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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL STUDIES OF NOVEL QUINAZOLINE DERIVATIVES

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ABSTRACT
Quinazoline nucleus is present in various compounds and it is responsible for diverse biological activities. The present work mainly focused on the Quinazolines with potential activities that are now in development. The objective of this research work is to synthesize various compounds containing Quinazoline moiety and their derivatives as well as characterising the compounds by spectral analysis and screening for antimicrobial and anticancer activities. The structures of synthesized compounds were confirmed by various spectroscopic methods such as IR, NMR and mass spectroscopy. The products were evaluated for their antimicrobial activity against several microbes. Some of the compounds exhibited potent anti-bacterial activity as well as anti-fungal activity. Among the Novel Quinazoline derivatives 8i, 8j, 8d shows Excellent Anti-microbial activity

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

INTRODUCTION:

Heterocyclic chemistry is a chemistry involving the Heterocyclic compounds, which has atoms of at least two different elements as number of ring. The heterocyclic atoms may be inorganic, though the compound contains carbon atoms in the ring. The word hetero means "different from carbon and hydrogen". Many heterocyclic compounds are biosynthesized by plants & animals are biologically active. Some heterocyclic compounds are fundamentals of life, like haeme derivatives in blood & chlorophyll essential for photosynthesis in plants. Also the DNA & RNA are containing heterocycles. Dyestuffs of plant origins include indigo blue used to dye jeans. Several heterocycles are the basic structure nucleus for nicotine, pyridoxine, cocaine, morphine etc.

Quinazoline Fig 1 is a compound made up of two fused six member simple aromatic rings-benzene & pyrimidine ring. It is a yellow colored 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, antiallergic, bronchodilating, antidiabetic, 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.

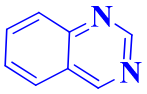


Fig 1 Quinazoline

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.

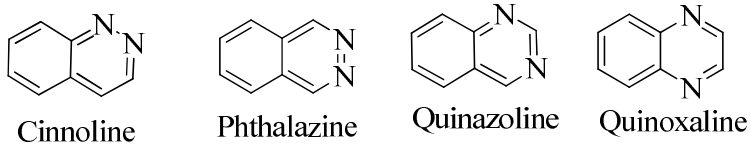


Figure 2. Quinazoline isomers.

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**]. Finally Quinazoline as a core structure contains so many popular drugs and their uses as shown in Table 1.

