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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL TRI SUBSTITUTED QUINAZOLINE-ISATIN MANNICH BASES BEARING MORPHOLINE AND BIPHENYL MOIETIES

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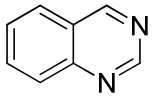
ABSTRACT
Quinazolines are a pharmacologically very attractive class of compounds and have shown activity in various assays. Several successfully launched drugs are based on this scaffold. As a consequence, a more intensive exploitation in drug discovery by various synthesis of quinazoline libraries has been initiated. To synthesize a Variety of Quinazoline derivatives 15(a-h) and their Biological activity was determined. Using 2-amino-4-nitrobenzoic acid and urea,new compounds were synthesized. Antimicrobial activity was done by Disc diffusion method. All the prepared compounds have been characterized by Elemental analysis, ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy. Therefore, The nature of groups is very important for antimicrobial activity in Disk Diffusion model.

Keywords: Heterocycles, Quinazoline derivatives, antibacterial activity, antifungal, synthesis, Isatin Mannich bases, Quinazoline Drugs

Introduction
The chemistry of quinazoline compounds has more than centuries old history; however the intense search for biologically active substances in this series began only in the last few decades. Evolution of quinazolines began only with discovery of febrifugine, a quinazolinone alkaloid, possessing anti-malarial potential from the Chinese plant aseru (Dichroa febrifuga Lour), which served as an impetus for initiation of the research on quinazolines. **Quinazoline (1)** is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. It is also called benzopyrimidine. It has the molecular formula $C_8H_6N_2$ and molecular mass 130.15 g/mol. It is isomeric with quinoxaline, phthalazine and cinnoline Quinazoline is the main six-membered heterocyclic ring system reported for their biological activities, compounds with multiple pharmacophores, which bring together knowledge of a target with understanding of the molecule types that might interact with the target family.

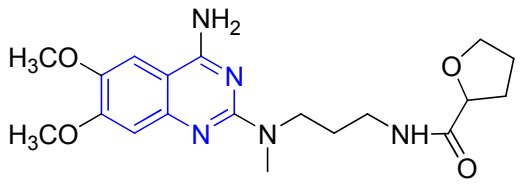


Quinazoline(1)

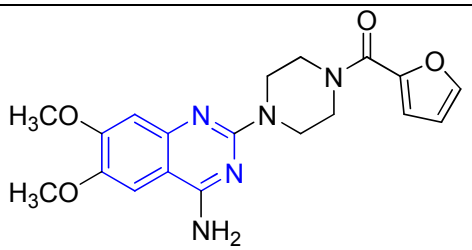
In the family of heterocyclic compounds, nitrogen-containing heterocycles are an important class of compounds in medicinal chemistry. There has been considerable interest in the development of preparative methods for the production of Quinazolines [**1**]. This is because Quinazolines and their ring-fused derivatives display a broad spectrum of biological activities [**2**] like antitubercular, analgesic, anti-inflammatory, and anti-bacterial. Quinazoline is the main six-membered heterocyclic ring system reported for their biological activities, compounds with multiple pharmacophores, which bring together knowledge of a target with understanding of the molecule types that might interact with the target family.

From a theoretical perspective Quinazolines are undoubtedly of intrest for study as they are multipurpose reactive centers . Among them are found highly effective agricultural compounds such as fungicides, bactericides, defoliants, plant growth stimulants[**3-5**]. According to recent data, Quinazoline nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity. In chemotherapy as antitumor drugs[**6-7**]. Varied biological activities have been attributed to Quinazoline compounds including analgesic, anti-inflammatory, antipyretic [**8-10**], antimicrobial [**11**], anticonvulsant [**12**], fungicidal[**13**],Antidepressant and other central nervous system affecting activities[**14**].

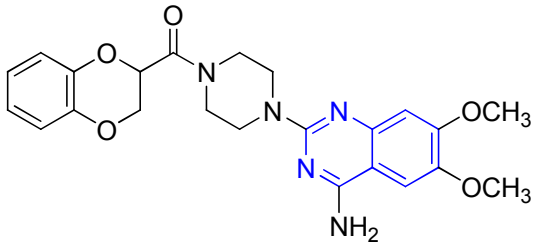
The quinazoline skeleton is present in a variety of biologically active compounds, among these are several marketed drugs such as Alfuzosine Hydrochloride(1), Prazosin hydrochloride(2), Doxazosine mesylate(3), Terazosine hydrochloride(4) (adrenergic blocker/Prostate disorders).



