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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL EVALUATION OF SOME NOVEL QUINAZOLINE DERIVATIVES AS POTENTIAL ANTI-MICROBIAL AGENTS

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ABSTRACT:
Objective: In search of new potential antimicrobial agents, the aim of the present study was to synthesize the series of Quinazoline analogs by a simple and accessible approach and evaluate for their antimicrobial activity.
Methods: Synthetic methodology involves the reaction of an anthranilic acid (1) with urea toget -2,4 di hydroxyl quinazoline (2) intermediate , which were further treated with $POCl_3$ to get 2,4 di chloro quinazoline (3) derivative. Next 2,4 di chloro quinazoline (3) reacts with hydrazine hydrate in methanol for 4 hrs to get compounds, which further reacts with different carboxylic acids in $POCl_3$ a series of novel fused 1,2,4 triazole derivatives, which were reacts with 4-thiomorpholinoaniline (7) in acetic acid to give target compounds (8a-k) in good yields.
Results: The structures of the synthesized compounds were provided by spectral analysis, and the Synthesised compounds were tested for their antimicrobial activity against different fungi and bacteria species in vitro.
Conclusion: The results of the study reveal that the new compounds possess promising antimicrobial activities.

Keywords: Quinazolines, thiomorpholine, cyclisation, Anti-microbial Screening.

1. Introduction

Hetero cyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact two thirds of organic compounds are heterocyclic compounds. Hetero cyclic chemistry comprises at least half of all organic chemistry research world wide.

Heterocyclic chemistry is the largest classical division of medicinal chemistry and display a broad range of industrial and pharmaceutical applications. 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. Medicinally it is used as antimalarial agent. It was first prepared by Gabriel in 1903 and first isolated from the Chinese plant aseru. The development of research on biological activity of quinazoline compounds started when the compound 2-methyl-1,3-aryl-4-quinazoline derivative was synthesized. This compound has soporific & sedative action. In last 10 to 15 years of research for medicinal has been characterized by significant advances. In 1968 only two derivatives were used, soporific & anticonvulsant- methaqualone and diuretic quinathazone. By 1980, about 50 kinds of derivatives of this class includes medicinal with different biological actions like 'soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, anti-allergic, bronchodilating, anti-diabetic, cholagogue, diuretic, cystatic, antimalarial, spermicidal etc. The search for substances of cardiovascular agents begun in quinazoline derivatives after pharmacological screening of hypotensive activity of quinazoline that have a glycine amide or β-alanine amide residue in 3rd position. But unfortunately due to volume & density of general material on quinazoline derivatives, more specific problem of investigation of cardiovascular agents not has been successfully reflected in some reviews.

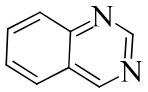


Fig 1 Quinazoline

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 di aza 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.

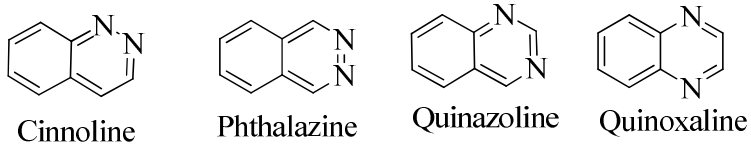


Figure 2. Quinazoline isomers.

Quinazoline derivatives, which belong to the nitrogen-containing heterocyclic compounds ,have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of Quinazoline derivatives , including anti-cancer[I-IV], anti-inflammatory[V-VI], anti-bacterial and anti-fungal[VII-X],anti-virus[XI],anti cytotoxin[XII], anti-spasm[XIII],anti tuberculosis[XIV], anti oxidation[XV], anti-malarial[XVI], anti-hypertension[XVII], anti-obesity[XVIII], antipsychotic[XIX], anti

diabetes[XX],etc. Heterocycles have a central position in medicinal as well as in organic chemistry [XXI-XXIII] and considerable attention has been focused on their synthesis. 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**].

