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PALLADIUM CATALYZED SUZUKI COUPLINGREACTION FOR SYNTHESIS OF NOVEL DI SUBSTITUTED QUINAZOLINE-SULPHONAMIDE DERIVATIVES AND THEIR BIOLOGICAL SCREENING

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ABSTRACT:
A novel series of compounds were synthesised by cyclisation reaction of anthranilic acid (1) with urea to get 2,4 di hydroxyl quinazoline (2) intermediate, which were further treated with $POCl_3$ to get 2,4- di chloroquinazoline (3) derivative. Next 2,4- di chloroquinazoline (3)reacts with N-(3-aminophenyl)-2-methylpropane-2-sulfonamide (4) for 16 hrsin t-Butanol to get compound 5 , which were reacted with different substituted phenyl boronic acids &heterocyclicboronic acids under Suzuki reaction conditions to get target compounds (7 a- 7j). The structures of new compounds were confirmed by IR. Mass and ^{1}H NMR ,^{13}C NMR spectral data.Anti-bacterial and anti-fungal activities were evaluated and compared with the standard drugs, some compounds of the series exhibited promising anti-microbial and anti-fungal activity compared to standard drugs.

KEYWORDS: Quinazolines, Synthesis, Spectral data, anti-bacterial activity, antifungal activity, Buchwald coupling, Suzuki coupling.

INTRODUCTION:

Quinazoline (1) is a fused six-member aromatic ring (a benzene ring and a pyrimidine ring are fused). Quinazoline is a fused bicyclic compound earlier known as benzo-1, 3-diazine. It was first prepared in the laboratory in 1903 by Gabriel [**1**] .Although its derivative were known much earlier. The name quinazoline (German: Chinazolin) was first proposed for this compound by Weddige on observing that this was isomeric with the compounds cinnoline and quinoxaline. Paal and Bush suggested the numbering of quinazoline ring system, which is currently used [**2-4**]. The other less commonly used names for this ring system are 'phenmiazine' and 5, 6-benzopyrimidine. However, the name quinazoline is now universally accepted.

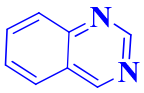


Fig 1 Quinazoline

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 azanaphthalenes 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 benzopyrazine, 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.

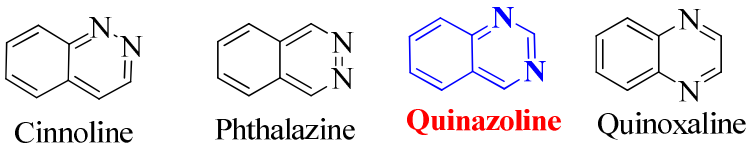


Figure2 Quinazoline isomers.

Quinazoline derivatives, which belong to the N-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 [**5-8**], anti-inflammation [**9-10**], anti-bacterial [**11-14**], analgesia [**9,13**], anti-virus [**15**], anti-cytotoxin [**16**], anti-spasm [**13,17**], anti-tuberculosis [**18**], anti-oxidation [**19**], anti malarial [**20**], anti-hypertension [**21**], anti-obesity [**22**], anti-psychotic [**23**], anti-diabetes [**24**], etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored.

Quinazoline derivatives have attracted much attention for their various biological and medicinal properties. For example, they act as the potent tyrosine kinase and cellular phosphorylation inhibitors[**25**], and they are also used as ligands for benzodiazepine and GABA receptors in the central nervous system (CNS) [**26**] or as DNA binders[**27**] Someof them show remarkable activity as anticancer[**28**], antiviral [**29**] and antitubercular agents [**30**]. Molecules containing the quinazoline unit have been popular drugs. For example, Erlotinib is used in the treatment of several types of tumors[**31**]Prazosin acts as an R-adrenergic blocker[**32**] and Iressa as an epidermal growth factor receptor inhibitor was approved by the Food and Drug Administration in USA for the treatment of lung cancer [**33**].

The Quinazoline skeleton is present in a variety of biologically active compounds, among these are several marketed drugs such as Trimetrexateglucuronate(**1**) (dihydrofolatereductase 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.

