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# SYNTHESIS AND EVALUATION OF ANTI-BACTERIAL ACTIVITIES OF NOVEL QUINAZOLINE DERIVATIVES

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**Abstract**
In this study, a series of Novel 7- substituted 4-Morpholine Quinazoline derivatives was designed and synthesized.The chemical structures of the synthesized compounds were confirmed by elemental analyses, FT-IR, $^{1}$H NMR,$^{13}$C NMRandmassspectralstudies.Eight newcompounds (11 a–h) were tested in vitro for their antimicrobial activity against clinically isolated strains. All the synthesized products were evaluated for their antimicrobial activity. All the compounds exhibited significant to moderate antimicrobial activity. Compounds 11h, 11e, and 11c demonstrated good antimicrobial activity against all the tested microbial strains.

**Key words:**Quinazolines, Anti-bacterial activity, Anti-fungal activity, bi phenyls, Synthesis, Heterocyclic compounds.

## Introduction:

Now a day's Heterocyclic compounds analogues and derivatives have become strong Interest in pharmaceutical research area because of their useful biological and pharmacological properties. Heterocyclic compounds are abundant in nature and have acquired more importance because their structural subunits are exhibit in many natural products such as vitamins, hormones, antibiotics etc. Quinazoline nucleus present in compounds possess variety of pharmacological activities such as antitumor, anti-microbial, antipsychotic, antifungal, antiviral and anti- inflammatory. The present review focuses on the Quinazoline derivativeswithpotential activities that are now in development.Quinazoline ( **Fig 1 )** is a compound made up of two fused six member simple aromatic rings- benzene &Pyrimidine ring. It is a yellow coloured compound, found usually in crystalline form.

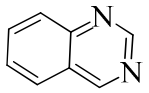


**Fig 1 Quinazoline**

**Quinazoline isomers**

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

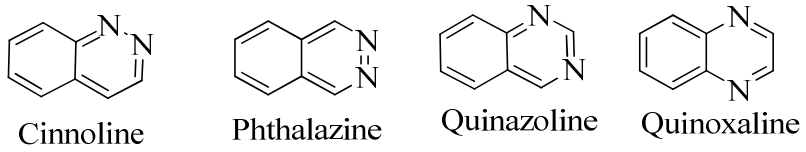



**Figure 2. Quinazoline isomers.**

Quinazoline derivatives, which belong to the N-containing Heterocyclic compounds, have caused universal concern due to widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [I-IV], anti-inflammation[V-VI], anti-bacterial[VII-X], analgesia[V,IX], anti-virus[XI], anti-cytotoxic[XII], anti-spasm[IX-, XIII], anti-tuberculosis[XIV], anti-oxidation[XV], anti-malarial [XVI], anti-hypertension [XVII], anti-obesty[XVIII], anti-psychotic [XIX], anti-diabetes[XX], etc.Medicinal chemists synthesised a variety of Quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods.

The Quinazoline skeleton is present in a variety of biologically active compounds, among these are several marketed drugs such as 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**].