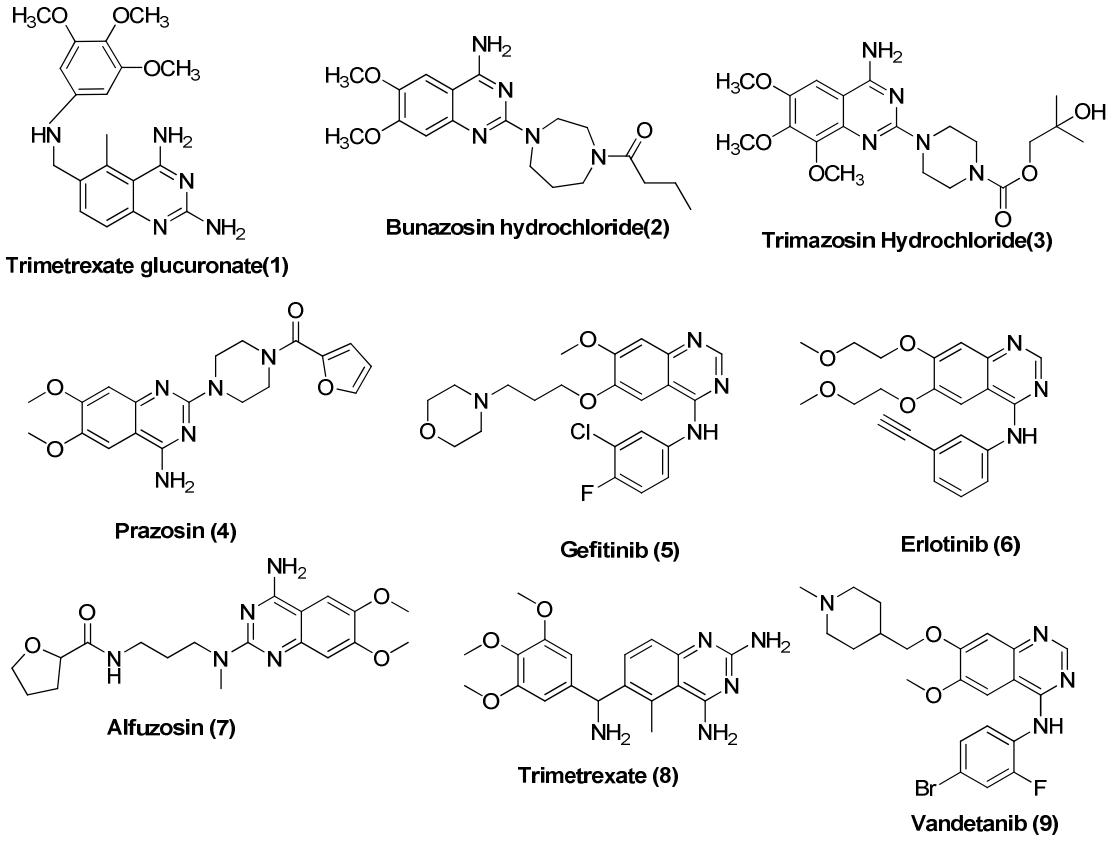


Fig .3. Quinazoline skeleton is present in a variety of biologically active compounds

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 2 , 4 di chloro quinazoline (3) was reacted with different substituted benzoic acids in $pocl_3$ at reflux condition to form compounds (6 a-k), which were further reacted with 4-thiomorpholinoaniline (7) in acetic acid to get target compounds (8a-8k). the synthesis of the compounds as per the following **scheme I** given below.

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

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.

2. 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 8 (a-k) respectively.

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

The title compounds 8(a-k) were synthesized in five sequential steps using different reagents and reaction conditions, the 8(a-k) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

3. EXPERIMENTAL SECTION

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-d or DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

3.1 General procedure for synthesis of 2,4 di hydroxy Quinazoline [compound (2)] :

The mixture of anthranilic acid (0.1 m.mol) and urea (0.5 m.mol) was stirred at 160^{0}c for 3 h. the reaction mixture was cooled to 100^{0}c and then water (50 ml) was added to quench the reaction. the crude product was obtained by filtration, and then washed with water (50 mlx3). after dried under vacuum condition, then obtained solid stireed in 0.5 n naoh solution at 50^{o}c, then cool to 0^{o}c, acidified with conc. hcl to get white solid, compound 2 was obtained as white solid

2,4 di hydroxy Quinazoline [Compound 2]:

Yield: 90%; M.p. above 300 ^{o}C; ^{1}H NMR (DMSO-d_6) δ ppm 7.15 (t, 2H, ArH), 7.6 (t, 1H, ArH), 7.85 (d, 1H, ArH).

^{13}C NMR (DMSO-d_6) (δ/ppm): 120 (Ar C-H), 125.6 (Ar C-H),133.5(Ar C-H), 126.6(Ar C-H), 185(Ar C-OH),187(Ar C-OH), 110(Ar C), , 151 (Ar C). IR (KBr, ν/cm^{-1}): 3469 (OH, broad), 3060 (Ar C-H), 1619 (C=N); LCMS Purity 99.63 %, RT 1.924, Mass 161.1

3.2 General procedure for synthesis of 2,4 di chloro Quinazoline [compound (3)] :

Quinazoline-2, 4-diol (2) (0.1 mol) was added to a stirred solution of $POCl_3$ (70 mL) at room temperature, and then N,N DIPEA (0.15 mol) was added drop wise to the mixture. The reaction mixture was heated to 110 °C for 6 h. The mixture was concentrated under reduced pressure. The residue was poured into ice water (500 mL), stirred at room temperature for 1 h and separated by filteration to give title compound 3 (95percent yield.).

Yield: 95%; M.p. 116-118 ^{o}C; ^{1}H NMR ($CDCl_3$-d_1) δ ppm 8.30-8.20 (d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H). ^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),136.5(Ar C-H), 127.6(Ar C-H), 161.3(Ar C-Cl),157(Ar C-Cl), 120(Ar C), , 151 (Ar C). IR (, KBr,ν/cm^{-1}): 750 (C-Cl), 3040 (Ar C-H), 1619 (C=N);

3.3 General procedure for synthesis of 2-chloro-4-hydrazinylquinazoline [compound (3)]:

A mixture of 2,4 di chloro quinazoline (Compound 2) (0.1 mol) in methanol was taken and cooled to 0^oC-5^oC in an ice bath. Tri Ethyl amine (0.3 mol) was added to the cold reaction mixture and then hydrazine hydrate (0.15 mol) was added slowly at 5^oC-10^oC. The reaction mass was allowed to stir at room temperature for 2 hrs, The Solid Thus obtained was filtered, washed with chilled water and dried to afford compound (3) as pale green Solid.