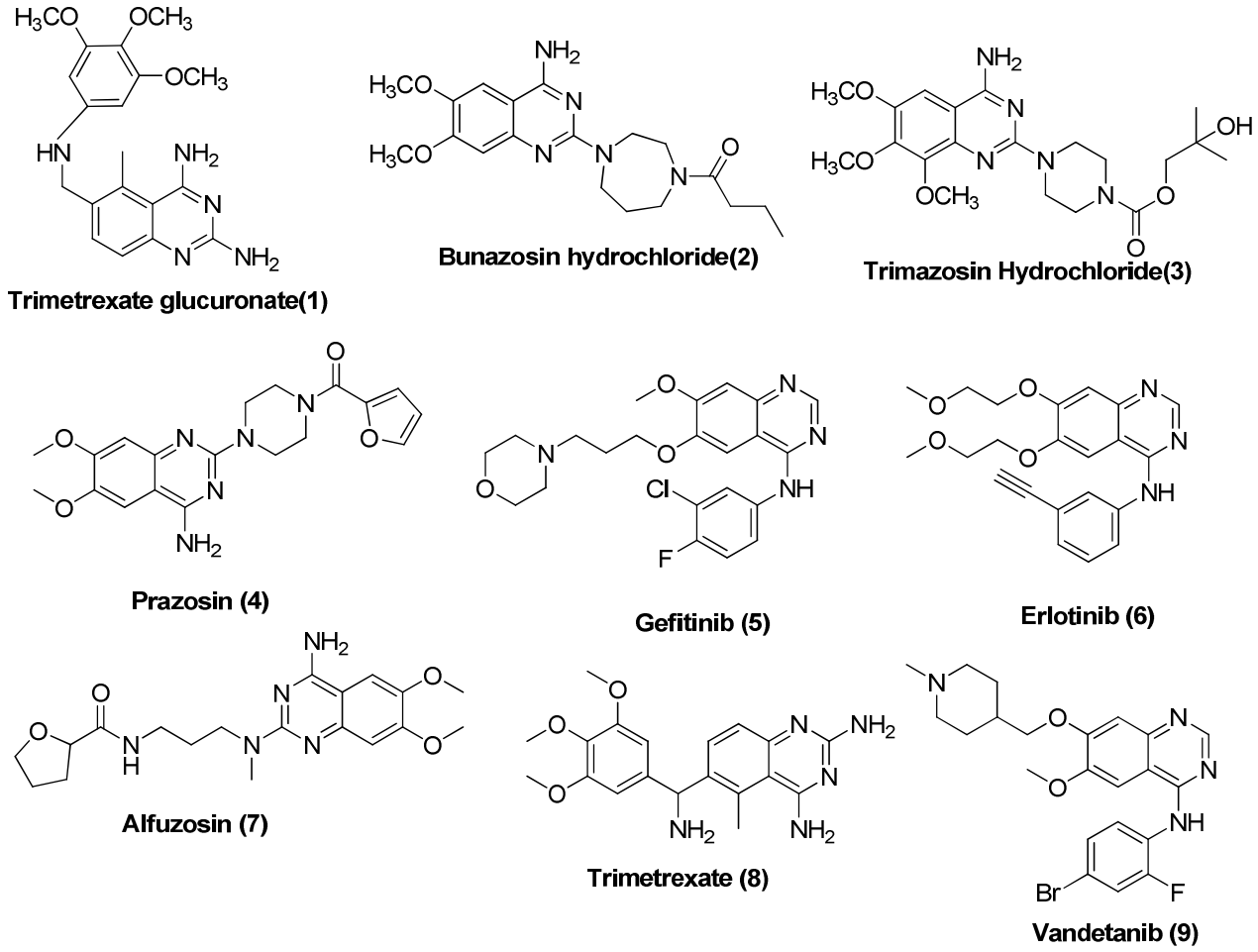


Fig .3. Quinazoline skeleton is present in a variety of biologically active compounds

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-chloro quinazolin-4-amine (4) was reacted with different substituted acid chloride in DCM at Room Temperature to form Compounds (6 a-j), which were further reacted with 4-thiomorpholinoaniline (7) in Acetic acid to get target compounds (8a-8j). 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.