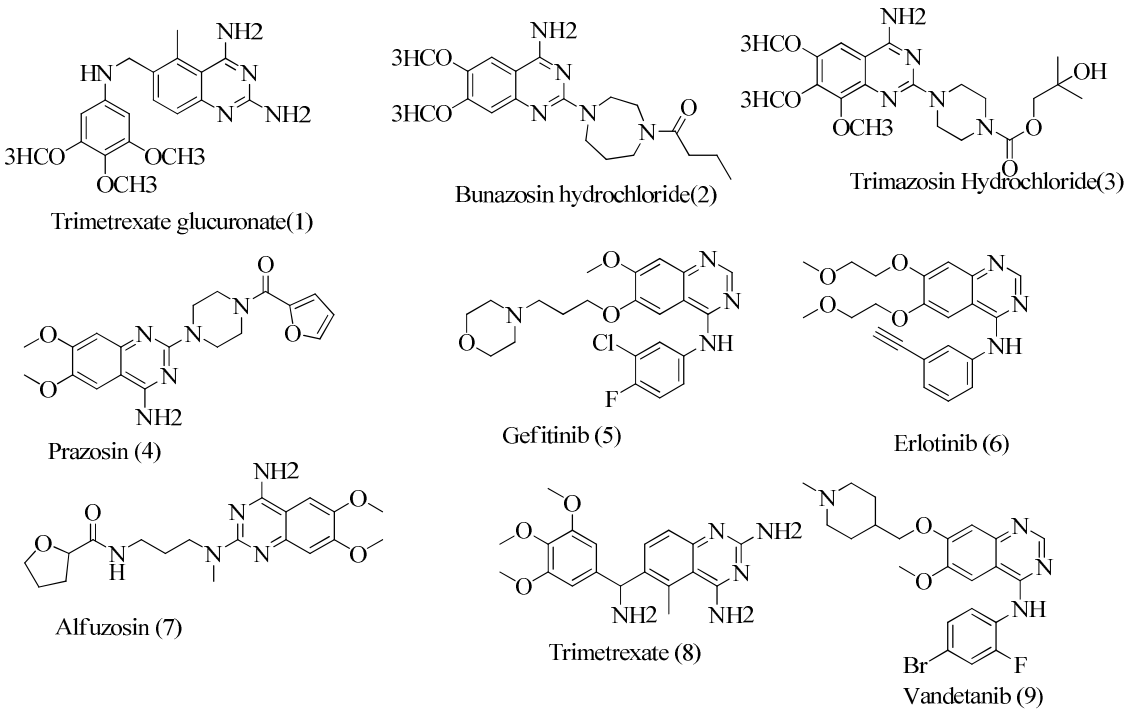



**Fig .3. Quinazoline core present in a variety of biologically active compounds**

Encouraged by the diverse biological activities of Quinazoline heterocyclic compounds, it was decided to prepare a new series of Quinazoline derivatives. Literature survey revealed that incorporation of different groups in Quinazolineheterocyclic ring enhanced antibacterial and antifungal activity. In the present communication 4-nitroAnthranilic acid(1) was reacted with urea at 200$^{O}$C to get 7-nitroquinazoline-2,4-diol (3), which was reacted with $POCl_3$ at reflux to get 2 , 4 di Chloro7-nitroQuinazoline (3) was reacted with Cis2,6-dimethylmorpholine in THF at RT to form Compound (6), which were further reacted with 4-(methoxycarbonyl)phenylboronic acid (7 ) under Suzuki reaction conditions to get compound ( 8). Compound (8) reacted with Zinc, Ammonium chloride in THF, water to get methyl 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (9), which were further reacted with Acid chlorides (10 a-h) to get compounds (11a-h).