Yield: 75%; M.p. 196-198 ^oC; ^1H NMR ($CDCl_3$-d_1) δ ppm 9.6(1H,bs),8.1 (d, IH), 7.7 (m, 2H), 7.4(d, I H). ^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 127.2 (Ar C-H),133.05(Ar C-H), 127.6(Ar C-H), 114(Ar C),151(Ar C), 120(Ar C), , 171 (Ar C-N), 158(Ar C-Cl). IR (, KBr,ν/cm^{-1}): 740 (C-Cl), 3340 & 3430 (N-H), 3080 (Ar C-H), 1646 (C=N); EI-MS (m/z): 195 [M^+], 197 [M+2] 3:1 it indicates molecule contains one –Cl atom.

3.4 General procedure for synthesis of compounds (6a-k):

Compound (3) (0.1 m. mol) and substituted benzoic acids (0.13 m.mol) were taken in $POCl_3$ (5 ml) and heated to reflux for 6 hrs.The reaction mass was concentrated under reduced pressure and then quenched in ice. The Solid obtained was filtered off , washed with water, dried and crystallized from methanol/ Ethanol solvent.

The following compounds were synthesized using this method:

5-chloro-3-phenyl-[1,2,4]triazolo[4,3-c]quinazoline (6a) :

Yield: 81%; M.p. 143-145 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.30-8.20 (d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.4-8.4 (5H,m). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(Ar C-N),167(Ar C-Cl), 120(Ar C), , 151 (Ar C), 135(Ar C), 128(2Ar CH), 130(2Ar CH), 132(1Ar CH). IR (ν/cm^{-1}): 750 (C-Cl), 3080 (Ar C-H), 1619 (C=N);

EI-MS (m/z): 281 $[M+H]^+$, 283 [M+2] 3:1, it indicates molecule contains one –Cl atom.

5-chloro-3-p-tolyl-[1,2,4]triazolo[4,3-c]quinazoline (6b) :

Yield: 76%; M.p. 163-165 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.30-8.20 (d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 8.6 (2H,d), 7.3(2H,d),2.36(3H,S). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 118(Ar C), 150(1ArC), 153 (Ar C, N-C-N), 132(Ar C), 126(2Ar C-H), 130(2Ar C-H), 132(1Ar C), 23(Aromatic Methyl Carbon). IR (ν/cm^{-1}): 2926 (C-H SP^3CH) 742 (C-Cl), 3100 (Ar C-H), 1629 (C=N);

EI-MS (m/z): 295$[M+H]^+$, 297 [M+2] 3:1, it indicates molecule contains one –Cl atom.

5-chloro-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-c]quinazoline (6c) :

Yield: 75%; M.p. 216-218 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.30 (d, IH), 7.6-7.9 (m, 3H), 7.80-7.70 (d, I H),7.86 (2H,d), 7.03(2H,d),3.86(3H,S). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 127(Ar C), 130(2Ar C-H), 115(2Ar C-H), 160(1Ar C), 57(Aromatic Methoxy Carbon). IR (ν/cm^{-1}): 2946 (C-H SP^3CH) 762 (C-Cl), 3110 (Ar C-H), 1610 (C=N); 1196(C-O-C).

EI-MS (m/z): 311 $[M+H]^+$, 313 [M+2] 3:1, it indicates molecule contains one –Cl atom.

5-chloro-3-(4-fluorophenyl)-[1,2,4]triazolo[4,3-c]Quinazoline (6d) :

Yield: 70%; M.p. 134-136 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.76 (2H,d), 7.33(2H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(Ar C, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 132(Ar C), 130(2Ar C-H), 115(2Ar C-H), 163(1Ar C-F). IR (ν/cm^{-1}): 1236 (C-F), 742 (C-Cl), 3120 (Ar C-H), 1616 (C=N); EI-MS (m/z): 299 $[M+H]^+$, 301 [M+2] 3:1, it indicates molecule contains one –Cl atom.

5-chloro-3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-c]quinazoline (6e) :
Yield: 67%; M.p. 186-188°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.76 (2H,d), 8.65(2H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 138(Ar C), 126(2Ar C-H), 125(2Ar C-H), 131(1Ar-C, CF_3),124(-**C**F_3). IR (ν/cm^{-1}): 1256 (C-F), 762 (C-Cl), 3130 (Ar C-H), 1616 (C=N); EI-MS (m/z): 349 $[M+H]^+$, 351 [M+2] 3:1, it indicates molecule contains one –Cl atom.