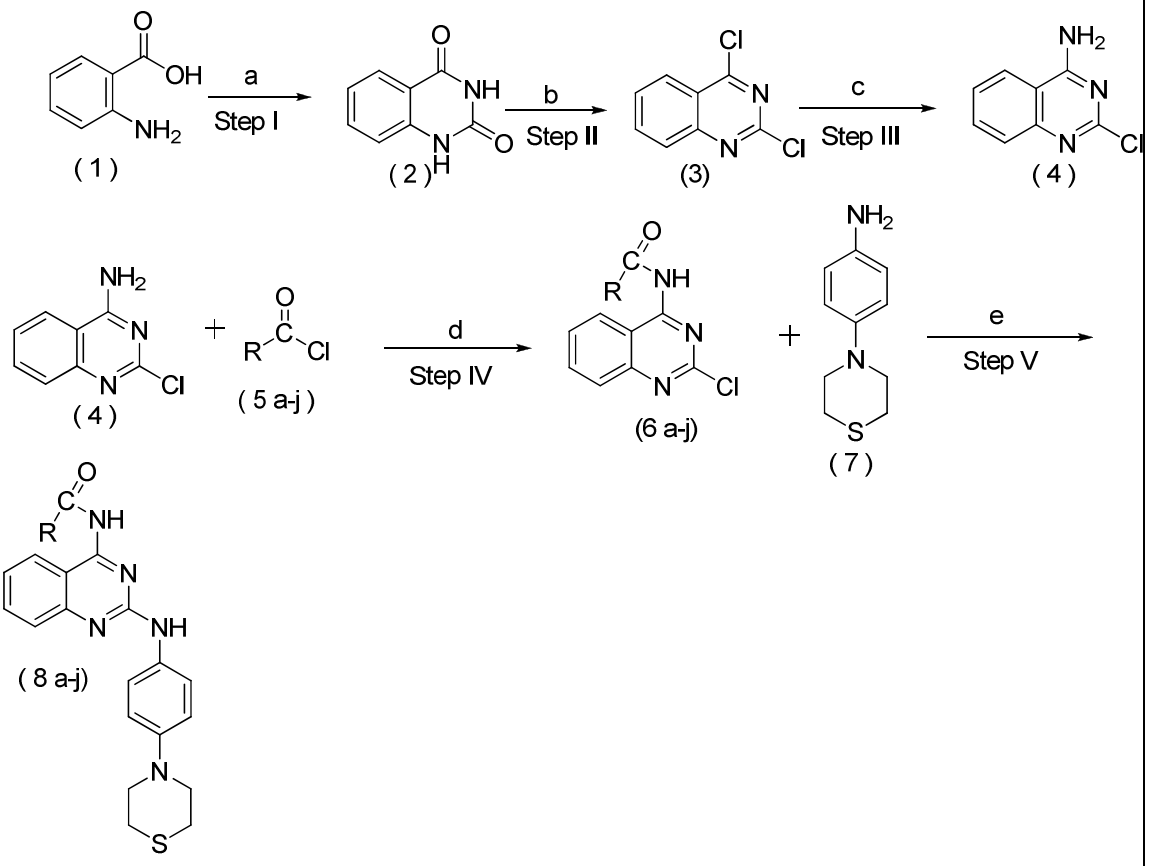
2. MATERIALS AND METHODS

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-j) respectively.

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

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

Synthetic Scheme



R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 Tri fluoro phenyl, -4 Tri Fluoro methoxy , -4 Chloro Phenyl, -4 Bromo Phenyl, -4 Nitro Phenyl, -2 Indole, -3 pyridine .

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

Reagents and Reaction conditions: (a) Urea, 150^{o}C, 3 hrs (d) $POCl_3$, Reflux, 16 hrs (c) THF, Na_2CO_3, Aqueous Ammonia, 0^{0}C-RT, 2 hrs. (d)DCM, TEA,RT, 6 hrs (e) Acetic Acid, 110^{0}C, 16 hrs

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

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

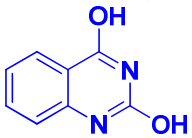
used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel, and concentrated 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 ^1H 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 (^1H NMR and ^{13}C NMR) were recorded using tetra methyl silane (TMS) in the solvent of $CDCl_3$-d_1 or DMSO-d_6 as the internal standard (^1H 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).

General procedure for synthesis of 2, 4 di hydroxyl Quinazoline [XXIV] ***[compound (2)] :***

The mixture of Anthranilic acid (1) (**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^{O}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 hydroxyl Quinazoline [Compound 2]:

Yield: 90%; M.p. above 300 ^{O}C;



(2)

^{1}H NMR (DMSO-d_6) δ ppm 7.15 (t, 2H, ArH), 7.6 (t, 1H, ArH), 7.85 (d, 1H, ArH), 11.05(1H,S), 11.1(1H,S).

^{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);

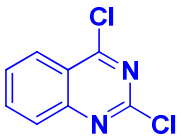
LCMS Purity 99.63 %, RT 1.924, Mass 161.1 [M$^+$, **100%**).

General procedure for synthesis of 2, 4 di chloro Quinazoline [XV] ***[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 filtration to give title compound 3 (90 % yield).

Yield: 95%;

M.p. 116-118 ^{O}C;



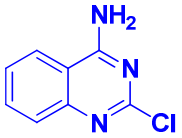
(3)

^{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);

General procedure for synthesis of 2-chloroquinazolin-4-amine [XXVI] ***[compound (4)]:***
A mixture of 2, 4 di chloro quinazoline (Compound 3) **(0.1 mol)** in THF and water (2:1) was taken and cooled to 0^oC-5^OC in an ice bath. Na_2CO_3 (**0.3 mol**) was added to the cold reaction mixture and then Aqueous ammonia (**0.3 mol**) was added slowly at 5^oC-10^oC. The reaction mass was allowed to stir at room temperature for 2 hrs, Then THF Concentrated under Reduced Pressure, then diluted with water Extract with Ethyl acetate, Concentrated the Ethyl acetate, Solid Thus obtained, dried with n-pentane and dried to afford compound (4) as white Solid.
Yield: 75%;



(4)

