1H), 8.27–8.28 (d, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 39.31, 108.64, 113.13, 115.91, 123.24, 127.38, 128.40, 130.10, 130.67, 132.73, 146.49, 149.49, 156.77, 159.44, 161.60, 164.07 ppm. MS (ESI), $m/z = 297.094$ $[M + H]^+$. EA calcd (%) for $C_{16}H_{10}F_2N_4$ (296.087): calcd. C 64.86, H 3.40, N 18.91; found. C 64.82, H 3.36, N 18.87.

3-Fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinic acid (9)

Yellow solid: mp 130–131 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.95 (s, 3H), 7.18–7.25 (t, 2H), 7.39–7.49 (m, 3H), 8.18–8.19 (d, 1H), 8.36–8.38 (d, 1H), 13.53 (bs, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 109.41, 115.64, 127.69, 129.55, 130.73, 133.49, 138.91, 144.98, 147.84, 153.42, 156.06, 160.66, 163.10, 164.47 ppm. MS (ESI), $m/z = 316.089$ $[M + H]^+$. EA calcd (%) for $C_{16}H_{11}F_2N_3O_2$ (315.082): calcd. C 60.95, H 3.52, N 13.33; found. C 60.91, H 3.48, N 13.29.

N-(1-(cyclohex-1-en-1-ylmethyl)piperidin-4-yl)-3-fluoro-4-(3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl)picolinamide (11a)

Yellow solid: mp 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53–1.58 (m, 5H), 1.91–2.19 (m, 9H), 2.89–3.35 (m, 3H), 4.18–4.22 (s, 3H), 5.84 (s, 1H), 7.18–7.22 (m, 2H), 7.29–7.51 (m, 4H), 8.19 (s, 1H), 8.32–8.33 (d, 1H), 8.72 (s, 1H), 9.70–10.9 (br s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): 21.90, 22.48, 25.26, 27.55, 109.94, 115.89, 116.11, 127.45, 129.90, 130.01, 130.08, 131.07, 131.20, 133.98, 141.59, 144.69, 148.29, 153.19, 155.83, 161.14, 162.97, 163.57 ppm. MS (ESI), $m/z = 492.256$ $[M + H]^+$. EA calcd (%) for $C_{28}H_{31}F_2N_5O$ (491.250): calcd. C 68.41, H 6.36, N 14.25; found. C 68.38, H 6.32, N 14.21.

Conclusions

In conclusion, a facile and simple catalytic method for the synthesis of fluorophenylpyrazole-picolinamide derivatives in high yields was developed using a cross-coupling reaction catalyzed by palladium-N-heterocyclic carbenes (Pd-NHCs). The proposed method represents a cost-effective, eco-friendly, and practical/scalable process for synthesis of fluorophenylpyrazole-picolinamide. The conditions applied and the results obtained in our work for the synthesis of pyrazole-picolinamides which is believed to be an improvement to other reported procedures. Pyrazole-picolinamide derivatives were evaluated for *in vitro* anticancer activity against a panel of four human tumor cell lines, i.e. HeLa (cervical), A-549 (Lung), MCF-7 (Breast) and IMR-32 (neuroblastoma), and features important for the structure-activity relationship (SAR) demonstrated. The derivatives with an electron-withdrawing group, i.e. F- & NO_2-aryl substituent displayed higher activity than the compounds containing electron-donating groups, i.e. CH_3- and aliphatic/aromatic N-heterocycle and without heteroatom substituents. The compounds **11c, 11e, 11j, and 11k** with F-aryl substituent on amide linker showed the highest antiproliferative activity which compared well with the standard drug cisplatin.

The broad spectrum of anticancer activity displayed by these pyrazole-picolinamides provide a valuable starting point for further optimization and biological studies *in vitro* and *in vivo*.

Experimental procedures, Spectral data of compounds 9 and 11a–k. Supplementary data associated with this article can be found, in the online version.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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CALL: AN ESSENTIAL APPROACH IN THE PANDEMIC PERIOD

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ABSTRACT

Computer Assisted Language Learning which is called CALL is an approach to language teaching and learning in which computer is used as the main source for the presentations and teaching language skills. The computer technology is used in teaching process at many stages as teaching, explanation, practice, and feedback. Is it possible to teach language skills through computers in rural areas and government schools and colleges? What are the benefits and demerits of usage of CALL? Why are the computer based classes given more importance in pandemic period? Is it emergency or compulsory to use computers for language learning?

Keywords: CALL (Computer-Assisted Language Learning), roles of teacher and learners, merits and demerits

Before 1990s in India, laboratories were utilized for simply science courses. The English teachers were supposed to teach English grammar and prescribed text only. Gaining pass marks in English was very tough for rural and regional medium background students in those days. The days were gone and there was necessity to introduce a new style of teaching with machines and so language laboratories were emerged as the replacement of general classrooms. The language lab is exceptionally helpful for surveying students' pronunciation. It furnishes learners with the specialized devices to get the best examples of way to express the language. The electronic gadgets utilized in the laboratory will energize the eyes and ears of the student to obtain the language rapidly and without any problem. The language laboratory facility offers broadcasting, TV programs, web-helped materials and recorded off-air chronicles in the objective language. In a word, we state that a student can acquire the experience of having cooperation with local speakers through the research facility. Thus, the language lab has become the need of great importance in any language learning process for correspondence. Language laboratory consists of so many computers that can work as tutor for language drills and as a tool for writing and explaining and of course it works as a medium of global communication. Teaching English for a second-language learner can take benefit from using computers. Indeed, a computer is a tool and medium that facilitates people in learning a language, although the effectiveness of learning depends totally

on the users (Hartoyo, 2006). Computers attract and motivate the students and provide a number of activities such as multiple choice questions, true and false quizzes, gap-filing exercise means cloze tests, matching, reordering and sequencing and crossword puzzles to the language teachers and learners. Computers can provide online communication for all. COVID-19 forced all teachers to use technology. Teachers interested in using technological apps and computers to get involved themselves and students in a number of different ways. Richards (2001) says: "The language laboratory exists to help one to use technology effectively to communicate. It is not merely for learning a single language, but can be used for teaching a number of languages efficiently. To acquire a sensibility for the sounds and rhythm of a language, one has to hear the best samples of a spoken language." There are so many benefits from language laboratory. It provides practices for students through experiential learning. It attracts the students and motivates the learners to learn a new language. It encourages greater interaction between teachers and students and helps one to learn pronunciation, accent, stress and all other aspects of the phonetics of a language. The labs help teachers and learners to use computer assisted language teaching also.

Computer Assisted Language Learning (CALL) is known as an approach of teaching and learning in which computer is mainly used to explain and receive the language. Levy (1997) defines CALL more succinctly and more broadly as "the search for and study of applications of the computer in language teaching and learning." CALL was originated during 1960s but it was not famous term until 1970s. Since computers started to dominate the world, the European counties start to use them in the classrooms and began to establish language laboratories. Chapelle (2001) mentioned that CALL was the expression agreed upon at the 1983 TESOL convention in a meeting of all interested participants. This term is widely used to refer to the area of technology and second language teaching and learning despite the fact that revisions for the term are suggested regularly. It is used to refer to any devices such as laptops, computers, smart mobiles, and whiteboards in English language teaching and learning. Language learners pick up language knowledge and enjoy learning process from CALL. Beatty says that CALL that accommodates its changing nature is any process in which a learner uses a computer and, as a result, improves his or her language (2003). In connection to this, Kumar and Sreehari (2007) say: "It is a form of student-centered learning materials, which promote self-paced accelerated learning. CALL is an interactive method of instruction that helps learners achieve their goal of learning, at their own pace and ability."

The old and conventional teaching in a classroom was used in the earlier days. Numerous English teachers need to teach English by utilizing current technology. It incorporates a ton of gainful focuses. The learners also like computer-assisted language learning because of visualization. Reinhard (1995) says that "80% of understanding comes from visualization and much less from hearing, although retention rate is higher for the latter." Computers can motivate the students and fill them with confidence. Learners effectively get the focus required utilizing PCs and they obtain the

specialized information too. Taylor (1980) expressed that "computer assisted language learning programs can be wonderful stimuli for second language learning. Currently, computer technology can provide a lot of fun games and communicative activities, reduce the learning stresses and anxieties, and provide repeated lessons as often as necessary. Those abilities will promote second language learners' learning motivation. Through various communicative and interactive activities, computer technology can help second language learners strengthen their linguistic skills, affect their learning attitude, and build their self-instruction strategies and self-confidence"

CALL gets numerous extreme changes the job of a teacher whose presence plays a great role in the exercises. Teachers ought to be comfortable with the assets and ought to have the option to foresee specialized issues and restrictions. The teacher's job as facilitator of learning—as guide and challenger, has expanded in significance. Students need the motivation from teachers and of course it teacher's obligation to persuade the learners in the conventional classrooms however in computer assisted language learning, PC will accept the position. Noemi (2007) says that "In other words, instead of being directly involved in students' construction of the language, the teacher interacts with students primarily to facilitate difficulties in using the target language (grammar, vocabulary, etc.) that arise when interacting with the computer and/or other people."

Newby et al. (2000) argued that when the computer-based learning environment is implemented in classrooms, there is a need for the modification of educational goals. Students must receive new technique to learn language skills. They should gain new experiences on their own terms. The students who are shy can easily participate in CALL. They would not actively spend their time in traditional classrooms and so learning from computers will help them. Robertson (1987) mentioned that "the participants who joined computer-assisted language learning programs also had significantly higher self-esteem ratings than regular students. Today, with the high development of computer technology, computers can capture, analyze, and present data on second language students' performances during the learning process." CALL presents numerous exercises that prepared by experts highly focusing on the language aptitudes. The objective language learning includes all language aptitudes: listening, speaking, reading and writing. In spite of the fact that the students get all the language aptitudes in classroom, CALL predominantly demands the students to perform tuning in and talking exercises. It spurs the students towards language learning. The progammes which are stacked by teachers may make the students to learn new things. It empowers the students to think in a basic manner. Utilizing the frameworks in the homerooms, the students can improve their authority of essential abilities. The following are some advantages that teachers and students get from computer assistance language learning.

i. Visual Learning

Most of the learners are generally visual learners. Computers are greatly helping them to understand the content and language skills. Students get

time to practice and speak loud. It can't be done among other classmates in traditional classrooms. As visualization attracted the students, the computers can teach pronunciation and sounds. With new technologies appearance, including their influences on people's life aspects and education, language learning and teaching seems to have entered a new area. CALL and listening comprehension L2 skill training stand considered bound together for good (Vandergrift, 2007).

ii. Interaction and Negotiation

Students have opportunities to interact and negotiate meaning. They can learn all subjects in a language include grammar, pronunciation, and vocabulary in the process of language learning by computer technology. They are allowed to focus on all the four skills i.e., listening, speaking, reading, and writing. For learners to have the ability to speak, good oral skills stand deemed as essential. Learners cannot respond or engage in conversation, if they do not understand what seems to be said by people or do not know word pronunciation, or the use of language in context (Redfield, 2003). Classical language teaching in classroom can be monotonous, boring, and even frustrating, and students can lose interest and motivation in learning. CALL programmers can provide student ways to learn English through computer games, animated graphics, and problem-solving techniques which can make drills more interesting (Ravichandran, 2000).

iii. Tests

Conducting online exams are easy through the help of computers. Stepping through exams on the PC can assist students feel less hurried and can cause them to feel as though they have more privacy than they would on the off chance that they were in a fully packed classroom. Students are advised to attempt the exams and improve their writing skills. Use of CALL and multimedia, now mean that there can be an equal development of listening skills, alongside writing and reading (Rost, 1990).

iv. Computer Helps

In traditional classes, students must go to the classes at meticulous time whereas computer assisted language learning; students can study at whatever time they want. If an educational institution has a satellite system of computer laboratories, students can learn English at a variety of places on campus at any time. Computer-supported learning environment is predicted to be one of the ways to give students an authentic learning environment and this condition helps students to learn English better than the daily classroom context (Egbert and Jessup, 1996).

v. Authentic Materials

CALL provides genuine materials to the learners for study. The material is generally very impressive and thought provoking. Since they are innovative, they attract the students quickly. Computer provides different types of

topics very rapidly. Teachers and students can use the time efficiently in the procedure of language learning by using computer technology. Nunan (1999) concludes that "interactive visual media which computers provided seem to have a unique instructional capability for topics that involve social situations or problem solving, such as interpersonal solving, foreign language or second language learning"

Even though CALL offers a lot of benefits to the students and teachers, there are some disadvantages of them. Gips, DiMattia, & Gips (2004) indicated that "the first disadvantage of computer and its attached language learning programs is that they will increase educational costs and harm the equity of education. When computers become a basic requirement for student to purchase, low budget schools and low-income students usually cannot afford a computer. It will cause unfair educational conditions for those poor schools and students. On the other hand, expensive hardware and software also becomes the big obligations for schools and parents." Besides it, most of the learners don't like to sit in front of the computers for many hours. Some of the teaching faculty and students may not have the basic knowledge of the programmes. Unless one has previous knowledge of computer use, the learning is not powerful. Computers would do what they are programmed to do. Classroom teaching, though with some weaknesses, is itself an art. In the classroom, teachers and students communicate with each other on both the knowledge they are learning and on their emotional feelings, which, in particular, makes the classroom teaching more attractive. Computers sometimes may have technical problems and then break down.

Conclusion

CALL programs have become an innovative approach in language learning in India. However, computer technology still has its limitations and weaknesses. Computers like other teaching tools would not promise to bring any benefit to students unless the practical use of computer in a particular context is explored in detail and implemented accordingly (Kern and Warschauer, 2000). To conclude that computers should be recognized as a teaching tool. They are very good teaching aids for language teachers and they provide language learners more freedom by being more accessible and versatile. Although they cannot replace the teachers, they assist the learners to learn English language. Therefore, when I attempt to apply CALL programs to help student learning, I remember the merits and demerits of usage of CALL programs and derive maximum benefits for ESL teaching and learning. It is expected that COVID 19 has shown the emergency of computers for English language teaching and learning.

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Phyto-pharmacological activity of *Tecoma copensis* (thumb.) lind. plant flowers

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Abstract
The liver and kidney disorders have been world major population problem. Despite its frequent occurrence, high morbidity and high mortality, its medical management is currently inadequate, no therapy has been successfully prevented the progression of nephritis and hepatic diseases. Plant drugs have been known to play vital role in the management of liver and kidney diseases. The plant *Tecoma capensis* belongs to family Bignoniaceae. The other species of this plant have reported for the hepato-protective activity but no activities were reported on the flowers of *Tecoma capensis.* The present study is performed to reveal that the hepatoprotective and nephroprotective activities of *Tecoma capensis* in rifampicin induced hepatotoxic and nephrotoxic in rats, to prove its claims in folklore practice against liver and kidney disorders.

Keywords: Rifampicin, *Tecoma capensis*, hepatotoxic, nephrotoxic and flower

Introduction
The largest organ in the human body is liver. Liver have been plays a very important role in the metabolism of foreign compounds entering the body. The exposure to the foreign compounds may be through consumption of alien/contaminated foods, from exposure to chemical substances in the occupation environment or through synthetic drugs consumed for various pathological conditions. These compounds have many toxic manifestations on the human liver [1]. The liver gets injured also by viruses, chemicals, alcohol and autoimmune diseases. Liver diseases remained one of the serious health problems, and medicinal plants and herbs have been in use for treating these in the Indian traditional systems of medicine, especially Ayurveda. The present modern age demands proof on a scientific basis to justify the various medicinal uses of herbs [2]
After decades of serious obsession with the modern medicinal system, people have started looking at the ancient healing systems like Ayurveda a, Siddha and Unani. This is because of the adverse effects associated with synthetic drugs [3]. *Tecomaria capensis* (Bignonaceae) is also known as Cape-honey suckles [4] is a climber common to the tropical zone. It is grown as an ornamental plant in gardens. Traditionally the leaves were used to treat pneumonia, enteritis, diarrhea and tonic. It was reported to contain analgesic, antimicrobial, anti-fungal and antipyretic, antioxidant activity [5]. Many researchers have screened for analgesic, anti-inflammatory, anti-pyretic, hepatoprotective, anti-ulcer, anti-oxidant, anti-microbial and anti–nociceptive activities on this plant on various parts. The other species of this plant have reported for the hepatoprotective activity but no activities were reported on the flowers of *Tecoma capensis.* The present study was performed to assess the hepatoprotective and nephroprotective activities of *Tecoma capensis* in rifampicin induced hepatotoxicity and nephrotoxicity in rat model, to prove its claims in folklore practice against liver and kidney disorders.

Materials and Method
Collection and preparation of extracts
The plant material was collected from the plant *Tecomaria Capensis*, which are collected during the month of June at Dept. of botony, Kakatiya University, Warangal (Dist.) of Telangna. Then it was authentified by Dr. P. Satyanarayana Raju, professor, Department of Botany, Kakatiya Universit. The flower part of *Tecomaria capensis* was dried at room temperature and grounded into powder and passed through 60# sieve. The powder (500gm) has been extracted successively in soxhlet extraction with methanol. The extraction sediments were filtered and the filtratate was dried at 40°C in an oven to get dried product. The extract was fractionated using methanol, ethanol and ethyl acetate. Plant extraction fractions obtained were prepared different concentrations and used for hepatoprotective and nephroprotective activities in-vitro and in-vivo modal.

Chemicals and instruments
All chemicals used in the study were pure. Reference standard Rifampicin obtained from Symed Pharm. Pvt. Ltd, Hyderabad.

Preliminary phytochemical screening
The extract was subjected to preliminary phytochemical screening was performed by using standard protocol. 5-7
The methanolic extract of the plant flowers part of *Tecomaria Capensis*, carried out test tube qualitative reactions were gave positive results for alkaloids, flavonoids, glycosides, saponins and tannins, phenols, steroids and tri-terpinoids. And also carried out TLC study for the methanolic extract.

Acute toxicity studies
Although medicinal plants may produce several biological activities in humans, but generally very little is known about their toxicity. Though, safety should be the overriding criterion in the selection of medicinal plants for use in healthcare systems, several drugs produce acute and obvious

signs of toxicity which are used in the traditional medicine. The present study was undertaken to investigate acute toxicity of methanolic extract prepared from flowers of *Tecomaria Capensis.*

Animal Model

The methanolic extract of *Tecomaria Capensis* was pharmacologically screened for its toxic and biological effects in selected animal models. All animal studies were performed as per the guidelines of CPCSEA and Institutional Animal Ethical Committee (IAEC). CPCSEA Reg. No: 1516/PO/a/11/CPCSEA dated 01-011- 2011. Albino mice of either sex weighing between 16 - 25 g procured from Sainath Agencies, Hyderabad - 48, for experimental purpose. Then the animals were acclimatized for 7 days under standard husbandry conditions.

Experimental design

A total of 36 animals were divided into 6 groups (6 no's in each group). Group 1 is served as normal control received only vehicle for 28 days (distilled water, p.o) whereas groups 2,3,4,5 and 6 received 20% ethanol (3.76 g / kg / day) to induce hepatotoxicy for *\][poiuy76t54320.

water and administered orally) respectively. After oral administration, the blood samples were withdrawn by retro-orbital puncture at 8th, 15th, 22nd and 29th days respectively. The collected blood samples were centrifuged at 2500 rpm for 15 min to get clear serum and were used to analyse the biochemical parameters such as serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alanine amino transaminase (ALP), bilirubin, and total protein. Finally, on the 29th day the animals were sacrificed using high dose of ether and the livers of all experimental animals were isolated.

Histopathological Evaluation

The liver and kidney organs were fixed in neutral buffered formalin for 24 h. Sections of tissue from liver and kidney organs were examined histopathologically to study the hepatoprotective and nephroprotective activity of *Tecomaria capensis*. The liver and kidney organs were fixed in 10% buffered formalin and were processed using a tissue processor. The processed tissues were embedded in paraffin blocks and about 5-µm.

Result

Acute toxicity studies were carried out on *Tecomaria capensis* up to the dose of 2000 mg/kg which demonstrated that the extract did not show any sign of toxicity and mortality. However, there was a decrease in physical activity, which was observed only at the dose of 2000 mg/kg. Thus, the present doses regime (100 and 200 mg/kg) was chosen for further studies. The results of hepatoprotective and nephroprotective activities of crude methanolic extracts of this plant at a dose of 100 mg/kg, 200mg/kg and 400mg/kg on rats intoxicated with standard silymarin (25 mg/kg) were illustrated in the table 1, fig-1and 2. The tables also showed the comparison of effects among the untreated (control) and Rifanpicin treated (negative control) group with the drug treated group of rats. Treatment with methanolic *Tecomaria capensis* at different dose levels (100, 200 and 400 mg/kg) and standard silymarin (25 mg/kg) significantly decreased the enzymes serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alanine amino transaminase (ALP) and bilirubin levels as compared to disease control group. Oral administration of methanolic *Tecomaria capensis* at different dose levels (100, 200 and 400 mg/kg) and standard silymarin (25 mg/kg) significantly increases the enzymatic antioxidants like superoxide dismutase, catalase, glutathione levels and reduces the lipid peroxidise levels when compared to the disease control group. All the above parameters indicating the hepatoprotective activity of METC against rifampicin-induced liver cell damage.

Methanolic extract of *Tecomaria capensis*, 400 mg/kg body weight was produced a significant reduction in the elevated serum biochemical parameter (Bilirubin, SGPT, SGOT and ALP) levels and elevated the decreased enzymatic anti-oxidant (SOD, catalase, glutathione) levels in Rifampicin induced hepatotoxic rats. These effects were found to be comparable and even more than that of the standard Silymarin (25 mg/kg). Oral administration of Rifampicin significantly decreased the body weight and increased the serum biochemical parameters such as blood urea nitrogen, serum creatinine and serum uric acid. Methanolic *Tecomaria capensis* at different dose levels (100, 200 and 400 mg/kg) significantly increased the body weights and lowers the serum bilirubin biochemical parameters inTable-1.

Table 1: Effect of METC on Bilirubin and % Reduction in Bilirubin Levels in Hepatotoxi Rats

Time in days (↓)	**Effect of The Flowers of *Tecoma Capensis* on Bilirubin Levels in Hepatotoxic Rats**						**% Reduction in Bilirubin Due to the Treatment with METC In Hepatotoxic Rats**					
Groups →	**Control**	**Rifampicin**	**Silymarin**	**Methanolic Extract of Flowers of *T. CAPENSIS***			**Control**	**Rifampicin**	**Silymarin**	**Methanolic Extract of Flowers of *T. CAPENSIS***		
Dose (mg/kg) →	-	1000	25	100	200	400	-	1000	25	100	200	400
0	0.516± 0.047	1.817± 0.030***	1.517± 0.030***	1.683± 0.030***	1.517± 0.030***	1.500± 0.025***	-	-	-	-	-	
8	0.600± 0.068	2.217± 0.030***	1.350± 0.022***	1.433± 0.033***	1.383± 0.016***	1.267± 0.021***	8.58± 14.52	17.22± 1.294***	10.88± 1.285***	14.57± 3.013***	7.60± 1.977***	15.47± 1.248***
15	0.566± 0.066	2.600± 0.036***	1.167± 0.021***	1.267± 0.021***	1.267± 0.021***	0.950± 0.022***	6.80± 14.81	34.42± 3.643***	22.83± 2.446***	24.52± 2.386***	15.40± 2.089***	36.63± 1.245***
22	0.516± 0.047	2.900± 0.036***	0.950± 0.042***	1.083± 0.040***	1.133± 0.033***	0.766± 0.021***	0.78± 11.46	37.27± 1.342***	37.32± 2.640***	35.57± 2.322***	25.22± 1.907***	48.77± 1.587***
29	0.583± 0.047	3.250± 0.042***	0.566± 0.033***	0.866± 0.021***	0.700± 0.044***	0.500± 0.036***	9.75± 10.22	44.03± 0.939***	62.55± 2.229***	48.43± 1.309***	53.22± 3.087***	66.67± 2.305***

n=6 significant at p<0.05*, 0.01**, 0.001***

Table 2: result isuric acid produced Rifampicin by nephrotoxicity was analysis for the nephroprotective effect produced by methanol extract of *Tecomaria capensis* is 400 mg/kg body weight was found to be same as that of the standard Silymarin (25 mg/kg).

Table 2: Effect of METC on Serum URIC Acid and % Reduction in Serum Uric Acid Levels in Toxic Rats

Time in days (↓)	**Effect of the Flowers of *Tecoma Capensis* on Serum Uric Acid Levels in Nephrotoxic Rats**						**% Reduction in Serum Uric Acid Due to the Treatment with Metc in Nephrotoxic Rats**					
Groups →	**Control**	**Rifampicin**	**Silymarin**	**Methanolic Extract of Flowers of *T. CAPENSIS***			**Control**	**Rifampicin**	**Silymarin**	**Methanolic Extract of Flowers of *T. CAPENSIS***		
Dose(mg/kg) →	-	1000	25	100	200	400	-	1000	25	100	200	400
0	5.633± 0.194	10.38± 0.047***	9.783± 0.030***	10.0± 0.036***	9.73± 0.033***	9.617± 0.047***	-	-	-	-	-	-
8	5.567± 0.316	10.82± 0.030***	9.350± 0.042***	9.73± 0.033***	9.46± 0.021***	9.10± 0.051***	1.45± 7.912	4.0± 0.559***	4.38± 0.508***	2.63± 0.483***	2.66± 0.333***	5.33± 0.311***
15	5.300± 0.178	11.42± 0.030***	8.967± 0.033***	9.23± 0.33***	9.00± 0.068***	8.58± 0.079***	5.80± 4.590	9.28± 0.583***	8.43± 0.212***	7.63± 0.542***	7.50± 0.506***	10.70± 0.390***
22	5.817± 0.299	12.28± 0.047***	7.650± 0.042***	8.75± 0.061***	8.48± 0.047***	7.23± 0.091***	2.63± 6.76	15.43± 0.391***	21.77± 0.332***	12.47± 0.730***	12.80± 0.256***	24.73± 1.010***
29	5.150± 0.172	13.28± 0.060***	5.833± 0.120***	7.83± 0.076***	6.85± 0.076***	6.01± 0.119***	7.90± 1.796	21.53± 0.491***	40.32± 1.219***	21.63± 0.780***	29.55± 0.815***	35.65± 0.996***

Table 3: result is serum creatinine levels produced by Rifampicin produced nephrotoxicity was analysis for the nephroprotective effect produced by methanol extract of *Tecomaria capensis* is 400 mg/kg body weight was found to be same as that of the standard Silymarin (25 mg/kg).

Table 3: Effect of Metc on Serum Creatinine and % Reduction in Serum Creatinine Levels in Toxic Rats

Time in days (↓)	**Effect of the Flowers of *Tecoma Capensis* on Serum Creatinine Levels in Nephrotoxic Rats**						**% Reduction in serum Creatinine Due to the Treatment with METC in Nephrotoxic Rats**					
Groups →	**Control**	**Rifampicin**	**Silymarin**	**Methanolic Extract of Flowers of *T. Capensis***			**Control**	**Rifampicin**	**Silymarin**	**Methanolic Extract of Flowers of *T. Capensis***		
Dose(mg/kg) →	-	1000	25	100	200	400	-	1000	25	100	200	400
0	1.083± 0.079	3.0± 0.035***	2.883± 0.030***	2.967± 0.021***	2.833± 0.021***	2.70± 0.025***	-	-	-	-	-	-
8	1.050± 0.076	3.50± 0.036***	2.483± 0.030***	2.767± 0.021***	2.058± 0.030***	2.417± 0.030***	3.88± 8.635	14.2± 1.354***	13.78± 1.175***	6.66± 0.852***	8.78± 0.801***	10.45± 1.114***
15	1.067± 0.080	4.0± 0.036***	1.950± 0.042***	2.267± 0.021***	2.0± 0.025***	1.883± 0.030***	1.75± 8.00	24.93± 0.978***	32.32± 1.381***	23.53± 0.785***	29.35± 1.055***	30.20± 1.060***
22	1.10± 0.089	4.50± 0.036***	1.045± 0.022***	1.950± 0.022***	1.750± 0.022***	1.450± 0.223***	1.28± 11.25	33.27± 0.954***	49.63± 1.039***	34.2± 0.883***	38.18± 0.560***	46.23± 0.988***

n=6 significant at p<0.05*, 0.01**, 0.001***

Fig 1: A. Group I (Normal control), B. Group II (Rifampicin) Section of liver with normal cell structure Section of liver showing centriolobular necrosis, C. Group III (Standard-Silymarin), D. Group IV (*Tecomaria capensis* -200), E. Group V (METC-400) Section of liver showing significantly reduced Necrotic area. The hepatoprotective effect produced by methanol extract of *Tecomaria capensis* is 400 mg/kg was found to be more than that of the standard Silymarin (25 mg/kg). Histological changes such as cortical glomerular, peritubular blood vessel congestion and interstitial inflammation were observed in disease control group. The Methanolic *Tecomaria capensis*, extract at 400 mg/kg had significantly prevented these histological changes.

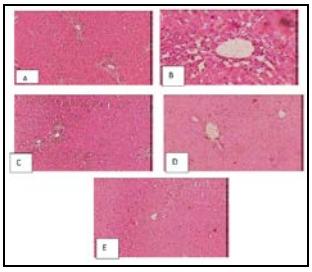

Fig 1: A. Group I (Normal control), B. Group II (Rifampicin) Section of liver with normal cell structure Section of liver showing centriolobular necrosis, C. Group III (Standard-Silymarin), D. Group IV (*Tecomaria capensis* -200), E. Group V (METC-400) Section of liver showing significantly reduced Necrotic area

Figure 2: A. Group I (Normal control, B. Group II Rifampicin induced Necrotic area, C. Group III (Standard-Silymarin), D.Group IV (*Tecomaria capensis* -200), E: Group V (METC-400) Section of liver showing significantly reduced Necrotic area. The nephroprotective effect produced by methanol extract of *Tecomaria capensis* is 400 mg/kg was found to be same as that of the standard Silymarin (25 mg/kg). Histological changes such as cortical glomerular, peritubular blood vessel congestion and interstitial inflammation were observed in disease control group. The Methanolic *Tecomaria capensis*, extract at 400 mg/kg had significantly prevented these histological changes.

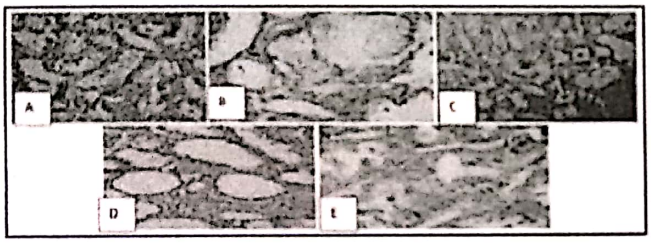

Fig 2: A. Group I (Normal control, B. Group II Rifampicin induced Necrotic area, C. Group III (Standard-Silymarin), D. Group IV (*Tecomaria capensis* -200), E: Group V (METC-400) Section of liver showing significantly reduced Necrotic area

Discussion

The plant *Tecoma capensis* belong to the family Bignoniaceae. The floweral parts of the above plants are selected for the investigation of hepatoprotective and nephroprotective activity. The methanolic extract of the flowers of *Tecoma capensis* gave positive results for steroids, alkaloids, tannins, glycosides, saponins, flavanoids, carbohydrates and proteins. An LD_{50} study of methanolic extract was conducted up to a dose of level of 2 mg/kg and no mortality was observed in any of the animals which induced the practically nontoxic nature and safety of the extract. There was a significant dose related decrease in serum biochemical parameters of liver like SGPT, SGOT, ALP and bilirubin at different dose levels (100, 200 and 400 mg/kg). Oral administration of methanolic extract of flowers of *Tecoma capensis* at different dose levels (100, 200 and 400 mg/kg) produced a significant dose dependent increase in the enzymatic antioxidants of liver like superoxide dismutase, catalase and glutathione levels. Administration of methanolic extract of flowers of *Tecoma capensis* at doses of 100, 200 and 400 mg/kg produced increase serum biochemical parameters of kidney like serum uric acid, serum creatinine and blood urea nitrogen levels.

From the Pharmacological screening, we can conclusively state that the methanolic extract of flowers of *Tecoma capensis* have hepatoprotective and nephroprotective activity and were comparable with that of standard silymarin. The hepatoprotective and nephroprotective activity produced by METC may be due to presence of steroids, triterpenes, alkaloids, glycosides, flavonoids, saponins, tannins and proteins.

Conclusion

In conclusion, this study provides evidences of methanolic extract for the hepatoprotective and nephroprotective activities of *Tecomaria Capensis* flowers, which could partly contribute to its ethno-medical use. However, further investigation is required to isolate the active constituents responsible for this activity and to elucidate the exact mechanism of action.

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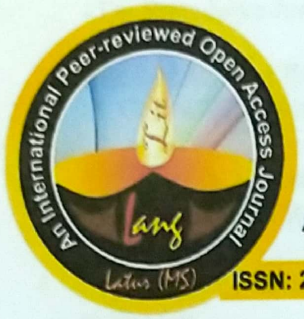

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INDIGENOUS PEOPLE AND WHITE SETTLERS IN KATE GRENVILLE'S *THE SECRET RIVER*

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ABSTRACT

Kate Grenville's novel The Secret River rewrites an Australian colonial history. It is about an early 19th century Englishman transported to Australia for theft. It depicts us the position of Aboriginal people after Europeans visit them and occupy the land and presents history and culture of two nations. Grenville explains exile, alienation, failure, success, dream, desire, and lifestyle of her own ancestors. The research paper aims to explore aboriginal people, white settlers from Kate Grenville's The Secret River.

Keywords: History, colonizers, exile, alienation

Catherine Elizabeth Grenville who is known as Kate Grenville is an Australian author. She has published a number of books including fictions and non-fictions. Her novels were translated into many languages. Her famous novel *The Secret River* was also shortlisted for the Man Booker Prize in 2006. The book has been compared to Thomas Keneally's *The Chant of Jimmie Blacksmith* and Peter Carey's *True History of the Kelly Gang*. The novel *The Secret River* attracted many readers across the world. It discusses the tragedy of Aboriginal people who were seen as enemy by the settlers. It has offered an invitation for criticism from readers and literati. Inga Clendinnen mentions the novel's creative historical interpretations as "opportunistic transpositions and elisions" which lend support to her accusations that "novelists have been doing their best to bump historians off the track" (16). Mark McKenna contends: "the rise of the novelist as historian, of fiction as history, has accompanied the decline of critical history in the public domain" (100). Australia is a "haunted country" (Wright, 30). It has great history. One should know history of one's country. Clendinne devoted a significant part of her *Quarterly Essay* to a historiographic criticism of *The Secret River*. She argues that, contrary to Grenville's claim, *The Secret River* is not history. As Clendinnen states:

> We need history, not Black Armband history and not triumphalist white-out history either, but good history, true stories of the making of this present land, none of them simple, some of them painful, all of them part of our own individual histories. (102)

The novel depicts the story of William Thornhill, a Thames boatman. After childhood poverty and small crimes in the slums of London, he is sentenced to death for stealing wood.

Luckily his sentence is commuted to transportation to New South Wales for the term of his natural life. He was transported with his wife, Sal and son, Willie to Australia in 1806. Sal attempts to have his sentence drove from death to transportation. Also, when the judge declares she may go with him, she goes with him to New South Wales, however different women "declined accepting that indulgence" (71). She gives birth to their second son Richard during the long voyage. Richard is called Dick. Thornhill shows good behavior at new place. He is unable to be in touch with Aboriginal people. He faces some problems to have a good friendship in the beginning. But he is closer with them after some days as he is attracted by them. After a few weeks, Thornhill went to work as a lighter man for Mr. King. Thornhill gets alcohol from Mr. King and sets up a bar named 'Pickled Herring.' Scabby Bill was a regular customer for him. He entertained customers by dancing for money.

Thornhill quits his job after three years and works for Thomas Blackwood, a former convict. Blackwood attempts himself with the place and its people. He lived on the Hawkesbury River near Sydney in the first two decades of the 19th century. Thornhill understands that the Aboriginal people of Australia have a different concept of land ownership when he compared to the white settlers. He observes that many of the Aboriginals were stealing his corn. He knows that Blackwood has an Aboriginal wife, and son. Meanwhile Saggity, a friend of Smasher Sullivan was killed after a raid on his farm by Aborigines. His death leads to the battle with the Aborigines. Blackwood tries to stop the fighting, but gets whipped by Smasher. Thornhill takes up land on the Hawkesbury River. It is still the home of the Darug people in 1813. There are threats between the Hawkesbury settlers and native people; Thornhill gets lot of property and lands. He participates in the massacre of an Aboriginal tribe. Soon, he becomes a prosperous property owner. The landscape itself will stand silent witness to the atrocity committed by the white settlers against the original owners of the land: "He would glance over at where river-oaks circled a patch of bare yellow earth beside the lagoon, marking where the bonfire had burned into the night. Something had happened to the dirt in that spot so that not as much as a blade of grass had grown there ever since. Nothing was written on the ground. Nor was it written on any page. But the blankness itself might tell the story to anyone who had eyes to see" (325). Towards the finish of the novel, he is a melancholic figure. He is obsessed by the disappearance of the Aborigines, and haunted by an inner feeling of great emptiness.

Kate Grenville said that her book was the result of a research that she had carried out. It is about the life of Solomon Wiseman, her ancestor, and the model for Thornhill. The writer didn't know much about interactions between the settlers and the Aboriginal people. She prepared to write it as a non-fiction but the novel became a fictional work written based on the life of Solomon Wiseman. In response to this need, Grenville had intended to write a factual work, believing that "this was a tale that drew its power from the fact that it was real" and that "this subject matter had to be handled in the authoritative voice of non-fiction" (146). The settlers dominate the Aborigional people as they received the settlers heartfully and helped them to show supremacy on them as the local people are illiterates and far from English culture. The culture of settlers here represents cunningness and politicism.

The exile of Thornhill has helped him a lot to learn and rule other land. The journey and banishment has taught life lessons to him. He as a banished man knows how to receive

other's freedom and assets. As a white settler, he has got an opportunity to rule the indigenous people. The writer has given in the novel that the Aboriginal people invited the white settlers to rule themselves.

Grenville's theme is very similar to the works of Ngugi, Chinua Achebe and J.M. Coetzee. The domineering attitude, desire to have power, and corruptive politics are main themes in the minds of settlers and Aboriginal people. The British settlers have to coexist with the Aboriginal people of Australia, yet the two gatherings have absence of communication and understanding. Besides, a few critics read the novel as an unpleasant illustration of the massacre of indigenous people. For instance, Kossew describes "Grenville's fiction as "a reassessment of what it means to be a white Australian." Kossew continues that "in so doing, she is situating her novel as a reworking of the narrative of settlement with a contemporary sensibility" (2007: 9). She argues:

> Grenville sees her novel as standing "outside that polarized conflict" of right and wrong by providing instead an empathetic and 'imaginative understanding of those difficult events' (Grenville in an interview with Ramona Koval). It is only by uncovering the painful scars of the past, the text suggests, by voicing the "Great Australian Silence", which a process of reconciliation and shared belonging can begin. But even then, from her own positionality as a "white" Australian, it is hedged about by moral ambiguities. (2007: 17)

The novel deals with exile and alienation also. The exile of Thornhills makes him forget his own place and learns about new country. Exile teaches him what a real society is. According to Said, "Exiles are cut off from their roots, their land, their past…Exiles feel, therefore, an urgent need to reconstitute their broken lives, usually by choosing to see themselves as part of triumphant ideology or a restored people." Said concludes that "the crucial thing is that a state of exile free from this triumphant ideology designed to reassemble an exile's broken history into a new whole is virtually unbearable, and virtually impossible in today's world." Then he gives some examples of "the fate of Jews, the Palestinians and the Armenians" (2000: 140-141).

Thus the Thornhills accepted the reality of exile. Herrero says that the merit of novels like *The Secret River* lies in their attempt to make non-Indigenous readers aware of the need to offer an apology to the Indigenous Australians so that a better and fairer future might someday be possible in the nation" (102) and the novel can be explained as clearly testifying to the settler's feelings of fault. It must be read by settlers, non-settlers, and local people to know what happens settlers dominate and aboriginal people dominate the settlers. It is clear that by focusing on the agony of Will Thornhill as a colonial victim of the atrocious and iniquitous British legal system, the plight of the Aborigines is conveniently diluted and minimized. To quote Weaver-Hightower: "By portraying their non-Indigenous protagonists as downtrodden but resilient settlers, as victims and not perpetrators of colonization, often with the non-settler English as the 'real' colonizers, [these novels] identify with the victim position and project colonial aggression. That is, these novels spend a great deal of time depicting non-Indigenous Australians as colonial victims of the British compared to the brief nod to non-Indigenous Australians as themselves colonizers of Indigenous Australians" (139).

Thus Grenville mixed history and realistic untold issues based on the problems of aboriginal people in the post-colonial period.

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Green Synthesis of Chromene Congeners *via* Multi-Component Reaction and Their Antimicrobial Studies

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A facile metal catalyst free, multi-component synthesis was established to afford tetrazolo dihydropyranochromenes and pyranochromeno pyridinediones in high yields starting from 7-hydroxy-4-methyl coumarin, aromatic aldehydes and malononitrile based on Green chemistry principles. This protocol is applied to a wide range of aldehydes and demonstrates excellent functional group tolerance. Further, the synthesized compounds were screened *in vitro* against a panel of clinically relevant bacteria and fungi and found that these compounds possess moderate antimicrobial efficacy. The compounds **6 d** & **7 d** were exhibited very impressive antimicrobial activity against four strains of bacteria and two strains of fungi. To know more about, their mechanism of action the lead compounds were virtually screened against a key microbial enzyme, tyrosyl-tRNA (TyrRS) synthetase and found that the compounds were bound with the enzyme through various interactions and thus able to inhibit the activity of the enzyme as evidenced by their binding energies. Further, the ADMET studies of the lead compounds were showed excellent favorable Druglikeness properties when they were tested with SwissADME programme.

1. Introduction

Heterocyclic compounds, particularly oxygen containing molecules like,*4H*-pyrans and its annulated heterocyclics like chromenes exhibit significant biological activities[1–4] such as anti-cancer,[5–9] anti-viral,[10] along with therapeutic activity towards anti-neurodegenerative disorders like Alzheimer's, Parkinson disease and Huntington's diseases.[11–13] *4H*-Pyrans represent an interesting building blocks of a series of natural products (Figure 1).[14–15] In addition, number of 2-amino-*4H*-pyrans are used as photoactive materials,[16] pigments,[17] and potential biodegradable agrochemicals,[18] some of the 2-amino-*4H*-pyrans derivatives are beneficial as photoactive materials.[19] Further, benzo*[g]*chromenes are also widely prevalent in nature as natural products, pigments and agrochemicals and exhibit very diverse biological activities.[20] Owing to their diverse applications in many fields, devising suitable synthetic strategies to afford various chromene bound heterocyclics bearing different pharmacophores have been a challenge for the chemistry commune for long time. We have many reports in the literature pertaining to chromene analogue compounds describing the synthetic methodologies to afford them and also focusing on their pharmacological profile.[21–26] However, our approach is very unique and we successfully built potent pharmacophores (tetrazole and pyridinedione rings) on the benzopyran scaffold to increase the binding interaction of the compounds with the targeted enzyme leading to enhanced antimicrobial activity.

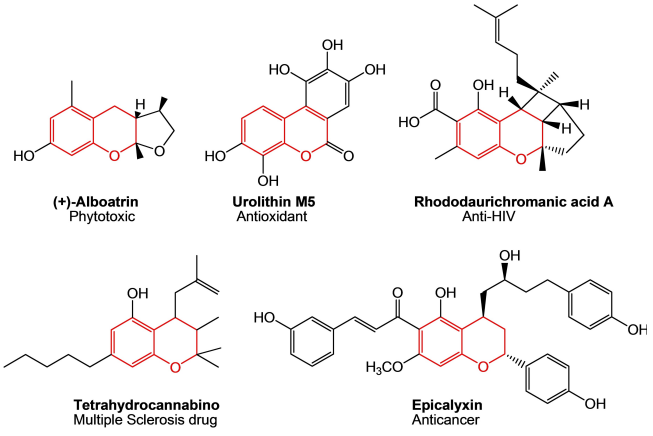

Figure 1. Natural products containing benzopyran/Chromene moiety.

2. Results & Discussion

2.1. Chemistry

In continuation to our previous work i.e., synthesis of biologically potent heterocyclics,[27] herein we report the facile and environmentally benign synthesis of tetrazolo dihydropyranochromene and pyranochromeno pyridinediones in good to excellent yields from readily available starting materials and using reagents like $AlCl_3$. Firstly, a mixture of 7-hydroxy-4-methylcoumarin (**1**), aromatic aldehydes (**2 a–j**) and malononitrile (**3**) were made to react in the presence of anhydrous K_2CO_3 to afford intermediate compounds i.e., 8-amino-4-methyl-2-oxo-6-(substituedphenyl)-benzodipyran-7-carbonitriles (**4 a–j**) (Table 1). This one-pot, multi-component reaction proceeded

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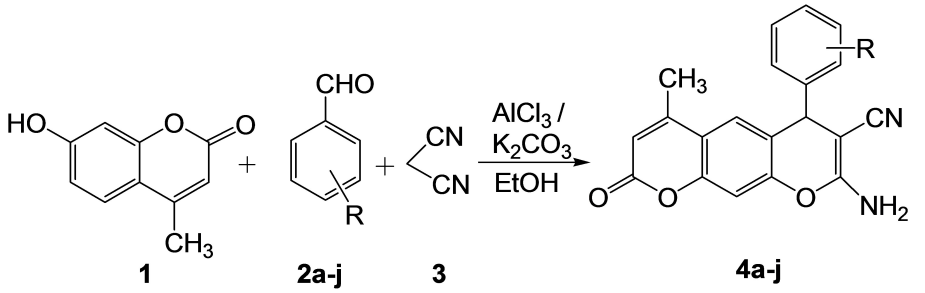
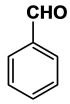
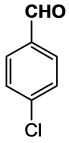
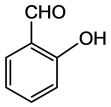
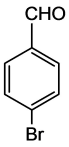
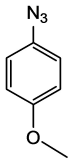
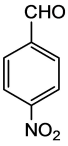
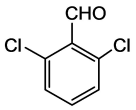
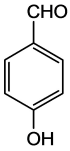
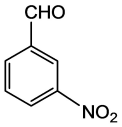
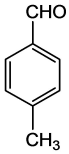
Table 1. Synthesis of 8-amino-4-methyl-2-oxo-6-(substituedphenyl)-benzodipyran-7carbonitriles.



1 **2a-j** **3** **4a-j**

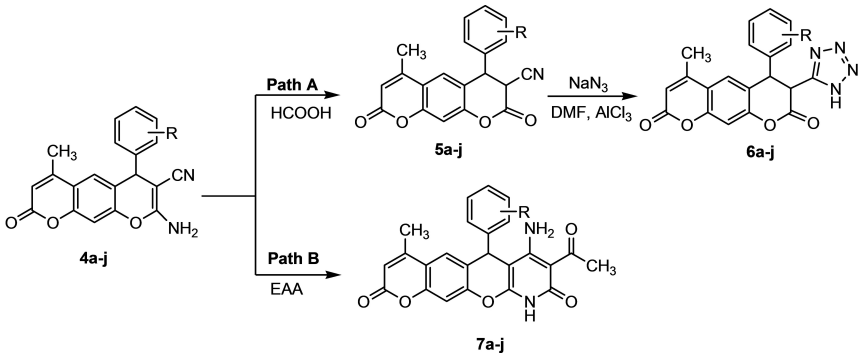
Entry	Ar-CHO	Product	Reaction time (h), (yield, %)[b]	Entry	Ar-CHO	Product	Reaction time (h), (yield, %)[b]
1		**4a**	10(90)	6		**4f**	11 (90)
2		**4b**	10(96)	7		**4g**	12 (86)
3		**4c**	12 (85)	8		**4h**	10(94)
4		**4d**	11(90)	9		**4i**	11(84)
5		**4e**	10 (92)	10		**4j**	12(86)

[a]All products were characterized by ^{1}H, ^{13}C NMR and mass spectral analysis. [b]Isolated yields after column chromatography.

to produce products in basic medium and ethanol as solvent without any need of heavy metal catalyst. Moreover, different aromatic aldehydes bearing both electron withdrawing and electron donating groups were used as partners with 7-hydroxy Coumarin and melononitrile to measure the reaction parameters like yields, reaction time etc., The aldehydes with electron withdrawing groups gave much better yields and the reaction completed in lesser time than the aldehydes with electron releasing groups. These results may be attributed to the increase in the electrophilic nature of carbonyl carbon of aldehydes with electron withdrawing groups and this in turn facilitates the smooth going of Knoevengel condensation between aldehyde and melononitrile.

These intermediate compounds (**4a–j**) (i) *via* path A, were deaminated with formic acid to get the compounds (**5a–j**) and followed by treatment with sodium azide to give tetrazolo dihydropyranochromenes (**6a–j**). (ii) *via* path B, were treated with ethylacetoacetate in the presence of piperidine (Scheme 1) to give pyranochromeno pyridinediones (**7a–j**). The pure compounds were obtained by recrystallisation from ethanol as solvent and no column or any other chromatographic methods are required to separate the final products. All the synthesized compounds were confirmed based on elemental analyses, IR, NMR and Mass spectral data.