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

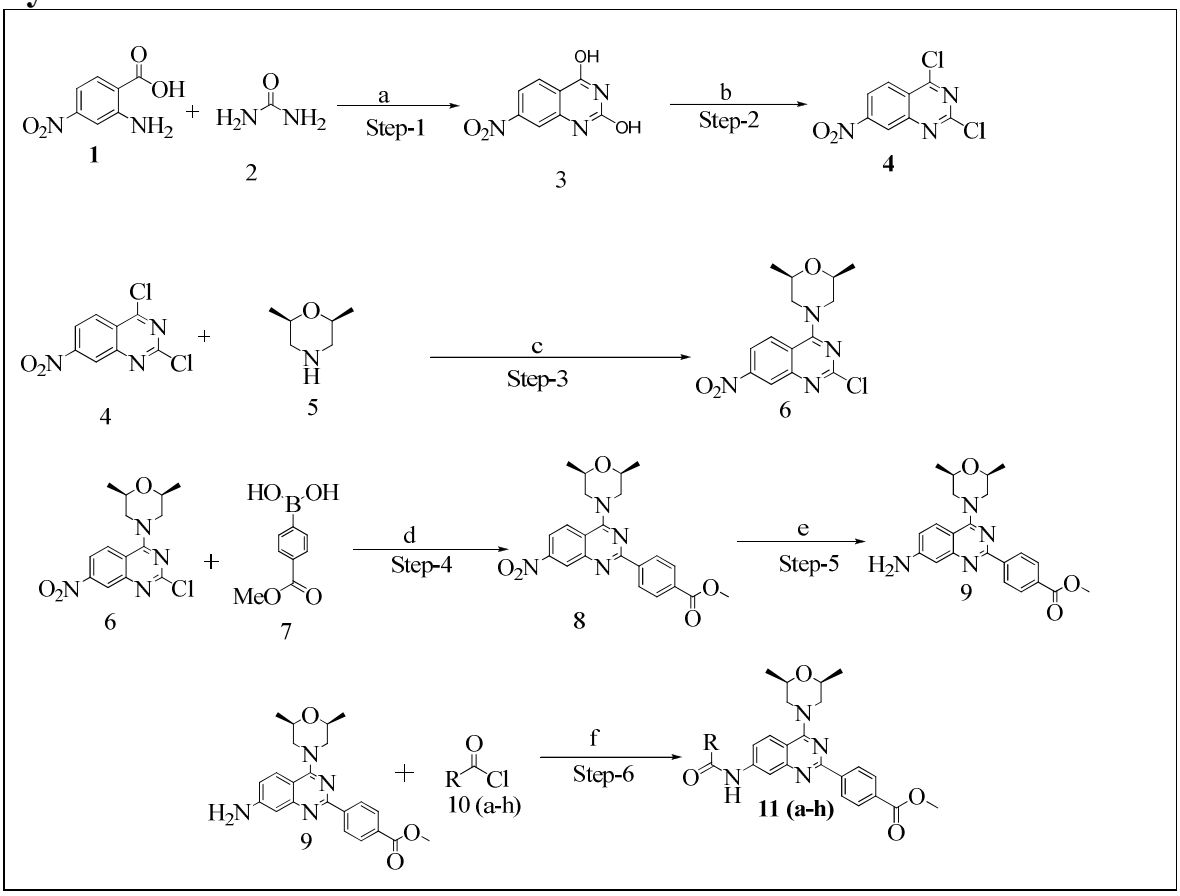
## Materials and methods

In this Investigation chemicals were purchased from local dealer with S.D fine make was used. Chemicals were 99 % pure; purity has been checked by thin layer chromatography and melting point. Conventional method has been used for synthesis of Quinazoline derivatives. Stirring and reflux method were used for synthesis of Quinazoline derivatives 11 (a-h) respectively.

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

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

## Synthetic Scheme




**R** = 4'-isopropylbiphenyl-4- carbonyl chloride, 4'-methoxybiphenyl-4- carbonyl chloride, 6-(4-isopropyl phenyl)nicotinic carbonyl chloride, 4'-methylbiphenyl-4- carbonyl chloride, 4'-nitrobiphenyl-4- carbonyl chloride, 4'-chloro biphenyl-4- carbonyl chloride, 4'-bromo biphenyl-4- carbonyl chloride, thiophene-2-carbonyl chloride.

**Scheme 1:** Synthetic path way for compounds **11 (a-h)**.

***Reagents and Reaction conditions:***(a) 160$^{o}$C, 6hrs (b) $POCl_3$, DIPEA, Reflux, 4hrs (c) Di Chloro methane, Tri Ethyl Amine, 0$^{0}$C-RT, overnight (d) $Pd(PPh_3)_2Cl_2$,$K_2CO_3$, 1,4 Dioxane, Reflux, 16 hrs (e) Iron, Acetic acid , Reflux , 6 hrs(f) DCM, Pyridine, 0$^{O}$C-RT .

## 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 $^{1}$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 ($^1H$ 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 7-nitroQuinazoline-2, 4-diol [XXI][ compound (3)] :**
2-Amino-4-nitro benzoic acid (1) **(10m.mol)**, and urea (2) (**100m.mol**) were stirred at $160^OC$ for 6 hrs, then cool to $100^OC$, and water (60 ml) was added. The solution was stirred for 10min. The formed precipitate was filtered off, washes with cold water and further suspended in 0.5N NaOH. The mixture was refluxed for 5 min, and then cool to RT, The $P^H$ was adjusted to 2 with Conc.HCl. Compound 2 was filtered off, wash with MeOH/water (1:1), dried in vacuum, to give compound (3) (**Yield 90%**) as a light-brown powder.
**$^1H$ NMR (400M.HZ, DMSO-$d_6$) δ** 8.14 (d, J = 9.0 Hz, 1H, ArH), 7.9 (S, 1H, ArH), 7.95 (d, J = 2.7 Hz, 1H, ArH).
**$^{13}C$ NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):** 124 (Ar C-H), 155.6 ( Ar C, Ar C-$NO_2$),120.5( Ar C-H), 122.6(1Ar C-H), 181.3(Ar ),150(Ar C), 190(Ar C, Ar C-OH), , 113 (Ar C, Ar C-OH).
**IR (KBr, *ν*/cm$^{-1}$):** 3469 (OH, broad), 3060 (Ar C-H), 1619 (C=N);1340& 1550 (N-OSymmetric & Asymmetric Stretching in Nitro group).
LCMS Purity 99.63 %, RT 1.924, Mass 210

**General procedure for synthesis of2, 4-dichloro-7-nitroquinazoline [XXI][compound (4)]:**
7-nitroQuinazoline-2, 4-diol (3) (**5m.mol**), DIPEA (**10 m.mol**) and $POCl_3$ were mixed and refluxed at $140^OC$ for 4 hrs. The Solution was slowly added poured into crushed ice and stirred vigorously, This aqueous mixture was Extracted with $CH_2Cl_2$, The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuum, The crystalline solid was re dissolved in $CH_2Cl_2$ filtered over a pad of silica using $CH_2Cl_2$as Eluent. Removal of the organic solvent gave compound 3 as graysolid (52% Yield, **$R_f$**=0.3in 10% EtoAc in Pet Ether).
Meltingpoint:110-112$^0$c
**$^1H$ NMR (400 MHz, DMSO-$d_6$)(δ/ppm):** 8.39 (d, 1H), 8.30 (S, 1H), 8.2 (d, 1H).
**$^{13}C$ NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):** 124 (Ar C-H), 158.6 ( Ar C, Ar C-$NO_2$),123.5( Ar C-H), 125.6(1Ar C-H), 161.3(Ar ),150(Ar C), 158(Ar C, Ar C-Cl), , 163 (Ar C, Ar C-Cl).
**IR (KBr, *ν*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N); 720 (C-Cl Stretching),1340& 1550 (N-O Symmetric & Asymmetric Stretching in Nitro group).
LCMS Purity 99.63 %, RT 5.924, Mass 244($M^+$), 246 (M+2), 248(M+4), 9:6:1 it indicates Molecule contains 2 chlorine atoms.

