Send Orders for Reprints to reprints@benthamscience.net

Letters in Drug Design & Discovery, 2019, *16*, *Page Enation*

ARTICLE TYPE

Facile Synthesis of 6-Phenyl-6*h*-chromeno [4, 3-*b*] Quinoline Derivatives using $NaHSO_4@SiO_2$ Re-usable Catalyst and Their Antibacterial Activity Study Correlated by Molecular Docking Studies

Kancharla Suman[a], Jyothi Prashanth[b], Koya Prabhakara Rao[*a], Madala Subramanyam[a], Vejendla Anuradha[a] and Mandava Venkata Basaveswara Rao[c]

[a]*New Generation Materials Lab (NGML), Department of Science and Humanities, Vignan's Foundation for Science Technology and Research (VFSTR) (Deemed to be University), Vadlamudi, Guntur-522 213, Andhra Pradesh, India;* [b] *Department of physics, Kakatiya University, Warangal-506009, Telangana, India;* [c]*Department of Chemistry, Krishna University, Machilipatnam-521001, Andhra Pradesh, India.*

ARTICLE HISTORY

Received:
Revised:
Accepted:

DOI:

Abstract Background: Heterocyclic compounds containing heteroatoms (**O**, **N** and **S**) as part of five or six-membered cyclic moieties exhibited various potential applications such as pharmaceutical drugs, agrochemical products and organic materials. Among many known heterocyclic moieties, quinoline and its derivatives are one of the privileged scaffolds found in many natural products. In general, quinoline derivatives could be prepared by utilizing *ortho*-substituted anilines and carbonyl compounds containing a reactive α-methylene group of well-known reaction routes like Friedlander synthesis, Niemantowski synthesis and Pfitzinger synthesis. Moreover, polysubstituted quinolones and their derivatives also had shown considerable interest in the fields of organic and pharmaceutical chemistry in recent years.

Objectives: The main objective of our research work is towards the design and synthesis of divergent biological-oriented, proactive analogues with potential pharmacological value inspired by the anti-tubercular activity of 2-phenylquinoline analogues. In this study, we have been interested in the design and synthesis of bioactive, 2, 4-diphenyl, 8-arylated quinoline analogues.

Methods: The 6-phenyl-6*h*-chromeno [4, 3-*b*] quinoline derivatives were synthesized from 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde and various substituted aromatic anilines as starting materials using sodium bisulfate embedded SiO_2 re-usable catalyst. All these fifteen new compound structures confirmed by spectral data ^1H & ^{13}C NMR, Mass, CHN analysis etc. Furthermore, all these new compounds antibacterial activity strains recorded using the paper disc method. The compound molecular structures were designed using molecular docking study by utilizing the crystallographic parameters of S. Areus Murb protein.

Results: A series of fifteen new quinoline derivatives synthesized in moderate to good yields using sodium bisulfate embedded SiO_2 re-usable catalyst. The molecular structures of these newly synthesized compounds elucidated by the combination of spectral data along with the elemental analysis. These compounds antibacterial activity study have shown moderate to good activity against, Escherichia coli (Gram-negative) and Staphylococcus aureus (gram-positive) organisms. These antibacterial activity results were also a very good correlation with molecular docking studies.

Conclusion: In this study, fifteen new quinoline derivatives synthesized and structures confirmed by spectral data. In fact, all the compounds have shown moderate to good antibacterial activity. In general, the compounds containing the electron donor group at R_1 position (R_1 = OMe) and the acceptor group at R_2 positions (R_2 = F or Cl) had shown good antibacterial activity. These antibacterial activity results were also a very good correlation with molecular docking studies showing strong binding energies with the highest value being, -12.45 Kcal mol^{-1} with **S. aureus MurB** receptor.

Keywords: Sodium bi sulfate silica, Aromatic snilines, Quinoline derivatives, Re-usable catalyst, Antibacterial, Docking studies.

*Address correspondence to Prof. Koya Prabhakara Rao at New Generation Materials Lab (NGML), Department of Science and Humanities, Vignan's Foundation for Science Technology and Research (VFSTR) (Deemed to be University), Vadlamudi, Guntur-522 213, Andhra Pradesh, India; Tel/Fax: +91-863-234-4762, +91-863-253-4468; E-mails:kprao2005@gmail.com, drkpr_sh@vignan.ac.in.

1570-1808/19 $58.00+.00

1. INTRODUCTION

Heterocyclic compounds attracted the attention of scientific community due to various applications (1-24) such as pharmaceutical drugs, agrochemical products and organic materials. In the literature, heteroatoms (O, N and S) containing verities of the heterocyclic skeleton based molecules exhibiting the above-mentioned applications were reported. Quinoline and its derivatives are one of the privileged scaffolds containing a group of heterocyclic compounds found in many natural products. One of the very important alkaloids found in many plants is quinine, which contains a quinoline heterocyclic scaffold [25] exhibits an antibiotic resistance.

In general, quinoline derivatives were prepared by utilizing *ortho*-substituted anilines and carbonyl compounds containing a reactive *α*-methylene group using various well-known reaction routes like Friedlander, Niemantowski and Pfitzinger synthetic methods. Moreover, the syntheses of polysubstituted quinolone derivatives are also attracting considerable interest in the fields of organic and pharmaceutical chemistry [1-24] in recent years due to their potential applications. Owing to their biological importance, the synthesis of these derivatives could be a primary goal for synthetic organic chemists and hence, many synthetic strategies described for the synthesis of these important heterocyclic scaffolds. Some of them are Skraup reaction [16-18], Combes synthesis, Friedlander synthesis and Doebner-Miller reaction [19] along with a few other well-recognized synthetic protocols employed for the preparation of these quinoline derivatives [26, 27]. However, many of these synthetic strategies suffered a few drawbacks such as prolonged reaction times, low yields of the products, high stoichiometric [28] quantities of the reagents and hard reaction conditions, etc. Moreover, the above-mentioned synthetic protocols suffered hard handling conditions and often do not grant sufficient diversity for substitution on the quinoline ring system [29-31], especially for the large-scale synthesis.

In continuing our ongoing research work in the design of divergent biological-oriented organic synthesis of bioactive molecules [32-36], exhibits potential pharmacological applications. In this study, we have been interested in the design and synthesis of bioactive, 2, 4-diphenyl, 8-arylated quinoline analogues inspired from the anti-tubercular activity of 2-phenylquinoline analogues [6-15]. In this article, we discussed synthesis, characterization, antibacterial activity and molecular docking studies of fifteen new quinoline derivatives.