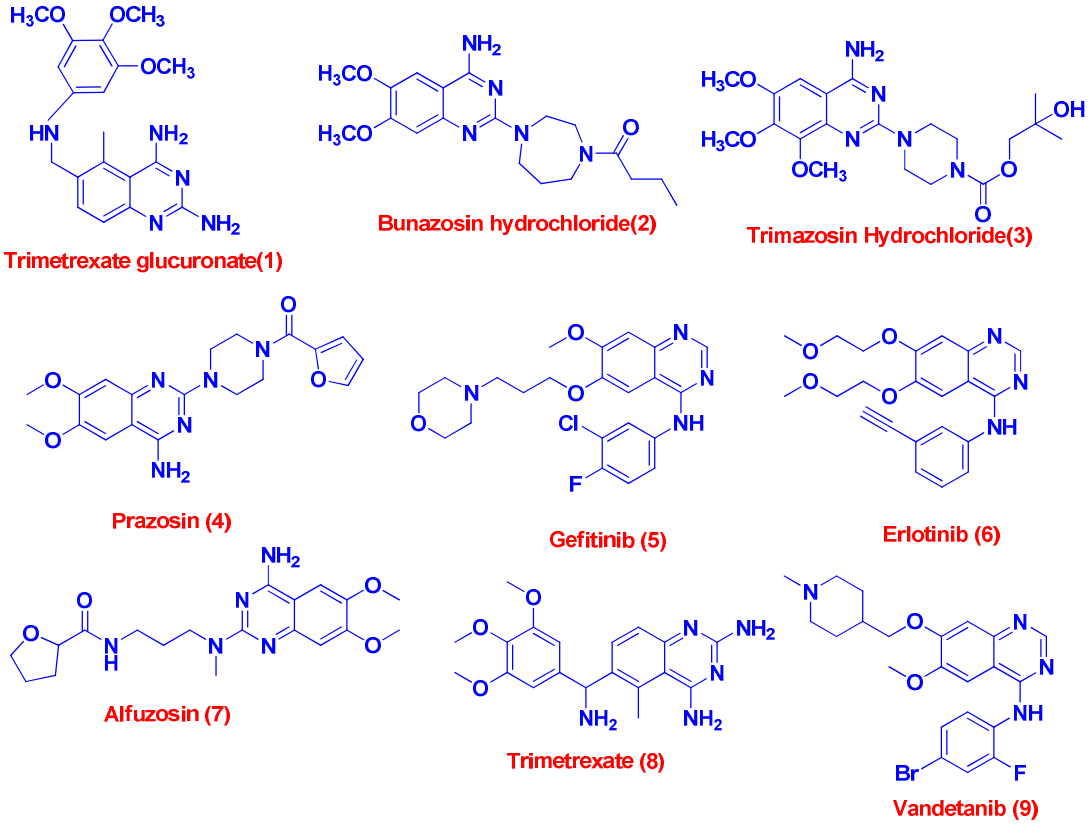
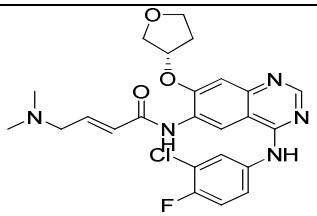
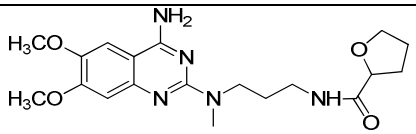
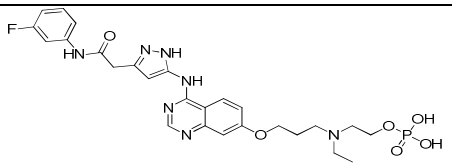
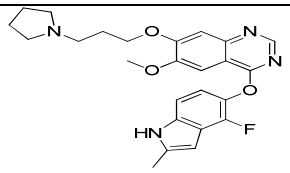
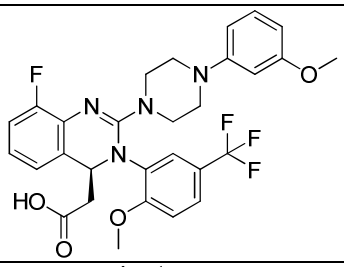
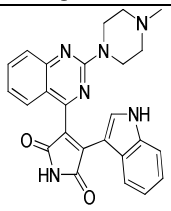
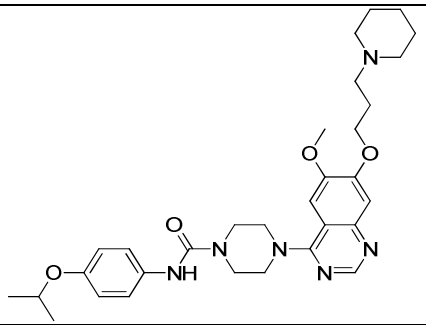
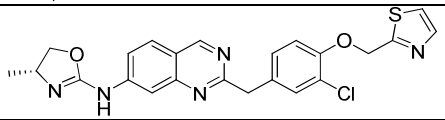
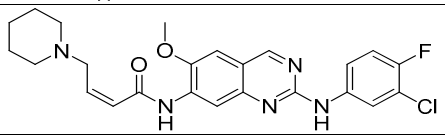
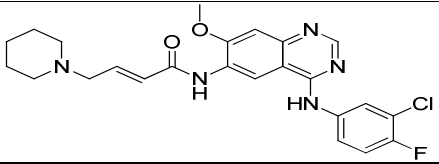
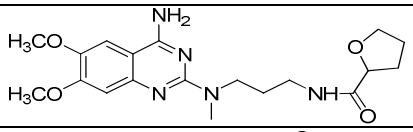
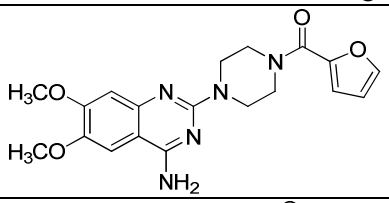
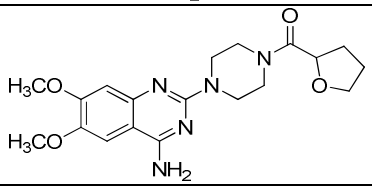


Fig .3. Quinazoline skeleton is present in a variety of biologically active compounds

***Table-1*Quinazoline compounds and their uses:**

S.NO	Quinazoline Derivative	Chemical structure	Use
1	Afatinib		**Anti-fungal activity**
2	Alfuzocin		**Anti Cancer activity**

3	Barasertib		**Acute myeloid leukemia**
4	Cediranib		**Heamatologicalcancer,Liver metastases**
5	Letermovir		**Human cytomegalovirus**
6	Sotrastaurin		**Psoriasis,ulcerative colitis.**
7	Tandutinib		**Glioblstoma.**
8	Varlitinib		**Anticancer drug.**
9	Verubulin		**Anticancer drug.**
10	Dacomitinib		**Antifungal**

11	Alfuzosine		**Anticancer**
12	Prazosin		**High blood pressure Treatment**
13	Terazosine		**Hyper Tension**

On the other hand, sulfonamides have a variety of biological activities such as antibacterial[**34-36**], insulin releasing [**37]**, carbonic anhydrase inhibitory [**38-39**], anti-inflammatory [**40**], andanti-tumor [**41]** activities. These findings encouraged us to exp lore the synthesis of sulfonamides containing Quinazoline moieties and to examine their antibacterial and antifungal properties. Sulphonamide core Structure present in various Drugs Such as Losartan, Irbesartan, Valsartan,.**Fig : 4** Structures of Sulphonamide Core Containing Various Biologically Active Drugs.