In more detailed manner, the synthesis can be explained as follows. The compounds 6-methyl-4-(substituted phenyl)-3-(1H-tetrazol-5-yl)-3,4-dihydropyrano[3,2 g]chromene −2,8-diones



Scheme 1. Synthesis of tetrazoles and pyridine diones.

6(**a–j**) were obtained after multiple reaction steps starting with 7-hydroxy-4-methylcoumarin, aromatic aldehydes and malononitrile under basic conditions gave the corresponding 2-amino-6-methyl-8-oxo-4-(substitutedphenyl)-4,8-dihydro pyrano*[3,2-g]*-chromene-3-carbonitrile **4**(**a–j**). Further these compounds are treated with formic acid and deamination takes place to produce corresponding 6-methyl-2,8-dioxo-4-(substituted phenyl)-2,3,4,8-tetrahydropyrano[3,2-g]-chromene-3-carbonitrile **5**(**a–j**). The compounds **5**(**a–j**) are treated with NaN_3 in the lewis acid mediated synthesis to afford corresponding tetrazoles **6**(**a–j**) in good yields (Figure 2). The compounds 8-acetyl-7-amino-4-methyl-6-(substituted phenyl) pyrano[3′,2′:6,7] chromeno[2,3- b]pyridine-2,9-(6H,1H)-diones **7**(**a–j**) (Figure 3) synthesized from 2-amino-6-methyl-8-oxo-4- (substituted phenyl) −4,8-dihydropyrano *[3,2-g]* chromene-3-carbonitrile by using ethyl acetoacetate in the presence of pipiridine.

2.2. Antimicrobial activity

The above synthesized compounds were then screened for their potential antibacterial and antifungal activity as benzopyrans possess a wide spectrum of pharmacological properties and the condensed Dihydropyranochromenes also possess appreciable clinical and commercial relevance. It was also made clear in the above discussion that 4H-pyrans and tetrazole units also possess significant physiological activities. Therefore it has been considered worthwhile to investigate the biological activity of the compounds synthesized. The novel synthesized heterocyclic compounds were screened for their *in vitro* antimicrobial activity using cup plate agar disc-diffusion method against two gram positive bacterial strains, *Bacillus polymyxa, Staphylococcus aureus and* two gram negative bacterial strains, *Escherichia coli, Pseudomonas aurignosa* and also two fungal strains *Aspergillus niger* and *Pencillus italicum.* All the compounds were taken at two concentrations. In this evaluation, the compounds **6d** & **7d** were shown to be more potent against all the microbial strains than the other chromene analogues. The observed potency of these compounds may be attributed to the presence of two chlorine atoms in them. In the literature, we have reports in which the biological activity significantly improved due to chlorine atoms.[28,29]

2.3. Antibacteral activity

The novel synthesized chromene compounds were screened for their *in vitro* antibacterial activity using cup plate agar disc-diffusion method against two gram positive bacterial strains namely *Bacillus polymyxa, Staphylococcus aureus* and two gram negative bacterial strains namely *Escherichia coli, Pseudomonas aurignosa.* The results were compared with Chloramphenicol as an antibacterial standard drug. The compounds **6**(**a–j**) and **7**(**a–j**) are showed good to moderate activity against both gram positive and gram negative bacterial strains. Notably, among them the compounds **6b**, **6d** & **7d** shown potential antibacterial efficacy against all the strains. The compound **6b** was more potent against *Pseudomonas aurignosa* (−) (18 mm at 400 μg/mL) whereas the compound **6d** was more toxic against *Bacillus polymyxa* (+) (18 mm at 400 μg/mL) (Figure 4).

2.3.1. Antifungal activity

All the compounds were screened against two fungi strains i.e., *Aspergillus niger* and *Pencillum italicum* and the results were compared with the fungal drug Fluconazole as the standard drug. The Compounds **6a**, **6b**, **6c**, **6d**, **7a**, **7b**, **7d** showed appreciable activity against *Aspergillus niger*, where as less activity against *Pencillus italicum.* **6b** found to be highly toxic and showed more than 90% inhibition of spore germination even at 120 μg/ml against *Aspergillus niger.* Compound **6d** is also found to be more active. It showed more than 70% inhibition at 120 μg/ml against both the fungi. From the present investigation, it can be concluded that all compounds of type **6b**, **6d** and **7d** are toxic to fungi and hence they may be exploited as future fungicides (Figure 5). We can draw some conclusions regrading SAR studies from the observed antifungal acitvity with respect to the structure of potent compounds. The compounds with phenyl, hydroxyphenyl and dichlorophenyl rings have shown more antifungal efficacy than the compounds bearing other substituents.

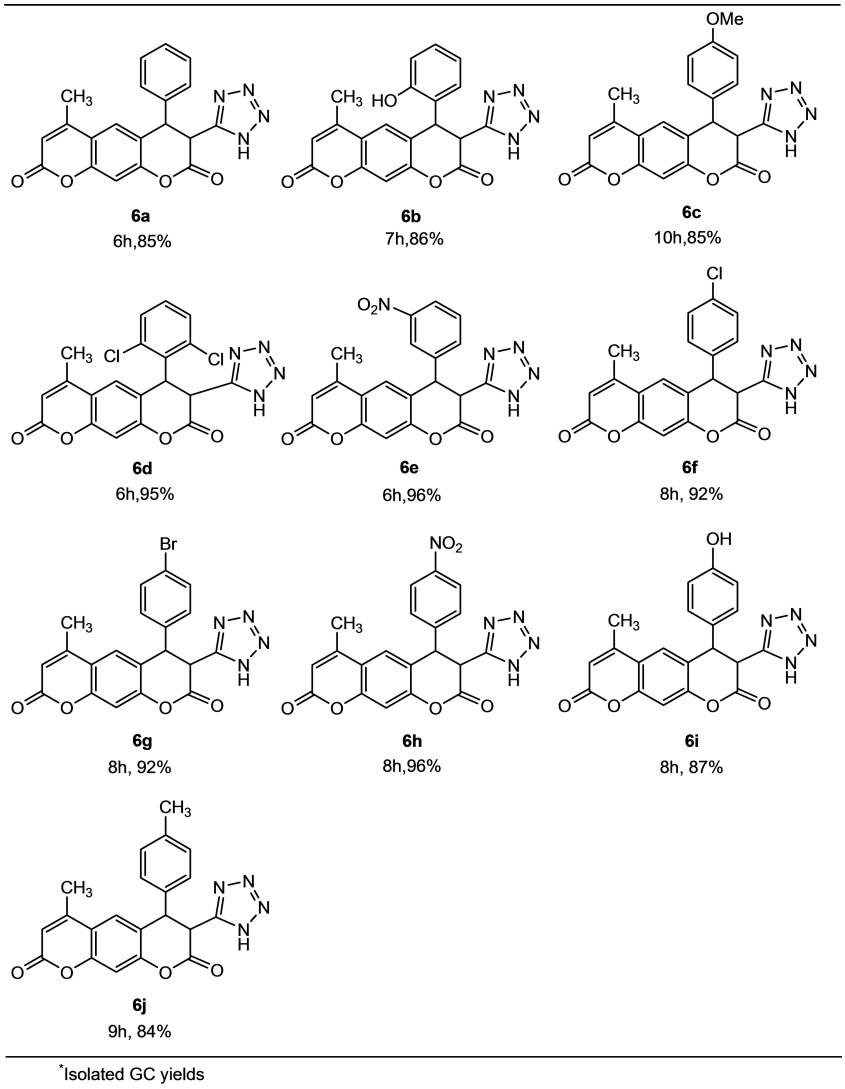


Figure 2. Substarte scope of tetrazole compounds.

2.4. Computational studies

The virtual screening of the lead compounds using AutoDock[30] (**6d** & **7d**) against a vital microbial enzyme, tyrosyl-tRNA (TyrRS) with PDB ID 1JIL was done to reveal their inhibitory capacity and strategic interaction with the binding sites of receptors. In addition, the *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of the lead compounds were also estimated using SwissADME[31] to know more about their Druglikeness.

2.4.1. Molecular Docking Studies

Docking studies of the active compounds **6d** & **7d** were conducted with AutoDock software to reveal the interactions of these compounds with the active sites of tyrosyl-tRNA (TyrRS) with PBD ID 1JIL. The screening results were very impressive showing high binding affinity of **6d** & **7d** with the active sites of enzyme and the corresponong docking scores observed were −8.8 & −10.5 kcal/mole. These scores were quite significant indicating that the lead compounds have the potential to inhibit the enzyme and thus they could be explored further as antibacterial and antifungal agents. The Docking studies of **6d** revealed that the compound docked well with the binding sites of enzyme through various types of interactions such as Hydrogen bonding, pi-alkyl and carbon hydrogen interactions (Figure 6). Interestingly, the newly constructed tetrazole ring of **6d** along with phenyl ring bearing two chlorine atoms were actively involved in binding with the enzyme sites mainly with amino acid residues like ASP A:194, LYS A:83, HIS A:49, ASP A:39, THR A:41 and ARG A:87 through H-bonding and other notable interactions. This clearly demonstarates the importance of the newly formed tetrazole ring and chlorine atoms in enhancing the antimicrobial activity.

On the other hand, the compound **7d** exhibited more pronounced interactions with the enzyme sites than the

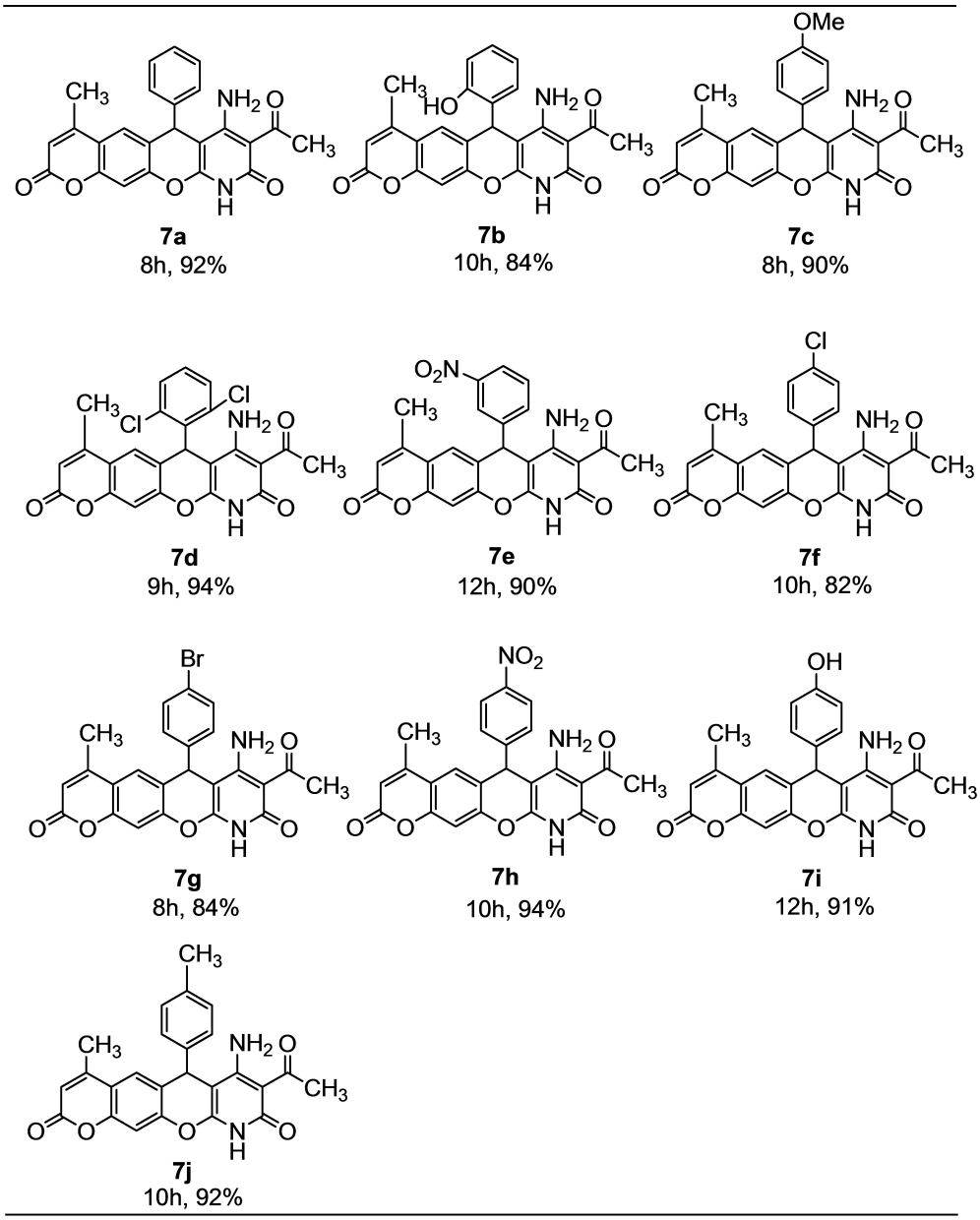


Figure 3. Substrate scope of pyridinedione compounds.

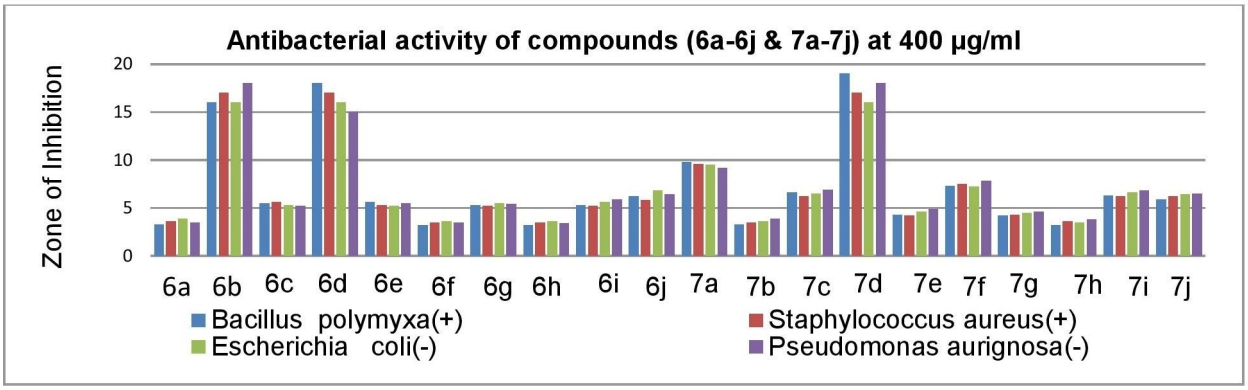


Figure 4. *in vitro* antibacterial activity data of compounds (**6a–j** & **7a–j**).

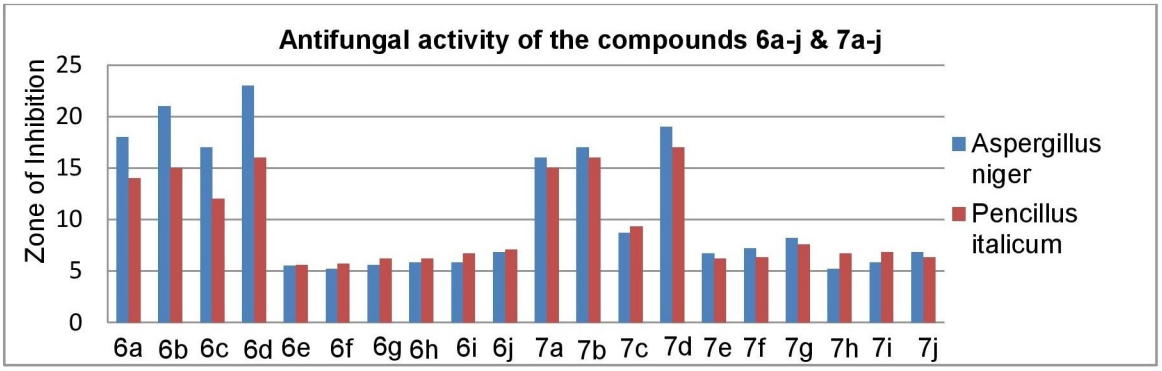


Figure 5. *in vitro* antifungal activity data of compounds (**6a–j** & **7a–j**).

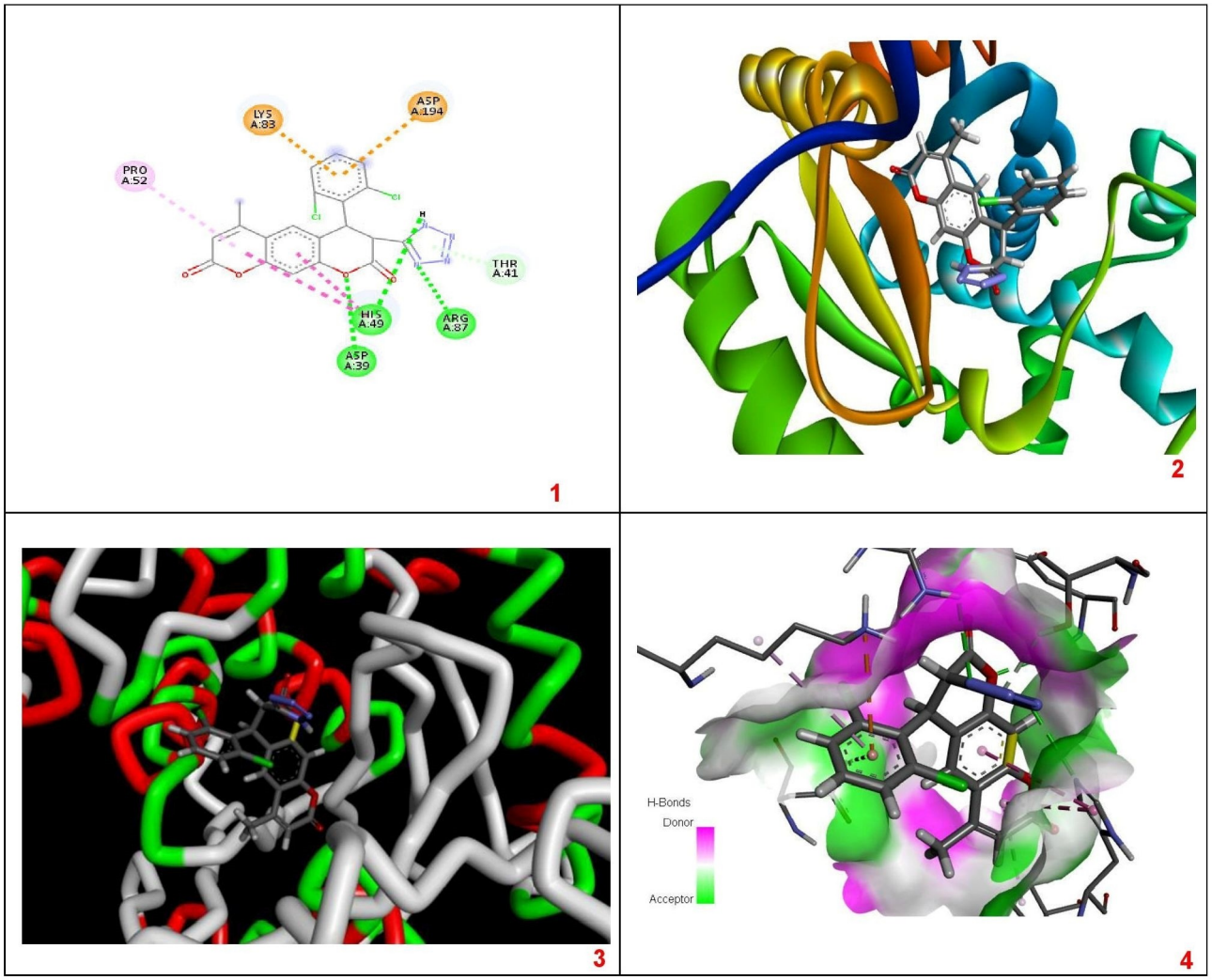


Figure 6. The docking poses of **6d** with tyrosyl-tRNA (TyrRS) with PDB ID 1JIL.

compound **6d** through various connections which include pi-pi stacked, pi-alkyl and hydrogen bonding. Its binding interactions were very extensive which includes but not limited to the amino acid residues like THR A:41, ARG A:87, ASP A:194, TYR A:5, ASP A:39, GLN A:195, HIS A:49, ALA A:38 and CYS A:36. (Figure 7). In this case, the newly formed pyridinedione ring and phenyl ring containing chlorine atoms were activily involved in the interaction and thus explaining its potent

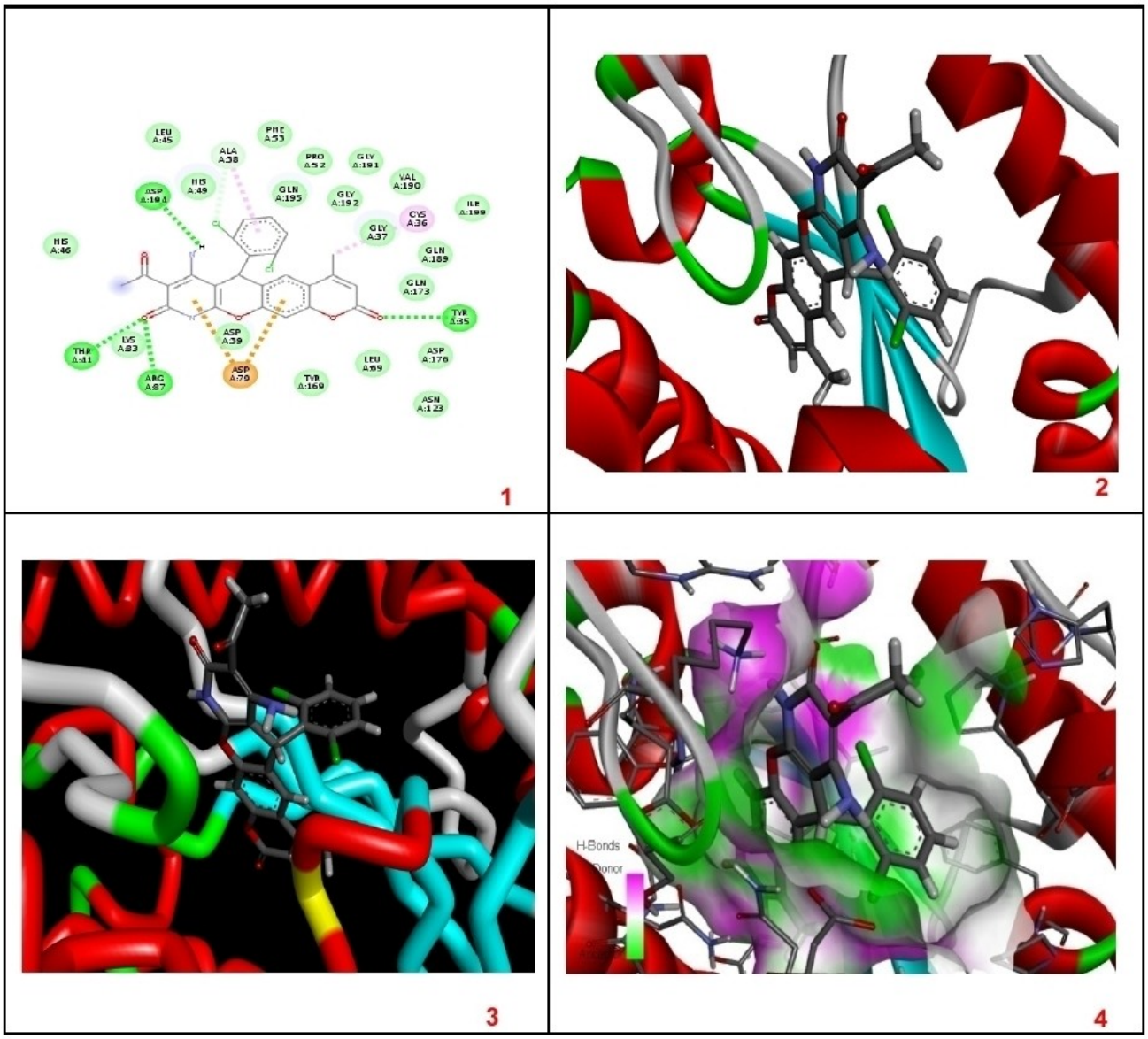


Figure 7. The docking poses of **7 d** with tyrosyl-tRNA (TyrRS) with PDB ID 1JIL.

antimicrobial efficacy. Finally, the molecular modeling results reasonably correalated with the observed antimicrobial values of the lead compounds.

2.4.2. ADMET Studies

ADMET studies are very important in the sense that they predict about the Druglikeness of synthesized compounds. In

Table 2. Druglikeness properties of lead compounds.

Properties / Compounds	Lipophylicity	Water Solubility	GI Absorption	Lipinski (Rule of five)	Bioavailability
6 d	Moderate (log $P = 3.36$)	Moderately soluble (log $S = -5.63$)	High (log $K_p = -6.44$)	Yes (Zero violations)	High (0.56)
7 d	Moderate (log $P = 4.26$)	Moderately soluble (log $S = -5.46$)	Low (log $K_p = -6.70$)	Yes (Zero violations)	High (0.56)

fact, half of all the late stage failures in drug development process could be attributed to poor pharmacokinetic properties (39%) and animal toxicity (11%). So it is wise to know these properties before realizing the actual synthesis. Thus, here the lead compounds (**6d** & **7d**) were further subjected to *in silico* screening for their ADMET properties using a robust SwissADME programme. The results were encouraging for both the lead compounds as they are following the rules of Druglikeness i.e., Lipinski, Ghose, Egan etc. Particularly, the tetrazole compound (**6d**) has Lipophilicity (Log $P_{O/W} = +3.36$), water solubility (Log $S = -5.25$) and Gastrointestinal absorption (high) values indicating its suitability for further advanced studies like *in vivo* and *ex vivo* evaluation (Table 2).

3. Conclusion

A new series of chromene analogue compounds were synthesized and characterized via catalyst free, one-pot green synthesis. This protocol is novel in its approach and methodology as it is accompanied by simple reaction setup and operation, simple separation and easy purification to avoid column chromatography, high yields and short reaction time. The *in vitro* antimicrobial evaluation and *in silico* computational techniques such as Docking and ADMET analysis identified two lead compounds (**6d** & **7d**) for further advanced studies such as *in vivo* & *ex vivo* screening.

Supporting Information Summary

Please find the general synthetic procedures, spectral data of the compounds, antimicrobial screening methods, MDS and ADMET procedures in the supporting information.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Multicomponent reactions · Chromene analogues · Biological activity · Molecular Docking Studies · ADMET Calculations

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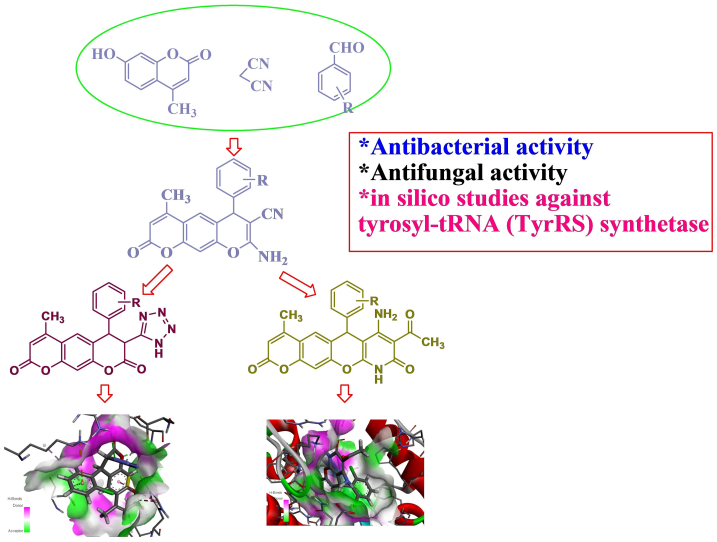
FULL PAPERS

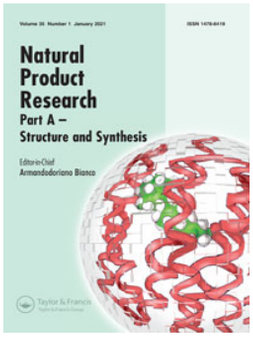


R. Vanam, V. Allam, Dr. S. Nerella, Dr. B. Gavaji**

A new series of chromene analogues were synthesized by using environmentally benign methods and screened for their antimicrobial activity. The chloro analogues were identified as leads in this study as they have shown very impressive activity against four bacterial and two fungal strains. The activity of these leads may be attributed to their effective inhibition of tyrosyl-tRNA (TyrRS) synthetase enzyme present in the most microbes as envisaged by molecular docking and ADMET studies.

Author Contributions

R.V. Conceptualization:Supporting



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Synthesis of podophyllotoxin-glycosyl triazoles *via* click protocol mediated by silver (I)-*N*-heterocyclic carbenes and their anticancer evaluation as topoisomerase-II inhibitors

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Synthesis of podophyllotoxin-glycosyl triazoles *via* click protocol mediated by silver (I)-*N*-heterocyclic carbenes and their anticancer evaluation as topoisomerase-II inhibitors

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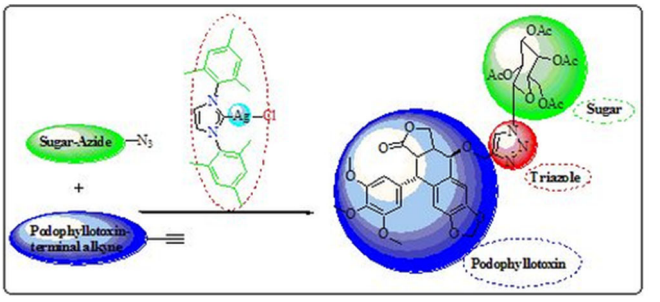
ABSTRACT

Herein we report the regioselective synthesis of podophyllotoxin-Glycosyl triazole hybrids catalysed by Ag(I)-*N*-heterocyclic carbene (Ag(I)-NHC) in a short reaction time (~30 min) at ambient conditions. In principle, it is the first report of Click alkyne-azide cycloaddition catalysed by Ag(I)-NHC catalyst and moreover, this new methodology yielded good results when compared with traditional CuAAC in terms of reaction time and selectivity. The synthesised compounds were further explored for *in vitro* anticancer activity against four human cancer cell lines Du145, HeLa, A-549, and MCF-7 and found that these synthesised compounds possess significant anticancer activity. Further, the compounds **5a** and **5e** were identified as promising leads due to their better activity across all cell lines than that of the standard drug etoposide. Molecular docking studies of 5a & 5e with DNA Topoisomerase-II were revealed that the free energy calculations of active compounds were in good agreement with observed IC_{50} values.



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Podophyllotoxin; click chemistry; Ag (NHC) catalyst; podophyllotoxin-glycosyl triazoles; anticancer studies

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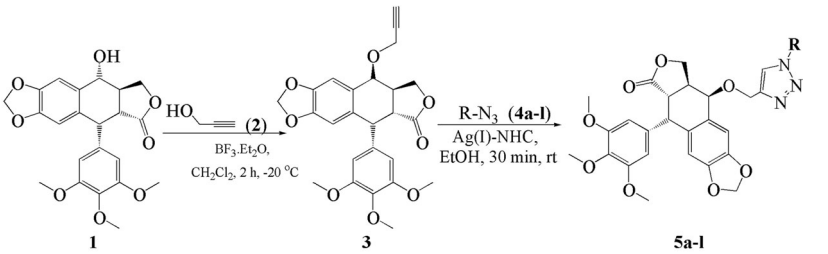
1. Introduction

Plants of Podophyllum species were known for their curative properties for many centuries. In folklore medicine, the plant parts and its crude extracts were used as cathartic, purgative and also to treat genital warts and molluscum contagiosum (Teillac-Hamel et al. 1996). Later on it was identified that Podophyllotoxin (**1**), is the main component present in Podophyllum species which is responsible for its healing properties. Podophyllotoxin is a naturally occurring cyclolignan that can be extracted from roots and rhizomes of Podophyllum species such as Podophyllum peltatum and Podophyllum hexandrum (You 2005).

Podophyllotoxin and its analogues exhibit very interesting and diverse pharmacological activities such as insecticidal, antiviral, antifungal, antitumor, anti-inflammatory, antioxidative and antispasmogenic (Gordaliza et al. 2004; Lv and Xu 2011). However, its severe gastrointestinal side effects restricted its use as therapeutic agent (Pettit et al. 2016). To overcome these side effects, several analogues were synthesised and reported by various groups. Among all the activities, its antitumor activity (Cheng et al. 2014) attracted much attention after the success of its semi synthetic derivatives etoposide and teniposide as effective anticancer drugs (Gupta et al. 2006). Some of these semi synthetic derivatives differ significantly from their parent compound i.e., podophyllotoxin, in their mechanism of action. Podophyllotoxin is a Tubulin inhibiting agent (Kamal et al. 2014) whereas etoposide and its analogues are inhibitors of DNA Topoisomerase-II (Mariani et al. 2015).

DNA Topoisomerases are set of enzymes which operate on topology of DNA and essential for unwinding of DNA strands during replication (Rybenkov et al. 1997). DNA strands must be separated during replication process, but super coiled nature of DNA doesn't allow this. At this juncture, Topoisomerase–II binds to DNA and causes breaks and seals to strands to ease the torsional strain leading to separation of DNA strands. Drugs which target Topoisomerase-II inhibit this action leading to stoppage of DNA replication and eventually leading to arrest of cell proliferation. Etoposide, a glycoside of podophyllotoxin also works on these lines (Byl et al. 2001). Hence we would like to synthesise etoposide like glycosides by reacting *O*-propargyl podophyllotoxin with glycosyl azides. On the other hand, triazoles also exhibit a broad spectrum of biological activities like Podophyllotoxin (Yempala et al. 2014). Triazole ring is a dynamic pharmacophore containing high dipole moment and thus able to participate actively in hydrogen bond formation as well as in dipole-dipole interactions with biological targets (Whiting et al. 2006). Especially Triazole moiety is prevalent in natural products and also in potential pharmaceutical compounds like carboxyamidotriazole (CAI), Tazobactum and cefatrizine. In addition to this, even glycosyl triazoles have their own significance in medicinal chemistry as chemical therapeutics (Zhang et al. 2005).

N-Heterocyclic Carbenes (NHCs) were already well established as versatile organo and organometallic catalysts and found diverse and myriad applications in organic transformations (Rafet and Naim 2017). Amidst diverse properties of NHCs, their catalytic property is the most significant and studied elaborately. We reported previously cooperative effect between Ag (I) and organo-NHCs in catalyzing a multicomponent one-pot reaction (Kankala et al. 2015). Literature survey revealed that the organo and organometallic NHCs have not yet been explored extensively for alkyne-azide



R=Tetracetylglucosyl (**5a**), Glucosyl (**5b**), Tetracetyl C2-glucosyl (**5c**), C2-Glucosyl (**5d**), Tetracetylgalactosyl (**5e**), galactosyl (**5f**), Tetracetyl mannosyl (**5g**), Mannosyl (**5h**), Tetracetylarabinosyl (**5i**), arabinosyl (**5j**), Tetracetylxylosyl (**5k**), xylosyl (**5l**).

Figure 1. Synthesis of Podophyllotoxin-glycosyl triazoles **(5a–l)**.

cycloaddition. Therefore we would like to employ diverse NHCs for the click 1, 3-dipolar cyclisation reaction to find out the efficacy of these catalysts and the best catalyst among them.

2. Results and discussion

This work describes a facile route for the regioselective synthesis of 1, 4- disubstituted podophyllotoxin-glycosyl triazoles *via* catalytic 1, 3-dipolar cycloaddition of sugar azides and 4β-*O*-propargyl podophyllotoxin. We have made 4β-*O*-propargylated podophyllotoxin to react with pre-synthesised sugar azides in cycloaddition to obtain podophyllotoxin-glycosyl triazole hybrids. The 4β-*O*-propargyl podophyllotoxin (**3**) was obtained from podophyllotoxin (**1**) and propargyl alcohol (**2**) in presence of Boron trifloride etherate in a single step synthesis (Figure 1). The synthesised compound (**3**) was then treated with sugar azides (**4a–l**) in the presence of Ag (I)-NHC catalyst to obtain podophyllotoxin-glycosyl triazole hybrids (**5a–l**).

Initially we chose to study 1, 3-dipolar cycloaddition reaction between 4β-*O*-propargyl podophyllotoxin (**3**) and galactose azide (**4e**) in ethanol. We would also like to explore the efficacy of a variety of potential catalysts in catalyzing 1, 3-dipolar cycloaddition as depicted in Table S1. There was no cycloaddition observed in the absence of catalyst (Table S1, entry 1). We are also interested to know the progress of click reaction employing widely used copper salts like CuI, $CuSO_4$ and $Cu(OAc)_2$, but obtained products in trace amounts after 24 h at reflux conditions (Table S1, entries 2–4). When silver salts (AgOAc and AgOTf) and zinc salts ($Zn(OAc)_2$ and $Zn(OTf)_2$) were employed as catalysts there was also no progress in the above cycloaddition reactions at reflux temperature (Table S1, entries 5–8).

However, when Ag(I)-NHC (NHC precursor = 1,3-Bis (2,4,6-trimesitylphenyl) imidazolium chloride) was employed as catalyst, the results were remarkable yielding podophyllotoxin-glycosyl triazole hybrid (**5e**) selectively just in 30 minutes with better yields (94%, Table S1, entry 9). On the other hand, previous reports revealed that alkyne-azide cycloaddition reaction employing catalysed and uncatalysed methodlogies was accomplished only under refluxing conditions with longer reaction times. The out come of these results clearly demonstarted the efficiency of Ag(I)-NHC as a potential catalyst for 1,3-dipolar cycloaddition.

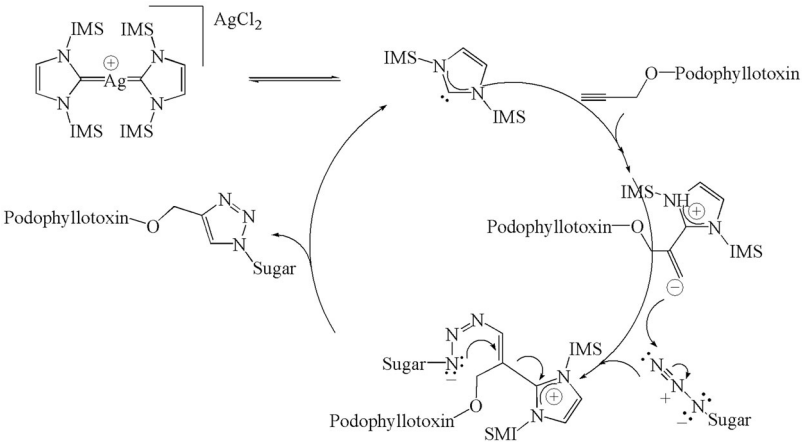


Figure 2. A plausible mechanism for the formation of 1, 4-disubstituted triazoles catalyzed by Ag (I)-NHC.

We have also interested to investigate the above cycloaddition reaction using other co-catalysts (CuI & $Zn(OTf)_2$) along with Ag(I)-NHC and the results were comparable with Ag(I)-NHC (Table S1, entries 10 and 11). We have also studied the same reaction using simple organo-NHC as a catalyst and found that the reaction was relatively slow and the yields of triazoles were moderate (Table S1, entry 12). However, we have got better yields when Silver salt (AgOTf) was introduced during the reaction course into the organo-NHC mediated cycloaddition (Table S1, entry 13) than the organo-NHC alone mediated 1,3-dipolar cycloaddition.

Employing the same optimised conditions (RT, 5 mol% Ag(I)-NHC, 30 min, ethanol), we investigated the scope of the reaction with a variety of structurally diverse sugar azides (**4a**–**l**) for the cycloaddition reaction and the results are depicted in Table S2. The structures of the podophyllotoxin-glycosyl triazole hybrids (**5a**–**l**) were established on the basis of elemental analysis and spectral data (^{1}H NMR, ^{13}C NMR and Mass).

The literature reports reveal that the synthesis of regioselective Podophyllotoxin-triazole hybrids from 4β-azidopodophyllotoxin and terminal alkynes was easy to achieve. However, the selective synthesis of these hybrids from 4β-*O*-propargylpodophyllotoxin and azides (simple or sugar) is still remain as a challenge to accomplish. All of the earlier efforts were not so successful and produced mixture of regioisomers (Hong et al. 2011; Mahesh et al. 2014). The results and conditions depicted in Table S2 for the regioselective synthesis of podophyllotoxin-glycosyl triazole hybrids (**5a**–**l**) suggest that our yields and reaction time are comparable or even better than those for the closely related synthesis of podophyllotoxin-triazole hybrids in earlier reports (Bhat et al. 2008; Reddy et al. 2011).

Based on the results obtained in the regioselective synthesis of 1, 4-disubstituted-1, 2, 3-triazoles a plausible mechanism has been deduced as depicted in Figure 2. The formation of triazole could occur in a domino fashion in cycloaddition. According to Figure 2, the organo-NHC catalyst will interact first with the 4β-*O*-Propargylated podophyllotoxin to form a zwitterion. The reactive zwitterionic species will now interact with sugar azide through nucleophilic attack and form another zwitterion *via* C-N

bond formation. This undergoes finally to C-N heterocyclisation to produce regioselectively the corresponding 1, 4-disubstituted-1, 2, 3-triazole.

2.1. In vitro anticancer activity

The anticancer activity of podophyllotoxin-glycosyl triazole hybrids (**5a–l**) was evaluated by MTT assay against human tumor cell lines Du145, HeLa, A-549 and MCF-7 and compared with etoposide as working standard, and the final inhibitory concentration to an extent of 50% was calculated using the reported methods (Mosmann 1983). The *in vitro* cytotoxicity values depicted in Table S3 indicate that the podophyllotoxin-glycosyl triazole hybrids (**5a**–**l**) show promising anticancer activity against all the tested cancer cell lines.

Among the synthesised compounds, **5a** and **5e** have shown more potent antitumor activity across all cell lines than the standard drug etoposide. The compound **5a** has shown the best activity against Prostate cancer cell lines (Du 145) with IC_{50} value $1.02 \pm 0.02\,\mu M$ whereas **5e** has shown the best activity against breast cancer cell lines (MCF-7) with IC50 value $1.25 \pm 0.02\,\mu M$. As far as the structure–activity relationship is concerned, some correlations can be drawn from the data to support the observed cytotoxic activity based on the type of the sugar substituents present on the triazole ring. The podophyllotoxin-glycosyl triazole hybrids bearing both protected and unprotected sugars have shown potential anticancer activity. However, the compounds with acetyl protected sugars particularly **5a** and **5e** have exhibited better anticancer activity than the unprotected sugars. This can be attributed to the presence of acetyl groups which have high binding affinity with the enzyme as supported by the docking studies. This effective drug-receptor interaction might be one of the promising reasons for the improvement in the activity of acetyl protected podophyllotoxin-glycosyl triazole hybrids.

2.2. Molecular docking studies

Docking studies of **5a** and **5e** were performed with Auto Dock software to reveal the interactions of these compounds with the active sites of Topoisomerase-II enzyme with PBD ID 1ZXN (Figure S1). The results were impressive showing high binding affinity of these compounds towards the enzyme and a free energy of −9.2 and −9.3 was observed for **5a** and **5e** respectively.

Docking studies of **5a** revealed that the molecule bound well with the enzyme through various types of interactions such as Hydrogen bonding, alkyl, pi-alkyl and carbon hydrogen interactions. Glycosyl moiety was shown strong binding affinity with the enzyme through hydrogen bonding with amino acids like Aspargine C92, Threonine C184, Arginine C-70, and Serine C-120. Triazole ring was interacted with Arginine C70 *via* pi-alkyl interactions. Other notable interactions of **5a** include the pi-alkyl interaction between aromatic rings (B and E) of Podophyllotoxin and Isoleucine D5.

The compound **5e** has shown strong interactions with the enzyme and formed hydrogen bonds with amino acid residues like ARG C70, SER C121, SER C120 and ASN

C122. It was clearly shown that the sugar moiety of the compound was actively participated in hydrogen bonding. The aromatic rings of Podophyllotoxin were interacted with amino acid residues such as ILE D5 and ARG C70 through pi-alkyl attractions. Other prominent interactions include pi-donor hydrogen between methyl hydrogens of E-ring of podophyllotoxin and ILE D5, ARG D4 and ASP C124. The docking studies and scores of **5a** and **5e** were in good agreement with observed IC_{50} values.

3. Experimental

3.1. General procedure for the synthesis of 4β-(prop-2-ynyloxy) epipodophyllotoxin (3)

Podophyllotoxin (**1**) and propargyl alcohol (**2**) was dissolved in dichloromethane (10 ml) and added Boron trifloride etherate slowly drop wise over a period of 10 minutes while maintaining the temperature at −20 °C and stirring was continued for 2 hours at the same temperature. The combined organic layers were washed consecutively with cold dilute HCl and brine solution. The extracted organic solution was dried under reduced pressure to afford a crude product which was subjected to column to afford pure product (**3**).

3.2. General procedure for the synthesis of sugar azides (4a-l)

Sugar azides were synthesised by the reported procedures in the literature based on Bertho's method. Firstly, Sugars are acetylated, then brominated with HBr in AcOH (33%) at 0 °C and finally made to react with NaN_3 under reflux conditions for 2 h in the presence of PTC to yield corresponding glycosyl azides, which were subjected to column chromatography to afford pure products (**4a**–**l**)

3.3. General procedure for the synthesis of podophyllotoxin-triazole hybrids (5a-l)

O-Propargylated podophyllotoxin (**3**) and Ag (I)-NHC was dissolved in dry EtOH and added sugar azide (**4a**–**l**). The reaction mass was stirred for 30 minutes. The organic layer was separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried and evaporated under reduced pressure to afford a crude product which was subjected to column chromatography to afford pure products (**5a**–**l**).

4. Conclusion

In conclusion, we have developed a simplistic catalytic approach for the regioselective synthesis of 1, 4-disubstiututed podophyllotoxin-glycosyl triazole hybrids in high yields and in short period of time. To our knowledge, this is the first methodology developed, optimised and extensively studied with Ag (I)-NHCs as catalyst for click reaction. These advantages make this methodology facile, appropriate and can be put into practice to create diverse compound libraries in future. The synthesised hybrid

molecules **5a** and **5e** have shown impressive *in vitro* anticancer activity and thus identified as promising lead compounds for future studies such as *in vivo* studies. The success of Ag (I)-NHCs as versatile catalysts for click reaction opens up entirely new vistas in this field and paves the way for further design and chemical modification of podophyllotoxin as anticancer agents. These promising findings and the computer modelling studies indicate that potent activities may be found in many related podophyllotoxin derivatives in the future.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Comparative analysis on various Natural Polymers

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Abstract: ***Any pharmaceutical formulation has two ingredients: an excipient and an active component. Excipients aid in the production of dosage forms and enhance their physicochemical characteristics. Any dosage form uses polymers as excipients, which are crucial. They should be compatible, non-toxic, stable, economical, etc., as they affect medication release. They fall into two general categories: synthetic polymers and natural polymers. The choice of polymer is the first step in constructing any dosage form since they have a wide variety of uses. Nowadays, producers are leaning toward employing natural polymers due to several issues with medication release and adverse effects. Since natural polymers are essentially polysaccharides, they are both biocompatible and ad-free.. This review discusses various natural polymers, their advantages over synthetic polymers and role of natural polymers in designing novel drug delivery systems.***

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Keywords: Agar, Cellulose, Chitin, Locust bean gum, Starch

INTRODUCTION

A big molecule (macromolecule) made up of repetitive structural units is referred to as a polymer. Covalent chemical bonds are frequently used to join these subunits. Both synthetic and natural polymers are available, however because they are affordable, widely accessible, and non-toxic, natural polymers are more appealing for use in pharmaceutical applications. With a few exceptions, they are also biocompatible, chemically modifiable, and perhaps biodegradable. 1 Plant-based substances can present a number of difficulties during the synthetic process, including the need for small amounts of complicated mixes that may vary depending on the location of the plants as well as other factors like the time of year. As a result, the separation and purification procedure could be time-consuming and costly.

The creation of solid monolithic matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable and injectable systems, as well as viscous liquid formulations, are just a few of the specialised uses for plant-derived polymers in pharmaceutical formulations. Polymeric polymers have served as binders, matrix formers or drug release modifiers, film coating formers, thickeners or viscosity enhancers, stabilisers, disintegrants, solubilises, emulsifiers, suspending agents, gelling agents, and bio adhesives among other functions within various dosage forms.

NEED OF HERBAL POLYMERS

•Biodegradable – Naturally occurring polymers produced by all living organisms. They show no adverse effects on the environment or human being.

•Biocompatible and non-toxic – Chemically, nearly all of these plant materials are carbohydrates in nature and composed of repeating monosaccharide units. Hence they are non-toxic.

•Economic - They are cheaper and their production cost is less than synthetic material.

•Safe and devoid of side effects – They are from a natural source and hence, safe and without side effects.

•Easy availability – In many countries, they are produced due to their application in many industries. 8

DISADVANTAGES OF HERBAL POLYMERS

•Microbial contamination – During production, they are exposed to external environment and hence, there are chances of microbial contamination.

•Batch to batch variation – Synthetic manufacturing is controlled procedure with fixed quantities of ingredients while

production of natural polymers is dependent on environment and various physical factors.

•The uncontrolled rate of hydration—Due to differences in the collection of natural

•materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. 8

•Slow Process – As the production rate is depends upon the environment and many other factors, it can't be changed. So natural polymers have a slow rate of production.