2. MATERIALS AND METHOD

2.1. General

All the solvents, reagents and reactants used for this work obtained from various commercial sources of the analytical grade used without any further purification. Melting points (MPs) determined by the open capillary method using on Stuart SMP3 melting-point apparatus and the values recorded are uncorrected. Mass spectra recorded on a VG micromass70-70H instrument. ^{1}H NMR ($CDCl_3$ 400 MHz) and ^{13}C NMR ($CDCl_3$ 100 MHz) were recorded on the Bruker Avance-400 spectrometer, trimethylsilane (TMS) as internal standard (chemical shifts and ppm). The reaction completeness monitored by thin layer chromatogram (TLC) on silica gel plates using a mixture of *n*-hexane and dichloromethane (DCM).

2.2. Synthesis

Synthesis of 1-(2-hydroxy-phenyl)-3-phenyl-propan-1-one (3):

To a mixture of water (7 mL) and sodium hydroxide flakes (3.0 mmol) solution, add 2-hydroxy acetophenone (1.0 mmol) at room temperature (RT). To this reaction, mixtures add benzaldehyde (1.3 mmol) and stir for 15 min. The whole reaction mixture was stirred for 4 hrs at 55 ^{o}C temperature. After completion of the reaction monitored by TLC, the product cooled to 15 ^{o}C. Later, adjust the pH to below 1.0 by adding HCl (3 mL) at below 15 ^{o}C and continued stirring for 2 hrs at the same temperature. Filtered the reaction mass and washed with water (10 mL) followed by methanol (3 mL), obtained crude product was purified in methanol to get the pure compound.

Synthesis of 2-phenyl chroman-4-one (4):

Compound (**4**), synthesized by adding ethanolic HCl (5 mL) to compound **3** (1.0 mmol) in a sealed tube. The reaction mixture stirred at 80 ^{o}C for 12 hrs. Later, the crude products extracted by distilling out the solvent under reduced pressure. To this crude product, 10 mL of distilled water added followed by neutralization the reaction mass with sodium carbonate solution. Finally, extract the compound with DCM 3x10 mL by washing with NaCl solution (5 mL) and dried with Na_2SO_4. The solvent distilled out under reduced pressure to get the pure compound.

Synthesis of 4-Chloro-2-Phenyl-2*H*-chromene-3-Carbaldehyde (5):

To the solution of flavan-4-ones (1.0 mmol) in dry DMF (5.0 mmol) with constant stirring at 0 ^{o}C, freshly distilled dry phosphorus oxychloride (1.0 mmol) was added. The whole reaction mixture stirred overnight poured onto crushed ice, after completion of the reaction. The yellow product separated out using filtration and washed with distilled water for few times. Later, the solid product purified by column chromatography by eluting with petroleum ether over silica gel yielded 70-85 % of 4-chloro-2-aryl-2H-3-chromenecarbaldehydes.

General Procedure for the synthesis of 6-phenyl-6H-chromeno [4, 3-b] quinolines (7a-o):

To a mixture of aldehyde (**5**) (1.0 mmol) and aniline (**6**) (1.0 mmol) in ethanol (5 mL) solvent, the catalysts sodium bisulfate embedded silica [37] (5.0 mmol) was added. The whole reaction mixture was stirred at room temperature for 30 min under halo photochemical light of wavelength 15000-18000 cm^{-1}. The reaction completion monitored by the thin layer chromatography (TLC). The solvent removed under reduced pressure from the crude product. Later, sodium bicarbonate solution (10 mL) added to the crude mixture and extracted with ethyl acetate (3x10 mL). From the collected organic layer, the solvent removed under reduced pressure. The resulting crude mixture was purified by the silica gel column using ethyl acetate/*n*-hexane (2:1) mixture to get 6-phenyl-6*H*-chromeno [4, 3-b] quinolines (**7a**) in good yield.

10-fluoro-6-phenyl-6H-chromeno [4, 3-b] quinoline (7a):

Yield 85 %, off white solid. IR spectrum (ν): 3027, 2965, 1779, 1038 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ .89 (dd, J =

7.5 Hz, 1-H), 8.15 (dd, J = 8.7, 5.3 Hz, 1-H), 7.85 – 7.42 (m, 4-H), 6.95 (d, J = 7.9 Hz, 2-H), 7.30 – 7.32 (m, 1-H), 7.21 (t, J = 7.4 Hz, 1-H), 7.15 (d, J = 8.1 Hz, 1-H), 6.37 (s, 1-H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 155.6, 150.1, 137.2, 133.4, 134.2, 129.8, 132.6, 130.5, 129.5, 128.9, 127.9, 127.9, 125.4, 125.6, 121.7, 118.7, and 81.2. Anal.Calcd for $C_{22}H_{14}FNO$: C, 80.72; H, 4.31; N, 4.28. Found: C, 81.72; H, 4.33; N, 4.58. Mass spectrum (ESI): m/z 328 $[M + H]^+$. M. P: 185-189 °C.

Similar procedure of **7a**, was employed for all other compounds **7b-o**, to get good yield. See supporting information (S. I) for complete spectral data.

9-Methyl-6-Phenyl-6H-chromeno [4, 3-b] quinoline (7b):

Yield 83 %, off white solid. IR spectrum (ν): 3027, 2965, 1784, 1036 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.55 (dd, J = 7.6 Hz, 1-H), 8.25 (dd, J = 8.5, 5.3 Hz, 1-H), 6.95 – 7.42 (m, 6-H), 7.35 (d, J = 7.5 Hz, 2-H), 7.25 – 7.28 (m, 1-H), 7.26 (t, J = 7.5 Hz, 1-H), 7.08 (d, J = 8.2 Hz, 1-H), 6.35 (s, 1-H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 155.6, 159.1, 137.2, 133.4, 131.2, 130.5, 131.6, 130.5, 128.1, 127.9, 127.1, 129.0, 125.4, 126.6, 123.7, 118.7, and 81.2. Anal.Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.81; H, 5.32; N, 4.35. Mass spectrum (ESI): m/z 324 $[M + H]^+$. M. P: 187-189 °C.

9-fluoro-6-(4-methoxyphenyl)-6H-chromeno [4, 3-b] quinoline (7c):

Yield 80 %, white solid. IR spectrum (ν): 3015, 2913, 1733, 1048 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.41 (s, 2-H), 7.33 (dd, J = 12.2, 8.3 Hz, 4-H), 7.22 (dd, J = 8.5, 2.1 Hz, 1-H), 7.11 (dt, J = 8.9, 4.4 Hz, 1-H), 6.98 - 6.88 (m, 4-H), 6.23 (s, 1-H), 3.78 (s, 3-H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 160.1, 158.7, 156.6, 133.5, 132.8, 129.5, 128.4, 125.9, 122.7, 122.6, 117.8, 114.2, 110.8, 79.6, and 55.3. Anal.Calcd for $C_{23}H_{16}FNO_2$: C, 77.30; H, 4.51; N, 3.92. Found: C, 77.32; H, 4.42; N, 3.99. Mass spectrum (ESI): m/z 359 $[M + H]^+$. M. P: 220-225 °C.