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H).
^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H), 133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 165 (Ar C-N), 158(Ar C-Cl).
IR (KBr,*ν*/cm^{-1}): 740 (C-Cl), 3340 & 3430 (N-H Symmetric & Asymmetric Stretching), 3080 (Ar C-H), 1646 (C=N);
LCMS Shows purity **99.98%** EI-MS (m/z): 180 [M^+], 182 [M+2] 3:1 it indicates molecule contains one –Cl atom.
General procedure for synthesis of N-(2-chloroquinazolin-4-yl)benzamide (6a), N-(2-chloroquinazolin-4-yl)-4-methylbenzamide(6b), N-(2-chloroquinazolin-4-yl)-4-methoxybenzamide (6c), N-(2-chloroquinazolin-4-yl)-4-(trifluoromethyl)benzamide (6d), N-(2-chloroquinazolin-4-yl)-4-(trifluoromethoxy)benzamide (6e), 4-chloro-N-(2-chloroquinazolin-4-yl)benzamide (6f), 4-bromo-N-(2-chloroquinazolin-4-yl)benzamide (6g), N-(2-chloroquinazolin-4-yl)-4-nitrobenzamide (6h), N-(2-chloroquinazolin-4-yl)thiophene-2-carboxamide(6i), N-(2-chloroquinazolin-4-yl)nicotinamide (6j) [XXVII] To the starting amine (Compound 4) (**6 m.mol**) suspended in anhydrous DCM(**10 mL**), appropriate Acidchlorides (5 a-i) (**6.3 m.mol**) was added gradually. The reaction mixture was stirred at RT for 4-5 hours, and then poured into ice water. The solid product was filtered, washed well with water, and re crystallized from Ethanol.
Table 3 Physical data of target compounds (6 a-j):

Compound	Yield (%)
6a	80
6b	75
6c	72
6d	71
6e	80
6f	76
6g	82
6h	77
6i	70
6j	60

N-(2-chloroquinazolin-4-yl)benzamide (6a):
IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Cl (736), C=N (1626.15), C=O (1685), N-H (3266),

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.6-7.9(5H, m).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H), 133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C), 151(Ar C), 165 (Ar C-N), 158(Ar C-Cl), 129.4(4Ar CH), 133(1Ar CH).

LCMS Shows EI-MS (m/z): 284 [M^+], 286 [M+2] (+VE MODE) 3:1 it indicates molecule contains one –Cl atom.

N-(2-chloroquinazolin-4-yl)-4-methylbenzamide (6b):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Cl (730), SP^3C-H (2910), C=N (1626.15), C=O (1685), N-H (3266).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.76(2H,d),7.4(2H, d), 2.3(3H,S).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H), 133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C), 151(Ar C), 165 (Ar C-N), 158(Ar C-Cl), 129.4(4Ar CH), 137(1Ar C), 23(Aromatic Methyl Carbon).

LCMS Shows EI-MS (m/z): 298[M^+], 300 [M+2] (+Ve mode) 3:1 it indicates molecule contains one –Cl atom.

N-(2-chloroquinazolin-4-yl)-4-methoxybenzamide (6c):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Cl (750), C-O-C (1160), SP^3C-H (2930), C=N (1626.15), C=O (1685), N-H (3266).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.66(2H,d),7.14(2H, d), 3.8(3H,S).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 165 (Ar C-N), 158(Ar C-Cl), 126.4(2Ar CH), 117(2Ar CH), 163(1 Ar C),58.8(Aromatic Methoxy Carbon).

LCMS Shows EI-MS (m/z): 314 [M^+], 316 [M+2] 3:1 it indicates molecule contains one –Cl atom.

N-(2-chloroquinazolin-4-yl)-4-(trifluoromethyl)benzamide (6d):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-F (1260), C-Cl (720), C=N (1616.15), C=C (1575), N-H (3266).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.76(2H,d),7.94(2H, d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 165 (Ar C-N), 158(Ar C-Cl), 127(4 Ar CH), 134(1 Ar C),125(Aromatic $–CF_3$ Carbon).

LCMS Shows EI-MS (m/z): 350 [M^+], 352 [M+2] (-ve mode) 3:1 it indicates molecule contains one –Cl atom.

N-(2-chloroquinazolin-4-yl)-4-(trifluoromethoxy)benzamide (6e):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-F (1270), C-Cl (780), C-O-C(1150), C=N (1616.15), C=O (1675), N-H (3266).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.66(2H, d), 7.14(2H, d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 127(2 Ar CH), 117(2 Ar CH), 153(1 Ar C),129(Aromatic $–OCF_3$ Carbon).

LCMS Shows EI-MS (m/z): 366 [M^+], 368 [M+2] (-VE MODE) 3:1 it indicates molecule contains one –Cl atom.

4-chloro-N-(2-chloroquinazolin-4-yl)benzamide (6f):

IR (KBr, cm^{-1}): Ar stretch C-H (3105), C-Cl (780), C=N (1646.15), C=O (1685), N-H (3286).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.86(2H, d), 7.64(2H, d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 127(2 Ar CH), 129.6(2 Ar CH), 138(1 Ar C).