•Heavy metal contamination – There are chances of Heavy metal contamination often associated with herbal excipients.

CLASSIFICATION OF NATURAL POLYMERS

•Plant origin - Cellulose, Hemicellulose, Glucomannan, Agar, Starch, Pectin, Inulin, Rosin, Guar gum, Locust bean Gum, Gum Acacia, Karaya gum, Gum Tragacanth, Aloe Vera gel.

•Animal origin - Chitin, Alginates, Carageenans, Psyllium, Xanthum gum.

NATURAL POLYMERS FROM PLANT ORIGIN

Cellulose

Cellulose was discovered in 1838 by the French chemist Anselme Payen, who isolated it from plant matter and determined its chemical formula. Cellulose is an organic polysaccharide with the formula $(C_6H_{10}O_5)_n$, consisting of a linear chain of several hundred to over ten thousand $\beta(1\rightarrow4)$ linked D-glucose units.

The polysaccharides of the plant cell wall consist mainly of cellulose, hemicelluloses and pectin.Cellulose is an essential structural component of cell walls in higher plants and is the most abundant organic polymer on earth. Many parallel cellulose molecules form crystalline microfibrils that are mechanically strong and highly resistant to enzymatic attack. These are aligned with each other to provide structure to the cell wall. Cellulose is insoluble in water and indigestible by the human body.

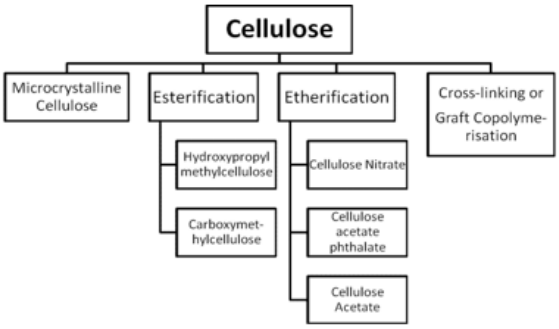

Fig. 1: Cellulose derivatives

Microcrystalline cellulose is mainly used in the pharmaceutical industry as a diluent/binder in tablets for both the granulation and direct compression processes. Controlled release applications for cellulose derivatives include the formulation of membrane-controlled drug release systems or monolithic matrix systems. Film coating techniques for the manufacture of membrane-controlled release systems include enteric coated dosage forms and the use of semi- permeable membranes in osmotic pump delivery systems.

Hydroxypropyl methylcellulose is a partly O- methylated and O-(2-hydroxypropylated) cellulose ether derivative that has been extensively investigated as an excipient in controlled release drug delivery systems due to its gel forming ability. In a study where two cellulose ethers; hydroxypropyl methylcellulose and carboxymethylcellulose were employed as polymeric carrier materials in matrix tablets for controlling the release of a soluble drug, diltiazem, it was found that each polymer on its own could sustain drug release over an extended period of time in these systems.

More importantly, a mixture of the two cellulose ethers in the matrix type tablets enabled zero order drug release kinetics at both pH 4.5 and 6.8 Hydroxypropyl methylcellulose monolithic matrix systems showed similar dissolution profiles as a commercial osmotic pump system for glipizide, a drug with low solubility. It was further found that the hydroxypropyl methylcellulose matrix systems have a stronger gel structure than those made of polyethylene oxide, which may provide superior in vivo performance in terms of matrix resistance to the destructive forces within the gastrointestinal tract.

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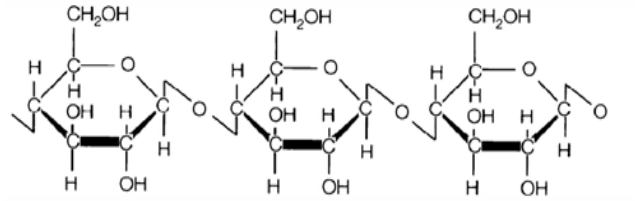

Fig. 2: Structure of Cellulose

Hemicellulose

A hemicellulose is a heteropolymer (matrix polysaccharides), such as arabinoxylans, present along with cellulose in almost all plant cell walls. While cellulose is crystalline, strong, and resistant to hydrolysis, hemicellulose has a random, amorphous structure with little strength.

Unlike cellulose, hemicellulose (also a polysaccharide) consists of shorter chains - 500-3,000 sugar units. In addition, hemicellulose is a branched

Pectin

Pectin is the purified carbohydrate product obtained by acid hydrolysis from the inner portion of the rind of citrus peels i.e. Citrus Simon or Citrus Aurantium, (Rutaceae). The main component of pectin is a linear polysaccharide composed of α-1,4-linked D- galacturonic acid residues interrupted by 1,2-linked L-rhamnose residues with a few hundred to about one thousand building blocks per molecule, corresponding to an average molecular weight of about 50,000 to about 1,80,000. The galacturonic acid polysaccharides are rich in neutral sugars such as rhamnose, arabinose, galactose, xylose and glucose. The composition of pectin can vary based on the botanical source, for example pectin from citrus contains fewer neutral sugars and has a smaller molecular size as compared to pectin obtained from apples.

Pectin has been investigated as an excipient in many different types of dosage forms such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, microparticulate delivery systems for ophthalmic preparations and matrix type transdermal patches. It has high potential as a hydrophilic polymeric material for controlled release matrix drug delivery systems, but its aqueous solubility contributes to the premature and fast release of the drug from these matrices.

It was investigated that the suitability of amidated pectin as a matrix patch for transdermal chloroquine delivery in an effort to mask the bitter taste when orally administered. The results suggest that the pectin-chloroquine patch matrix preparation has potential applications for the transdermal delivery of chloroquine and perhaps in the management of malaria. Calcium pectinate nanoparticles to deliver insulin were prepared as a potential colonic delivery system by ionotropic gelation.

Micro particulate polymeric delivery systems have been suggested as a possible approach to improve the low bioavailability characteristics shown by standard ophthalmic vehicles (collyria). In this context pectin microspheres of piroxicam were prepared by the spray drying technique. In vivo tests in rabbits with dispersions of piroxicam-loaded microspheres also indicated a significant improvement of piroxicam bioavailability in the aqueous humour (2.5-fold) when compared with commercial piroxicam eye drops.

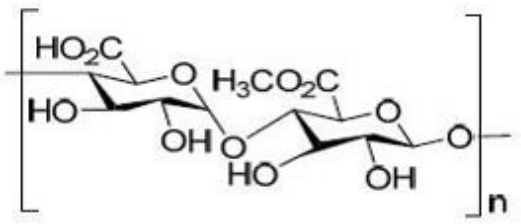

Fig. 3: Structure of Pectin

Rosin

Rosin, also called colophony or Greek pitch (Pix græca), is a solid form of resin obtained from pines and some other plants, mostly conifers, produced by heating fresh liquid resin to vaporize the volatile liquid terpene components. Rosin is a natural polymer with a low molecular weight of 400 Da obtained from the oleoresin of pine trees, with the principle sources being Pinus soxburghui, Pinus longifolium and Pinus toed a. Rosin is primarily composed of abietic and pimaric acids and has excellent film-forming properties. Rosin and its derivatives are biopolymers that are increasingly used for their pharmaceutical applications. In the pharmaceutical context it has been investigated for microencapsulation, film-forming and coating properties, matrix materials in the tablets for sustained and controlled release.1 Derivatives of rosin synthesized by a reaction with polyethylene glycol 200 and maleic anhydride proofed suitable for sustaining the drug

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release from matrix tablets and pellets.Polymerized rosin films containing hydrophobic plasticizers showed excellent potential as coating materials for the preparation of sustained release dosage forms. Different studies on the film forming and coating properties of rosin and the glycerol ester of maleic rosin demonstrated their potential to be used as coating materials for pharmaceutical products as well as in sustained release drug delivery systems. It was shown that hydrocortisone loaded nanoparticles prepared from rosin could slowly release this model drug, which was dependent on the rosin content. This in vitro study demonstrated the potential of rosin for the production of effective nanoparticulate drug delivery systems.

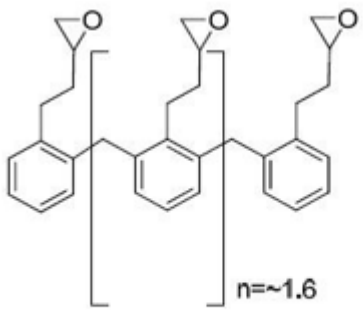

Fig.4: Structure of Rosin

CONCLUSION

Polymers play a vital role in the drug delivery. So, the selection of polymer plays an important role in drug manufacturing. But, while selecting polymers care has to be taken regarding its toxicity, drug compatibility and degradation pattern. By this review, we can say that natural polymers can be good substitute for the synthetic polymers and many of the side effects of the synthetic polymers can be overcome by using natural polymers.

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A Special Issue on

Recent Trends in English Language Teaching

| Editors |
Dr. Adi Ramesh Babu
Yeldi Ramesh

Recent Trends in English Language Teaching

Along with the flow of time, everything undergoes appropriate changes and takes turns in compliance with time. Academy is no exception in this matter. From the recent past a drastic change in teaching & learning process has been beings visualized. Advent of technology brought some noteworthy changes in all the educational institutions. The research papers in this special issue cover a variety of topics related to 'Recent Trends in English Language Teaching,' including teaching & learning English through mobile learning, the role of technology in language teaching, Computer Assisted Language Learning (CALL), & the importance of phonetics in teaching English to Indians, role of mother tongue in teaching English as a second language, communication skills in the modern days, innovative teaching methods & techniques, challenges in multi - cultural English language classrooms, learning English through Youtube etc. The unique nature of this work contents will interest professionals in applied linguistics and in ELT also.

Dr Adi Ramesh Babu is presently working as Asst. Professor, Department of English, Government City College (A), Hyderabad, Telangana State. He obtained his M.Phil and Ph.D degrees from Kakatiya University, Warangal. He also did PGCTE and PGDTE from EFLU (Hyderabad). His edited books are: *Indian English Literature: A Memento of Feminist Minds, Indian Women Literature: A Montage of Leitmotiv, English Language Teaching and Learning: Problems & Remedies, Principles and Techniques in English Language Teaching & Learning, Subaltern Spaces in New Literatures : An Anthology Presented to K. Damodar Rao, Commonwealth Literature: An Anthology of Mosaic Themes, and Postcolonial Literature : Controversial concepts of Silence & Violence.* He has published several articles & presented scholarly papers in national and international seminars. He is one of the Editors of The Criterion : An Online International Journal ; International Journal of English Language, Literature & Translation Studies; International Journal on Studies in English Language & Literature.

Yeldi Ramesh is presently working as an Asst. Professor, Department of English, Government Degree College, Thorrur, Mahabubabad Dist. He is pursuing his Ph.D. He has published two books on English Literature for NET /SET under Pragma Publication, Hyderabad. He has published several papers in national & international seminars. He has presented a number of research papers in internationals seminars. He has completed 'Annual Refresher Programme in English Language Teaching' successfully.

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Preface

The paper 'Importance of Phonetic Symbols for Indian Learners of English' written by Dr. Alka Bansal tries to give the importance of phonetics in the present days, pronunciation of Indian learners. Mahammad Azam in his paper "Computer Assisted Language Learning (CALL): An Interactive Method of Teaching and Learning in English" has critically given how CALL would help the language learners. It also gives us the merits and demerits of CALL. The paper entitled "An English Teacher: A Creator of Innovative Activities in English Language Classroom" by Dr. E. Brijesh attempts to examine the role of English teacher in the modern English language classrooms. Adepu Priyanka and Yelagonda Anjaneyulu in their paper "Useful Techniques in Pronunciation Practice: A Special Focus on Stress and Intonation" argue for the innovative techniques that teachers should follow in teaching pronunciation. They have pointed out by focusing on stress and intonation.

The paper titled "Native Language vs. Foreign Language: Role of Mother Tongue in Teaching English as a Second Language" written by Brishti Mukherjee deals with the difference between mother tongue and foreign language. It also aims to study the role of mother tongue in English language teaching which is significant & will also elaborate the methods of English teaching which employ mother tongue. Dr. Dandu Swamy in his paper "Role of Print Media in English Language Learning for ESL Learners" discusses how the newspapers, magazines, and other print media play a vital role in teaching and learning language skills.

The paper "Analysis of Impressive Schemes in English Language Teaching" by Dr. Ch. Jaiwanth Rao reveals that there are many teaching methods that the teachers have been using in the language classrooms but argues that some innovative schemes must be brought in the English language classrooms. The paper "Communication Skills in English: Overcoming Barriers of Speaking Skills" by S. Kavitha focuses on the hurdles encountered by the rural students while learning English language. It also explores the reasons for the failure of the students in communicating in English in spite of academic excellence. Dr. I.M. Khairdi's paper 'Methods of Teaching English' presents important methods in teaching English. The paper tries to attempt to show the merits and demerits of each teaching method.

Dr. Adi Ramesh Babu in his interesting paper "Teaching Tactics and Experimental Techniques in English Language Classroom" makes an attempt to give some innovative methods and approaches in teaching foreign language. The paper shows us important tactics that must be come from the mind of the classroom teachers. The research paper "Innovative Techniques in English Language Teaching" tries to examine into the methods, techniques, and innovative ideas in teaching English. The research paper by Dr. Reena Dewan "Challenges of a Multicultural English Language Classroom" focus on the above challenges and seek to elucidate possible strategies to not only overcome them but make the class more interesting and effective for students coming from heterogeneous background.

Dr. N. Swamy in his critical research paper "Personal Learning Networks: The Future of ELT" talks about Personal Learning Networks are one of the best alternatives to bring the

needed changes in the field of ELT. The paper "The Efficient Methods of Teaching in English Language Classroom" by Dr. Tulshiram Laxman Dabde aims to point out some effective teaching methods focusing attention on the characteristic features, teacher-student role and example of a lesson in English as a second Language (ESL) classroom. Yeldi Ramesh in his paper "English Language Teaching: Problems and Remedies" discuses that the purpose of the paper is to learn about the difficulties that teachers face when teaching English in high school and college, with a focus on regional medium schools. It also emphasizes the importance of English in Indian education. The scholar P. Yellaiah in the paper "Using Youtube as an Effective Tool to Enhance Speaking Skills: An Experimental Study" argues that the modern English language classroom should have techno support and mentions that Youtube is an effective tool to get language skills especially speaking skills.

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ENGLISH LANGUAGE TEACHING: PROBLEMS AND REMEDIES

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ABSTRACT:

English teachers at regional medium schools face a slew of issues, including a lack of audiovisual tools, a lack of a suitable setting in which to teach English, a lack of cooperation from students' parents, a flawed testing system, and inappropriate textbooks. The purpose of this study is to learn about the difficulties that teachers face when teaching English in high school and college, with a focus on regional medium schools. It also emphasizes the importance of English in Indian education.

Key words: English class, English teacher, problems, remedies

What is the difference between a subject and a language when it comes to English? It's a form of communication. It's a skill that needs to be developed. It is not possible to test it in the same way that other subjects are. Instead of a fragmented approach to language training, a complete and integrated curriculum is required. Learning English is a process that takes time and effort to master. The educational curricula should not be segmented from elementary school to college. In connection to this, Narayanan (2009) says that "because of the great ethnic and linguistic diversity found within our nation, English acts as an indispensable 'link' language. English symbolizes in Indians' minds, better education, better culture and higher intellect."

It is a controversial issue whether teaching English in regional medium schools is simple is a contentious question. Some argue that it is simple since an English teacher can teach in his own language, whereas we cannot find it in English medium schools. Other professors said that teaching English to regional medium students is a difficult task since the students are unable to understand English terms because they do not have a clear understanding of their meaning. The English language does not enjoy the same status in free India as it did prior to independence. We now teach English as a second language or as a practical language in our classrooms. However, there are some issues that necessitate extra attention and effort. They're as follows:

i. Lack of correspondence between alphabets and sounds: The fundamental distinction between the 26 alphabets and 44 sounds of the English language is rarely taught to Indian students. We don't see such lessons at the elementary school level. Vowels and consonants do not have their own chapter. Instead, students are taught incorrectly that the English language has five vowels: a, e, i, o, and u. Alphabets and phonetic symbols are sometimes

confused. Students want to pronounce all of the letters, but some aren't. As a result, they never learn about the proper sounds that result from articulating these phonetic symbols. It is critical to comprehend vowels and consonants as different from alphabets in order to pronounce and spell words correctly.

ii. Dictionaries: Most English speakers are unaware of the various functions of dictionaries and are astonished to realize that dictionaries are an excellent resource for learning how to pronounce English words correctly. Few people consult dictionaries to learn how to pronounce difficult words correctly. The accent and pronunciation of people who speak it as a second language are inextricably influenced by their mother tongue. Using dictionaries can help us become closer to the RP model of English pronunciation.

iii. Class-room Conditions: These conditions include the number of students in a class, physical arrangements for the class, teaching materials such as chalk, blackboard, audio-visual aids, and a library, among others. A class of roughly fifty students becomes un-widely while teaching a second language, and students cannot receive individual attention. The issue is that our students in Indian schools and universities do not have access to audio or visual assistance. Leave aside the tape recorder, lingua-phone, film strips, and other essentials for learning English worthy of the name in our schools. In government schools and institutions, online education is never used. About the importance of online education, Anderson (2004) claims: "The Net provides expanded opportunities for students to plunge ever deeper into knowledge resources, thus affording a near limitless means for students to grow their knowledge, to find their way around the knowledge of the discipline, and to benefit from its expression in thousands of formats and contexts" The availability of appropriate instructional materials and audio-visual aids can undoubtedly improve English teaching in India.

iv. Reverse Teaching: In the United States, native English speakers listen to the language in order to learn how to speak it before being taught the script; but, in India, the process is reversed. Students are first taught how to write and read a script, with speech and listening abilities falling to the wayside. Furthermore, the emphasis is placed on writing English without completely grasping its meaning. The general criticism is that speaking and reading abilities have been entirely disregarded. The Indians learnt "English not mainly in order to talk in English, but in order to get at the knowledge and thought which is stored in English. They are learning English to read" (West, 1926) and so the aim of teaching English in India should be "to create a class of one-way values of people who can read English and set vital ideas" (West, 1926).

v. Translation Issues: A bilingual approach to English instruction is used in many institutions and colleges. When learners try to synchronise their mental processes in the vernacular with the tempo of English language, they run into problems. The structure of English differs between regional languages and English, and it is critical that this distinction be highlighted to young learners so that they are aware of the differences between the two languages. In English, subject, verb, and object are subject, verb, and object, whereas in many regional languages, for instance in Telugu, subject, verb, and object are disordered as subject, object, and verb.

vi. Textbooks: English textbooks suffer from a variety of problems. Despite the fact that these text books were prepared by renowned professors, the course editors failed to focus on the learners' issues. They don't follow the students' English standards. By providing useless and uninteresting material, they are leading the learner down the incorrect path. Students' speaking skills aren't always tested in the texts. Different states' education boards have implemented similar policies. Many flaws can be found in the textbooks. While reading these texts, a number of students have difficulties. Subject professors notice a number of flaws in them, as well. These publications fail to deliver the goods when placed in the hands of typical English teachers. The topic has little to do with the learners' immediate surroundings. Learners face challenges with vocabulary and structures as well. Many of the events in the novels are out of step with the learners' mental abilities.

vii. State Policy: Each state is responsible for its own set of policies. They almost never stick to their guns when making a decision. Depending on the situation, policies are occasionally amended. They could have one policy for one year and a different policy the following year. English was once required of third-year undergraduate students in Andhra Pradesh, but it was removed from the curriculum after only a few years. "There have been regular changes in Government policy toward the teaching and learning of English in numerous states," according to the report of the study group on English education. Teachers and language learners are both affected by the government's changing policy.

viii. Syllabi: The English syllabi for various classes are far from adequate. Many students complain that the syllabi's prose and poems aren't funny; instead, they're essays that don't focus on abilities. The students pass the exams, but they are unable to apply what they have learned in their real-life situations. Many essays, stories, and letters/applications are taught in their schools. They can write on occasion, but their errors entertain the audience. Even a graduate student nowadays would struggle to create a basic application because he had studied everything from an examination point of view rather than from a practical point of view.

ix. Methods: There are a variety of ways to teach English, including the following: The classic translation-cum-Grammar Method of teaching is still used in most Indian colleges. Our professors are not fond of the new approaches, which include structural, communicative, and situational. Grammar and composition continue to play a significant role in the educational curriculum. However, they are unaware of the fundamentals of language instruction. Teachers spend time by teaching grammar under the influence of compasses, which does not foster the four fundamental abilities of language learning. As a result, this sort of instruction should be phased out, and teachers should strive to help students speak, read, and write fluently in English.

x. Teaching of literary forms: Introduction of literary forms like as poetry, plays, short tales, and other finer nuances of the language in the syllabi before the student has learned the fundamentals of the language is a complete waste of time for everyone. In the recent past, using literature to teach English has yielded dismal outcomes, as it has failed to meet the goal of improving students' language skills. Furthermore, it has exacerbated the problem by

adding to the sorrows of English-language-challenged Indian students, leading to a linguistic aversion among them.

xi. Passive Students: In India's educational system, students are lectured rather than encouraged to produce English. As a result, English teachers instill the importance of speaking in their students. Students are not given enough opportunities to speak the language and are not exposed to proper English. As a result of their lack of practice listening to the language, kids are unable to comprehend spoken English. The continual practice of the four skills is necessary and should be emphasized when learning a language.

xii. Parental Intervention: Parental interference in the work of teachers obstructs progress. When a teacher tries to implement new methods of teaching English, he is hampered by the parents whose children are enrolled in the school. It is possible that the parents are religious. They were educated in some way, and they want their children to be educated in the same manner. In such situations, the teacher must adapt his or her teaching methods and teach in the manner that the parents prefer. As a result, the problem is worsened by the parents' interference.

xiii. Correction Work: When teaching a language, correction work is crucial. When teaching a foreign language, such as English, correction work is even more critical. However, we have discovered that it receives little attention. This is a huge problem in India because there are just a few English professors and lecturers. The school administration makes no attempt to determine what is causing the rectification work to be neglected. The number of periods for English teachers is the same as for other disciplines. When dispersing workload, their weight of labour due to rectification work is not taken into account. Teachers are unable to do justice to their responsibility of correcting students due to their overworked schedules. It was agreed upon by all teachers.

xiv. Examination System: The Indian examination system is a sham at all universities. It does not assess a student's knowledge; rather, it assesses how many marks he can obtain by writing down anything he reads. It does not appear to be trustworthy. Exams have become a priority for both students and teachers. Everything they do is solely for the sake of a test. The person who sets the paper, the examiner, the teacher, and others are unconcerned about actual language learning. The questions are set by the paper setter, who only assesses the learner's packed information. The teacher and students do their assignments while keeping the examination schedule in mind. Things that are crucial for the examination are addressed. In academic exams, there is no question about spoken English. This vital part of language learning is overlooked by everyone. If the board of studies introduces it, students may strive to train even harder in order to gain higher scores on the exam and be able to speak more effectively. Teachers and students continue to be concerned about the upcoming assessment.

xv. Web based Learning: English has become easier to learn more than ever before with the availability of many sources to help people learn very easily and enjoyable. Web based learning drags the attention of the learners very quickly but most of the schools and colleges in India have limited resources. Web based learning is one of the fastest growing areas in education. It is widely accepted that advances in information technology and new

developments in learning science provide opportunities to create well-designed, learner-centered, interactive, affordable, efficient, flexible e-learning environments (Khan, 2005).

It is important for course designers and teachers to familiarize themselves with the ways to classify tasks. The different components of a syllabus can be fulfilled as to be made up of different types of tasks. (Hosseni, 2010) It must not be forgotten that mere knowledge of the fundamental concepts of grammar or literary works does not translate into fluency in spoken English. So, there should be equal focus on practising of all the skills related to the language. There should be a practical examination in all these classes, where students' spoken and listening skills are also to be tested along with their reading and writing skills. Though it is difficult to completely overhaul the system or change the deeply entrenched practises overnight, a slow and gradual change will make a difference in the times to come. Rooting out some of the anomalies will pave the way for the future good of English language teaching in India.

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Isolation and Screening of Indigenous Rhizobia from BlackGram Cultivated in Fallow Rice Soils for Plant Growth Promoting Traits

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ABSTRACT

Bio fertilisers are relatively safer, environmentally friendly and a cost-effective approach to chemical fertiliser usage. The selection of bacterial strains with multiple beneficial characteristics is important to maximise their effectiveness on the host plant. In the present study, four native and indigenous rhizobial strains (VM-2, VM-8, VM-9 and VM-15) were isolated from root nodules of blackgram (*Vignamungo*) cultivated in fallow rice soils of Andhra Pradesh, India. All the four strains were screened *in vitro* for their plant growth-promoting (PGP) characteristics viz. production of indole acetic acid (IAA), exopolysaccharide (EPS), hydrogen cyanide (HCN) and phosphate solubilisation. The results indicated that the rhizobial strains varied in their plant growth promoting activities. All the four strains produced IAA, EPS and also solubilised the insoluble phosphate. The amount of IAA produced varied from strain to strain and relatively high amounts were recorded in VM-8 (43.4 µg/ml) followed by VM-15 with 43.1 µg/ml. Maximum EPS production was recorded in VM-9 (527 mg/ml) followed by VM-8 (483 mg/ml). The phosphate solubilisation efficiency of *Rhizobium* strains on solid media ranged between 16% and 17%. In liquid medium, strain VM-2 recorded maximum solubilisation (799µg/ml) followed by VM-8 (372µg/ml). All the strains except strain VM-8 were HCN producers. Among these three strains, VM-2 and VM-15 showed strong HCN production. These isolates were identified as *Rhizobium* sp. strain VM-2 (KJ 704783), *Brady rhizobium* sp. strain VM-8 (KJ 704784), *Brady rhizobium* sp. strain VM-9 (KJ 704785) and *Achromobacter* sp. strain VM-15 (KJ501696) after 16S rRNA sequencing. The pot culture experiment showed that VM-8, VM-9 and VM-15 inoculated plants had good results both

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in inoculated sterilised and inoculated unsterilised soils than the plants grown in sterilised uninoculated soils and control soils. The VM-2 strain showed moderate results under plant inoculation test. This study suggests that these four native rhizobial strains of PGP can be used as bio fertilisers as well as a bio control agent for enhancing the yield of blackgram in rice fallows.

Keyword: Rice fallows, black gram, plant growth promoting characteristics.

INTRODUCTION

Blackgram (*Vignamungo*) is a short duration crop belonging to the Leguminaceae family. It is also called urad bean. Our (1993) reported that millions of people in many countries are consuming it as a part of their diet and is a cheap source of protein (17-34% seed protein). Reddy *et al*. (2011) reported that this legume increases soil fertility by fixing 38 kg N/ha/year in soil from atmosphere. It is mainly cultivated in the rice fallows after rice cultivation to conserve soil nutrients and utilise the left-over soil moisture present in the rice fallows. Cultivation of legumes in rice fallows can prevent the loss of soil nitrate and additionally capture atmospheric nitrogen through biological nitrogen fixation process (George *et al.* 1992).

Most of the rhizospheric microorganisms promote plant growth and development either directly (nitrogen fixation, phosphate solubilisation and plant growth regulators) or indirectly (by controlling the pathogenic microorganisms) and are referred to as plant growth promoting rhizobacteria (PGPR). Besides symbiotic nitrogen fixation, *Rhizobium* can also produce phytohormones like Indole acetic acid (Halda-Alija 2003), siderophores and HCN, thereby decreasing the damage due to plant pathogens and ultimately improving plant growth and yield (Deshwal *et al*. 2003; Weller and Cook 1983; Raajjmakers *et al.* 1999; Kranthi Kumar and Raghu Ram 2016; Manasa *et al.* 2017).

Phosphorous is one of the most important macro nutrients that plays an important role in plant metabolism (Sashidhar and Podile 2010). Several microorganisms in the rhizosphere (rhizobacteria) solubilise inorganic phosphate by the production of organic acids (Rodriguez and Fraga1999). Rhizobia is also a good phosphate solubiliser and tends to increase phosphorous availability to plants by solubilising the insoluble phosphates (Halder *et al.* 1990; Johri *et al*. 2003).

Another important characteristic feature of PGPR is EPS production which helps in nitrogen fixation by protecting the dinitrogenase enzyme from high oxygen concentrations (Tank and Saraf 2003). The EPS produced by the *Rhizobium* species play a prominent role in the *Rhizobium*-legume symbiosis (De and Basu 1996) particularly in root hair infection and nodule formation (Phillip-Hollings worth *et al*.1989; Kranthi Kumar and Raghu Ram 2016).

Less information is available on these important plant growths promoting traits of native or indigenous *Rhizobium* strains isolated from blackgram particularly cultivated in rice fallows. The present investigation was undertaken

to isolate and screen the indigenous Rhizobium bacteria from root nodules of *Vignamungo* plants for their PGPR activities like IAA, EPS, HCN production and phosphate solubilisation followed by plant inoculation test.

MATERIALS AND METHODS

Isolation of Rhizobium Strains from Blackgram Root Nodules

In the present investigation, the nodulated roots of mature black gram plants cultivated in rice fallows of Krishna and Guntur districts of Andhra Pradesh, India were collected. Rhizobium strains were isolated from freshly collected healthy root nodules on yeast extract mannitol agar (YEMA) medium with 0.1% Congo red. The pure cultures of all isolates were maintained on YEMA slants and preserved at 4ºC (Vincent 1970). The identity of the strains was confirmed by tests such asGram staining, growth on culture media such as YEMA with Congo red (Vincent 1970; 1982), Hofer's alkaline broth and Glucose Peptone Agar (Vincent 1970), Ketolactose test (Bernaertz and Deley 1963) and nodulating ability on homologous hosts (Somasegaran and Hoben 1985).

Screening of Rhizobial Strains for Their Plant Growth Promoting Activities

Indole Acetic Acid(IAA) Production

IAA production was determined by the (Gorden and Weber, 1951) method. For IAA production, all the four strains were grown separately in 100 ml conical flasks containing 30 ml of YEM broth (Skerman 1959) supplemented with L-tryptophan (1.5 mg/ml) at pH 7.0 in triplicate on a rotatory shaker for 54 h at 30±2°C. Bacterial growth was determined by taking optical density (OD) at 540 nm using a Spectrophotometer (Elico-Cl 157). The broth cultures were centrifuged at 5000 rpm for 20 min and the cell free supernatant was analysed for IAA extraction according to Sinha and Basu (1981). To the 10 ml of supernatant, 2 ml of Salkowsky's reagent (0.5 M $Fecl_3$ in 35% perchloric acid) was added and the mixture was left in the dark for 30 min. The development of pink colour indicated IAA production and the optical density was measured at 540 nm using a spectrophotometer. The yield of IAA was calculated by using the standard graph of authentic IAA (Merck). Data on three replications was maintained.

Exopolysaccharide (EPS) Production

The *Rhizobium* strains were inoculated into Erlenmeyer flasks containing 100 ml of YEM broth supplemented with 1% Mannitol. The inoculated flasks were incubated at 30±2°C on a rotator shaker at 300 rpm for 72 h. After incubation, the culture broth was centrifuged at 3000 rpm and the supernatant was mixed with two volumes of chilled acetone. The crude polysaccharide developed was collected by centrifugation at 3000 rpm for 30 min. The EPS was washed with distilled water and acetone alternatively, then transferred on to a filter paper and weighed after overnight drying at 105°C (Damery and Alexander 1969). Data on three replications was maintained.

Phosphate Solubilisation

The phosphate solubilising ability of the strains was tested on Pikovskaya's solid agar medium (Pikovskaya 1948) with Tricalcium phosphate (TCP) as insoluble phosphate source. The solubilisation efficiency (SE) on solid agar medium was expressed interms of SE (%) (Sri Ram Kumar and Kannapiran 2011; Srivastava *et al.* 2004). The strains which showed a solubilisation zone on solid agar medium were further tested in flasks containing 100ml of Pikovskaya's broth having an initial pH 7. One ml of the inoculum was inoculated into the broth and the flasks were incubated on a rotary shaker (200rpm) at 28±2ºC for 72h. The supernatant was separated from the bacterial cells by centrifugation of flasks at 3000rpm. Later the final pH of the supernatant was measured and the liberated P_2O_5 was estimated by adding 2.5 ml of Barton's reagent to 10ml aliquot of the clear culture supernatant and the volume was made up to 50 ml. After 10 min, the resultant yellow colour was read in a calorimeter at 430 nm (Jackson 1973) and the liberated P_2O_5 was estimated by comparing the values with a standard curve prepared with K_2HPO_4.Data on three replications was maintained.

Hydrogen cyanide (HCN)Production

All the isolates were screened for their ability to produce HCN. Production of HCN was assayed by the method given by Miller and Higgins (1970) with slight modifications. Actively growing bacterial cultures were streaked on YEMA plates supplemented with 4.4 g glycine/L. Filter paper soaked in 0.5% picric acid and 1% Na_2CO_3 was attached to the upper Petri dish lids and the plates sealed with parafilm. Plates without inoculum served as control. HCN production was estimated after seven days of incubation at room temperature, by observing a colour change in the filter paper from yellow to light brown (low), brown (moderate) or reddish brown (strong). Data on three replications was maintained.

PCR Amplification and Partial Sequencing of 16S rRNA Gene

The amplification of PCR and sequencing of 16S rRNA gene of the four isolates, VM-2, VM-8, VM-9 and VM-15,was done by using the commercial services of Macrogen Inc. Korea.

Phylogenetic Analysis of Bacterial Strains

The gene sequences of VM-2, VM-8, VM-9 and VM-15 were submitted to BLAST for comparison with Gen Bank sequences employing the Basic Local Alignment Search Tool (*http://www.ncbi.nlm.nih.gov/GenBank/*). For the phylogenetic analysis, Gene Sequences greater than 600 bp in length were used.

Plant Inoculation Test

Pot culture experiment and experimental design

Symbiotic efficiency and persistence of inoculated Rhizobium in soil are necessary for the success of an inoculation program. Screening for these traits is therefore an important component of inoculation studies. A pot culture experiment was carried

out using the most cultivated rice fallow black gram variety, LBG-752, in the Botanical garden of Acharya Nagarjuna University, Guntur, Andhra Pradesh, India to evaluate the effect of indigenous *Rhizobium* strains (VM-2, VM-8, VM-9 and VM-15) isolated from rice fallows on the growth, nodulation, nitrogen fixation and yield of black gram. All the pots used in this experiment were of uniform size (27×25 cm) and 5 kg of soil was used in all pots. The experiment was conducted in RBD with three replications and three treatments. The treatments were as follows: Treatment-1: Seed inoculation with isolated native strains in sterilised soil; Treatment-2: Seed inoculation with isolated native strains in unsterilized soil; Treatment-3:Growth of seedlings in sterilised soil without inoculation; and Control: Growth of seedlings in unsterilized soil without inoculation.

Materials used

The materials used include rice fallow soils collected from different rice fields, black gram seeds obtained from Regional Agriculture Research Station (RARS), Lam, Rhizobium cultures, autoclave, earthen pots, plastic tag for labeling, broth culture for multiplying the Rhizobium strain and electric orbital shaker.

Soil sterilisation

Rice fallow soils collected from different rice fields were heat sterilised using (electric soil steriliser at 65°C for 90 min) and then autoclaved for 30 min at 130 kpa and 121°C. Then the soil was left to cool and stored in air tight bags.

Sowing and inoculation

Seeds of black gram LBG-752 which were uniform in size, shape and weight were surface sterilised with 1% mercuric chloride ($HgCl_2$) for 3-4 min and were repeatedly washed with sterilised water. No fertilizer was applied at the time of sowing. For seed inoculation, seeds were coated with a paste of *Rhizobium* inoculum containing approximately 10^8 cells per seed (Somasegaran and Hoben 1994) and eight such seeds were sown per pot containing 5 kg soil for Treatments 1&2. The non-coated sterilised seeds were sown in pots of Treatment-3 and Control. The experiment was conducted under natural conditions by following all agronomic practices which were uniform and normal for all the treatments.

Data Collection

Data was collected from all the treatments at 35 DAS and at 50% flowering stage on morphological and yield characters such as number of nodules, nodule fresh weight (mg), nodule dry weight (mg), leg haemoglobin content (µg/ml), root length (cm), shoot length (cm), root fresh weight (gm), root dry weight (gm), shoot fresh weight (gm), shoot dry weight (gm), number of leaves per plant, number of branches per plant, number of clusters per plant, number of pods per plant, seeds per pod, pod length (cm), nodule nitrogen (%), root nitrogen (%), shoot nitrogen (%), leaf nitrogen (%), seed nitrogen (%), seed protein and seed yield per plant.

Statistical Analysis

Statistical analysis of the PGPR data was performed by using SPSS software (version 2.0). Correlation coefficient and ANOVA were calculated for the PGPR data wherever necessary. The data onpot inoculation was statistically analysed using AGRISTAT software. Correlation coefficients between traits regarding pot experiment were calculated by MINITAB 16 software.

RESULTS AND DISCUSSION

Isolation of Rhizobial Strains

Four isolates were obtained from the nodules of blackgram plants grown in the rice fallows of Krishna and Guntur districts of Andhra Pradesh, India. The *Rhizobium* colonies on Congo red medium appeared as white, round, transparent, and elevated with entire margin. They were Gram-negative rods and did not grow on Hofer's medium and glucose peptone agar. All the strains were negative for the production of 3-ketolactose from lactose and were finally confirmed as rhizobia by the nodulation test (Satyanandam *et al*. 2014).

Screening of Rhizobial Strains for Various Plant Growth Promoting Activities

In this study all the four strains were screened in vitro for their plant growth promoting properties like Indole Acetic Acid production, EPS production, Phosphate solubilisation and HCN production. The results revealed that all the four strains were IAA, EPS producers and phosphate solubilisers. Except for strain VM-8, all the other strains showed HCN production (Table 1).

TABLE 1
Plant growth promoting activities of different rhizobial isolates

Strains	IAA	EPS	Phosphate solubilisation	HCN
VM-2	+	+	+	+
VM-8	+	+	+	−
VM-9	+	+	+	+
VM-15	+	+	+	+

' + ' indicates positive ' − ' indicates negative

IAA Production

All the four strains showed IAA production. The amount of IAA produced varied from strain to strain and relatively high amounts were recorded in VM-8 (43.4 µg/ml) followed by VM-15 with 43.1 µg/ml incubated for 54 h when YEM medium was supplemented with 1.5 mg/ml L-tryptophan. A low amount of IAA was produced

byVM-9 (35.0 µg/ml) and VM-2(19.0 µg/ml) respectively (Table 2). In earlier reports, the *Rhizobium* sp. isolated from root nodules of *Dalbergial anceolaria* produced a high amount of IAA at 2.5 mg/ml L-tryptophan concentration (Ghosh and Basu 2002) while the *Rhizobium* sp. from root nodules of *Roystonearegia* produced a maximum amount of IAA at 3 mg/ml L-tryptophan concentration (Basu and Ghosh 2001). Kranthi Kumar and Raghu Ram (2016) reported that *Ensifer* sp. isolated from *Vigna trilobata* produced a maximum of 42.5 µg/ml of IAA in the presence of L-tryptophan 2mg/ml concentration. Manasa *et al.* (2017) mentioned that out of 15 Rhizobial strains isolated from different legume crops such as groundnut, black gram, green gram, soy bean and redgram,11 were able to produce IAA. Further, out of 11 isolates, the *Rhizobium* strain from ground nut showed maximum IAA (24.12 µg/ml).

TABLE 2
Production of IAA by *Rhizobium* strains from Vigna mungo

S. No	Name of strain	IAA production (µg/ml)
1	VM-2	19.0
2	VM-8	43.4
3	VM-9	35.0
4	VM-15	43.1

Notes: Each value in the table is a mean of three replicates
F-calculated (4.256); F-tabulated (1.925); significant at 5% level

EPS production

Maximum EPS production was recorded in VM-9 (527 mg/ml) followed by VM-8 (483mg/ml). The lowest EPS production was recorded byVM-2 (341mg/ml) followed by VM-15 (287 mg/ml) (Table 3). The above results clearly indicate that these isolates are considered as copious EPS producers. The *Rhizobium* strain isolated from the root nodules of *Crotalaria saltiana* produced 16 µg/ml (Mukhurjee *et al*. 2011) while that of *Rhizobium* DL 10 from *Dalbergia lanceolaria* produced maximum EPS 765 µg/ml (Ghosh *et al.* 2005) and *Rhizobium* strain from blackgram produced maximum EPS 346 mg/l (Mandal *et al.* 2007).

Phosphate Solubilisation

All the four strains of VM-2, VM-8, VM-9 and VM-15 produced a clear zone around the colonies after 24 h of incubation on Pikovskaya's agar medium, which gradually increased up to 72h. The solubilisation efficiency (SE) of *Rhizobium* strains on solid media ranged between 16% and 170%. The *Rhizobium* strainVM-2 showed maximum solubilisation efficiency (Figure 1) followed by VM-8, VM-

TABLE 3
EPS production by *Rhizobium* strains from Vigna mungo

S.No	Name of strain	EPS production (mg/100 ml)
1	VM-2	341
2	VM-8	483
3	VM-9	527
4	VM-15	287

Notes: Each value in the table is an average of three replicates
F-calculated (5.637); F-tabulated (2.295); significant at 5% level

15 and VM-9. In liquid medium, *Rhizobium* strain VM-2 recorded maximum solubilisation (799µg/ml) followed by VM-8 (372µg/ml), VM-15(353µg/ml) and VM-9 (261µg/ml) (Table 4). A drop in a pH was accompanied by phosphate solubilisation. Phosphate solubilising microorganisms dissolve insoluble phosphates by the production of inorganic or organic acids and/or by a drop in pH value (Sperber1958; Rodroguez and Fraga 1999; Sridevi *et al.* 2007; Kranthi Kumar and Raghu Ram 2016).

In earlier reports, solubilisation efficiency (SE) of *Rhizobium* isolates from *Cassiaabsus, Vigna trilobata* and three strains from *Sesbania sesban* on solid media ranged between 33% and 150%. In liquid medium, maximum solubilisation was recorded with *Rhizobium* isolate from *Cassiaabsus* (620 µg/ml) (Sri devi and Mallaiah 2009) while the *Rhizobium* sp isolated from root nodules of *Crotalaria retusa* recorded maximum solubilisation (840 µg/ml) in liquid medium (Sri devi *et al.* 2007). In the study of Muhammad Adnan (2016) it was observed that 21% of the tested rhizobia were phosphate solubilising bacteria. Among 15 *Rhizobial* isolates, 7 isolates were able to solubilise phosphate on Pikovskaya's media containing Tricalcium phosphate as phosphate source. The solubilisation efficiency of *Rhizobium* strains on solid media ranged between 38% and 270% (Manasa *et al*. 2017).

Figure 1. Phosphate solubilised zone of Rhizobium strain VM-2

TABLE 4
Solubilisation of tricalcium phosphate by *Rhizobium* strains from Vigna mungo

S. No	P_2O_5 liberated strain	(µg/ml)
1	VM-2	799
2	VM-8	372
3	VM-9	261
4	VM-15	353

Notes: Each value in the table is an average of three replicates
Significant at 1% (p = 0.000)

Hydrogen Cyanide Production

Among the four strains screened, except forVM-8 strain, the other three strains (VM-2, VM-9 and VM-15) produced HCN. Among these three strains VM-2and VM-15 showed strong HCN production by a change in colour of filter paper from yellow to reddish brown (Figure 2) and Strain VM-9 showed low HCN production by change in colour of filter paper from yellow to light brown (Table 5). Control plate did not show any colour (Figure 3).

The isolates of *Rhizobium meliloti* from ground nut were able to produce HCN (Arora *et al.* 2001). Thirty-three isolates (7.26%) from 454 rhizobial isolates had the ability to produce HCN as reported by Pellock *et al.* (2002). Yogendra *et al.* (2013) reported that out of the 25 Rhizobium strains tested, only one strain produced hydrogen cyanide (HCN). Muhammad *et al.* (2016) reported that their studies on PGPR features of the Rhizobium strains obtained from different summer

legumes, only 9% of the tested rhizobial strains produced HCN. Kranthi Kumar and Raghu Ram (2016) reported that four *Rhizobium* strains out of six strains isolated from *Vignatrilobata* showed HCN production. Monika *et al*. (2017) reported that four rhizobial strains from 14 rhizobial isolates had the ability to produce HCN. Out of 15 *Rhizobium* isolates, eight produced HCN. Further, out of eight, the *Rhizobium* strain obtained from red gram exhibited strong HCN production and the *Rhizobium* strains obtained from ground nut scored as moderate for HCN production (Manasa *et al*. 2017).

TABLE 5
Production of hydrogen cyanide (HCN) by *Rhizobium* strains

S. No.	Strain	Colour
1.	VM-2	Reddish brown
2.	VM-8	–
3.	VM-9	Light brown
4.	VM-15	Reddish brown

Figure 2. HCN production by VM-2

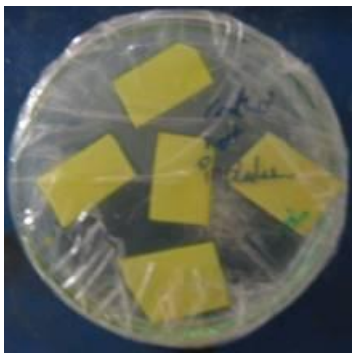

Figure 3. HCN control plate

Phylogenetic Analysis of Four Representative Isolates

The phylogenetic analysis of the four gene sequences of 16S r RNA of VM-2, VM-8, VM-9 and VM-15 was blasted against the nucleotide database of the NCBI and the sequences were aligned with a set of published sequences on the basis of the conserved primary sequence and also by nucleotide BLAST similarity search analysis. Based on the 16S rRNA gene sequences, the strain VM-2 showed a close relation with *Rhiobium* sp. strain, VM-8 and VM-9 with *Bradyrhizobium* sp. and VM-15 with *Achromobacter* sp. The 16S rRNA sequences were deposited in NCBI with the accession numbers KJ 704783 (VM-2), KJ 704784 (VM-8),KJ 704785 (VM-9) and KJ 501696 (VM-15).

The above results clearly indicate that the strains belong to Rhizobiaceae (VM-2), Bradyrhizobiaceae (VM-8, VM-9) and Alcaligenaceae (VM-15) families which are phylogenetically distinct.

Plant Inoculation Test

Pot culture experiment

Among the different morphological and yield parameters studied under pot culture experiment (Figure 4), indigenous strains such as VM-8, VM-9, and VM-15 inoculated plants showed good results both in inoculated sterilised and Inoculated unsterilised soils than the plants grown in sterilised uninoculated soils and control soils both at 35 DAS and at 50% flowering stage. The strain VM-2 showed moderate results among the different parameters studied under pot culture experiment.

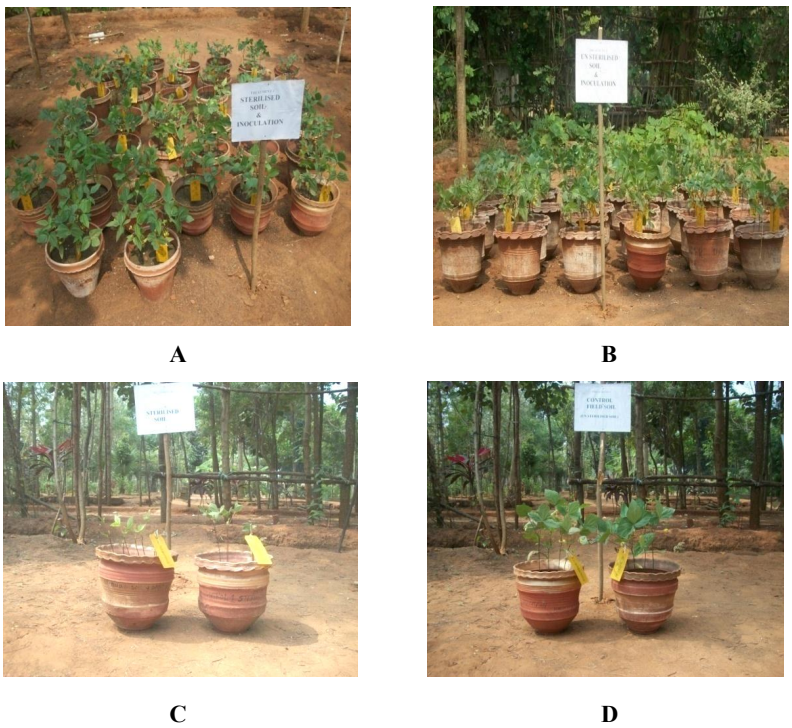

Figure 4. Experimental view of pot experiment

A. Treatment 1: Seed inoculation with isolated native strains in sterilised soil.
B. Treatment 2: Seed inoculation with isolated native strains in unsterilised soil.
C. Treatment 3: Growth of seedlings in sterilised soil without inoculation
D. Control : Growth of seedlings in unsterilised soil without inoculation

Similar reports of variation among the native or indigenous rhizobial strains inoculation in different crops on different parameters have been reported by so many authors. Arroyo *et al.* (1998) inoculated common bean with native Bradyrhizobia, Pant and Prasad (2004) treated soybean with native Bradyrhizobia while Hungria *et al.* (2015)and Samudin and Kuswantoro (2018) inoculated soybean with native *Rhizobium*. Other researchers carried out studies on the Bengal gram (Bhattarai and Maskey1992; Tippannavar and Desai 1992) the soybean (Palaniappan *et al*.1997), black gram (Neemar *et al.* 2007), chick pea (Yadav *et al.* 2011), green gram (Bhat *et al*. 2010) and in dry bean (Karaca and Uyanoz 2012).