6-(4-methoxyphenyl)-9-methyl-6H-chromeno [4, 3-b] quinoline (7d):

Yield 85 %, light yellow solid. IR spectrum (ν): 3087, 2965, 1733, 1059 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 9.35 (d, J = 8.2 Hz, 2-H), 7.55-7.65 (m, 7-H), 7.12 – 6.59 (m, 3-H), 6.25 (s,1-H), 3.75 (s, 3-H), 2.48 (s, 3-H).^{13}C NMR: (100 MHz, $CDCl_3$): δ 161.6, 158.8, 152.7, 147.3, 141.8, 141.1, 138.3, 138.9, 138.7, 130.8, 129.5, 128.6, 127.8, 127.5, 125.1, 121.1, 118.7, 116.1, 115.7, 81.39, 56.5, 30.7. Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.76; H, 5.32; N, 3.86. Mass spectrum (ESI): m/z 354 $[M + H]^+$. M. P: 225-227 °C.

9-chloro-6-(4-methoxyphenyl)-6H-chromeno [4, 3-b] quinoline (7e):

Yield 86 %, light yellow solid. IR spectrum (ν): 3085, 2966, 1734, 1059 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 9.26 (d, J = 8.1 Hz, 2-H), 7.56-7.64 (m, 7-H), 7.15 – 6.55 (m, 3-H), 6.25 (s,1-H), 3.76 (s, 3-H), 2.45 (s, 3-H).^{13}C NMR: (100 MHz, $CDCl_3$): δ 160.6, 158.8, 154.7, 147.3, 140.8, 142.1, 138.3, 138.9, 138.7, 135.8, 127.5, 129.6, 127.8, 127.5, 1254.1, 121.1, 118.7, 116.1, 115.7, 81.39, 56.5, 30.7. Anal.Calcd for $C_{23}H_{16}ClNO_2$: C, 73.90; H, 4.31; N, 3.75 Found: C, 74.30; H, 4.42; N, 3.79. Mass spectrum (ESI): m/z 374 $[M + H]^+$. M. P: 224-225 °C.

6-phenyl-6H-chromeno [4, 3-b] quinoline (7f):

Yield 85 %, White solid. IR spectrum (ν): 3035, 2925, 1722, 1024 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.55 (dd, J = 7.7, 1.9 Hz, 1-H), 8.07 (dd, J = 8.2 Hz, 1-H), 7.66-7.59 (m, 1-H), 7.51-7.42 (m, 1-H), 7.45 – 7.40 (m, 7-H), 7.35 (m, 1-H), 7.20 – 7.15 (m, 1-H), 7.04 (dd, J = 8.1, 0.8 Hz, 1-H), 6.32 (d, J = 0.9 Hz, 1-H).^{13}C NMR: (100 MHz, $CDCl_3$): δ 154.6, 149.2, 144.4, 138.3, 131.3, 130.5, 130.4, 130.2, 130.1, 129.6, 129.4, 128.5, 128.3, 128.1, 126.5, 125.4, 122.7, 122.5, 117.6, 80.25. Anal.Calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.52; H, 4.93; N, 4.58. Mass spectrum (ESI): m/z 310 $[M + H]^+$. M. P: 185-188 °C.

10-chloro-6-(4-methoxyphenyl)-6H-chromeno [4, 3-b] quinoline (7g):

Yield 83 %, white solid. IR spectrum (ν): 3046, 29144, 1715, 1024 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.55 (d, J = 7.5 Hz, 1-H), 8.35 – 8.13 (m, 1-H), 7.52 – 7.42 (m, 2-H), 7.46 – 7.36 (m, 3-H), 7.25 (dt, J = 6.5, 3.3 Hz, 1-H), 7.17 (dd, J = 11.2, 3.8 Hz, 1-H), 7.05 (t, J = 7.7 Hz, 1-H), 6.95 – 6.92 (m, 2-H), 6.25 (s, 1-H), 3.83 (s, 3-H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 161.1, 157.6, 148.2, 145.1, 133.4, 131.2, 130.9, 130.5, 130.4, 130.2, 129.5, 129.2, 128.4, 126.5, 125.7, 122.5, 116.7, 113.2, 79.5, and 55.2. Anal.Calcd for $C_{23}H_{16}ClNO_2$: C, 73.90; H, 4.31; N, 3.75. Found: C, 74.09; H, 4.20; N, 3.80. Mass spectrum (ESI): m/z 374 $[M + H]^+$. M.P: 234-236 °C.

9-chloro-6-phenyl-6H-chromeno [4, 3-b] quinoline (7h):

Yield 82 %, off white solid. IR spectrum (ν): 3026, 2963, 1784, 1033 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.45 (dd, J = 7.6 Hz, 1-H), 8.15 (dd, J = 8.5, 5.2 Hz, 1-H), 7.48 – 7.42 (m, 6-H), 7.36 (d, J = 7.8 Hz, 2-H), 7.25 – 7.21 (m, 1-H), 7.18 (t, J = 7.5 Hz, 1-H), 7.05 (d, J = 8.2 Hz, 1-H), 6.35 (s, 1-H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 156.5, 149.4, 138.3, 132.2, 132.5, 130.5, 130.5, 129.3, 129.4, 128.7, 128.2, 128.1, 126.5, 125.4, 122.5, 118.7, and 80.5. Anal.Calcd for $C_{22}H_{14}ClNO$: C, 76.86; H, 4.10; N, 4.07. Found: C, 76.79; H, 4.21; N, 4.17. Mass spectrum (ESI): m/z 345 $[M + H]^+$. M. P: 187-189 °C.

6-(4-methoxyphenyl)-10-methyl-6H-chromeno [4, 3-b] quinoline (7i):

Yield 85 %, light yellow solid. IR spectrum (ν): 3087, 2965, 1733, 1059 cm^{-1}. 1H NMR: (400 MHz, CDCl3): δ 9.35 (d, J = 8.2 Hz, 2-H), 7.55-7.65 (m, 7-H), 7.12 – 6.59 (m, 3-H), 6.25 (s,1-H), 3.75 (s, 3-H), 2.48 (s, 3-H).13C NMR: (100 MHz, CDCl3): δ 161.6, 158.8, 152.7, 147.3, 141.8, 141.1, 138.3, 138.9, 138.7, 130.8, 129.5, 128.6, 127.8, 127.5, 125.1, 121.1, 118.7, 116.1, 115.7, 81.39, 56.5, 30.7. Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.76; H, 5.32; N, 3.86. Mass spectrum (ESI): m/z 354 $[M + H]^+$. M. P: 225-227 °C.