LCMS Shows EI-MS (m/z): 318 [M^+], 320 [M+2], 322[M+4] (+VE MODE)

4-bromo-N-(2-chloroquinazolin-4-yl)benzamide (6g):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Br (560), C-Cl (760), C=N (1616.15), C=O (1675), N-H (3266).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.81(2H, d), 7.9(2H,
d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 130(2 Ar CH), 133.6(2 Ar CH), 128(1 Ar C-Br).

LCMS Shows EI-MS (m/z): 363 [M^+], 365 [M+2], 367[M+4] (+VE MODE)

N-(2-chloroquinazolin-4-yl)-4-nitrobenzamide (6h):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), 1360 & 1537 (N-O Symmetric and asymmetric Stretching in Nitro group), C-Cl (740), C=N (1616.15), C=O (1685), N-H (3266), 1360& 1150(S=O Symmetric and asymmetric Stretching in Sulphonamide group).

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 8.1(2H, d), 8.4(2H,
d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 130(2 Ar CH), 123.6(2 Ar CH), 151(1 Ar **C**-NO_2).

LCMS Shows EI-MS (m/z): 327 [M^+], 329 [M+2], (-VE MODE) it indicates molecule contains one–Cl atom and even Number of Nitrogen atoms According to Nitrogen rule.

N-(2-chloroquinazolin-4-yl)thiophene-2-carboxamide (6i):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Cl (740), C=N (1616.15), C=O (1675), N-H (3266),.

^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 8.1(2H, d), 7.3(1H,
d), 7.2(dd), 7.7(1H,d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 127(2 Ar CH), 125.6(1 Ar CH).

LCMS Shows EI-MS (m/z): 288 [M^+], 289 [M+2], (-VE MODE) it indicates molecule contains one–Cl atom.

N-(2-chloroquinazolin-4-yl)nicotinamide (6j):

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Cl (740), C=N (1616.15), C=O (1685), N-H (3266).

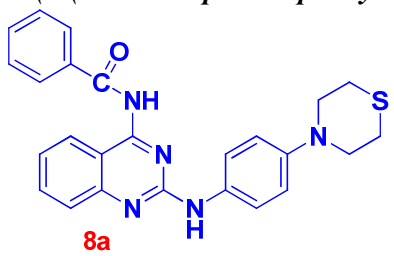
^{1}H NMR ($CDCl_3$-d_1) δ ppm 7.56(1H, t), 8.16 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 8.91(1H, S), 8.43(1H,
d), 7.62(d), 8.47(1H,d).

^{13}C NMR ($CDCl_3$-d_1) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 147(1 Ar CH), 152.6(1 Ar CH), 124(1ArC-H), 133(1 Ar CH).

LCMS Shows EI-MS (m/z): 285 [M^+], 287 [M+2], (+VE MODE) it indicates molecule contains one–Cl atom.

General procedure for N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8a),
4-methyl-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8b),
4-methoxy-N-(2-(4-thiomorpholinophenylamino)quinazolin-4-yl) benzamide (8c),
N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl)-4-(trifluoromethyl) benzamide (8d),
N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl)-4-(trifluoromethoxy) benzamide (8e),
4-chloro-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8f),
4-bromo-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8g),
4-nitro-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8h),
N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) thiophene-2-carboxamide (8i),
N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) nicotinamide (8j) [XXVIII]:
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 di chloro methane and 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-8j).
Table 1 Physical data of target compounds (8 a-j):

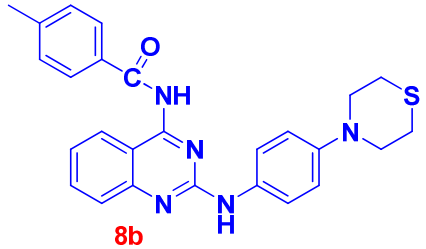
N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8a):



8a

IR (KBr, cm^{-1}): Ar stretch C-H (3010), C=N (1646.15), C=O (1685), N-H (3266).
^{1}H NMR (DMSO-d_6) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.8 (t, 1H), 7.56(d, 1 H), 7.6-7.9(5H, m), 6.4-6.7(4H,m), 3.8(4H,t, -N-$(CH_2)_2$), 2.7(4H,t, -S-$(CH_2)_2$).
^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 169 (Ar C-NH-SO_2-), 129.4(4Ar CH), 133(1Ar CH), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).
LCMS Shows EI-MS (m/z): 442 [M^+], 443 [M+1] (+VE MODE).