CONCLUSION

Based on our study, it is concluded that all the four isolates (VM-2, VM-8,VM-9 and VM-15) exhibited plant growth promoting traits like production of IAA, EPS, HCN and phosphate solubilisation. Inoculation of most cultivated rice fallow black gram variety LBG-752 with these four indigenous rhizobial strains promoted plant growth which could be directly attributed to the beneficial effects from biological N_2 fixation and phytohormones, EPS production and indirectly to phosphate solubilisation. These strains belong to *Rhiobium* sp., *Bradyrhizobium* sp. and *Achromobacter* sp. respectively. In this investigation, *Achromobacter* sp. (VM-15) is reported for the first time to nodulate the Indian blackgram. This study, therefore suggests that these four native rhizobial strains of PGP potential can be used as biofertilisers as well as bio control agent for enhancing the yield of blackgram in rice fallows.

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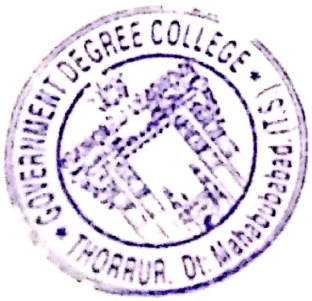

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Synthesis and bioevluation of BIS (Indolyl) methane derivatives using copper halide catalyst

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Abstract

A mild and an efficient method catalyzed by copper iodide in TMEDA as solvent was used for the synthesis of bis(indolyl) methanes through a cascade process between indole and substituted aromatic aldehyde to produce the corresponding bis (indolyl) alkanes in moderate to good yields under reflux conditions. All structures of the desired products were evaluated using spectroscopic techniques ^{1}H NMR, ^{13}C NMR spectroscopy and LCMS.

The structure of the compounds was determined by elemental analysis. The antibacterial activity of newly synthesized compounds was investigated against gram positive bacteria (Escherichia coli and Pseudomonas) and gram negative bacteria (Bacillus subtilis and Staphylococcus aureus). Anti fungal activity of some newly synthesized compounds was examined against three pathogens such as Aspergillus Niger, Aspergillus favus and Candida albicans.

Keywords: Indole, Substituted aromaticaldehydes, CuI_2/ TMDEA, Bis (indolyl) alkanes, Antimicrobial activity.

Introduction

Functionalized nitrogen containing fused hetero cyclic compounds plays a key role in synthetic organic chemistry as well as medicinal chemistry and intensively used as scaffolds for development of drug moiety. Nowadays one pot multi-component reactions (MCR's) have emerged as a powerful technique for producing the molecular diversity required in the combinatorial approaches for the synthesis of bioactive fused heterocyclic compounds.

The structural moiety of indole possesses more than 3000 types of isolated natural products and effective numerous biological active systems[1-3]. So, this area has been attracted a considerable attention recent time for the development of new synthetic[4,5] and catalytic[6-11] methods leading to functionalized indole analogues with applications in drug discovery[12].

Indole is an important structural core unit of Bis(indolyl)methane derivatives (BIMs), these derivatives are isolated from marine natural sources[13] and are an important class of indole analogues showing wide range of biological activity such as antibacterial, antifungal, anti-inflammatory, among others[14]. Interestingly, BIMs exhibit to be active potent derivatives of anticancer agent and also showed anti metastatic activity. They could be actively and potentially used as chemotherapeutic agents against different forms of cancer demonstrated by the clinical studies[15].

The great significance of bisindolylmethane is due to the development of new moiety strategies for their synthesis after the pioneering work reported by Fischer in 1886.

Material and Methods

All chemicals, synthetic reagents and solvents were procured from Merck and used without further purification. All known organic compounds were identified by comparison of their spectral and physical data with those of authentic samples. The melting point of the title compound was measured by open capillary tube and uncorrected. Thin layer chromatography (TLC) was performed on UV-active precoated plates of silica gel (TLC Silica gel60 F254). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruckner AVANCE 400 MHz spectrometer operating at 400 and 100MHz respectively and $CDCl_3$ with TMS as an internal standard. Coupling constants J was reported in Hertz units (Hz). Spin multiplicities are shown as s (singlet), d (doublet), t (triplet) and m (multiplet) Elemental analyses were performed by Vario EL equipment. The molecular weights of the compounds were determined by LC-MS spectrometry.

General procedure: 25mL TMEDA is taken in a dry and clean 100mL RBF four neck which is fitted with magnetic stirrer. The mixture of substituted aromatic aldehyde (2.5mmol), indole (4mmol) and copper iodide (0.5mmol) is taken in a RBF. It was stirred at room temperature for appropriate period of time. The reaction mixture was monitored with TLC (4:6-EtOAC: n-Hexane). After completion of the time, filter the catalyst. The filtrate is poured into ethyl acetate. The mixture was washed with saturated brine solution and separate the organic layer purify and analyze. The spectral data of some of the Bis (indolyl) methane are summarized below:

Spectroscopic data:

1) 3,3'-(phenylmethylenene)bis(1H-indole(3a): Colorless solid,Yield-85%, mp:200-201^{0}C, ^{1}H-NMR (400 MHz, $CDCl_3$)δppm: 9.746 (s,2H, Indole), 7.576(d, J= 7.6Hz, 2H,Indole), 7.310-7.084 (m,10H,Ar-H), 6.245(s,2H,Indole), 5.177(s,1H,-CH-),^{13}C-NMR (100 MHz,$CDCl_3$)δppm: 137.25, 135.76(2c), 129.34, 128.72, 127.45, 126.08, 123.96

(2c), 121.08, 119.66(2c), 117.98(2c), 113.46(2c), 110.92 (2c), 51.49. LCMS(m/z); 322.55(M-H), Molecular Formula: C_{23}, $H_{18}N_2$, Elemental Analysis: Calculated: C-85.68, H-5.63, N-8.69. Obtained: C-85.62, H-5.61, N-8.75.

2) 4-(di(1H-indol-3-yl)methyl)-2-Ethoxyphenol(3b): Colorlesssolid,Yield-87%,mp:201-203^{0}C, ^{1}H-NMR (400 MHz,$CDCl_3$)δppm : 9.745 (s,2H, Indole-N-H), 8.682(s,1H,-OH),7.546(d, J = 7.0 Hz,2H,Indole-Ar-H), 7.310-6.892 (m,6H,Ar-H,Indole), 6.845 (s,1H,Ar-H), 6.812(d, J=5.6Hz ,1H,Ar-H), 6.785(d, J=5.70 Hz ,1H,Ar-H),6.548(d, J=7.61 Hz,1H,Ar-H),6.256(s,2H,pyroles), 5.175(s,1H,-CH-),4.024-3.874(m,2H,-CH_2-),0.956(t,3H,-CH_3); ^{13}CNMR (100 MHz, $CDCl_3$): 147.85, 145.05, 135.46, 130.66, 128.15(2c), 124.46(2c), 122.16, 121.96(2c), 119.37(2c), 118.08(2c), 116.76,114.87,112.76(2c),110.64(2c),52.97. LCMS**(*m/z)***; 382.39(M^+); Molecular Formula: $C_{25}H_{22,}$ N_2 O_2, Elemental Analysis: Calculated: C-78.50, H-5.80,N-7.30. Obtained: C-78.46, H-5.79, N-7.38.

3) 4-bromo-3-(di(1H-indol-3-yl)methyl)phenol(3c): Pale red solid, Yield-90%, mp:231-232^{0}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:9.925(6s2H,N-H,Indole), 8.766(s,1H,-OH), 7.584(d, J = 7.6 Hz,2H,Ar-H),7.478(d,J=7.0Hz,1H,Ar-H), 7.257-6.852(m,8H,Ar-H),6.457(s,2H, Indole),5.157 (s,1H,-CH-);^{13}CNMR(100MHz,$CDCl_3$)δppm:154.45, 140.08, 135. 39,129.66, 128.49(2c), 123.55(2c), 122.04(2c), 120.15(2c), 118.65(2c), 117.43,116.73,115.77,112.89(2c), 110.96 (2c), 51.94; LCMS(*m/z)*:418.22 (M+2); Molecular Formula: $C_{23}H_{17}BrN_2O$, Elemental Analysis: Calculated: C-66.14,H-4.10,N-6.78. Obtained: C-66.19, H-4.09, N-6.85.

4) 4-(di(1H-indol-3-yl)methyl)benzoic acid(3d): Colorless solid,Yield-88%, mp:221.223^{0}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm 11.378(s,1H,-COOH), 10.218(s,2H,N-H, pyrrole), 8.105(d, J= 5.6 Hz,2H,Ar-H),7.557(d,J=6.8Hz, 2H, Indole, Ar-H), 7.418(d, J=7.8Hz,2H,Ar-H), 7.298-6.968(m ,6H,Ar-H,Indole), 6.298(s,2H,Indole). 5.451 (s,1H, -CH). ^{13}CNMR (100 MHz, $CDCl_3$) δppm: 167.48,141.72, 137.34(2c), 130.36, 128.75, 128.04, 127.47(2c), 124.66(2c), 121.38(2c), 120.14(2c), 118.56(2c), 111.96(2c), 110.77(2c), 53.63. LCMS *m/z*; [M−H]367.03(M+H), Molecular Formula: $C_{24}H_{18}N_2O_2$), Elemental Analysis: Calculated: C-78.67, H-4.95,N-7.65. Obtained: C-78.63, H-4.94, N-7.69.

5) 4-(di-(1H-indol-3-yl)methyl)benzonitrile(3e): Pale reddish solid, Yield-86%, mp:210-212^{0}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm :10.197 (s,1H,N-H,pyrrole), 7.567(d, J=7.6Hz,2HAr-H),7.503(d, J=6.4MHz,2H,Ar-H), 7.387 (d, J=8.4 Hz, 2H,A-H), 7.242-7.096(m,6H,Ar-H,Indole), 6.325(s,2H,Pyrole),5.215(s,1H,-CH-).^{13}CNMR (100 MHz, $CDCl_3$) δ ppm :141.58, 135.72(2c), 131.35, 129.18, 127.74(2c), 123.54(2c), 120.96(2c), 119.27(2c), 118.89(2c), 117.64(2c), 113.56(2c), 110.77(2c), 52.48.LCMS *m/z* [M−H] 346.29(M-H), Molecular Formula: $C_{24}H_{17}N_3$), Elemental Analysis: Calculated: C-82.97,H-4.93,N-12.10. Obtained: C-82.93, H-4.92, N-12.18.

6) 3,3^1 -(3,4,5-Trimethoxy phenyl)methylenebis(1H-Indole)(3f): Pale yellow solid, Yield-90%, mp:197-199^{0}C, ^{1}H-NMR (400 MHz, $CDCl_3$)δppm:10.096(s,1H,-N-H,indole),7.613(d, J=6.4Hz,2H,Ar-H),7.345-7.156(m,6H, Ar-H),6.725(d, J=7.4Hz, 2H, Ar-H), 5.092 (s,1H-CH-),3.526(s,9H,(OCH_3). ^{13}CNMR (100MHz, $CDCl_3$) δppm: 151.88, 136.68(2c), 134.47, 131.35, 128.45(2c), 125.72(2c), 122.86(2c), 120.97(2c), 118.78(2c), 112.98(2c), 110.84(2c),107.4(2c), 60.09, 55.76, 53.25. LCMS[m/z] 412.38(M+), MolecularFormula:$C_{26}H_{24}N_2O_3$), Elemental Analysis: Calculated: C-76.70, H-5.25, N-67.3. Obtained: C-76.66, H-5.25, N-67.36.

7) 2-(di(1H-indole-3-yl)methyl-5-(dimethylamino)phenol (3g): Red solid,Yield-89; mp: 223–226^{0}C; 1H-NMR (400 MHz,CDCl3) δppm:10.89(s,2H,N-H,indole), 8.15 (d, J = 8.7 Hz, 2H),7.61 (d, *J* = 8.7 Hz, 2H), 7.38(d, J = 8.1 Hz, 2H),7.30(d, J = 7.9 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 2H),7.08–6.89(m,4H),5.214(s,1H,-CH-);^{13}CNMR(100MHz, $CDCl_3$) δppm: 157.68,148.46,135.25, 130.36,129.38,128.06,127.55, 126.08,124.47, 121.49, 120.36,119.62,118.86,110.73, 109.93,35.37. LCMS:381.56; molecular formulae: $C_{25}H_{23}N_3O$.

8) 3,3-((4-nitrophenyl)methylene)bis(1H-indole)(3h): Reddish solid, Yield-88%, mp:221-230^{0}C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm:10.174(s,1H-N-H,pyrrole),8.073 (d,J=7.0Hz,2HAr-H),7.517-7.029 (m,10H,Ar-H),6.397 (s, 1H,pyrrole), 5.587(s, 1H,-CH-).^{13}CNMR (100 MHz, $CDCl_3$) δppm:142.45,138.94,135.89(2c),130.86,128.03, 126.55, 124.07(2c), 122.77(2c), 120.08(2c), 118.36(2c), 115.76(2c), 112.66(2c), 50.64. LCMS [m/z]:366.18(M-H); Molecular formule:$C_{23}H_{17}N_3O_2$; Elemental Analysis: Calculated: C-75.19, H-4.66, N-11.44. Obtained: C-75.14, H-4.65, N-11.52.

9) 3,3'((2-bromo-3,5-dimethoxyphenyl)methylene)bis (1H-indole)(3i): Redsolid,mp:Yeild-92%,MP-223–226^{0}C; ^{1}H-NMR(400MHz,$CDCl_3$) δppm:10.585 (s,2H,NH,indole), 8.146(d,J=8.0Hz,2H), 7.775(d,J=7.6Hz, 2H,indole),7.437 (d,J=8.4Hz,2H,Indole), 7.287 (d,J=7.0Hz,2H,Indole),7.145 (t,J=7.0Hz,2H.Ar-H),7.102–6.924(m,4H,Ar-H),5.446(s,1H, -CH-); ^{13}CNMR(100MHz,CDCl3)δppm:162.29,158.18, 142.55,137.35, 129.53, 128.38,127.16,126.03,123.78, 121.67,120.07, 118.29,111.54,50.67, 46.75, 43.74;LCMS (m/z): 462.15(M+2); Molecular formuler: $C_{25}H_{21}BrN_2O_2$.

Biological Evaluation

Antibacterial assay: The nutrient broth was prepared in 100mL sterile conical flask and incubated with the test organisms and incubated at 30^{0}Cover night. By using a sterile pipette, 0.7 mL of the broth culture of each test organism was added to 70 mL of molten agar, it was mixed well and maintained at 35^{0}C.Test organism of sterile agar test plates was prepared by pouring inoculated medium with uniform thickness. The agar was allowed to stand and harden and wells of 5 mm diameter were cut at equidistant using a sterile cork borer. Agar plugs were removed. 100 µg/mL of

test solutions (3a–3i) were prepared in DMSO and were introduced into the wells using micropipette.

The plates were kept at room temperature for 2 h for better diffusion of solution into the medium. The plates were incubated for 36h at 35^0C. After incubation the diameter of inhibitory zones formed around each well was measured in millimeter (mm) using antibiotic zone scale. The assay was carried out in duplicate. DMSO was used as control and the antibacterial activity of the test compounds was compared with standard "streptomycin".

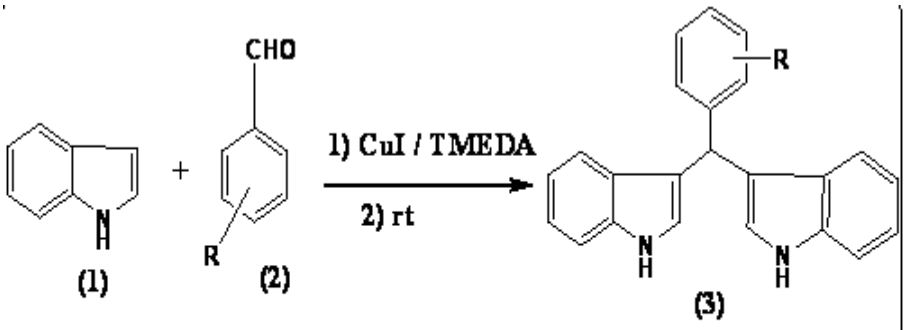
Antifungal assay: Sterile molten potato dextrose agar (PDA) medium was inoculated with 50 µg/mL of fungal spore suspension aseptically and maintained at 45^0C temperature. The inoculated medium was mixed well and poured immediately in sterilized Petri plates. Then five wells of 6 mm diameter were punched using sterile borer and filled with 100 µg/mL of test compounds (3a-3i) as well as sterile DMSO 100% as negative control. Plates were incubated for 24 h at 35^0C. Antifungal activity was determined by measuring the zone of inhibition. The zones produced by the test compounds were compared with the "ketoconazole".

Results and Discussion

Initially substituted aromatic aldehyde (1.5mmol) reacted with indole (2mmol) for the synthesis of Bis (indolyl) Methane. We observed that copper iodide is an effective catalyst in TMDEA as solvent for this reaction. It is an important point of view after completion of the reaction; the catalyst can be separated by simple filtration in subsequent reactions without significant decrease in activity. It is clear that it is economically beneficial procedure for the synthesis of bis (indolyl) methane in presence of copper iodide and TMEDA as solvent.

We observed that the reaction of substituted aromatic aldehyde with indole (1.25:2 molar ratios) was investigated to optimize the reaction conditions with respect to molar ratio of catalyst to the substrate and Lewis acid catalyst. It was observed that 75 mol% of catalyst was sufficient to obtain the titled bis(indolyl)methane in 85-92% yield within 20 min in TMDEA solvent at reflux. Various substituted aldehyde were studied under optimized conditions to understand the scope and generality of this procedure (Table 1).

To determine the appropriate concentration of the catalyst CuI, we investigated the model of the reaction at different concentrations of catalyst, i.e. 0.1, 0.2, 0.3, 0.4, 0.5 and 1 mol%. The product yielded from different concentrations was 64%, 71%, 78%, 83%, 92% and 92% respectively. It was observed that the product yield remained constant at 92% when concentration of the catalyst was increased from 0.5 to1 mol%. This indicates that 0.5 mol% of CuI is sufficient for the best result considering the reaction time and yield of product. The results are summarized in table 1.



Scheme 1: Synthesis of BIS (Indolyl) methaneanalogs

Table 1
Optimization of catalyst at different concentrations (catalyst %) for the Preparation of (3i).

S.N.	Catalyst	No. of moles(%)	Reaction Time	Yeild (%)
1	CuI	0.1	60	64
2	CuI	0.2	45	71
3	CuI	0.3	35	78
4	CuI	0.4	20	83
5	CuI	0.5	10	92
6	CuI	1	10	92

Table II
Optimization of different solvents for the synthesis of derivative"3i".

S.N.	Catalyst	Solvent	Time(hrs)	Yeild(%)
1	CuI	H_2O	15	66
2	CuI	K_2CO_3/H_2O	12	58
3	CuI	DMF	5	70
4	CuI	THF	8	73
5	CuI	TMEDA	≤1 hr	92

Reaction Conditions: 1.Mole (%) is 0.1, Reaction time 60 min, Room Temperature; 2. Mole (%) is 0.2, Reaction time 45 min, Room Temperature; 3. Mole (%) is 0.3, Reaction time 35min, Room Temperature. 4. Mole (%) is 0.4, Reaction time 20min. 5.Mole (%) is 0.5, Reaction time 10min and 6.Mole (%) is 1, Reaction time is 10min.

The various solvents used during the reaction, percentage of product yield as well as time of the reaction were developed. It is observed that aqueous medium and base such as K_2CO_3 are used, the reaction time is more as well as percentage of yield is low. Other solvents like DMF and THF are used in this reaction and then time of the reaction reduced and percentage of the reaction improved. During the reaction, TMEDA is used as solvent. The reaction time and product percentage increased compared with remaining solvents before used as shown in table II.

Interestingly, the catalyst was effectively used for the synthesis of bis(indolyl)methane from indole and substituted aromatic aldehyde (Scheme). The reaction of 2 equivalents of indole with 1.25 equivalent substituted aromatic aldehyde proceeded successfully to scaffold bis(indolyl)methane (I) with good to an excellent yield. The chemical structures of (3a–i) were confirmed by ^{1}H,^{13}C NMR and LCMS mass spectral data. The –COOH proton showed a singlet in region 11.378. The–NH protons gave a singlet in the region and the methoxy protons at 3.646 of the derivative"3i" and 3.526 of the derivative "3f". The alkenes protons gave a singlet in the region of 6.73–6.31. Similarly, the Ar-CH– protons also gave a singlet in the region of 5.587–5.092, methyl protons showed triplet at 0.956.

The ^{13}C NMR value gave 162ppm of the compound "3i". The molecular weight peaks exhibited (M+2) value of the derivatives "3C" and "3i".

Bio evaluation

Antimicrobial activity: The newly synthesized and well characterized compounds (3a-3i) were evaluated for *in vitro* antibacterial activity against gram positive bacteria, gram negative bacteria and antifungal activity against *Aspergillus niger*, *Candida albicans* and *Aspergillus favus* using agar well diffusion assay and zones of inhibition of the test compounds were expressed in mm as shown in table III and table IV.

Antibacterial activity: The *in vitro* antibacterial activity of the newly synthesized compounds (3a-3i) was compared with standard" streptomycin'' as in table III. As observed in table III, most of the newly synthesized compounds generally showed activity against all the tested bacterial strains. Compound "3b, 3f and 3i" exhibited excellent antibacterial activity against gram-positive bacterial strains viz. *E.coli*, *P.aeruginosa* and gram negative bacterial strains viz. *B.subtilis* and *Staphylococcus aureus* respectively.

Table III
Antibacterial activity of the newly synthesized compounds (3a-3i):
Zones of inhibition (mm) of compounds (3a–3i) against tested bacterial strains:

Compound	Anti Bacterial Activity			
	Gram(+ve) bacteria		Gram(-ve) bacteria	
	Escherichia coli	*Pseudomonas aureoginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
3a	09	08	12	10
3b	20	22	22	21
3c	19	18	20	22
3d	15	13	16	18
3e	07	10	11	13
3f	21	22	24	23
3g	15	12	17	19
3h	17	15	16	19
3i	23	22	25	23
Streptomycin	27	27	30	30
DMSO				

Streptomycin was used as standard.
Values are average of three readings

The derivatives 3c, 3d, 3g and 3h exhibited moderate to good potent activity against bacterial strains. The compounds ”3a and 3e” showed low activity against bacterial stains due to compounds having highly electron withdrawing groups. These results indicated that the compounds having electron releasing groups showed moderate to good activity than the compounds having electron withdrawing groups. The compounds containing halogen atoms showed excellent active potential against antibacterial strains.

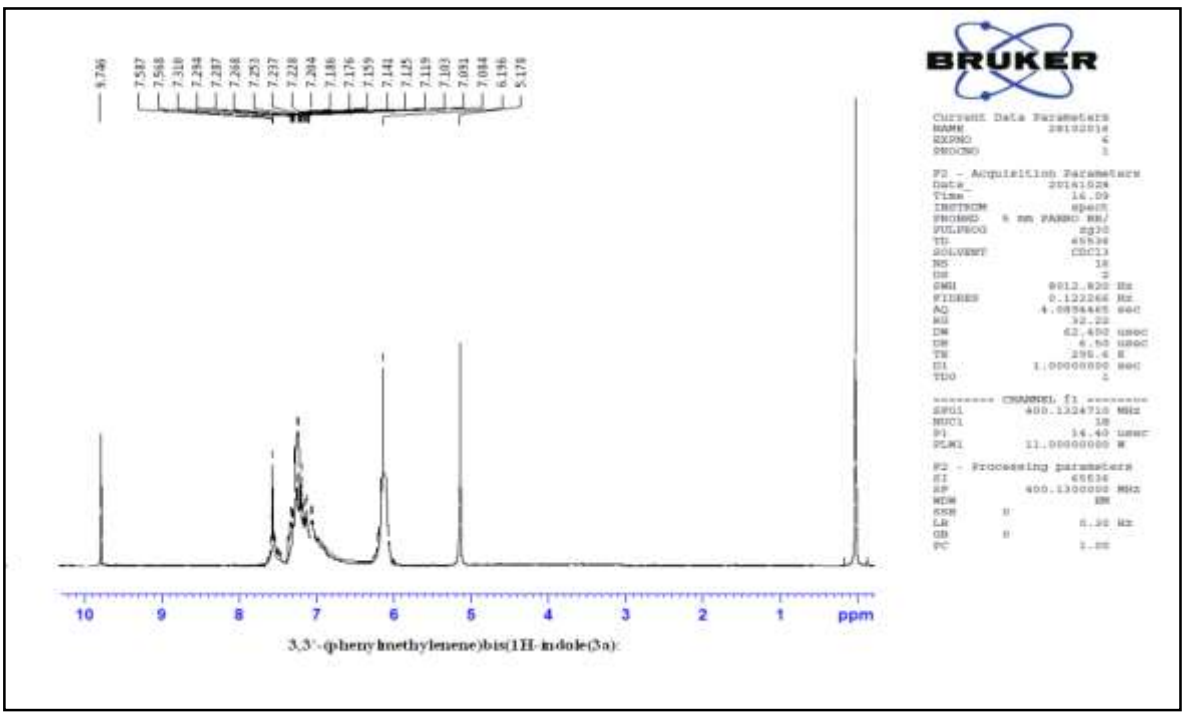
Antifungal activity: The *in vitro* antifungal activity of the newly synthesized compounds (3a-3i) was compared with standard drug” Ketonozole.’’ as shown in (Table-IV). The *in vitro* antifungal activity of the titled derivatives(3a-3i) was investigated against *Aspergillus niger*, *Candida albicans* and *Aspergillus favus* using agar well diffusion assay and zones of inhibition of the test Compounds were expressed in mm as shown in table IV. Compounds “3h” as well as ’3i” and “3c” exhibited significant activity against the fungal strain. The compounds “3d” and”3e” were found to be moderate to good active against tested fungal strain.

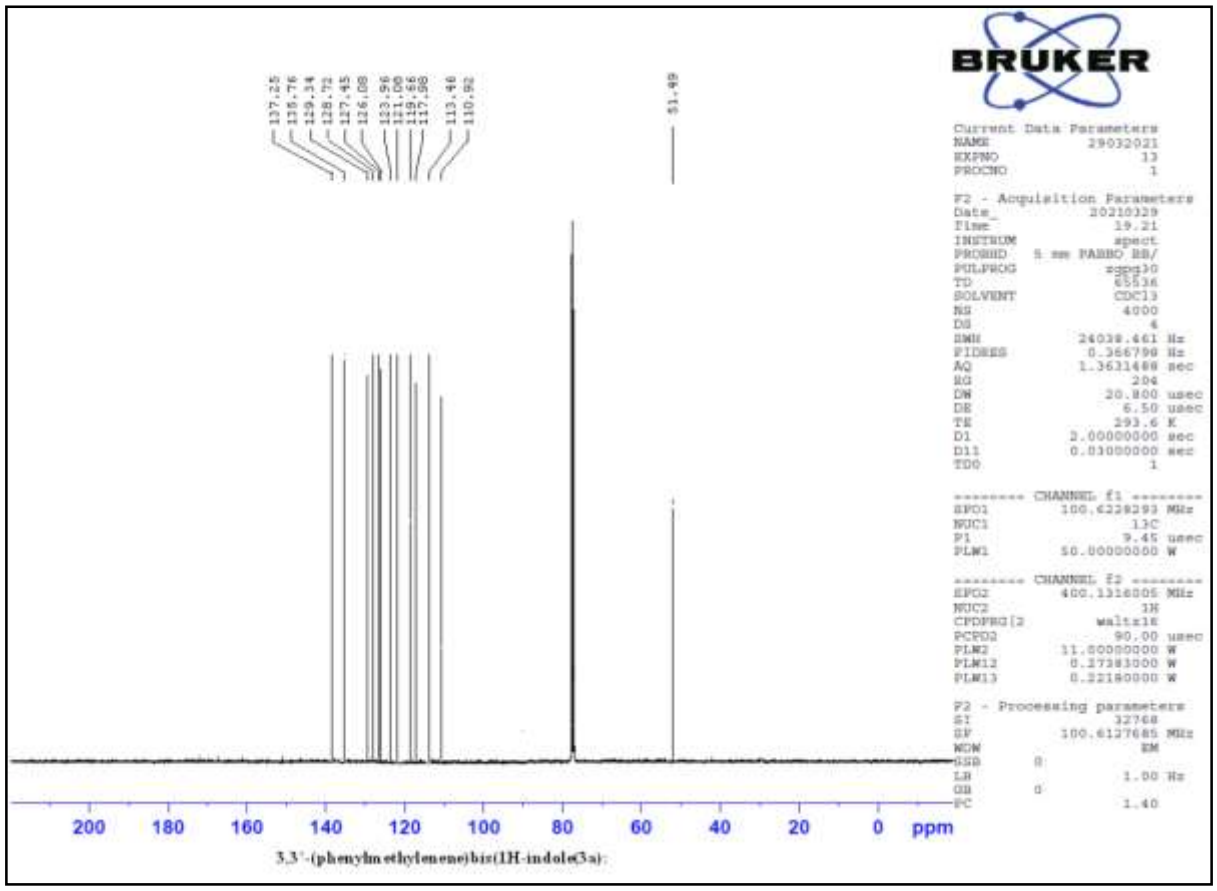
Compounds “3a”,”3b”,”3g” and “3f” have demonstrated low fungal activity compared to standard. Therefore, the results indicated that most of the compounds exhibited significant activity and few are moderately active as shown in table IV. The remaining derivatives showed moderate potent activities against *Aspergillus favus*. These results prove that the compounds possess electron donating groups exhibiting moderate activity while the compounds having electron attracting groups exhibited moderate to good against the fungal stains.

Table IV
Antifungal activity of the synthesized compounds (3a-3i)
Zones of inhibition (mm)[a] of compounds (3a–3i) against tested fungal strains:

Entry	Anti Fungal Activity		
	Aspergillus Niger	***Aspergillus favus***	***Candida albicans***
3a	08	09	11
3b	11	13	14
3c	18	20	18
3d	13	12	14
3e	16	14	16
3f	12	09	11
3g	10	12	09
3h	20	21	21
3i	19	20	20
Ketonozole	25	25	25
DMSO			

Values are the average of three readings.
Ketoconazol was used as standard.

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119.66
117.98
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110.92
51.49
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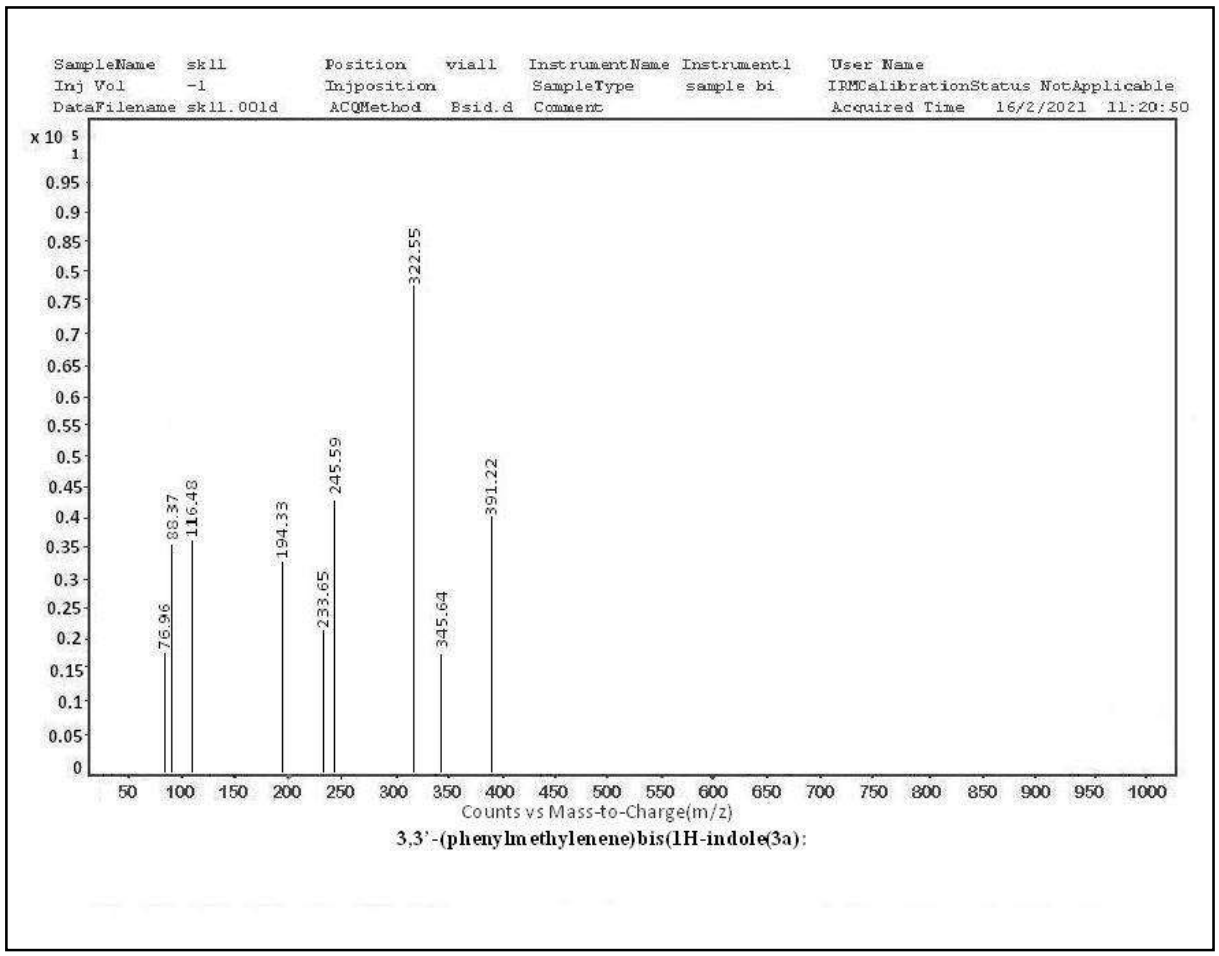
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88.37
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Counts vs Mass-to-Charge(m/z)
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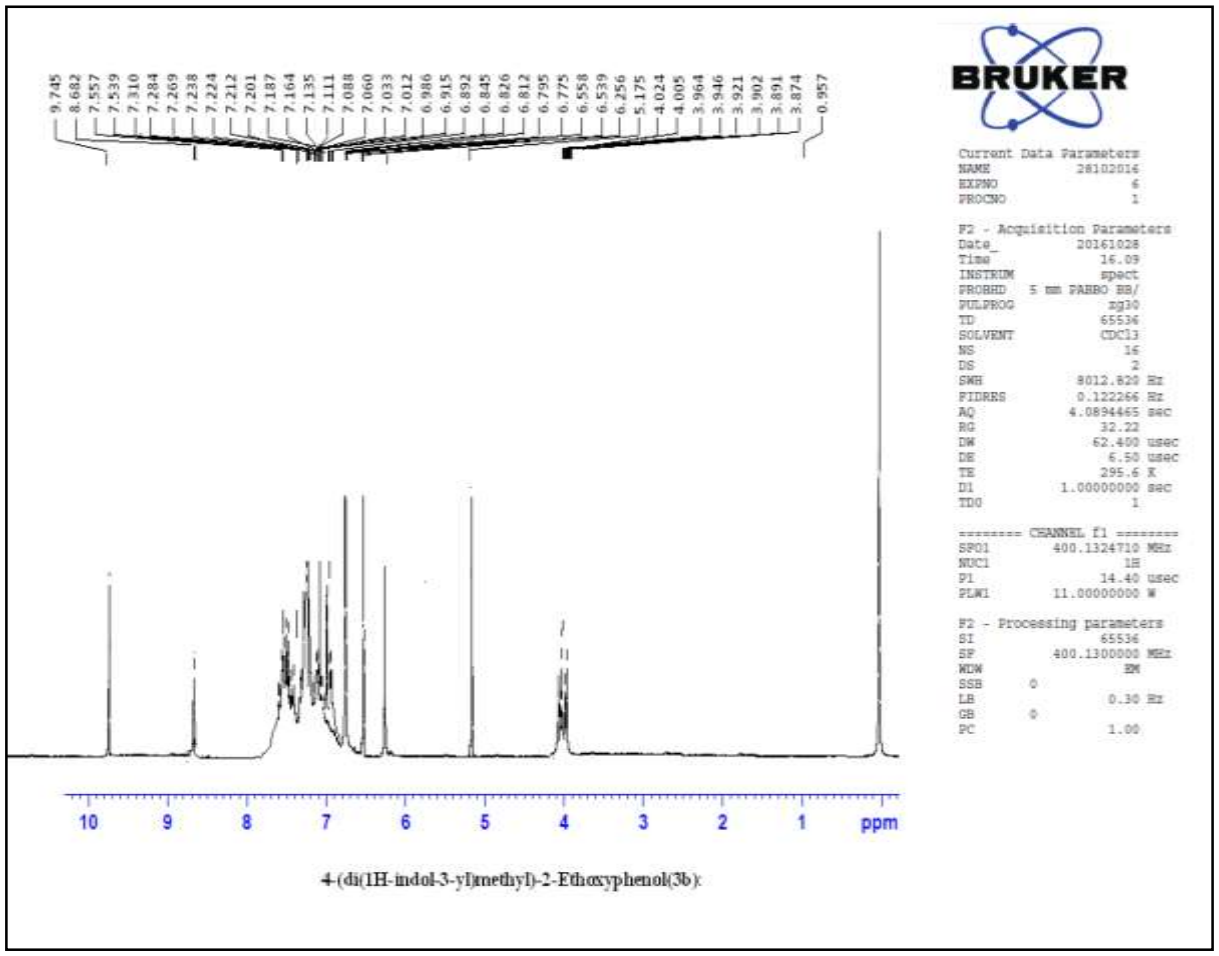
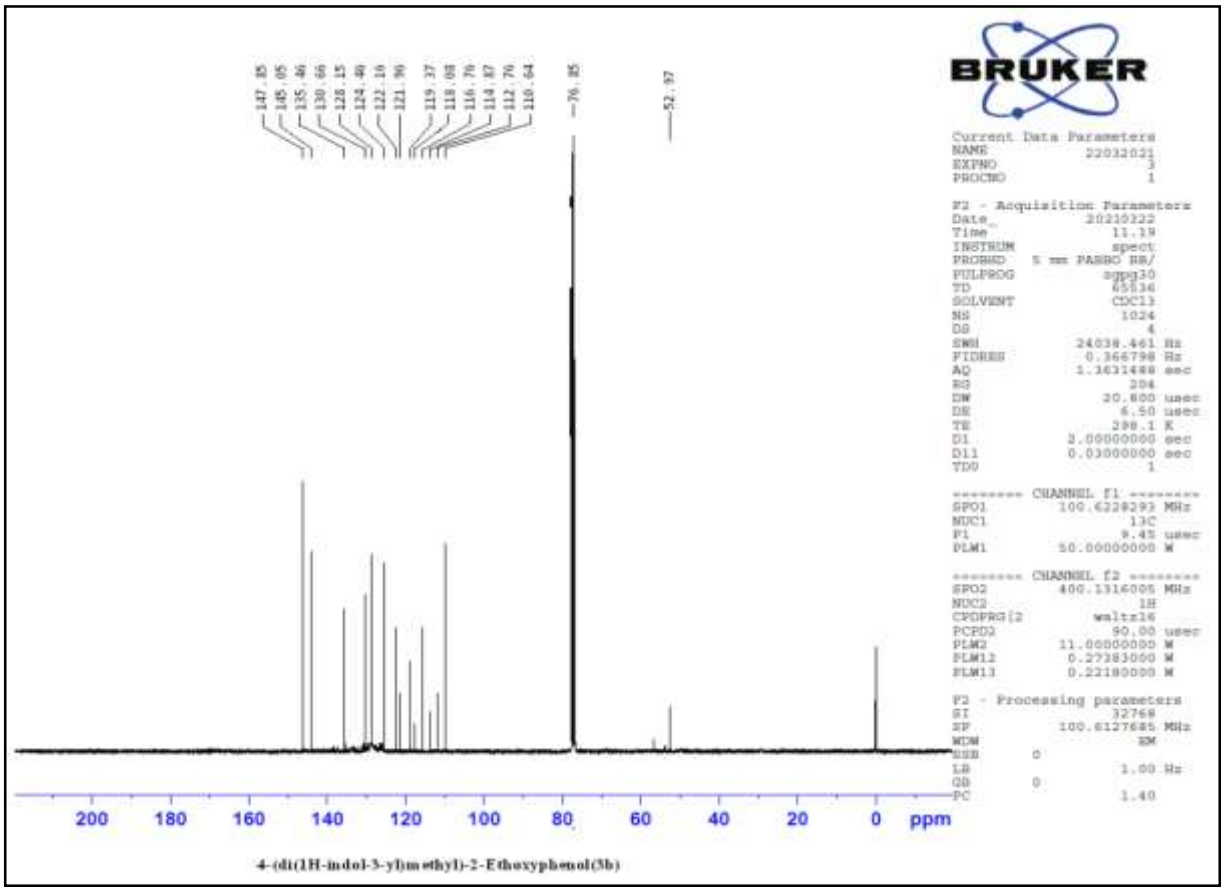


4-(di(1H-indol-3-yl)methyl)-2-Ethoxyphenol(3b)



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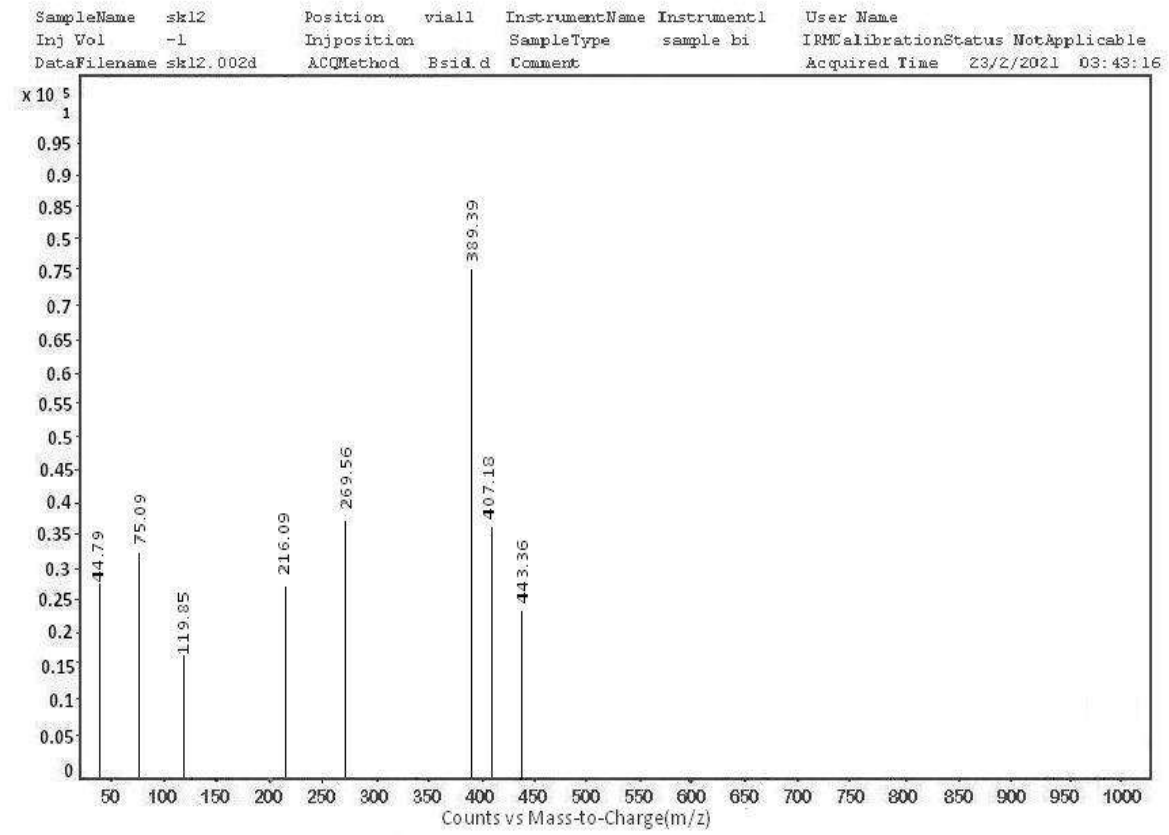

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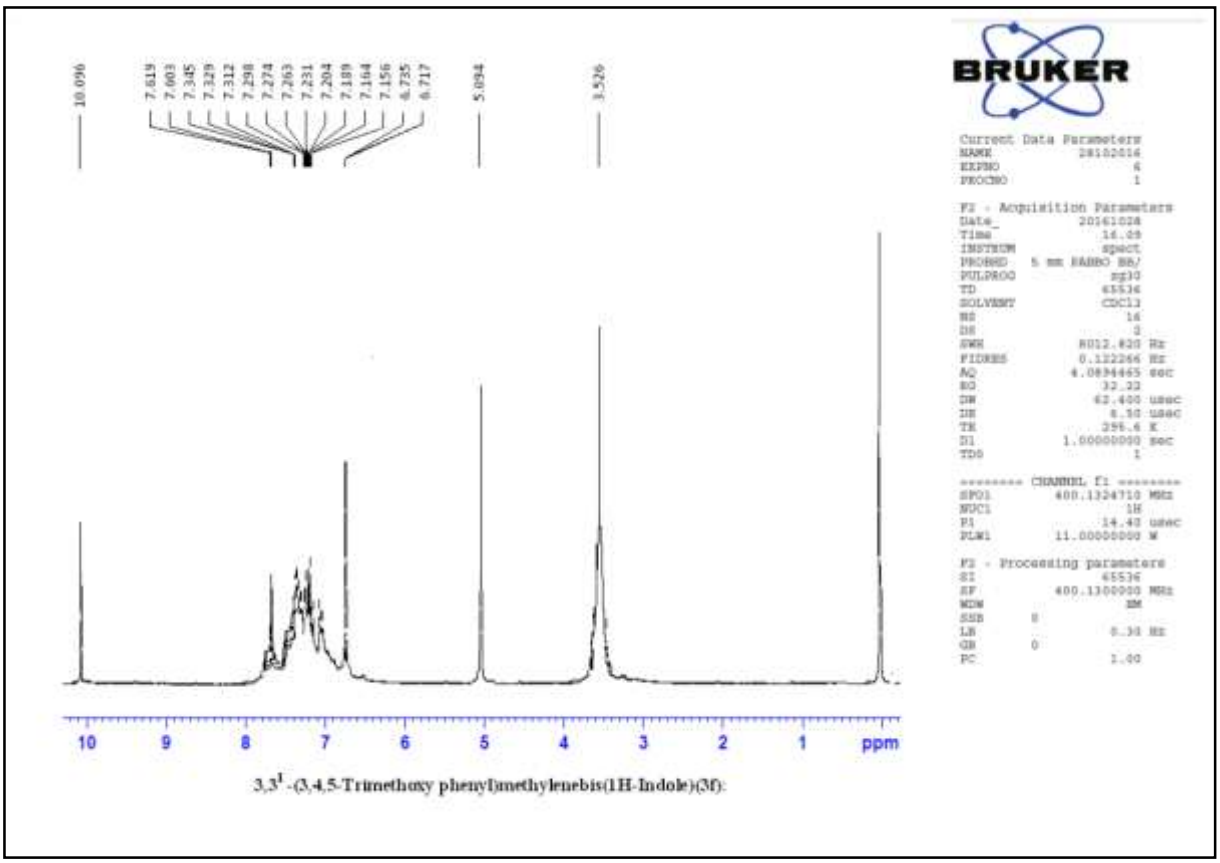
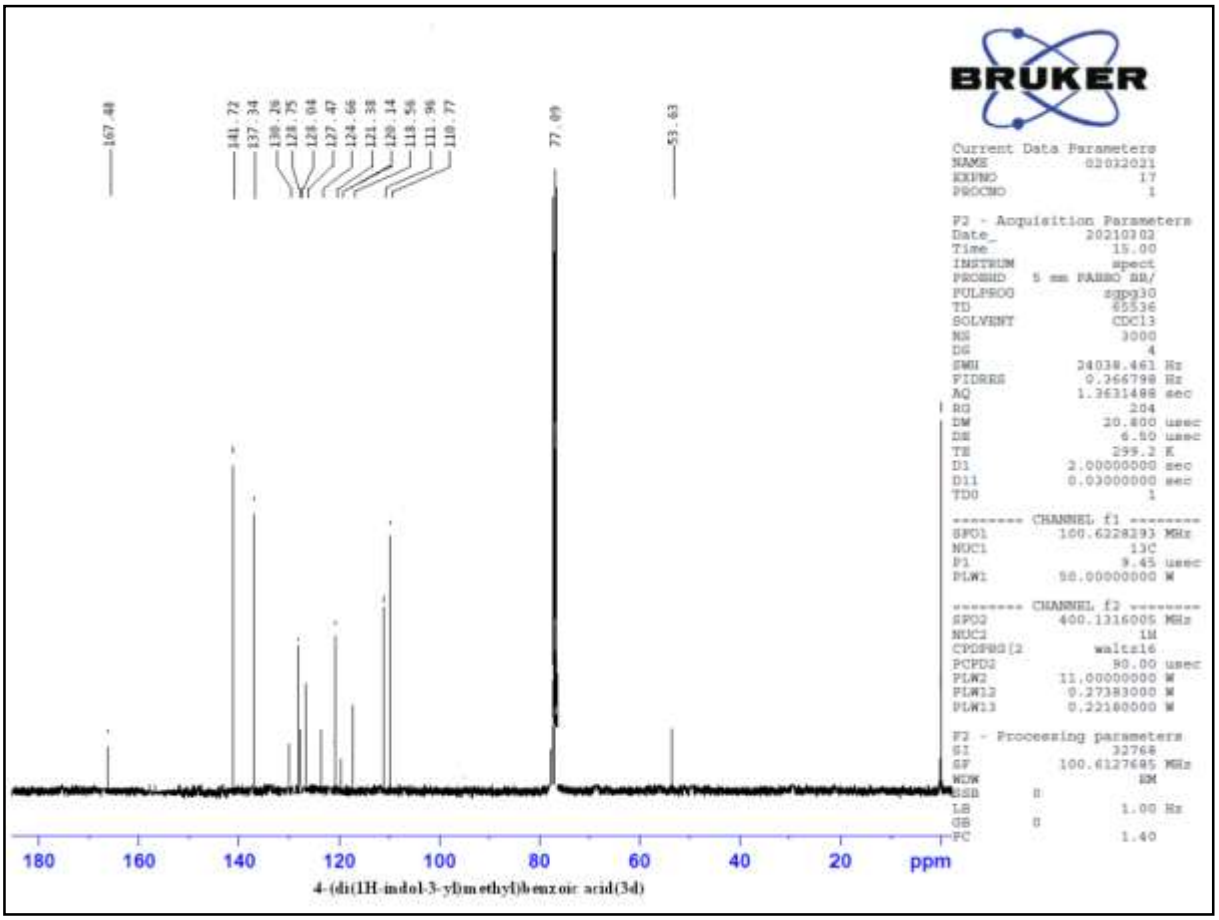