10-fluoro-6-(4-methoxyphenyl)-6H-chromeno [4, 3-b] quinoline (7j):

Yield 85 %, white solid. IR spectrum (ν): 3016, 2915, 1735, 1046 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.45 (s, 2-H), 7.35 (dd, J = 12.3, 8.3 Hz, 4-H), 7.25 (dd, J = 8.5, 2.1 Hz, 1-H), 7.11 (dt, J = 8.9, 4.4 Hz, 1-H), 6.99 – 6.88 (m, 4-H), 6.25 (s, 1-H), 3.78 (s, 3-H). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 161.1, 158.7, 155.6, 135.5, 133.8, 129.7, 128.5, 125.7, 122.5, 122.5, 117.5, 114.4, 110.5, 79.7, and 55.5. Anal.Calcd for $C_{23}H_{16}FNO_2$: C, 77.30; H, 4.51; N, 3.92. Found: C, 77.44; H, 4.35; N, 3.98. Mass spectrum (ESI): m/z 358 $[M + H]^+$, M. P: 225-228 °C.

10-bromo-6-phenyl-6H-chromeno [4, 3-b] quinoline (7k):

Yield 82 %, off white solid. IR spectrum (*v*): 3089, 2925, 1787, 1025 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): *δ* 8.57 (dd, J = 7.2, 1.6 Hz, 1-H), 8.18 (d, J = 8.2 Hz, 1-H), 7.69 – 7.58 (m, 2-H), 7.45 – 7.42 (m, 7-H), 7.35-723 (m, 1-H), 7.20 (s, 1-H), 6.32 (s, 1-H). ^{13}C NMR: (100 MHz, $CDCl_3$): *δ* 155.6, 148.2, 147.4, 139.3, 135.3, 131.6, 129.5, 128.5, 128.3, 126.5, 125.7, 122.5, 117.4, and 80.5. Anal.Calcd for $C_{22}H_{14}BrNO$: C, 68.06; H, 3.63; N, 3.61. Found: C, 68.35; H, 3.55; N, 3.63. Mass spectrum (ESI): m/z 388 $[M + H]^+$. M. P: 195-198 °C.

10-nitro-6-phenyl-6H-chromeno [4, 3-b] quinoline (7l):

Yield 80 %, yellow solid. IR spectrum (*v*): 3013, 2928, 1765, 1046 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 8.55 (d, J = 6.9 Hz, 1-H), 8.16 (s, 1-H), 7.65 (dd, J = 12.0, 3.0 Hz, 2-H), 7.45 – 7.35 (m, 7-H), 7.20 (t, J = 7.4 Hz, 1-H), 7.07 (t, J = 12.2 Hz, 1-H), 6.34 (s, 1-H). ^{13}C NMR: (100 MHz, $CDCl_3$): *δ* 155.5, 149.9, 148.1, 139.7, 133.9, 131.0, 129.8, 129.5, 128.5, 128.7, 128.4, 128.3, 127.5, 127.3, 126.5, 124.5, 123.4, 121.6, 115.7, 81.5.: Anal.Calcd for $C_{22}H_{14}N_2O_3$: C, 74.57; H, 3.98; N, 7.91. Found: C, 74.63; H, 3.89; N, 7.21. Mass spectrum (ESI): m/z 355 $[M + H]^+$. M. P: 235-237 °C.

10-methoxy-9-methyl-6-phenyl-6H-chromeno [4, 3-b] quinoline (7m):

Yield: 84 %, white solid. IR spectrum (*v*): 3014, 2915, 1725, 1013 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): *δ* 8.56 (d, J = 2.5 Hz, 1-H), 8.05 (d, J = 9.2 Hz, 1-H), 7.45 – 7.35 (m, 2-H), 7.35 – 7.32 (m, 3-H), 7.25 (d, J = 7.5 Hz, 2-H), 6.95 (d, J = 2.8 Hz, 1-H), 6.92 (d, J = 8.5 Hz, 1-H), 6.32 (s,1-H), 3.85 (s, 3-H), 2.45 (s, 3-H). ^{13}C NMR: (100 MHz, $CDCl_3$): *δ* 161.7, 158.8, 145.3, 141.8, 140.1, 138.3, 136.7, 136.5, 129.6, 129.7, 128.2, 127.2, 127.5, 124.4, 122.2, 118.7, 114.5, 80.2, 55.65, and 28.7. Anal.Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.65; H, 5.35; N, 4.09. Mass spectrum (ESI): m/z 354 $[M + H]^+$. M. P: 198-199 °C.

10-bromo-8-chloro-11-methyl-6-phenyl-6H-chromeno [4, 3-b] quinoline (7n):

Yield 82 %, yellow solid. IR spectrum (*v*): 3087, 2911, 1724, 1024 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): *δ* 8.65 (d, J = 2.5 Hz, 1-H), 8.05 (d, J = 8.9 Hz, 1-H), 7.65 – 7.62 (m, 2-H), 7.47 (dd, J = 8.6, 2.5 Hz, 1-H), 7.42 (s, 1-H), 7.32 (d, J = 8.1 Hz, 2-H), 7.26 (d, J = 7.9 Hz, 2-H), 6.94 (d, J = 8.6 Hz, 1-H), 6.35 (s, 1-H), 2.40 (s, 3-H). ^{13}C NMR: (100 MHz, $CDCl_3$): *δ* 158.6, 151.0, 137.5, 135.8, 131.5, 129.6, 129.5, 127.7, 125.4, 124.5, 124.2, 121.5, 115.9, 114.3, 113.5, 108.5, and 55.5. Anal.Calcd for $C_{23}H_{15}BrClNO$: C, 63.25; H, 3.46; N, 3.21. Found: C, 63.5; H, 3.36; N, 3.35. Mass spectrum (ESI): m/z 437 $[M + H]^+$. M. P: 224-226 °C.

9, 10, 11-trimethoxy-6-phenyl-6H- chromeno [4, 3-b] quinoline (7o):

Yield 95 %, White solid. IR spectrum (*v*): 3097, 2985, 1765, 1083 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): *δ* 9.45 (d, *J* = 7.3 Hz, 1-H), 9.02 (s, 1-H), 8.15 (s, 1-H), 7.56 (t, *J* = 7.8 Hz, 1-H), 7.45 – 7.43 (m, 3-H), 7.45 (dt, *J* = 6.2, 3.2 Hz, 2-H), 7.35 (t, *J* = 7.3 Hz, 1-H), 7.07 (d, *J* = 8.2 Hz, 1-H), 6.42 (s, 1-H), 4.19 (s, 3-H), 4.05 (s, 3-H), 3.94 (s, 3-H). ^{13}C NMR: (101 MHz, $CDCl_3$): *δ* 158.08, 148.02, 143.78, 137.97, 135.23, 128.70, 128.19, 126.97, 124.51, 124.05, 119.45, 118.42, 79.12, 61.96, 61.37, and 57.34. Anal.Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.25; H, 5.20; N, 3.55. Mass spectrum (ESI): *m/z* 400 $[M + H]^+$. M. P: 203-205 °C.