4-methyl-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8b):

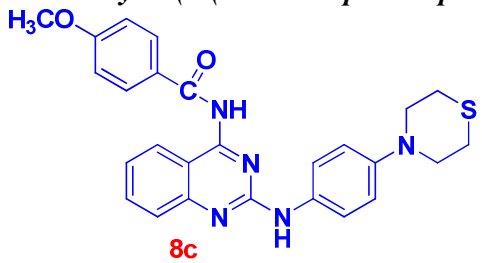


8b

IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3C-H (2910), C=N (1626.15), C=O(1685), N-H (3266).
^{1}H NMR (DMSO-d_6) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.87 (t, 1H), 7.56(d, 1 H), 7.76(2H,d),7.4(2H, d), 2.35(3H,S), 6.5(2H,d), 6.7(2H,d), 3.78(4H,t, -N-$(CH_2)_2$), 2.72(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 165 (Ar C-N), 138(1Ar-C which is attached to Sulphur carbon), 129.4(4Ar CH), 137(1Ar C), 23(Aromatic Methyl Carbon), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).
LCMS Shows EI-MS (m/z): 456 [M^+], 457 [M+1] (+ve MODE).

4-methoxy-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8c):



8c

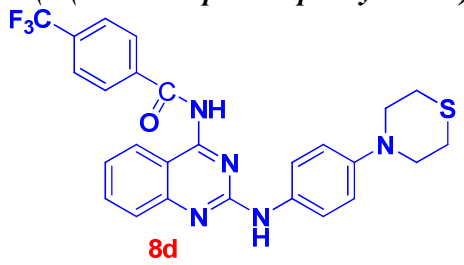
IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-O-C (1160) SP^{3}C-H (2930), C=N (1626.15), C=O (1675), N-H (3266).

^{1}H NMR (DMSO-d_6) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.66(2H,d),7.14(2H, d), 3.8(3H,S), 6.5(2H,d), 6.67(2H,d), 3.72(4H,t, -N-$(CH_2)_2$), 2.74(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 165 (Ar C-N), 126.4(2Ar CH), 117(2Ar CH), 163(1 Ar C),58.8(Aromatic Methoxy Carbon), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 472 [M^+], 473 [M+1] (+VE MODE).

N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl)-4-(trifluoromethyl) benzamide (8d):



8d

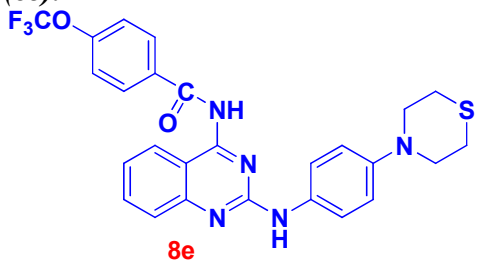
IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-F (1256.50), C=N (1616.15), C=O (1685), N-H (3266).

^{1}H NMR (DMSO-d_6) δ ppm 7.36(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.76(2H,d),7.94(2H, d), 6.5(2H,d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 165 (Ar C-N), 127(4 Ar CH), 134(1 Ar C),125(Aromatic –CF_3 Carbon), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 510 [M^+]. (+ve MODE).

N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl)-4-(trifluoromethoxy) benzamide (8e):



8e

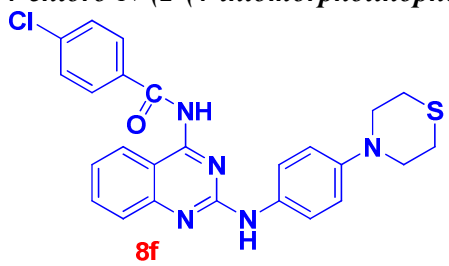
IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-F (1270), C-O-C(1150), C=O (1686.15), C=C (1595), N-H (3266).

^{1}H NMR (DMSO-d_6) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.66(2H, d), 7.14(2H, d), 6.5(2H,d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 127(2 Ar CH), 117(2 Ar CH), 153(1 Ar C),129(Aromatic –OCF_3 Carbon), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 526 [M^+] (+VE MODE).

