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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL QUINAZOLINE DERIVATIVES AS POTENTIAL ANTI-BACTERIAL AGENTS

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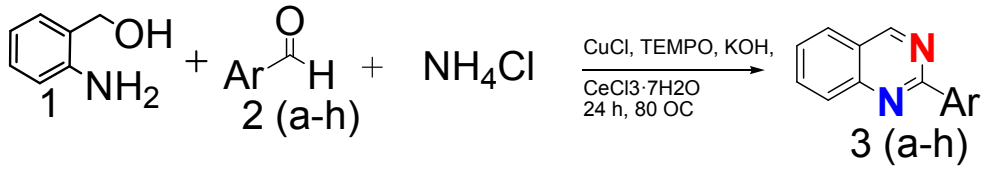
ABSTRACT
In this study, a series of Novel Quinazoline derivatives was designed and synthesized. The chemical structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral studies. Eight new compounds (3a–h) were tested in vitro for their antimicrobial activity against clinically isolated strains. All the synthesized products were evaluated for their antimicrobial activity. All the compounds exhibited significant to moderate antimicrobial activity. Compounds 3h, 3g, and 3e demonstrated good antimicrobial activity against all the tested microbial strains.

KEY WORDS: Quinazolines, Anti-bacterial activity, Anti-fungal activity, different aldehydes, Synthesis, Heterocyclic compounds.

SCHEME



INTRODUCTION:

Now a day's Heterocyclic compounds analogues and derivatives have become strong Interest in pharmaceutical research area because of their useful biological and pharmacological properties. Heterocyclic compounds are abundant in nature and have acquired more importance because their structural subunits are exhibit in many natural products such as vitamins, hormones, antibiotics etc. Quinazoline nucleus present in compounds possess variety of pharmacological activities such as antitumor[I], anti-microbial[II], antipsychotic[III], antifungal and anti- inflammatory[IV]. The present review focuses on the Quinazoline derivatives with potential activities that are now in Development. Quinazoline (**Fig 1)** is a

compound made up of two fused six member simple aromatic rings- benzene & Pyrimidine ring. It is a yellow coloured compound, found usually in crystalline form.

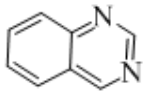


Fig 1 Quinazoline

Quinazoline isomers

The class of bi cyclic aromatic ring structures comprising a benzene ring linked to two-nitrogen containing aromatic ring such as pyridazine, pyrimidine, pyrazine are known in four isomers with the structural formulas as shown in **figure 2**. These isomers, also called as diaza naphthalenes are identified by the position of nitrogen in the heterocyclic ring.

Quinazoline is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a Pyrimidine ring.

- Phthalazine, also called benzo-orthodiazine or benzo-pyridazine bears a benzene ring and a pyridazine ring.
- Quinoxaline, also called a benzo pyrazine, consists of a benzene ring and a pyrazine ring.
- Cinnoline is a Heterocyclic double-ring structure compound containing a benzene ring and a pyridazine ring.

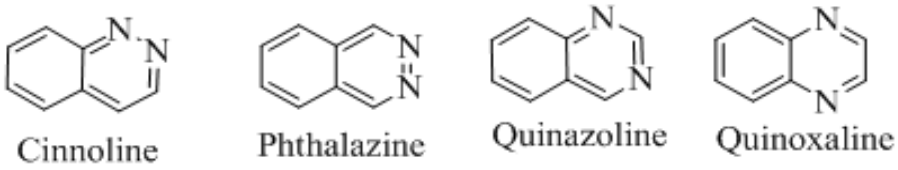


Figure 2. Quinazoline isomers.

Nitrogen-containing heterocycles are present in a wide variety of bioactive natural products and biological molecules that may be good drug candidates. Specifically, They possess a wide range of biological and pharmacological activities including anticancer[V], antiviral[VI], antitubercular[VII], and anti-malarial properties[VIII]. Medicinal chemists synthesised a variety of Quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods.