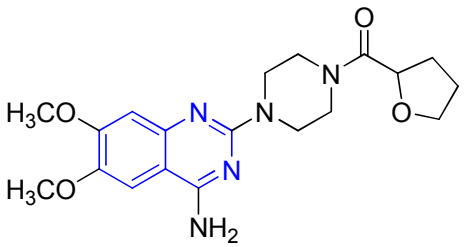
Alfuzosine Hydrochloride (1)



Prazosin hydrochloride(2)



Doxazosine mesylate (3)

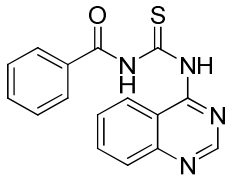
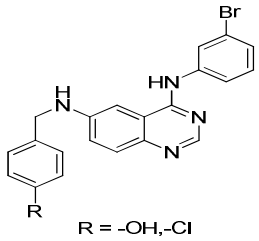
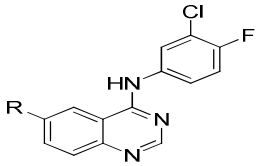
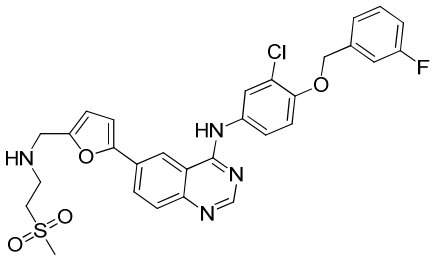
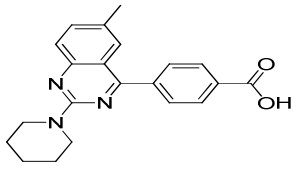
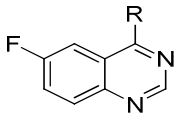


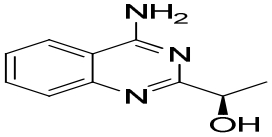
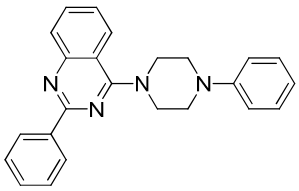
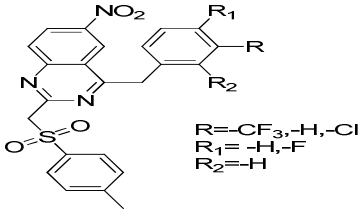
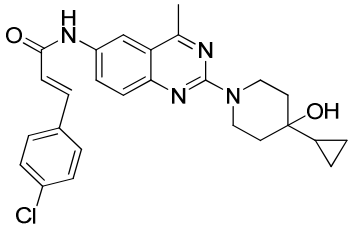
Terazosine hydrochloride(4)

The Quinazoline scaffold is present in many classes of biologically active compounds. Quinazolines are classes of fused Heterocycles that are of considerable interest because of the

diverse range of their biological properties, for example, anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities [**15**] .

Table-1 Biologically potent Quinazoline derivatives

S.NO	Compound	Activity	Reference
01		antitumor	J. He et al [**16**]
02	 R = -OH,-Cl	antitumor	H.-Q. Li et al [**17**]
03	 R = --NH_2	EGFR inhibitors	C. Fernandes et al [**18**]
04		ErbB-1/ErbB-2 tyrosine kinase inhibitor	K. G. Petrov et al [**19**]
05		Antibacterial	P. M. S. Bedi et al [**20**]
06	 R = -S-CH_2-CH=CH_2, -S-CH_2-CH_3	Antifungal	G.-F. Xu et al [**21**]