5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-c]quinazoline (6f) :
Yield: 64%; M.p. 226-228°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.66 (2H,d), 8.15(2H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 133(Ar C), 129(2Ar C-H), 132(2Ar C-H), 135(1Ar-C, -C-Cl). IR (ν/cm^{-1}): 742 (C-Cl), 3130 (Ar C-H), 1616 (C=N); EI-MS (m/z): 315 $[M+H]^+$, 317[M+2], 319 [M+4] 9:6:1, it indicates molecule contains two –Cl atoms.

3-(4-bromophenyl)-5-chloro-[1,2,4]triazolo[4,3-c]quinazoline (6g) :
Yield: 65%; M.p. 262-263°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.66 (2H,d), 7.8(2H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 135(Ar C), 131(2Ar C-H), 133(2Ar C-H), 125(1Ar-C, -C-Br). IR (ν/cm^{-1}): 542 (C-Br), 3130 (Ar C-H), 1616 (C=N); EI-MS (m/z): 359 $[M+H]^+$, 361[M+2], 363 [M+4] it indicates molecule contains one –Cl atom and one –Br atom.

5-chloro-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-c]quinazoline (6h) :
Yield: 60%; M.p. 212-213°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 8.05 (2H,d), 8.4(2H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 135(Ar C), 127(2Ar C-H), 125(2Ar C-H), 148(1Ar-C, -C-NO_2). IR (ν/cm^{-1}): 762 (C-Cl), 3180 (Ar C-H), 1350 & 1530 (N-O),1616 (C=N); EI-MS (m/z): 326 $[M+H]^+$, 328[M+2], it indicates molecule contains one –Cl atom.

5-chloro-3-(thiophen-2-yl)-[1,2,4]triazolo[4,3-c]quinazoline (6i) :
Yield: 68%; M.p. 112-113°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.9 (1H,d), 7.2(1H,dd), 7.9(1H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 152 (Ar C, N-C-N), 145(Ar C), 129(1Ar C-H), 127(1Ar C-H), 129(1Ar-CH). IR (ν/cm^{-1}): 732 (C-Cl), 3110 (Ar C-H), 687 (C-S-C),1626 (C=N); EI-MS (m/z): 285 $[M-H]^+$, 287[M+2], it indicates molecule contains one –Cl atom.

5-chloro-3-(1H-indol-2-yl)-[1,2,4]triazolo[4,3-c]quinazoline (6j):
Yield: 65%; M.p. 205-207°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 6.8 (1H, S), 7.52(1H,d), 6.9(1H,t), 7.05(1H,t), 7.7(1H,d), 9.2(1H,bs). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),142(1ArC), 124 (Ar C), 105(1Ar CH), 129(1Ar C), 121(1Ar C-H), 120(1Ar-CH),122(1Ar CH), 111(1Ar CH). IR (ν/cm^{-1}): 762 (C-Cl), 3110 (Ar C-H), 3340 (-NH),1626 (C=N); EI-MS (m/z): 318$[M-H]^+$, 320[M+2], it indicates molecule contains one –Cl atom.

5-chloro-3-(pyridin-4-yl)-[1,2,4]triazolo[4,3-c]quinazoline (6k):
Yield: 64%; M.p. 122-123°C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 8.95 (2H,d), 8.04(2H,d). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(1Ar C-Cl),

117(1Ar C),150(1ArC), 153 (1Ar C, N-C-N), 134(1Ar C), 122(2Ar C-H), 155(2Ar C-H). IR (ν/cm^{-1}): 752 (C-Cl), 3180 (Ar C-H), 1616 (C=N); EI-MS (m/z): 282 $[M+H]^+$, 284[M+2], it indicates molecule contains one –Cl atom.

3.5 General procedure for synthesis of compounds (8a-k):

A screw-cap vial was charged with 4-thio-morpholino aniline (7, 1.00 m.mol), compounds(6a 1.20 m.mol), and acetic acid (5 mL). The mixture was stirred for 16 h at 110 °C, and cooled to room temperature. The residue was diluted with dichloromethaneand 1N Na_2CO_3 Solution, and brine sequentially, dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography to provide the title product in a yield of 85%.Its applicable to synthesis of remaining compounds (8b-8k).

3-phenyl-N-(4-thiomorpholinophenyl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8a) :

Yield: 61%; M.p. 123-125 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.30-8.20 (d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.4-8.4 (5H,m), 6.5(2H,d), 6.8(2H,d), 3.8(4H,t), 2.7(4H,t). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(Ar C-N),167(Ar C-Cl), 120(Ar C), , 151 (Ar C), 135(Ar C), 128(2Ar CH), 130(2Ar CH), 132(1Ar CH), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 55(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 3080 (Ar C-H), 1619 (C=N); 680(C-S-C), 3310 (-NH).

EI-MS (m/z): 437 $[M-H]^+$.