3,3^1-(3,4,5-Trimethoxy phenyl)methylenebis(1H-Indole)(3f):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137.34
130.26
128.75
128.04
127.47
124.66
121.38
120.14
118.56
111.96
110.77
77.09
53.63
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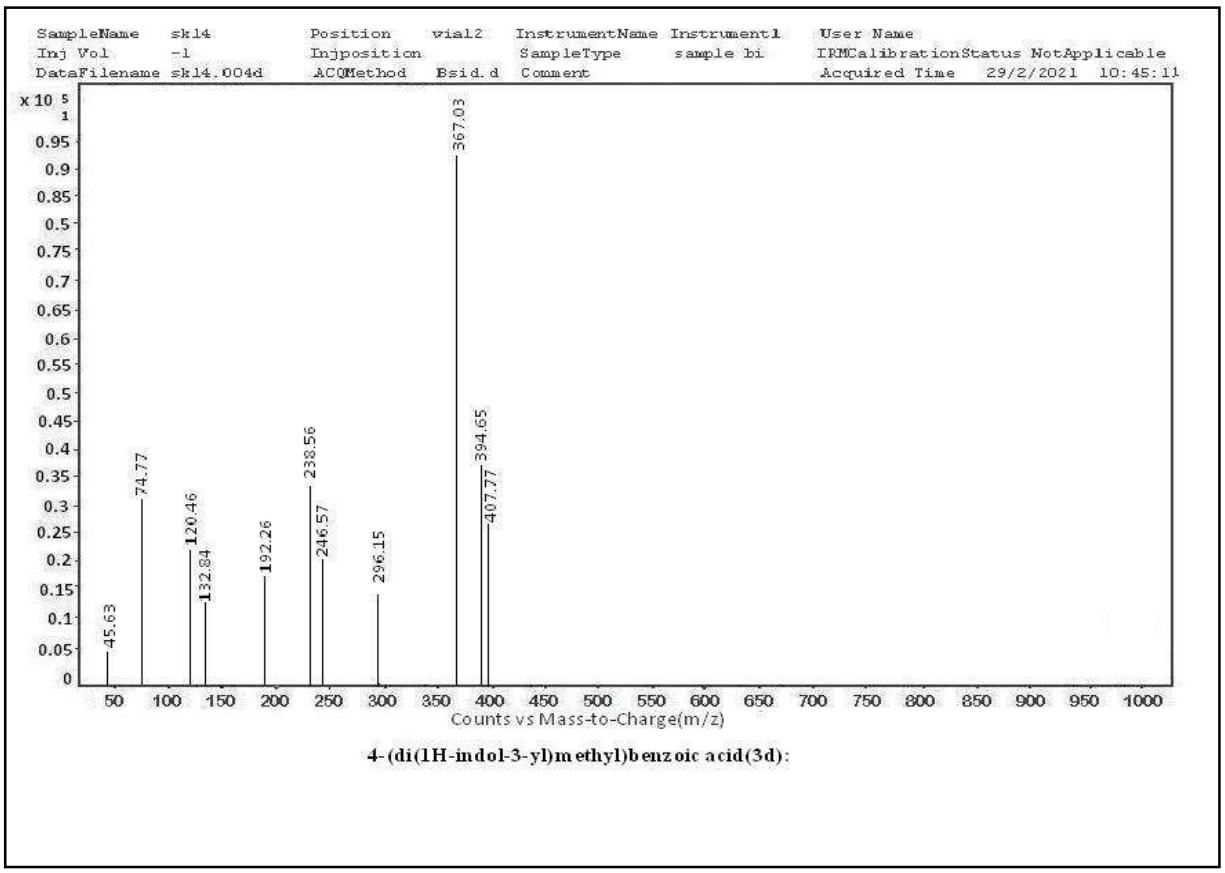
140
120
100
80
60
40
20
ppm
4-(di(1H-indol-3-yl)methyl)benzoic acid(3d)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74.77
120.46
132.84
192.26
238.56
246.57
296.15
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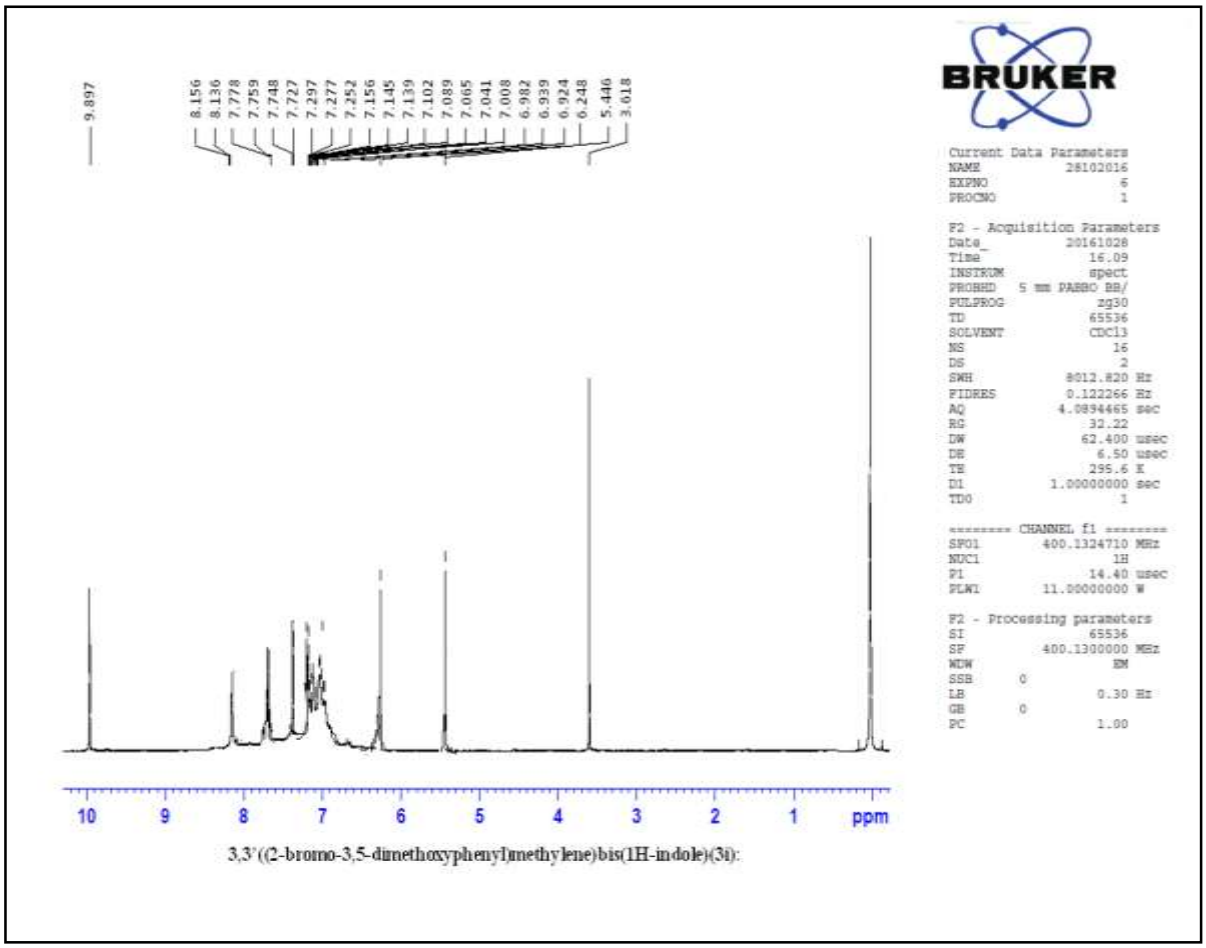
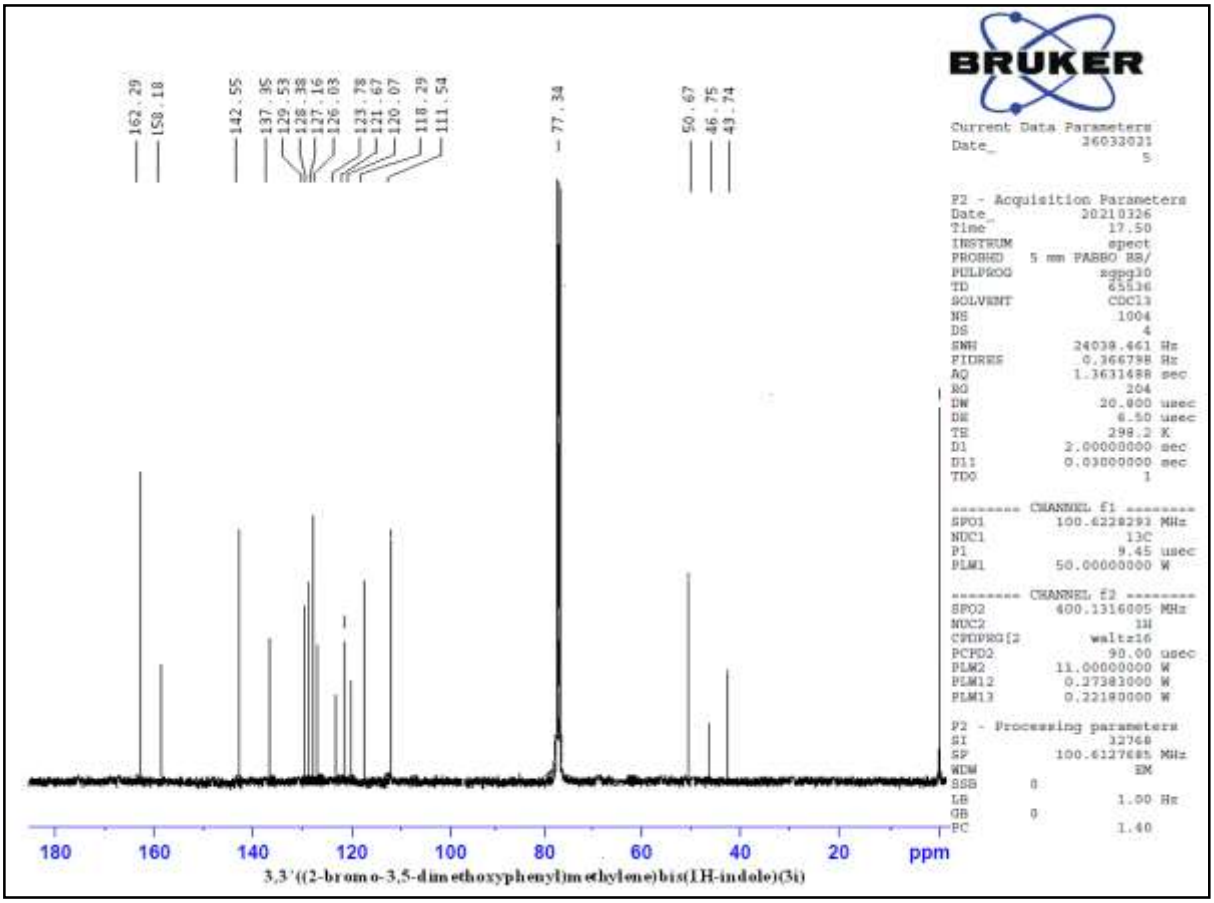
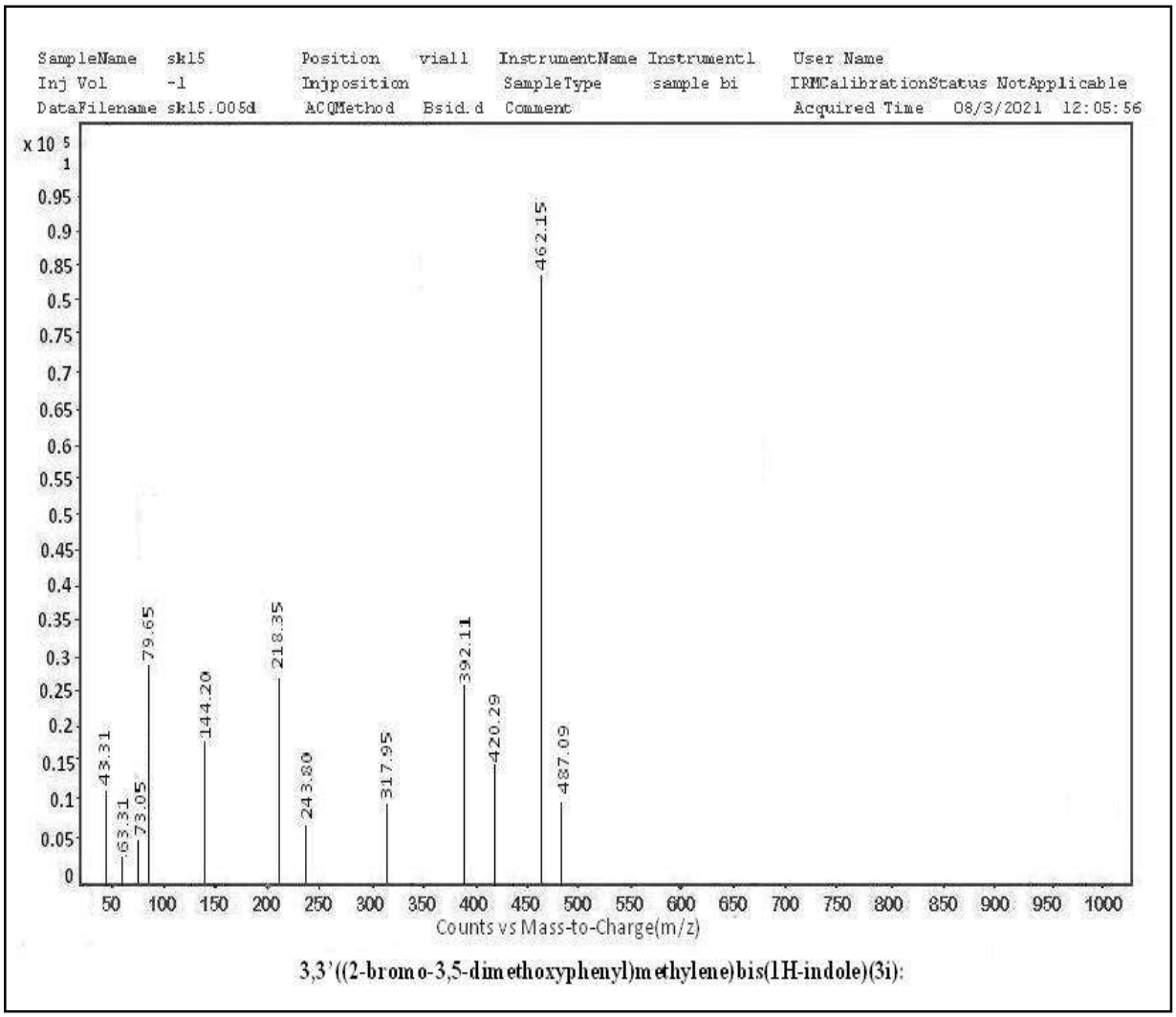
394.65
407.77
Counts vs Mass-to-Charge(m/z)
4-(di(1H-indol-3-yl)methyl)benzoic acid(3d):



3,3'((2-bromo-3,5-dimethoxyphenyl)methylene)bis(1H-indole)(3i):



3,3'((2-bromo-3,5-dimethoxyphenyl)methylene)bis(1H-indole)(3i)



Conclusion

We reported for the synthesis of BIM approach of CuI catalyzed addition of indole to substituted aromatic aldehyde to give good yields. This catalytic system is active under mild reaction conditions and is effective for wide application in the synthesis of aromatic substituted bisindolylmethane derivatives. In this reaction, the small amount of catalyst is used. Anti microbial activity of titled products exhibited different values of the different compounds. The compound bearing halogen substitution as well as electron donating group substituent exhibited excellent potent activity.

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IMPACT OF COVID-19 PANDEMIC ON INDIAN ECONOMY: AN ANALYSIS

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Abstract: The outbreak of Covid-19 pandemic in China in 2019 is such one type of worst impact on world after influenza in the decade of 1911-20. The socio-economic conditions of every country and every person are affected by covid-19. The lockdown imposed by almost all countries in the world to prevent the virus spread, worsened the daily life of human beings.. There is decline in growth rate, production, employment opportunities, business transactions and increase in inflation etc. are economically impacted aspects. Due to the Covid-19 pandemic, the Governments have to take various measures like lockdown, diverting the funds to increase the health facilities, medicines and vaccines, support the front warriors financially and morally. The world economic growth rate declined as well as of India. This article is intended to understand the Covid-19 pandemic origin, spread worldwide, to assess the impact on Indian Economy and to know the sectoral changes in India during the Covid-19 pandemic. As per the data revealed by the Ministry of Statistics, India's growth rate was fallen to 3.1 percent in the Quarter 4 of the 2020 Financial Year. The unemployment has risen to 26% in April, from 6.7% in March 2020. The Indian economy was likely to lose $4.5 billion every day during the first phase of lockdown period from 25 March to 14 April 2020. The economic loss expected to almost $2.8 trillion in the country during complete lockdown period. The area sown under Kharif and Rabi crops and the production of wheat and rice has been steadily increasing over the years. The area sown under food grains in the Kharif cycle of 2021-22 was higher (743 Lakh Hectars) than in the previous year (732 Lakh Hectars). During the first lockdown period in March 2020, the industrial output declined in core industry and indices. All the sectors in Services registered negative growth in the covid-19 period. The negative growth is very high in respect to Trade, hotels, transport, communication and services related to broadcasting with -18.2 in 2020-21. Anyhow, the Covid-19 made learnt new things in all sectors of economy viz. work from home, online payments, increased use of technology, health awareness, telemedicine, social distance, online teaching and learning.

Index Terms: Covid-19, Indian Economy, Agriculture, Industries, Services

1. INTRODUCTION: There is proverb that History Repeats. The outbreak of Covid-19 pandemic in China in 2019 is such one type of worst impact on world after influenza in 1911-20 decade. After 100 years almost such type of pandemic reoccurred. It is a biggest blow to world economy after the great economic depression, 1929-30. It has an impact on world in all aspects that the modern world history may be written as world before covid-19 and after. The countries irrespective of developed and under developed suffered a lot with the pandemic. Even the advanced countries with well equipped health facilities are also unable to control and cope with up in facing the pandemic. In this case the situation of middle income and poor countries is worse in the battle against the covid-19. The socio-economic conditions of every country and every person are affected by covid-19. The lockdown imposed by almost all countries in the world to prevent the virus spread, worsened the daily life of human beings. Of course, like the two sides of coin, covid-19 has impact of positive as well as negative on the world. There is decline in growth rate, production, employment opportunities, business transactions and increase in inflation etc. are economically impacted aspects. There are anxiety, loneliness, quarrels in the families, decrease the human relations etc., found in social impact. In health sector, practicing experimental methods on patients, costly treatment in hospitals, following the indigenous treatments other than Allopathy i.e. Ayurvedic, Naturopathy, Unani, Siddha, Homoeopathy are utilized by the public, research and development of medicine and vaccines, Awareness on health issues also enhanced in the country. The social media plays vital role in spreading the positive and negative information worldwide such a speed than the virus spread. In India also, covid-19 has impact in all the above aspects. Repeated waves of infection, supply-chain disruptions and, more recently, inflation have created particularly challenging times for policy-making. The Government of India's immediate response was a bunch of safety to cushion the impact on vulnerable sections of society and economic sector (Economic Survey 2021-22). The Government of India has taken many precautions and economy boosting activities to minimise the impact of Covid-19 on Indian Economy.

2. REVIEW LITERATURE: The Covid-19 pandemic is causing unprecedented disruptions to economic activities across countries worldwide, and India is no exception. The complete lockdown and presently the ongoing partial lockdowns have both demand-side and supply-side effects on the Indian economy. On the supply side, the restrictions of movement of goods, services and personnel affect the production networks (Sahoo and Ashwani, 2020). The impact of the virus spread to lead to a huge loss as international trade is mostly affected. The Indian growth model generally depends on the export-led-growth (Mishra, 2019). It can be noticed sever impact on Indian Economy due to the lock down. It is expected to plunge in a range of 13–32 per cent under

optimistic and pessimistic scenarios, respectively on the international trade (WTO, 2020). McKibbin and Fernando (2020) used the Computable General Equilibrium (CGE) modeling and explained that global GDP would be reduced by around US$ 2.4 trillion in 2020 under a low-end pandemic taking in to consideration the Hong Kong Flu as a reference point. Ozili and Arun (2020) revealed the spillover effects of Covid-19 and opined that the lockdown and social distancing measure of virus controlling led to the shutdown of financial markets, corporate offices, businesses, industries and events which in turn may have significant impact on the economy. International Labour Organization (ILO) estimated the total value added of industrial enterprises in China declined by 13.5% during the first 2 months of 2020 (National Bureau of Statistics of China, 2020). There are numerous projections and estimations by institutions and research scholars impact of Covid-19 pandemic on the economic aspects. In its latest estimations in June 2020, IMF projected that the global economy may shirk by 4.9% to almost three times more than Global Financial Crisis and the Indian economy is likely to witness 4.5% negative growth for the 2020.

3. STATEMENT OF THE PROBLEM: Due to the Covid-19 pandemic, the Governments have to take various measures like lockdown, diverting the funds to increase the health facilities, medicines and vaccines, support the front warriors financially and morally. The economic activities are almost minimized due to lockdown which leads to low production, shut down of marginal firms, removal of employees from work. The world economic growth rate declined as well as of India. As the world economies connected with foreign trade, the Globalization acted as medium of worsening the economies of various countries in the pandemic period. In India also the covid-19 pandemic brought changes in all sectors of economy. The agriculture, industry and services sectors in India are adversely affected by Covid-19 pandemic. The long march of migrant labours in India from the place of work to their home places during lockdown, in which time of transport system and the toll of deaths in the journey, shows the severity of the Covid-19 pandemic. The decline of the stocks of food and related items, increase in rate of inflation, non availability of works to do, no wages etc. deeply worsened the state of poor people in country. In this back drop, it is oblige to study the sectoral changes and impact of Covid-19 pandemic on Indian Economy.

4. OBJECTIVES: This article is intended

- To understand the Covid-19 pandemic origin, spread worldwide
- To assess the impact on Indian Economy
- To know the sectoral changes in India during the Covid-19 pandemic

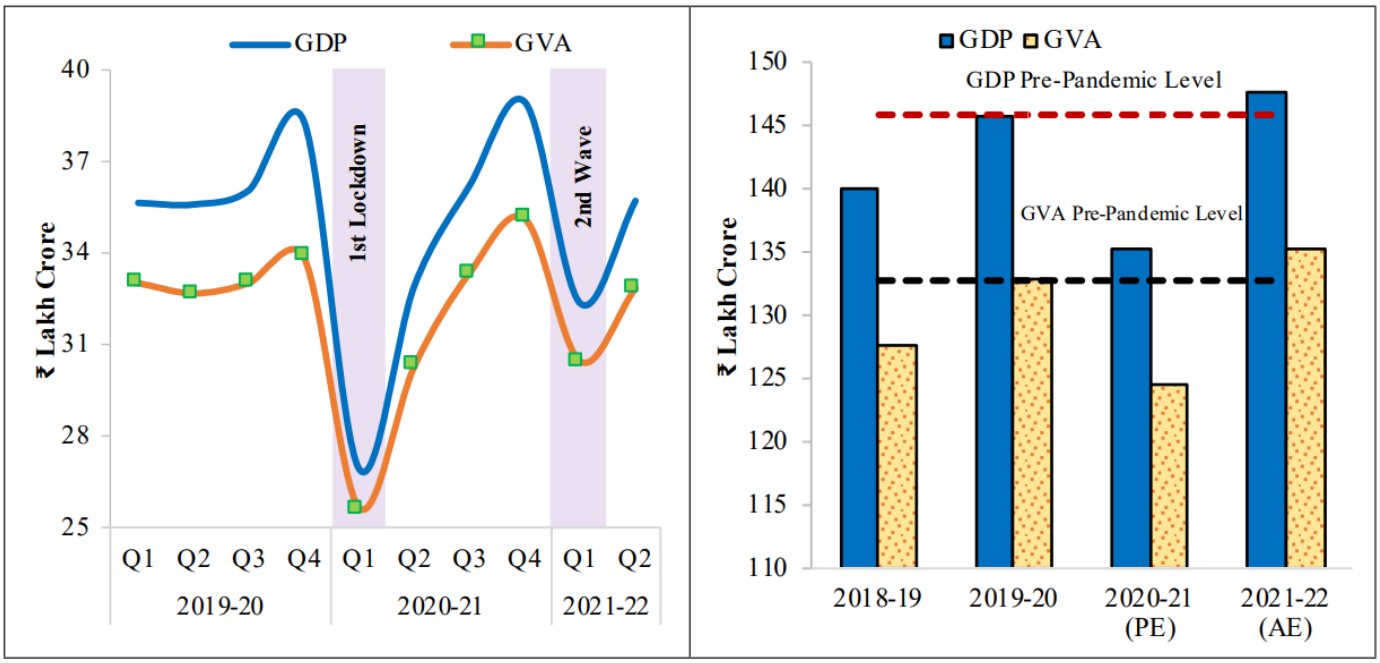
5. METHODOLOGY: The present study is based on the secondary data collected from various Journals, Text Books, News Papers, Reports and Websites etc. And, different published and unpublished data of Public and Private Institutions are also referred. The data analyzed and assessed the impact of Covid-19 pandemic on Indian Economy.

6. COVID-19: Covid-19 is a contagious disease caused by a newly discovered corona virus (Novel Corona Virus) called SARS-CoV-2. The first case of Novel Corona Virus (Covid-19) was reported in the month of December, 2019 in Wuhan province, China. Then it has very fast spread all over the countries in the world. The people affected by the novel corona virus would develop mild to moderate respiratory illness depending upon their immunity power and health status. In general, children and older people are more vulnerable to covid-19 as they have low immunity power. People with reported health problems such as heart disease, diabetes, chronic respiratory disease like pneumonia and cancer are also more vulnerable to be attacked by corona virus. The symptoms of Novel Corona Virus are cough, fever, shortness of breath or difficulty in breathing, muscle or body aches, sore throat, loss of taste or smell, diarrhea, headache, fatigue, runny nose and nausea or vomiting etc. Though, the 98% of the Covid-19 positive cases are reported recovery, many are losing their life to the virus due various causes. There is still no perfect vaccine for corona virus, people are advised to maintain social distancing, frequent washing of hands and wearing of the face mask to prevent them from the virus infection and spreading (World Health Organization, 2020). These precautions only protect the people from Covid-19 pandemic.

7. IMPACT ON INDIAN ECONOMY: The Lockdown has put an immediate end to almost all economic activities nationwide. The fluctuations of demand and supply, taken place during the lockdown, are continuing though the lockdown has been lifted. It will take time to the Indian Economy to return to its normal state. As per the data revealed by the Ministry of Statistics, India's growth rate was fallen to 3.1 percent in the Quarter 4 of the 2020 FY. The unemployment has also risen to 26% in April 2020 from 6.7% in March 2020. Almost 140 million people lost their employment during the lockdown period and others got salaries cut. The Indian economy was likely to lose $4.5 billion every day during the first phase of lockdown period from 25 March to 14 April 2020. The economic loss expected to almost $2.8 trillion in the country during complete lockdown period.

Figure 1 reveals the Gross Domestic Output's fluctuations during Covid-19 period. It can be seen the 'V' shaped growth rate in GDP. The GDP has declined in First Quarter of 2020-21 due to Lockdown and then recovered. Again in First Quarter of 2021-22 GDP declined. It has been staging a sustained recovery since the second half of 2020-21 in Indian Economy. Though the second wave of the Covid-19 pandemic in April - June 2021 was more severe from a health point of view, the economic impact was muted compared to the national lockdown of the previous year. Advance estimates suggest that GDP will register an expansion of 9.2 per cent in 2021-22. It shows that the level of real economic output will surpass the pre-Covid level of 2019-20 (Economic Survey, 2021-22).

Figure 1: Gross Domestic Output (Constant Prices, Base Year: 2011-12)



Source: Economic Survey 2021-22

Table 1: Annual Growth of GVA at constant (2011-12) prices (per cent)

Sectors	2019-20 (1st Revised Estimates)	2020-21 (Provisional Estimates)	2021-22 (1st Advance Estimates)	Recovery over 2019-20.
1. Agriculture & Allied Sectors	**4.3**	**3.6**	**3.9**	**107.7**
2. Industry	**-1.2**	**-7.0**	**11.8**	**104.1**
Mining and Quarrying	-2.5	-8.5	14.3	104.6
Manufacturing	-2.4	-7.2	12.5	104.4
Electricity, Gas, Water Supply & Other Utility Services	2.1	1.9	8.5	110.5
Construction	1.0	-8.6	10.7	101.2
3. Services	**7.2**	**-8.4**	**8.2**	**99.2**
Trade, Hotels, Transport, Communication & Services related to Broadcasting.	6.4	-18.2	11.9	91.5
Financial, Real Estate and Professional Services	7.3	-1.5	4.0	102.5
Public Administration, Defence & Other Services	8.3	-4.6	10.7	105.6
GVA at basic price	**4.1**	**-6.2**	**8.6**	**101.9**

Source: NSO

The Table 1 shows the Annual Growth Rate of GVA at constant prices of 2011-12. Due to Covid-19 pandemic situation and lockdown, the Agricultural Sector and Allied Sectors recorded decline growth rate from 4.3 in 2019-20 to 3.6 in 2020-21 and slightly increased to 3.9 in 2021-22. The industrial Sector was already in minus growth rate -1.2 in 2019-20 to further more minus growth -7.0 in 2020-21. This sector recovered in 2021-22 with a growth rate of 11.8 recording the 104.1 recovery over 2019-20. The Mining & Quarrying and manufacturing recorded negative growth while Electricity, gas, water supply & other utility services and Construction recorded positive growth during the Covid-19 pandemic period. In the case of Service sector, there is decline in growth rate to -8.4 in 2020-21 compare to that of 7.2 in 2019-20. Again the services sector recovered with 8.2 in 2021-22. All the sectors in Services registered negative growth in the covid-19 period. The negative growth is very high in respect to Trade, hotels, transport, communication and services related to broadcasting with -18.2 in 2020-21. Financial, real estate & professional services and Public administration, defence and Other Services are also registered negative growth in 2020-21. Later the services sector recovered with a 99.2 recovery over 2019-20. The GVA is declined with -6.2 growth rate in 202-21 compared to that of 4.1 in 2019-20. And, it registered as growth rate 8.6 in 2021-22 with a recovery of 101.9 over 2019-20.

8. IMPACT ON AGRICULTURE SECTOR: The covid-19 pandemic shown adverse impact on Agriculture and Allied activities. Due to the shutdown of hotels, restaurants, tea stalls, and transport restrictions reduced the demand for fresh agricultural commodities. The farmers in general and the farmers producing perishable commodities such as fruits and vegetables in particular faced problems in marketing their produce as transport facilities are stopped. During the lockdown period, perishable agricultural commodities such as fruits and vegetables were become wasted. And, the farmers were unable to harvest and send those commodities to market. Most of the farmers sold their produce at low price to get some revenue in the local market. The wage rate has declined as migrant workers came from cities to rural areas. There is a notion that rural people would be get infection to the Covid-19 contacting the returned migrant workers. However, it is observed that the spread of the virus is not as fast as expected in the urban areas as the density of population is low in rural areas. When compared with urban people the ability of the rural people is low in meeting their health expenditure, hence, they lack in copping the virus infection. Enough vigilance should be given in containing the virus infection in the rural areas (Sahoo and Ashwani, 2020).

Figure 2 : Area Sown under Food Grains

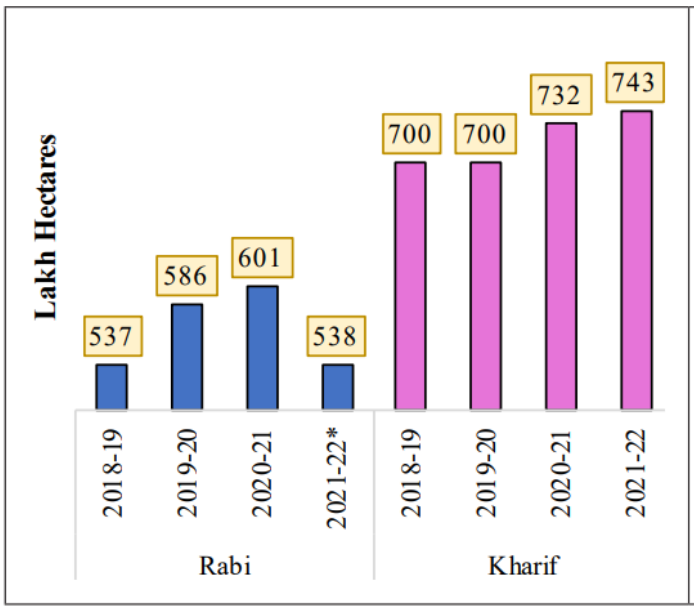
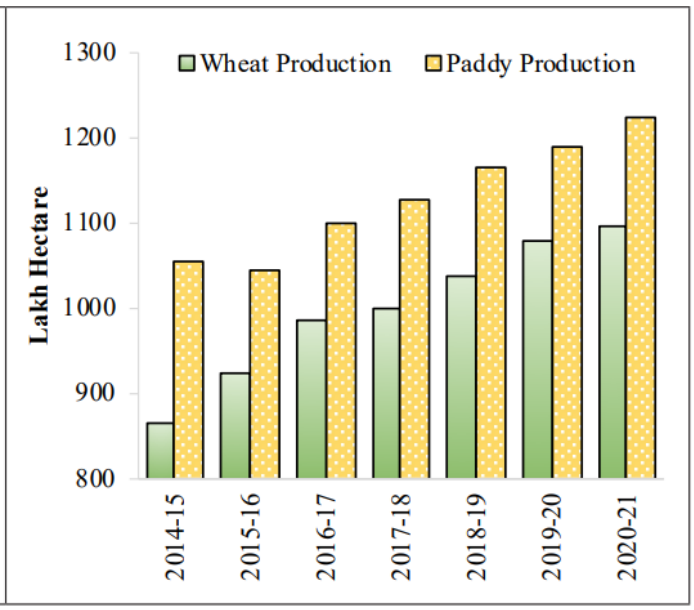


Figure 3: Production of Wheat and Rice



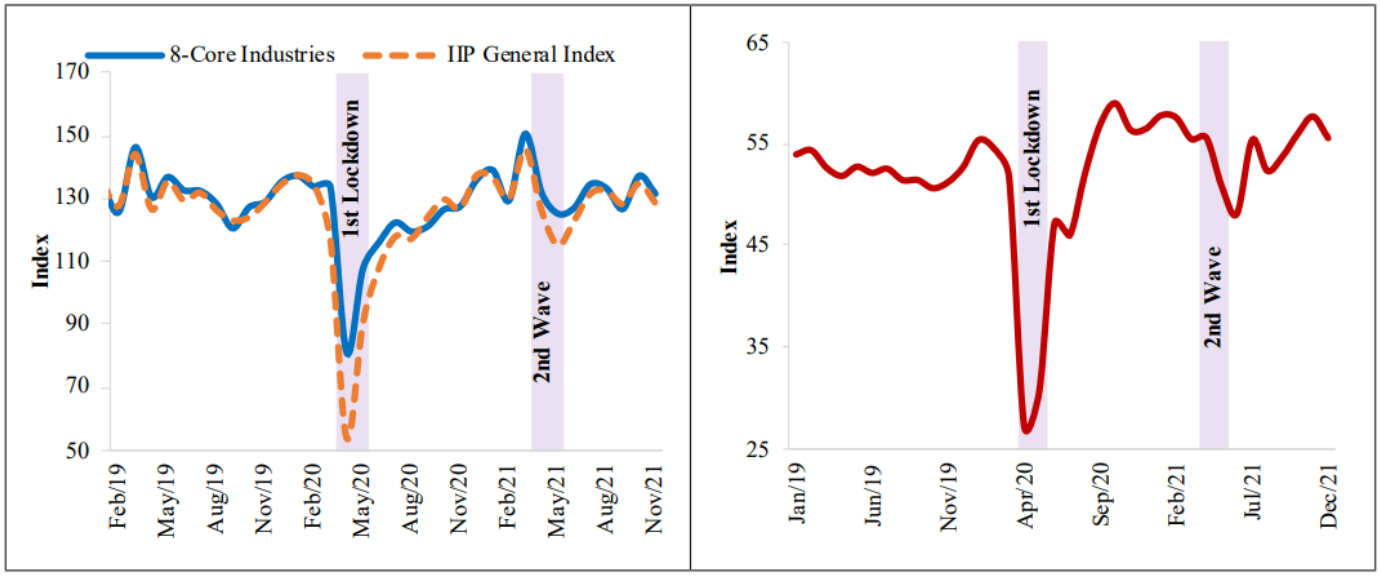
Source: Economic Survey 2021-22

As shown in Figures 2 and 3 above, the area sown under Kharif and Rabi crops and the production of wheat and rice have been steadily growing over the years. The area sown under food grains in the Kharif cycle of 2021-22 was higher (743 Lakh Hectars) than in the previous year (732 Lakh Hectars). In the current year, food grains production for the Kharif season is estimated to post a record level of 150.5 million tonnes. The national wide policy of procurement of food grains under the central pool maintained its increasing trend in 2021-22 along with minimum support prices (MSP) which promises for national food security and farmers' incomes (Economic Survey, 2021-22).

The Government of India has taken a number of policy measures to protect the agriculture and allied sectors from the adverse impact of the Covid-19 pandemic situation and lockdown. Rs.1 lakh crore was allotted for the agriculture sector. Rs. 20,000 crores was allotted for the welfare of the fishermen. Rs.10,000 crores was allotted for the improvement of the micro food industries. Rs.15,000 crores was allotted for the development of animal husbandry. Rs.4,000 crores was allotted for the promotion of herbal cultivation. Rs.500 crores was allotted for the development of beekeeping with many other initiatives and Rs.500 crores was allotted to improve the marketing infrastructure for the fruits and vegetables. Government is continuously taking many initiatives to protect the agriculture sector. However, the steps taken by the Government is inadequate, Government should increase its spending for pandemic relief to meet the needs of the agriculture sector to ensure the higher growth rate of the agriculture sector in the coming period (Balamurugan P., 2021). Then only the Agriculture sector may fully recovered.

9. IMPACT ON INDUSTRIAL SECTOR: In the month of November, 2021, the Index of Industrial Production (IIP) and Core Industry indices have both followed a similar pattern and went past their pre-pandemic level for the corresponding month of 2019. Figure 4 shows the Industrial Output trends. During the first lockdown period in March 2020, the industrial output declined in core industry and indices. The Purchasing Managers' Index-Manufacturing, which is widely used, has remained in the expansionary zone (i.e. over 50) since January 2021 except for one month when the second wave had slowed down economic activity as shown in Figure 5 below.

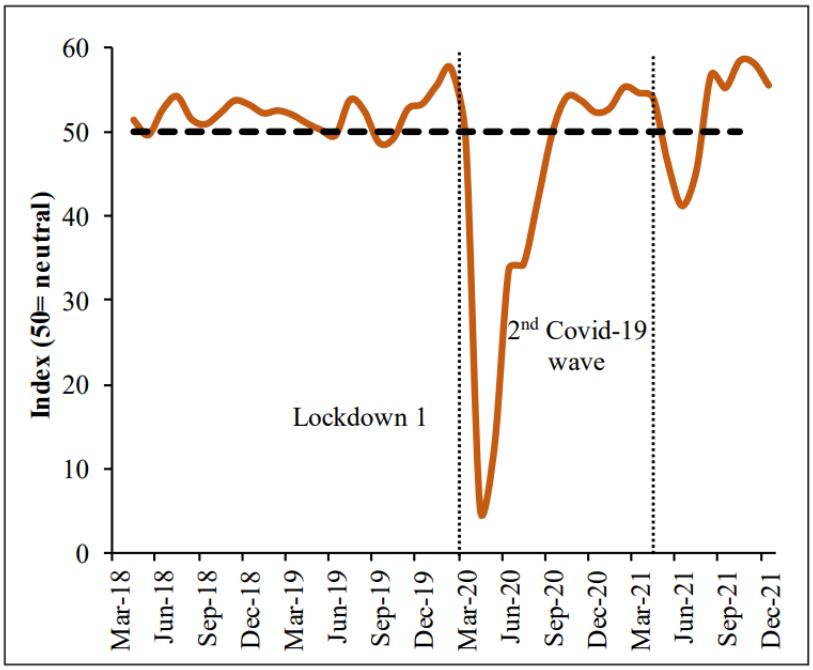
Figure 4: Industrial Output Figure 5: PMI Manufacturing



Source: Economic Survey

10. IMPACT ON SERVICE SECTOR: Services sector is accounting for more than half of the Indian economy's GDP. It was the most impacted sector by the COVID-19 related restrictions, especially for activities that need human contact. Although, the service sector first contracted by 8.4 % in 2020-21, it is estimated to grow by 8.2% in 2021-22. It may be noted that there is a wide dispersion of performance by different sub-sectors in Services. Both the Finance and Real Estate and the Public Administration areas are recovered and now well above pre-COVID levels. However, segments like Travel, Trade and Hotels are yet to fully recover. It should be added that the stop-start nature of repeated pandemic waves makes it especially difficult for these sub-sectors to gather. There is increase in Services GVA with the trend in high frequency indicators such as Purchasing Managers Index (PMI) Services Index, freight and passenger traffic point to a pickup in economic momentum (Economic Survey, 2021-22). As shown in Figure 6, Services PMI Index shows a steep decline during First Quarter of 2020-21 FY due to lockdown and then recorded a recovery stage in remaining Quarters. And, in Second Quarter of 2021-22 FY also it is registered as light decline in Services PMI Index.

Figure 6: Services PMI Index



Source: Economic Survey 2021-22

11. CONCLUSION: The covid-19 pandemic originated in China and spread worldwide in a short period and shown adverse effect on almost all economies in the world. In India also we can see the changes in all sectors in economy due to covid-19 and lockdown to control the spread of virus. Among the three sectors in Indian Economy, only Agriculture and Allied sector registered slightly declined growth rate during Covid-19 pandemic period whereas other sectors i.e. Industrial and Services Sectors registered negative growth rate in its sub sectors also. Later in 2021-22, all the three sectors recovered over the situation in 2019-20. Anyhow, the Covid-19 made learnt new things in all sectors of economy viz. work from home, online payments, increased use of technology, health awareness, telemedicine, social distance, online teaching and learning.

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ONE POT SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF METHYL- 6-METHYL-4-PHENYL-2-THIOXO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE

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ABSTRACT

The present work deals with the exploration of chemistry and medicinal diversity of pyrimidine-2-thiones. An efficient three component one pot synthesis of Methyl-6-methyl-4-phenyl -2-thioxo-1, 2, 3, 4-tetrahydro pyrimidineidin-5-yl)ethanone based on the reaction of readily available substituted aryl aldehyde, active methyl group of compound and thiourea, followed by camphor sulphonic acid as catalysed cyclocondensation. The desired products are prepared in excellent yield under mild, solvent less condition. The structure of the desired products has been analysed by their advanced spectroscopic data ^{1}HNMR, ^{13}CNMR and LCMS spectral data and also structural determination was calculated by elemental analysis. In addition to examined the biological activity.

KEYWORDS: Substituted aryl aldehyde, acetylacetonate, thiourea, camphorsulfonicacid, cyclocondensation antimicrobial activity.

1. INTRODUCTION

Six-member heterocyclic compounds containing nitrogen compounds have been play an important role in synthetic and medicinal chemistry. Heterocyclic compounds are possesses

with at least two different or same elements as ring members' atoms, the commonest atoms include nitrogen, oxygen and sulphur. The existence of several naturally occurring hetero cyclic compounds viz; as hormones, antibiotics, caffeine etc. are abundance in nature and are very significant in our lives.

Literature survey represented that the partially reduced pyridine and derivatives of Pyrimidines which having anti-hypertensive property of the clinically used calcium channel blockers such as nifedipine, amlodipine have 1,4-dihydropyridine ring system possess methyl carboxylate side chain at 3rd position of compound of pyrimidines and its derivatives. Pyrimidine thiones represents a broad range of compounds which have acquired to considerable attention due to their biological properties activities.[11-14] In addition to the chemistry and the synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione have attracting wide spread attention in recent years. The present popularity of these tetrahydropyrimidines thiones is mainly because of their close structural relationship to the clinically important dihydropyridines such as calcium-channel blockers and related compounds.[15-22] The tetrahydropyrimidine-2-thione is known as versatile heterocyclic compound that has been subjected to a major variety of structural modification in order to synthesized derivatives with different biological properties. Pyrimidines derivatives possessing anti-inflammatory and analgesic activities have been reported in the literature.[23-30] In addition to the a aforementioned activities, Pyrimidine thiones and its derivatives containing antitumor[31], antimicrobial.[32] Antibacterial[33], antifungal[34] and anti-infective[35] activities have also been reported in the literature. The various synthetic approaches have been reported for the synthesis of fused heterocyclic Pyrimidine thiones derivatives[36-38] organic and medicinal chemistry. The main three component one pot reactions are acquiring importance for different reasons. Synthesis of 5-acetyl-1, 2, 3, 4-Tetrahydro pyrimidine-2-thiones by Biginell's reaction is one among them. This protocol is an brownstd acid catalyzed three component reaction between an substituted aryl aldehyde, 1,3-dicorbanyal components and Thiourea. The Pyrimidines skeleton available in a wide range variety of natural available compounds and also in clinically useful molecules having diverse biological activities and here it is great importance to Chemistry and Biology. Organic reactions under solvent free conditions are of interest from both industrial and academic viewpoints.

2. METHODS AND MATERIALS

All the synthetic grade reagents and chemicals were purchased from Sigma Aldrich. These chemicals, solvents and reagents were used without further purification. The melting points of newly synthesized compounds were measured by Agarwal thermometer in open capillaries and are uncorrected. ^{1}H NMR and ^{13}CNMR spectra were recorded on a Brucker 400MHz spectrometer using $CDCl_3$ as solutions. Chemical shifts are measured given in ppm relative to TMS, multiplicative are reported as singlet(s),doublet (d), triplet(t), quartet (q), some consideration of these, multiplicative (m). Molecular weight of the newly synthesized compounds were recorded by LCMS spectrometer. Elemental analysis was performed on a Carlo ErbaEA 1108 elemental analyzer. Reaction mixture was monitored on Merck aluminium thin layer chromatography (TLC, UV254nm) plates. Visualisation was accomplished either an UV chamber (or) in Iodine Vapour. Coloumnchromotogrphy was carried out on silica gel (100mesh) Merck chemicals.

2.1. General Procedure

The synthesis of the Methyl 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate-2-thiones derivatives from a mixture of methyl acetate, substituted aromatic aldehyde and thiourea in the presence of camphor sulfonic acid was stirred and heated at RT for 2hrs. The reaction mixture was checked by thin layer chromatography (4:6 = ethyl acetate: n-hexane**).** After completion of the reactants were consumed during the completion of the reaction conditions by using thiourea. The reaction mixture poured in a beaker containing ethyl acetate and washed with saturated solution of sodium bicarbonate. The distillation of organic solvent in crude and compound was recrystallized from ethanol.