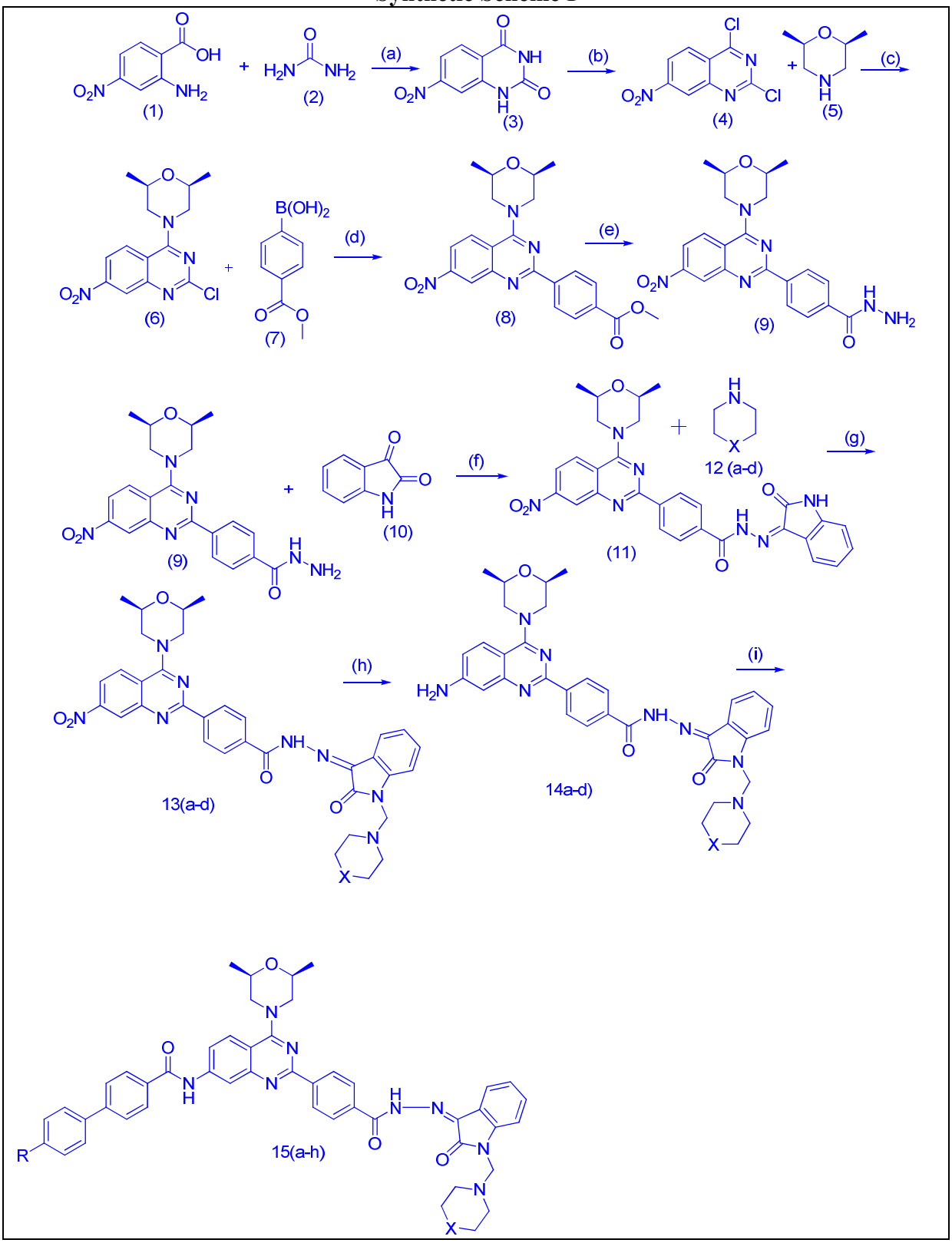
07		Anti mutagenic	D. Kohli et al [**22**]
08		Analgesic	A. M. Alafeefy et al [**23**]
09		Anti plasmodial	Y. Kabri et al [**24**]
10		Anti obesity	H. R. Kanna Reddy et al[**25**]

Materials and Methods

Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. 1H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer using TMS as internal standard. The mass spectra were obtained on a JEOL 5x102/DA-6000 mass spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. Elemental analyses of the newly synthesized compounds were carried out on Perkin Elmer model 2400 C H N analyzer. All the compounds gave satisfactory elemental analysis within ±0.4% of theoretical values.

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

Synthetic Scheme I



Reagents and conditions : (a) *150^0c* ***(b)*** *$POCl_3$, TEA* **(c)**Ethanol,0^0C-RT
(d)CS_2CO_3 **,**1,4 Dioxane,$Pd(PPh_3)_4$ **(e)**Hydrazine Hydrate,Ethanol
(f) Isatin,DMF **(g)**HCHO,DMF,Heating **(h)**Fe powder,NH_4Cl,ethanol,Reflux **(i)** Substituted Bi Phenyl acid chlorides,TEA, DCM,0^0c-RT

Compound	**15(a)**	**15(b)**	**15(c)**	**15(d)**	**15(e)**	**15(f)**	**15(g)**	**15(h)**
R	OMe	OMe	OMe	OMe	Isopropyl	Isopropyl	Isopropyl	Isopropyl
X	$-CH_2$	-O	-S	$N-CH_3$	$-CH_2$	-O	-S	$N-CH_3$

The title compounds 15(a-h) were synthesised in nine sequential steps using different reagents and reaction conditions the 15(a-h) were obtained in moderate yields. The structures of 15(a-h) were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

EXPERIMENTAL SECTION:

All materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame dried glassware, which was then cooled under nitrogen or argon gas. Tetrahydrofuran (THF), toluene was distilled over Na/Ph_2CO under nitrogen or argon atmosphere. Dichloromethane (CH_2Cl_2), tertiary butyl methyl ether (TBME), benzene, pentane, acetonitrile, dimethylsulfoxide, triethylamine (TEA) and diethyl ether (Et_2O) were dried over Calcium Hydride (**CaH_2**) and distilled prior to use. 4 Å molecular sieves were flame dried and then cooled under high vacuum prior to use. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates (AL SIL G/UV, aluminum back) and analyzed with 254 nm UV light and / or anisaldehyde – sulfuric acid or potassium permanganate or PMA treatment. Silica gel for column chromatography was purchased from acme's (Silica Gel 60-120, 100-200 mesh). All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Gemini 200, Avance 300, Inova 400, Inova 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ as an internal reference (^{1}H: δ 7.26 ppm, ^{13}C: δ 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet).

