DESIGN, SYNTHESIS AND CHARACTERIZATION OF NEW 1,8-NAPHTHYRIDINE SUBSTITUTED HETEROCYCLES AND THEIR BIOLOGICAL EVALUATION

ज्ञान-विज्ञान विमुक्तये
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C O N T E N T S

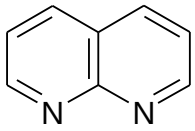
CHAPTER I

Introduction to 1,8-Naphthyridines and microwave organic synthesis

CHAPTER-I

1.1 Chemistry of 1,8-Naphthyridines : Nitrogen containing heterocyclic compounds are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications. Heterocyclic compounds containing naphthyridine moiety are interesting as potential biologically active substances.

Literature survey reveals that nitrogen containing heterocyclic compounds have attracted considerable attention as they endowed with a wide range of biological activity. 1,8-Naphthyridines **1** are an important class of nitrogen containing heterocyclic compounds, several derivatives of which have been found to possess diverse types of biological and pharmacological activities. The bioactive nature of substituted and fused 1,8-naphthyridines has made their synthesis an important target.



1

The first naphthyridine derivative was prepared in 1893 by Reissert[1] who suggested the name, but the first unsubstantiated 1,5-naphthyridine[2] and 1,8-naphthyridine[3] were not obtained until 1927.

Increasing interest in the chemistry of naphthyridines is reflected in the number of previous reviews made by Allen, [4] by Weiss and Hauser,[5] by Paudler and Kress[6], by Czuba[7] and by Brown[8].

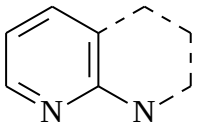
When compared to other isomeric compounds, 1, 8-naphthyridines are well known from their varied biological activities. Therefore a brief account of the methods of synthesis of 1,8-naphthyridines is abridged below.

1.2 Various approaches for the synthesis of 1,8-Naphthyridines: The methods of synthesis of 1,8-naphthyridines may be divided into two types.

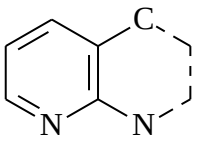
Type - I involves cyclization into a pyridine ring and these methods require adaptations of the synthesis of quinolines by the following methods.

(a) Ethoxymethylenemalonic ester (EMME)
(b) Conrad-Limpach and Knorr
(c) Combes
(d) Chichibabin
(e) Skraup and related syntheses

All these ring closure reactions involved carbon-to-carbon condensations of the ionic type in which a pyridine ring acts as electron donar and a carbonyl group as the electron acceptor.



TYPE - I



TYPE - II

Type - II involves the cyclization with 3-substituted 2-aminopyridines. These syntheses are generally analogous methods of synthesis of quinolines including the

(a) Von-Niementowski, and
(b) Friedlander method

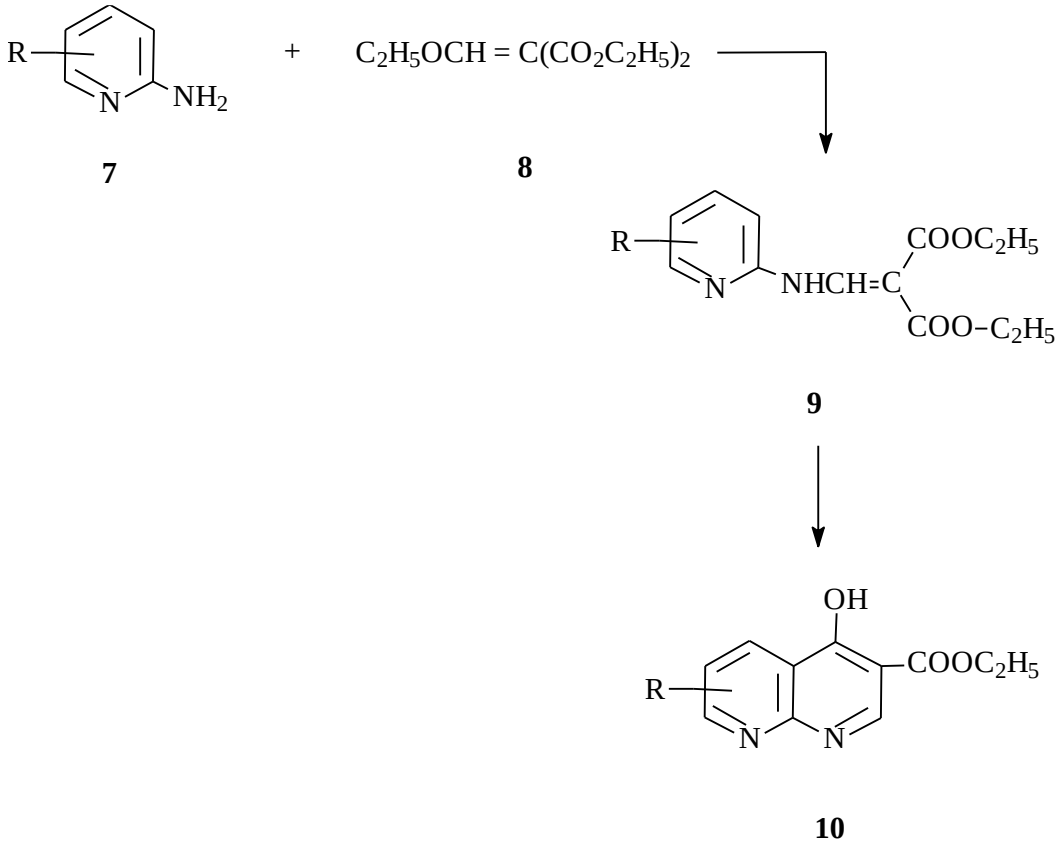
In these methods, the formation of the new pyridine ring requires two condensations, nitrogen to carbon and carbon to carbon. The nitrogen-carbon condensation involves anil and amide formation. The carbon-carbon condensation is generally of the aldol or acylation type. Since **Type-II** procedures usually do not involve cyclization into pyridine ring, they are not limited by the factors encountered in the methods of **Type-I**.

Type - I Syntheses

Cyclization of 2-aminopyridine derivatives

(a) Ethoxymethylenemalonic ester (EMME) method

Reaction of 2-aminopyridine **7** with ethoxymethylenemalonic ester (EMME) **8** results in the formation of a crotonate **9**, which on cyclization give 3-carbethoxy-4-hydroxy-1,8-naphthyridine **10**.[9]

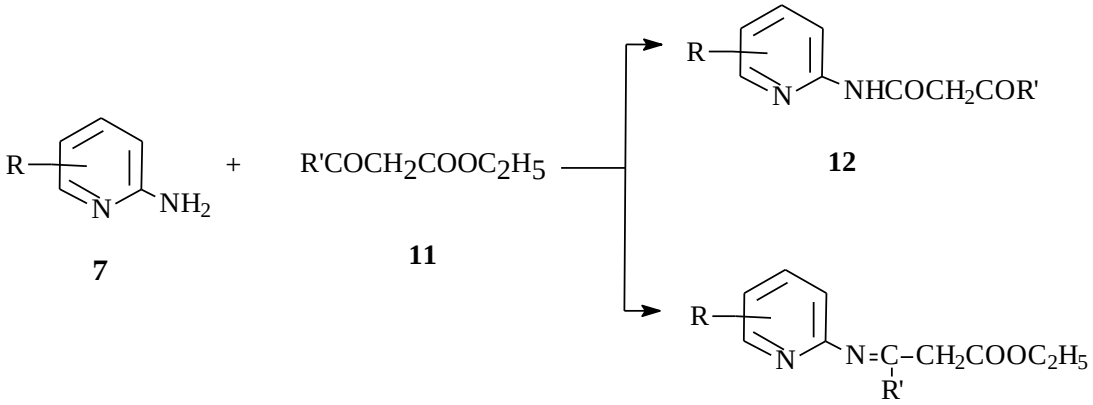


7 **8** **9** **10**

(b) Conrad-Limpach and Knorr method : (Syntheses with β-keto esters)

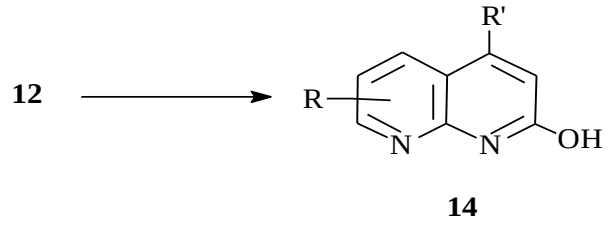
These syntheses involve the condensation of 2-aminopyridines **7** and β-keto esters **11** in two ways. The former reaction involves the ester group of the β-

keto ester to form an amide **12**, whereas the latter reaction involves the ketonic group of the β-keto ester to form anil **13**.



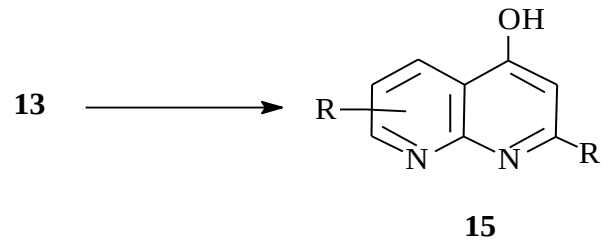
Knorr reaction

The amide **12** can give 2-hydroxy-1,8-naphthyridine **14** on cyclization. The amide **12**, (R = 6-NH_2, R′ = CH_3) from 2,6-diaminopyridine and ethyl acetoacetate undergoes the Knorr reaction to give 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine in good yield.[10,11]



Conrad-Limpach reaction

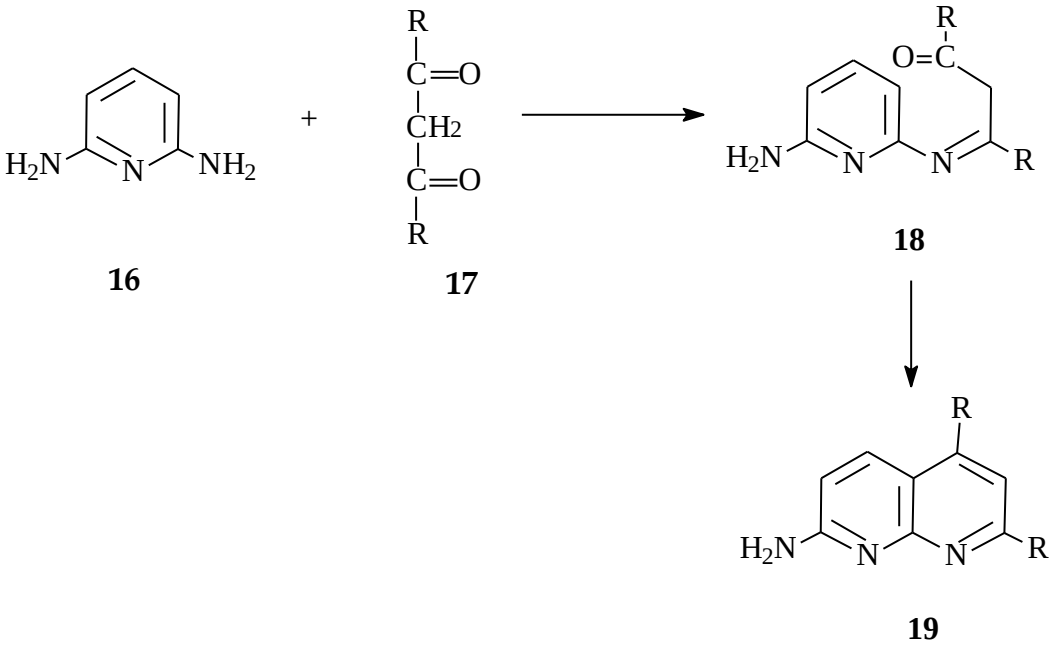
The anil **13** on cyclization gives 4-hydroxy-1,8-naphthyridine **15**. The anil **13** (R = 6-NH_2, R′ = CH_3) from 2,6-diaminopyridine and ethyl acetoacetate undergoes the Conrad-Limpach reaction conditions to give 2-methyl-4-hydroxy-7-amino-1,8-naphthyridine in poor yield.[12]