2.3. Antibacterial activity study:

The antibacterial activity screenings for the compounds, **7a-o,** were carried out by the paper disc method using organisms, Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive) for this study. The growing culture of Escherichia coli and Staphylococcus aureus micro-organisms were monitored separately, after solidification of media, petri-plates inoculated for 24 hrs at 37 °C as follows [40, 41]. Filter paper discs of 5 mm diameter dipped in the test solution of different concentrations of all fifteen compounds (**7a-o**). After drying, the discs placed on the antibiotic med-3 agar in petri-plates seeded with 1 mL bacterial culture of Escherichia coli and Staphylococcus aureus.

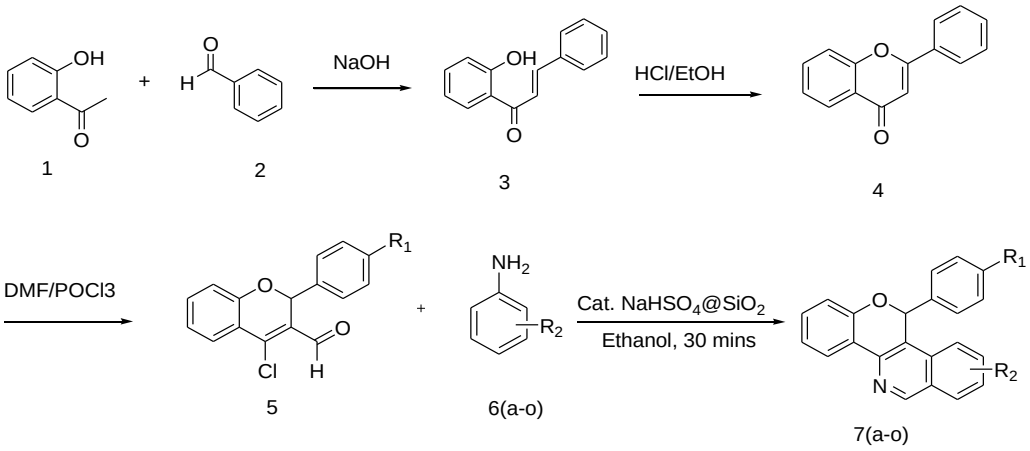
2.4. Molecular Docking study:

The molecular structures of all the newly synthesized compounds designed using Gauss view program 5.0 [33]. The geometries of the ligands were optimized using the standard density functional triply-parameter hybrid model DFT/RPM6 using ZDO basis set with Gaussian 09w [42]. The crystallographic parameters of S. Areus Murb protein collected from RCSB protein data bank (www.rscb.org) with PDB ID: 1HSK for S. Areus Murb. The water molecules removed from the downloaded protein structure using UCSF chimera 1.10.1 software. Later, the molecular docking studies carried out using Auto Dock Tools (ADT) version 1.5.6 and Auto Dock 4.2 package suite (http://mgltools.scripps.edu). Gasteiger charges, Non-polar hydrogens and torsions degrees of freedom assigned by employing the ADT program to merge non-polar hydrogens into related carbon atoms of the receptor S. Areus Murb. The donor-acceptor hydrogen bonding interactions adjusted to be 1.9 Å. The grid box built with dimensions of 60 × 60 × 60 $Å^3$ on the receptor S. Areus Murb with the aid of the ADT program with a grid point spacing of 0.3750 Å. The graphical output results illustrated using Discovery Studio 4.1.0 software [43].

3. RESULTS AND DISCUSSION

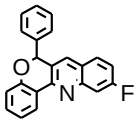
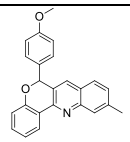
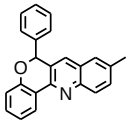
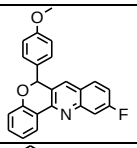
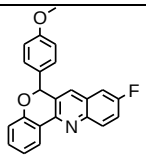
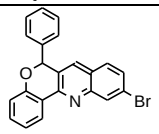
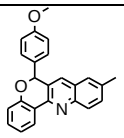
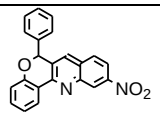
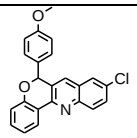
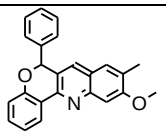
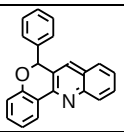
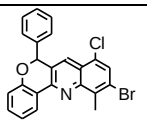
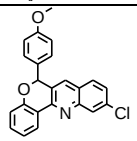
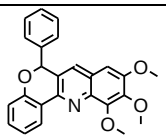
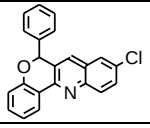
3.1. Synthesis

The compound, **3**, synthesized by taking a mixture of water and sodium hydroxide flakes and 2-hydroxy acetophenone at room temperature. To this reaction, mixture added benzaldehyde and stirred for 15 min followed by increased the temperature to 55 ^oC along with 4 hrs constant stirring. The next intermediate, 2-phenyl chroman-4-one **(4)** synthesized by mixing ethanolic HCl to the compound **3,** in a sealed tube stirred at 80 ^oC for 12 hrs. Next intermediate, 4-Chloro-2-Phenyl-2*H*-chromene-3-carbaldehyde **(5)** was synthesized by using compound **4**, in dry DMF and freshly distilled dry phosphorus oxychloride along with constant stirring at 0 ^oC (Scheme 1).



Scheme 1: Synthesis of final compounds, 6-phenyl-6*H*-chromeno [4, 3-b] quinolones, **7**(**a-o**).

Table 1: Structures of quinoline derivatives, **7** (**a-o**) and their synthetic conditions.

S. NO	Compound R, R^1	Product	Time (Min)	Yield (%)	S. NO	Compound R, R^1	Product	Time (Min)	Yield (%)
7a	R_1= H R_2= 3-F		30`	85	**7i**	R_1= OMe R_2= 3-Me		30`	85
7b	R_1= H R_2= 4-Me		30`	83	**7j**	R_1= OMe R_2= 3-F		30`	84
7c	R_1= OMe R_2= 4-F		30`	85	**7k**	R_1= H R_2= 3-Br		30`	82
7d	R_1= OMe R_2= 4-Me		30`	80	**7l**	R_1= H R_2= 3-NO_2		30`	80
7e	R_1= OMe R_2= 4-Cl		30`	80	**7m**	R_1= H R_2= 3-OMe, 4-Me		30`	84
7f	R_1= H R_2= H		30`	85	**7n**	R_1= H R_2= 2-Me, 3-Br, 5-Cl		30`	82
7g	R_1= OMe R_2= 3-Cl		30`	84	**7o**	R_1= H R_2= 2-OMe, 3-OMe, 4-OMe		30`	95
7h	R_1= H R_2= 4-Cl		30`	86					

Synthesis of 6-phenyl-6*H*-chromeno [4, 3-b] quinolines (7a-o):

A Series of fifteen 6-phenyl-6*H*-chromeno [4,3-*b*] quinoline derivatives, **7(a-o**) were prepared from 4-Chloro-2-Phenyl-2*H*-chromene-3-Carbaldehyde (**5**) with various aromatic anilines (**6**) in good yields using sodium bisulfate embedded SiO_2 catalyst at room temperature (Scheme. 1, Table 1). The catalyst was prepared slightly modified method used earlier [37] by taking the solution of $NaHSO_4.H_2O$ in the water added to SiO_2 slowly. The whole catalyst reaction mixture stirred for 15 min at room temperature. Later, the mixture heated gently on a hot plate until free-flowing solid obtained. Finally, this catalyst mixture further dried at 120 °C for 48 hrs and stored in hot condition to give desired sodium bisulfate embedded silica catalyst.