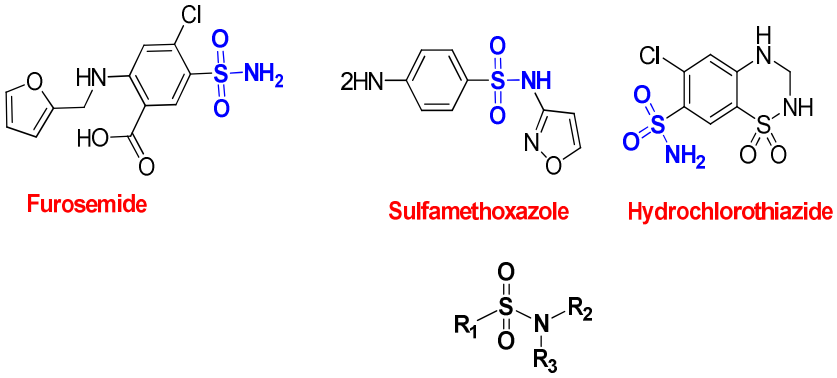


Fig : 4 Structures Of Sulphonamide Core Containing Various Biologically Active Drugs

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 ChloroQuinazoline(3) was reacted with M-Amine Sulphonamide (4) in t-butanol at 90^{O}C to form Compound5, which was further reacted with Different Substituted Boronic acids under Suzuki reaction conditions to get target compounds (7a-7j). The synthesis of the compounds as per the following Scheme **I** given below.
The synthetic route was depicted in scheme **I.**

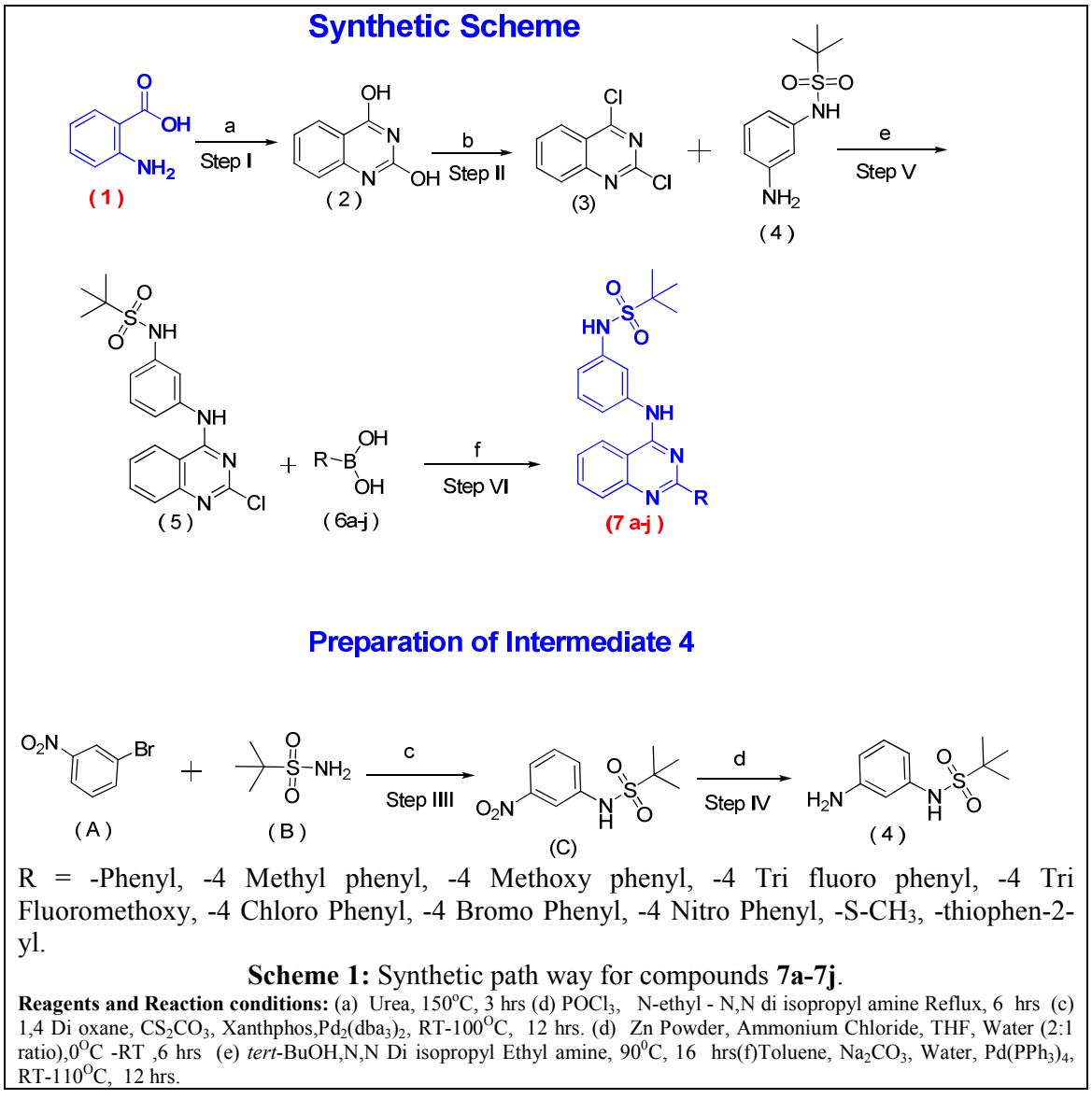
The structures of all synthesized compounds were assigned on the basis of IR, Mass, ^{1}H &^{13}C NMR spectral data analysis. Further these compounds were subjected for antifungal and antibacterial activity.