(c) Combes method

(i) Syntheses with β-diketones

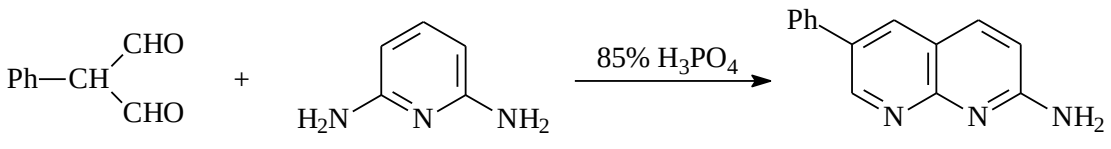
2,6-Diaminopyridine **16** reacts with β-diketones **17** to give an anil **18**, which undergoes cyclization to give 2,4-disubstituted-7-amino-1,8-naphthyridine **19**.[13,14] The percentage of yield is increased when conc. H_2SO_4 is used in place of $ZnCl_2$.[15]



16 **17** **18** **19**

(ii) Syntheses from β-dialdehydes

2,6-Diaminopyridine **16** reacts with phenylmalonaldehyde **20** to afford 2-amino-6-phenyl-1,8-naphthyridine **21**.[16]

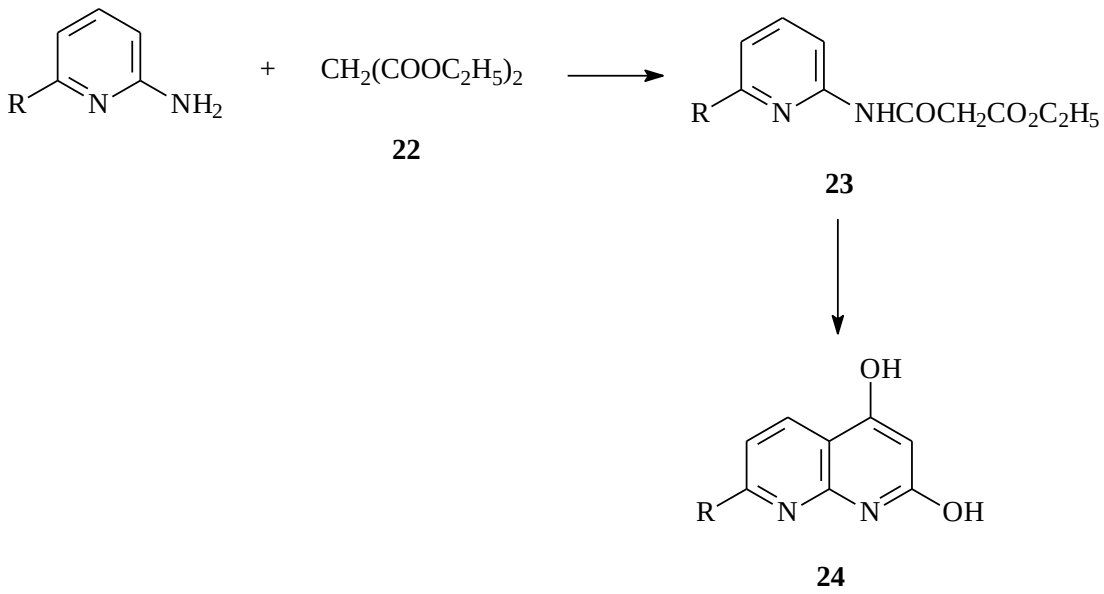


20 **16** **21**

(d) Chichibabin method (Syntheses with diethyl malonoate)

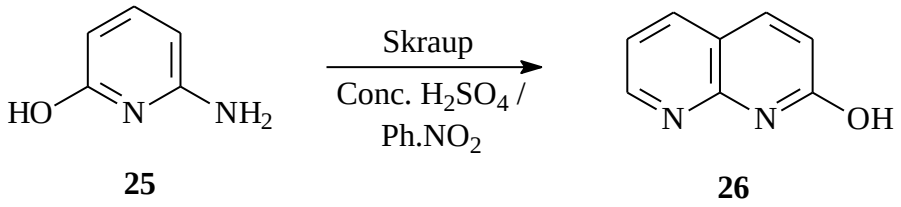
2-Aminopyridines react with diethyl malonoate **22** to produce intermediate amide **23**, which on cyclization give 2,4-dihydroxy-1,8-naphthyridines **24**. However,

the cyclization takes place, only when an electron donating group like amino, acetamido or ethoxy occupy 6-position.[17]



Skraup synthesis

The Skraup reaction on 2-amino-6-hydroxypyridine **25** using H_2SO_4 and nitrobenzene has yielded 2-hydroxy-1,8-naphthyridine **26**.[18]

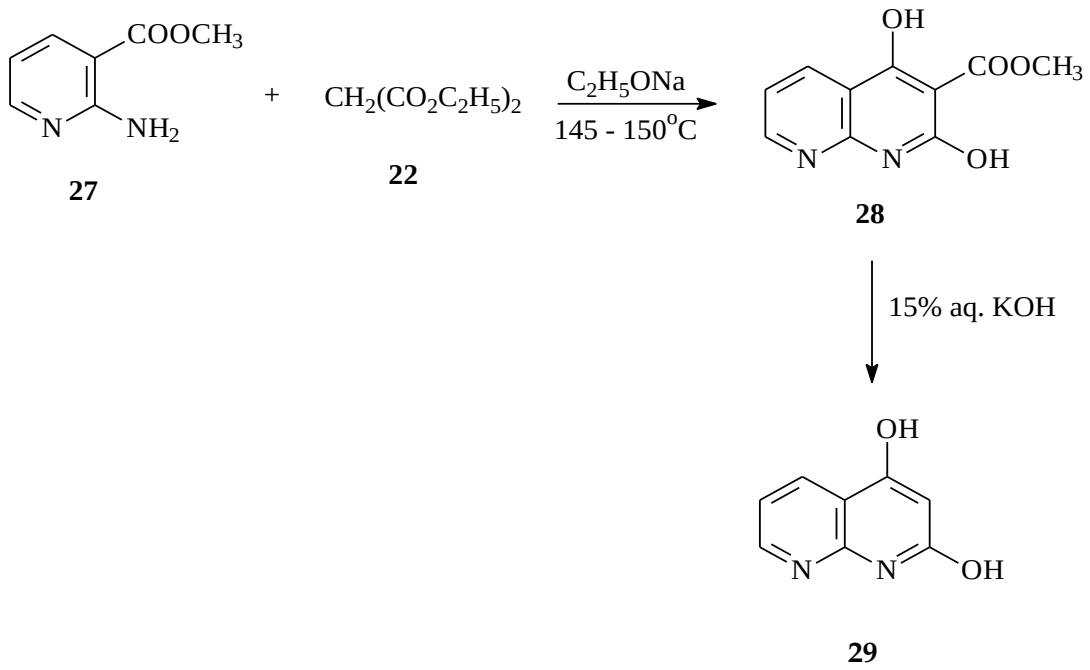


Type - II Syntheses

Cyclization with 3-substituted-2-aminopyridine derivatives

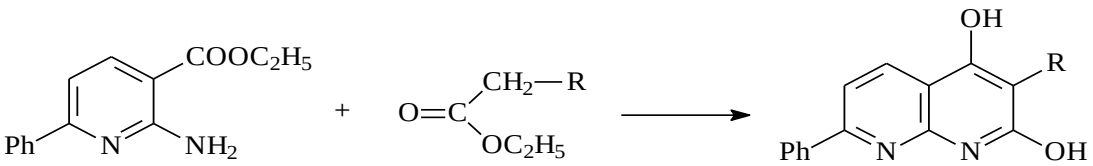
(i) Von-Neimentowski method

The reaction of methyl 2-aminonicotinate **27** with diethyl malonoate **22** gave 2,4-dihydroxy-3-carbomethoxy-1,8-naphthyridine **28** which on hydrolysis and decarboxylation, furnished 2,4-dihydroxy-1,8-naphthyridine **29**. The occurrance of an ester interchange is note-worthy.[19]



27 **22** **28** **29**

Ethyl 2-amino-6-phenylnicotinate **30** reacts with more reactive esters (ethyl nitroacetate, ethyl cyanoacetate, diethyl malonoate) to form into the corresponding 1,8-naphthyridines **31**.[20]

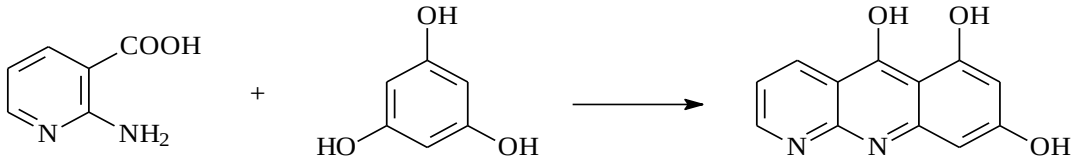


30 **31**

R = NO_2, CN, -COOEt

(ii) From 2-aminonicotinic acid

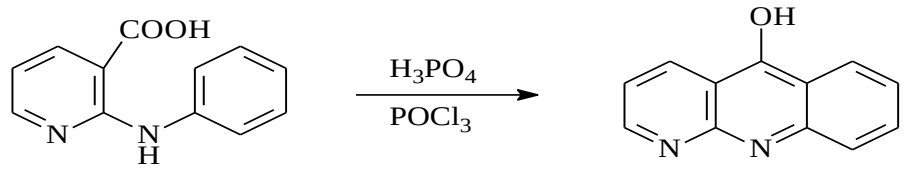
Condensation of 2-aminonicotinic acid **32** with phloroglucinol **33** afforded **34**.[21]



32 **33** **34**

(iii) From 2-anilinonicotinic acid

The cyclization of 2-anilinonicotinic acid **35** with H_3PO_4 and $POCl_3$ has yielded **36**.[22]