2.2. Characterisation

1) Methyl 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (4a)

Yield: 84%, yellow solid; mp (ºC): 225-227 ;**^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm:9.287(1H, s, NH-1), 8.874 (1H, s, NH-3), 7.487-7.273 (5H, m, Ar-H), 5.104 (1H, d, J = 7.6Hz, CH), 3.662 (s,3H, OCH_3), 2.247 (s,3H, CH_3); **^{13}C NMR (**100 MHz, $CDCl_3$): δ ppm:176.45, 165.66, 146.58, 142.83, 128.59, 127.76, 126.94, 101.82, 54.17, 49.48, 16.85; LC-MS (m/z) : = 262.45. **Molecular formulae**: $C_{13}H_{14}N_2O_2S$.**Elemental Analysis**: calculated: C- 59.54, H-5.38. N-10.67, Obtained: C-59.47, H-5.37, N-10.74.

2).Methyl4-(4-hydroxy-3,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate(4b).

Yield: 90%, pale-yellow solid; m.p (ºC): 224-226;^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.155 (1H, s, NH-1),8.815(1H, s, NH-3), 7.984 (1H, s, OH), 6.817 (2H, s, Ar-H), 5.012 (1H, d, J = 7.2Hz, CH), 3.571 (s,3H, OCH_3), 3.558 (s,3H,OCH_3), 2.114 (s,3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$)δppm:174.88,166.76,148.16,143.68, 136.38,133.77, 103.78, 101.24, 55.97, 54.84,49.68,17.86;LC-MS(m/z):338.38;.**Molecularformule**:$C_{15}H_{18}N_2O_5S$..**Elemental Analysis**:calculated:C-53.25, H-5.36.N-8.29,Obtained:C-53.18,H-5.35,N-8.35.

3).Methyl4-(3,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4c)

Yield: 92%, yellow solid; m.p (ºC): 223-225; ^{1}H NMR (400 MHz,$CDCl_3$)δ ppm: 9.148 (s,1H, NH-1),8.794 (s,1H, NH-3), 6.948 (d, J =6.8Hz,2H, Ar-H), 6.472 (t, J = 7.6Hz, Ar-H), 6.987 (d, J =7.2Hz,1H, -CH-), 3.615 (s,6H, OCH_3),3.665 (3H, s, OCH_3), 2.124 (s,3H, CH_3); ^{13}CNMR(100MHz,$CDCl_3$)δppm:176.89,164.56,158.65,145.64,145.80,103.35,100.87,98.82, 54.69,52.44,51.88,17.04;LC-MS(m/z)=322.38.**Molecularformule**:$C_{15}H_{18}N_2O_2S$.**Elemental Analysis**:calculated:C-55.84,H-5.62.N-8.68,Obtained:C-55.78,H-5.61,N-8.76.

4).Methyl4-(3, 4, 5-trimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4d)

Yield: 94%, yellow solid; m.p (ºC): 218-219; ^{1}H NMR (400 MHz,$CDCl_3$)δppm : 9.117(s,1H, NH-1),8.964(s,1H,NH-3),6.557(s,2H,Ar-H),5.106(d,J=6.4Hz,1H,-CH),3.668(s,9H,OCH_3), 2.227(s,3H,-CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm;176.01,165.58,151.97,146.36,138.05, 135.63,103.78,101.72,60.59,55.84,53.87,48.37,17.58;LC-MS(m/z)=352.47. **Molecular formule**: $C_{16}H_{20}N_2O_5S$.ElementalAnalysis:calculated:C-54.54,H-5.71.N-7.96,Obtained:C-54.46,H-5.70,N-8.05.

5).Methyl4-(4-acetamidophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4e).

Yield: 86%, pale-yellow solid; m.p (ºC):232-233;^{1}H NMR(400 MHz, CDCl3) δ ppm: 9.272 (s,1H, NH-1), 9.039 (s,1H, NH-3), 8.998 (s,1H,$NHCOCH_3$),7.894 (d, J = 8.0Hz,2H, Ar-H), 7.218 (d, J = 8.0Hz,2H Ar-H), 5.118 (d, J =7.6Hz, -CH), 3.517 (s,3H,- OCH_3), 3.312 (s,3H, CH_3),2.129(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:174.98,166.75,163.87,145.88, 138.17,136.84,127.58,118.87,100.84,52.54,50.57,23.45,17.81;LC-MS:(m/z)=319.02.

Molecularformule: $C_{15}H_{17}N_2O_2S$. **ElementalAnalaysis**: calculated: C-56.45, H-5.36.N-13.15, Obtained: C-56.38,H-5.35,N-13.21.

6).Methyl4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4f):

Yield: 90%, yellow solid; m.p (ºC): 212-214; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:9.446 (s,1H, NH-1), 9.126 (s,1H NH-3), 7.454(d, J = 8.8Hz,2H, Ar-H), 7.218 (t, J = 7.6, 2H,Ar-H), 5.102(d, J = 7.0Hz,1H,-CH-), 3.558 (s, 3H,-OCH_3), 2.247(s,3H,- CH_3); 13C NMR (100 MHz, $CDCl_3$)δppm: 175.88, 165.72, 161.78, 145.56, 139.44, 128.77, 115.28, 100.18, 53.86,50.45,17.83;LC-MS(m/z)=280.24.**Molecularformule**:$C_{13}H_{13}FN_2O_2S$.**Elemental Analysis**: calculated: C-55.71,H-4.67.N-9.98,Obtained:C-55.66,H-4.66,N-10.07.

7).Methyl4-(2,4-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-arboxylate(4g):

Yield: 91%, yellow solid; m.p (ºC): 242-244; ^{1}H NMR (400 MHz, $CDCl_3$) δppm = 9.578 (s,1H, NH-1), 9.139 (s,1H, NH-3), 7.240 (s,1H, Ar-H), 7.436-7.326 (m,2m, Ar-H), 5.128 (d,J=7.6Hz,1H,- CH), 3.662(s,3H,-OCH_3), 2.232 (s,3H,- CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δppm=175.99,165.88,146.32,138.18,133.58,131.36,129.59,128.84,127.21,98.89,50.27, 48.53,16.77;LCMS(m/z)=331.45.**Molecularformule**:$C_{13}H_{12}Cl_2N_2O_2S$.ElementalAnalaysis: calculated:C-47.15, H-3.65.N-8.47,Obtained : C-47.08,H-3.64,N-8.53.

8).4-(5-(methoxycarbonyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzoic acid (4h): Yield: 87%, pale-yellow solid; m.p (ºC): 250-252; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm = 9.656(s,1H, NH-1),9.217 (s,1H, NH-3),7.886 (d, J = 8.8Hz,2H Ar-H), 7.346 (d, J = 8.0Hz, Ar-H), 5.326 (d, J =6.8Hz,1H,-CH), 3.569(3H,s,-OCH_3), 2.232 (s,3H,-CH_3); ^{13}C NMR(100MHz,$CDCl_3$)δppm:176.55,166.71,164.7,146.83,144.99,130.86,129.35,126.87, 99.84,53.46,50.27,17.37;LC-S(m/z)=306.10.**Molecularformule**:$C_{14}H_{14}N_2O_2S$.**Elemental Analysis**:calculated:C-54.88, H-4.61.N-9.16,Obtained:C-54.82,H-4.60,N-9.21.

3. BIOLOGICAL ACTIVITY

3.1. Anti-Bacterial Activity

The anti-bacterial activities of newly synthesized compounds are screened against 5 pathogenic bacteria strains. The result of antibiotic activity reported for the compounds as shown in table-I. The gram negative bacteria screened were E. Coli, P. aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus. The target compounds were used at the

concentration of 250 µglml and 500 µglml using DMSO as a solvent the Ciprafloxin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested micro-organism.

3.2. Anti-Fungal Activity

Anti-fungal activities of new synthesized compounds were examined by disc diffusion method against the organism of AspergillusNiger and Candida albicans 1. Compared were treated at the concentrations of 500 µglml and 1000 µglml using DMSO as a solvent. The standard drug was used as **Ketonozole** 50 µglml against both organisms.

Table-I: Antimicrobial activity screening activity synthesized scaffold.

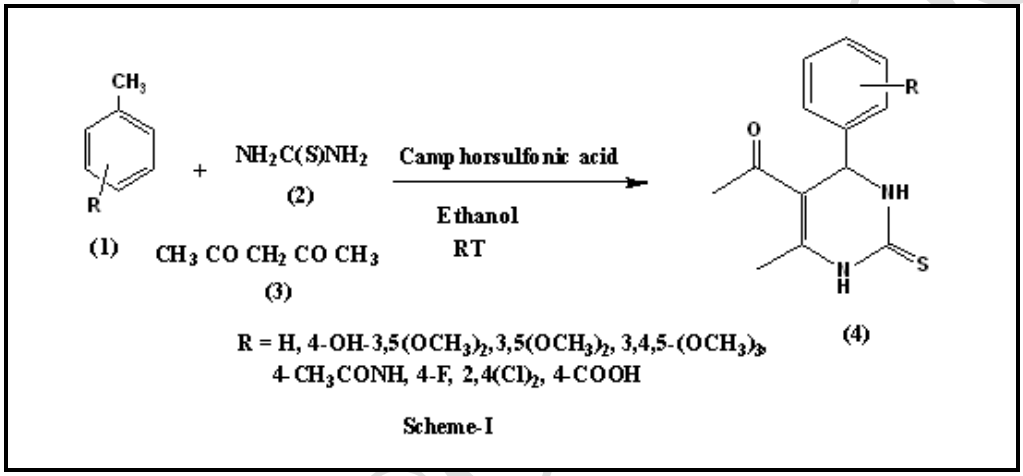
Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	P.aeruginosa	E.coli	S.aureus	B.substill	A. niger	C. albicans
4a	05	08	07	07	08	07
4b	21	18	18	18	12	14
4c	20	18	18	17	10	13
4d	21	19	17	19	16	16
4e	10	13	12	11	10	09
4f	18	17	18	19	14	15
4g	22	21	19	19	17	16
4h	11	17	10	18	16	17
Ciprafloxin	25	25	22	22	NA	NA
Ketonozole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

4. RESULTS AND DISCUSSION

The present work deals with Biginelli-type reactions to be found in the scientific literature, The fast approach for the synthesis of this Methyl- 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivate were on the application of Bronstd acid such as caphorsulfonic acid and a one pot multicomponent of starting from equimolar amounts of substituted aromatic aldehyde and 3 molar equivalent of thiourea. However RT followed by cooling room temperature, pouring the crude product mixture over crushed, filtration of the yellow solid the precipitated and recrystallization from ethanol.

Substituted aryl aldehydes having both electron-withdrawing and electron-donating group of substituent molecules were employed as reactants, the synthesis of desired compounds being in short reaction times, using a small amount of camphor sulfonic acid as solvent and acid catalyst under reflux **(Scheme -1).** The isolated yields were generally very good, ranging

from4a-4h of 1,2,3,4-tetrahydropyrimidine-2(1H)-thiones.Methyl-6-methyl -4- phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate and its analogues can be prepared by the camphor sulfonic acid as a promoter of Biginelli cyclocondensation reaction of acetyl acetone, substituted aromatic aldehyde and thiourea at RT. The role of this camphor sulfonic acid acts as catalyst and ethanol as solvent. The yields of the desired products as excellent yield. In this synthesis, the product of the synthesized compound can be obtained 85-94% of the yield. ^{1}HNMR signals of N-H-1 protons showed at 9.656-9.117 and NH-3 protons showed at 9.257 to 8.815. These values indicate that two different protons is the Pyrimidines ring. ^{1}HNMR values of –OH protons of 4b compounds exhibited 7.984.The proton values of ^{1}HNMR values of –OCH_3 group 4b,4c and 4d compounds exhibited different values at 3.668 to 3.558. The proton value of $NHCOCH_3$ is 8.998.



Scheme-I

The anti-microbial activities of desired compound exhibited different values potent active. Among the titled compounds, electron releasing group of moieties such as **4b,4c,4d** and halogen substituent **4f,4g** exhibited good active potent value where as electron withdrawing substituent **4h** showed poor active potent. Anti fungal activity of 4g exhibited good active potent as shown **Table-I.**

5. CONCLUSIONS

An optimized procedure for the preparation of pyrimidine-2-thione derivatives under room temperature conditions was described. The advantages of catalyst in chemical reactions is shorter reaction times, higher yields and room temperature conditions, could be of use in industrial applications in the pharmaceutical or fine chemical industries. The compounds screened good anti-microbial activity.

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BRONSTED ACID CATALYST PROMOTED FOR BIOACTIVE SYNTHESIS OF 2, 4, 5-TRIPHENYL IMIDAZOLE DERIVATIVES

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ABSTRACT

The highly versatile and an efficient synthesis of 2,4,5-trisubstituted imidazoles is obtained by three component cyclocondensation of 1,2-dicarbonyl compounds, substituted aromatic aldehydes and ammonium acetate in thermal solvent free condition using Brønsted acidic methane sulfonic acid as catalyst. All the compounds were evaluated by advanced spectroscopic data (1H NMR, 13C NMR& LCMS) and the structural determination of the novel derivations was calculated by elemental analysis. The main focus of this process is cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short time reactions. Multicomponent reactions were encouraged an outstanding status in synthetic organic and medicinal chemistry for their high degree of atom economy and application in the diversity oriented convergent synthesis of complex organic moiety from simple and readily available substrates in a single vessel. In the present study, ten hybridized imidazoles derivatives were synthesized via cyclo condensation and evaluated for their invitro antimicrobial activity and antioxidant properties.

KEYWORDS: 2, 4, 5-triarylimidazoles, benzil, aromatic aldehydes, bioevluation.

1. INTRODUCTION

Imidazoles are a class of heterocyclic compounds that contain nitrogen atom and are currently under intensive focus due to their wide range of applications.[1] Synthetic study of imidazole units is very important due to their potent biological activity[2] and synthetic utility.[3] Imidazoles are an important class of heterocycles being the core fragment of different natural products and biological systems. Compounds containing imidazole moiety have many pharmacological properties and play important roles in bio chemical processes.[4] The potency and wide applicability of the imidazole pharama cophores can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active sites 3b.[5,6]

Naturally occurring substituted imidazoles, as well as synthetic derivatives thereof, exhibit wide ranges of biological activities, making them attractive compounds for organic chemists. They act as inhibitors of p38 MAP kinase[7], B-Raf kinase[8], transforming growth factor b1 (TGF-b1) type 1 active in receptor-like kinase (ALK5)[9], cyclooxygenase-2 (COX-2)[10] and biosynthesis of interleukin-1 (IL-1).[11] Appropriately substituted imidazoles are extensively used as glucagon receptors[12] and CB1 cannabinoid receptor antagonists[13], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR)[14], antibacterial and antitumor agents[15] and also as pesticides.[16] Recent advances in green chemistry and organometallic catalysis has extended the application of imidazoles as ionic liquids[17] and Nheterocyclic carbenes.[18] Ionic liquid (IL) technology offers a new and environmentally benign approach toward modern synthetic chemistry. Ionic liquids have interesting advantages such as extremely low vapour pressure, excellent thermal stability, reusability, and talent to dissolve many organic and inorganic substrates. Ionic liquids have been successfully employed as solvents and catalyst for a variety of reactions which promise widespread applications in industry and organic syntheses.[19]

We report here a simple and efficient producers for the preparation of the 2, 4, 5-triarylimidazoles using methanesulphonic acid Brønsted acidic as catalyst that is considered as efficient catalyst. The methodology reported here in, consequently, the represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles derivatives.

2. METHODS AND MATERIALS

2.1. Experimental

All reagents, chemicals and solvents were procured from Aldrich and Merck and used without further purification. The newly synthesized derivatives of melting points that determined by open capillary method using a Galen Kamp melting point apparatus and is uncorrected. The desired products were characterized by spectroscopy data (FTIR, ^{1}H NMR and ^{13}C NMR spectra and Mass) and melting points. SHIMADZU FT-IR-8400s spectrometer was used to record IR spectra using KBr pellets. NMR spectra were recorded by the compounds on a Bruker (400-MHz) Ultrasheild NMR and $CDCl_3$ was used as a solvent. The purity of the compounds and the progress of the reactions were monitored by use of TLC.

2.3. General Methods for Synthesis of 2,4,5-Trisubstituted Imidazoles

The mixture of Benzil (1mol), aldehyde (1mol), and ammonium acetate (2mol) were introduced in clean and dry 50mL four neck rounded bottom flask and Bronsted acid catalyst added in a above the mixture(3mmol) in an oil bath at room temperature as in Scheme-I. Then the reaction mixture was heated to 100°C for the appropriated period of time. After completion of the reaction, progress of the reaction was monitored by TLC; the mixture was cooled, poured in crushed ice and also neutralised with sodium carbonate solution. The mixture was taken in ethyl acetate and washed with water. The ethyl acetate layer was separated followed by distillation U/vacuumed and the solid product purified by recrystallization from ethanol. The entire desired product was characterized by comparison of their physical data with those of known compounds. Some characterization data for selected known products are given below**.**

3. SPECTRAL AND ANALYTICAL DATA

1). 2, 4, 5-Triphenyl-1H-imidazole (4a)

M.p. 269–271°C; FTIR (KBr, cm−1): 3436 (NH), 2989, 2479, 1638(C=C), 1510 (C=N); ^{1}HNMR (400 MHz, $CDCl_3$): 11.372 (s, 1H, NH, imidazole), 8.068 (d, J=7.6 Hz, 2H, aromatic), 7.845–7.287 (m, 13H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$): 149.08, 137.44, 135..54, 130..78, 130.66, 129.72, 128.83, 128.23, 127.65, 127.07, 125.88; LCMS (m/z); 297.41(M^{+}+H); Molecular formulae: $C_{21}H_{16}N_2$; Elemental analysis: Calculated: C- 85.11, H- 5.43, N- 9.44; Obtained: C- 85.05, H -5.41, N- 9.53.

2). 4-(4, 5-Diphenyl-1H-imidazol-2-yl)-phenol (4b)

M.p: 267–269°C. FTIR (KBr, cm^{-1}): 3590 (OH), 3454 (NH), 3284, 3064, 1701(C=C), 1283; 1HNMR (400 MHz, CDCl3): 11.742 (s, 1H, NH-imidazole), 9.158 (s, 1H, OH), 7.90 (d, J=7.6 Hz, 2H), 7.578–7.298 (m, 10H, Ar-H), 6.947 (d, J=8.8 Hz, 2H); ^{13}C NMR (400MHz, $CDCl_3$): 158.36, 147.61, 128.12, 126.74, 124.53, 121.89, 114.74, 114.85, 99.67, 95.46; LCMS (m/z); 313.17(M++H); Molecular formulae: C_{21} H_{16} N_2O; Elemental analysis: Calculated: C-80.74, H- 5.15, N- 8.97; Obtained: C-80.67,H – 5.14, N- 9.08.

3). 2-(2, 5-Dimethoxyphenyl)-4,5-diphenyl-1Himidazole (4c)

M.p-181-183°C. FTIR (KBr, cm-1):3333(NH), 3059(C-H), 2962, 2834, 1648(C=N), 1524, 1221, 1175, 1047, 742, 696. ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.690 (s, 1H, NH-imidazole),8.057-7.435(m,13H,Ar-H), 3.745(s,3H,OCH_3), 3.685(s. 3H,OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$):158.35, 152.66, 148.23, 144.21, 141.95, 138.46, 136.07, 134.19, 131.15, 130.83, 128.72, 128.61, 128.41, 128.13, 127.22, 126.35, 126.12, 119.71, 115.014, 115.38, 113.76, 55.91, 55.47; LCMS (m/z);357.44 (M+H); Molecular formulae : C_{23} H_{20} N_2 O_2; Elemental analysis: Calculated: C- 77.51, H-5.65, N-7.86; Obtained: C- 77.48, H – 5.64 , N- 7.92.

4). 2-(2, 4, 6-Trimethoxyphenyl)-4, 5-diphenyl-1Himidazole (4d)

M.p:180-182°C. FTIR (KBr, cm-1): 3392(NH), 3049(C-H), 2936, 2848, 1656 (C=N), 1525, 1222, 1196, 1039, 742, 693.^{1}HNMR (400MHz,$CDCl_3$) ppm: 11.455 (s, 1H, NH imidazole), 7.895-7.451 (m, 10H, Ar-H), 6.868-6.545(m, 2H, Ar-H), 3.690(s,3H, OCH_3), 3.612(s,6H,2.OCH_3);^{13}CNMR(400MHz,$CDCl_3$)ppm:153. 55,151.26,146.19,141.32, 136.71,131.66,130.95, 128.71, 128.54, 128.27, 128.01, 126.96,119.67,116.58,114.82, 112.76,55.55, 54.70. LCMS (m/z); 387.31 (M+H); Molecular formulae:
C_{24} H_{22} N_2 O_3; Elemental analysis: Calculated: C- 74.59, H- 5.73, N-7.25; Obtained: C- 74.52, H- 5.72, N- 7.35.

5). 2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (4e)

M.p 262-264°C. FTIR (KBr, cm^{-1}): 3250 (NH), 3082 (C-H), 2914, 2902, 1601(C=N), 1520, 1156, 1087, 728, 692, 639. ^{1}HNMR (400MHz, CDCl3) ppm: 11.857 (s, 1H, NH-imidazole), 8.245 (d, J=8.4 Hz, 2H, Ar-H), 7. 874-7.562 (m, 12H, Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$):148.28, 138.96, 135.08, 131.74, 130.52, 129.20, 128.87, 128.56, 128.26, 128.12, 128.00, 127.85, 127.37, 126.83, 126.25; LCMS (m/z); 322.22 (M+2);: Molecular formulae: C_{21} $H_{15}Cl$ N_2; Elemental analysis: Calculated: C- 76.25 , H-4.56 , N- 8.46; Obtained: C- 76.17, H- 4.55, N- 8.54.

6). 2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (4f)

M.p: 249-252°C. FTIR (KBr, cm-1): 3420(NH), 3027(C-H), 2924, 2835, 16034(C=N), 1501, 1126, 1069, 826, 728, 715, 696. 1HNMR (CDCl3, 400MHz) ppm: 11.247(s, 1H, NH), 8.106(d, J= 8.0 Hz, 2H), 7.846 (d, J= 8.4 Hz, 2H), 7.720-7.274 (m, 10H, Ar-H); ^{13}C NMR (400MHz, $CDCl_3$): 145.59, 138.62, 135.19, 131.78, 130.88, 129.72, 129.13, 128.96, 128.51, 128.15, 127.88, 127.36, 127.09, 126.55, 121.63. LCMS (m/z); 376.18 (M+2); Molecular formulae: C_{21} $H_{15}Br$ N_2; Elemental analysis: Calculated: C- 67.21, H- 4.02, N-7.46; Obtained : C- 67.14, H -4.01, N- 7.53.

7). 2-(2-iodo-3,4-dimethoxyphenyl)-4,5-diphenyl-1H)-imidazole (4g)

M.p: 248-250°C. FTIR (KBr, cm-1):3333 (NH-imidazole), 3055(C-H), 2954, 1588 (C=N), 1691 (C=O), 1512, 1345, 874. ^{1}HNMR (400 MHz, $CDCl_3$) ppm:11.569 (s,1H,NH-imidazoles), 7.547 – 7.291 (m, 10H, Ar-H) 6.955(s,1H,Ar-H), 6.667(s,1H,Ar-H), 3.715 (s,6H,2OCH3); ^{13}C NMR (400 MHz, $CDCl_3$) ppm: 158.44, 153.65, 148.36, 136.19, 130.21, 129.53, 128.66, 127.74, 110.31, 108.47, 100.65, 50.95. LCMS (m/z); 484.28 (M+2); Molecular formulae: C23 H19 N2O2; Elemental analysis : Calculated : C- 57.28, H- 3.97, N-5.81; Obtained: C- 57.21, H – 3.95, N-5.89.

8).4-(4,5-diphenyl-1H-imidazol-2-yl)benzaldehyde (4h)

M.p: 221-223°C. FTIR (KBr, cm-1): 3300 (NH), 3052(C-H), 2980, 1593 (C=N), 1696 (C=O), 1504, 1345, 876. 1H NMR (400 MHz, $CDCl_3$) ppm: 11.779 (s, 1H, NH-imidazoles) 10.548 (s, 1H, Aldehyde), 8.214 – 7.287 (m, 14H, Ar-H). 13C NMR (400 MHz, $CDCl_3$) ppm: 195.07, 138.58, 134.55, 132.47, 130.15, 129.67, 129.17, 128.95, 128.76, 128.51, 128.39, 128.78, 128.16, 128.08, 127.48. LCMS (m/z); 325.07; Molecular formulae: C22 H16 N2O; Elemental analysis : Calculated : C- 81.45, H-4.96, N-8.64; Obtained: C- 81.38, H – 4.95, N- 8.74.

9). 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzonitrile (4i)

M.p:234-236°C. FTIR (KBr, cm-1): 3365 (NH), 3048(C-H), 2976, 1585 (C=N), 1694 (C=O), 1515, 1342, 873. ^{1}H NMR (400 MHz, $CDCl_3$): 11.845 (s, 1H, NH-imidazoles) 8.014 – 7.295 (m, 14H, Ar-H). 13C NMR (400 MHz, CDCl3) ppm: 147.07, 137.79, 135.15, 130.36, 129.75, 129.18, 128.96, 128.57, 128.19, 127.64,119.09,114.76; LCMS (m/z); 322.34; Molecular formulae: C22 H15 N3; Elemental analysis: Calculated: C- 82.22, H-4.70, N-13.08; Obtained: C- 82.14, H – 4.68, N- 13.17.

10). 2-(4-Nitrophenyl)-4.5-diphenyl-1H-imidazole (4j)

MP 199-201 ºC (lit. [24] 199-201,ºC). IR spectrum,□, cm-1: 3421 (NH), 2928, 1596 (C=N), 1515 (NO2), 1345 (NO2), 856. 1H NMR (400MHz, CDCl3) ppm : 11.754 (s,NH-imidazole,1H),8.218-7.347 (m, 14H, Ar-H). 13C NMR (400MHz, CDCl3) ppm: 118.5, 122.0, 124.0, 125.4, 126.1, 126.9, 127.0, 128.4, 129.7, 130.6, 136.1, 141.0, 147.0. Calculated: C 73.89, H 4.43; N 12.31. LCMS (m/z); 342.37(M+H); Molecular formulae: C_{21} H_{15} N_2O_3; Elemental analysis : Calculated: C- 73.89, H-4.43, N- 12.31; Obtained : C- 73.81, H -4.41, N- 12.39.

BIOLOGICAL ACTIVITY

Anti-Bacterial Activity

The anti-bacterial activities of newly desired compounds are examined against four pathogenic bacteria strains (24, 25). The results of this bacterial activity were observed for tested compounds. The gram negative bacteria were examined against E.coli, P. aeruginosa. The gram positive bacteria screened were examined against S-aureas and Bacillus. The target compounds were used at the different concentration and average value calculated and using DMSO as a solvent the amoxylin 10 µg/ml discs were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

Anti-Fungal Activity

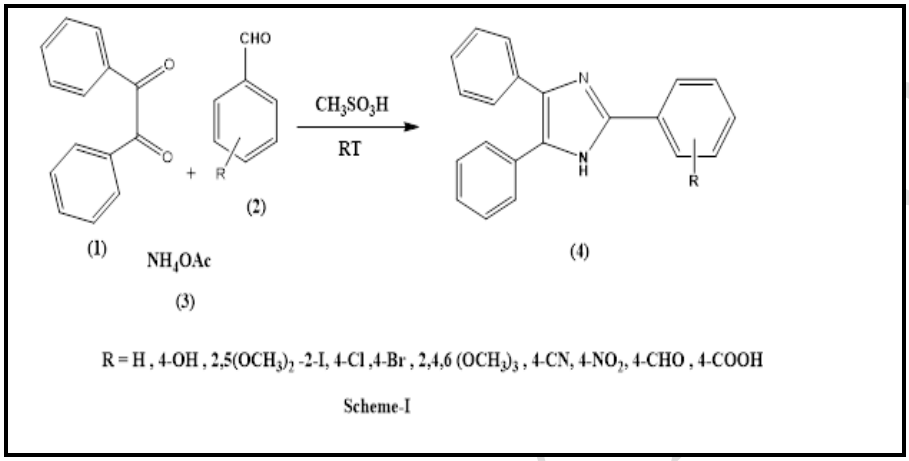
Anti-fungal activities of new synthesized compounds were examined by disc diffusion method against the organism of A.Ngier and C.albicans. The target compounds were used at the different concentration and average value and using DMSO as a solvent. The standard drug was used as ketoconazole 50 µg/ml against both organisms.

RESULTS AND DISCUSSION

As a result of the versatile biological potent activities of substituted imidazoles of different conventional process for the synthesis of these derivatives have been reported (20,21).[28,29] In typical methods, benzil, different functional group aromatic aldehydes and ammonium acetate are condensed in the presence of strong Bronsted acid methane sulphonic acid under RT conditions. These Bronsted acid catalysts present limitations due to the use of corrosive reagents and the necessity of neutralization of the base media. In addition, the synthesis of these heterocycles in polar organic solvents such as ethanol, methanol, acetic acid, DMF and DMSO lead to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed of. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in large amounts for organic reactions have posed a serious threat to the environment. Thus, design of solvent-free catalytic reaction has attracted tremendous attention in recent times in the area of green synthesis (22).[33] 2,4,5-Trisubstituted imidazole were synthesised in excellent yield by condensing benzil (10mmol), ammonium acetate with substituted aromatic aldehyde derivatives (10mmol), in the presence of Brønsted acid catalyst methane sulphonic acid (3mmol), as a catalyst in solvent free condition at RT. The stoichiometric amount of ammonium acetate in the preparation of 2, 4, 5-trisubstituted imidazoles is two. We can synthesised 2,4,5-trisubstituted imidazoles using two equivalents of ammonium acetate but we observed in our experiment and other published papers, if we use inexpensive and available ammonium acetate having more than two equivalents, the reaction will show better results. Thus, small amount of the ammonium acetate was found to be advantageous and hence the molar ratio of benzil to ammonium acetate was kept at 1:2. The efficiency and versatility of the methane sulphonic acid as a catalyst for the preparation of 2,4,5-trisubstituted imidazoles were demonstrated by the broad range of substituted and structurally diverse substituted aromatic aldehydes to synthesize the corresponding products in high to excellent yields (Table 2).

Table 2: Comparison between our catalyst methane sulfonic acid and the other used catalyst about 2-(2-iodo-3, 4-dimethoxyphenyl)-4, 5-diphenyl-1H)-imidazole.

S.NO	Catalyst	Conditions	Time (min)	Yield (%)
1	PTSA	RT	150	74
2	Sulphanilic acid	RT	180	70
3	Silica sulphuric acid	RT	150	75
4	Camphor sulphonic acid	RT	120	84
5	Silica per sulphuric acid	RT	150	78
6	Methane sulfonic acid	RT	60	95



Scheme-I

In Vitro Antioxidant Activity Assay

2.3.1. 1, 1-Diphenyl-2-Picrylhydrazyl (DPPH) Radical-Scavenging Assay

For the determination of the radical-scavenging potent activity newly synthesized derivatives, we used our implementation of the Salazar-Aranda et al.[20] method. A set of serial dilutions in methanol were prepared for each test sample. Then, 0.5 mL aliquots of each dilution were mixed with a solution of 1, 1-diphenyl-2-picryl hydrazyl (DPPH) in methanol(0.5 mL, 76 µM). The resulting mixtures were kept in the dark at room temperature for 30 min. The absorbance of each sample was measured at 517 nm (A517) and methanol was used as the blank. To calculate the radical-scavenging activity as DPPH decolouration percentage, the formula below was used.

$$\text{DPPH (\%)} = [1 - (B/A)] \times 100$$

Where A indicates the absorbance value of the DPPH solution (used as control) and B is the absorbance of the DPPH solution with the sample. Results were expressed as EC50, which represents the required concentration to diminish the absorbance of DPPH by 50%. Quercetin was employed as the reference compound.

3.2. Antioxidant Activity

The DPPH assays of newly prepared imidazole presented EC50 of >16 and >10 mg/mL, respectively **(Table 1**), which compared to most of the results shown by its derivatives, suggests that the 2, 4, 5-triphenylsubstitution in the imidazole heterocyclic is relevant for the antioxidant activity of these compounds, where the effect of their substitutions on their ring is further developed below.

The DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging method is widely used to examined antioxidant activities in a relatively short period of time compared to other methods. The results of this assay are shown in Table 1, comparing the synthesized products with the standard quercetin, where the most active synthesized imidazole derivatives were 4d, 4e and 4f with excellent values. These results exhibited that the presence of halogen substituted on an aromatic ring bonded to imidazole are essential in the antioxidant activity. The consulted literature showed that this could be due to the free pair of electrons in nitrogen in imidazole, which can react with free radicals, being favoured due to their aromatic ring stabilization.[23]

Table 1: Antioxidant activity (EC50) of synthesized compounds 1–10.

Compounds	DPPH
4a	3.227 ± 0.135
4b	1.379 ± 0.629
4c	0.1391 ± 0.092
4d	16.68 ± 0.003
4e	16.78 ± 0.634
4f	7.14 ± 1.908
4g	0.339 ± 0.101
4h	12.227± 3.041
4i	0.172 ± 0.039
4j	4.00 ± 0.133
* Quercetin	0.051 ± 0.036

* Served as the reference compound. Values are mean ± SD, DPPH n = 2, ABTS n = 3. EC_{50} = Concentration required to decrease the absorbance by 50%.

Table I: Antimicrobial activity screening activity synthesized scaffold.

Entry	Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
4a	05	07	05	08	04	06
4b	12	11	14	16	12	14
4c	10	14	12	15	11	12
4d	14	13	11	15	12	13
4e	14	15	18	17	14	17
4f	15	15	17	16	16	15
4g	12	14	18	20	12	14
4h	10	08	11	09	10	08
4i	08	09	07	10	09	08
4j	10	08	11	10	05	06
Amoxicillin	22	22	25	25	-	-
Ketoconazole					20	20
DMSO	-	-	-	-	-	-

Biological Activity

All the synthesized derivatives were evaluated by anti-oxidant properties. The compounds containing halogen derivatives exhibited good active potent against Quercetin. All the synthesized derivatives were evaluated by anti-bacterial activity as well as antifungal Activity. The electron attracting group of compounds and electron donating group compounds showed different activity against the all bacterial and fungal strains. Therefore, electron withdrawing group of derivatives exhibited poor biological activity compared with electron releasing groups. All halogen compounds exhibited good to excellent activity even though, these are electron attracting groups but also having lephoplic nature. The compound which possess electron donating group showed moderate activity as shown in Table-I. The compound containing chloro aldehydes, which exhitbited maximums at S-aureus, E-coli and B.substill at 21, 19,18. S. typhi showed "13'. The compound possesses Br-aldehydes, which is exhibited at E.coli as well as S.typhi at 20 and 21. Whereas S.aureus and B.substill showed at 18,18. Derivatives of these compounds exhibited antifungal activity at '17' of A.Ngier and '20' of C.albicans whereas electron donating group of substituents showed low potent activity against fungal strains.

4. CONCLUSION

Multicomponent reactions encouraged an outstanding status in organic synthesis and medicinal chemistry for their high degree of atom economy and application in the diversity-oriented convergent synthesis of complex organic molecules from simple and readily available substrates in a single vessel. A simple highly versatile and efficient synthesis of 2,4,5-trisubstituted imidazoles is acquired by three component cyclocondensation of benzil, substituted aromatic aldehydes and ammonium acetate as ammonia source in solvent free condition using Brønsted acidic catalyst methane sulphonic acid as catalyst. The key advantages of this process are cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, excellent yields and very short time reactions.

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Review on Analysis of polymers and its blends and applications

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Abstract: Polymeric mixes are crucial materials, yet it can be difficult to control and comprehend their behaviour. Although it gives a rudimentary grasp of the underlying thermodynamic processes, the original Flory-Huggins theoretical technique has little to no predictive ability and fails to appropriately characterise the majority of actual systems. It computes statistical thermodynamics using a lattice model. In this study, we provide a method that we have developed based on the lattice integral equation theory, which not only provides fresh insights into the behaviour of polymers and their mixes but also accurately depicts the data from the literature on polymer mixtures.

INTRODUCTION

Both naturally occurring and synthetically produced polymers are made of macromolecules, which are very massive molecules that are variants of the less complicated chemical building blocks known as monomers. These are only a few examples of the polymers that may be found in living things, along with proteins, cellulose, and nucleic acids. They also serve as the basis for minerals like feldspar, quartz, and diamond as well as man-made products including concrete, glass, paper, plastic, and rubber.

In this sense, a "polymer" is any collection of monomer units. When there are several monomers present, the combination is referred to as a high polymer. Monomers need not have the same molecular weight, shape, or chemical make-up for polymers to form from them.

Natural polymers: organic and inorganic

Both the basic structural elements of living beings and their involvement in essential life processes depend heavily on organic polymers. For instance, polymers make up all of the solid components of plants. Some of them are cellulose, lignin, and other resins. A polysaccharide, or polymer made of sugar molecules, is cellulose. A complex three-dimensional network of polymers makes up lignin. Isoprene, a simple hydrocarbon, is a component of wood resins. Rubber is an additional well-known isoprene polymer.

In addition to their apparent everyday applications, polymeric materials are widely used and crucial in high-tech sectors including electronics, aircraft, and medicine. For many years, theoretical and practical research has focused heavily on the connection between their molecular structures and how they function as materials. Thanks to computer modelling, theoretical advancement, and chemists' ability to create precisely controlled structures to test and validate theory, the potential for controlling electrical, mechanical, and rheological behaviour not only through choice of chemical repeat unit but also through molecular weight, molecular weight distribution, stereo-regularity, and degree of branching (and thus crystallinity) has become well understood in recent years.

It quickly became clear that theoretical advancements well beyond those used for mixtures of simple liquids were required in order to explain polymer molecules in mixes—with solvents or with other polymeric species. Polymer mixtures are challenging to make and control due to their extremely high viscosity, even at high temperatures, as well as for

thermodynamic reasons. Or, to put it another way, for high molecular weight materials, the entropy of mixing, which so readily tends to promote mixing of small molecules, becomes a relatively modest contribution, amplifying all the other variables that contribute to mixing. Additionally, polymers usually only create thermodynamically stable combinations at particular concentrations, pressures, and temperatures.

Polymers for new Applications

(i) Seasickness patches, Prostheses—hip cups, lenses, orthopaedic implants, denture bases, fillings, sutures, heart valves, organs, vascular grafts, hernia mesh, catheters, syringes, diapers, blood bags, artificial limbs, ligaments, and packaging are a few examples of how polymers are used as biomaterials. controlled release of diagnostics and medications.

(ii) Dielectrics, synthetic metals and battery materials, sensors, lithographic resists, photonic materials, light-emitting diodes and displays, electrophotography, holography, fuel cells, and solar cells are a few examples of applications for high-quality electronic polymers.

(iii) Increasingly, blends and composites are used to create materials with "tailored" properties, such as high-strength, high-modulus fibres, enhanced matrix options, "tailored" mechanical properties, high-stability toughening additives, high-temperature options, and an understanding of failure mechanisms.

(iv) Continual replacement of metals and other materials with polymers for use in marine structures and vehicles, clothing, automobiles, aircraft, spacecraft, and machined components.

(v) A growing number of military equipment, including uniforms, bulletproof apparel, and lighter aircraft, are being made from polymeric materials.

Techniques

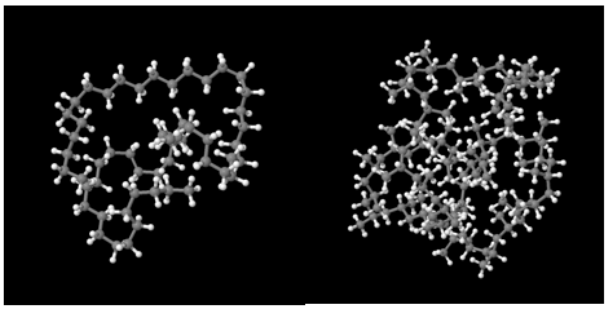
• A greater capacity to characterise data: This is made possible by technological developments in computer and electronic systems, such as the following: collimative, light scattering, centrifuged separation, NMR, UV, FTIR, and RAMAN spectroscopy for molecular research; rheology, diffusion, viscosity and acoustical studies, neutron scattering; synchrotron x-ray and electron spectroscopy for solid state studies; The development of synthetic tools for manipulating polymer structures Examples include enzyme synthesis, ring-opening metathesis polymerization, hybrid organic-inorganic materials synthesis, sol gel formation, dendritic polymers, coordination catalysts, biocatalysts, and creatures that produce monomers and polymers biologically. composites having specialised electrical, optical, or transport characteristics

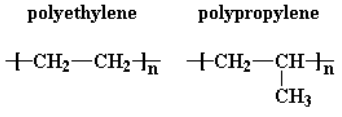
• Evolution of polymer theory: Evolution of polymer theory is being done with emphasis on computer modelling and simulation, for States of matter: solutions, crystalline, amorphous, LCs, blends, block polymers, copolymers, interfaces, surfaces; Dynamic properties: rheology, mechanical properties, electro-activity.

• Growing understanding of structure-property relationships: such as Finite-element analysis, Flow modelling, rheology, Simulation of structures of composites, blends, crystalline polymers.

• Continuing reduction of environmental threats: such as Elimination of toxic components, Replacement of plastics by natural materials, Continuing search for viable recycling strategies, Blending: properties of mixtures.

We occasionally require a material that combines some of the benefits of one polymer with those of another. Instead of going back to the lab and trying to make a brand-new polymer with all the needed properties, we try to mix two polymers to make a new material that, hopefully, combines the best features of both. Even though it might appear easy, combining two different kinds of polymers can be rather difficult. You know, it's pretty uncommon to combine two different kinds of polymers. This appears to be problematic. In this case, have a look at polyethylene and polypropylene.





According to the second rule of thermodynamics, when anything changes, it will go from being in an orderly state to being in a

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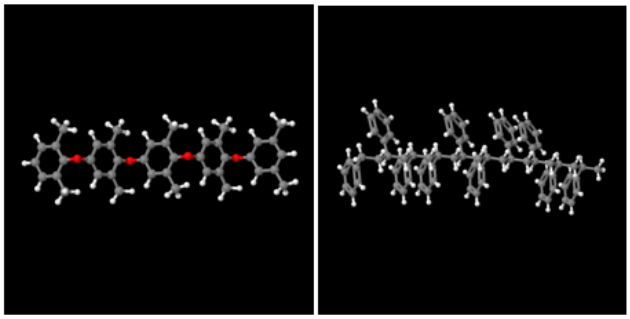
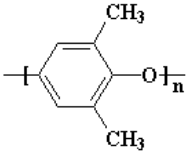
chaotic one. It is quite challenging to make things change in the other direction. Your place is simple to mess up but challenging to clean. A automobile is simple to crash, but considerably more difficult to repair. A change is more likely to occur in your room, in life, or in polymers if the thing that's changing goes from a state of more order to a state of less order, or from a state of less entropy to greater entropy. one particular kind of polymer, in its amorphous form.

This presents a problem if you're trying to make polymer blends. You see, one of the biggest reasons two compounds will ever mix together is that they are more disordered mixed together than they are separate. So, mixing is favored by the second law of thermodynamics. But an amorphous polymer is so disordered as it is, that it really doesn't gain that much entropy when it's blended with another polymer. So, mixing is disfavored.

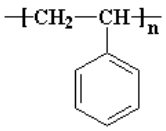
Making Polymers Mix

The first law of thermodynamics says that when things change, they change from a state of more energy to a state of less energy. it's easier to go to sleep than it is to get out of bed in the morning. For example, a rock on top of a mountain will roll down to the bottom of the mountain more easily than a rock on the bottom will roll to the top. in order to make two polymers mix, we have to make them have less energy when mixed than they would be separate. Assume Two polymers that do actually mix are polystyrene and poly (phenylene oxide). 3D models of the two polymers as shown below, right and left.





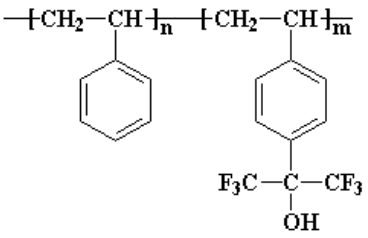
poly(phenylene oxide)



polystyrene

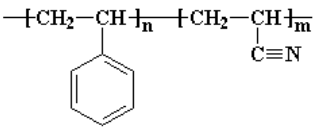
Copolymers

But most of the time, the two polymers you want to blend won't be miscible. So you have to play some tricks on them to make them mix. One is to use copolymers. Polystyrene doesn't blend with many polymers, but if we use a copolymer made from styrene and p-(hexafluoro-2-hydroxyisopropyl) styrene, blending is a lot easier.

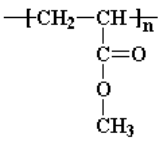


poly[styrene-*co*-(*p*-hexafluoro-2-hydroxyisopropyl)styrene]

There's another way copolymers can be used to help polymers blend. Let's consider a random copolymer of styrene and acrylonitrile. This copolymer will blend with poly(methyl methacrylate) (PMMA). This is where it gets weird. PMMA won't blend with either polystyrene or polyacrylonitrile.



poly(styrene-*co*-acrylonitrile)



poly(methyl methacrylate)

Why then does the arbitrary copolymer mix with PMMA? The rationale goes something like this: the random copolymer's styrene and acrylonitrile segments may not like PMMA, but they like each other even less. While the acrylonitrile segments are very polar, the styrene segments are non-polar. To prevent coming into touch with one another, the styrene and acrylonitrile segments merge with the PMMA.

Blends are usually made in two ways. The first method involves dissolving two polymers in the same solvent and letting it evaporate. If the two polymers are miscible, you will have a mix in the bottom of your beaker once the solvent has completely evaporated.

Although this procedure is effective in the lab, using it in an industrial setting might be costly. Solvents are expensive, so you'll spend a lot of money evaporating hundreds or thousands

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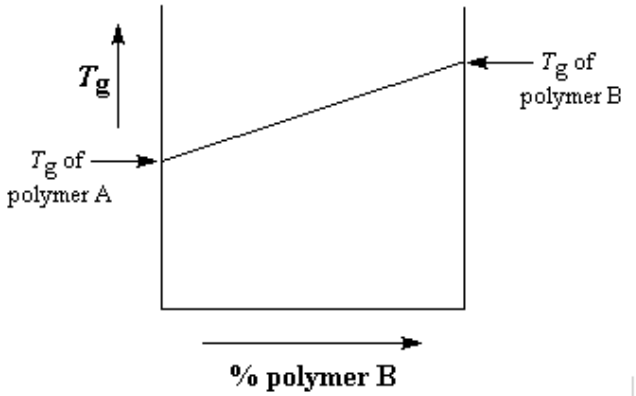
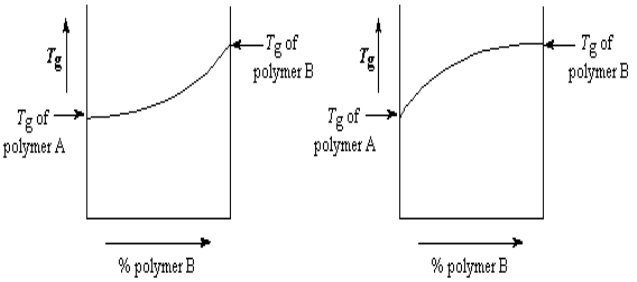
of litres of them. Not to mention the harm your hazardous solvent emissions do to the environment or the added expense of recapturing all that solvent for future usage. In order to create blends in large quantities, heat the two polymers together until you are above their respective glass transition temperatures. They will be lovely and gooey at this time, and you may combine them like a cake batter. This is frequently carried out by devices like extruders. Again, if your two polymers are miscible, your material will cool with a good mix.

Properties of Blends

The properties of two polymers that are miscible together frequently resemble those of the two polymers alone. Think about Tg, often known as the glass transition temperature. The Tg of a mix of polymers A and B is determined by the ratio of polymer A to polymer B. As evidence, consider the graph below.



If polymer B has a higher Tg than polymer A, the Tg of the mix will increase as the amount of polymer B in the blend changes. The graph shows that the increase is frequently linear. The plot isn't fully linear, though. When the two polymers bond more strongly to one another than to themselves, chain mobility is decreased, which causes the Tg to occasionally be bigger than expected. The plot will resemble the graph you can see to the right below.



The Tgs of the blends are often a little lower than anticipated because, in the majority of situations, the two polymers bind less strongly with one another than with themselves. The Tg plot will resemble the one on the left in the image above.

Tgs has been the subject of our discussion up to this point, but what is true for Tgs is often true for other properties. Mechanical characteristics, chemical, radiation, or heat resistance—they all typically plot according to the relative proportions of each polymer in the mix in the same way that the Tg does.

This allows changing the blend's qualities quite easy. The characteristics change depending on how much of the two polymers are present. This is extremely helpful. To demonstrate, I'll use poly(phenylene oxide), sometimes known as PPO. PPO is a polymer that resists heat well. This is fantastic. Heat-resistant materials are required for people. But there are some shortcomings. Processing this is quite difficult. It's too heat resistant, as you can see. Typically, amorphous polymers are treated by heating them over their Tgs, which causes them to become goopy and squishy. With a Tg of 210 oC, however, it is difficult and costly to heat PPO to the point where it becomes mushy and gooey.