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 7 (a-j) respectively.

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

The title compounds 7 (a-j) were synthesized in six steps using different reagents and reaction conditions, the 7 (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.

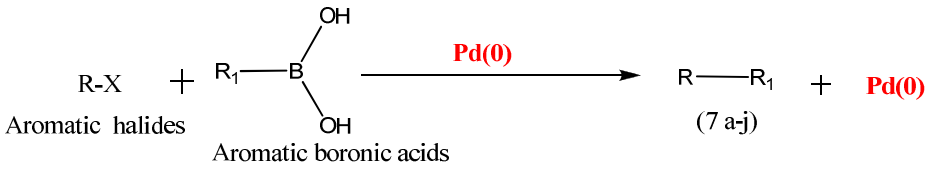


R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 Tri fluoro phenyl, -4 Tri Fluoromethoxy, -4 Chloro Phenyl, -4 Bromo Phenyl, -4 Nitro Phenyl, -S-CH_3, -thiophen-2-yl.

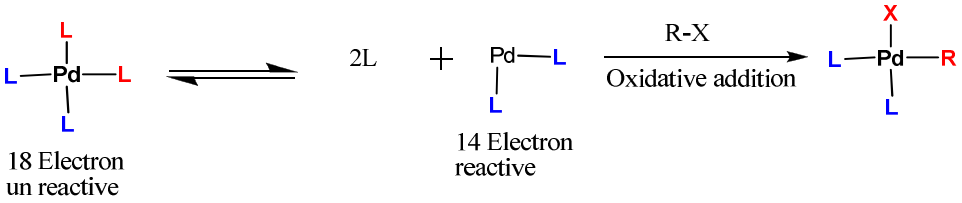
Scheme 1: Synthetic path way for compounds **7a-7j**.

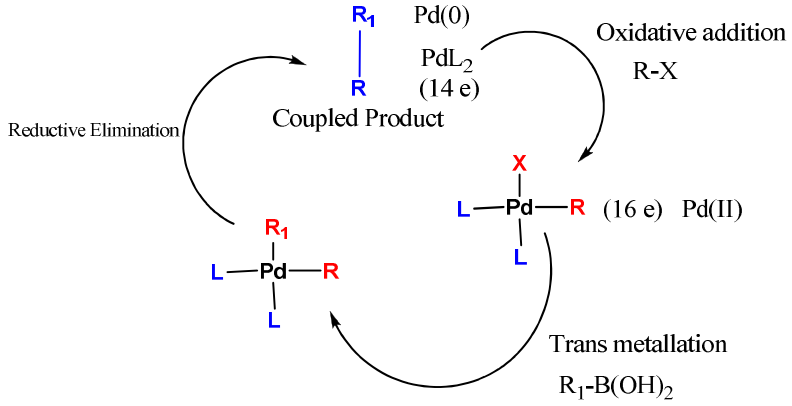
Reagents and Reaction conditions: (a) Urea, 150^{o}C, 3 hrs (d) $POCl_3$, N-ethyl - N,N di isopropyl amine Reflux, 6 hrs (c) 1,4 Di oxane, CS_2CO_3, Xanthphos,$Pd_2(dba_3)_2$, RT-100^{O}C, 12 hrs. (d) Zn Powder, Ammonium Chloride, THF, Water (2:1 ratio),0^{O}C -RT ,6 hrs (e) *tert*-BuOH,N,N Di isopropyl Ethyl amine, 90^{0}C, 16 hrs(f)Toluene, Na_2CO_3, Water, $Pd(PPh_3)_4$, RT-110^{O}C, 12 hrs.

POSSIBLE MECHANISM FOR SUZUKI COUPLING:



Here **R = Chloro Quinazoline derivative (5)**
R_1 = Different substituted boronic acids (6a-j)



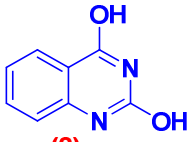


3. EXPERIMENTAL SECTION:

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 benzophenoneketyl 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 BrukerAvance 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 tetramethylsilane (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 hydroxyQuinazoline*[42] *[compound (2)] :
The mixture of Anthranilicacid(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.

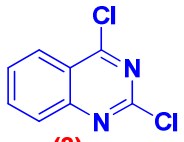
2,4 di hydroxyQuinazoline [Compound 2]:
Yield: 90%; M.p. above 300^{O}C;



(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}): 3428 (OH, broad), 3079 (Ar C-H), 1604 (C=N);
LCMS Purity 99.63 %, RT 1.924, Mass 161.1 [M$^+$, **100%**).

General procedure for synthesis of 2,4 di chloroQuinazoline*[43]*[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);
GCMS Purity 89.75 %, RT 8.738, Mass 198 [M$^+$], 200 [M+2], 202 [M+4], 9:6:1 It indicates molecule contains Two chlorine atoms& Even no. of Nitrogen atoms According to Nitrogen rule.