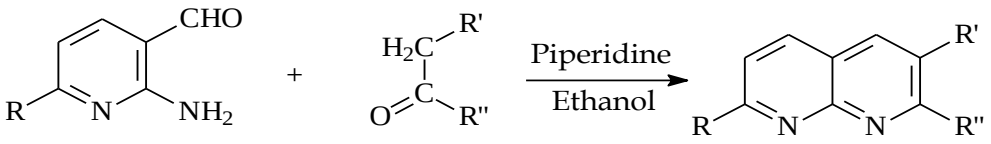


35 **36**

(iv) Friedlander method

Syntheses with 2-aminonicotinaldehydes

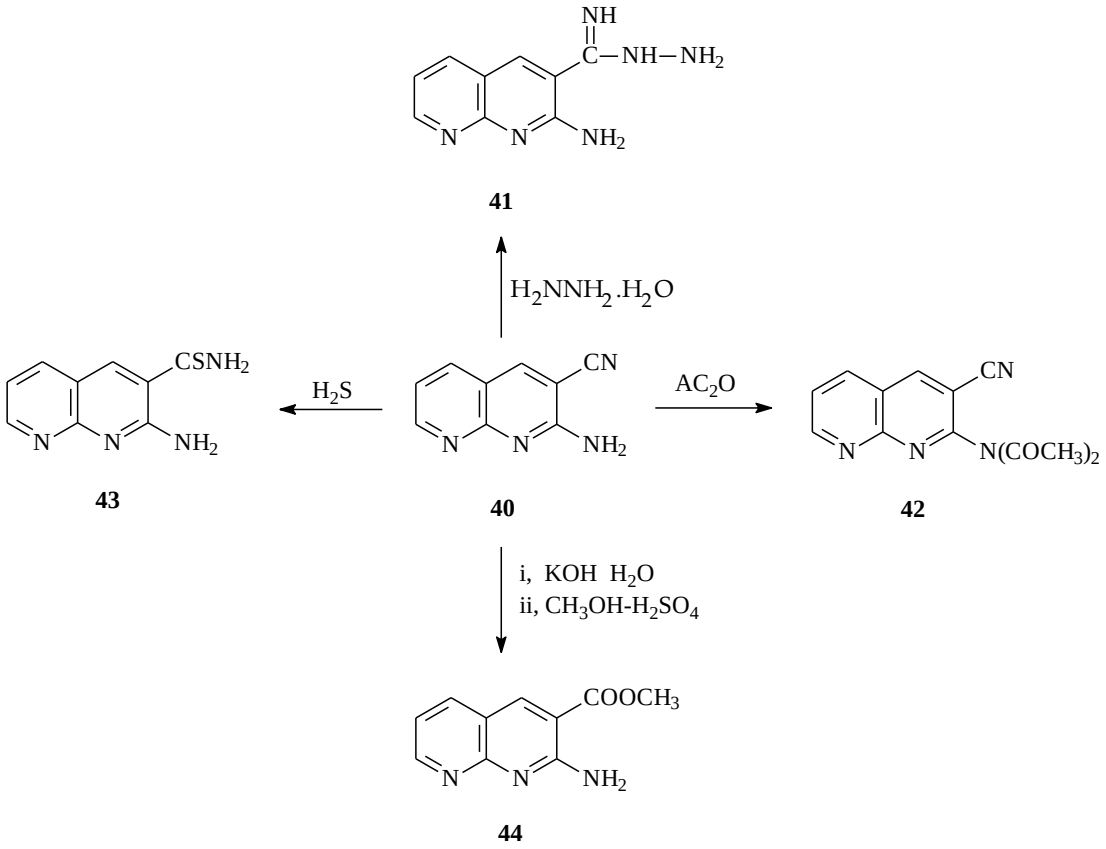
2-Aminonicotinaldehydes **37** are potentially more reactive than 2-aminonicotinates. The condensation of keto methylene compounds **38** with **37** with piperidine as catalyst has proved to be an excellent method for the synthesis of 2,3-disubstituted 1,8-naphthyridines **39**.[20]



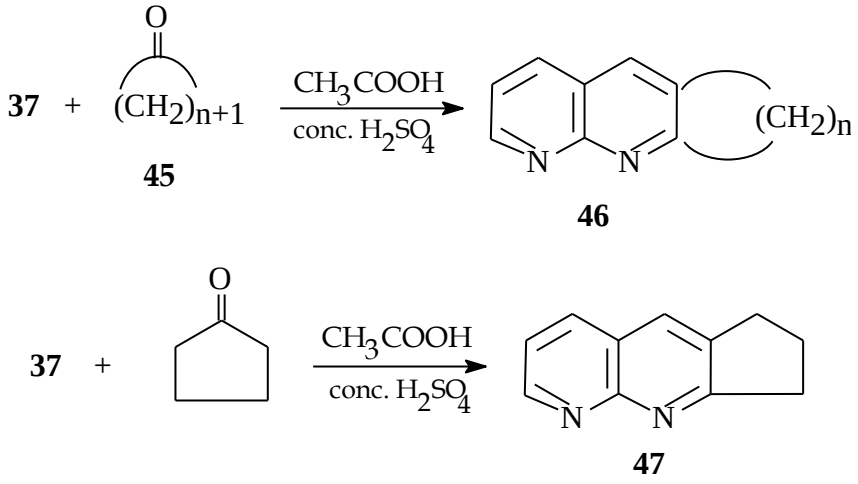
37 **38** **39**

R = H or Ph
R' = H, aryl / heteryl, NO_2, $COCH_3$, COOEt, CN, $CONH_2$
R" = CH_3, NH_2, OH

A number of 2,3-disubstituted-1,8-naphthyridines (**41**-**44**) were synthesized either directly by the Friedlander reaction or by subsequent reaction of the bicyclic compounds[23].

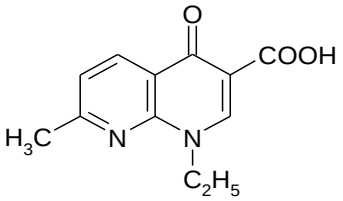


The Friedlander condensation of 2-aminonicotinaldehyde **37** (R=H) with cyclic ketones **45** furnished 2,3-fused-1,8-naphthyridines **46**.[24]



1.3 Role of 1,8-Naphthyridines in the field of medicinal chemistry

Nalidixic acid **2** (1-ethyl-3-carboxy-7-methyl-1,8-naphthyridin-4-one) has been found to be particularly effective against Gram-negative bacteria found in chronic urinary tract infections[25]. 1,8-Naphthyridine derivatives are known for their antibacterial[26], diuretic[27], antimalarial[28] antiinflammatory[29], gastric antisecretary[30], antiallergic[31], local anaesthetic[32] and benzodiazepine receptor activity[33]. These compounds were also reported to be associated with antitumor[34] β-adrenergic blocking[35] and antihypertensive[36] properties.



2

1.4 Role of microwave technology in organic synthesis

Green chemistry is placed in the frontier areas of research and has been focused for considerable recent research. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical process. One of the thrust areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformation with minimized by-products or waste as well as eliminating the use of conventional organic solvents, where ever possible.

Microwave-induced Organic Reaction Enhancement (MORE) chemistry reactions are extremely fast, cleaner than conventional reactions and lead to higher atom economy (less chemical waste).[37-40] Because of short time requirement, ease of workability and eco-friendliness, microwave provide an alternative green approach to environmentally unacceptable procedures using toxic and expensive reagents. Recently use of inorganic solid supports[41] as catalysts has been developed for solvent-free reactions resulting in higher selectivity, milder conditions and easy experimental procedures.

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CHAPTER II

Chloramine-T mediated synthesis of 9-aryl-6-(3-methoxyphenyl)[1,2,4]triazolo[4,3-*a*]-[1,8]naphthyridines

CHAPTER II

Fused 1,2,4-triazoles are the biologically interesting molecules and their chemistry has received considerable interest[1-6]. The synthesis of a fused 1,2,4-triazole system is possible by two distinct routes either by treatment of a suitably substituted 1,2,4-triazole with appropriate reagents to give rise either to the fused 1,2,4-triazole system as such or an intermediary product which may be cyclized subsequently[7] or more conventionally by starting from a suitable α-hydrazino heterocycle and creating the triazole unit thereon. The latter method for the formation of fused 1,2,4-triazoles has been discussed in a review[8] and is the one more frequently employed for the synthesis. The wide applicability of this approach was recognized by a number of workers and a variety of fused 1,2,4-triazoles were prepared by a proper choice of conditions and reagents[9-12]. However, these methods are not very satisfactory due to drawbacks such as low yields, expensive reagents, longer reaction time at higher reaction temperature and tedious work-up procedures. Therefore, the development of new methods with greater efficacy, straightforward procedures and better yields still is desirable. The 1,8-naphthyridine nucleus is the ubiquitous future of various compounds possessing many pharmacological and biological activities and therefore, they are useful materials[13-15]. In recent years, chloramine-T (*p*-CH_3 $C_6H_4SO_2N^-$-$ClNa^+$.$3H_2O$ or CAT) has emerged as a potential oxidizing agent in different areas of organic synthesis[16,17] because it is non-toxic, easy to handle and readily available.

Microwave (MW) activation has become a very popular and useful technology in synthetic organic chemistry[18-21]. Several methods have been developed for performing reactions with MW irradiation in solution and under solvent-free conditions, but a homogeneous mixture is preferred to obtain uniform heating. The solvents with higher dielectric constants are superheated and reactions take place rapidly.

Encouraged by these facts, herein is reported a convenient and efficient method for the synthesis of 9-aryl-6-(3-methoxyphenyl)[1,2,4]-triazolo[4,3-*a*] [1,8]naphthyridines using chloramine-T in ethanol under MW irradiation.

In this chapter we present the synthesis of

I **3-(3-Methoxyphenyl)[1,8]naphthyridin-2-amine 3**

II **3-(3-Methoxyphenyl)-1,2-dihydro[1,8]naphthyridin-2-one 4**

III **2-Chloro-3-(3-methoxyphenyl)[1,8]naphthyridine 5**

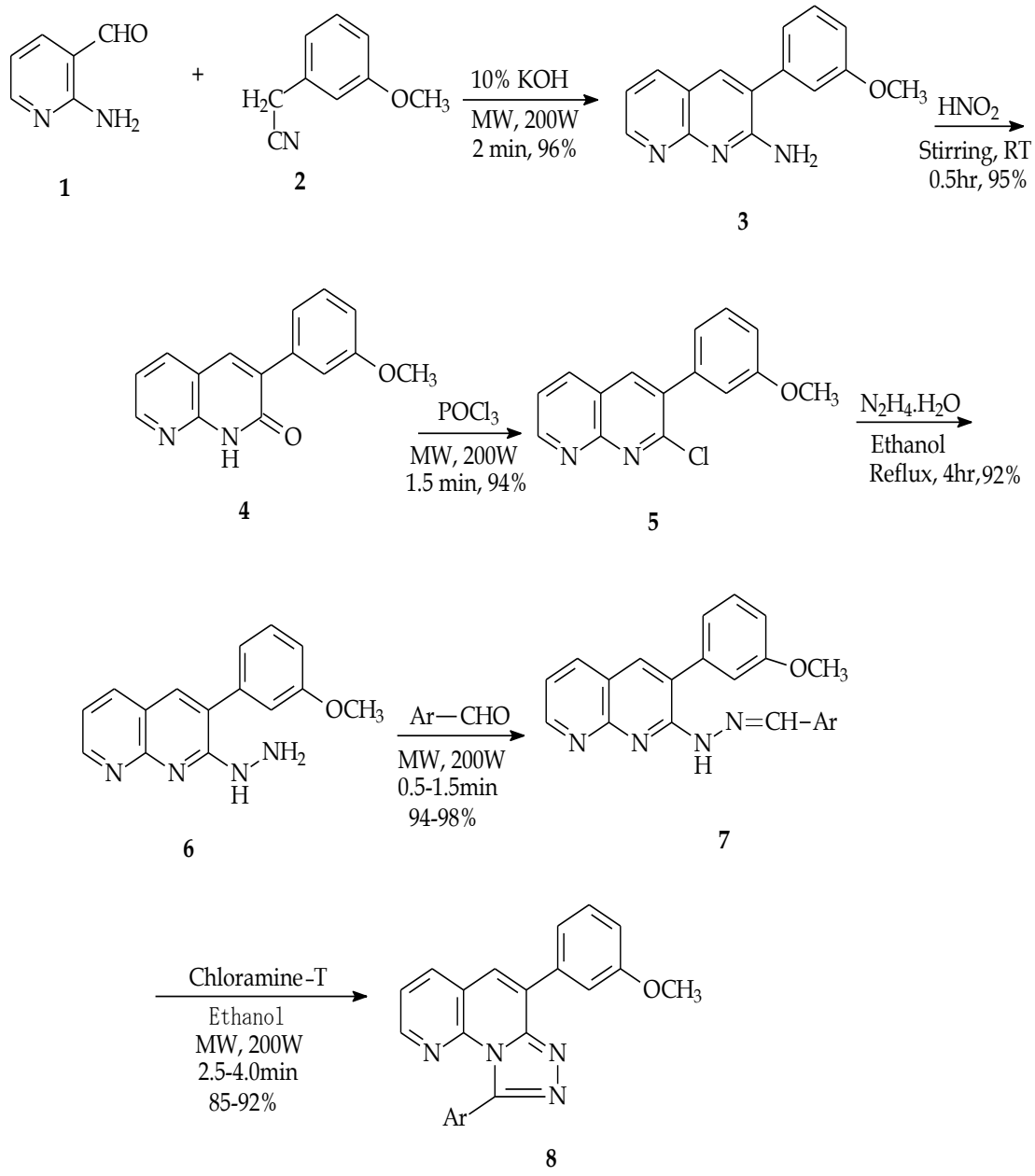
IV **1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazine 6**