N-(4-thiomorpholinophenyl)-3-p-tolyl-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8b) :

Yield: 66%; M.p. 184-185 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.30-8.20 (d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 8.6 (2H,d), 7.3(2H,d),2.36(3H,S), 3.6(1H,bs), 6.5(2H,d), 6.8(2H,d), 3.8(4H,t, N-CH in Thiomorpholine ring), 2.7(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 118(Ar C), 150(1ArC), 153 (Ar C, N-C-N), 132(Ar C), 126(2Ar C-H), 130(2Ar C-H), 132(1Ar C), 23(Aromatic Methyl Carbon), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 55(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 2920 (SP^3CH), 3110 (Ar C-H), 1629 (C=N); 650(C-S-C), 3310 (-NH).EI-MS (m/z): 453$[M+H]^+$, 454 [M+1] 3.5:1, it indicates molecule contains 26 Carbon atoms.

3-(4-methoxy phenyl)-N-(4-thio morpholine phenyl)-[1,2,4] triazolo [4,3-c] quinazolin-5-amine (8c) :

Yield: 75%; M.p. 216-218 ^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.30 (d, IH), 7.6-7.9 (m, 3H), 7.80-7.70 (d, I H),7.86 (2H,d), 7.03(2H,d),3.86(3H,S), 3.1(1H,bs), 6.5(2H,d), 6.8(2H,d), 3.73(4H,t, N-CH in Thiomorpholine ring), 2.72(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 127(Ar C), 130(2Ar C-H), 115(2Ar C-H), 160(1Ar C), 57(Aromatic Methoxy Carbon), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 55(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 2946 (C-H SP^3CH), 3110 (Ar C-H), 1610 (C=N); 680(C-S-C), 3310 (-NH), 1196(C-O-C).

EI-MS (m/z): 467$[M-H]^+$, 468 [M+1] 3:1, 3.5:1, it indicates molecule contains 26 Carbon atoms.

3-(4-fluoro phenyl)-N-(4-thiomorpholino phenyl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8d) :

Yield: 70%; M.p. 234-235^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.76 (2H,d), 7.33(2H,d) 5.1(1H,bs), 6.5(2H,d), 6.8(2H,d), 3.70(4H,t, N-CH in Thiomorpholine ring), 2.70(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(

Ar C, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 132(Ar C), 130(2Ar C-H), 115(2Ar C-H), 163(1Ar C-F) 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 55(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 1256 (C-F), 3100 (Ar C-H), 1616 (C=N); 680(C-S-C), 3310 (-NH). EI-MS (m/z): 457 $[M+H]^+$, 458 [M+1] 3.5:1, it indicates molecule contains 25 Carbon atoms.

N-(4-thiomorpholinophenyl)-3-(4-(tri fluoro methyl) phenyl)- [1,2,4] triazolo [4,3-c]quinazolin-5-amine (8e) :

Yield: 60%; M.p. 146-148^{o}C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.76 (2H,d), 8.65(2H,d), 5.1(1H,bs), 6.5(2H,d), 6.8(2H,d), 3.70(4H,t, N-CH in Thiomorpholine ring), 2.70(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 138(Ar C), 126(2Ar C-H), 125(2Ar C-H), 131(1Ar-C, CF_3),124(-**C**F_3), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 55(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 1276 (C-F), 680(C-S-C), 3310 (-NH) , 3130 (Ar C-H), 1626 (C=N); EI-MS (m/z): 507 $[M+H]^+$, 508 [M+1] 3.5:1, it indicates molecule contains 26 Carbon atoms.

5-chloro-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-c]quinazoline (8f) :

Yield: 64%; M.p. 136-138^{o}C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.66 (2H,d), 8.15(2H,d), 9.1(1H,bs), 6.5(2H,d), 6.8(2H,d), 3.76(4H,t, N-CH in Thiomorpholine ring), 2.76(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 133(Ar C), 129(2Ar C-H), 132(2Ar C-H), 135(1Ar-C, -C-Cl), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 55(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 762 (C-Cl), 3130 (Ar C-H), 680(C-S-C), 3310 (-NH), 1616 (C=N); EI-MS (m/z): 473 $[M+H]^+$, 475[M+2], 3:1, it indicates molecule contains One –Cl atom.

3-(4-bromophenyl)-N-(4-thiomorpholinophenyl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine

(8g) :

Yield: 60%; M.p. 222-223^{o}C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.66 (2H,d), 7.8(2H,d) 9.1(1H,bs), 6.5(2H,d), 6.9(2H,d), 3.74(4H,t, N-CH in Thiomorpholine ring), 2.74(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 135(Ar C), 131(2Ar C-H), 133(2Ar C-H), 125(1Ar-C, -C-Br), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 57(2 Ali CH, N-C in Thiomorpholine ring), 29(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 582 (C-Br), 3130 (Ar C-H), 1616 (C=N); 670(C-S-C), 3320 (-NH). EI-MS (m/z): 517$[M+H]^+$, 519[M+2] it indicates molecule contains one –Br atom.

3-(4-nitrophenyl)-N-(4-thiomorpholinophenyl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8h) :

Yield: 62%; M.p. 162-163^{o}C; ^{1}H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 8.05 (2H,d), 8.4(2H,d), 5.1(1H,bs), 6.45(2H,d), 6.89(2H,d), 3.78(4H,t, N-CH in Thiomorpholine ring), 2.70(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 153 (Ar C, N-C-N), 135(Ar C), 127(2Ar C-H), 125(2Ar C-H), 148(1Ar-C, -C-NO_2), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 59(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 670(C-S-C), 3180 (Ar C-H), 1360 & 1555 (N-

O),1626 (C=N); EI-MS (m/z): 484 $[M+H]^+$, 485[M+1], 3.5:1, it indicates molecule contains 25 Carbon atoms.