General procedure for synthesis of N-(3-(2-chloroquinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide [43]*[compound (5)] :*
To a well stirred solution of N-(3-aminophenyl)-2-methylpropane-2-sulfonamide (4)**(1 m.mol)**and N, N Di isopropyl Ethyl amine (**1.3m.mol**) in *tert*-BuOH (15 ml) at Room Temperature, 2, 4-dichloroQuinazoline compound- (3) (**1 m.mol**) was added. The reaction mixture was allowed to stir at 60-70^{O}C for 9-10 hrs. After completion of reaction as monitored by TLC, *tert*-BuOH was evaporated under reduced pressure and the residue was

treated with water. The mixture was Extracted with EtoAc (3 x 30 ml) and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography to give the N-(3-(2-chloroquinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (compound 5).
Yield: 90%;
M.p. 196-198^{O}C;
^{1}H NMR ($CDCl_3$-d_1) δ ppm9.5 (S, IH), 9.10 (S, 1H), 8.2 (d, I H), 7.6(1H, S), 7.5(2H,m), 7.3(1H,m),7(1H, t), 6.9(1H,d), 1.2(9H,S).
^{13}C NMR (DMSO-d_6) (δ/ppm): 127 (Ar C-H), 125.6 (Ar C-H),133.5(Ar C-H), 121.6(Ar C-H), 171(Ar C-NH),151(1Ar C), 114(Ar C),, 157 (Ar C-Cl), 143(1ArC), 102.7(1Ar CH), 138(1ArC), 110(1 Ar CH), 130(1 Ar CH), 108(1 Ar CH), 67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2910), C-Cl(759), C=N (1626.15), C=C (1575), N-H (3292), 1365& 1150(S=O Symmetric and asymmetric Stretching in Sulphonamide group).
LCMS Purity 96.33 %, RT 4.211, Mass 391.1(positive mode) [M^+, **100%**], 393 [M+1, 33%] It indicates molecule contains one chlorine atom &Even no. of Nitrogen atoms According to Nitrogen rule.

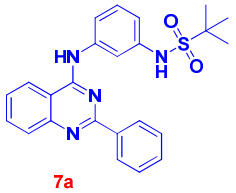
***General procedure for synthesis of2-methyl-N-(3-(2-phenylquinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7a),2-methyl-N-(3-(2-p-tolylquinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7b), N-(3-(2-(4-methoxyphenyl)quinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (7c), 2-methyl-N-(3-(2-(4-(trifluoromethyl)phenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7d), 2-methyl-N-(3-(2-(4-(trifluoromethoxy)phenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7e), N-(3-(2-(4-chlorophenyl)quinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (7f), N-(3-(2-(4-bromophenyl)quinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (7g), 2-methyl-N-(3-(2-(4-nitrophenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7h),2-methyl-N-(3-(2-(4-(methylthio)phenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7i), 2-methyl-N-(3-(2-(thiophen-2-yl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7j)*[45]:**
A mixture of N-(3-(2-chloroquinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (5), (**2.55 m.mol**), boronic acids 6(a-j) (**3.825 m.mol**), $Pd(PPh_3)_4$ (**0.078 m.mol**), toluene (15 mL) and Na_2CO_3 (2.7 mL, **2M**) was flushed with N_2 for 5 min under magnetic stirring. The reaction mixture was stirred and heated under reflux (temperature of oil bath 120^{O}C) under a N_2 atmosphere until the starting material has disappeared. After cooling, the reaction mixture was evaporated under reduced pressure to dryness. EtOAc (80 ml) was added and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered, washed thoroughly with EtOAc (200 ml) and the filtrate evaporated under reduced pressure to dryness. The residue was purified by flash column chromatography on silica gel.
The following compounds were prepared in this manner.

Table 2 Physical data of target compounds (7 a-j):

Compound	Melting Point (^{O}C)	R_f	Yield (%)
7a	145-147	0.64	70
7b	106-107	0.62	68
7c	165-168	0.69	62
7d	160-163	0.63	61

7e	145-147	0.65	70
7f	158-160	0.63	66
7g	177-180	0.67	62
7h	132-135	0.65	67
7i	123-125	0.64	60
7j	196-197	0.7	64

2-methyl-N-(3-(2-phenylquinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7a):

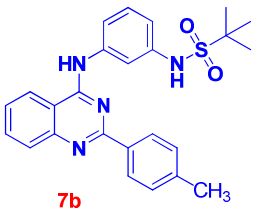


7a

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.5 (bS, IH), 9.10 (bS, 1H), 8.2 (d, I H), 7.6(1H, S), 7.5(2H,m), 7.3(1H,m),7(1H, t), 6.9(1H,d), 1.2(9H,S), 8.3(2H, t), 7.6(t,2H), 7.4(1H, t).
^{13}C NMR (DMSO-d$_6$) (δ/ppm): 127 (Ar C-H), 125.6 (Ar C-H),133.5(Ar C-H), 121.6(Ar C-H), 171(Ar C-NH),151(1Ar C), 114(Ar C), 161 (Ar C), 143(1ArC), 102.7(1Ar CH), 138(1ArC), 110(1 Ar CH), 130(1 Ar CH), 108(1 Ar CH), 67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 134(Ar CH), 128(Ar CH), 130(Ar CH), 131(Ar CH).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2910), C=N (1626.15), C=C (1575), N-H (3292), 1365& 1150(S=O Symmetric and asymmetric Stretching in Sulphonamide group).