3.2. Antibacterial Activity:

Table 2: Antibacterial activity of 6-phenyl-6*H*-chromeno [4, 3-b] quinolones, **7(a-o)**.

Comp.	Zone of inhibition (mm)*					
	Escherichia coli (Gram-negative) (Conc. µg/ml)			*Staphylococcus aureus* (Gram-positive) (Conc. µg/ml)		
	200	**100**	**50**	**200**	**100**	**50**
7a	20	22	20	19	21	10
7b	18	19	15	31	24	22
7c	15	16	18	19	15	11
7d	15	18	11	18	19	11
7e	18	19	30	28	19	23
7f	12	12	22	20	32	22
7g	14	15	16	11	15	13
7h	11	13	15	12	15	16
7i	12	11	17	13	11	15
7j	10	12	13	9	11	14
7k	13	12	11	14	13	11
7l	14	11	11	16	19	15
7m	12	6	8	3	6	8
7n	3	6	9	12	6	9
7o	12	18	10	11	14	15
Chloramphenicol	31	30	21	33	30	23
*indicates average of triplicate						

As we designed to perform the biological activity, all the newly synthesized compounds **(7a-o),** screened for the antibacterial activity study using the paper disc method. For antibacterial activity study, two organisms, Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive) organisms were used. The antibacterial activity screening data (Table 2) exhibited that, all the compounds **7(a-o),** are active towards above-mentioned organisms by showing moderate to good antibacterial activity. However, among the fifteen screened compounds, **7a**, **7b, 7c, 7d,** and **7e** showed high activity against the entire microorganism employed for this study. Indeed, the activities shown by these compounds are close to that of the reference standards. The remaining ten compounds also have shown good to moderate antibacterial activity against the same microorganisms. In general, the compounds containing electron donor group at R_1 position (R_1 = OMe) and acceptor group at R_2 positions (R_2 = F or Cl) had shown good antibacterial activity.

3.3. In silico molecular docking studies

The in silico molecular docking studies of the titled compounds **7(a**-o) have performed, in order to understand the binding interaction energy with protein S. Areus UPA-N-Acetylenol pyruvyl-glucosamine reductases including Helicobacter pylori and Bacillus subtilis (S. Areus Murb) (PDB ID: I HSK). This protein is a promising target for antimicrobial drug therapy [38, 39]. According to molecular docking studies, all the ligands shown good binding energies with the protein receptor represented in table 3. Docking results revealed that all the ligands shown good to moderate binding energies with the protein receptor.

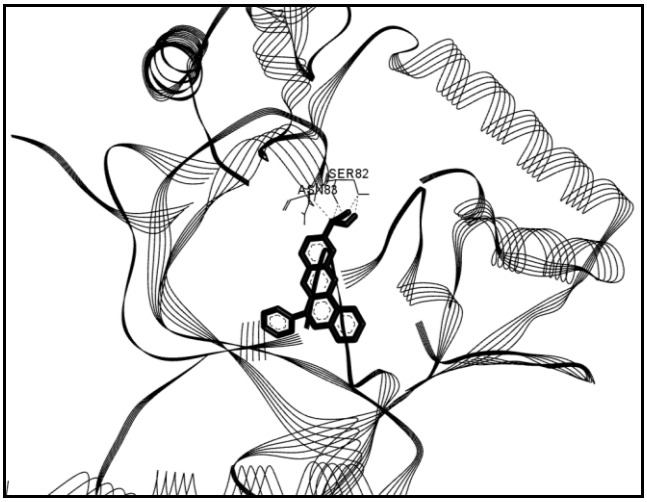


Figure 1. Showing the binding posture and interactions of **7l**, to the amino acid residues (SER 82 and ASN 83) target protein: S. arecus murb (**PDB ID: I HSK**).

The compound, **7l** exhibited the highest binding energy 12.45 Kcal mol^{-1} with five hydrogen bonds with amino acid residues (Fig 1, see SI for all the figures). Among five *H*-bonds, four of them are between oxygen and nitrogen atoms of a nitrite group of SER 82 (3) amino acid residue with bond distances 1.998 (1), 2.046 (1) and 2.421(1) Å. The

remaining two *H*-bonds are between the oxygen and nitrogen of a nitrite group of ASN 83 amino acid with a bond distance of 2.220 (1) and 1.909 (1) Å, respectively. The corresponding hydrogen bond energies vary from -1.8 to -4.3 Kcalmol^{-1} [44]. The free energy for hydrogen bonding in biological systems varies between −1.5 Kcal mol^{-1} to −4.7 Kcal mol^{-1} [44, 45]. The present protein-ligand *H*-bonding values reasonably agreed with the range of biological systems reported in the literature. The calculated AIM intermolecular *H*-bonding energies are lower than calculated binding energy values of our systems. The topological parameters kinetic and potential energy density at the BCP depicting intermolecular hydrogen-bonding, using AIM theory [46] have been computed by the Multiwfn software [47] employing the output file of the optimized geometry of **7l** using DFT/B3LYP/6-31^{++} (d, p) basis set.

Table 3. Binding energies of 6-phenyl-6*H*-chromeno [4, 3-b] quinolone, (**7a-o**) compounds substituted against receptor S. aureus MurB inhibitors.

Compound	Binding Energies (Kcal mol^{-1})		
	S. aureus MurB (PDB ID : I HSK)		
	Binding energy	No. of H Bonds	Residues involved in bonding
7a	-10.72	02†	SER82, ASN83
7b	-10.43	03*	GYL146, GYL145,VAL199
7c	-11.43	02†	ASN83, HIS196
7d	-10.51	02*	TYR149, GYL145, SER143, GLY146
7e	-10.28	02*	TYR149, GLY145. GLY146, SER143
7f	-10.71	03*	GLY146, SER143, GLY145, TYR149
7g	-11.40	01†	HIS196
7h	-10.57	03*	VAL199, GLY146, SER115, GLY145, SER143
7i	-11.40	1†	HIS196
7j	-11.43	03†	HIS196, ASN83, SER82
7k	-10.78	05*	VAL199, GLY145, TYR149, SER143, SER115, LEU78
7l	-12.45	05†	SER 82 (3), ASN83 (2)
7m	-10.78	01†	VAL199
7n	-11.77	03*	GLY146, SER115, GLY81, GLY79, VAL199
7o	-10.15	01†	VAL199
† Protein and ligand H-bond; * Hydrophobic H-bond			

CONCLUSION

In summary, fifteen new quinoline derivatives synthesized in moderate to good yields from, 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde and various substituted aromatic anilines as starting materials using sodium bisulfate embedded SiO_2 as a re-usable catalyst. Molecular structures of all these fifteen newly synthesized compounds elucidated using spectral data and elemental analysis. In fact, all the compounds have shown moderate to good antibacterial activity against, Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive) organisms. In general, the compounds containing the electron donor group at R_1 position (R_1 = OMe) and acceptor group at R_2 positions (R_2 = F or Cl) had shown good antibacterial activity. These antibacterial activity results are a very good correlation with molecular docking studies showing strong binding energies with the highest value being, -12.45 Kcal mol^{-1} with **S. aureus MurB** receptor.