Synthesis of 7-nitroquinazoline-2,4(1H,3H)-dione(compound 3):

The mixture of 2-amino-4-nitrobenzoic acid(**0.1 m.mol**) and urea (**0.5 m.mol**) was stirred at 150^0C for 10 h. The reaction mixture was cooled to 100^0C 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, compound 3 was obtained as yellow solid (**Yield** 80%); mp >300^0C;

^{1}H NMR (DMSO-d_6) δ ppm 8.24 (d, J = 9.0 Hz, 1H, ArH), 8.16 (dd, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H, ArH), 8.95 (d, J = 2.7 Hz, 1H, ArH).

Synthesis of 2,4-dichloro-7-nitroquinazoline(compound 4):

Quinazoline-2,4-diol 2 (**0.3 m.mol**) was a*dded* to a stirred solution of $POCl_3$ (**1 m.mol**) at room temperature, and then DIPEA (**1.5 m. mol**) was added dropwise to the mixture. The reaction mixture was heated to 90^0C for 6 h. The mixture was concentrated under reduced pressure. The residue was poured into ice water ,stirred at room temperature for 1 h and separated by filteration to give title compound 3 as a Yellow colour solid.

Yield 95%

Meltingpoint:110-112^{0}c

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 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).

Synthesis of (2S,6R)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylmorpholine (compound 6):

To a cooled (0^0C.) suspension of 2,4-dichloro-7-nitroquinazoline(4) (0.1 m.mol) in ethanol (5 ml), which was stirred under an inert atmosphere, was added triethylamine (0.5 m.mol) and then Cis 2,6,di methyl morpholine (0.15 m.mol). The mixture was maintained at this temperature for 3 hours where upon it was concentrated in vacum, diluted with NaOH (10 ml, 1M) and extracted with EtOAc (3x 20 ml). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated in vacuo to give a colorless solid. The crude residue was re-crystallised using EtOAc/Hexanes to give the title compound (90% **Yield**) as a colourless solid which required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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× C**H**$_3$),3.6(2H,O-C**H**),2.9(4H,N-C**H**$_2$)

Synthesis of methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)benzoate(compound 8):

To a solution of the compound(6) (**0.1 m.mol**) in anhydrous 1,4-dioxane (**10 volumes**) in a sealed tube was introduced 4-(methoxycarbonyl) phenylboronic acid (7) (**0.5 m.mol**) and finely grind CS_2CO_3 (**2.0 m.mol**). The solution was degassed (N_2 bubbling) for 5 min, $Pd(PPh_3)_4$ (5 mol %) introduced and degassing continued for a further 5 min. The tube was sealed under nitrogen and heated with rapid stirring at 100^0C for 5 h. After cooling, the reaction mixture was filtered in vacuo through a celite pad and the precipitated material washed with 1,4-dioxane. The combined filtrates were evaporated and purified by flash column chromatography (neat hexane to 1:1 hexane/EtOAc gradient containing 2.5percent by volume Et_3N) to furnish the compound 8.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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×C**H**$_3$),3.6(2H,O-C**H**),2.9(4H,N-C**H**$_2$),8(4H,Ar-H), 3.9(S,3H,-O-C**H**$_3$)

Synthesis of 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl) benzohydrazide (compound 9) :

A mixture of compound (8) (**0.1 m.mol**) and of 99% hydrazine hydrate (**0.5 m.mol**) was refluxed for 4 h. After cooling, a precipitate formed and was filtered off and recrystallized from a ethanol to get off white solid with 80% yield,

Melting point: 95-97^{0}c.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S),2(2H,broad S)

Synthesis of 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)-N'-(2-oxoindolin-3-ylidene)benzohydrazide(compound 11):

A mixture of compound (9) (**0.1 m.mol**) and Isatin(10) (**0.12 m.mol**) were dissolved in toluene (10 ml) and stirred under reflux for 16 h. The solution was cooled to RT and toluene was removed under reduced pressure. After recrystallization from hexanes the product was obtained as a white solid

Yield : 77%

Melting point: 134-136^{0}c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H)

Synthesis of 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)-N'-(2-oxo-1-(piperidin/morpholine/thio morpholine/N-Methyl piperazine)-1-ylmethyl)indolin-3-ylidene)benzohydrazide(compound 13 a-d):

A methanolic solution of Compound 11 (**0.1m.mol**) was charged into a three neck flask equipped with a stirred and dropping funnel. The solution was stirred to dissolve it completely. To this methanolic solution, formaldehyde (7 ml, 37%) was added drop wise during 15-20 minutes. The resulting mixture was stirred during half an hour to complete reaction of formaldehyde and To this reaction mixture, the methanolic solution of compound 12(a-d) (**0.12 m.mol**) was added drop wise with stirring in about half an hour at 30^0 C temperature and refluxed for two hour at 65-70^0C. it was allowed to cool and poured in ice water. The solid obtained was filtered off washed thoroughly with hot water and dried.