Mass Spectra shows that 433(positive mode) [M$^+$, **100%**], 434 [M+1, 26%] It indicates molecule contains 24 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

2-methyl-N-(3-(2-p-tolylquinazolin-4-ylamino) phenyl) propane-2-sulfonamide (7b):

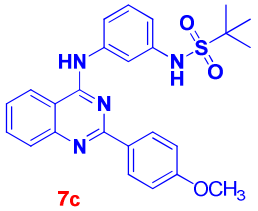


7b

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.5 (bS, IH), 9.10 (bS, 1H), 8.2 (d, I H), 7.6(1H, S), 7.5(2H,m), 7.3(1H,m),7(1H, t), 6.9(1H,d), 1.3(9H,S), 8.53(2H, d), 7.36(d,2H), 2.34(3H, S).
^{13}C NMR (DMSO-d$_6$) (δ/ppm): 127 (Ar C-H), 125.6 (Ar C-H),133.5(Ar C-H), 121.6(Ar C-H), 171(Ar C-NH),151(1Ar C), 114(Ar C), 161 (Ar C), 143(1ArC), 102.7(1Ar CH), 138(1ArC), 110(1 Ar CH), 130(1 Ar CH), 108(1 Ar CH), 67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 131(Ar C), 129(Ar CH), 131(Ar CH), 133(Ar C), 21(Aromatic Methyl carbon).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2910), C=N (1626.15), C=C (1575), N-H (3292), 1355& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).

Mass Spectra shows that 447(positive mode) [M^+, **100%**], 448 [M+1, 27%] It indicates molecule contains 25 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

N-(3-(2-(4-methoxyphenyl)quinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (7c):



7c

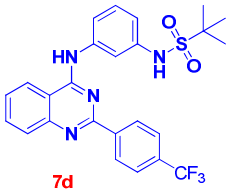
^{1}H NMR (DMSO-d_6) (δ/ppm) δ ppm9.15 (bS, IH), 9.10 (bS, 1H), 8.2 (d, I H), 7.6(1H, S), 7.5(2H,m), 7.3(1H,m),7(1H, t), 6.9(1H,d), 1.3(9H,S), 7.83(2H, d), 7.06(d,2H), 3.84(3H, S).

^{13}C NMR (DMSO-d_6) (δ/ppm): 127 (Ar C-H), 125.6 (Ar C-H),133.5(Ar C-H), 121.6(Ar C-H), 171(Ar C-NH),151(1Ar C), 114(Ar C), 161 (Ar C), 143(1ArC), 102.7(1Ar CH), 138(1ArC), 110(1 Ar CH), 130(1 Ar CH), 108(1 Ar CH), 67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 128(Ar C), 130(Ar CH), 116(Ar CH), 160(Ar C), 55(Aromatic Methoxy carbon).

IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2910), C-O-C(1159), C=N (1626.15), C=C (1575), N-H (3292), 1355& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).

Mass Spectra shows that 463(positive mode) [M^+, **100%**], 464 [M+1, 27%] It indicates molecule contains 25 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

2-methyl-N-(3-(2-(4-(trifluoromethyl)phenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7d):



7d

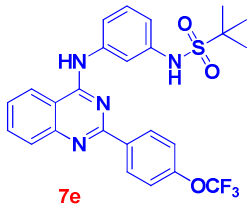
^{1}H NMR (DMSO-d_6) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,q), 7.83(1H,d),5.7(1H, S), 6.9(1H,d), 7(1H,d), 6(1H,d), 1.3(9H,S), 8.83(2H, d), 7.66(d,2H).

^{13}C NMR (DMSO-d_6) (δ/ppm): 127 (Ar C-H), 126.6 (Ar C-H),133.5(Ar C-H), 128.6(Ar C-H), 161(Ar C-NH),151(1Ar C), 114(Ar C), 161 (Ar C), 143(1ArC), 102.7(1Ar CH), 138(1ArC), 110(1 Ar CH), 130(1 Ar CH), 108(1 Ar CH), 67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 138(Ar C), 127(Ar CH), 126(Ar CH), 130(Ar C), 125(Aromatic –CF_3Carbon).

IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2930), C-Fstretching (1340), C=N (1666.15), C=C (1615), N-H (3298), 1350& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).

Mass Spectra shows that 499(negative mode) [M^+, **100%**], 500 [M+1, 27%] It indicates molecule contains 25 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

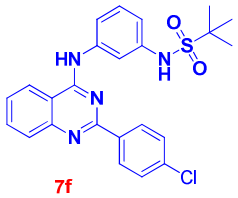
2-methyl-N-(3-(2-(4-(trifluoromethoxy)phenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7e):



7e

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,q), 7.83(1H,d),5.78(1H, S), 6.9(1H,d), 7(1H,d), 5.96(1H,d), 1.13(9H,S), 8.03(2H, d), 7.06(d,2H).
^{13}C NMR (DMSO-d$_6$) (δ/ppm): 127 (Ar C-H), 126.6 (Ar C-H),133.5(Ar C-H), 128.6(Ar C-H), 161(Ar C-NH),151(1Ar C), 114(Ar C), 161 (Ar C), 143(1ArC), 107.7(1Ar CH), 130(1ArC), 110(1 Ar CH), 138(1 Ar CH), 102(1 Ar CH), 67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 128(Ar C), 130(Ar CH), 116(Ar CH), 150(Ar C), 129(Aromatic –OCF_3 Carbon).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2920), C-F stretching (1360), C=N (1666.15), C=C (1615), N-H (3298), 1350& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).
Mass Spectra shows that 515(negative mode) [M^+, **100%**], 516 [M+1, 27%] It indicates molecule contains 25 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

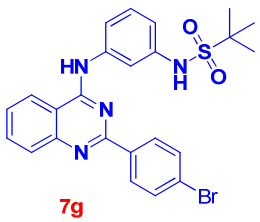
N-(3-(2-(4-chlorophenyl)quinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (7f):



7f

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,t), 7.83(1H,d),5.7(1H, S), 6.9(1H,d), 7.1(1H,d), 6(1H,d), 1.3(9H,S), 8.13(2H, d), 7.56(d,2H).
^{13}C NMR (DMSO-d$_6$) (δ/ppm):67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 100-160(18 Aromatic carbons).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2920), C-Cl stretching (740), C=N (1666.15), C=C (1615), N-H (3298), 1360& 1170(S=O Symmetric and asymmetric Stretching in Sulphonamide group).
Mass Spectra shows that 467(positive mode) [M^+, **100%**], 469 [M+1, 33%] It indicates molecule contains one –Cl atom& Even no. of Nitrogen atoms According to Nitrogen rule.