V **Aryl aldehyde 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazones 7**

VI **9-Aryl-6-(3-methoxyphenyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridines 8**

The reaction sequence leading to the formation of these compounds is outlined in **Scheme I**.

The convenient starting material for the synthesis of 1,8-naphthyridines is 2-aminonicotinaldehyde **1** which was prepared according to the method of Majewicz and Caluwe.[22] The 3-methoxyphenylacetonitrile **2** was purchasedfrom Aldrich Chemical Company.



Ar		Ar	
a :	C_6H_5	**f** :	4-F C_6H_4
b :	4-$CH_3C_6H_4$	**g** :	2-NO_2 C_6H_4
c :	4-$CH_3OC_6H_4$	**h** :	3-NO_2 C_6H_4
d :	2-Cl C_6H_4	**i** :	4-NO_2 C_6H_4
e :	4-Cl C_6H_4	**j** :	3,4-$(CH_3O)_2C_6H_3$

Scheme I

I 3-(3-Methoxyphenyl)[1,8]naphthyridin-2-amine 3

Condensation of 2-aminonicotinaldehyde **1** with 3-methoxyphenyl-acetonitrile **2** in the presence of 10% KOH without any solvent under MW irradiation afforded 3-(3-methoxyphenyl)[1,8]naphthyridin-2-amine **3** in 96% yield. The structure of the compound **3** was established on the basis of its elemental analysis and spectral (IR, ^{1}H NMR and MS) data.

Spectral data

IR (KBr): 3479, 3079 (NH_2), 1633(C-NH_2), 1594 cm^{-1} (C=N)

^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6):δ 3.85 (s, 3H, OCH_3), 5.42 (s, 2H, NH_2), 7.43(m, 1H, C_6-H), 7.78 (s, 1H, C_4-H), 7.96 (m, 1H, C_5-H), 8.85 (m, 1H, C_7-H), 6.98-7.27 (m, 4H, Ar-H)

MS(LC-MSD): *m/z* 252.2 $[M+H]^+$

II 3-(3-Methoxyphenyl)--1,2-dihydro[1,8]naphthyridin-2-one 4

The interaction of 3-(3-methoxyphenyl)[1,8]naphthyridin-2-amine **3** with HNO_2 furnished 3-(3-methoxyphenyl)-1,2-dihydro[1,8]naphthyridine-2-one **4** in 95% yield. The structure of the compound **4** was confirmed by its spectral (IR, ^{1}H NMR and MS) and analytical data.

Spectral data

IR (KBr): 3404 (NH), 1660 (C=O), 1594 cm^{-1} (C=N)

^{1}H NMR (300MHz, $CDCl_3$): δ 3.88 (s, 3H, OCH_3), 7.58 (m, 1H, C_6-H), 7.84 (s, 1H, C_4-H), 8.00 (m, 1H, C_5-H), 8.25 (m, 1H, C_7-H), 6.92-7.42 (m, 4H, Ar-H), 9.14 (brs, 1H, NH)

MS(LC-MSD): *m/z* 253.2 $[M+H]^+$

III 2-Chloro-3-(3-methoxyphenyl)[1,8]naphthyridine 5

Treatment of 3-(3-methoxyphenyl)--1,2-dihydro[1,8]naphthyridin-2-one **4** with $POCl_3$ under MW irradiation produced 2-chloro-3-(3-methoxyphenyl) [1,8]naphthyridine **5** in 94% yield. The structure of the compound **29** was assigned from its analytical and spectral (IR, ^1H NMR and MS) data.

Spectral data

IR (KBr): 1592 cm^{-1} (C=N)

^1H NMR (300MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 7.42 (m, 1H, C_6-H),
8.13 (s, 1H, C_4-H), 7.57 (m, 1H, C_5-H),
8.22 (m, 1H, C_7-H), 6.98-7.16 (m, 4H, Ar-H)

MS(LC-MSD): *m/z* 271.2 $[M+H]^+$

IV 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazine 6

Hydrazinolysis of **5** with hydrazine hydrate in boiling ethanol yielded 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazine **6** in 92% yield. The characterization of the compound **6** has been done by its spectral (IR, ^1H NMR and MS) and analytical data.

Spectral data

IR (KBr): 3423, 3304, 3120 ($NHNH_2$), 1621 (C-$NHNH_2$), 1597 cm^{-1} (C=N)

^1H NMR (300MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 6.38 (brs, 2H, NH_2),
7.40 (m, 1H, C_6-H), 7.68 (s, 1H, C_4-H),
8.00 (m, 1H, C_5-H), 8.84 (m, 1H, C_7-H),
6.96-7.43 (m, 5H, NH, 4Ar-H)

MS(LC-MSD): *m/z* 305.3 $[M+K]^+$

V Aryl aldehyde 1-[3- (3-methoxyphenyl)[1,8]naphthyridin-2-yl]-hydrazones 7

The hydrazine **6** on condensation with various aromatic aldehydes in the presence of catalytic amount of DMF under MW irradiation resulted in the formation of the corresponding aryl aldehyde 1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]hydrazones **7** in excellent yields.

In a typical case, a mixture of **6**, benzaldehyde (Ar=C_6H_5) and DMF (5 drops) was exposed to MW irradiation at 200 W intermittently at 10 sec intervals for 0.5 min. The reaction mixture was cooled to RT, digested with cold water and filtered off. After usual work-up benzaldehyde 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazone **7a** (Ar=C_6H_5) was obtained in 95% yield.

The condensation reaction was extended to nine other aromatic aldehydes and the corresponding aryl aldehyde 1-[3-(3-methoxyphenyl)-[1,8]naphthyridin-2-yl]hydrazones **7b-j(**Ar=4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3,4-$(CH_3O)_2C_6H_3$) were isolated in 94-98% yields(**Table V**).

The structures of the compounds **7** were established on the basis of their elemental analyses and spectral (IR, ^{1}H NMR and MS) data.

IR spectra

The IR (KBr) spectra of aryl aldehyde 1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]hydrazones **7** exhibited absorption bands around 3352 and 1622 cm^{-1} due to NH and C=N functions, respectively. The data are presented in **Table I.**

Mass spectra

The LC-MSD mass spectra of aryl aldehyde 1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]hydrazones **7** exhibited strong $[M+H]^+$ ions (**Table I**).

Table I — IR and mass spectral data of Aryl aldehyde 1-[3-(3-methoxy-phenyl)[1,8]naphthyridin-2-yl]hydrazones **7**

Compd	Ar	ν_{max} in cm^{-1}		MS(LC-MSD) $[M+H]^+$ *m/z*
		NH	C=N	
7a	C_6H_5	3351	1623	355.3
7b	4-$CH_3C_6H_4$	3351	1622	369.3
7c	4-$CH_3OC_6H_4$	3350	1622	385.3
7d	2-ClC_6H_4	3352	1621	389.2
7e	4-ClC_6H_4	3351	1622	389.3
7f	4-FC_6H_4	3353	1624	373.3
7g	2-$NO_2C_6H_4$	3353	1621	400.3
7h	3-$NO_2C_6H_4$	3351	1623	400.3
7i	4-$NO_2C_6H_4$	3352	1622	400.3
7j	3,4-$(CH_3O)_2C_6H_3$	3353	1623	415.3

^{1}H NMR spectra

The ^{1}H NMR (300 MHz) spectra of aryl aldehyde 1-[3-(3-methoxy-phenyl) [1,8]naphthyridin-2-yl]hydrazones **7** were measured in $CDCl_3$ and the data are listed in **Table II.**

Table II — ^{1}H NMR spectral data of Aryl aldehyde 1-[3-(3-methoxyphenyl)-[1,8]-naphthyridin-2-yl]hydrazones 7

Compd	Ar	^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm)
7a	C_6H_5	3.84 (s, 3H, OCH_3), 7.65 (m, 1H, C_6-H), 7.70 (m, 2H, C_4-H, C_5-H), 8.26 (m, 1H, C_7-H), 8.38 (s, 1H, N=CH), 6.85-7.60 (m, 9H, Ar-H), 10.15 (s, 1H, NH).
7b	4-$CH_3C_6H_4$	2.40 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.70 (m, 3H, C_4-H, C_5-H, C_6-H), 8.30 (m, 1H, C_7-H), 8.42 (s, 1H, N=CH), 6.85-7.40 (m, 8H, Ar-H), 10.18 (s, 1H, NH).
7c	4-$CH_3OC_6H_4$	3.84 (s, 6H, 2XOCH_3), 7.63 (m, 1H, C_6-H), 7.78 (m, 2H, C_4-H, C_5-H), 8.28 (m, 1H, C_7-H), 8.42 (s, 1H, N=CH), 6.85-7.40 (m, 8H, Ar-H), 10.22 (s, 1H, NH).
7d	2-ClC_6H_4	3.85 (s, 3H, OCH_3), 7.68 (m, 2H, C_4-H, C_6-H), 8.24 (m, 1H, C_5-H), 8.35 (m, 1H, C_7-H), 8.85 (s, 1H, N=CH), 6.92-7.40 (m, 8H, Ar-H), 10.25 (s, 1H, NH).
7e	4-ClC_6H_4	3.83 (s, 3H, OCH_3), 7.75 (m, 2H, C_4-H, C_6-H), 8.02 (m, 1H, C_5-H), 8.37 (m, 1H, C_7-H), 8.42 (s, 1H, N=CH), 6.90-7.44 (m, 8H, Ar-H), 10.24 (s, 1H, NH).
7f	4-FC_6H_4	3.86 (s, 3H, OCH_3), 7.67 (m, 1H, C_6-H), 7.80 (m, 2H, C_4-H, C_5-H), 8.34 (m, 1H, C_7-H), 8.44 (s, 1H, N=CH), 6.94-7.40 (m, 8H, Ar-H), 10.20 (s, 1H, NH).
7g	2-$NO_2C_6H_4$	3.84 (s, 3H, OCH_3), 7.70 (m, 1H, C_6-H), 8.22 (m, 2H, C_4-H, C_5-H), 8.40 (m, 1H, C_7-H), 8.56 (s, 1H, N=CH), 6.98-7.65 (m, 8H, Ar-H), 10.26 (s, 1H, NH).
7h	3-$NO_2C_6H_4$	δ 3.86 (s, 3H, OCH_3), 7.75 (m, 1H, C_6-H), 8.20 (m, 2H, C_4-H, C_5-H), 8.38 (m, 1H, C_7-H), 8.60 (s, 1H, N=CH), 6.95-7.62 (m, 8H, Ar-H), 10.28 (s, 1H, NH).
7i	4-$NO_2C_6H_4$	3.85 (s, 3H, OCH_3), 7.72 (m, 1H, C_6-H), 8.18 (m, 2H, C_4-H, C_5-H), 8.42 (m, 1H, C_7-H), 8.58 (s, 1H, N=CH), 7.00-7.67 (m, 8H, Ar-H), 10.24 (s, 1H, NH).
7j	3,4-$(CH_3O)_2C_6H_3$	3.84 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.38 (m, 1H, C_6-H), 7.65 (m, 1H, C_5-H), 7.45 (s, 1H, C_4-H), 8.30 (m, 1H, C_7-H), 8.42 (s, 1H, N=CH), 6.84-7.32 (m, 7H, Ar-H), 10.18 (s, 1H, NH).