Compound 13a:

Yield : 77%

Melting point : 134-136^0c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),1.6(6H,m)

Compound 13b:

Yield : 75%

Melting point:104-106^0c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),3.6(4H,m)

Compound 13c:

Yield : 78%

Melting point : 94-96^0c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.8(4H,N-CH_2,m),2.5(4H,S-CH_2,m)

Compound 13d:

Yield : 80%,

Melting point: 185-187^0c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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), 8(1H, -NH,broad S), 7.3-7.9 (4H, Ar-H), 4 (2H,S), 2.4 (4H, N-C$\mathbf{H_2}$, m), 2.4 (4H, H_3C-N-C$\mathbf{H_2}$, m), 2.3 (3H, S, N-C$\mathbf{H_3}$)

Synthesis of 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)-N'-(2-oxo-1-(piperidin/Morpholin/Thio morpholine/N-methyl piperazine-1-ylmethyl)indolin-3-ylidene)benzohydrazide 14 a-d):

A suspension of 13(a-d)(**0.1 m.mol**) in ethanol (6 ml), THF (2 ml), and water (1 ml) was treated with ammonium chloride(**3 m.mol**)and iron powder(20 m.mol). After being stirred at 80^0C for 2 h, the mixture was diluted with ethanol (4 ml) and filtered through a pad of diatomaceous earth (Celite) while still hot. The pad was washed with ethanol, and the filtrate was concentrated. The concentrate was diluted with water and extracted with ethyl acetate three times. The combined extracts were washed with brine,dried(Na_2SO_4),filtered,and concentrated to provide the title compounds (**14 a-d**).

Compound 14a:

Yield : 90%,

Melting point : 144-146^0c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),1.6(6H,m) ,6.3(2H.br singlet,-NH_2)

Compound 14b:

Yield : 88%

Melting point:130-132^{0}c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),3.6(4H,m) , 6.3(2H.br singlet,-NH_2)

Compound 14c:

Yield : 90%

Melting point: 124-126^{0}c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.8(4H,N-CH_2,m),2.5(4H,S-CH_2,m), 6.2(2H.br singlet,-NH_2)

Compound 14d:

Yield : 90%

Melting point: 85-87^{0}c

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.4(4H,N-C**H**$_2$,m),2.4(4H,H_3C-N-C**H**$_2$,m),2.3(3H,S,N-CH_3), 6.3(2H.br singlet,-NH_2)

Synthesis of N-(4-((2S,6R)-2,6-dimethylmorpholino)-2-(4-((Z)-2-(2-oxo-1-(piperidin/Morpholin/Thio morpholine/N-Methyl piperazine-1-ylmethyl)indolin-3-ylidene)hydrazinecarbonyl)phenyl)quinazolin-7-yl)-4'-methoxybiphenyl-4-carboxamide(15 a-h):

The compound Substituted bi phenyl acid chlorides(**0.12 m.mol**) was added drop wise to a mixture of 14(a–d)(**0.1 m.mol**) and tri ethyl amine (**1 m.mol**) in dichloromethane (2 ml) at 0^{0}C temperature with stirring. Then the reaction mixture was refluxed for 4–6 h. After cooling to room temperature, the mixture was slowly poured to ice water (50 ml). The solution was extracted with dichloromethane (3×30 ml) and the organic phase was dried over with sodium sulfate anhydrous. After removal of the dichloromethane, the solid residue was purified by recrystallization with petroleum ether–ethyl acetate to give compounds **15 a–h** as colourless liquids.