**General procedure for synthesis of(2S, 6R)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylmorpholine[XXI][compound (6)]:**
To a Stirred solution of 2, 4-dichloro-7-nitroquinazolinecompound (4) (**40m.mol**) in $CH_2Cl_2$ (10 ml) was added a solution of Cis 2,6 di methyl morpholinecompound (5) (**40 m.mol**) and Tri Ethyl amine (**80 m.mol**) in $CH_2Cl_2$ at $0^OC$. The resulting mixture was stirred at RTover night and diluted with $CH_2Cl_2$The organic solution was washed with water and brine, dried over $Na_2SO_4$. The Solvent was removed the residue was purified by silica gel column chromatography with $CH_2Cl_2$to give compound 6 as a yellow solid (85% **Yield**, **$R_f$** =0.3 in $CH_2Cl_2$).
**$^1H$ NMR (400 MHz, $CDCl_3$)(δ/ppm):** 8.7 (d, J=2.4 Hz, 1H), 8.17 (dd, J=9.2, 2.5 Hz, 1H), 8.18 (d, J=9.2 Hz, 1H),1.3(6H,d, 2× $CH_3$),3.6(2H,O-C**H**), 4.5 (2H, d,N-$CH_2$),2.9(4H,N-$CH_2$).

**$^{13}$C NMR (100M.HZ, $CDCl_3$-$d_1$) (δ/ppm):** 124 (Ar C-H), 157.6 ( Ar C, Ar C-$NO_2$),123.5( Ar C-H), 125.6(1Ar C-H), 181.3(Ar ),123(1ArC), 150(Ar C), 159(Ar C, Ar C-Cl), 69 (N-$CH_2$), 73(2 O-CH), 20(Methyl carbon).
**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N); 730 (C-Cl Stretching),1340& 1550 (N-O Symmetric & Asymmetric Stretching in Nitro group).
LCMS Purity 96.63 %, RT 2.924, Mass 323($M^+$), 325 (M+2), 3:1 it indicates Molecule contains One chlorine atom.

**General procedure for synthesis ofmethyl 4-(4-((2S, 6R)-2, 6-dimethylmorpholino)-7-nitro Quinazolin-2-yl) benzoate [XXII][compound (8)]:**
A mixture of compound-6 (**0.6 m.mol**), compound-7 (**0.9m.mol**), $K_2CO_3$ (**3.2 m.mol**) degassed with argon for 10 min.and $Pd(PPh_3)_2Cl_2$ (**0.0033 m.mol**) in 5 ml 1,4 Di Oxane solvent at 100$^o$C in a sealed tube for 16 hrs. Reaction progress was monitored by TLC. Then reaction mixture was diluted with water and Extracted with EtoAc, dried over $Na_2SO_4$ filtered and evaporated to dryness. The crude product was purified by Column Chromatography affording product 8 (**Yield 60%).**
**$^1$H NMR (400 MHz, $CDCl_3$):** 8.9 (d, J=2.4 Hz, 1H), 8.75 (dd, J=9.2, 2.5 Hz, 1H), 8.18 (d, J=9.2 Hz, 1H),1.2(6H,2×$CH_3$),3.6(2H,O-C**H**),2.9(4H,N-$CH_2$),8(4H,Ar-H),3.9(3H,-$OCH_3$).
**$^{13}$C NMR (100M.HZ, $CDCl_3$-$d_1$) (δ/ppm):** 124 (Ar C-H), 157.6 ( Ar C, Ar C-$NO_2$),123.5( Ar C-H), 125.6(1Ar C-H), 181.3(Ar ),123(1ArC), 150(Ar C), 159(Ar C), 69 (N-$CH_2$), 73(2 O-CH), 20(Methyl carbon), 139(1ArC), 127(2Ar CH), 127.8(2Ar C), 130(1Ar C, 170(carbonyl carbon in ester), 53(methoxy carbon).
**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1730 (C=O Stretching), 1160(C-O-C Stretching), 1340 & 1550 (N-O Symmetric & Asymmetric Stretching in Nitro group).
Mass 423($M^+$)