N-(4-thiomorpholinophenyl)-3-(thiophen-2-yl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8i) :

Yield: 61%; M.p. 126-128^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 7.9 (1H,d), 7.2(1H,dd), 7.9(1H,d), 5.1(1H,bs), 6.45(2H,d), 6.89(2H,d), 3.78(4H,t, N-CH in Thiomorpholine ring), 2.70(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),150(1ArC), 152 (Ar C, N-C-N), 145(Ar C), 129(1Ar C-H), 127(1Ar C-H), 129(1Ar-CH), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 56(2 Ali CH, N-C in Thiomorpholine ring), 29(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 660(C-S-C), 3100 (Ar C-H), 3320 (-NH),1646 (C=N); EI-MS (m/z): 445 $[M-H]^+$, 446[M+1], 4:1, it indicates molecule contains 23 Carbon atoms.

3-(1H-indol-2-yl)-N-(4-thiomorpholinophenyl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8j):

Yield: 61%; M.p. 187-188^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 6.8 (1H, S), 7.52(1H,d), 6.9(1H,t), 7.05(1H,t), 7.7(1H,d), 9.2(1H,bs), 5.1(1H,bs), 6.45(2H,d), 6.9(2H,d), 3.8(4H,t, N-CH in Thiomorpholine ring), 2.70(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(Ar C-Cl), 117(Ar C),142(1ArC), 124 (Ar C), 105(1Ar CH), 129(1Ar C), 121(1Ar C-H), 120(1Ar-CH),122(1Ar CH), 111(1Ar CH), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 59(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 640(C-S-C), 3110 (Ar C-H), 3340 (-NH),1626 (C=N); EI-MS (m/z): 476$[M-H]^+$, 478[M+1], 3.4:1, it indicates molecule contains 27 Carbon atoms.

3-(pyridin-4-yl)-N-(4-thiomorpholinophenyl)-[1,2,4]triazolo[4,3-c]quinazolin-5-amine (8k):

Yield: 60%; M.p. 182-183^oC; ^1H NMR (DMSO-d_6) (δ/ppm): 8.32-8.25(d, IH), 8.10-8.00 (m, 2H), 7.80-7.70 (d, I H), 8.95 (2H,d), 8.04(2H,d), 5.1(1H,bs), 6.45(2H,d), 6.9(2H,d), 3.8(4H,t, N-CH in Thiomorpholine ring), 2.70(4H,t, S-CH in Thiomorpholine ring). ^{13}C NMR (DMSO-d_6) (δ/ppm): 124 (Ar C-H), 128.6 (Ar C-H),133.5(Ar C-H), 127.6(Ar C-H), 158.3(ArC, N-C-N),167(1Ar C-Cl), 117(1Ar C),150(1ArC), 153 (1Ar C, N-C-N), 134(1Ar C), 122(2Ar C-H), 155(2Ar C-H), 129(1Ar C), 119(2Ar CH), 114(2Ar CH), 140(1ArC), 59(2 Ali CH, N-C in Thiomorpholine ring), 28(2 Ali CH, S-C in Thiomorpholine ring). IR (ν/cm^{-1}): 656(C-S-C), 3180 (Ar C-H), 3340 (-NH), 1616 (C=N);
EI-MS (m/z): 440 $[M+H]^+$, 441[M+1], 3.84:1, it indicates molecule contains 24 Carbon atoms.

4.Anti-microbial screening :

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 againstGram 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 order of activity was 8i>8k>8j>8e>8h >8d >8g>8f>8b>8c>8a.

Table 1: Anti-microbial Screening data of Novel Quinazoline derivatives (8a-8k)

Compound	**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
8a	07	14	09	07	14	14
8b	09	12	07	11	12	13
8c	08	13	08	06	15	11
8d	11	12	09	12	19	18
8e	14	16	09	12	24	11
8f	09	07	10	08	11	17
8g	10	08	07	09	09	21
8h	13	15	13	11	10	06
8i	20	24	19	14	27	23
8j	15	12	12	13	12	13
8k	18	14	17	12	16	25
Sparfloxacin	24	25	22	22	---	---
Benzyl penicillin	19	18	16	16	---	---
Fluconazole	---	---	---	---	22	20

5. Results and Discussions

5.1Chemistry:

The title Compounds Novel Quinazoline based derivatives (8a-8k) were synthesized in good yields (scheme-I). All these compounds were tested for Anti-microbial activity showed considerable activity when compared to the standard drug .