N-(3-(2-(4-bromophenyl)quinazolin-4-ylamino)phenyl)-2-methylpropane-2-sulfonamide (7g):

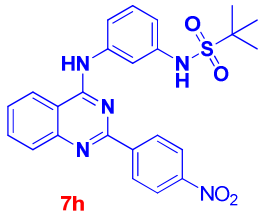


7g

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,t), 7.83(1H,d),5.7(1H, S), 6.9(1H,d), 7.1(1H,d), 6(1H,d), 1.3(9H,S), 7.7(2H, d), 7.46(d,2H).

^{13}C NMR (DMSO-d$_6$) (δ/ppm):67(Quaternary carbon in t-butyl sulphonamide group), 21(methyl carbon), 100-160(18 Aromatic carbons).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2915), C-Br stretching (540), C=N (1666.15), C=C (1615), N-H (3278), 1350& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).
Mass Spectra shows that 509(negative mode) [M$^+$, **100%**], 511 [M+2, 98%] It indicates molecule contains one –Br atom & Even no. of Nitrogen atoms According to Nitrogen rule.

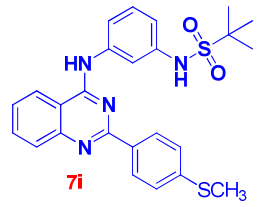
2-methyl-N-(3-(2-(4-nitrophenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7h):



7h

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,t), 7.83(1H,d),5.7(1H, S), 6.9(1H,d), 7(1H,d), 6(1H,d), 1.3(9H,S), 8.03(2H, d), 8.42(d,2H).
^{13}C NMR (DMSO-d$_6$) (δ/ppm):65(Quaternary carbon in t-butyl sulphonamide group), 20(methyl carbon), 100-160(18 Aromatic carbons).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), SP^3 C-H stretching (2908), 1550& 1360 (N-OSymmetric and asymmetric Stretching in Nitro group), C=N (1666.15), C=C (1615), N-H (3298), 1350& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).
Mass Spectra shows that 476(negative mode) [M$^+$, **100%**], 477 [M+1, 26%] It indicates molecule contains 24 carbon atoms &odd no. of Nitrogen atoms According to Nitrogen rule.

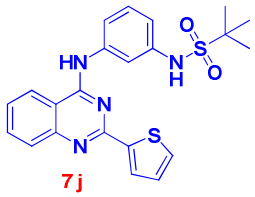
2-methyl-N-(3-(2-(4-(methylthio)phenyl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7i):



7i

^{1}H NMR (DMSO-d$_6$) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,t), 7.83(1H,d),5.7(1H, S), 6.9(1H,d), 7(1H,d), 6(1H,d), 1.43(9H,S), 7.63(2H, d), 7.46(d,2H).
^{13}C NMR (DMSO-d$_6$) (δ/ppm):65 (Quaternary carbon in t-butyl sulphonamide group), 20(methyl carbon), 15(methyl carbon), 100-160(18 Aromatic carbons).
IR (KBr, cm^{-1}): Ar stretch C-H (3095), C=N (1666.15), C=C (1615), N-H (3298), 1350& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).
Mass Spectra shows that 479(positive mode) [M$^+$, **100%**], 500 [M+1, 27%] It indicates molecule contains 25 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

2-methyl-N-(3-(2-(thiophen-2-yl)quinazolin-4-ylamino)phenyl)propane-2-sulfonamide (7j):



7j

^{1}H NMR (DMSO-d_6) (δ/ppm) δ ppm9.10 (bS, 1H), 8.2 (d, I H), 7.86(1H, t), 7.5(1H,t), 7.83(1H,d),5.7(1H, S), 6.9(1H,d), 7(1H,d), 6(1H,d), 1.3(9H,S), 7.83(1H, d), 7.16(t,1H), 7.7(1H,d).

^{13}C NMR (DMSO-d_6) (δ/ppm):65 (Quaternary carbon in t-butyl sulphonamide group), 20(methyl carbon), 100-160(18 Aromatic carbons).

IR (KBr, cm^{-1}): Ar stretch C-H (3095), C=N (1666.15), C=C (1615), N-H (3298), 1350& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group).

Mass Spectra shows that 439(positive mode) [M^+, **100%**], 440 [M+1, 24%] It indicates molecule contains 22 carbon atoms & Even no. of Nitrogen atoms According to Nitrogen rule.

Synthesis of Preparation of Intermediate 4:

General procedure for synthesis of 2-methyl-N-(3-nitrophenyl)propane-2-sulfonamide[Buchwald coupling] (Compound C):

A mixture of 1-bromo-3-nitrobenzene (A), (**2.55 m.mol**), 2-methylpropane-2-sulfonamide (B) (**3.06 m.mol**), Xanthophos (**1.1eq.**), in 1,4-Dioxane (15 mL) and CS_2CO_3 (**2.5 eq.)** was flushed with Argon for 15 min under magnetic stirring. Then adeed$Pd_2(dba_3)_2$(**10 mol%, 0.01 eq.**)Again flushed with Argon for 15 min, The reaction mixture was stirred and heated under reflux (temperature of oil bath 100^{O}C) under a Aratmosphere until the starting material has disappeared. After cooling, the reaction mixture was filtered through celite pad,Celite pad washed thoroughly with EtOAc (200 ml) and the filtrate evaporated under reduced pressure to dryness. The residue was purified by flash column chromatography on silica gel.