The Quinazoline skeleton is present in a variety of biologically active compounds, among these are several marketed drugs such as Trimetrexate glucuronate(**1)** (dihydrofolate reductase inhibitor), Bunazosin hydrochloride**[2]** and Trimazosin Hydrochloride**[3]** (hypotensive properties), prazosin (4), Gefitinib (5), Erlotinib (6), Alfuzosin (7), Trimetrexate (8), Vandetanib (9). [**Fig 3**].

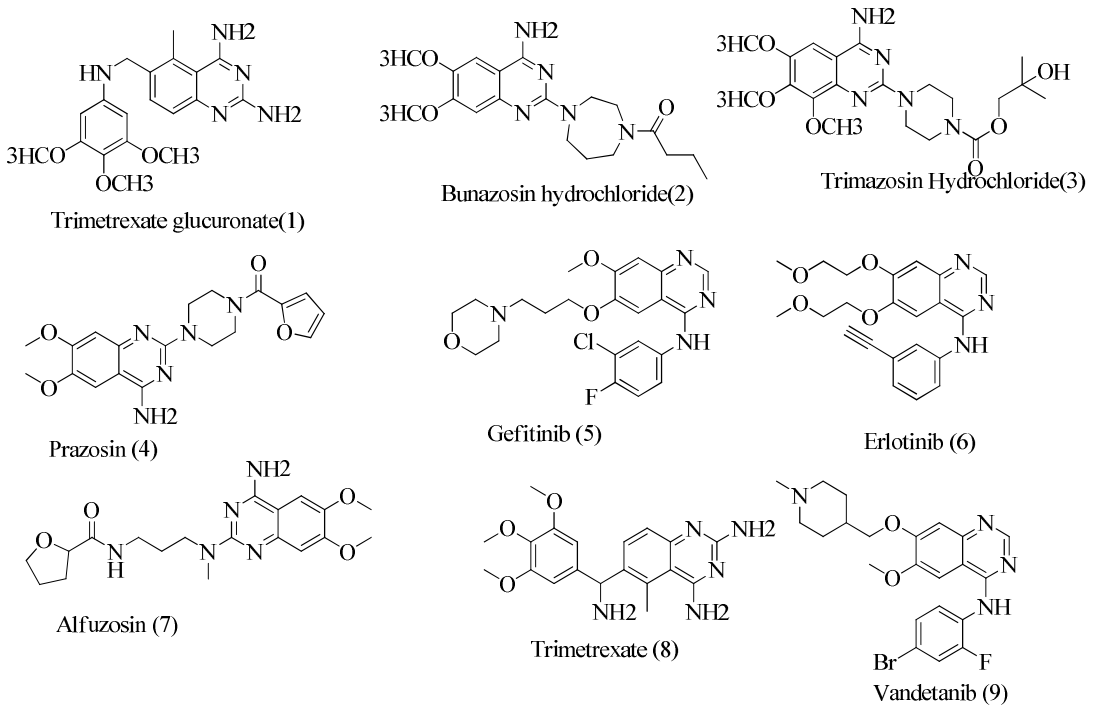


Fig .3. Quinazoline core present in a variety of biologically active compounds

Encouraged by the diverse biological activities of Quinazoline Heterocyclic compounds, it was decided to prepare a new series of Quinazoline derivatives. Literature survey revealed that incorporation of different groups in Quinazoline Heterocyclic ring enhanced antibacterial and antifungal activity. In the present communication copper-catalyzed cascade reaction of (2-aminophenyl) methanols with different aldehydes using the combination of cerium chloride hepta hydrate and ammonium chloride has been developed, leading to a wide range of different 2-substituted quinazolines in moderate to excellent yields.

The structures of all synthesized compounds were assigned on the basis of IR, Mass, ^{1}H & ^{13}C NMR spectral data analysis. Further these compounds were subjected for antifungal and antibacterial activity.