VI 9-Aryl-6-(3-methoxyphenyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridines 8

Oxidative cyclization of hydrazones 7 with chloramine-T in ethanol under MW irradiation furnished the respective 9-aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **8**(**Scheme I**). The oxidative transformation is clean and efficient. The high yield transformation did not form any undesirable by-products. The products that are obtained are pure and do not require purification. The experimental procedure is very simple.

In a typical case, equimolar amounts of hydrazone **7a** (Ar=C_6H_5) and chloramine-T in ethanol was subjected to MW irradiation at 200 W intermittently at 20 sec intervals for 2.5 min. Work-up of the reaction mixture afforded 6-(3-methoxyphenyl)-9-phenyl[1,2,4]triazolo[4,3-*a*][1,8]-naphthyridine **8a** (Ar=C_6H_5) in 90% yield.

The generality of the facile oxidative transformation was checked by treating other hydrazones **7b-j** with chloramine-T in ethanol under MW irradiation and in all cases the respective 9-aryl-6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*] [1,8]naphthyridines **8b-j(**Ar=4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3,4-$(CH_3O)_2C_6H_3$) were obtained in 85-92% yields (**Table VI**).

Interestingly, this oxidative reaction proceeds only to a minor extent (6-8% in 2.5-4.0 min) when conducted under conventional conditions in an oil-bath preheated to 110^oC (temperature measured at the end of exposure during MW experiment), which confirms the rate increase during MW heating.

The structures of the compounds **8** were confirmed by their spectroscopic (IR, ^1H NMR and MS) and analytical data. The significant advantages of this procedure are: short reaction times, operational simplicity, pure products and high yields.

IR spectra

The IR (KBr) spectra of 9-aryl-6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*] [1,8]naphthyridines **8** did not show any absorption in the region 3353- 3350 cm^{-1}, indicating the absence of NH group. The spectra showed absorption band around 1609 cm^{-1} characteristic of νC=N (**Table III**).

Table III — IR and mass spectral data of 9-Aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **32**

Compd	Ar	ν_{max} in cm^{-1}	MS (LC-MSD) $[M+H]^+$
		C=N	*m/z*
8a	C_6H_5	1603	353.2
8b	4-$CH_3C_6H_4$	1606	367.3
8c	4-$CH_3OC_6H_4$	1611	383.3
8d	2-ClC_6H_4	1611	387.2
8e	4-ClC_6H_4	1597	387.3
8f	4-FC_6H_4	1609	371.3
8g	2-$NO_2C_6H_4$	1612	398.2
8h	3-$NO_2C_6H_4$	1613	398.3
8i	4-$NO_2C_6H_4$	1611	398.3
8j	3,4-$(CH_3O)_2C_6H_3$	1607	413.3

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^{1}H NMR spectra

The ^{1}H NMR (300 MHz) spectra of 9-aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **8** were recorded in $CDCl_3$ and the data are presented in **Table IV.**

Table IV — ^{1}H NMR spectral data of 9-Aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **8**

Compd	Ar	^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm)
8a	C_6H_5	3.90 (s, 3H, OCH_3), 7.90 (m, 2H, C_3-H, C_5-H), 8.16 (m, 1H, C_4-H), 8.42 (m, 1H, C_2-H), 7.00-7.75 (m, 9H, Ar-H).
8b	4-$CH_3C_6H_4$	2.45 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.80 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.45 (m, 1H, C_2-H), 7.01-7.67 (m, 8H, Ar-H).
8c	4-$CH_3OC_6H_4$	3.90 (s, 6H, 2×OCH_3), 7.86 (m, 2H, C_3-H, C_5-H), 8.17 (m, 1H, C_4-H), 8.43 (m, 1H, C_2-H), 7.00-7.75 (m, 8H, Ar-H).
8d	2-ClC_6H_4	3.93 (s, 3H, OCH_3), 7.68 (m, 2H, C_3-H, C_5-H), 8.15 (m, 1H, C_4-H), 8.38 (m, 1H, C_2-H), 7.02-7.58 (m, 8H, Ar-H).
8e	4-ClC_6H_4	3.95 (s, 3H, OCH_3), 7.70 (m, 2H, C_3-H, C_5-H), 8.16 (m, 1H, C_4-H), 8.37 (m, 1H, C_2-H), 7.00-7.56 (m, 8H, Ar-H).
8f	4-FC_6H_4	3.94(s, 3H, OCH_3), 7.88 (m, 2H, C_3-H, C_5-H), 8.20 (m, 1H, C_4-H), 8.42 (m, 1H, C_2-H), 7.02-7.74 (m, 8H, Ar-H).
8g	2-$NO_2C_6H_4$	3.92 (s, 3H, OCH_3), 7.72 (m, 2H, C_3-H, C_5-H), 8.30 (m, 1H, C_4-H), 8.45 (m, 1H, C_2-H), 7.00-7.62 (m, 8H, Ar-H).
8h	3-$NO_2C_6H_4$	3.95 (s, 3H, OCH_3), 7.70 (m, 2H, C_3-H, C_5-H), 8.26 (m, 1H, C_4-H), 8.43 (m, 1H, C_2-H), 7.03-7.60 (m, 8H, Ar-H).
8i	4-$NO_2C_6H_4$	3.96 (s, 3H, OCH_3), 7.75 (m, 2H, C_3-H, C_5-H), 8.24 (m, 1H, C_4-H), 8.46 (m, 1H, C_2-H), 7.02-7.64 (m, 8H, Ar-H).
8j	3,4-$(CH_3O)_2C_6H_3$	3.92 (s, 6H, 2xOCH_3), 4.00 (s, 3H, OCH_3), 7. 65 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.48 (m, 1H, C_2-H), 6.98-7.56 (m, 7H, Ar-H).

Mass spectra

The LC-MSD mass spectra of 9-aryl-6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*] [1,8]naphthyridines **8** showed strong $[M+H]^+$ ions (**Table III**).

Experimental Section

Chloramine-T mediated synthesis of 9-aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines

I 3-(3-Methoxyphenyl)[1,8]naphthyridin-2-amine 3

a) 2-Aminonicotinaldehyde 1

A mixture of nicotinamide (36.5 g) and ammonium sulphamate (52 g) was heated in an oil bath at 150°C. After a clear melt was obtained, the temperature was raised slowly to 200°C. The mixture was kept at this temperature for 6 hr, after which the contents of the flask had completely solidified. Water was added and the precipitate collected and washed with ether to remove nicotinonitrile. The solid material thus obtained was refluxed in 2 N HCl for 4 hr, made alkaline and extracted with ether. The resulting ether solution was dried (K_2CO_3) and evaporated to give pure 2-aminonicotinaldehyde **1,** m.p. 98°C (lit[28], m.p. 98°C).

b) 3-(3-Methoxyphenyl)[1,8]naphthyridin-2-amine 3

A mixture of 2-aminonicotinaldehyde **1** (0.01 mole), 3-methoxyphenylacetonitrile **2** (0.01 mole) and 10% KOH (5 drops) was subjected to MW irradiation at 200 W intermittently at 30 sec intervals for 2.0 min. On completion of the reaction, as monitored by TLC, the reaction mixture was cooled. The solid thus deposited was filtered, washed with water and purified by recrystallization from methanol to obtain **3,** yield 96%; m.p. 222°C. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.82; H, 5.23; N, 16.77%.

II 3-(3-Methoxyphenyl)--1,2-dihydro[1,8]naphthyridin-2-one 4

To a cold solution of **3** (0.01 mole) in 2 M HCl (25 mL) was added $NaNO_2$ solution (0.01 mole in 25 mL water) and the reaction mixture was stirred at RT for 0.5 hr and treated with cold water. The solid precipitated solid was filtered, washed

with water and purified by recrystallization from methanol to give **4,** yield 95%; m.p. 174°C. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.55; H, 4.80; N, 11.14%.

III 2-Chloro-3-(3-methoxyphenyl)[1,8]naphthyridine 5

A mixture of **4** (0.01 mole) and $POCl_3$ (10 mL) was exposed to MW irradiation at 200 W intermittently at 10 sec intervals for 1.5 min. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled and poured onto a mixture of crushed ice and $NaHCO_3$. The product that separated was filtered, washed with water and purified by recrystallization from ethanol to obtain **5,** yield 94%; m.p. 127°C. Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found : C, 66.67; H, 4.12; N, 10.39%.

IV 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazine 6

A mixture of **5** (0.01 mole) and hydrazine hydrate (0.015 mole) 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 that separated was filtered, washed with water and purified by recrystallization from ethanol to give **6,** yield: 92%; m.p. 185°C. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.78; H, 5.32; N, 21.09%.

V General procedure for the synthesis of aryl aldehyde 1-[3- (3-methoxyphenyl)[1,8]naphthyridin-2-yl]hydrazones 7

A mixture of **6** (0.01 mole), aromatic aldehyde (0.01 mole) and DMF (5 drops) was exposed to MW irradiation at 200 W intermittently at 10 sec intervals for the specified time (**Table V)**. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The resultant product was filtered, washed with water and purified by recrystallization from ethanol to obtain **7** (**Table V)**.

VI General procedure for the synthesis of 9-aryl-6-(3-methoxyphenyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridines 8

To a solution of appropriate hydrazone **7** (0.01 mole) in ethanol (10 mL), chloramine-T (0.01 mole) was added. The reaction mixture was subjected to MW irradiation at 200 W intermittently at 20 sec intervals for the specified time (**Table VI**). On complete conversion as indicated by TLC, the reaction mixture was cooled and digested with cold water. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol to give **8** (**Table VI**).