CONFLICT OF INTEREST

All the authors declare no competing financial interest.

ACKNOWLEDGEMENTS

K. Suman (K. S) thanks VFSTR (Deemed to be University) for the research avenues and funding. Koya Prabhakara Rao (K. P. Rao) thanks DST-SERB, financial support, project no. **EMR/2014/001114.**

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article like all the spectral data and molecular docking interactions can find in the online version, at xxxxxxxxx. File name and description: Suman-LDDD-Supporting Information.

REFERENCES

[1] Cagir, A.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. Synthesis and topoisomerase I inhibitory properties of luotonin A analogues. *Bio org & Med Chem.* **2004**, *12*, 6287-6299.

[2] Akguna, H.; Yilmaza, D.U.; Atalay, R.C.; Gozen, D.A Series of 2,4(1*H*,3*H*)-Quinazolinedione derivatives: synthesis and biological evaluation as potential anticancer agents. *Lett. In. Drug. Des & Disc*. **2016**, *13*, 64 – 76.

[3] Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, Ch.; Harikishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. Synthesis of multisubstituted quinolines from Baylis–Hillman adducts obtained from substituted 2-chloronicotinaldehydes and their antimicrobial activity *Bioorg Med Chem*. **2006**, *14*, 4600-4609.

[4] Reddy, T. N.; Rao, V. J. Importance of Baylis-Hillman adducts in modern drug discovery. *Tet. Lett*. **2018**, *59*, 2859-2875.

[5] Mareddy, J.; Praveena, K. S. S.; Suresh, N.; Jayashree, A.; Roy, S.; Rambabu, D.; Murthy, N. Y. S.; Pal, S. A remarkably faster approach towards 1, 2, 3-triazolyl quinolines via CuAAC in water: their crystal structure analysis and antibacterial activities. Lett Drug Des & Disc. **2013**, *10*, 343-352.

[6] McKay, M. J.; Carroll, A. R.; Quinn, R. J. Perspicamides A and B, Quinolinecarboxylic acid derivatives from the Australian ascidian botrylloides perspicuum. *J Nat Prod*. **2005**, *68*, 1776-1778.

[7] Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. Practical route to a new class of LTD4 receptor antagonists. *J Org Chem*. **1996**, *61*, 3398-3405.

[8] Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. Synthesis and antibacterial evaluation of certain quinolone derivatives. *J Med Chem.* **2001**, *44*, 2374-2377.

[9] Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. 1,8-Naphthyridines IV. 9-substituted N,N-dialkyl-5-(alkylamino or cycloalkylamino) [1,2,4]triazolo[4,3-a][1, 8] naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities. *Eur J Med Chem*. **2000**, *35*, 1021-1035.

[10] Reddymasu, S.; Pombala, S.; Singh, J. S.; Jawed, A. M.; Kumar, C. G.; Raju, R. R. Synthesis, antitumor evaluation, and molecular docking studies of indole–indazolyl hydrazide–hydrazone derivatives. *Monatsh Chem*. **2017**, *148*, 305-314.

[11] Dube, D.; Blouin, M.; Brideau, C.; Chan, C. C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530. *Bio org Med Chem Lett.* **1998**, *8*, 1255-1260.

[12] Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. A new series of PDGF receptor tyrosine kinase inhibitors: 3-substituted quinoline derivatives. *J Med Chem.* **1994**, *37*, 2129-2137.

[13] Bilker, O.; Undo, V.; Panico, M.; Etiene, A. E.; Paxton, T.; Dell, A.; Rogers, M.; Sinden, R. E.; Morris, H. R.; Identification of xanthurenic acid as the putative inducer of malaria development in the mosquito. *Nature*. **1998**, *392*, 289-292.

[14] Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. Cu(I)-catalyzed three component coupling protocol for the synthesis of quinoline derivatives. *Tet Lett*. **2002**, *43*, 6485-6488.

[15] Legros, J. Y.; Primault, G.; Fiaud, J. C. Syntheses of acetylquinolines and acetylisoquinolines via palladium-catalyzed coupling reactions. *Tetrahedron*. **2001**, *57*, 2507-2514.

[16] Agrawal, A. K.; Jenekhe, S. A. Electrochemical properties and electronic structures of conjugated polyquinolines and polyanthrazolines. *Chem Mater*. **1996**, *8*, 579-589.

[17] Jenekhe, S. A.; Lu, L.; Alam, M. M. New conjugated polymers with donor−acceptor architectures: synthesis and photophysics of carbazole−quinoline and phenothiazine−quinoline copolymers and oligomers exhibiting large intramolecular charge transfer. *Macromolecules*. **2001**, *34*, 7315-7324.

[18] Jegou, G.; Jenekhe, S. A. Highly fluorescent poly(arylene ethynylene)s containing quinoline and 3-alkylthiophene. *Macromolecules*. **2001**, *34*, 7926-7928.

[19] Niementowski, *S.* Synthesen der chinolin derivative. *Ber*. **1894**, *27*, 1394-1403.

[20] Sakamoto, R.; Rao, K. P.; Nishihara, H. Arylethynylanthraquinone and Bis (arylethynyl) anthraquinone: Strong donor–acceptor interaction and proton-induced cyclization to form pyrylium and dipyrylium salts. *Chem. Lett*. **2011**, *40*, 1316-1326.

[21] Rao, K. P.; Kondo, M.; Kume, S.; Sakamoto, R.; Nishihara, H. Protonation-induced cyclization of 1, 8-bis (arylethynyl) anthraquinones: monopyrylium salt formation and intensification of donor–acceptor interaction.*Chem Lett.* **2011**, *40*, 1456-1458.

[22] Rao, K. P.; Kusamoto, T.; Kume, S.; Yamamoto, Y.; Sakamoto, R.; Nihei, M.; Oshio, H.; Nishihara, H. Platinadithiolene-conjugated pyrylium salt with strong intramolecular donor–acceptor interaction. *Chem. Comm.* **2011**, *47*, 2330-2332.