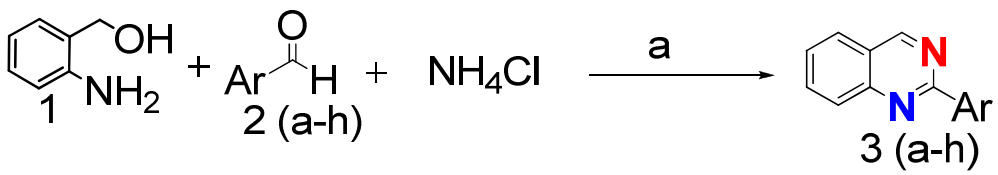
MATERIALS AND METHODS

In this Investigation chemicals were purchased from local dealer with S.D fine make was used. Chemicals were 99 % pure; purity has been checked by thin layer chromatography and melting point. Conventional method has been used for synthesis of Quinazoline derivatives. Stirring and reflux method were used for synthesis of Quinazoline derivatives 3 (a-h) respectively.

The synthetic route was depicted in scheme **I**

The title compounds 3(a-h) were synthesised in single step using different reagents and reaction conditions the 11(a-h) were obtained in moderate yields. The structures of 3(a-h) were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

SYNTHETIC SCHEME



Scheme 1: Synthetic path way for compounds **11 (a-h)**.
Reagents and Reaction conditions: CuCl (20 mol %), bpy (20 mol %), TEMPO (10 mol %), KOH (2.5 equiv), $CeCl_3 \cdot 7H_2O$ (10 mol %) and CH_3CN (2 mL), O_2, 30^OC, 24 h then 80 ^OC for 24 h.

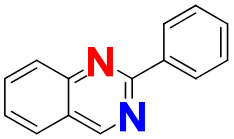
EXPERIMENTAL SECTION :

General Information. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were measured on a 500 or 300 MHz spectrometer (1H at 500 or 300 MHz, ^{13}C at 125 or 75 MHz), with deuterated dimethyl sulfoxide (DMSO-d6) or $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra (HRMS) were recorded on an electrospray quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer. Other commercially obtained reagents were used without further purification. All reactions were conducted by use of standard Schlenk techniques. Column chromatography was performed on EM silica gel 60 (300−400 mesh).

General Procedure for Synthesis of Quinazolines (3a-h):

To a sealed tube were added (2-aminophenyl) methanols (1) (0.5 m.mol, 1eq.), aldehyde 2a (1.5eq.), NH_4Cl (2.5 eq.), CuCl (20 mol %), bpy (20 mol %), TEMPO (10 mol %), KOH (2.5 equiv), $CeCl_3 \cdot 7H_2O$ (10 mol %), and dry CH_3CN (2 mL). Next the tube was charged with O_2 (1 atm), and the mixture was was stirred constantly at 30 ^OC for 24 h and then at 80°C for 24 h. After completion of the reaction, as monitored by TLC analysis, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products 3.

2-Phenylquinazoline (3a):



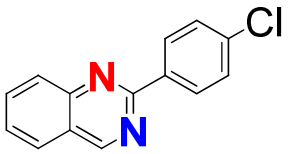
2-phenylquinazoline (3a)

pale yellow solid (73% yield), mp 98−99 °C

^1H NMR (DMSO-d_6, 300 MHz) δ 9.70 (s, 1H), 8.55−8.59 (m, 2H), 8.17 (d, J = 8.1 Hz, 1H), 8.00−8.08 (m, 2H), 7.71−7.76 (m, 1H), 7.55−7.59 (m, 3H);

^{13}C NMR (DMSO-d_6, 75 MHz) δ 161.3, 159.8, 149.8, 137.4, 134.8, 130.8, 128.7, 128.1, 127.9, 127.8, 123.3. ESI m/z calcd for $C_{14}H_{11}N_2$ $[M + H]^+$ 207.0917.