Conclusion:

The foundation of modern materials science is polymers. Researchers are examining a variety of cutting-edge methods for producing customised, high-value polymers. In doing so, they are attempting to develop solutions to the long-standing costs and inefficiencies related to the production of polymers. The potential of such techniques for cutting-edge biological and pharmacological substances is also being developed. Researchers are paving the way for several ambitious applications by combining several strategies for the creation of novel polymeric materials. Researchers are discovering ways to comprehend and regulate molecular processes by examining the use of nanotechnology, creating polymers at the molecular level, and using chemical agents. By doing so, they will be able to produce useful goods like thin but strong polymers. For the foreseeable future, the broad field will continue to have a significant effect on all spheres of society. Noble polymeric materials provide a wealth of research prospects that are enticing fresh scholars to pick up the cause.

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KNOWLEDGE AND ATTITUDE TOWARDS COVID-19 AMONG RURAL PEOPLE -AN EMPIRICAL STUDY

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Abstract:

The study focused on examining the knowledge and attitudes of the rural respondents in the rural area of Telangana State. The study presents that 48% of respondent are between 31-40 years. 54%of respondents are male, while 46% are female. 28%of sample rural people had primary school level education. 66% of sample respondent are married, and 78% follow the nuclear family system. 34% of respondents are farmers, earningRs.150000 per annum. Knowing Covid19, 90% of respondents knew that coronavirus transmits through droplets, touching an infected surface and other touches face less than the 1-meter distance from an infected person. 88% of respondents knew the symptoms of Covid-19, i.e. hyperthermia, malaise and breathing difficulty.74%of respondents said that novel coronavirus could infect all age group.70% of respondents do not know that an Asymptomatic person with Coronavirus infection cannot transmit the virus to others. Surprisingly, 42% of respondents do not know that there is currently no specific coronavirus treatment, but a patient can be recovered by early symptomatic treatment.

The present study reveals that 52% of respondents agree that infection is controlled. The majority of respondents, 72%, opined that India would win the battle against novel corona. 60% of respondents opined that the lockdown could slow the Spread of Infection. 50% of respondents are approved that their family members are at risk. 76% of respondents are worried if they have a common cold. 56% of respondents think that the coronavirus changed their daily routine life. 54%opined that they feel uncertain about frequent modification of infection control procedures. 74% of respondents spend most of their time watching information related to coronavirus, and 76% of respondents have developed anxiety from watching the news.

Key words: Covid-19, knowledge, attitude, and rural people.

Introduction

The COVID-19 pandemic has become a significant public health challenge globally, with countries of the world adopting unprecedented infection prevention and control (IPC) measures to curtail the spread of the COVID-19 virus urgently. The knowledge, attitudes and practices (KAP) of the people toward COVID-19 are critical to understanding the epidemiological dynamics of the disease and the effectiveness, compliance and success of IPC measures adopted in a country.

COVID 19 and the measures to control it have caused devastations beyond imagination to people in every sphere of life. More than 185 million people have been infected with the virus across the globe, and more than 4 million deaths have been reported to date, and the numbers keep adding up every day. India is one of the worst-hit countries, having more than 30 million confirmed cases and more than 4 lakh deaths. The virus, though dominantly attacks an individual's health, its repercussions are reflected in aspects beyond health – be it work, education, career, social life, family life, and so on, WHO (2021).

Review of Literature

Severe acute respiratory syndrome coronavirus-2 is the causative agent of the 2019 novel coronavirus disease pandemic, which originated from Wuhan in China and has now spread to 6 continents, including more than 214 countries. A coronavirus is a group of viruses categorized into alphacoronavirus and beta coronavirus, often causing cold and other mild upper respiratory tract infections in the human body, Lal (2020).

Developing an initial policy revolving around the use of Telemedicine to boost capacity in identifying and treating COVID-19 will serve as a helpful pilot following which subsequent uses can

be developed. In the first phase, the application should attempt to identify with a high degree of sensitivity and specificity likely COVID-19 cases, which can then be confirmed by laboratory testing Chattu (2020).

The unheralded inroads that the pandemic has managed to make well past the defences of major economies on a multi-pronged level (be it socio-economic, health, or environmental) have left indubitable dents economy-wide across the spectrum of countries, Lal(2020a).

Recent epidemiological models have explored various mitigation strategies for pandemic influenza in the United States. The study has shown the effectiveness of targeted antiviral use, low-efficacy vaccines, and nonmedical interventions such as school closure, case isolation, and household quarantine in reducing peak or cumulative illness attack rates, even for highly transmissible viruses, Lal (2020). There has been widespread apathy among the public since the epidemic has been kept under control in the country. As a result, many people are seen not wearing a face mask when they leave home for outdoor activities, Lal(2020b).

A key difference is that epidemiologists and economists often think differently about human behaviour during a pandemic. However, both groups recognize feedback mechanisms between the pathogen, the population, and individual choices, Michael (2022). Water-borne communicable diseases like gastrointestinal disorders, including acute diarrhoea, are responsible for higher morbidity and mortality due to poor sanitation, unhygienic conditions and lack of safe drinking water in the banjaras thandas. For example, the acute diarrheal problem was due to poor environmental hygiene, lack of safe drinking water, and improper disposal of human excreta, Lal (2015).

A wide range of psychiatric morbidities has been found, such from depression, anxiety, panic attacks, somatic symptoms, and posttraumatic stress disorder (PTSD) symptoms, to delirium, psychosis, and even suicidality, Toosi (2020).

Inadequate sanitation, poor hygiene and lack of safe water supply result not only in more sickness and death but also in higher health costs, lower worker productivity, lower school enrolment and retention rates of girls and perhaps most importantly, the denial of the rights of all people to live in dignity Kavitha (2013). Safe water and sanitation are the two primary components of hygiene, which have a solid cultural determination and a key influence on people's health, perhaps comparable only to food Lal (2010).

The outbreak has given humanity a lifetime opportunity to understand the natural world and the importance of a reassessment lifestyle. Every child is given their own time to learn at their place, which will lead to the child's personal growth. This is the time to teach the students how to learn to live in harmony with nature- working from home presents new challenges, mainly when it comes to cyber security, Sen (2020).

India's services industry suffered a substantial setback during the COVID-19 pandemic-mandated shutdown. Because of its contact-intensive nature, the industry shrank by about 16% in the first half of the fiscal year 2020-21, Deepika (2022). Information regarding the present occupation pursued by the tribals subjects is given. Majority of the subjects have practicing agriculture i.e., 64.5 percent. Followed by Agri Labour and others their percent is 25.5 and 10 respectively Lal(2011). Education is the most potent tool on which we would successfully build an equitable and just society with the feature of dynamic social-economic mobility as education provides skills and competencies for economic well-being for the whole society and the whole nation too, Lal (2019).

The illiterate people trapped in a cycle of poverty with limited opportunities for employment or income generation and higher chances of poor health, turning to crime and dependence on social welfare. Therefore, illiteracy is a curse to humanity and socioeconomic development Lal(2015a).

Educating in a pandemic and beyond" talks about how COVID 19 is threatening the current education system and how technology-based learning solutions like remote learning and approaches like blended learning can pave the way ahead. Mary Jo Jean-Francois, Rotary International's area of focus manager for primary education and literacy, believes that the pandemic's impact on education will continue long even after developing a COVID-19 vaccine, Weiner (2020). Preventing the spread of Coronavirus (COVID-19) is almost impossible without clean water, decent sanitation and

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good hygiene. Currently, 785 million people globally lack access to clean water, and 2.3 billion are without safe, private toilets. In the poorest countries, almost half (45%) of health care facilities do not have clean water on site. One in five healthcare facilities (21%) globally do not provide decent toilets and one in six health care facilities have no handwashing facilities at all, Lal(2020c).

Methods

We explored KAPs among rural people from rural Telangana State using a physical mode-based questionnaire. The questionnaire explored individuals' knowledge about COVID-19; their attitudes. We also collected demographic data.

Objectives of the Study

1. To study the demographic background of sample rural respondents, and
2. To assess the knowledge and attitude on coronavirus infection among rural people areas.

Research Design

A descriptive survey was used in this study as it was deemed most appropriate for identifying and describing rural people opinions about a phenomenon, in this case, knowledge and attitudes. Fifty respondents were selected from rural Thorrur Mandal of Warangal using a purposive sampling technique.

Results and Discussion

The following table presents social and demographic characteristics like age group, gender, education particulars, marital status of the sample respondents, type and size of family, occupation and income particulars of the sample student respondents in the study area.

Table.1 - Demographic Information of the Respondents

Sl.No.	Particulars	Description	Frequency	Percentage
1	Age Group	21-30 Years	15	30.0
		31-40 Years	24	48.0
		41-50 Years	5	10.0
		51-60 Years	6	12.0
		Total	**50**	**100.0**
2	Gender	Male	27	54.0
		Female	23	46.0
		Total	**50**	**100.0**
3	Education Particulars	Illiterate	13	26.0
		Primary school Level	14	28.0
		High School Level	9	18.0
		Plus 2 level	6	12.0
		Under Graduation	4	8.0
		Above UG	4	8.0
		Total	**50**	**100.0**
4	Marital Status	Married	33	66.0
		Unmarried	17	34.0
		Total	**50**	**100.0**
5	Type of Family	Nuclear Family	39	78.0
		Joint Family	11	22.0
		Total	**50**	**100.0**
6	Size of Family	Below 4 Members	33	66.0
		5-7 Members	15	30.0
		Above 7 Members	2	4.0

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		Total	**50**	**100.0**
7	Occupational Particulars	Students	15	30.0
		Cooli	11	22.0
		farmers	17	34.0
		Employee	7	14.0
		Total	**50**	**100.0**
8	Income Particulars (per annum)	Below150000	26	52.0
		1.5 - 3 Lakh	11	22.0
		3 -4.5 Lakh	10	20.0
		4.5- 6 Lakh	3	6.0
		Total	**50**	**100.0**

Sources: Field study

The demographic information is an essential aspect by which it is easy to understand the respondents' nature, attitudes, needs, income and consumption patterns, their surroundings, and their responses to the socio-economic conditions. The table-1 depicts the demographic information of respondents. Regarding the age group, most of the respondents (48 per cent) are between 31-40 years old. The next age group is 21-30 years, in which 30 per cent of respondents are there. The age groups 41-50 years and 51-60 years have 10 per cent and 12 per cent of respondents, respectively. In the present study, 78 per cent of respondents lie in the age group of 21- 40 years.

Regarding gender, 54 per cent of respondents are male while 46 per cent are female. The educational details can be known from the above table that most of the respondents (28 per cent) have Primary school level education while 26 per cent are illiterates. High School level respondents are 18 per cent, whereas plus 2 level respondents are 12 per cent. Under Graduation and above Under Graduation level respondents are 8 per cent each. The marital status shows that Most of the respondents (66 per cent) are married, and only 34 per cent are unmarried. Notably, 78 per cent of respondents reside in Nuclear Family, whereas 22 per cent are still enjoying the joint family system. Sixty-six per cent of respondents have below four members size of family, and 30 per cent of respondents have 5-7 size of family members. Only four percentage respondents have more than seven members of family size. Most of the respondents give priority to a small family. As it is a rural area, 34 per cent of respondents are farmers, and 30 per cent are students. Twenty-two per cent of respondents are working as coolie, while 14 per cent are employees in various departments. The income particulars per annum are shown in the table. Fifty-two per cent of respondents are getting below 150000 incomes, while 22 per cent are between 1.5 to 3 lakhs. The 20 respondents are getting income between 3 to 4.5 lakhs, while six percentage respondents' income is between 4.5 to 6 lakhs.

Table.2 - Knowledge of Covid-19 Information of the Respondents

Sl. No.	Item of Knowledge	Yes		No		Do not know		Total	
		Frequency	%	Frequency	%	Frequency	%	Frequency	%
1	Corona Virus Transmit through droplets, touching an infected surface and further touches the face and less than the 1-meter distance from an infected person	45	90	3	6	2	4	50	100
2	The symptoms of Corona are hyperthermia, malaise and breathing difficulty	44	88	3	6	3	6	50	100
3	The first case of Novel Coronavirus was identified in Wuhan	8	16	20	40	22	44	50	100
4	WHO announced the official name of Novel	37	74	1	2	12	24	50	100

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	Coronavirus is COVID-19								
5	Novel Coronavirus can infect all age groups	37	74	8	16	5	10	50	100
6	Common Cold and rhinorrhea and sneezing are not found in infected persons	31	62	9	18	10	20	50	100
7	An asymptomatic person with Coronavirus infection cannot transmit the virus to others	9	18	6	12	35	70	50	100
8	Not all people with coronavirus infection will become severe cases. Only children, the elderly and have chronic diseases are more likely to be severe cases	33	66	3	6	14	28	50	100
9	Currently, there is no specific treatment for coronavirus, but by early symptomatic treatment, a patient can recover	15	30	14	28	21	42	50	100
10	Pet animals can be spread the Infection	13	26	17	34	20	40	50	100
11	Infection can be spread by mosquitoes & flies	16	32	20	40	14	28	50	100
12	All must wear a mask	49	98	0	0	1	2	50	100
13	Isolation and treatment of infected people can reduce the spread of Infection	32	64	4	8	14	28	50	100
14	The coronavirus is not related to SARS/MERS	12	24	17	34	21	42	50	100
15	People in contact with corona virus-infected person should keep isolated and observed for 14 days	47	94	2	4	1	2	50	100

Sources: Field study

Table.2 reveals the knowledge of Covid-19 information of the respondents. Ninety per cent of respondents knew that Coronavirus is Transmitted through droplets, touching an infected surface and other touches faces and less than the 1-meter distance from an infected person. At the same time, 6% were unaware of this knowledge, and 4% of respondents said they do not know about the transmission of Covid-19. Furthermore, the symptoms of Covid-19, i.e. hyperthermia, malaise and breathing difficulty, are known to 88 per cent of respondents. However, six per cent of respondents do not know about the symptoms of Covid-19, and another 6 per cent are ignorant about the symptoms.

Most respondents (44%) do not know that the first case of Novel Coronavirus was identified in Wuhan; while 40 per cent answered negative, only 18 per cent responded YES. It is known to 74 per cent of respondents that WHO announced an official name of Novel Coronavirus is COVID-19, but 24 per cent do not know it. In comparison, only 2 per cent said NO. 74 per cent of respondents said Novel Coronavirus could infect all age groups. However, 16 per cent disagreed with it, while 10 per cent did not know about it. As per the knowledge of 62 per cent of respondents, the Common Cold and rhinorrhoea and sneezing are not found in infected persons, but 18 per cent answered negatively. Twenty per cent of respondents are unaware of it. Seventy per cent of respondents do not know that an Asymptomatic person with Coronavirus infection cannot transmit the virus to others. At the same time, 18 per cent are positive, and 12 per cent are pessimistic about the fact. There is a positive response from 66 per cent of respondents towards the knowledge that 'Not all people with coronavirus infection will become a severe case. Only children, the elderly, and chronic diseases are more likely to be severe cases. Twenty-eight percentage respondents do not know it, while six per cent are pessimistic. Surprisingly 42 percentage respondents do not know there is currently no specific Coronavirus treatment, but a patient can recover by early symptomatic treatment.

Thirty per cent of respondents said YES, while 28 per cent said NO. Another fact is ' Pet animals can be spread the infection is not known to 40 percentage respondents while 34 percentage agreed and 26 percentage are disagreed it. 40 percentage of respondents said NO to the statement that infection can spread by mosquito & flies while 32 percentage said YES but 28 percentage said

they do not know it. The lock down and Government propaganda became fruitful in inculcating the knowledge about Covid-19 among the people. For the evidence, the 98-percentage people knew that All must wear a mask while only 2 percentage do not know. The control measure of Covid-19 that Isolation and treatment of infected people can reduce the spread of infection is known to 64 percentage of respondents while 28 percent do not know, but only 8 per cent denied it. The information the coronavirus is not related to SARS/MERS dragged the 42 per cent of respondents as do not know while 34 per cent said NO and 24 per cent said YES. It is worth knowing that 94 per cent of respondents know that People in contact with corona virus-infected persons should keep isolated and observed for 14 days. Only four per cent disagreed with it, while 2 per cent did not know. The above knowledge of respondents about Covid-19 reflects the awareness of the pandemic. The Government activities to improve the knowledge about Covid-19 among the people are successful.

Table.3 - Attitude towards Covid-19 information of the Respondents

Sl. No	Item of Attitude towards Covid-19	Agree		Neutral		Disagree		Total	
		Frequency	%	Frequency	%	Frequency	%	Frequency	%
1	Do you think the infection is successfully controlled?	26	52	15	30	9	18	50	100
2	Do you feel India will win the battle against novel corona?	36	72	10	20	4	8	50	100
3	Do you think the lockdown can slow the spread of infection?	30	60	11	22	9	18	50	100
4	Do you think Novel Corona Virus can infect you?	19	38	24	48	7	14	50	100
5	Do you think your family members are at risk?	25	50	16	32	9	18	50	100
6	Do you get worried if you have a common cold?	38	76	5	10	7	14	50	100
7	Do you think the Corona Virus changed your daily routine life?	28	56	15	30	7	14	50	100
8	Do you feel uncertain about frequent modification of infection control procedures?	27	54	16	32	7	14	50	100
9	Do you spend most of your time watching information related to coronavirus?	37	74	8	16	5	10	50	100
10	Do you think the news about coronavirus increases your anxiety?	38	76	8	16	4	8	50	100

Sources: Field study

Table.3 depicts the attitude toward Covid-19 information of the respondents. Fifty-two per cent of respondents agreed that infection is successfully controlled, while 30 per cent are neutral and 18 disagree. The majority of respondents (72%) opined that India would win the battle against novel corona, while 20 per cent disagreed and eight per cent were neutral. Sixty per cent of respondents opined that the lockdown could slow the spread of infection, while 22 were neutral and 18 per cent disagreed. Forty-eight per cent of respondents are neutral to the attitude that they can be infected by Novel Corona Virus, while 38 per cent of respondents agreed, but 14 per cent said that they do not know. Fifty per cent of respondents are approved that their family members are at risk, while 18 per cent of respondents said that they do not know, but 16 per cent denied it. For the question do they get worried if they have a common cold, 76 per cent of respondents said YES, while ten per cent said NO, and 14 per cent said that they do not know? Fifty-six per cent of respondents think that the

Corona Virus changed their daily routine, but 30 per cent denied it while 14 per cent could not. Out of the total respondents, 54 per cent opined that they feel uncertain about frequent modification of infection control procedures, while 32 per cent do not agree that, and 14 per cent are on neither side of opinion. Seventy-four per cent of respondents spent most of their time watching information related to coronavirus, while 16 per cent did not spend and ten per cent could not say any. As per the opinion of 76 per cent of respondents, the news about coronavirus increases their anxiety. However, 16 per cent denied it, and 8 per cent do not know.

Discussion

COVID-19 is an emerging infectious disease that significantly threatens public health. Given the severe threats imposed by COVID-19 and the absence of a COVID-19 vaccine, preventive measures play an essential role in reducing infection rates and controlling the spread of the disease. This indicates the necessity of public adherence to preventive and control measures, which is affected by their knowledge and attitudes. Thus, this study aimed to assess the knowledge and attitudes of rural people in Thorrur mandal of Warangal district.

The study examined that most respondents (48 per cent) are between 31-40 years old. Fifty-four percentage respondents are male, while 46 per cent are female. Most of the respondents (28 per cent) have Primary school education. Most of the respondents (66 per cent) are married. It can be observed that 78 per cent of respondents reside in nuclear families. Sixty-six per cent of respondents have below four members size of the family. As it is a rural area, 34 per cent of respondents are farmers, and 52 per cent are getting below 150000 incomes.

The study assessed that knowing Covid19, 90 per cent of respondents knew that Coronavirus transmit through droplets, touching an infected surface and others touches the face and less than the 1-meter distance from an infected person. The symptoms of Covid-19, i.e. hyperthermia, malaise and breathing difficulty, are known to 88 per cent of respondents. Most respondents (44 per cent) do not know that the first case of Novel Coronavirus was identified in Wuhan. It is known to 74 per cent of respondents that WHO announced an official name of Novel Coronavirus is COVID-19. Seventy-four percentage respondents clearly said that Novel Coronavirus could infect all age groups. As per the knowledge of 62 per cent of respondents, the Common Cold and rhinorrhoea and sneezing are not found in infected persons. Seventy per cent of respondents do not know that an Asymptomatic person with Coronavirus infection cannot transmit the virus to others. There is a positive response from 66 per cent of respondents towards the knowledge that 'Not all people with coronavirus infection will become a serious case. Surprisingly 42 percentage respondents do not know that there is currently no specific treatment for coronavirus, but by early symptomatic treatment, a patient can recover. The fact 'Pet animals can be spread the infection is not known to 40 per cent of respondents. Forty per cent of respondents said NO to the statement that infection can be spread by mosquitoes & flies. The 98-percentage people knew that 'All must wear a mask'. The control measure of Covid-19 that isolation and treatment of infected people can reduce the spread of infection is known to 64 per cent of respondents. 42 percentage is of respondents were unaware that 'the coronavirus is not related to SARS/MERS, and 94% of respondents knew that People in contact with a coronavirus-infected person should keep isolated and observed for 14 days.

The present study reveals that 52 per cent of respondents agreed that infection is successfully controlled. Most respondents (72%) opined that India would win the battle against novel corona. Sixty per cent of respondents opined that the lockdown could slow the Spread of Infection. Forty-eight per cent of respondents are neutral to the attitude that Novel Corona Virus can infect them. Fifty per cent of respondents agree that their family members are at risk. Seventy-six per cent of respondents get worried if they have a common cold. Fifty-six per cent of respondents think the Corona Virus changed their daily routine. Out of the total respondents, 54 per cent opined that they feel uncertain about frequent modification of infection control procedures. A total of 74 per cent of respondents spend most of their time watching information related to coronavirus. As per the opinion of 76 per cent of respondents, the news about coronavirus increases their anxiety too.

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Conclusion

Minimal studies have been done on rural people. To limit the spread of COVID-19, one needs to educate the people play a more significant role in rural areas regarding the disease and its preventive methods. A vast majority of rural families and people do not have access to the internet; hence, they need to utilize the different modes of information through television, radio channels and print media more effectively for the same and also emphasize to the population the role of asymptomatic carriers in spreading the disease. The adherence of the general population to the control strategies is greatly influenced by their knowledge and practice towards current pandemic infection.

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Diclofenac Induced Genotoxicity in the Gill Tissue of *Channa Punctatus*

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ABSTRACT

Pharmaceuticals have emerged as priority pollutants in recent times. The enormous usage of these drugs has led to pollution of the aquatic systems all over the globe. Diclofenac is the most widely prescribed non-steroidal anti inflammatory drug. The drug Diclofenac has been detected in surface waters in the magnitude of ng/L to µg/L. There are many investigations on the toxicity of the drug Diclofenac in aquatic flora and fauna. This study aims to examine diclofenac induced genotoxicity in the gill tissue of *Channa punctatus*. The acute toxicity test was conducted by exposing the fish to ten different concentrations of diclofenac for 96 hours. The median lethal concentration was found to be 25.28 ppm. Genotoxicity was evaluated by exposing the fish to median lethal concentration (25.28 ppm) and sub lethal concentration (8.42 ppm) of Diclofenac. DNA damage was estimated by Comet assay (Singh *et al*., 1988). There was an increase in the percentage of tail DNA, tail length and tail moment in the gill cells of the exposed fish in both the set concentrations of Diclofenac. The present study clearly indicates that the drug Diclofenac damages DNA of the aquatic organisms like fish. This study also signifies that genotoxic studies are effective biomarkers in the assessment of pollution.

Key words: Diclofenac, genotoxicity, *Channa punctatus*, DNA, Gill

INTRODUCTION

Pharmaceutical residues have become prominent emerging pollutants in recent times. The increased consumption of these drugs has led to their discharge into the environment. A large number of pharmaceuticals both prescription and over the counter drugs have been detected in influents and effluents of wastewater, surface water, ground water and even in drinking water. They enter into water bodies through many routes and the foremost being excretion from treated patients either in the form of parent compound or its metabolites, direct release from manufacturing units, hospitals, disposal of unused drugs and leaching from terrestrial deposits.

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Though pharmaceuticals have been detected in traces from ng/L to µg/L they show adverse effects on aquatic life. There are several experimental evidences on the toxicity of different classes of pharmaceuticals. They are known to cause behavioral alterations, changes in biochemical constituents, genotoxicity, endocrine disruption in non-target organisms like fish and selection of antibiotic resistance in pathogenic microorganisms.

Diclofenac is the widely prescribed drug for treating both acute and chronic pain in various disorders like rheumatoid arthritis, osteoarthritis, spondylitis, ocular inflammation, gout and dysmenorrhea (Skoutakis *et al*., 1988). It is available in the form of tablets, capsules, suppositories, intravenous solutions and injections. It is usually supplied in the form of either sodium or potassium salt. It is sold with the common brand names as Voltaren, Pennsaid, Arthrotec, Flector, Solaraze etc,. Diclofenac has been detected in surface waters of rivers, lakes, seas, influents and effluents of wastewater treatment plants, groundwater, drinking water, soil and sediment worldwide (Nikolaou *et. al.*, 2007). It was detected in the magnitude of high ng/L to µg/L in many countries in the world including India.

Fish is the best bioindicator for assessing environmental risk caused due to various pollutants (Chavonec, 2003). *Channa punctatus* was selected as the test animal due to its wide distribution, availability throughout the year and easy maintenance in the laboratory.

Diclofenac was found to induce many potential toxic effects in aquatic flora and fauna. The subchronic and chronic studies have reported the toxicity of diclofenac in the aquatic organisms. However, the acute toxicity data in fish is very scarce. There are little evidences of genotoxicity in fish. Therefore, DNA damage has been taken as parameter to find out acute toxicity of diclofenac. Several investigations have shown that gill was the suitable tissue for conducting genotoxicological studies in fish. (Masud *et al*., 2003). Hence gill tissue has been taken up for study of DNA damage.

Materials and Methods

Warangal district, Telangana, India. The experiments were performed according to the standard methods to determine the LC_{50} of *Channa punctatus.* The healthy fish weighing about 100-110g and 20±1.21cm in length were transported to laboratory in large plastic tanks and filled with water. The fish were washed in 1% potassium permanganate to free from microbial infections. The fishes were acclimatized in 50 litres capacity plastic tubs filled with dechlorinated water prior to experimentation. The fish were fed *ad libitum* with commercial feed rice bran and oil cake twice a day. Proper aeration was provided with the help of aerators. The fish were maintained in tanks under 12:12 hour light : dark period. The dead fish were removed immediately to keep the water afresh. During acclimatization and test period, water was renewed for every 12 hours followed by the addition of desired concentration of the test compound. The fish were starved one day before experimentation.

Analytical grade of Diclofenac sodium (2- [(2-6 Dichlorophenyl) amino] benzene acetic acid sodium salt, 99% pure (CAS 15307- 86-5) was purchased from Sara Exports, Ghaziabad, Uttar Pradesh, India. Diclofenac stock solution was prepared with acetone and ten different concentrations 5 ppm, 10 ppm, 15 ppm, 20 ppm, 25 ppm, 30 ppm, 35 ppm, 40 ppm, 45 ppm and 50 ppm were prepared from stock solution. The fish were exposed for 96 hours to ten different concentrations and median lethal concentration was analysed. The experiment was carried out for six times.

The molecular abnormalities were evaluated by exposing the healthy fish to sub lethal (8.42ppm) and median lethal concentrations (25.28ppm) of Diclofenac for 96 hours along with a control. The live fish were sacrificed after 96 hours and the tissues were isolated from gill to examine DNA damage.

The alkaline Single Cell Gel Electrophoresis or comet assay was performed by Singh *et al*. (1988) with minor modifications. Microscopic slides were precoated with 1% NMP agarose on pre cleaned and methanol treated dry slides. The 30 µL of cell suspension was gently mixed with 70 µL of 0.1% Low Melting Point Agarose (LMPA) and was layered on a frosted slide which was precoated with a layer of 1% 200 µL normal agarose. Then again, it was layered with LMPA (100 µL) and covered with a coverslip and kept for 5 minutes at 4°C. Then coverslip was removed and slides were kept submerged in freshly prepared, prechilled lysis buffer overnight at 4°C. The slides were positioned side by side in horizontal unit of gel electrophoresis, dipped in fresh cold alkaline electrophoresis buffer and left for 20 min. at 4°C in the same solution in order to unwind DNA and convert alkali-labile sites to single strand breaks. The same alkaline buffer was used for carrying out alkaline electrophoresis using 300 mA, 15 V (0.8 v/cm) for 20 min. at 4°C. Then the slides were gently neutralized using 0.4 M tris buffer (pH 7.5). The slides were stained with ethidium bromide and were inspected under an epifluorescent microscope. The microscopic images of comets were scored using Comet IV computer software. Fifty nuclei were analysed per slide.

The data obtained from the experiment was expressed as Mean±SE. The data was analysed by using one way analysis of variance (ANOVA) followed by Tukey pair wise multiple comparison test. The value of $p<0.05$ was considered statistically significant.

Results and Discussion

There was significant DNA damage in the gill tissue of fish exposed to both 8.42ppm and 25.28ppm concentrations of Diclofenac on comparison to control. The comet images of gill from control group have shown circular DNA without any tail formation. (Fig:1a). The results of DNA damage are expressed as percentage of DNA damage, tail length and olive tail moment. The results are shown in the Tables 1, 2 and 3 respectively.

Gill cells of fish exposed to 8.42ppm and 25.28ppm concentrations of diclofenac have shown significant increase in percentage of tail DNA, tail length and olive tail moment on comparison to control. Nuclear DNA with tail formation was observed in gill cells of the exposed fish. The percentage of DNA damage, tail length, and olive tail moment are given in the tables below and graphically represented.

Table: 1 Percentage of DNA damage in gill cells of *Channa punctatus* on exposure to Diclofenac

Diclofenac exposure	% of DNA Damage
Control	4.21 ± 2.4
8.42ppm	14.22 ± 0.8
25.28ppm	48.64 ± 1.6

DNA damage is the most serious consequence of aquatic pollution. DNA damage is primarily a kind of chemical damage which involves changes in molecular structure of DNA. It may be breakage in single strand or double strand of DNA, alkali-labile sites, single base alterations or two base alterations, intra strand cross linkages or inter strand cross linkages. DNA damage during replication process will lead to base mismatch or absence of base and some other related damages.

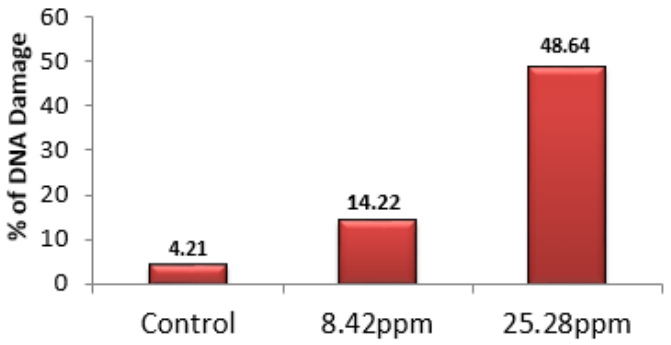

Figure-1. DNA damage in gill cells of *Channa punctatus* on exposure to 8.42 ppm and 25.28 ppm concentrations of Diclofenac against Control

Single cell gel electrophoresis or Comet assay is a versatile, sensitive and cost effective technique used to measure DNA damage and repair in individual cells (Nandakumar *et al*., 2011). The comet assay helps to measure single or double strand DNA breaks, alkali labile sites (apurinic/ apyrimidinic sites), DNA cross-links, base or base-pair damages and apoptotic nuclei in the cells.

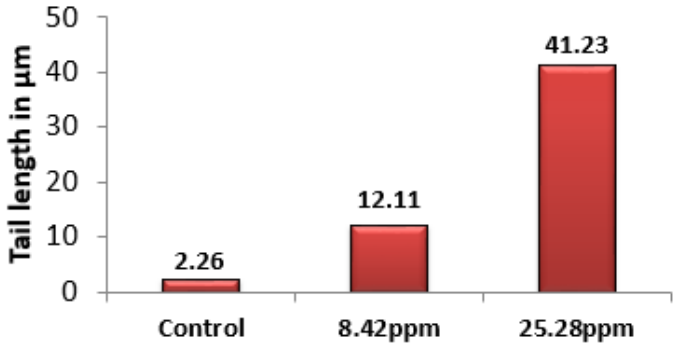

Figure-2. Tail length observed in µm in gill cells of Channa punctatus on exposure to Diclofenac

The three parameters of genotoxicity usually used to evaluate DNA are tail moment, tail length, and tail intensity. The shape, size and amount of DNA in the comet are crucial in the determination of the level of damage of DNA. The extent of DNA migration positively corresponds with the DNA damage present in the cells. It is quantified in terms of an increased amount of determined fluorescence in the tail region, as well as by tail length. The resulting comet like structure is quantified by measuring the length of the tail and or tail moment (the intensity of the migrated DNA multiplied by the respective tail length with respect to DNA (Akpoilih, 2012).

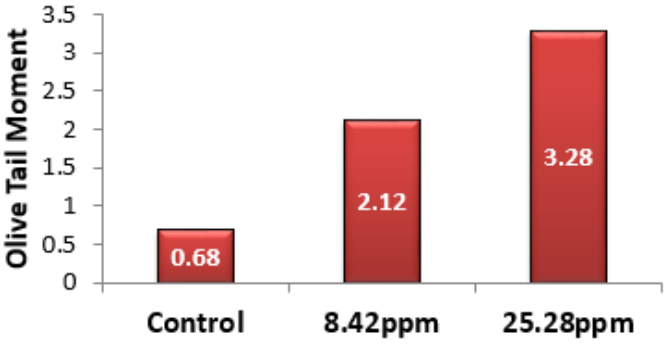

Figure-3. Olive Tail Moment observed in gill cells of *Channa punctatus* on exposure to Diclofenac

A few studies have reported DNA damage in different fish on exposure to Diclofenac. Pandey *et al*., (2017) have reported DNA damage in the liver of *Oreochromis niloticus* after 30 days of exposure to sub lethal doses of diclofenac. Ghelfi *et al*., (2016) have reported that there was no DNA damage in the liver, kidney and blood of *Rhamdia quelen* on exposure to 0.2 µg/L, 2 µg/L, and 20 µg/L concentrations of diclofenac for 96 hours.

Bolognesi *et al*., (1999) have reported a statistical increase of DNA damage in mussels on exposure to Cadmium and also an increase of DNA single strand breaks and micronuclei frequency on exposure to Copper and Mercury. Abbas and Ali (2007) have revealed that there was concentration dependent increase in percentage of DNA damage in liver and kidney cells on exposure to sub lethal concentrations of Cr (VI) in *Oreochromis species*. Sharma *et al*., (2007) have noticed DNA damage in gill, kidney, and erythrocytes of *Mystus vittatus* on exposure to sublethal and nonlethal concentrations of Endosulfan.

Goodale *et al*., (2008) have noticed DNA double strand breaks in medaka fin cell lines exposed to Cr (VI) and chromosome damage in a concentration dependent manner. Ali and Kumar (2008) have reported significant DNA damage in gill followed by kidney and lymphocyte cells in *Channa punctatus* on exposure to different sublethal and nonlethal concentrations of monocrotophos. Ali *et al*., (2009) have reported DNA damage in lymphocyte and gill cells of *Channa punctatus* exposed to chloropyrifos.

Jin *et al*., (2011) have studied the effects of cypermethrin exposure on the induction of hepatic oxidative stress and DNA damage in adult zebra fish and found that even low concentration of pesticide can cause heavy DNA damage and defects in gene expression. Pandey *et al*., (2011) have reported DNA damage in gill cells of *Channa punctatus* on exposure to profenofos. There was an increase in DNA damage in gill and liver on

exposure to Roundup, a glyphosate based herbicide in *Anguilla anguilla* (Guilherme *et al*., 2012).

Kumar *et al*., (2013) have reported the genotoxic potential of Arsenic at different exposure concentrations in *Channa punctatus* and *Carassius auratus*. Ismail *et al*., (2014) have noticed more DNA damage in gill than blood in *Labeo rohita* on exposure to chlorpyriphos. Kousar and Javed (2014) have reported higher percentage of DNA damage in *Cirrhinus mrigala* on exposure to Arsenic, Copper, Zinc and their mixtures in peripheral blood erythrocytes. Arsenic has induced DNA damage in terms of percentage of damaged cells, genetic damage index and cumulative tail length of comets in peripheral blood erythrocytes of *Labeo rohita, Cirrhinus mrigala, Catla catla and Ctenopharyngodon idella* (Kousar and Javed, 2015).

Ullah *et al*., (2016) have noticed DNA damage in the gill tissue of *Labeo rohita* on exposure to Malathion and revealed that there was a linear relation between exposure and DNA damage. Cypermethrin exposure has induced DNA damage in erythrocytes of *Labeo rohita* (Gadhia *et al*., 2016). Sharma and Chada (2017) have reported DNA damage in *Channa punctatus* after subchronic exposure to 4- Nonylphenol. Vieira *et al*., (2018) and Ashwini Ravichandra Jatap (2013) have reported DNA damage in liver, kidney and gills of *Prochilodus lineatus* exposed to imidacloprid.

The decrease of DNA contents in kidney may be due to reduction or absence of the essential factors controlling DNA synthesis which are the substrates (4-Deoxyribonucleoside triphosphates), enzymes (polymerase), template activity of deoxyribonucleic-protein and activators like Mg^{2+} and other divalent ions (Jaya and Shettu, 2015). Velma and Tchounwou (2010) have opined that DNA damage at higher test concentrations in the liver and kidney could be due to elevated levels of hydroperoxides compared to control. Induction of ROS under metallic stress could attack DNA and damage its integrity. The oxidative damage due to reactive oxygen species causes DNA strand breakage.

The higher DNA damage in gills might be due to the fact that the gills are constantly, directly and continuously exposed to the toxicant (Pandey *et al*., 2006). There are several reports on various species of fish which reported higher sensitivity of gills to DNA damage than other cells including lymphocytes, erythrocytes, liver and kidney (Ali *et al*., 2009). The toxicants cause DNA damage in cells through different mode of action such as cellular transformation, gene amplification, breaking DNA protein crosslinks and rupturing of DNA strand (Ullah *et al*., 2016a).

The biotransformation of xenobiotic leads to an increase in the production of Reactive Oxygen Species (ROS) which is highly toxic to fish. ROS can directly break DNA through OH and H_2O_2 resulting in oxidized bases of DNA (Akcha *et al*., 2004). Fish have an antioxidant defence system against ROS but when higher production of ROS surpasses the defence systems of fish, cellular lesions and DNA damage occur (Jha, 2008).

Oxidative DNA damage due to production of ROS is attributing for variable and higher DNA damage in the cells of the gills (Pavlica *et al*., 2001). Sureda *et al*., (2006) have established that there is a close correlation between oxidative stress and DNA damage. Pollution induced ROS can provoke oxidative damage of DNA including strand breaks and base and nucleotide modifications, particularly in sequences with high guanosine content (Viarengo *et al*.,1990).

Conclusion

The present study has clearly indicated that the drug diclofenac would cause DNA damage in the aquatic organisms like fish. The pharmaceuticals should be rationally used and properly disposed before releasing into the aquatic environment at different stages like manufacturing, consumption and waste management.

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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IMAGE RECOGNITION USING DEEP NEURAL NETWORK ALGORITHMS

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Abstract— Deep learning algorithms are a subset of the machine learning algorithms, which target various stages of appropriated depictions. Starting late, different deep learning algorithms have been proposed to settle common human-made intellectual prowess issues. This work means to review the best in deep learning algorithms in PC vision by including the responsibilities and troubles from late assessment papers. It first gives a graph of various deep learning moves close, and their new developments, and a short time later, quickly portrays their applications in different vision tasks.

Keywords:- Deep learning, pooling layers, machine learning, ImageNet

I. INTRODUCTION

Deep learning is a subfield of machine learning that tries to learn raised level considerations in data utilizing reformist structures. It is an emerging methodology and has been comprehensively applied in standard computerized reasoning spaces, for instance, semantic parsing, move learning, formal language preparing, PC vision, and some more[1]. There are generally three huge clarifications behind the impact of deep seeing today the radically extended chip getting ready capacities (with regards to model GPU units), the inside and out cut down the cost of handling gear, and the considerable advances in the machine learning algorithms. Diverse deep learning approaches have been comprehensively investigated and discussed in progressing years. Stressed the critical inspirations and particular responsibilities in an undeniable plan association investigated deep learning research challenges and proposed two or three forward-looking assessment headings[2]. Deep networks have been exhibited to help PC vision tasks since they can remove legitimate features while commonly performing separation. In late ImageNet Large Scale Visual Recognition Challenge (ILSVRC) contentions, different investigators have typically grasped deep learning strategies and achieved top accuracy scores. This survey is proposed to be significant to general neural handling, PC vision, and intelligent media experts who are enthusiastic about the bleeding edge in deep learning in PC vision[3]. It gives a survey of various deep learning algorithms and their applications, especially those applied in the Computer vision space.

II. CHALLENGES

Theoretical Understanding

Despite the advancement accomplished in the hypothesis of deep learning, there is critical space for better understanding in developing and upgrading the CNN architectures toward improving attractive properties, for example, invariance and class segregation[4].

Training with restricted data

Larger models exhibit possible limits and have gotten the inclination of ongoing developments. However, the lack of training data may limit such models' size and learning capacity, mainly when it is costly to entirely acquire marked data. As deep learning related algorithms have pushed ahead the-best in-class consequences of different PC vision tasks by an enormous edge, it turns out to be additionally testing to gain ground what's more. There may be a few headings for all the more impressive[5]. The first bearing is to expand the speculation capacity by increasing the size of the networks.

III. CONVOLUTIONAL NEURAL NETWORKS (CNNS)

The Convolutional Neural Networks (CNN) is quite possibly the most eminent deep learning approaches where numerous

layers are prepared in a lively manner. It has been found exceptionally successful and is additionally the most ordinarily utilized in various PC vision applications.

The pipeline of the overall CNN architecture has appeared in Fig.1. For the most part, CNN comprises three primary neural layers: convolutional, pooling layers, and complete associated layers. Various types of layers play unique jobs.

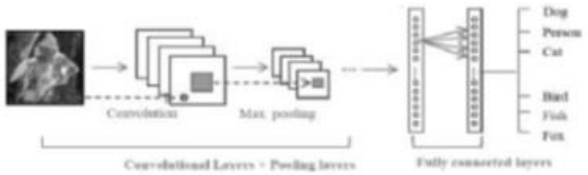

Figure 1: The pipeline of the general CNN architecture

In Fig. 1, an overall CNN engineering for picture classification is demonstrated layer-by-layer[6]. There are two phases for training the organization: a forward stage and an in reverse stage. In the first place, the forward stage's fundamental objective is to speak to the info picture with the current boundaries (loads and inclination) in each layer. The expected output is utilized to figure the misfortune cost with the ground truth names. Second, the regressive stage computes every boundary's angles with chain rules in light of the misfortune cost. All the parameters are refreshed dependent on the inclinations and are ready for the following forward calculation. After adequate cycles of the bold and in reverse stages, network learning can be halted. Next, we will initially present the capacities alongside the new developments of each layer, and afterward, sum up the usually utilized training techniques of the networks[7]. Finally, we present a few notable CNN models, inferred models, and close with the current propensity for utilizing these models in simple applications.

Convolutional layers

In the convolutional layers, CNN utilizes various pieces to convolve the whole picture similarly as the middle of the road part maps, producing other component maps, as showed up in Fig.2.There are three principle inclinations of the convolution activity:

1. The weight sharing instrument in a comparative part map lessens the number of boundaries

2. Close by accessibility learns connections among neighboring pixels

3. Invariance to the territory of the article. Because of the preferences presented by the convolution activity. Use it as a trade for the related layers to enliven the learning cycle.

One fascinating philosophy of taking care of the convolutional layers is the Network in Network (NIN) strategy. The fundamental idea is to substitute the ordinary convolutional layer with a little multilayer perceptron comprising of different connected layers with nonlinear commencement limits, supplanting the straight channels with nonlinear neural networks.

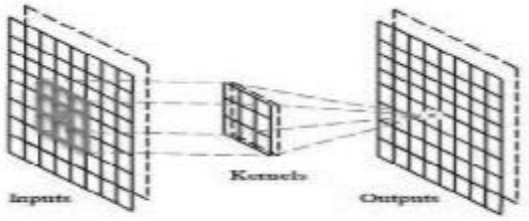

Figure 2: The operation of the convolutional layer

Pooling layers

A pooling layer follows a convolutional layer. Moreover, it can be used to reduce the parts of feature maps. Like convolutional layers, pooling layers are like manner translation-invariant because their computations think about neighboring pixels. Standard pooling and max pooling are the most by and large used systems[8]. Fig. 3 gives a model for a full pooling measure. For 8x8 segment maps, the output maps lessened to 4x4 estimations, with a most extreme pooling size 2x2. For max pooling and standard pooling, given a nitty hypothetical assessment of their presentations. A relationship between the two pooling tasks found that most extreme pooling could provoke faster association, select overwhelming invariant features, and improve the theory.

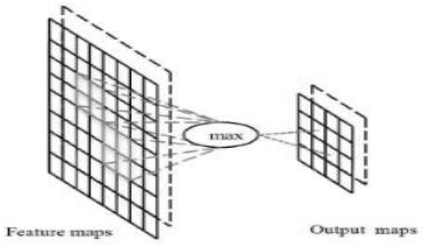

Figure 3: The operation of the max-pooling layer

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Stochastic Pooling

An inconvenience of max-pooling is that it is sensitive to overfit the preparation set, making it hard to summarize well to test tests. It expects to address this issue, a stochastic pooling approach that replaces the regular deterministic pooling tasks with a stochastic methodology by discretionarily picking the authorization inside each pooling district as indicated by a multinomial flow. It is indistinguishable from standard max-pooling yet with various copies of the information picture, each having little neighborhood disfigurements. This stochastic nature is helpful to hinder the overfitting issue[9].

Spatial Pyramid Pooling (SPP)

Ordinarily, the CNN-based strategies require a fixed-size input picture. This restriction may decrease the recognition accuracy for photos of an optional size. To wipe out this limitation, He et al. utilized the by and large CNN design; be that as it may, replaced the last pooling layer with a spatial pyramid pooling layer[10]. The spatial pyramid pooling can isolate fixed-length depictions from inspirational pictures, creating a versatile response for dealing with different scales, sizes, perspective extents. It can be applied in any CNN structure to help the show of this structure.

Deep Belief Networks (DBNs)

The Deep Boltzmann Machine (DBM) is another deep learning calculation where the units are again coordinated in layers. Diverged from DBNs, whose principle two layers structure an undirected graphical model whose lower layers structure a planned generative model, the DBM has an undirected relationship across its structure. In like manner, various strategies hope to improve the practicality of DBMs[11]. The upgrades can either occur at the pre-preparing stage or the preparation stage. The multi-gauge preparing plan was utilized to prepare the DBM, which beats past picture portrayal methods.

Deep Energy Models (DEMs)

The Deep Energy Model (DEM) is a later method to manage deep train architectures. Not under any condition like DBNs and DBMS, which share the property of having diverse stochastic covered layers, the DEM has a solitary layer of stochastic hid units for pragmatic preparing and surmising. Even though RBMs are not as sensible as CNNs for vision applications, some authentic models embrace RBMs to vision tasks[12]. To manage the task of modeling similar shape pictures, which learns extraordinary probability courses over article shapes, both credibility of tests from the transport and hypothesis to new occasions of a comparative shape class.

IV. RESULTS

Despite being constrained by larger models, they experienced overfitting and underfitting issues when there is little preparation information or short preparation time. To avoid this deficiency, Wu et al. has developed new approaches, such as Image, for information increment and multi-scale pictures. They moreover amassed a large supercomputer for deep neural networks. They created a significantly improved coordinating calculation. The course of action result achieved a general 20% improvement in the last one with a focal five error speed of 5.33%.

Figure 4: Image classification examples from AlexNet

Parametric Rectified Linear Unit to make the standard reviewed incitation units and deduced a reliable statement method. This plot incited 4.94% top-5 test error and beat human-level execution (5.1%) out of the blue. Tantamount yields were refined whose technique showed up at a 4.8% test error by using a get-together of normalized bunch networks.

V. CONCLUSION

Deep learning and develops an arrangement that intends to separate the current significant learning composing. It isolates the deep learning algorithms into four classes based on the basic model they got from Convolutional Neural Networks, Boltzmann Machines, and Sparse Coding. The bleeding edge

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approaches of the three categories are discussed and separated in detail. For the PC vision area applications, the paper principally reports the movements of CNN-based plans, as it is the most broadly utilized and by and large proper for pictures. Most strikingly, some new articles have point-by-point motivating advances demonstrating that some CNN-based algorithms have quite recently outperformed human raters' precision. Despite the promising results declared up until this point, there is a necessary space for extra advances. For example, the hidden theoretical foundation doesn't yet clarify under what conditions they will perform well or beat various approaches and decide the ideal structure for a particular task.

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DEEP RESIDUAL NETWORKS BASED IMAGE RECOGNITION-REVIEW

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Abstract:- Deep neural networks show to have an elite on image order undertakings while being more hard to prepare. The unpredictability and disappearing angle issue ordinarily take a great deal of time and more computational capacity to prepare deeper neural networks. Deep residual networks (ResNets) can make the training cycle quicker and accomplish more precision contrasted with their identical neural networks. ResNets accomplish this improvement by adding an essential skip association corresponding to the layers of convolutional neural networks. In this venture, we first plan a ResNet model to play out the image arrangement task on the Tiny ImageNet dataset with high precision. At that point, we think about the presentation of this ResNet model with its identical Convolutional Network (ConvNet). Our discoveries show that ResNets are more inclined to overfitting regardless of their higher exactness

Keywords: Deep neural networks, ResNet, ReLU.