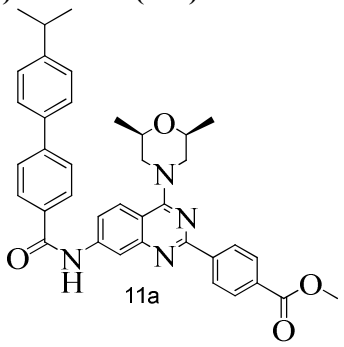
**General procedure for synthesis ofmethyl 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate[XXIII] (Compound 9 ) :**
Methyl 4-(4-((2S, 6R)-2, 6-di methyl morpholino)-7-nitro Quinazolin-2-yl) benzoate (compound 8) (**7 m.mol**), Iron (**45 m.mol**), acetic acid (**90 m.mol**) were suspended in aqueous Ethanol, and heated at reflux about 70-80$^O$C for 6 hrs. The reaction mixture was cooled to room temperature slowly and alkalinized by addition of Concentrated Ammonia (40 ml). Insoluble material was removed byfilteration through celite and the filtrate was evaporated under reduced pressure. The resulting solid was extracted with Ethyl acetate for column chromatography was performed using silica gel (200-300 mesh) eluting with Ethyl acetate and petroleum Ether (3:1 V/V) to give 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (Compound 9).

**$^1$H-NMR of methyl 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate(compound-9):**
**$^1$H NMR (400 MHz, DMSO-$d_6$):** 7.3 (S, 1H), 6.75 (d, J=9.2HZ, 1H), 7.6 (d, J=9.2 Hz, 1H),6.3(2H, bs),1.2(6H,d, 2×$CH_3$),3.6(2H,O-C**H,**m),2.9(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(3H,-$OCH_3$).
**$^{13}$C NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-$NH_2$),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 69 (N-$CH_2$), 73(2 O-CH), 20(Methyl carbon), 139(2ArCH), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon).
**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1730 (C=O Stretching), 1160(C-O-C Stretching), 3350&3410 (N-H Symmetric & Asymmetric Stretching in Amine group).
Mass 393($M^+$),394 (M+1).

**General procedure for synthesis ofmethyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-isopropylbiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11a), methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-methoxybiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11b), methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(6-(4-isopropylphenyl)nicotinamido)quinazolin-2-yl)benzoate (11c), methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-methylbiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11d), methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-nitrobiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11e), methyl 4-(7-(4'-chlorobiphenyl-4-ylcarboxamido)-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (11f), methyl 4-(7-(4'-bromobiphenyl-4-ylcarboxamido)-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (11g), methyl 4-(4-((2S,6R)-2,6-dimethylmorpholine)– 7-(thiophene-2-carboxamido)quinazolin – 2 – yl)benzoate (11h)[XXIV] :**

methyl 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (compound 9) (**7 m.mol, 1eq.**), Acid chlorides (10 a-h) (**1.2 eq.**), pyridine (**2 eq.**) were suspended in Dry DCM, and Stirred at 0-RT for 6 hrs. The reaction mixture was diluted with aqueous $Na_2CO_3$ Solution. The resulting Aqueous layer was extracted with Ethyl acetate and concentrated under reduced pressure to give Compounds (11 a-h).

**Methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-isopropylbiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11a) :**



11a

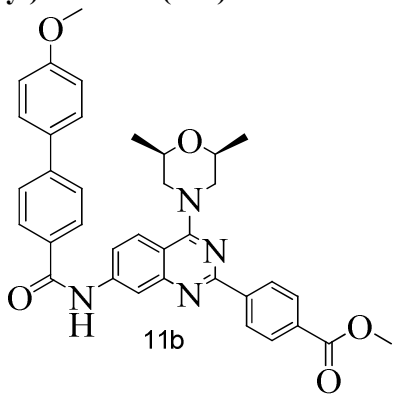
**$^1$H NMR (400 MHz, DMSO-$d_6$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.13(1H, bs),1.2(6H,d, 2×$CH_3$),3.6(2H,O-C**H,**m),2.9(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(3H,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.9(2H,d,J=8HZ), 7.4(4H,dd), 2.9(m,1H), 1.3(6H,d).

**$^{13}$C NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 69 (N-$CH_2$), 73(2 O-CH), 20(Methyl carbon), 139(2ArCH), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in ester),133(1Ar C), 130(2Ar CH), 128(2Ar CH), 144(1Ar C), 128(4Ar CH), 147(1Ar C),33(-CH), 23.5(2 $CH_3$).

**IR (KBr, *ν*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 1160(C-O-C Stretching), 3350 (N-H Stretching in Amide group).

LCMS Shows RT at 6.64, Mass 613($M^+$).