[23] Rao, K. P.; Kusamoto, T.; Toshimitsu, F.; Inayoshi, K.; Kume, S.; Yamamoto, Y.; Sakamoto, R.; Nishihara, H. Double protonation of 1, 5-bis (triarylaminoethynyl) anthraquinone to form a paramagnetic pentacyclic dipyrylium salt. *J. Am. Chem. Soc*. **2010**, *132*, 12472-12479.

[24] Rao, K. P.; Kondo, M.; Sakamoto, R.; Kusamoto, T.; Kume, S. Nihei, M.; Oshio, H.; Nishihara, H. Double protonation of 1, 5-bis (triarylaminoethynyl) anthraquinone to form a paramagnetic pentacyclic dipyrylium salt. *Chem. Eur. J.* **2011**, *17*, 14010-14019.

[25] Luckner, M.; Ritter, C. On the biosynthesis of the 2-n-alkyl-4-hydroxyquinolines of pseudomonas aeruginosa (Schroet.) Migula. *Tet Lett.* **1965**, *12*, 741-744.

[26] Ramann, G. A.; Cowen, B. J. Recent advances in metal-free quinoline synthesis. *Molecules*. **2016**, *21*, 986.

[27] Ranu, B. C.; Hajra, A.; Jana, U. Microwave-assisted simple synthesis of quinolines from anilines and alkyl vinyl ketones on the surface of silica gel in the presence of indium (III) chloride. *Tet Lett.* **2000**, *41*, 531-533.

[28] Bose, D. S.; Kumar, R. K. High-yielding microwave assisted synthesis of quinoline and dihydroquinoline derivatives under solvent-free conditions. *Heterocycles.* **2006**, *68*, 549-559.

[29] Pasau, P.; Knerr, L.; Demaude, T. New synthetic pathway to diverse 2-substituted quinolines based on a multicomponent reaction: solution-phase and solid-phase applications. *J Comb Chem*. **2004**, *6*, 768-775.

[30] Mehata, P. K.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. Reaction of α-oxoketene-N, S-arylaminoacetals with Vilsmeier reagents: an efficient route to highly functionalized quinolines and their benzo/hetero-fused analogues. *J Org Chem*. **2003**, *68*, 3966-3975.

[31] Sangu, K.; Fuchibe, K.; Akiyama, T. A novel approach to 2-arylated quinolines: electrocyclization of alkynyl imines via vinylidene complexes. *Org Lett.* **2004**, *6*, 353-355.

[32] Srinivas, B.; Suryachandram, J.; Devi, Y. K.; Rao, K. P. Synthesis and antibacterial activity studies of 8,9-dihydro [7*H*] benzo 1,2,4-oxadiazoles and its coumarin derivatives. *J Hetro Cyclic Chem.* **2017**, *54*, 3730-3734.

[33] Boddupally, S.; Jyothi, P.; Rao, M. V. B.; Rao, K. P. Design and synthesis of antimicrobial active (E)-(3-(substituted-styryl)-7H-furo[2,3-f]chromen-2-yl)(phenyl)methanone derivatives and their in silico molecular docking studies. *J Hetro Cyclic Chem.* **2019**, *56*, 73-80.

[34] Suman, K.; Rao, K.P.; Anuradha, V.; Rao, M.V.B.; Pal, M. Ultrasound assisted synthesis of 3,4-diyne substituted isocoumarin derivatives: identification of potential cytotoxic agents. *Mini reviews in Med Chem.* **2018**, *18*, 1064-1070.

[35] Subramanyam, M.; Sreenivasulu, R. Varala, R.; Rao, M. V. B.; Rao, K. P. A facile, efficient and convenient synthesis of 1,8-dioxodecahydroacridines with PMA-SiO_2 reusable catalyst. *Lett Org Chem*. **2018**, *15*, 915-921.

[36] Subramanyam, M.; Sreenivasulu, R.; Gundla, R.; Rao, M. V. B.; Rao, K. P. Synthesis, Biological Evaluation and Docking Studies of 1,3,4-Oxadiazole Fused Benzothiazole Derivatives for Anticancer Drugs. *Lett. Drug. Des. Disc*. **2018**, *15*, 1299-1307.

[37] Azarifar, D.; Forghaniha, A. J. A novel chemoselective reaction of aldehydes with 2-mercaptoethanol catalyzed by SiO_2-$NaHSO_4$ under solvent-free condition. Chin. Chem. Soc. **2006**, *53*, 1189-1192.

[38] Timothy, E. B.; Melissa, S. H.; Gil, H. C.; Joyce, I. C.; John, T.H.; Joseph, P. M.; Eric, T. B. A structural variation for MurB: X-ray crystal structure of staphylococcus aureus UDP-N-acetylenolpyruvylglucosamine reductase (MurB). *Biochemistry*. **2001**, *40*, 2340-2350.

[39] Eleni, P.; Evangelia, T.; Athina, G.; Jovana, P.; Jasmina, G.; Marina, S.; Emmanuele, C.; Giovanni, M.; Shome, S. B.; Anil, K. S. 4-Thiazolidinone derivatives as potent antimicrobial agents: microwave-assisted synthesis, biological evaluation and docking studies. *Med Chem Commun.* **2015**, *6*, 319-326.

[40] Home, W. S.; Stout, C. D.; Ghadiri, M. R. A Heterocyclic Peptide Nanotube. *J Am Chem Soc.* **2003**, *125*, 9372-9376.

[41] Chandrashekhar, S.; Basu, D.; Rambabu, Ch. Three-component coupling of alkynes, Baylis–Hillman adducts and sodium azide: a new synthesis of substituted triazoles. *Tet Lett.* **2006**, *47*, 3059-3063.

[42] Frisch MJ, Trucks GW, et al., Gaussian, Inc., Wallingford CT. **2009**.

[43] Diego, S.; Calif. *Discovery Studio Modeling Environment.* USA Accelrys Software Inc. Release 4.1.0. Accelrys Software Inc; **2013**.

[44] Freitas, R. F. D.; Schapira, M. A systematic analysis of atomic protein–ligand interactions in the PDB. *Med. Chem. Commun*. **2017**, *8*, 1970-1981.

[45] Davis, A. M.; Teague, S. J. Hydrogen bonding, hydrophobic interactions, and failure of the rigid receptor hypothesis. *Angew. Chem., Int. Ed.*,**1999**, *38*, 736–749.

[46] Schlegel, H. B.; Millam, J.; Iyengar, S. S.; Voth, G. A.; Daniels, A. D.; Scuseria, G. E.; Frisch, M. J. *Ab initio* molecular dynamics: propagating the density matrix with Gaussian orbitals. *J. Chem. Phys.*, **2001**, *114*, 9758-9763.

[47] Lu, T.; Chen, F. Multiwfn: a multifunctional wave function analyzer. *J. Comput. Chem.*, **2012**, *33*, 580–592.