Table V — Physical and analytical data of Aryl aldehyde1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]hydrazones **7**

Compd	Ar	Reaction Time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd) C	H	N
7a	C_6H_5	0.5	172	95	$C_{22}H_{18}N_4O$	74.70 (74.56	5.13 5.12	15.86 15.81)
7b	4-$CH_3C_6H_4$	1.0	144	97	$C_{23}H_{20}N_4O$	75.10 (74.98	5.49 5.47	15.25 15.21)
7c	4-$CH_3OC_6H_4$	1.5	138	94	$C_{23}H_{20}N_4O_2$	71.99 (71.86	5.25 5.24	14.62 14.57)
7d	2-ClC_6H_4	0.5	152	95	$C_{22}H_{17}ClN_4O$	68.08 (67.95	4.43 4.41	14.46 14.41)
7e	4-ClC_6H_4	0.5	155	98	$C_{22}H_{17}ClN_4O$	68.09 (67.95	4.42 4.41	14.45 14.41)
7f	4-FC_6H_4	1.0	166	96	$C_{22}H_{17}FN_4O$	71.08 (70.96	4.62 4.60	15.08 15.04)
7g	2-$NO_2C_6H_4$	1.0	176	94	$C_{22}H_{17}N_5O_3$	66.30 (66.16	4.30 4.29	17.58 17.53)
7h	3-$NO_2C_6H_4$	0.5	165	96	$C_{22}H_{17}N_5O_3$	66.28 (66.16	4.31 4.29	17.58 17.53)
7i	4-$NO_2C_6H_4$	0.5	182	97	$C_{22}H_{17}N_5O_3$	66.29 (66.16	4.30 4.29	17.57 17.53)
7j	3,4-$(CH_3O)_2C_6H_3$	1.0	162	96	$C_{24}H_{22}N_4O_3$	69.69 (69.55	5.37 5.35	13.57 13.52)

Table VI — Physical and analytical data of 9-Aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **32**

Compd	Ar	Reaction Time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
						C	H	N
8a	C_6H_5	2.5	175	90	$C_{22}H_{16}N_4O$	75.11 (74.98	4.60 4.58	15.94 15.90)
8b	4-$CH_3C_6H_4$	2.5	165	91	$C_{23}H_{18}N_4O$	75.53 (75.39	4.96 4.95	15.34 15.29)
8c	4-$CH_3OC_6H_4$	3.0	159	88	$C_{23}H_{18}N_4O_2$	72.38 (72.24	4.75 4.74	14.69 14.65)
8d	2-ClC_6H_4	3.0	196	88	$C_{22}H_{15}ClN_4O$	68.45 (68.31	3.92 3.91	14.53 14.48)
8e	4-ClC_6H_4	2.5	215	92	$C_{22}H_{15}ClN_4O$	68.44 (68.31	3.93 3.91	14.52 14.48)
8f	4-FC_6H_4	3.0	219	90	$C_{22}H_{15}FN_4O$	71.47 (71.34	4.09 4.08	15.18 15.13)
8g	2-$NO_2C_6H_4$	4.0	258	85	$C_{22}H_{15}N_5O_3$	66.62 (66.49	3.82 3.80	17.66 17.62)
8h	3-$NO_2C_6H_4$	4.0	281	86	$C_{22}H_{15}N_5O_3$	66.63 (66.49	3.81 3.80	17.67 17.62)
8i	4-$NO_2C_6H_4$	3.0	276	88	$C_{22}H_{15}N_5O_3$	66.61 (66.49	3.82 3.80	17.66 17.62)
8j	3,4-$(CH_3O)_2C_6H_3$	3.5	188	87	$C_{24}H_{20}N_4O_3$	70.02 (69.89	4.90 4.89	13.62 13.58)

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CHAPTER III

Green synthesis of 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes under microwave irradiation using solid support

CHAPTER III

Among five membered heterocycles, pyrazoles represent a class of compounds of great importance in medicinal industry and in many other ways[1-3]. The literature review shows that the Vilsmeier-Haack reaction of acetophenone phenylhydrazone resulted in the formation of pyrazole-4-carboxaldehyde[4,5]. In Vilsmeier-Haack reaction, DMF-$POCl_3$ has a dual role of regent as well as solvent. $POCl_3$ is a highly toxic solvent and its use is hazardous to health and is also pollutant of the environment. Derivatives of 1,8-naphthyridine[6,7] and 2*H*-2-chromenone[8,9] are also known to have a broad spectrum of biological and pharmacological activities. In light of these interesting biological activities, it was of interest to synthesize some new pyrazole derivatives bearing 1,8-naphthyridine and 2*H*-2-chromenone and evaluate their antimicrobial potential.

Eco-friendly chemical process is the vital part of the current chemical research and development. In recent years reports on the MW assisted synthesis under solvent-free reaction condition[10,11] in general and on inorganic solid supports[12,13] in particular is promising alternative to conventional methods as these reactions represent a clean, efficient, safe, economical and eco-friendly procedure.

In view of this, we now wish to report a facile and efficient protocol for the synthesis of 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-chromenyl)-1*H*-4-pyrazolecarbaldehydes using $POCl_3$-DMF over silica gel under MW irradiation.

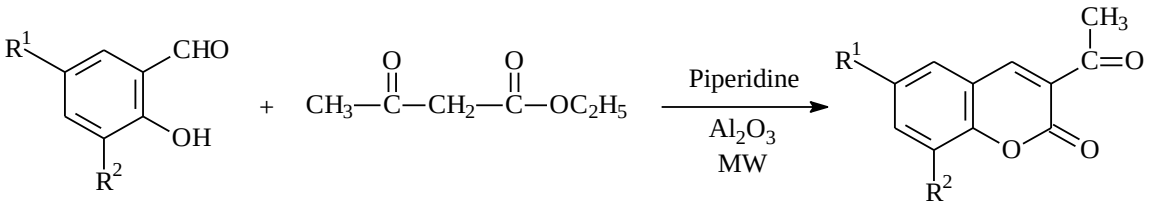
In this chapter we present the MW assisted synthesis of

I 3-(1-{2-[3-(3-Methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) 35

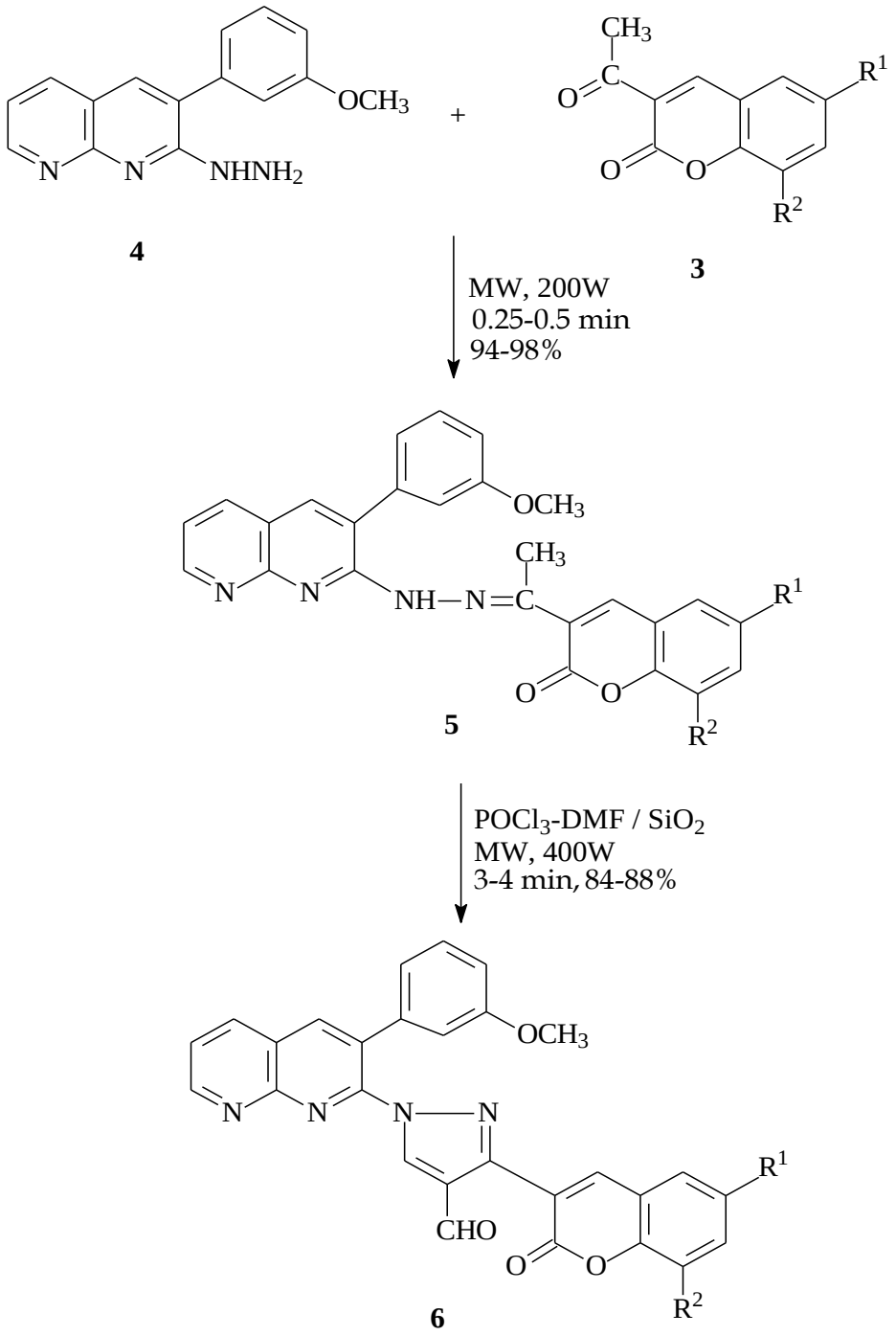
II 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes 36

The synthetic approach to these compounds is profiled in **Scheme I.**

The starting compounds, 3-acetylcoumarines(3-acetyl-2*H*-2-chromones) **3** were prepared by the condensation of different salicylaldehydes **1** with ethyl acetoacetate **2** in presence of piperidine under MW irradiation using basic Al_2O_3 as solid support.[14]



1 **2** **3**



	R^1	R^2		R^1	R^2
a :	H	H	e :	Br	H
b :	H	OCH_3	f :	Br	Br
c :	Cl	H	g :	NO_2	H
d :	Cl	Cl	h :	5,6- Benzo	

Scheme I

I Synthesis of 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) 5

Condensation of 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-hydrazine **4** with different 3-acetylcoumarins(3-acetyl-2*H*-2-chromenones) **3** in the presence of catalytic amount of DMF under MW irradiation afforded the corresponding 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5** in excellent yields.

In a typical case, a mixture of **4**, 3-acetylcoumarin **3a (**R^1 = H; R^2= H) and DMF (5 drops) was subjected to MW irradiation at 200 W intermittently at 10 sec intervals for 0.25 min. On completion of the reaction (monitored by TLC), the reaction mixture was cooled and poured into ice-cold water. After usual work-up, 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenone (hydrazone) **5a** (R^1 = H; R^2= H) was obtained in 95% yield.

The reaction was extended to seven other substituted 3-acetyl-coumarins **3b-h** and the corresponding 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5b-h** (R^1=H, R^2=OCH_3; R^1=Cl, R^2=H; R^1=Cl, R^2=Cl; R^1 = Br, R^2= H; R^1 = Br, R^2= Br; R^1 = NO_2 , R^2= H; R^1= R^2 =5,6-benzo) were isolated in 95-98% yields (**Table V**).