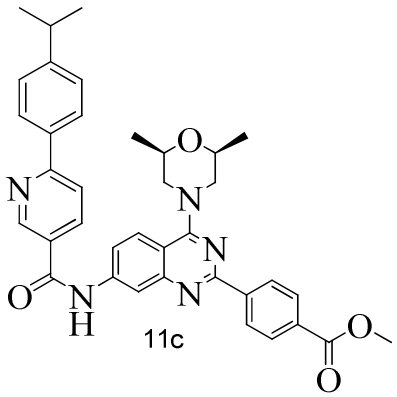
**methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-methoxybiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11b) :**




11b

**$^1$H NMR (400 MHz, DMSO-d$_6$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.10(1H, bs),1.2(6H,d, 2×$CH_3$),3.6(2H,O-C**H,**m),2.9(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(3H,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.9(2H,d,J=8HZ), 7.4(4H,dd).
**$^{13}$C NMR (100M.HZ, DMSO-d$_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 69 (N-$CH_2$), 73(2 O-CH), 20(Methyl carbon), 139(2ArCH), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide),133(1Ar C), 130(2Ar CH), 128(2Ar CH), 144(1Ar C), 128(4Ar CH), 147(1Ar C),33(-CH), 23.5(2 $CH_3$).
**IR (KBr, *ν*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 1160(C-O-C Stretching), 3350 (N-H Stretching in Amide group).
Mass Shows 603(+ve mode, $M^+$).

**Methyl4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(6-(4-isopropylphenyl)nicotinamido)quinazolin-2-yl)benzoate (11c) :**

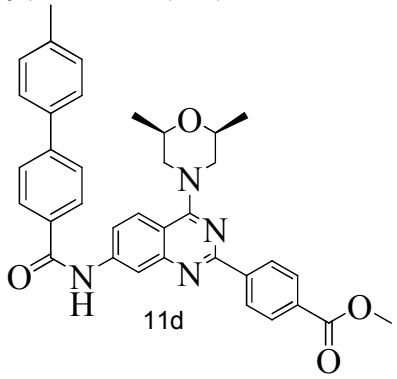



11c

**$^1$H NMR (400 MHz, DMSO-d$_6$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.15(1H, bs),1.2(6H,d, 2×$CH_3$),3.6(2H,O-C**H,**m),2.9(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(6H,S,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.09(2H,d,J=8HZ), 8.8(1H,S), 7.96(d,2H), 8.3(2H,d), 2.9(m,1H), 1.3(6H,d).

**$^{13}$C NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 68 (N-$CH_2$), 75(2 O-CH), 20(Methyl carbon), 139(2ArCH), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide ),128(1Ar C), 155(1Ar C), 138(1Ar CH), 124(1Ar CH), 155(1Ar C),132(1 Ar C), 128(2Ar CH), 115(2Ar CH),147(1Ar C),33(-CH), 23.5(2 $CH_3$).
**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 2900(C-H Stretching in methyl group), 1160(C-O-C Stretching), 3350 (N-H Stretching in Amide group).
Mass Shows 616(+ve mode, $M^+$).

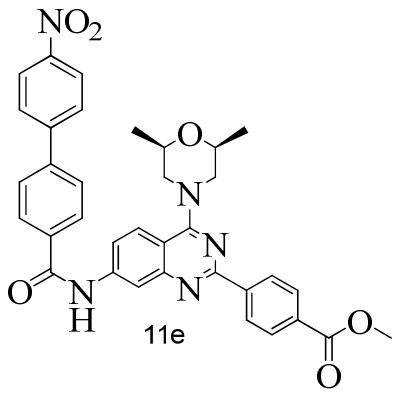
**methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-methylbiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11d):**



11d

**$^{1}$H NMR (400 MHz, DMSO-$d_6$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.13(1H, bs),1.2(6H,d, 2×$CH_3$),3.6(2H,O-C**H,**m),2.9(4H,d, N-$CH_2$),8(4H,Ar-H),3.8(3H,S,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.09(2H,d,J=8HZ), 7.96(2H,d), 8.3(2H,d),2.3(3H,s).
**$^{13}$C NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 68 (N-$CH_2$), 75(2 O-CH), 20(Methyl carbon), 139(1ArC), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide ),128(1Ar C), 155(1Ar C), 138(1Ar CH), 124(1Ar CH), 155(1Ar C),132(1 Ar C), 128(2Ar CH), 115(2Ar CH),147(1Ar C), 23.5(2 $CH_3$).
**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 2900(C-H Stretching in methyl group), 1160(C-O-C Stretching), 3350 (N-H Stretching in Amide group).
Mass Shows 587(+ve mode, $M^+$).