In the present communication quinazoline-2,4(1H,3H)-dione (2) was synthesized from anthranilic acid (1) according to the reported procedure [XXIV]. 2, 4 Di chloro quinazoline was synthesized from compound (2) reflux in $POCl_3$ according to the reported procedure [XXV]. 2 , 4 Di Chloro Quinazoline (3) was reacted with hydrazine hydrate in methanol at room temperature to form compound 2-chloro-4-hydrazinyl quinazoline (4) According to the reported procedure [XXVI] , which were further reacted with 4-Substituted benzoic acids and heterocyclic acids (5 a-k)in $POCl_3$ at Reflux temperature to get compounds (6a-6k) According to the reported procedure [XXVI], which were further reacted with 4-thiomorpholinoaniline (7) to get Target Compounds (8 a-k) according to the reported procedure [XXVII] .

Structures of Compounds 8a-8k were confirmed by IR, ^{1}H & ^{13}C NMR, mass Spectroscopic Techniques. All of the Quinazoline Derivatives possesses similar basic skeletal structure.

5.2 Spectroscopic data analysis:

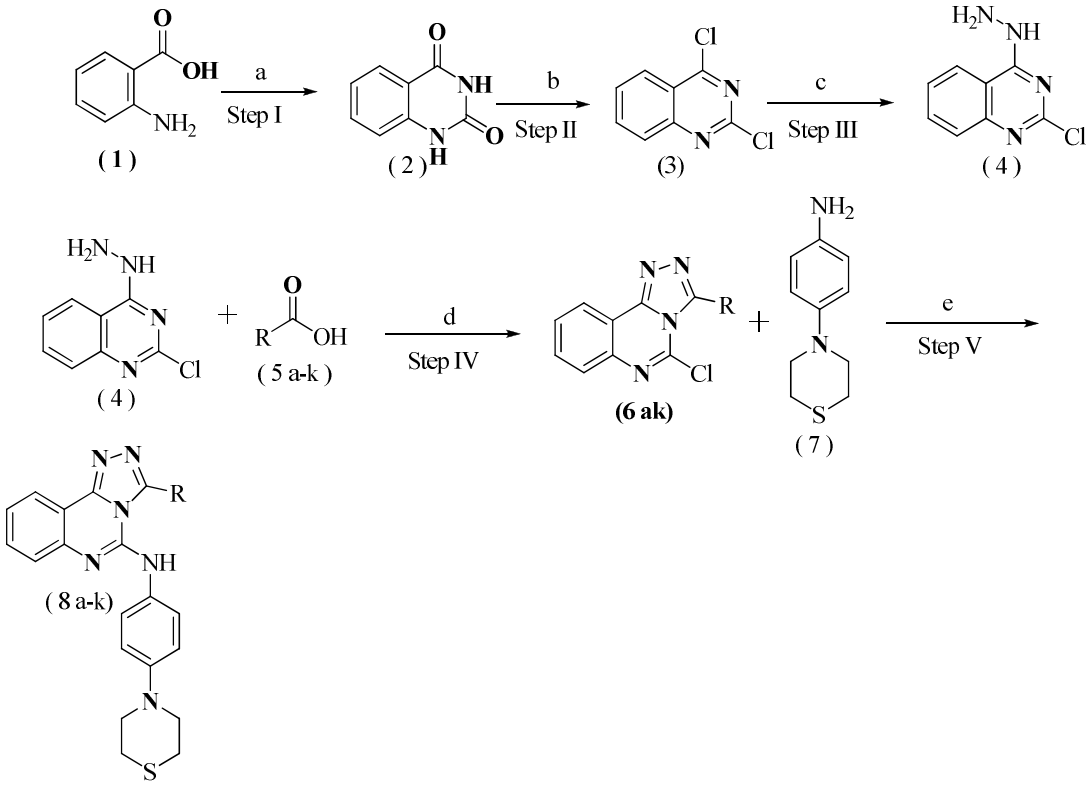
The structures of the title compounds **8a-8k** were confirmed by spectral data. The IR spectra of the obtained compounds showed strong absorption band in the 3280-3250 cm^{-1} region corresponding to NH of the ring. The FT-IR spectra of 8a–8l were recorded using KBr pellets in the range of 4,000–400 cm^{-1}.The IR spectrum of the title Compounds 8(a-l) has given stretching vibration 3420 cm^{-1} due to the stretching vibration corresponding to N-H Stretching vibrations. 3100cm^{-1}, due to the stretching vibration corresponding to Ar C-H Stretching vibrations. The absorption peak at 2930 cm^{-1} is due to The stretching vibration

corresponding to the SP^3 C-H (methyl gp).The strong Intensity absorption at 1150 cm^{-1} is due to The stretching vibration of -C-O-C Stretching, 1260 cm^{-1} is due to The stretching vibration of C-F bond. 750 cm^{-1} is due to The stretching vibration of C-Cl bond. 580 cm^{-1} is due to The stretching vibration of C-Br bond. The weak Intensity absorption at 1620 cm^{-1} corresponds to a C=N Stretching vibration.

It has been observed from chemical structure of compounds 8(a-k) that different pair of protons. The protons of Methyl group which is attached to benzene ring appeared as a singlet at δ =2.3 ppm, The protons of Methoxy group appeared as a Singlet at δ =3.85 ppm,. The protons attached Aromatic ring protons appeared between δ =7 -8.45 ppm respectively.