Compound 15a:

Yield : 80%

IR(KBr, cm-^{1}): 1050(C-O-C stret),2900(SP^3 C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),1.6(6H,m),9.15(1H,S,-NH), 7.8(2H,d,J=7HZ),8(2H,d,J=7HZ),7(2H,d,J=8.3HZ),7.6(2H,d,J=8.3HZ),3.8(3H,S)

^{13}CNMR(100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, ,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,55, 55,75,25,23,55(aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)

The EIMS m/z values and corresponding percentage were as follows: 830 (**M+H** 100%) and Anal. calculated for Chemical Formula $C_{49}H_{48}N_8O_5$ (in %) C, 71.00; H, 5.84; N, 13.52; Found: C, 71.00; H, 5.82; N, 13.50

Compound 15b:

Yield : 82%,

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),3.6(4H,m) , 9.15(1H,S,-NH), 7.8 (2H, d, J=7HZ), 8(2H, d, J=7HZ), 7 (2H, d, J=8.3HZ), 7.6 (2H,d, J=8.3HZ), 3.8 (-O-C**H**$_3$,3H, S)

^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, ,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,75 (aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)

The EIMS m/z values and corresponding percentage were as follows: 831 (M+1 100%) and Anal. calculated for Chemical Formula $C_{48}H_{46}N_8O_6$ C, 69.38; H, 5.58; N, 13.49 Found: C, 69.36; H, 5.54; N, 13.46

Compound 15c:

Yield : 79%

IR(KBr,cm-^{1}): 1050(C-O-C stret),2900(SP^3 C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending) , 1125 (C-S str.)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.8(4H,N-CH_2,m),2.5(4H,S-CH_2,m), 9.15(1H,S,-NH), 7.8(2H,d,J=7HZ),8(2H,d,J=7HZ),7(2H,d,J=8.3HZ),7.6 (2H, d, J=8.3HZ), 3.8 (-O-C**H**$_3$,3H, S)

^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, ,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,75 (aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)

The EIMS m/z values and corresponding percentage were as follows: 848 (M+1 100%) and Anal. calculated for Chemical Formula $C_{48}H_{46}N_8O_5S$ C, 68.07; H, 5.47; N, 13.23 Found: C, 68.05; H, 5.45; N, 13.21

Compound 15d:

Yield : 75%

IR(KBr,cm-^{1}): 1050(C-O-C stret), 2900(SP^3 C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending)

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.4(4H,N-C**H**$_2$,m), 2.4(4H,H3C-N-C**H**$_2$,m),2.3(3H,S,N-C**H**$_3$), 9.15(1H,S,-NH), 7.8 (2H, d, J=7HZ), 8 (2H, d, J=7HZ), 7 (2H, d, J=8.3HZ),7.6 (2H, d, J=8.3HZ), 3.8 (3H, S)

^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, 123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,75, 56,57,45,55(aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)

The EIMS m/z values and corresponding percentage were as follows: 845 (M+1 100%) and Anal. calculated for Chemical Formula $C_{49}H_{49}N_9O_5$ C, 69.73; H, 5.85; N, 14.94; Found: C, 69.70; H, 5.83; N, 14.92

Compound 15e:
Yield : 78%
IR(KBr,cm-^{1}): 1050(C-O-C stret),2900(SP^{3} C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending)
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),1.6(6H,m),9.15(1H,S,-NH), 7.8(2H,d,J=7HZ),8(2H,d,J=7HZ),7(2H,d,J=8.3HZ),7.6(2H,d,J=8.3HZ), 2.87(1H,m,J=7HZ),1.2(6H,d,j=7HZ)
^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, ,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,33, 23,55,75,25,23,55(aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)
The EIMS m/z values and corresponding percentage were as follows: 842 (M+1 100%) and Anal. calculated for Chemical Formula $C_{51}H_{52}N_8O_4$: C, 72.83; H, 6.23; N, 13.32 Found: C, 72.81; H, 6.20; N, 13.30
Compound 15f:
Yield :82%
IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^{3} C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending)
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.5(4H,N-CH_2,m),3.6(4H,m) , 9.15(1H,S,-NH), 7.8(2H,d,J=7HZ),8(2H,d,J=7HZ),7(2H,d,J=8.3HZ),7.6(2H,d,J=8.3HZ),2.87(1H,m,J=7HZ),1.2(6H,d,j=7HZ), 1.2(6H,d,j=7HZ)
^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, ,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,54, 65,33,75,22(aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon).
The EIMS m/z values and corresponding percentage were as follows: 844 (M+1 100%) and Anal. calculated for Chemical Formula $C_{50}H_{50}N_8O_5$ C, 71.24; H, 5.98; N, 13.29; Found: C, 71.22; H, 5.96; N, 13.26
Compound 15g:
Yield : 79%
IR(KBr,cm-^{1}): 1050(C-O-C stret),2900(SP^{3} C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending) , 1125 (C-S str.)
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.8(4H,N-CH2,m),2.5(4H,S-CH_2,m), 9.15(1H,S,-NH), 7.8 (2H , d, J=7HZ), 8 (2H, d, J=7HZ), 7 (2H, d, J=8.3HZ),7.6 (2H, d, J=8.3HZ), 2.87 (1H, m, J=7HZ),1.2 (6H, d, j=7HZ), 1.2 (6H, d, j=7HZ)
^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135, ,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,75, 58,30.33,23(aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)
The EIMS m/z values and corresponding percentage were as follows: 860 (M+1 100%) and Anal. calculated for Chemical Formula $C_{50}H_{50}N_8O_4S$ C, 69.91; H, 5.87; N, 13.04; Found: C, 69.90; H, 5.85; N, 13.02