4-chloro-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8f):



8f

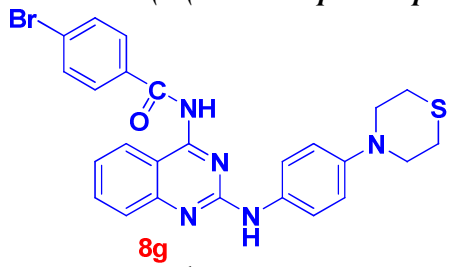
IR (KBr, cm^{-1}): Ar stretch C-H (3105), C-Cl (760), C=N (1646.15), C=O (1685), N-H (3286).

^{1}H NMR (DMSO-d_6) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.86(2H, d), 7.64(2H, d), 6.5(2H,d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 127(2 Ar CH), 129.6(2 Ar CH), 138(1 Ar C), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 476 [M^+], 478 [M+2], (+VE MODE),3:1 it indicates molecule contains one –Cl atom

4-bromo-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8g):



8g

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C-Br (560), C=N (1616.15), C=O (1685), N-H (3266).

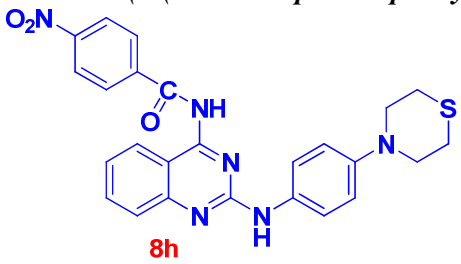
^{1}H NMR (DMSO-d_6) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 7.81(2H, d), 7.9(2H,

d), 6.5(2H,d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 130(2 Ar CH), 133.6(2 Ar CH), 128(1 Ar C-Br), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 520 [M^+], 522 [M+2] 1:1 it indicates molecule contains one –Br atom, (+VE MODE).

4-nitro-N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) benzamide (8h):



8h

IR (KBr, cm^{-1}): Ar stretch C-H (3095), 1360 & 1537 (N-O Symmetric and asymmetric Stretching in Nitro group), C=N (1616.15), C=O (1685), N-H (3266).

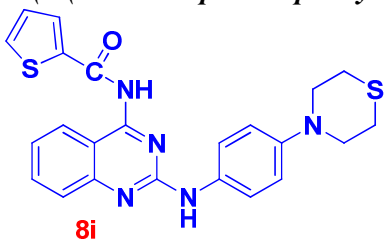
^{1}H NMR (DMSO-d_6) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 8.1(2H, d), 8.4(2H,

d), 6.5(2H, d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 130(2 Ar CH), 123.6(2 Ar CH), 151(1 Ar **C**-NO_2), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30(-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 485 [M^+] , (-VE MODE).

N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) thiophene-2-carboxamide (8i):



8i

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C=N (1616.15), C=O (1685), N-H (3266).

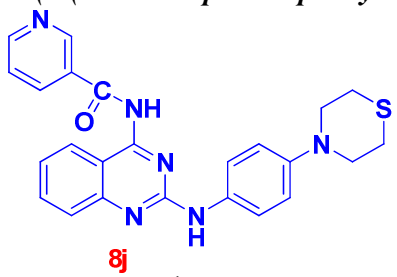
^{1}H NMR (DMSO-d_6) δ ppm 7.56(1H, t), 8.06 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 8.1(2H, d), 7.3(1H,

d), 7.2(dd), 7.7(1H,d), 6.5(2H,d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).

^{13}C NMR (DMSO-d_6) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 127(2 Ar CH), 125.6(1 Ar CH), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).

LCMS Shows EI-MS (m/z): 448 [M^+] (+VE MODE).

N-(2-(4-thiomorpholinophenylamino) quinazolin-4-yl) nicotinamide (8j):



8j

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C=N (1616.15), C=O (1675), N-H (3266).
^{1}H NMR (DMSO-d$_6$) δ ppm 7.56(1H, t), 8.16 (d, IH), 7.7 (t, 1H), 7.56(d, 1 H), 8.91(1H, S), 8.43(1H,
d), 7.62(d), 8.47(1H,d), 6.5(2H,d), 6.67(2H,d), 3.74(4H,t, -N-$(CH_2)_2$), 2.78(4H,t, -S-$(CH_2)_2$).
^{13}C NMR (DMSO-d$_6$) (δ/ppm): 128 (Ar C-H), 126.8 (Ar C-H),133.05(Ar C-H), 121.6(Ar C-H), 114(Ar C),151(Ar C), 171 (Ar C-N), 158(Ar C-Cl), 147(1 Ar CH), 152.6(1 Ar CH), 124(1ArC-H), 133(1 Ar CH), 177(Ar C-NH-Phenyl Thio Morpholino),128(1Ar C), 119(2Ar CH), 115(2 Ar CH), 55(-N-$(CH_2)_2$), 30((-S-$(CH_2)_2$).
LCMS Shows EI-MS (m/z): 443 [M$^+$] (+VE MODE).