2-(4-Chlorophenyl)quinazoline (3b):



2-(4-Chlorophenyl)quinazoline (3b)

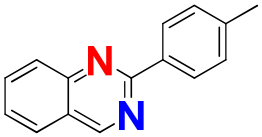
white solid (70% yield), mp 135−136 °C

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.72 (s, 1H), 8.57 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.0 Hz, 1H), 8.04−8.08 (m, 2H), 7.75−7.78 (m, 1H), 7.64 (d, J = 8.5 Hz, 2H);

^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.5, 158.8, 149.8, 136.3, 135.8, 135.1, 129.9, 128.9, 127.93, 127.90, 123.4.

ESI m/z calcd for $C_{14}H_{10}ClN_2$ $[M + H]^+$ found 241.0538.

2-p-Tolylquinazoline (3c):



2-*p*-tolylquinazoline (3c)

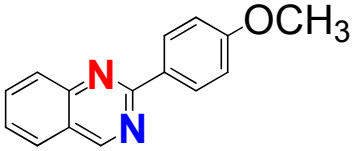
yellow solid (70% yield), mp 109−110 °C

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.44 (s, 1H), 8.52 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.87−7.90 (m, 2H), 7.56−7.60 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H);

^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.1, 160.4, 150.8, 140.8, 135.3, 134.0, 129.4, 128.52, 128.50, 127.1, 127.0, 123.5, 21.5.

ESI m/z calcd for $C_{15}H_{13}N_2$ [M + H]+ found 221.1063.

2-(4-Methoxyphenyl)quinazoline (3d):



2-(4-methoxyphenyl)quinazoline (3d)

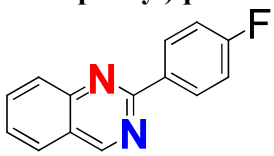
white solid (71% yield), mp 93−94 ^{O}C

^{1}H NMR (CDCl3, 500 MHz) δ 9.40 (s, 1H), 8.57−8.59 (m, 2H), 8.03 (d, J = 8.9 Hz, 1H), 7.86 (t, J = 9.7 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9, 160.9, 160.4, 150.9, 134.0, 130.9 130.2, 128.4, 127.1, 126.8, 123.3, 114.0, 55.4.

ESI m/z calcd for calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ found 237.1

2-(4-Fluorophenyl)quinazoline (3e):



2-(4-fluorophenyl)quinazoline (3e)

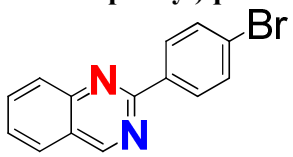
white solid (67% yield), mp 136−138 °C

^{1}H NMR (CDCl3, 500 MHz) δ 9.44 (s, 1H), 8.60− 8.65 (m, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.91 (t, J = 7.8 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.7 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 163.7, 160.5, 160.1, 150.7, 134.2, 130.7, 130.6, 128.6, 127.3, 127.1, 123.5, 115.6, 115.5.

ESI m/z calcd for $C_{14}H_{10}FN_2$ $[M + H]^+$ found 225.0827.

2-(4-Bromophenyl)quinazoline (3f):



2-(4-bromophenyl)quinazoline **(3f)**

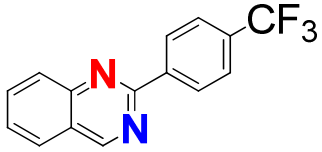
white solid (49.4 mg, 87% yield), mp 120−121 °C

^{1}H NMR (CDCl3, 500 MHz) δ 9.43 (s, 1H), 8.50 (d, J = 8.5 Hz, 2H), 8.06 (d, J = 9.0 Hz, 1H), 7.89−7.92 (m, 2H), 7.60− 7.66 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 160.1, 150.7, 137.0, 134.2, 131.8, 130.2, 128.6, 127.4, 127.1, 125.4, 123.6.

ESI m/z calcd for $C_{14}H_{10}BrN_2$ $[M + H]^+$ found 285.0034.