The ^{13}C NMR spectra show the expected resonance signals of the different carbons, The carbon nucleus under the influence of a strong electronegative environment appeared down field, The carbon chemical shift of the methyl group at δ= 23 ppm. The carbon chemical shift of the Methoxy group at δ= 58 ppm.

Synthetic Scheme

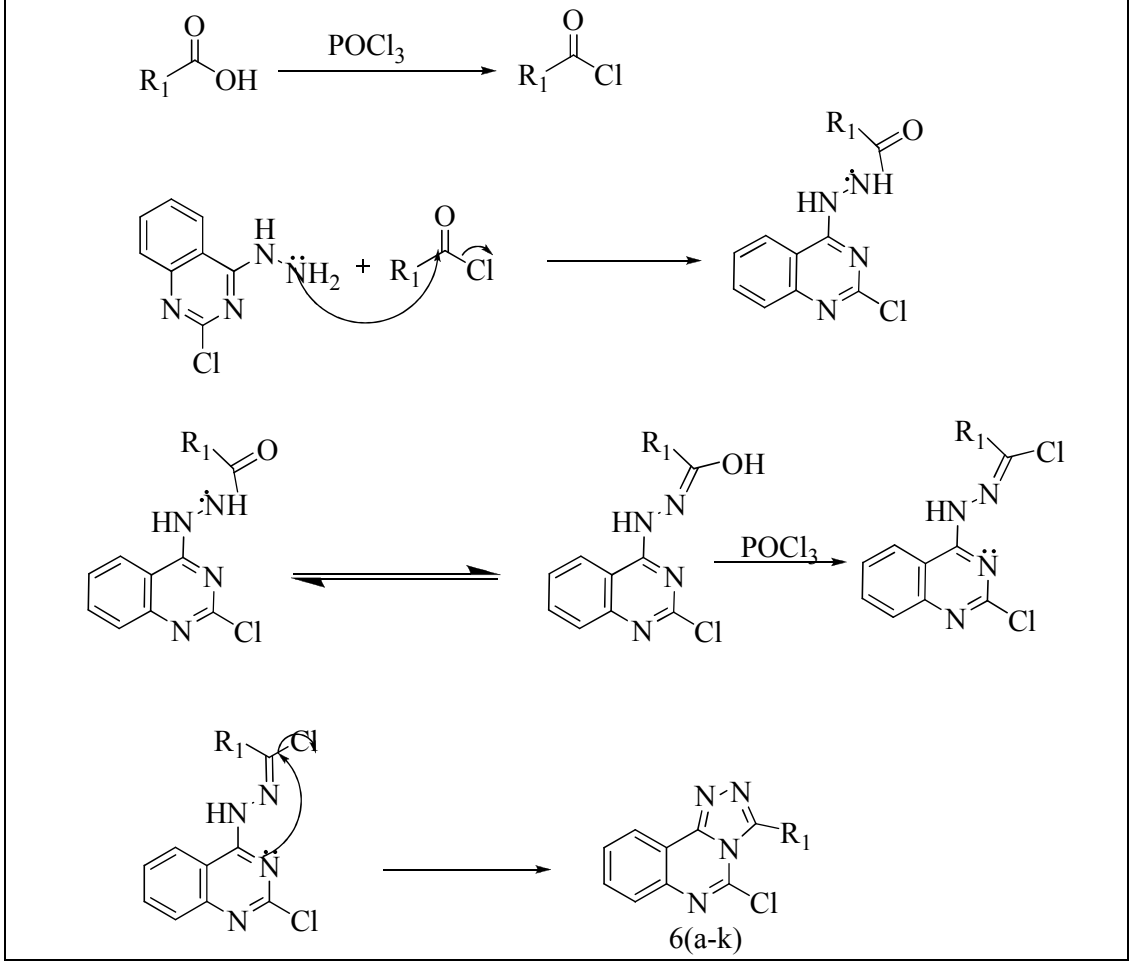


R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 Fluoro phenyl, -4 Tri fluoro phenyl, -4 Chloro Phenyl, -4 Bromo Phenyl, -4 Nitro Phenyl, -2 thiophene, -2 Indole, iso nicotinic acids.

Scheme 1: Synthetic path way for compounds **8a-k**.

Reagents and Reaction conditions: (a) Urea, 150^oC, 3 hrs (d) $POCl_3$, N-ethyl - N,N di isopropyl amine Reflux, 6 hrs (c) Methanol, Tri Ethyl Amine, 0^0C-RT, 2 hrs. (d) $POCl_3$, Reflux, 6 hrs (e) Acetic Acid, 110^0C, 16 hrs

Possible mechanism for formation of 6 (a-k) :



6. Conclusions

In conclusion, a series of new quinazoline analogs (8a-8k) were synthesized in good yield, characterized by different spectral studies and their antibacterial and antifungal activity have been evaluated. various derivatives of quinazoline that showed potent anti-bacterial and anti-fungal acivity. among the synthesised compounds 8i and 8k, 8j showed excellent anti-bacterial and anti-fungal activity when compared to other compounds in the series.

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