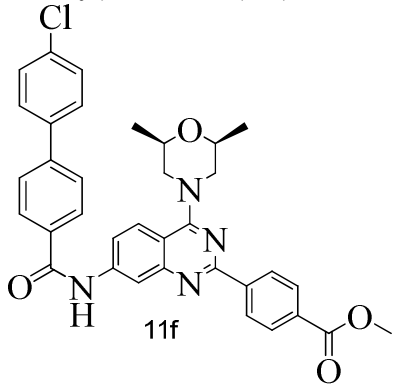
**methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-(4'-nitrobiphenyl-4-ylcarboxamido)quinazolin-2-yl)benzoate (11e) :**



11e

**$^1$H NMR (400 MHz, DMSO-$d_6$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.13(1H, bs),1.2(6H,d, 2×$CH_3$),3.6(2H,O-C**H,**m),2.9(4H,d, N-$CH_2$),8(4H,Ar-H),3.89(3H,S,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.89(2H,d,J=8HZ), 7.8(2H,d), 8.4(2H,d).
**$^{13}$C NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 68 (N-$CH_2$), 75(2 O-CH), 20(Methyl carbon), 139(1ArC), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide ),133(1Ar C), 135(2Ar CH), 128(2Ar CH), 144(1Ar C), 147(1Ar C),129(2Ar CH), 125(2Ar CH), 147(1Ar C).
**IR (KBr, *ν*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N); 1730 (C=O Stretching), 1340 & 1542 (N-O Stretching in –NO2 Symmetric &asymmetric), 1680(C=O Stretching in amide), 2900(C-H Stretching in methyl group), 1160(C-O-C Stretching), 3350 (N-H Stretching in Amide group).
Mass Shows 618(+ve mode, $M^+$).

**methyl 4-(7-(4'-chlorobiphenyl-4-ylcarboxamido)-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (11f) :**

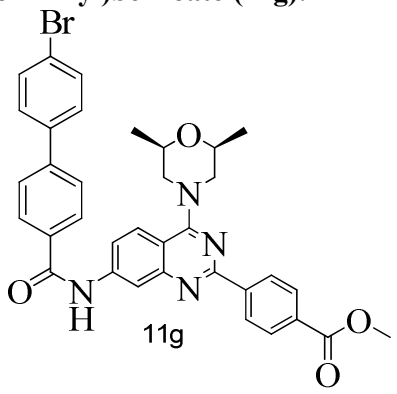


11f

**$^1$H NMR (400 MHz, $CDCl_3$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.13(1H, bs),1.2(6H,d, 2×$CH_3$),3.8(2H,O-C**H,**m),2.79(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(3H,S,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.89(2H,d,J=8HZ), 8.1(2H,d), 8.4(2H,d), 8.05(2H,d).
**$^{13}$C NMR (100M.HZ, $CDCl_3$-$d_1$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 68 (N-$CH_2$), 75(2 O-CH), 20(Methyl carbons), 139(1ArC), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide ),133(1Ar C), 130(2Ar CH), 128(2Ar CH), 144(1Ar C), 138(1Ar C),129(2 Ar CH), 125(2Ar CH), 133(1Ar C).

**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 743 (C-Cl Stretching), 2900(C-H Stretching in methyl group), 1160(C-O-C Stretching), 3350 (N-H Stretching in Amide group).
Mass Shows 607(+ve mode, $M^+$), 609(M+2, 33%).

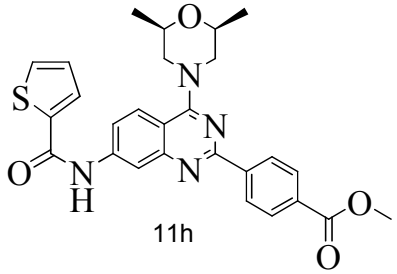
**methyl 4-(7-(4'-bromobiphenyl-4-ylcarboxamido)-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (11g):**



11g

**$^1$H NMR (400 MHz, $CDCl_3$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.13(1H, bs),1.2(6H,d, 2×$CH_3$),3.8(2H,O-C**H,**m),2.79(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(3H,S,-$OCH_3$), 8.1(2H,d, J=8HZ), 7.89(2H,d,J=8HZ), 7.6(2H,d), 7.77(2H,d).
**$^{13}$C NMR (100M.HZ, $CDCl_3$-$d_1$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 68 (N-$CH_2$), 75(2 O-CH), 20(Methyl carbons), 139(1ArC), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide ),133(1Ar C), 130(2Ar CH), 128(2Ar CH), 144(1Ar C), 138(1Ar C),129(2 Ar CH), 125(2Ar CH), 123(1Ar C).
**IR (KBr, *v*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 533 (C-Br Stretching), 2900(C-H Stretching in methyl group), 1160(C-O-C Stretching), 3350 (N-H Stretchingin Amide group).
Mass Shows 651(+ve mode, $M^+$, 100%), 653(M+2, 98%).