Compound 15h:
Yield : 75%

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1680(C=O Stret in amide),1550(C=C Stret),3300(-NH Stret),1240(C-N Stretch),1600(-NH bending)
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 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),8(1H,-NH,broad S), 7.3-7.9(4H,Ar-H), 4(2H,S),2.4(4H,N-C**H**2,m),
2.4(4H, H_3C-N-C$\mathbf{H_2}$, m), 2.3 (3H, S, N-CH_3) , 9.15 (1H, S, -NH), 7.8 (2H, d, J=7HZ), 8 (2H, d, J=7HZ),7 (2H, d, J=8.3HZ),7.6 (2H, d, J=8.3HZ), 2.87 (1H, m, J=7HZ),1.2 (6H, d, j=7HZ), 1.2 (6H, d, j=7HZ)
^{13}CNMR (100 MHz, $CDCl_3$): δ ppm 124,118,150,110,150,115,170,125,130,135,,123,129,124,131,115,145,,130,128,133,144,133,130,115,160(Aromaticcarbons),69,19,72,75,52,57,4533,23(aliphatic carbons),165,168,175(carbonyl carbons),162(N=C in Isatin carbon)
The EIMS m/z values and corresponding percentage were as follows: 857 (M+1 100%) and Anal. calculated for Chemical Formula $C_{51}H_{53}N_9O_4$: C, 71.56; H, 6.24; N, 14.73 Found: C, 71.54; H, 6.22; N, 14.70

ANTI-MICROBIAL ACTIVITY

Media and chemicals

Nutrient Broth, Nutrient agar and 5 mm diameter antibiotic assay were obtained from Hi-Media Laboratories Limited, India. Barium chloride dehydrate GR, concentrated sulphuric acid GR, Dimethyl sulphoxideGR, Sodium chloride AR and Potassiumdichromate were obtained from Ranbaxy Laboratories Ltd, Chemical Division, India. The standard bacterial and fungal strains were procured from National Centre from Cell Science (NCCS), Pune, India. The bacterial included two Gram positive bacterial isolates Staphylococcus aureus NCCS 2079 and Bacillus cereus NCCS 2106 and two Gram negative bacterial isolates Escherichia coli NCCS2065 and Pseudomonas aeruginosa NCCS 2200. The fungicidal organisms included were Aspergillus nigeri NCCS 1196 (AN) and Candida albicans NCCS 3471(CA). The bacteria were grown and maintained on nutrient agar (Hi-Media, Mumbai) and were subculture when needed.

Glass wares and Apparatus

Glass petridish, Glass tubes, Beakers, Erlenmeyer flasks, Bacterial loop and measuring cylinder. All the glass wares were of Borosilicate grade. Digital electronics balance (Shankar Scientific supplies, India), Yorco Horizontal Laminar air flow bench (Yorco sales Pvt. Ltd, New Delhi, India), Ausco incubator, Zone reader (Cintex industrial Corporation, India), hot air oven, autoclave and UV/Visible spectrophotometer (Shimadzu corporation, Japan).

Antibacterial activity

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacterial screened were Staphylococcus aureus NCCS 2079 (SA) and Bacillus cereus NCCS 2106 (BC). The gram negative bacterial screened were Escherichia coli NCCS 2065 (EC) and Pseudomonas aeruginosa NCCS 2200 (PA). The synthesized compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The amoxicillin 10 µg/disc and Streptomycin 30 µg/disc were used as a standard (Himedia laboratories limited, Mumbai).

Disc Diffusion Method

A suspension of Staphylococcus aureus (SA) was added to sterile nutrient agar at 45ºC. The mixture was transferred to sterile petridishes to give a depth of 3 to 4 mm and allowed to solidify. Precautions were observed to reduce uniform layer of medium on the plate. Sterile discs 5mm in diameter (made from Whatman Filter paper) were immersed in the solutions of

synthesized compounds (250µg/ml) and maintain an untreated control sample for comparison.

Leave the plates to stand for 1hour at room temperature as a period of preincubation diffusion to minimize the effects of variations in different time. Then the plates were incubated at 37ºC for 24 hours and observed for antibacterial activity. The diameter of the zone of inhibition was measured for each plate in which the zone of inhibition was observed. The average zone of inhibition was calculated and compared with that of standard. A similar procedure was adopted for studying the antibacterial activity against the other organisms. Antifungal activity The antifungal activity3 of synthesized compounds were studied by disc diffusion method against the organisms of Aspergillus nigeri NCCS 1196 (AN) and Candida albicans NCCS 3471(CA).