The structures of the hydrazones **5** were assigned on the basis of their spectral **(**IR, ^{1}H NMR and MS) and analytical data.

IR spectra

The IR (KBr) spectra of 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5** exhibited NH, lactone C=O, C=N and C=C groups around 3415, 1734, 1616 and 1586 cm^{-1}, respectively. The data are listed in **Table I**.

Table I — IR and mass spectral data 3-(1-{2-[3-(3-Methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5**

Compd	R^1	R^2	ν_{max} in cm^{-1}				MS (ESI) (M^+) *m/z*
			NH	Lactone, C=O	C=N	C=C	
5a	H	H	3432	1728	1623	1592	436
5b	H	OCH_3	3342	1736	1622	1590	466
5c	Cl	H	3435	1735	1611	1580	470
5d	Cl	Cl	3329	1725	1616	1585	504
5e	Br	H	3435	1736	1623	1592	514
5f	Br	Br	3415	1734	1610	1586	592
5g	NO_2	H	3435	1737	1614	1582	481
5h	5,6-Benzo		3436	1717	1622	1590	486

^{1}H NMR spectra

The ^{1}H NMR (400 MHz) spectra of 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5** were recorded in $CDCl_3$ and the data are dispalyed in **Table II**.

Table II — ^{1}H NMR spectral data of 3-(1-{2-[3-(3-Methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5**

Compd	R^1	R^2	^{1}H NMR (400 MHz, $CDCl_3$) (δ,ppm)
5a	H	H	2.53 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 7.85 (m, 1H, C_6-H), 8.21 (m, 2H, C_4-H, C_5-H), 8.42 (m, 1H, C_7-H), 8.52 (s, 1H, C_4-H of coumarin), 6.92-7.80 (m, 8H, Ar-H), 10.28 (s, 1H, NH).
5b	H	OCH_3	2.42 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.70 (m, 1H, C_6-H), 8.26 (m, 2H, C_4-H, C_5-H), 8.38 (m, 1H, C_7-H), 8.50 (s, 1H, C_4-H of coumarin), 6.86-7.65 (m, 7H, Ar-H), 10.37 (s, 1H, NH).
5c	Cl	H	2.40 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H), 8.16 (m, 2H, C_4-H, C_5-H), 8.26 (m, 1H, C_7-H), 8.40 (s, 1H, C_4-H of coumarin), 6.82-7.72 (m, 7H, Ar-H), 10.20 (s, 1H, NH).
5d	Cl	Cl	2.42 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.82 (m, 1H, C_6-H), 7.95 (m, 2H, C_4-H, C_5-H), 8.42 (m, 1H, C_7-H), 8.56 (s, 1H, C_4-H of coumarin), 6.98-7.67 (m, 6H, Ar-H), 10.46 (s, 1H, NH).
5e	Br	H	2.43 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 7.82 (m, 1H, C_6-H), 8.16 (m, 2H, C_4-H, C_5-H), 8.35 (m, 1H, C_7-H), 8.52 (s, 1H, C_4-H of coumarin), 7.00-7.65 (m, 7H, Ar-H), 10.20 (s, 1H, NH).
5f	Br	Br	2.40 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.32 (m, 1H, C_7-H), 8.55 (s, 1H, C_4-H of coumarin), 7.02-7.72 (m, 6H, Ar-H), 10.35 (s, 1H, NH).
5g	NO_2	H	2.42 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.86 (m, 1H, C_6-H), 8.16 (m, 2H, C_4-H, C_5-H), 8.22 (m, 1H, C_7-H), 8.45 (s, 1H, C_4-H of coumarin), 7.05-7.70 (m, 7H, Ar-H), 10.27 (s, 1H, NH).
5h	5,6-Benzo		2.44 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.78 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.48 (m, 1H, C_7-H), 9.00 (s, 1H, C_4-H of coumarin), 6.96-7.85 (m, 10H, Ar-H), 10.38 (s, 1H, NH).

Mass spectra

The ESI mass spectra of 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5** showed strong (M^+) ions (**Table I**).

II Synthesis of 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes 6

The hydrazones **5** were subjected to the Vilsmeier-Haack reaction with $POCl_3$-DMF/SiO_2 under MW irradiation to furnish the respective 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6** (**Scheme I**). The reaction proceeds efficiently in very good yields at ambient pressure within a few minutes time and in the absence of solvent. The purity of the products is excellent. The process is environmentally benign. The experimental procedure is very simple.

In a typical case, to the Vilsmeier-Haack reagent, prepared from DMF and $POCl_3$ at 0-5ºC, hydrazone **5a** (R^1= H; R^2= H) and silica gel was added and was exposed to microwaves at 400 W intermittently at 30 sec intervals for 3.0 min. The reaction mixture was cooled and treated with water and $NaHCO_3$. After usual work-up 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehyde **6a** (R^1= H; R^2= H) was obtained in 85% yield.

The reaction is of general applicability and the various 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6b-h** (R^1= H, R^2= OCH_3; R^1= Cl, R^2= H; R^1= Cl, R^2= Cl; R^1= Br, R^2= H; R^1 = Br, R^2= Br; R^1 = NO_2 , R^2= H; R^1= R^2 =5,6-benzo) synthesized are obtained in 84-88% yields (**Table VI**).

Alternatively, the Vilsmeier-Haack reactions when conducted under conventional conditions in an oil-bath preheated to 110◦C (highest temperature measured at the end of exposure during MW experiment), where the reactions took 3.5-4.5 hr for completion giving the products in 30-40% yields.

The structural assignments of compounds **6** were based on their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. The procedure is simple, milder, faster and is also consistent with the green chemistry theme since no solvent is needed and affords very good yields with excellent purity.

IR spectra

The IR spectra of 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]- 3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6** showed absorption bands around 1735, 1682, 1610 and 1565 cm^{-1} due to lactone C=O, aldehyde C=O, C=N and C=C groups, respectively. The data are summarized in **Table III**.

Table III — IR and mass spectral data of 1-[3-(3-Methoxyphenyl)-[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6**

Compd	R^1	R^2	ν_{max} in cm^{-1}				MS (ESI) $[M+H]^+$ *m/z*
			Lactone C=O	Aldehyde C=O	C=N	C=C	
6a	H	H	1736	1685	1609	1562	475
6b	H	OCH_3	1726	1682	1609	1568	505
6c	Cl	H	1734	1680	1612	1566	509
6d	Cl	Cl	1727	1680	1605	1575	543
6e	Br	H	1735	1676	1610	1561	553
6f	Br	Br	1736	1684	1608	1565	631
6g	NO_2	H	1743	1685	1612	1562	520
6h	5,6-Benzo		1725	1684	1609	1572	525

^{1}H NMR spectra

The ^{1}H NMR (400 MHz) spectra of 1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazole- carbaldehydes **6** were measured in $CDCl_3$ and the data are presented in **Table IV**.

Table IV— ^{1}H NMR spectral data of 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6**

Compd	R^1	R^2	^{1}H NMR (400 MHz, $CDCl_3$) (δ,ppm)
6a	H	H	3.90 (s, 3H, OCH_3), 7.79 (m, 1H, C_6-H of naphthyridine), 8.05 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.30 (m, 1H, C_7-H of naphthyridine), 8.50 (s, 1H, C_4-H of coumarin), 6.94-7.67 (m, 8H, CH of pyrazole, 7Ar-H), 9.62 (s, 1H, CHO).
6b	H	OCH_3	3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.90 (m, 1H, C_6-H of naphthyridine), 8.12 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.44 (s, 1H, C_4-H of coumarin), 6.92 – 7.78 (m, 8H, CH of pyrazole, 7Ar-H), 9.60 (s, 1H, CHO).
6c	Cl	H	3.95 (s, 3H, OCH_3), 7.78 (m, 1H, C_6-H of naphthyridine), 8.18 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.48 (s, 1H, C_4-H of coumarin), 6.92-7.65 (m, 8H, CH of pyrazole, 7Ar-H), 9.60 (s, 1H, CHO).
6d	Cl	Cl	3.94 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H of naphthyridine), 8.20 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.42 (m, 1H, C_7-H of naphthyridine), 8.44 (s, 1H, C_4-H of coumarin), 6.96-7.72 (m, 7H, CH of pyrazole, 6Ar-H), 9.65 (s, 1H, CHO).
6e	Br	H	3.94 (s, 3H, OCH_3), 7.92 (m, 1H, C_6-H of naphthyridine), 8.10 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.38 (m, 1H, C_7-H of naphthyridine), 8.43 (s, 1H, C_4-H of coumarin), 6.90 – 7.76 (m, 8H, CH of pyrazole, 7Ar-H), 9.60 (s, 1H, CHO).
6f	Br	Br	3.92 (s, 3H, OCH_3), 7.90 (m, 1H, C_6-H of naphthyridine), 8.12 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.45 (s, 1H, C_4-H of coumarin), 6.95-7.80 (m, 7H, CH of pyrazole, 6Ar-H), 9.62 (s, 1H, CHO).

- Contd.

Table IV — ^{1}H NMR spectral data of 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6** -- *Contd..*

Compd	R^1	R^2	^{1}H NMR (400 MHz, $CDCl_3$) (δ,ppm)
6g	NO_2	H	3.95 (s, 3H, OCH_3), 7.88 (m, 1H, C_6-H of naphthyridine), 8.08 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.34 (m, 1H, C_7-H of naphthyridine), 8.45 (s, 1H, C_4-H of coumarin), 6.84-7.72 (m, 8H, CH of pyrazole, 7Ar-H), 9.94 (s, 1H, CHO).
6h	5,6-benzo		3.92 (s, 3H, OCH_3), 7.93 (m, 1H, C_6-H of naphthyridine), 8.18 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.43 (m, 1H, C_7-H of naphthyridine), 8.60 (s, 1H, C_4-H of coumarin), 6.92-7.86 (m, 11H, CH of pyrazole, 10Ar-H), 9.65 (s, 1H, CHO).

Mass spectra

The ESI mass spectra of 1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6** exhibited strong $[M+H]^+$ ions (**Table III**).

Experimental section

Green synthesis of 1-[3-(3-methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes under microwave irradiation using solid support

I General procedure for the synthesis of 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) 5

i) 3-Acetylcoumarins(3-acetyl-2H-2-chromenones) 3

Salicylaldehyde **1** (0.01 mole), ethyl acetoacetate **2** (0.01 mole) and piperidine (0.02 mole) were taken in a borosil beaker (100ml). To this 5g of basic alumina was added and properly mixed with the help of a glass rod. The solid matrix so obtained was irradiated in a microwave oven at 450 W for the period 1.5–3.0 min. After cooling, the reaction mixture was treated with glacial acetic acid and filtered. Dilution of acetic acid solution with ice-cold water gave the product, which was filtered, washed with water, dried and recrystallized from a suitable solvent to give 3-acetylcoumarins **3**.

ii) Synthesis of 3-(1-{2-[3-(3-methoxyphenyl)[1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) 5

A mixture of 2-hydrazino-3-(3-methoxyphenyl)[1,8]naphthyridine **4** (0.01 mole), 3-acetylcoumarin **3** (0.01 mole) and DMF (5 drops) was exposed to MW irradiation at 200 W intermittently at 10 sec intervals for the specified time (**Table V**). On completion of reaction as indicated by TLC, the reaction mixture was cooled and treated with water. The resulting solid product was filtered, washed with water and purified by recrystallization from ethanol to give **5** (**Table V**).