**methyl 4-(4-((2S,6R)-2,6-dimethylmorpholine)– 7-(thiophene-2-carboxamido)Quinazolin – 2 – yl)benzoate (11h) :**



11h

**$^1$H NMR (400 MHz, DMSO-$d_6$):** 8.4 (S, 1H), 8.1 (d, J=9.2HZ, 1H), 7.9 (d, J=9.2 Hz, 1H),9.13(1H, bs), 1.2(6H,d, 2×$CH_3$),3.8(2H,O-C**H,**m),2.79(4H,d, N-$CH_2$),8(4H,Ar-H),3.9(3H,S,-$OCH_3$), 8.14(1H,d, J=8HZ), 7.29(1H,d,J=8HZ), 7.96(1H,d).

**$^{13}$C NMR (100M.HZ, DMSO-$d_6$) (δ/ppm):**110 (Ar C-H), 151.6 ( Ar C, Ar C-NH),118.5( 1Ar C-H), 124.6(1Ar C-H), 171.3(1ArC ),115(1ArC), 151(1Ar C), 160(1Ar C), 68 (N-$CH_2$), 75(2 O-CH), 20(Methyl carbons), 139(1ArC), 127(4Ar CH), 130(1Ar C), 170(carbonyl carbon in ester), 53(methoxy carbon), 165(carbonyl carbon in amide ),139(1Ar C), 130(1Ar CH), 128(1Ar CH).

**IR (KBr, *ν*/cm$^{-1}$):** 3030 (Ar C-H), 1629 (C=N);1680(C=O Stretching in amide), 1730 (C=O Stretching), 580 (C-S Stretching), 2900(C-H Stretching in methyl group), 1160(C-O-C Stretching), 3350 (N-H Stretchingin Amide group).

Mass Shows 503(+ve mode, $M^+$, 100%), 504(M+1, 30%).

**Biological Activity**

The samples of synthesized Novel Quinazoline derivatives(8a-8k) for antimicrobial activity were prepared at concentration 40μg/ml in DMSO solvent. In case of antibacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked 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 Aspergillusniger (A. niger) and Candida albicans (C. albicans). The results were compared with stand drugs Sparfloxacin, Benzyl penicillin and Fluconazole.

The Quinazoline derivates11h, 11e and11c showed more activity than other substituent's

The order of activity was11h>11e>11c>11f>11g>11d>11a>11b

**Table 1:** Anti-microbial Screening data of Novel Quinazoline derivatives( 11a-11h ) :

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

**Results and Discussions :**

**Synthesis:**

The present scaffold **11(a-h)** is a part of the synthesis of new chemical entities in the form of antimicrobial agents. The title compounds **11(a-h)** were synthesized in six steps. The first step involves coupling of 2-amino-4-nitrobenzoic acid (1) with urea (2) to give 7-nitroquinazoline-2,4-diole(Compound3), Compound(3) on treatment with $POCl_3$ at reflux condition to get 2,4-dichloro-7-nitroquinazoline (4), which is reacted with (2R,6S)-2,6-dimethylmorpholine(5) to get compound 6 i.e.,(2S,6R)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylmorpholine**.** compound (6) on reaction with 4-(methoxycarbonyl)phenylboronic acid (7) under Suzuki reaction conditions furnished methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)benzoate (compound 8), Compound(8) reacts with Iron powder in Acetic acid to give methyl 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)benzoate (compound 9). Compound(9) reacts with different Bi phenyl acid chlorides and Heterocyclic acid chlorides (10 a-h ) in DCM to get Target Compounds 11(a-h).

The scheme of synthetic procedure for preparation of title compounds is given in **Scheme I.**

**IR spectra:** The characteristic absorption peaks were observed for all relevant groups. The absorption peaks around 1600 $cm^{-1}$ indicates the formation of C=N ring atoms of quinazoline, amide N-H stretching vibrations were observed in the region of 3450-3140 $cm^{-1}$. Amide C=O stretching vibrations were observed near 1690-1640 $cm^{-1}$ and all other relevant groups absorption were observed for all the synthesized compounds.

**NMR spectra:** Aromatic protons were observed 6.68- 8.13 δ ppm. Amide N-H proton were observed at 9.15 δ ppm, for all the synthesized compounds.

Readily available starting materials and simple synthesizing procedures make this method is very attractive and convenient for the synthesis of quinazoline derivatives .Formation of products was confirmed by recording their $^{1}H$ NMR, $^{13}C$,FT-IR,mass spectra. The Elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values with in ±0.4% .

**Anti microbial screening:**

The results of anti microbial studies of newly synthesized compounds reveal that the compounds possess significant antibacterial and anti fungal activities. The results of these studies are given in (Table 1).From Anti bacterial screening results, it has been observed that compounds 11h and 11e possess good activity.

**Conclusion**

The newly synthesized Quinazoline derivatives( 11 a-11h ) exhibited moderate to promising antimicrobial activity against standard strains. This class of compounds certainly holds great promise to discover novel classes of anti-microbial agents. All these reactions are very easy to carry out giving high yield. These results make interesting lead molecule for further synthetic and Biological evaluation.

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