4. Anti-microbial Screening:

The samples of synthesized Novel Quinazoline derivatives (8a-8j) 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 Novel Quinazoline derivates containing Phenyl Thio morpholine derivatives Thiophene (8i) and Pyridine (8j) showed more activity than other substituent's The order of activity was **8i>8j>8d>8e>8h>8f>8g>8a>8b>8c**.

Table 2: Anti-microbial Screening data of Novel Quinazoline derivatives (8a-8j):

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

penicillin						
Fluconazole	---	---	---	---	22	20

Results and Discussions:

The Title compounds 8a-8j were synthesized in good yields (scheme-I). All these compounds were tested for anti-bacterial and anti-fungal activity showed considerable activity when compared to the standard drugs Sparfloxacin, Benzyl penicillin, Fluconazole. It is interesting to note that the compound **8i, 8j** possessed the maximum activity. It clearly indicates the favourable effect of substituent's on the anti-bacterial and anti-fungal activity of the Novel Quinazoline derivatives (8a-8j).

Chemistry:

The target compounds were synthesized as shown in **Scheme 1**. Anthranilic acid (1) on cyclisation with urea gave 2,4 di hydroxyl Quinazoline (2), which on Chlorination by using $POCl_3$ gave 2,4 di chloro Quinazoline (3). 2, 4 di chloro Quinazoline (3) reactions of with Aqueous Ammonia in the presence of Na_2CO_3 in THF to get 2-chloroquinazolin-4-amine compound (4). Compound (4) on reacts with different Acid chlorides in the presence of pyridine yielded Corresponding compounds (6a–6j) respectively. Compounds 6a-6j further undergoes Substitution reaction with 4-Thio Morpholine anilines to afford Target compounds 8a-8j.

All the synthesized compounds (8a-8j) were characterized by IR, ^{1}H NMR, ^{13}C NMR.

Characterization:

The IR spectrum of the title compounds 8(a-j) has given stretching vibration at 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2930 cm^{-1} is due to the stretching vibration corresponding to the SP^3 C-H (methyl group).The strong intensity absorption at 1350 & 1530 cm^{-1} is due to the stretching vibration of **-**N-O stretching in nitro group, 1360 cm^{-1} is due to the stretching vibration of C-F bond. 760 cm^{-1} is due to the stretching vibration of C-Cl bond.

560 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. 1680 C=O Stretching in amide group.

It has been observed from chemical structure of compound 8(a-j) 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 methyl group appeared as a singlet at δ =3.8 ppm,. The protons attached to benzene ring appeared between δ =7.2-8.4 ppm respectively.

The chemical shifts of the final compound carbon vary from δ = 165 to 23 ppm. 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 tri fluoro methyl carbon group at δ= 124 ppm. The carbon chemical shift of the methoxy group at δ= 58 ppm.

Readily available starting materials and simple synthesizing procedures make this method very attractive and convenient for the synthesis of Novel Quinazoline derivatives (8a-8j). Formation of products was confirmed by recording their ^{1}H NMR, ^{13}C, FT-IR.

Biological Activity Screening:

The results of biological studies of newly synthesized compounds reveal that the compounds possess significant anti-bacterial and anti-fungal activities. The results of these studies are given in **Table 5**. From anti-bacterial and anti-fungal activity screening results, it has been observed that compounds **8i, 8j** possess good activity.

Conclusion:

The approach of the present study was to synthesize various Novel Quinazoline derivatives (8a-8j) and evaluate the anti-bacterial and anti-fungal activities. From result generated it can be concluded that test compounds 8i, 8j, 8d were found to possess moderate antibacterial activity against gram positive bacteria and gram negative bacteria compared with Benzyl penicillin. These results suggest that the Novel Quinazoline derivatives (8a-8j) of appropriately substituted Substituents have good potential for further development as antimicrobial agents. The data reported in this article may be helpful guide for the medicinal chemist as well as synthetic chemist who is working in this area.

Acknowledgments:

Authors are thankful to PRAGNA Life Sciences Pvt Ltd, Hyderabad for providing us facilities of IR Spectra, ^{1}H NMR for characterization of novel synthesized compounds.

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