Compounds were treated at the concentrations of 250 µg/ml using DMSO as a solvent. The standard used was Ketaconazole 50 µg/ml and Griseofulvin 50 µg/ml against both the organisms. Disc Diffusion Method A suspension of Aspergills nigeri NCCS 1196 (AN) was added to a sterile sabouraud dextrose agar at 45^0C. The mixture was transferred to sterile petridishes and allowed to solidify. Sterile discs 5 mm in diameter (made from Whatmann Filter paper) immersed in the solutions of synthesized comopounds and control were placed on the surface of agar medium with forceps and pressed gently to ensure even contact. Leave the plates to stand for 1 hour at room temperature as a period of preincubation diffusion to minimize the effects of variation at 37^0C for 13 hours and observed for antibacterial activity. The diameters of the zone of inhibition were measured for the plates in which the zone of inhibition was observed. The average zone of inhibition was calculated with that of standard.

The order of activity was **15g>15f>15c>15b>15h>15d>15e>15a.**

The results were described in the **TABLE 2**

Table-2 Antibacterial activity of synthesized compounds (15a-15h):

S.NO	Compound	Zone of inhibition (mm)					
		Antibacterial Activity				Antifungal Activity	
		Gram+ve		Gram-ve			
		SA	BC	EC	PA	AN	CA
1	15a	6	8	9	10	12	10
2	15b	12	14	10	12	13	11
3	15c	13	14	11	12	16	13
4	15d	9	10	8	9	12	10
5	15e	7	9	5	7	11	11
6	15f	14	15	12	13	15	15
7	15g	15	16	14	15	18	16
8	15h	10	11	9	10	14	12
Amoxicillin		22	25	21	23	-	-
Streptomycin		27	29	25	27	-	-
Ketaconazole		-	-	-	-	22	25
Griseofulvin		-	-	-	-	24	27

RESULTS AND DISCUSSIONS :

In our study, New series of compounds 15c, 15b and 15h showed moderate to significant antibacterial and antifungal activity when compared with standard drugs. However it is less than standard drugs like Ampicillin and Griseofulvin. but compounds 15g and 15f showed significant antibacterial activity .

7-Nitroquinazoline-2,4(1H,3H)-dione (2) was synthesised according to the reported procedure [**26].** The reaction of 2-amino-4-nitrobenzoic acid and urea was stirred at 150 °C to afford the corresponding 7-nitroquinazoline-2,4(1H,3H)-dione (2) which was reacted with $POCl_3$ as per the reported procedure [**27]** to afford 2,4-dichloro-7-nitroquinazoline (4) Which was reacted with Cis 2,6,di methyl morpholine to afford (2S,6R)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylmorpholine(compound**6)** according to the reported procedure.[**28**], which was reacted with phenylboronic acid in 1,4 dioxane to afford methyl 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)benzoate(compound8) according to the reported procedure[**29**],which was reacted with hydrazine hydrate in ethanol to afford as 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)benzohydrazide (compound 9) according to the reported procedure[**30**], which was reacted with Isatin in toluene to afford 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)-N'-(2-oxoindolin-3-ylidene)benzohydrazide(compound 11) according to the reported procedure [**31**],which was reacted with formaldehyde and secondry amines(piperidine,morpholine,thio morpholine,N-Methyl piperazine) to afford 4-(4-((2S,6R)-2,6-dimethylmorpholino)-7-nitroquinazolin-2-yl)-N'-(2-oxo-1-(piperidin/morpholine/thio morpholine/N-Methyl piperazine)-1-ylmethyl)indolin-3-ylidene)benzohydrazide(compound 13 a-d) according to the reported procedure **[32]** ,which was reacted with iron powder and ammonium chloride to afford 4-(7-amino-4-((2S,6R)-2,6-dimethylmorpholino)quinazolin-2-yl)-N'-(2-oxo-1-(piperidin/Morpholin/Thio morpholine/N-methyl piperazine-1-ylmethyl)indolin-3-ylidene)benzohydrazide 14 (a-d) as per the reported procedure [**33]**,which was reacted with substituted bi phenyl acid chlorides to afford Title compounds(15 a-h) as per the reported procedure [**34]**.

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 3500-3140 cm^{-1}. Amide C=O stretching vibrations were observed near 16901640 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 6.05-6.40 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 Elemental analysis, ^{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%.

Conclusions:

In conclusion a series of new quinazoline derivatives 15(a-h) were synthesized in good yield, characterized by different spectral studies and their biological activity have been evaluated. various derivatives of quinazoline derivatives showed potent anti fungal activity. Among the synthesized compounds 15g,15f showed excellent anti bacterial and antifungal activity.

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