2-[4-(Trifluoromethyl)phenyl]quinazoline (3g):



2-(4-(trifluoromethyl)phenyl)quinazoline**(3g)**

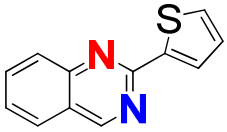
white solid (70% yield), mp 144− 146 °C

^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.76 (s, 1H), 8.75 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.06−8.12 (m, 2H), 7.93 (d, J = 8.5 Hz, 2H), 7.78−7.81 (m, 1H);

^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 158.4, 149.7, 141.2, 135.1, 130.7, 150.5, 128.7, 128.4, 128.0, 127.9, 125.8, 125.7, 125.3, 123.6, 123.1.

ESI m/z calcd for $C_{15}H_{10}F_3N_2$ $[M + H]^+$ found 275.07.

2-(Thiophen-2-yl)quinazoline (3h):



2-(thiophen-2-yl)quinazoline**(3h))**

white solid (73% yield), mp 132−133 °C

^{1}H NMR (CDCl3, 500 MHz) δ 9.35 (s, 1H), 8.14− 8.16 (m, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.85−7.90 (m, 2H), 7.51−7.59 (m, 2H), 7.18−7.21 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 157.9, 150.7, 143.9, 134.3, 129.9, 129.2, 128.3, 128.2, 127.2, 127.0, 123.4.

ESI m/z calcd for $C_{12}H_9N_2S$ $[M + H]^+$ found 213.04.

Biological Activity

The samples of synthesized Novel Quinazoline derivatives(8a-8k) for antimicrobial activity were prepared at concentration 40µg/ml in DMSO solvent. In case of antibacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked against Gram positive bacteria Staphylococcus aureus (S. aureus) and Bacillus subtilis (B. subtilis), Gram negative bacteria Pseudomonas aeruginosa (P. aeruginosa) and Escherichia coli (E. coli). The antifungal activity was checked against fungi Aspergillus niger (A. niger) and Candida

albicans (C. albicans). The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole.

The Quinazoline derivates 3h, 3g and 3e showed more activity than other substituent's. The order of activity was 3h>3g>3e>3f>3c>3d>3b>3a

Table 1: Anti-microbial Screening data of Novel Quinazoline derivatives (3a-3h) :

Compounds	**Antibacterial activity** (Zone of inhibition in mm)			**Antifungal Activity** (Zone of inhibition in mm)		
	S. aureus	B. subtilis	P. aeruginosa	E. coli	A. niger	C. albicans
3a	09	07	10	08	11	17
3b	10	08	07	09	09	21
3c	13	15	13	11	10	06
3d	11	12	09	12	19	18
3e	15	12	12	13	12	13
3f	14	16	09	12	24	11
3g	18	14	17	12	16	25
3h	20	24	19	14	27	23
Sparfloxacin	24	25	22	22	---	---
Benzyl penicillin	19	18	16	16	---	---
Fluconazole	---	---	---	---	25	30

RESULTS AND DISCUSSIONS :

NMR spectra: Aromatic protons were observed 6.68- 8.13 δ ppm. Readily available starting materials and simple synthesizing procedures make this method is very attractive and convenient for the synthesis of quinazoline derivatives .Formation of products was confirmed by recording their ^{1}H NMR, ^{13}C, FT-IR, mass spectra.

Anti microbial screening:

The results of anti microbial studies of newly synthesized compounds reveal that the compounds possess significant antibacterial and anti fungal activities. The results of these studies are given in (Table 1).From Anti bacterial screening results, it has been observed that compounds 3h, 3g and 3e possess good activity.

CONCLUSION:

The newly synthesized Quinazoline derivatives (3a-3h) exhibited moderate to promising antimicrobial activity against standard strains. This class of compounds certainly holds great promise to discover novel classes of anti-microbial agents. All these reactions are very easy to carry out giving high yield. These results make interesting lead molecule for further synthetic and Biological evaluation.

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