Yield: 55%;

M.p. 146-148^{O}C;

^{1}H NMR ($CDCl_3$-d_1) δ ppm8 (S, IH), 7.63 (d, 1H), 7.5 (t, I H), 7.06(1H, d), 1.5(9H,S) 4.3(1H,bs).

IR (KBr, cm^{-1}): Ar stretch C-H (3110), C=N (1646.15), C=C (1585), N-H (3292), 1361& 1145(S=O Symmetric and asymmetric Stretching in Sulphonamide group), 1412& 1594(N-O Symmetric and asymmetric Stretching in Nitro group).

Mass Spectrum shows Mass 257(Negative mode) [M^+, **100%**], It indicates Even no. of Nitrogen atoms According to Nitrogen rule.

General procedure for synthesis ofN-(3-aminophenyl)-2-methylpropane-2-sulfonamide (Compound 4):

A mixture ofCompound (C) **(0.1 mol, 1 eq.)** was added to a stirred solution of Zn powder**(0.5 mol, 5 eq.)** at 0^{O}C temperature, and then NH_4Cl **(0.5 mol, 5 eq.)** was added lot wise to the mixture. The reaction mixture was Stirred at RT for 6 h. The mixture was filtered through celitepad, washed with thoroughly with EtoAc (50 ml). The residue was poured into ice water (500 mL), and the filtrate evaporated under reduced pressure to dryness. The residue was purified by flash column chromatography on silica gel. (60 % yield).

Yield: 55%;

M.p. 166-168^{O}C;

^{1}H NMR (DMSO-d_6) δ ppm5.6 (S, IH), 6.1 (d, 1H), 7 (t, I H), 5.9(1H, d), 1.5(9H,S) 4.3(1H,bs), 6.5(2H,bs).
IR (KBr, cm^{-1}): Ar stretch C-H (3110), C=N (1646.15), C=C (1585), N-H (3266), 1345& 1160(S=O Symmetric and asymmetric Stretching in Sulphonamide group), 3320 &3440 (N-H Symmetric and asymmetric Stretching in primary amine group).
LCMS Purity 92.75 %, RT 3.161, Mass 227.1(Negative mode) [M^+, **100%**], It indicates molecule contains one chlorine atom & Even no. of Nitrogen atoms According to Nitrogen rule.

Anti-Microbial Screening:

The samples of synthesized Novel Quinazoline derivatives(7a-7j) 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 Aspergillusniger (A. niger) and Candida albicans (C. albicans). The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole.The Novel Quinazoline-Sulphonamide derivates containing Thiophene ring (7j) and -SCH_3 group (7i) showed more activity than other substituent's The order of activity was **7j>7i>7d>7e>7h>7f>7g>7a>7b>7c**.

Table 3: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
7a	14	16	09	12	24	11
7b	08	13	08	06	15	11
7c	13	15	13	11	10	06
7d	10	08	07	09	09	21
7e	11	12	09	12	19	18
7f	15	12	12	13	12	13
7g	09	12	07	11	12	13
7h	09	07	10	08	11	17
7i	20	24	19	14	27	23
7j	18	14	17	12	16	25
Sparfloxacin	24	25	22	22	---	---
Benzyl penicillin	19	18	16	16	---	---
Fluconazole	---	---	---	---	22	20

RESULTS AND DISCUSSIONS:

The Title compounds 7a-7j 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 drugsSparfloxacin,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 Quinazolinederivatives (7a-7j).

Chemistry:

The target compounds were synthesized as shown in **Scheme 1**. Anthranilic acid (1) on cyclisation with urea gave 2,4 di hydroxyQuinazoline(2), which on Chlorination by using $POCl_3$ gave 2,4 di chloroQuinazoline(3). 2,4 di chloroQuinazoline(3)reactswith Compound (4) in the presence of N,N Di isopropyl Ethyl aminein t-butanol to get compound (5). Compound (5) reactswithdifferent Aromatic Substituted boronic acids (6a-6j) in the presence of Pd (0) catalyst yielded Correspondingcompounds (7a–7j) respectively with good yields.

All the synthesized compounds (7a-7j) were characterized by IR, ^{1}H NMR,^{13}C NMR.

Characterization:

The IR spectrum of the title compounds 7(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 gp).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.1365& 1150 S=O Symmetric and asymmetric Stretching in Sulphonamide group.

It has been observed from chemical structure of compound 7(a-j) that different pair of protons. The protons of methylgroup which is attached to benzene ring appeared as a singlet at δ =2.3 ppm,The protons of methylgroup 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 chemicalshift 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 Quinazolinederivatives (7a-7j). Formation of products was confirmed by recording their ^{1}H NMR, ^{13}C,FT-IR.

Biological Activity Screening:

The results of biologicalstudies of newly synthesized compounds reveal that the compounds possess significant anti-bacterial and anti-fungalactivities. The results of these studies are given in **Table 3**.From anti-bacterial and anti-fungalactivity screening results, it has been observed that compounds 7i, 7jpossess good activity.

CONCLUSION:

The approach of the present study was to synthesize various Novel Quinazolinederivatives (7a-7j) and evaluate the anti-bacterial and anti-fungal activities. From result generated it can be concluded that test compounds 7j, 7i, 7d 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 (7a-7j) 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:

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