II General procedure for the synthesis of 1-[3-(3-methoxyphenyl) [1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes 6

To the Vilsmeier-Haack reagent (0.03 mole) at 0-5°C, compound **5** (0.01 mole) was added portion wise. After the addition was complete, the reaction flask was kept at RT for 5 min and silica gel (3 g) was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder was then irradiated in microwave oven at 400 W intermittently at 30 sec intervals for the specified time (**Table VI**). After completion of reaction (monitored by TLC), the reaction mixture was cooled, treated with chilled water and filtered. The solid that precipitated by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from ethanol to obtain **6** (**Table VI**).

Table V — Physical and analytical data of 3-(1-{2-[3-(3-Methoxyphenyl) [1,8]-naphthyridin-2-yl]hydrazono}ethyl)-2*H*-2-chromenones (hydrazones) **5**

Compd	R^1	R^2	Reaction time (min)	m.p. C°	Yield (%)	Mol. formula	Found (%) (Cacld) C	H	N
5a	H	H	0.25	173	95	$C_{26}H_{20}N_4O_3$	71.68 (71.55	4.64 4.62	12.88 12.84)
5b	H	OCH_3	0.5	149	96	$C_{27}H_{22}N_4O_4$	69.65 (69.52	4.76 4.75	12.06 12.01)
5c	Cl	H	0.25	196	98	$C_{26}H_{19}ClN_4O_3$	66.44 (66.32	4.09 4.07	11.94 11.90)
5d	Cl	Cl	0.5	250	94	$C_{26}H_{18}Cl_2N_4O_3$	61.94 (61.80	3.61 3.59	11.14 11.09)
5e	Br	H	0.5	191	97	$C_{26}H_{19}BrN_4O_3$	60.72 (60.60	3.74 3.72	10.92 10.87)
5f	Br	Br	0.5	193	95	$C_{26}H_{18}Br_2N_4O_3$	52.67 (52.54	3.07 3.05	9.50 9.45)
5g	NO_2	H	0.25	208	95	$C_{26}H_{19}N_5O_5$	64.99 (64.86	3.99 3.98	14.60 14.55)
5h	5,6-Benzo		0.5	254	96	$C_{20}H_{22}N_4O_3$	74.19 (74.06	4.58 4.56	11.56 11.52)

Table VI – Physical and analytical data of 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes **6**

Compd	R^1	R^2	Reaction time (min)	m.p. C°	Yield (%)	Mol. formula	Found (%) (Cacld)		
							C	H	N
6a	H	H	3.0	183	85	$C_{28}H_{18}N_4O_4$	71.02 (70.88	3.83 3.82	11.86 11.81)
6b	H	OCH_3	3.5	195	87	$C_{29}H_{20}N_4O_5$	69.16 (69.04	4.02 4.00	11.15 11.11)
6c	Cl	H	3.0	165	88	$C_{28}H_{17}ClN_4O_4$	66.21 (66.08	3.39 3.37	11.06 11.01)
6d	Cl	Cl	3.5	188	84	$C_{28}H_{16}Cl_2N_4O_4$	62.02 (61.89	2.99 2.97	10.35 10.31)
6e	Br	H	3.0	156	87	$C_{28}H_{17}BrN_4O_4$	60.90 (60.77	3.11 3.10	10.16 10.12)
6f	Br	Br	4.0	158	84	$C_{28}H_{16}Br_2N_4O_4$	53.33 (53.19	2.57 2.55	8.91 8.86)
6g	NO_2	H	3.5	193	84	$C_{28}H_{17}N_5O_6$	64.86 (64.74	3.31 3.30	13.52 13.48)
6h	5,6-Benzo		3.5	172	86	$C_{32}H_{20}N_4O_4$	73.42 (73.28	3.86 3.84	10.71 10.66)

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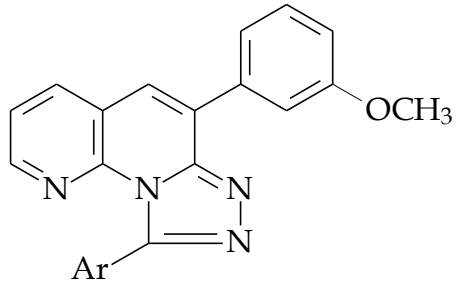
CHAPTER IV

BIOLOGICAL ACTIVITY

CHAPTER IV

1,8-Naphthyridine ring system is an important pharmacophoric element in medicinal chemistry. The incorporation of various heterocyclic moieties with 1,8-naphthyridine may show enhanced biological activity. Further, incorporation of halogen substituent generally enhances the antibacterial activity. Synthesis and biological evaluation of 1,8-naphthyridine derivatives have been a topic of special interest to organic and medicinal chemists. Fascinated by the varied biological profile of 1,8-naphtyridines, it was considered worthwhile to synthesize certain new 1,8-naphthyridines and assess their antibacterial and anti-fungal activities.

I 9-Aryl-6-(3-methoxyphenyl)[1,2,4]-triazolo[4,3-*a*][1,8]naphthyridines 8



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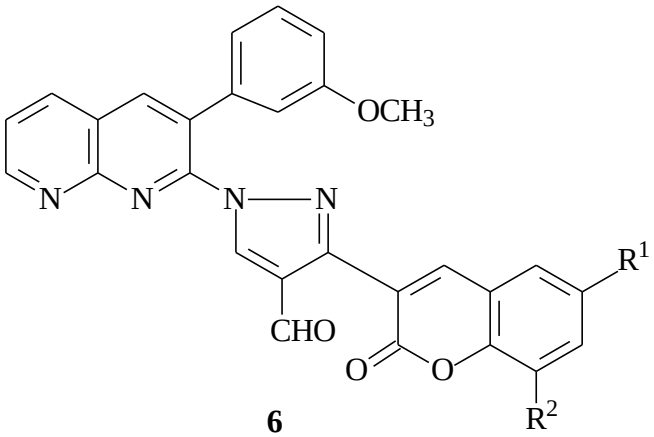
II 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes 6



6

Antibacterial activity

The newly synthesized compounds **8** and **6** were screened for their *in vitro* antibacterial activity against *Escherichia coli* (Gram-negative) and *Bacillus subtilis* (Gram-positive). The activity assay was carried out using the 250 and 500μg/disc concentration filter paper disc method of Vincent and Vincent[19] by measuring the zones of inhibition in mm. Gentamycin was used as a standard drug for comparison. The results are presented in **Table I** and **II**.

I 9-Aryl-6-(3-methoxyphenyl)[1,2,4]-triazolo[4,3-*a*] [1,8]naphthyridines 8

From the antibacterial activity results obtained (Table I**), it was evident that all the compounds** 8 **were active against both Gram-negative and Gram-positive bacteria at the concentration of 250 μg/disc. The compounds showed varying degree of antibacterial activity against these organisms. The activity of the compound depends upon the nature and position of the substituent at the aryl moiety. Compounds having chloro, fluoro and dimethoxy substituents are more antibacterial than the other substituents. On the other hand, compounds having nitro group diminishes the activity of the compounds. Compounds** 8e, 8f **and** 8j **showed promising antibacterial activity. The most active compound of the series was** 8e**.**

II 1-[3-(3-Methoxyphenyl)[1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-1*H*-4-pyrazolecarbaldehydes 6

From **Table II**, it was established that all the compounds **6** exhibited antibacterial activity against both the test bacteria at 250 μg/disc concentration. Compounds **6b**, **6c, 6d** and **6f** showed significant activity and remaining compounds showed moderate activity. The compound **6c** exhibited antibacterial activity similar with that of the Gentamycin.

Antifungal activity

The antifungal activity of the newly synthesized compounds **8** and **6** was examined against the fungi *Curvularia lunata* and *Fusarium oxysporum* using filter paper disc technique of Vicent and Vincent at 250 and 500 μg/disc concentrations. Carbendazim was used as standard. None of the screened compounds displayed antifungal activity.

Experimental Section

Antibacterial activity

The antibacterial activity of the compounds prepared was evaluated by the filter paper disc technique of Vincent and Vincent. The bacteria used in the present study were *Escherichia coli*, (Gram-negative) and *Bacillus subtilis* (Gram-positive). The compounds were dissolved in acetone and tried at two different concentrations (250 and 500 μg/disc). The Whatman filter paper discs (6 mm diameter) with different compounds were placed aseptically on seeded nutrient agar plates with different bacteria and incubated for 72 hours at 37±1°C. At the end of the incubation period, the diameter of the growth inhibition zones was measured. At least 10 paper discs were observed and repeated twice.

Antifungal activity

The antifungal activity of the compounds synthesized was determined by the filter paper disc method[19]. The fungi *Curvularia lunata* and *Fusarium oxysporum* were employed as the test organisms in the present investigation. The compound were dissolved in acetone and tried at two different concentrations (250 and 500 μg/disc). The Whatman filter paper discs (6 mm diameter) with different compounds were placed aseptically on seeded nutrient agar plates with different fungi and incubated for 7 days at 28±2°C. At the end of the incubation period, the diameter of the growth inhibition zones was measured. At least 10 paper discs were observed and repeated twice for each concentration of each test compound.

Table I - Antibacterial screening results of 9-Aryl-6-(3-methoxyphenyl) [1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **8**

Compd	Ar	Inhibition zone (in mm)			
		E. coli at		*B. subtilis* at	
		250 µg/disc	500 µg/disc	250 µg/disc	500 µg/disc
8a	C_6H_5	7.5	15.5	5.0	8.0
8b	4-$CH_3C_6H_4$	8.0	14.0	5.5	9.0
8c	4-$CH_3OC_6H_4$	7.0	12.5	4.5	8.5
8d	2-ClC_6H_4	8.5	18.0	5.5	11.0
8e	4-ClC_6H_4	10.0	20.0	6.0	13.0
8f	4-FC_6H_4	9.0	18.5	6.0	12.0
8g	2-$NO_2C_6H_4$	8.0	9.5	4.0	6.0
8h	3-$NO_2C_6H_4$	5.5	8.5	4.5	9.0
8i	4-$NO_2C_6H_4$	7.0	11.0	5.5	9.5
8j	3,4-$(CH_3O)_2C_6H_3$	9.0	18.0	5.5	10.0
	Gentamycin	12.0	22.0	8.0	15.0

Table II - Antibacterial activity data of 1-[3-(3-Methoxyphenyl) [1,8]naphthyridin-2-yl]-3-(2-oxo-2*H*-3-chromenyl)-

1*H*-4-pyrazolecarbaldehydes **6**

Compd	R^1	R^2	Inhibition zone (in mm)			
			E. coli at		*B. subtilis* at	
			250 μg/disc	500 μg/disc	250 μg/disc	500 μg/disc
6a	H	H	8.0	12.5	5.5	10.0
6b	H	OCH_3	10.0	17.5	6.5	12.0
6c	Cl	H	11.0	20.0	7.0	13.5
6d	Cl	Cl	9.5	16.0	6.0	10.5
6e	Br	H	9.0	14.0	5.0	8.5
6f	Br	Br	9.5	15.5	5.5	9.5
6g	NO_2	H	6.0	9.0	5.0	8.0
6h	5,6-Benzo		8.0	12.0	6.0	11.0
	Gentamycin		12.0	22.0	8.0	15.0