I. INTRODUCTION

Recently deep convolutional neural networks have achieved a movement of revelations in the field of image classifications. Inspired by fundamental cells and responsive field divulgences in neuroscience by Hubel and Wiesel, Deep convolutional neural nets (CNNs) have a layered structure, and each layer is included convolutional stations. By convolving these channels with the data image, incorporate vectors for the accompanying layer are conveyed, and through sharing limits, they can be adjusted with no issue[1]. Early layers in convolutional neural networks address low-level area features, for instance, edges and concealing differentiations, while deeper layers endeavor to find more incredible shapes and are more expressive. One can improve the gathering execution of CNNs by propelling these convolutional channels' assortment and un equivocality through deepening the network. Along these lines, deep CNNs, despite having better classification execution, are more diligently to prepare[2]. One compelling approach to tackle these issues recommended is Residual Networks (ResNets). The fundamental distinction in ResNets is that they have easy route associations corresponding to their typical convolutional layers. Despite convolution layers, these alternate route associations are consistently alive, and the slopes can undoubtedly back spread through them, which brings about quicker training. This way, profound CNNs, despite having better arrangement execution, are more enthusiastic about preparing. One successful approach to take care of these issues recommended is Residual Networks (ResNets). The fundamental contrast in ResNets is that they have easy route connections corresponding to their typical convolutional layers. As opposed to convolution layers, these easy route connections are consistently alive, and the angles can occur without much of a stretch back spread through them, which brings about quicker training. One could depict ResNets as various fundamental blocks that are sequentially associated with one another, and there are likewise alternate route connections corresponding to every essential square, and it gets added to its output. Figure 1 shows an essential square presented in. If the info and output size for a total square are equivalent, the alternate way association is just

a character framework [3]. Else one can utilize regular pooling (for decrease) and zero cushioning (for development) to change the size.

Has looked at changed fundamental blocks for one alternate way association in ResNets (Figure 1) and shows that adding a parameter layer after option can sabotage ResNet favorable circumstances since there is no quick route for gradients to back through spread any longer. However, considering that condition, there is no tremendous favorable position or hindrance for adding an un-parameter layer like ReLU after the option module[4]..

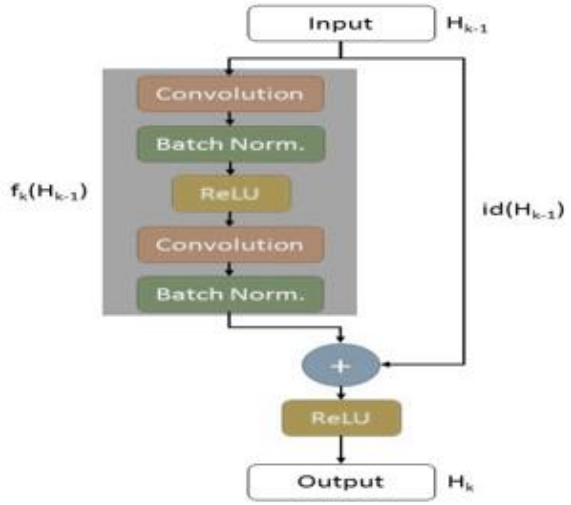

Figure 1: ResNet Basic Block

II. NETWORK DESIGN

The ResNet model presented is our beginning stage for the organization plan. This model is explicitly intended for images in ImageNet and acknowledges images with size 256*256 and characterizes them in 1000 classes. One can utilize various techniques, to begin with, this prepared model and modify it to acknowledge small ImageNet images with size 64*64 and group them into 200 classifications. A nave strategy could be merely up-inspecting a 64*64 picture to a 256*256 and afterward offer it to the prepared model, or entirely skipping the primary layer and addition the first picture as the contribution of the second convolutional layer, and afterward adjusting a couple of the last layers to get higher exactness[5].

1. Network Architectures

We will see that this model experiences overfitting on the off chance that we train the first 18-layer ResNet presented in on little ImageNet dataset. To lessen overfitting, we presented another Basic Block (BB) that appeared in figure 2 by adding a dropout layer with a boundary 0:5 between the two convolution layers in the essential square that appeared in figure 1.

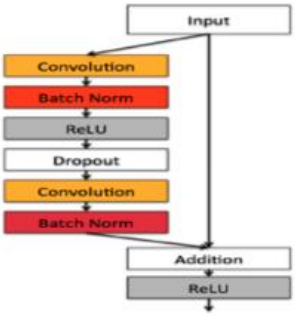

Figure 2: New basic block with a dropout layer to reduce overfitting

Figure 2 shows one of the ResNets we intended for the picture order undertakings. This model gives a Top-1 arrangement exactness of 49% on the approval set of little ImageNet[6].

2. Dataset

This dataset comprises a training set of 100 000 images, an approval set of 10,000 images, and a test set of 10,000 images from 200 unique classes of items. All images in tiny ImageNet are 64*64, thus multiple times less than images in the first ImageNet dataset, 256*256. Figure3 shows a couple of test images from various classes of small imagenet datasets[12].

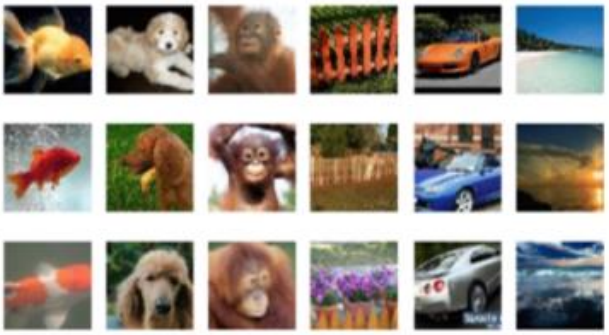

Figure 3: Few sample images from tiny imagenet datasets

3. Torch

The torch is a logical open-source figuring system with comprehensive help for neural network implementations. In this

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task, we utilized this structure to actualize and prepare diverse ResNet and ConvNet Models[7]. The torch has numerous predefined neural network layers and bundles that empower us to run our GPUs' training algorithms

III. RESULTS

As referenced previously, even though the evaporating inclination is a significant issue for deep neural networks, in shallow ConvNets, it is anything but a severe deal. To notice this impact, we contrasted two external networks and 7 and 9 layers. Figure 4 shows the misfortune work and training and approval exactness of these two networks on the CIFAR-10 dataset. As we see for the nine-layer network, ResNet and ConvNet have comparable execution, and for even shallower networks (7 layers), the ResNet execution is far more terrible than plain ConvNets[8]. This result bodes well since when you add the output of a convolutional layer with its information, you are fundamentally averaging a trained, prepared data with the crude data, and that would hurt the training if there were no other advantage to it. At that point, we attempted to prepare numerous deep ResNets shifting from 12 to 21 layers and see which one performs better on the Tiny Imagenet data set[9]. One could see that the ResNet has a lot higher exactnesses than plain ConvNet, and it prepares a lot quicker. In this ResNet, the approval precision, 13%, and training exactness 30% percent higher than its ConvNet same. The contrast between training exactness and approval precision is a decent marker of over fitting, and dependent on our results, we understood that ResNets are more inclined to overfitting[10].

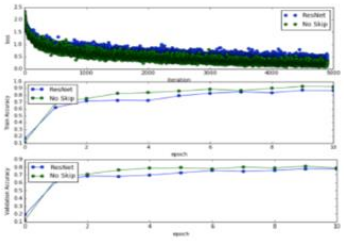

Figure 4: Validation accuracy and loss at every epoch for a 7-layer network over CIFAR-10 dataset

Initially, this distinction was considerably higher for ResNet (around 30%), yet we utilized the dropout and stochastic expansion method that was depicted to decrease this overfitting; however, it could diminish it by 6%[11]. Another approach to diminish the overfitting is to have a more modest boundary set, which implies fewer convolution layers.

IV. CONCLUSION

As we clarified in our results, adding an essential easy route association can improve the picture grouping errand's accuracy and make the training cycle a lot quicker. However, the exchange is that residual networks are more inclined to overfitting, which is unfortunate. We demonstrated that by utilizing distinctive machine learning techniques like drop out layer and stochastic enlargement, we could lessen this overfitting, and whenever planned appropriately, we can have fewer boundaries that result in a lot more modest overfitting (14%). We likewise noticed that results are all the more remarkable for profound networks, and if utilized inappropriately, it could even damage the presentation for too shallow networks.

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Efficient synthesis, antibacterial and anti-inflammatory properties of 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridines

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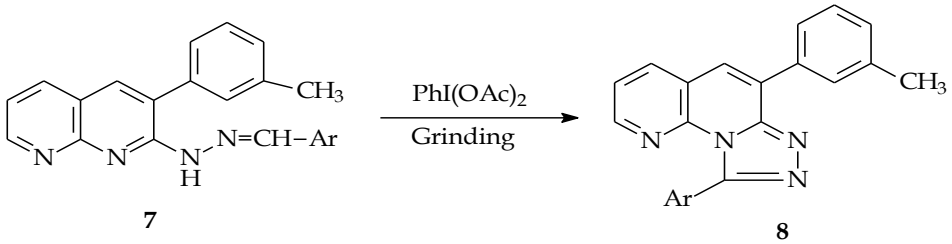
Abstract-A simple and highly efficiently method for the synthesis of 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo [4,3-*a*][1,8]naphthyridines **8** by the oxidation of the corresponding aryl aldehyde 1-[3-(3-methylphenyl)[1,8]naphthyridin-2-yl]hydrazones **7** using iodobenzene diacetate [$PhI(OAc)_2$] in the solid state at RT under grinding conditions is described. The yields are very good and purity is high. The structures of compounds **3-8** were confirmed by their spectroscopic (IR, ^1H NMR and MS) and analytical data. The compounds **8** have been tested for their antibacterial and anti-inflammatory activities.

Keywords: 1,2,4-Triazole, 1,8-naphthyridine, iodobenzene diacetate [$PhI(OAc)_2$] , solid state, antibacterial activity, anti-inflammatory activity.

Graphical abstract



7 **8**

Introduction:

Fused 1,2,4-triazoles have emerged as an important class of nitrogen heterocycles attracting significant synthetic interest because of their pharmacological and biological activities[1-4]. Though various methods for the synthesis of these compounds are known[5-10], some involve long reaction times, toxic oxidants and high reaction temperatures and even then may produced low yields. Therefore a convenient and eco-friendly method for the synthesis of fused 1,2,4-triazoles is highly desirable. 1,8-Naphthyridines are very interesting compounds with wide ranging biological properties[11-13]. In recent years, iodobenzene diacetate [$PhI(OAc)_2$] has emerged as a potential oxidizing agent in different areas of organic synthesis[14-16], because it is non-toxic and easy to handle. Solid state reactions without using harmful organic solvents is of great interest especially in relation to environmental concerns today. So, the grinding method has increasingly been used in organic synthesis in recent years. Compared to traditional methods, many organic reactions occur more efficiently

in the solid state than in solution and in some cases even more selectively. Furthermore, the solid state reaction has many advantages: reduction pollution, low costs and simplicity in process and handling[17,18]. These factors are beneficial to industry as well as to environment.

Inspired by these facts and in continuation of our interest on solid state(solvent-free) organic transformations of 1,8-naphthyridine derivatives[19-21], we report herein, a simple, efficient and convenient method for the 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo[4,3-*a*][1,8]-naphthyridines using iodobenzene diacetate [$PhI(OAc)_2$] in the solid state.

Results and Discussion

Condensation of 2-aminonicotinaldehyde **1** with 3-methylphenyl-acetonitrile **2** in the presence of solid KOH under solvent-free grinding conditions at RT afforded 3-(3-methylphenyl)[1,8]naphthyridin-2-amine **3,** which is converted into 3-(3-methylphenyl)-1,2-dihydro[1,8]naphthyridin-2-one **4** by the reaction with HNO_2. Treatment of **4** with $POCl_3$ under microwave irradiation yielded 2-chloro-3-(3-methylphenyl)[1,8]naphthyridine **5**, which on hydrazinolysis with refluxing hydrazine hydrate furnished 2-hydrazino-3- (3-methylphenyl) [1,8]naphthyridine **6**.

The hydrazine **6** on condensation with various aromatic aldehydes in the presence of catalytic amount of PTSA in solvent-free grinding conditions at RT afforded the corresponding aryl aldehyde 1-[3-(3-methylphenyl) [1,8]naphthyridin-2-yl] hydrazones **7** in excellent yields.

Oxidative cyclization of hydrazones **7** with $PhI(OAc)_2$ in the solid state at RT yielded the respective 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo[4,3-*a*][1,8]-naphthyridines **8** (**Scheme I**). The reaction is facile, clean, efficient and is devoid of any by-products. The reactions proceed efficiently in very good yields (85-94%) within a few minutes. Furthermore, it is to be noted highly pure products were obtained using this simple procedure and in most cases no further purification was needed. The process is enviro-friendly. The experimental procedure is very simple and avoids sophistication.

In a typical case, a mixture of hydrazone **7a** (Ar = C_6H_5) and $PhI(OAc)_2$ was ground in a mortar by pestle at RT for 7.0 min. The solid was combined with cold water and filtered to give 6-(3-methylphenyl)-9-phenyl [1,2,4]triazolo[4,3-*a*][1,8]-naphthyridine **8a** (Ar = C_6H_5) in 87% yield.The generality of this oxidative transformation was established by treating other hydrazones **7b-j** with $PhI(OAc)_2$ under solid state grinding conditions and in all cases respective 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo [4,3-*a*][1,8]naphthyridines **8b-j** were obtained in 84-94% yields (**Table II**).

The structural assignment of compounds **3-8** were based on their elemental analysis and spectral (IR, ^{1}H NMR and MS) data (**Table I** and **II**). The advantages of this protocol include a simple reaction set-up not requiring specialized equipment, short reaction times, non-toxicity of the reagent, mild reaction conditions and high product yields with excellent purity.

Antibacterial activity

All the compounds **8** were screened for their antibacterial activity against *Escherichia coli* and *Bacillus subtilis* using Gentamycin as standard drug. The activity was determined using filter paper disc technique of Vincent and Vincent[22] at 250 and 500 μg/disc concentrations. The results are given in **Table-III.** All the compounds were active against both the bacteria at the concentration of 250 μg/disc. The activity of the compound depends upon the nature and position of the substituent at the phenyl group. Compounds **8b**, **8d**, **8e** and **8f** promising significant antibacterial activity and the remaining compounds exhibited either good or moderate antibacterial activity. Introduction of nitro group at aryl moiety decreases the activity of the compounds. The compound **8e** showed significant activity against both the organisms comparable with that of Gentamycin.

Anti-inflammatory activity

The anti-inflammatory activity of the compounds **8** were tested by applying carrageenan induced rat paw edema method[23], using Diclofenac sodium as reference drug for comparison. The results are presented in **Table IV**. The screening data indicate that all the compounds **8a-j** exhibited interesting activity, however with a degree of variation. The compounds **8c**, **8d**, **8e**, **8i** and **8j** exhibited significant anti-inflammatory activity. Rest of the compounds showed moderate anti-inflammatory activity.

Experimental Section

Melting points were measured on a Cintex melting point apparatus and are uncorrected. Homogeneity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) were recorded on a Perking-Elmer FT-IR spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer (chemical shifts in δ ppm) and mass spectra on a *PE-SCIEX* API 3000 LC-MS/MS System. The 3-methylphenylacetonitrile **2** was purchased from Aldrich Chemical Company.

3-(3-Methylphenyl)[1,8]naphthyridin-2-amine 3

A mixture of 2-aminonicotinaldehyde **1** (0.01 mol), 3-methylphenylacetonitrile **2** (0.01 mol) and solid KOH (0.01 mole) was ground by pestle and mortar at RT for 2.0 min. After completion of the reaction, as monitored by TLC, the reaction mixture was treated with cold water. The solid obtained was filtered, washed with water and purified by recrystallization from methanol to afforded **3,** yield 97%; m.p. 195^{o}C. Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.68; H, 5.58; N, 17.90%. IR (KBr): 3466, 3076 (NH_2), 1634 (C-NH_2), 1591 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s 3H, CH_3), 5.46 (s, 2H, NH_2), 7.40 (m, 1H, C_6-H), 7.74 (s, 1H, C_4-H), 7.96 (m, 1H, C_5-H), 8.83 (m, 1H, C_7-H), 7.18-7.32 (m, 4H, Ar-H); LC-MS: *m/z* 236.1568 $[M+H]^+$

3-(3-Methylphenyl)-1,2-dihydro[1,8]naphthyridin-2-one 4

To a cold solution of **3** (0.01 mol) in 2 M HCl (25 mL) was added $NaNO_2$ solution (0.01 mol in 25 mL water) and the reaction mixture was stirred at RT for 0.5 hr and treated with chilled water. The precipitated solid was filtered, washed with water and purified by recrystallization from methanol to obtain **4,** yield 96%; m.p. 182^{o}C. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.35; H, 5.14; N, 11.89%. IR (KBr): 3163 (NH), 1649 (C=O), 1598 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s 3H, CH_3), 7.55 (m, 1H, C_6-H), 7.81 (s, 1H, C_4-H), 7.96 (m, 1H, C_5-H), 8.70 (m, 1H, C_7-H), 7.20-7.42 (m, 4H, Ar-H), 9.75 (brs, 1H, NH); LC-MS: *m/z* 237.1849 $[M+H]^+$

2-Chloro-3-(3-methylphenyl)[1,8]naphthyridine 5

A mixture of **4** (0.01 mol) and $POCl_3$ (10 mL) was refluxed for 1.5 hr. The reaction mixture was cooled and poured onto a mixture of crushed ice and $NaHCO_3$. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford **5,** yield 95%; m.p. 142^{o}C. Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.84; H, 4.37; N, 11.04%. IR (KBr): 1593 cm^{-1} (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s 3H, CH_3), 7.55 (m, 1H, C_6-H), 8.12 (s, 1H, C_4-H), 8.23 (m, 1H, C_5-H), 9.15 (m, 1H, C_7-H), 7.22-7.42 (m, 4H, Ar-H); LC-MS: *m/z* 255.1691 $[M+H]^+$

2-Hydrazino-3-(3-methylphenyl)[1,8]naphthyridine 6

A mixture of **5** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water bath for 4.0 hr. The reaction mixture was cooled and poured into ice-cold water. The solid separated was filtered, washed with water and purified by recrystallization from ethanol to yield **6,** yield: 96%; m.p. 108^{o}C. Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C,

72.09; H, 5.65; N, 22.42%. IR (KBr): 3433, 3328, 3171 ($NHNH_2$), 1616 (C-$NHNH_2$), 1560 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s 3H, CH_3), 6.15 (brs, 2H, NH_2), 7.62 (m, 2H, C_4-H, C_6-H), 7.98 (m, 1H, C_5-H), 8.83 (m, 1H, C_7-H), 7.18-7.38 (m, 5H, NH, 4Ar-H); LC-MS: *m/z* 251.1852$[M+H]^+$

General procedure for the synthesis of aryl aldehyde 1-[3-(3-methylphenyl)[1,8]naphthyridin-2-yl]hydrazones 7

A mixture of **6** (0.01 mole), aromatic aldehyde (0.01 mol) and PTSA (0.015 mol) was ground by pestle and mortar at RT for the specified time (**Table II**). On completion of the reaction (monitored by TLC), the reaction mixture was treated with ice-cold water. The product which separated was filtered, washed with water and purified by recrystallization from ethanol to give **7** (**Table II**).

General procedure for the synthesis of 9-aryl-6-(3-methylphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines 8

A mixture of appropriate hydrazone **7** (0.01 mol) and $PhI(OAc)_2$ (0.01 mol) was ground in a mortar by pestle at RT for the period indicated in **Table II**. After complete conversion as indicated by TLC, the reaction mixture was digested with cold water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to furnish **8** (**Table II**).

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Table I — IR, ^{1}H NMR and mass spectral data of compounds **7** and **8**

Compd	IR (KBr) ν_{max} in cm^{-1}	^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm)	LC-MS $[M+H]^+$ *m/z*
7a	3344 (NH), 1619 (C=N)	2.40 (s, 3H, CH_3), 7.65 (m, 1H, C_6-H), 7.80 (m, 2H, C_4-H, C_5-H), 8.30 (m, 1H, C_7-H), 8.47 (s, 1H, N=CH), 6.98-7.60 (m, 9H, Ar-H), 10.28(s, 1H, NH).	339.2237
7b	3353 (NH), 1618(C=N)	2.40 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.68(m, 1H, C_6-H), 7.75 (m, 2H, C_4-H, C_5-H), 8.32 (m, 1H, C_7-H), 8.43 (s, 1H, N=CH), 6.97-7.65 (m, 8H, Ar-H), 10.26 (s, 1H, NH).	353.2607
7c	3346 (NH), 1614 (C=N)	2.42 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.76(m, 2H, C_4-H, C_6-H), 8.03 (m, 1H, C_5-H), 8.30 (m, 1H, C_7-H), 8.45 (s, 1H, N=CH), 6.90-7.65 (m, 8H, Ar-H), 10.25 (s, 1H, NH).	369.2565
7d	3352 (NH), 1621 (C=N)	2.43 (s, 3H, CH_3), 7.70 (m, 2H, C_4-H, C_6-H), 8.00 (m, 1H, C_5-H), 8.38 (m, 1H, C_7-H), 8.43 (s, 1H, N=CH), 6.98-7.65 (m, 8H, Ar-H), 10.24 (s, 1H, NH).	373.2253
7e	3343 (NH), 1619 (C=N)	2.45 (s, 3H, CH_3), 7.72 (m, 2H, C_4-H, C_6-H), 8.02 (m, 1H, C_5-H), 8.36 (m, 1H, C_7-H), 8.42 (s, 1H, N=CH), 7.00-7.63 (m, 8H, Ar-H), 10.27 (s, 1H, NH).	373.2253
7f	3349 (NH), 1623 (C=N)	2.43 (s, 3H, CH_3), 7.76 (m, 1H, C_6-H), 7.97 (m, 2H, C_4-H, C_5-H), 8.40 (m, 1H, C_7-H), 8.53 (s, 1H, N=CH), 7.08-7.52 (m, 8H, Ar-H), 10.35 (s, 1H, NH).	357.2415
7g	3334 (NH), 1620 (C=N)	2.44 (s, 3H, CH_3), 7.76 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.40 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 7.04-7.48 (m, 8H, Ar-H), 10.28 (s, 1H, NH).	384.2152
7h	3350 (NH), 1623 (C=N)	2.43 (s, 3H, CH_3), 7.73 (m, 1H, C_6-H), 8.02 (m, 2H, C_4-H, C_5-H), 8.36 (m, 1H, C_7-H), 8.48 (s, 1H, N=CH), 7.02-7.46 (m, 8H, Ar-H), 10.35 (s, 1H, NH).	384.2152
7i	3342 (NH), 1622 (C=N)	2.45 (s, 3H, CH_3), 7.75 (m, 1H, C_6-H), 7.95 (m, 2H, C_4-H, C_5-H), 8.38 (m, 1H, C_7-H), 8.52 (s, 1H, N=CH), 7.07-7.50 (m, 8H, Ar-H), 10.32 (s, 1H, NH).	384.2152
7j	3353 (NH), 1619 (C=N)	2.41 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.50 (m, 2H, C_4-H, C_6-H), 7.65 (m, 1H, C_5-H), 8.32 (m, 1H, C_7-H), 8.40 (s, 1H, N=CH), 6.85-7.36 (m, 7H, Ar-H), 10.17 (s, 1H, NH).	399.2757

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Table I — IR, ^{1}H NMR and mass spectral data of compounds **7** and **8 -** *Contd..*

Compd	IR (KBr) ν_{max} in cm^{-1}	^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm)	LC-MS $[M+H]^+$ *m/z*
8a	1608 (C=N)	2.45 (s, 3H, CH_3), 7.88 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.42(m, 1H, C_2-H), 7.23-7.60 (m, 9H, Ar-H).	337.1918
8b	1610(C=N)	2.46(s,3H,CH_3)2.48 (s, 3H, CH_3), 7.80 (m, 2H, C_3-H, C_5-H), 8.30 (m, 1H, C_4-H), 8.45 (m, 1H, C_2-H), 7.25-7.58 (m, 8H, Ar-H)	351.2147
8c	1611 (C=N)	2.45 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.85 (m, 2H, C_3-H, C_5-H), 8.16 (m, 1H, C_4-H), 8.43 (m, 1H, C_2-H), 7.00-7.60 (m, 8H, Ar-H).	367.2282
8d	1606(C=N)	2.48(s, 3H, CH_3), 7.83 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.42 (m, 1H, C_2-H), 7.23-7.62 (m, 8H, Ar-H).	371.1838
8e	1608(C=N)	2.46 (s, 3H, CH_3), 7.86 (m, 2H, C_3-H, C_5-H), 8.24 (m, 1H, C_4-H), 8.40 (m, 1H, C_2-H), 7.20-7.58 (m, 8H, Ar-H).	371.1838
8f	1607(C=N)	2.49 (s, 3H, CH_3), 7.85(m, 2H, C_3-H, C_5-H), 8.16(m, 1H, C_4-H), 8.42 (m, 1H, C_2-H), 7.18-7.60 (m, 8H, Ar-H).	355.2121
8g	1606 (C=N)	2.46 (s, 3H, CH_3), 7.87 (m, 2H, C_3-H, C_5-H), 8.20 (m, 1H, C_4-H), 8.46 (m, 1H, C_2-H), 7.24-7.62 (m, 8H, Ar-H).	382.2120
8h	1604 (C=N)	2.45 (s, 3H, CH_3), 7.85 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.43 (m, 1H, C_2-H), 7.22-7.63 (m, 8H, Ar-H).	382.2120
8i	1601 (C=N)	2.48 (s, 3H, CH_3), 7.86 (m, 2H, C_3-H, C_5-H), 8.16 (m, 1H, C_4-H), 8.45 (m, 1H, C_2-H), 7.20-7.60 (m, 8H, Ar-H).	382.2120
8j	1610 (C=N)	2.45 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.87 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.45(m, 1H, C_2-H), 6.98-7.58 (m, 7H, Ar-H).	397.2562

Table II — Physical and analytical data of compounds **7** and **8**

Compd	Reaction time (min)	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calcd)		
					C	H	N
7a	1.5	78	95	$C_{22}H_{18}N_4$	78.19 (78.08	5.37 5.36	16.60 16.56)
7b	2.0	91	97	$C_{23}H_{20}N_4$	78.48 (78.38	5.74 5.72	15.95 15.90)
7c	2.0	97	94	$C_{23}H_{20}N_4O$	75.09 (74.98	5.49 5.47	15.25 15.21)
7d	1.5	102	95	$C_{22}H_{17}ClN_4$	70.97 (70.87	4.62 4.60	15.06 15.03)
7e	2.0	165	98	$C_{22}H_{17}ClN_4$	70.98 (70.87	4.61 4.60	15.07 15.03)
7f	1.5	105	96	$C_{22}H_{17}FN_4$	74.25 (74.14	4.83 4.81	15.76 15.72)
7g	2.0	143	94	$C_{22}H_{17}N_5O_2$	69.03 (68.92	4.48 4.47	18.31 18.27)
7h	1.5	112	96	$C_{22}H_{17}N_5O_2$	69.01 (68.92	4.49 4.47	18.32 18.27)
7i	2.0	156	97	$C_{22}H_{17}N_5O_2$	69.02 (68.92	4.48 4.47	18.30 18.27)
7j	2.0	178	96	$C_{24}H_{22}N_4O_2$	78.78 (78.66	6.07 6.05	15.34 15.29)
8a	7.0	160	87	$C_{22}H_{16}N_4$	78.65 (78.55	4.80 4.79	16.71 16.66)
8b	7.5	178	90	$C_{23}H_{18}N_4$	79.02 (78.83	5.20 5.18	16.02 15.99)
8c	8.0	195	88	$C_{23}H_{18}N_4O$	75.49 (75.39	4.96 4.95	15.32 15.29)
8d	7.5	220	92	$C_{22}H_{15}ClN_4$	71.35 (71.25	4.09 4.08	15.15 15.11)
8e	7.0	256	94	$C_{22}H_{15}ClN_4$	71.34 (71.25	4.10 4.08	15.16 15.11)
8f	7.5	208	92	$C_{22}H_{15}FN_4$	74.66 (74.56	4.28 4.27	15.84 15.81)
8g	7.5	236	84	$C_{22}H_{15}N_5O_2$	69.37 (69.28	3.98 3.96	18.39 18.36)
8h	8.0	222	85	$C_{22}H_{15}N_5O_2$	69.39 (69.28	3.97 3.96	18.41 18.36)
8i	8.0	278	88	$C_{22}H_{15}N_5O_2$	69.38 (69.28	3.98 3.96	18.40 18.36)
8j	7.5	215	87	$C_{24}H_{20}N_4O_2$	72.82 (72.71	5.09 5.08	14.17 14.13)

Table III - Antibacterial screening results of compounds **8**

Compd	Inhibition zone (in mm)			
	E. coli at		*B. subtilis* at	
	250 μg/disc	500 μg/disc	250 μg/disc	500 μg/disc
8a	9.0	15.5	6.0	9.5
8b	10.0	16.5	6.5	12.5
8c	9.0	15.0	5.5	9.0
8d	10.5	18.5	6.5	13.0
8e	11.0	21.0	7.0	13.5
8f	10.0	17.0	6.5	12.5
8g	6.5	9.0	5.0	8.0
8h	7.5	10.5	5.5	9.0
8i	8.0	12.0	6.5	11.5
8j	9.5	16.0	6.0	9.0
Gentamycin	12.0	22.0	8.0	15.0

Table IV – Anti-inflammatory activity date of compounds **8**
(Carrageenan-induced paw edema test in rats)

Compd[a]	Rat paw edema in mL[b] (Treatment in hours)			
	1h	2h	3h	4h
8a	2.42±0.295 11.67	2.08±0.310** 27.52	1.42±0.254** 54.48	1.02±0.265** 67.61
8b	2.24±0.278 18.24	1.82±0.297** 36.58	1.12±0.309** 64.10	0.98±0.284** 68.88
8c	2.26±.0267 17.51	1.91±0.281*** 33.44	1.21±0.302*** 61.21	0.85±0.262*** 73.01
8d	2.21±0.285 19.34	1.88±0.292*** 34.49	1.18±0.275*** 62.17	0.82±0.270*** 73.96
8e	2.11±0.264 22.99	1.68±0.289*** 41.46	1.06±0.284*** 66.02	0.72±0.308*** 77.14
8f	2.14±0.289 21.89	1.96±0.276*** 31.70	1.09±0.266*** 65.06	0.81±0.254*** 74.28
8g	2.22±0.254 18.97	1.87±0.263** 38.84	1.15±0.255** 63.14	0.96±0.268** 69.52
8h	2.30±0.305 16.05	1.78±0.304** 37.97	1.13±0.249** 63.78	0.93±0.302** 70.47
8i	2.18±0.308 20.40	1.72±0.295*** 40.06	1.11±0.278*** 64.42	0.75±0.249*** 76.19
8j	2.16±0.310 21.16	1.69±0.306*** 41.11	1.10±0.256*** 64.74	0.78±0.251*** 75.23
control	2.74±0.242 NA	2.87±0.254 NA	3.12±0.289 NA	3.15±0.291 NA
Diclofenac sodium	1.84±0.251*** 32.84	1.32±0.254*** 54.01	0.91±0.257*** 70.83	0.52±0.309*** 83.49

[a]Dose level: test compounds (100mg/kg b.wt), Diclofenac sodium (10mg/kg b.wt)
[b]Values are expressed as mean± SD (number of animals N= 6 rats)
Statistically significant compared to respective control values, ***P<0.001, **P<0.01, *P<0.05 (Dunnet's test)

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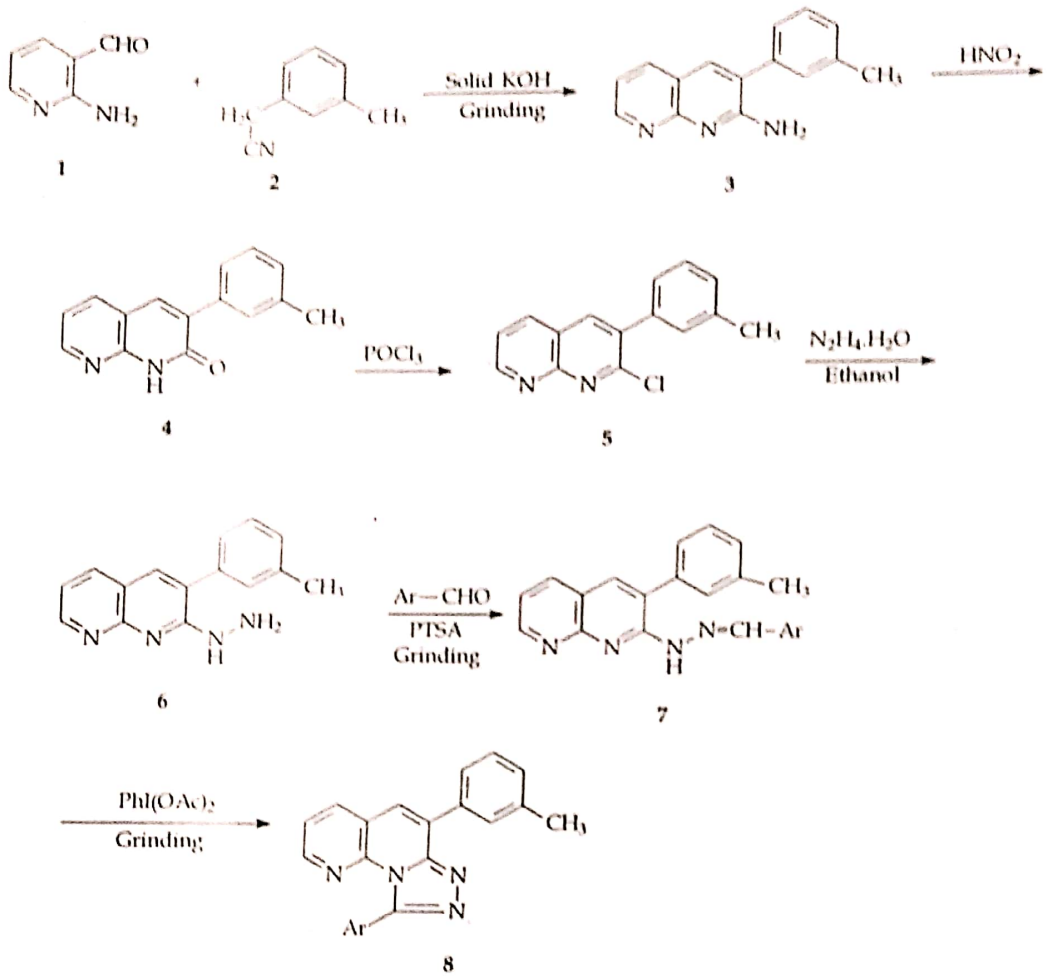

Ar		Ar	
a :	C_6H_5	f :	4-F C_6H_4
b :	4-$CH_3C_6H_4$	g :	2-$NO_2C_6H_4$
c :	4-$CH_3OC_6H_4$	h :	3-$NO_2C_6H_4$
d :	2-Cl C_6H_4	i :	4-$NO_2C_6H_4$
e :	4-Cl C_6H_4	j :	3,4-$(CH_3O)_2C_6H_3$

Scheme I

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$CeCl_3.7\ H_2O$ catalyzed Friedlander synthesis of 1, 8-naphthyridines under solvent-free conditions

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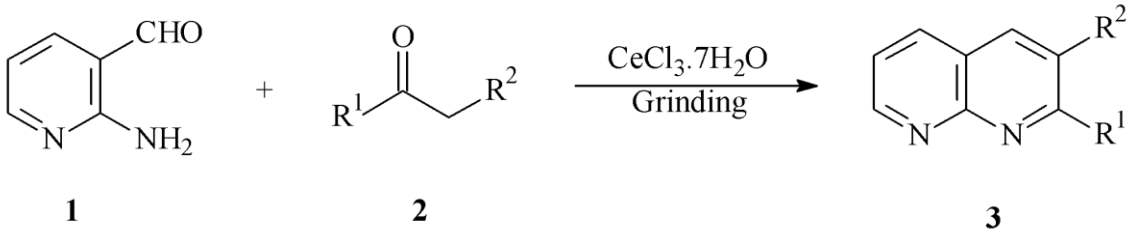
Abstract

The Friedlander condensation of 2-aminonicotinaldehyde **1** with various carbonyl compounds containing α-methylene group **2** in the presence of catalytic amount of reusable catalyst $CeCl_3.\ 7H_2O$ in solvent-free grinding conditions at RT furnished the corresponding 1, 8-naphthyridines**3** (**Scheme I**). The development of new methods with greater efficacy, straightforward procedures and better yields still is desirable.

Keywords: 1, 8-naphthyridines**,** Friedlander condensation, solvent-free conditions.



1 **2** **3**

Graphical Abstract

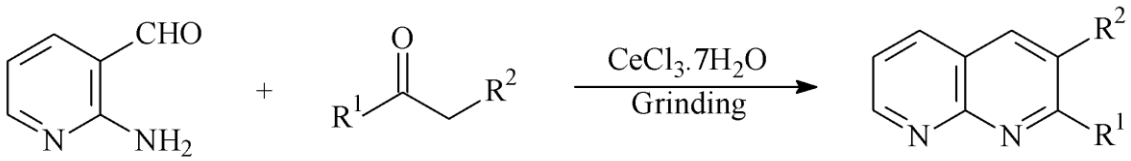
INTRODUCTION

The reaction proceeds efficiently in high yields at ambient temperature within a few minutes. Various 1,3-dicarbonyl compounds including alkyl acetoacetates, acetylacetone, benzoylacetone, ω-benzoylacetophenone, acetoacetamides and benzoylacetanilides give the corresponding substituted 1,8-naphthyridines without any side products. In general the reaction is very clean, rapid and efficient and involves a simple work-up procedure. Unlike previous methods, the present protocol does not require high temperature to produce 1,8-naphthyridine derivatives.

Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone with the carbonyl compound containing a reactive α-methylene group. 2-Aminonicotinaldehyde condense readily with active methylene compounds in the presence of base[1] and acid[2] catalysts to give 1,8-naphthyridines. However, some of these methods suffer from disadvantages such as long reaction times, lower yields and requirement of severe conditions. Therefore, the development of new methods with greater efficacy, straightforward procedures and better yields still is desirable.

Interest in solvent-free reactions has increased in recent years, though reactions in solution are much more common. This is due to the fact that, in many cases, ground state organic reactions occur more effectively and selectively than the solution reactions. Furthermore, the solvent-free reaction has many advantages such as reduced pollution, low costs and simplicity in process and handling.

In view of this, herein we report the $CeCl_3.7H_2O$ catalyzed Friedlander condensation under solvent-free grinding conditions at RT. The synthetic route is presented in **Scheme I**.



1 **2** **3**

3	**R^1**	**R^2**
a	CF_3	$COOC_2H_5$
b	CH_3	$COOC_2H_5$
c	OH	$COOC_2H_5$
d	C_6H_5	$COOC_2H_5$
e	CH_3	$COCH_3$
f	CH_3	COC_6H_5
g	C_6H_5	COC_6H_5
h	CH_3	C_6H_5NHCO
i	CH_3	*4*-$CH_3C_6H_4NHCO$
j	CH_3	*4*-$CH_3OC_6H_4NHCO$
k	CH_3	2-ClC_6H_4NHCO
l	CH_3	4-ClC_6H_4NHCO
m	C_6H_5	C_6H_5NHCO
n	C_6H_5	*4*-$CH_3C_6H_4NHCO$
o	C_6H_5	*4*-$CH_3OC_6H_4NHCO$
p	C_6H_5	2-ClC_6H_4NHCO
q	C_6H_5	4-ClC_6H_4NHCO

Scheme I

EXPERIMENTAL SECTION

A mixture of 2-aminonicotinaldehyde **1** (0.01 mole), active methylene compound **2** (0.01 mole) and $CeCl_3.7H_2O$ (0.01 mole) was ground by pestle and mortar at room temperature for the period indicated in **Table II**. On completion of the reaction as monitored by TLC, the reaction mixture was treated with cold water. The solid separated was filtered, washed with water and recrystallized from appropriate solvent to furnish **3** (**Table II**). The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The catalyst was recovered and reused in subsequent

reactions, three times without losing any significant activity. The newly synthesized compounds were further confirmed by IR and ^{1}HNMR analysis data.

RESULTS AND DISCUSSION

Spectral and analytical physical data were described below tables I & II.

Table I – IR and ^{1}H NMR spectral data of 1,8-naphthyridines **3**

Compd	R^1	R^2	IR (KBr) ν_{max} in cm^{-1}	^{1}H NMR (200 MHz, DMSO-d_6) (δ, ppm)
3a	CF_3	$COOC_2H_5$	1734 (C=O) 1605 (C=N)	1.50 (t, 3H, CH_2CH_3), 4.50 (q, 2H, CH_2CH_3), 8.76 (s, 1H, C_4-H), 8.40 (m, 1H, C_5H), 7.70 (m, 1H, C_6-H), 9.35 (m, 1H, C_7-H).
3b	CH_3	$COOC_2H_5$	1720 (C=O) 1608 (C=N)	1.50 (t, 3H, CH_2CH_3), 2.72 (s, 3H, CH_3), 4.42 (q, 2H, CH_2CH_3), 8.31 (s, 1H, C_4-H), 8.68 (m, 1H, C_5H), 7.62 (m, 1H, C_6-H), 9.12 (m, 1H, C_7-H).
3d	C_6H_5	$COOC_2H_5$	1705 (C=O) 1605 (C=N)	1.45 (t, 3H, CH_2CH_3), 4.43 (q, 2H, CH_2CH_3), 8.40 (m, 2H, C_4-H, C_5-H), 8.00 (m, 1H, C_6-H), 9.15 (m, 1H, C_7-H), 7.35-7.82 (m, 5H, Ar-H).
3e	CH_3	$COCH_3$	1685(C=O) 1610 (C=N)	2.40 (s, 3H, $COCH_3$), 2.82 (s, 3H, CH_3), 8.40 (m, 2H, C_4-H, C_5-H), 7.72 (m, 1H, C_6-H), 9.10 (m, 1H, C_7-H).
3f	CH_3	COC_6H_5	1656(C=O) 1600 (C=N)	2.73 (s, 3H, CH_3), 8.45 (m, 2H, C_4-H, C_5H), 7.93 (m, 1H, C_6-H), 9.00 (m, 1H, C_7-H), 6.98-7.52 (m, 5H, Ar-H).
3g	C_6H_5	COC_6H_5	1654(C=O) 1602 (C=N)	7.92 (s, 1H, C_4-H), 8.35 (m, 1H, C_5-H), 9.12 (m, 1H, C_7-H), 6.83-7.62 (m, 11H, C_6-H, 10Ar-H).
3h	CH_3	C_6H_5NHCO	3248(N-H) 1679 (C=O) 1602 (C=N)	2.92 (s, 3H, CH_3), 8.32 (m, 2H, C_4-H, C_5-H), 9.10 (m, 1H, C_7-H), 7.03-7.82 (m, 6H, C_6-H, 5Ar-H), 10.38 (s, 1H, NH).
3m	C_6H_5	C_6H_5NHCO	3200(N-H) 1655 (C=O) 1600 (C=N)	8.10 (s, 1H, C_4-H), 8.65 (m, 1H, C_5-H), 7.86 (m, 1H, C_6-H), 9.16 (m, 1H, C_7-H), 6.97-7.78 (m, 10H, Ar-H), 10.25 (s, 1H, NH).

Table II –Yield %, Reaction period and Physical data of 1, 8-Naphthyridines **3**

Compd	R^1	R^2	Reaction Period (min)	Yield (%)	m.p. °C		Mol. Formula
					Found	Reported	
3a	CF_3	$COOC_2H_5$	5.5	92	125	125[8]	$C_{12}H_9F_3N_2O_2$
3b	CH_3	$COOC_2H_5$	5.0	94	85	85-86[1]	$C_{12}H_{12}N_2O_2$
3c	OH	$COOC_2H_5$	5.0	90	206	205-07[1]	$C_{11}H_{10}N_2O_3$
3d	C_6H_5	$COOC_2H_5$	5.5	92	104	104[7]	$C_{17}H_{14}N_2O_2$
3e	CH_3	$COCH_3$	5.0	94	147	146-147[1]	$C_{11}H_{10}N_2O$
3f	CH_3	COC_6H_5	5.0	92	143	143[6]	$C_{16}H_{12}N_2O$
3g	C_6H_5	COC_6H_5	5.5	90	160	160[6]	$C_{21}H_{14}N_2O$
3h	CH_3	C_6H_5NHCO	5.0	92	215	215[5]	$C_{16}H_{13}N_3O$
3i	CH_3	$4\text{-}CH_3C_6H_4NHCO$	7.0	94	170	170[5]	$C_{17}H_{15}N_3O$
3j	CH_3	$4\text{-}CH_3OC_6H_4NHCO$	8.0	89	149	150[5]	$C_{17}H_{15}N_3O_2$
3k	CH_3	$2\text{-}ClC_6H_4NHCO$	7.0	92	150	150[5]	$C_{16}H_{12}ClN_3O$
3l	CH_3	$4\text{-}ClC_6H_4NHCO$	6.5	96	206	205[5]	$C_{16}H_{12}ClN_3O$
3m	C_6H_5	C_6H_5NHCO	7.0	90	279	285[7]	$C_{21}H_{15}N_3O$
3n	C_6H_5	$4\text{-}CH_3C_6H_4NHCO$	6.5	92	277	278[7]	$C_{22}H_{17}N_3O$
3o	C_6H_5	$4\text{-}CH_3OC_6H_4NHCO$	7.0	90	218	218[7]	$C_{22}H_{17}N_3O_2$
3p	C_6H_5	$2\text{-}ClC_6H_4NHCO$	8.0	92	276	277[7]	$C_{21}H_{14}ClN_3O$
3q	C_6H_5	$4\text{-}ClC_6H_4NHCO$	6.5	95	200	201[7]	$C_{21}H_{14}ClN_3O$

CONCLUSION

We have demonstrated a simple and efficient procedure for the synthesis of 1, 8-naphthyridines by employing $CeCl_3.7H_2O$ as a reusable catalyst. The salient features of this method include operational simplicity, improved reaction rates, high yields of products and avoidance of the use of hazardous acids or bases.

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Table II –Yield %, Reaction period and Physical data of 1, 8-Naphthyridines 3

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3a	CF_3	$COOC_2H_5$	5.5	92	125	125[8]	$C_{12}H_9F_3N_2O_2$
3b	CH_3	$COOC_2H_5$	5.0	94	85	85-86[1]	$C_{12}H_{12}N_2O_2$
3c	OH	$COOC_2H_5$	5.0	90	206	205-07[1]	$C_{11}H_{10}N_2O_3$
3d	C_6H_5	$COOC_2H_5$	5.5	92	104	104[7]	$C_{17}H_{14}N_2O_2$
3e	CH_3	$COCH_3$	5.0	94	147	146-147[1]	$C_{11}H_{10}N_2O$
3f	CH_3	COC_6H_5	5.0	92	143	143[6]	$C_{16}H_{12}N_2O$
3g	C_6H_5	COC_6H_5	5.5	90	160	160[6]	$C_{21}H_{14}N_2O$
3h	CH_3	C_6H_5NHCO	5.0	92	215	215[5]	$C_{16}H_{13}N_3O$
3i	CH_3	$4\text{-}CH_3C_6H_4NHCO$	7.0	94	170	170[5]	$C_{17}H_{15}N_3O$
3j	CH_3	$4\text{-}CH_3OC_6H_4NHCO$	8.0	89	149	150[5]	$C_{17}H_{15}N_3O_2$
3k	CH_3	$2\text{-}ClC_6H_4NHCO$	7.0	92	150	150[5]	$C_{16}H_{12}ClN_3O$
3l	CH_3	$4\text{-}ClC_6H_4NHCO$	6.5	96	206	205[5]	$C_{16}H_{12}ClN_3O$
3m	C_6H_5	C_6H_5NHCO	7.0	90	279	285[7]	$C_{21}H_{15}N_3O$
3n	C_6H_5	$4\text{-}CH_3C_6H_4NHCO$	6.5	92	277	278[7]	$C_{22}H_{17}N_3O$
3o	C_6H_5	$4\text{-}CH_3OC_6H_4NHCO$	7.0	90	218	218[7]	$C_{22}H_{17}N_3O_2$
3p	C_6H_5	$2\text{-}ClC_6H_4NHCO$	8.0	92	276	277[7]	$C_{21}H_{14}ClN_3O$
3q	C_6H_5	$4\text{-}ClC_6H_4NHCO$	6.5	95	200	201[7]	$C_{21}H_{14}ClN_3O$

CONCLUSION

We have demonstrated a simple and efficient procedure for the synthesis of 1, 8-naphthyridines by employing $CeCl_3.7H_2O$ as a reusable catalyst. The salient features of this method include operational simplicity, improved reaction rates, high yields of products and avoidance of the use of hazardous acids or bases.

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