Synthesis, Characterization and Biological Evaluation of Novel Trisubstituted Quinazoline Thiazole Derivatives Bearing Trans Substituted Thiomorpholine and Tetrazoles Moieties.

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Abstract

Quinazolinones is considered as an important chemical, synthesis of various physiological significance and pharmacological utility. Quinazolines are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans. To synthesize a variety of Quinazoline linked with Trans 2.6 Di Methyl Thio Morpholine, Tetrazoles and Thiazoles and Their Antimicrobial activity was determined .Using 2,4-dichloro-7-nitroquinazoline, new compounds were synthesized. The structures of all the new compounds are established on the basis of FT-IR,^{1}H &^{13}C NMR,Mass spectral Data

Key words: Thiazoles, Quinazolines, Tetrazoles, Anti microbial activity, Heterocyclic compounds

Introduction

Nitrogen-containing heterocycles are present in a wide variety of bioactive natural products and biological molecules that may be good drug candidates**[1]** Specifically, quinazolines and their derivatives represent a medicinally and pharmaceutically important class of heterocyclic molecules that are found as the core structural skeletons in a variety of drug molecules such as prazosin**[2],** lapatinib**[3]**, and icotinib**[4]** (Figure 1). They possess a wide range of biological and pharmacological activities including anticancer**[5]**, antiviral**[6]**, antitubercular**[7]**, and antimalarial properties**[8]**. Yang and co-workers**[9]** recently reported that substituted quinazolines have novel potent and selective FLT3 inhibitory and anti-acute myeloid leukemia (AML) activities. Therefore, the development of different synthetic strategies for the preparation of substituted quinazolines has received much attention.

Tetrazole and its derivatives have attracted much attention because of their unique structure and applications as antihypertensive, antialergic, antibiotic and anticonvulsant agents **[10-17]**. Development of tetrazole chemistry has been largely associated with wide scale of applications of these classes of compounds in medicine, biochemistry, agriculture **[18-21]** and also a large number of medicinally important tetrazole heterocyclic incorporated drugs approved by the FDA **[22-23]**. The medicinal activity

of tetrazole functionality is due to its ability to serve as bioequivalent (bioisostere) of the carboxylic acid group. 1, 5-disubstituted tetrazoles can be used as isosteres of the cis-amide bond of peptides **[24-26]**.

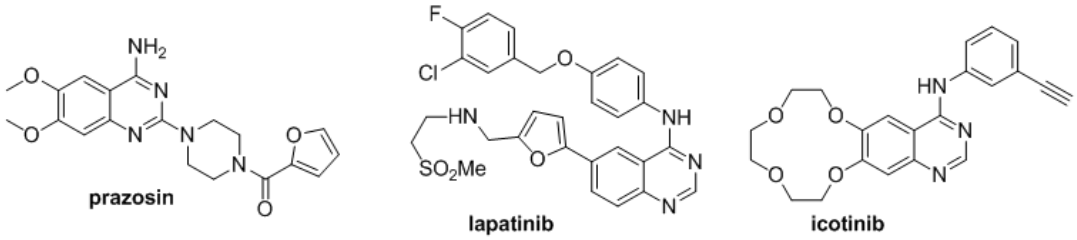


Figure 1. Structures of some biologically active quinazoline cores.

Thiazole derivatives a wide range of biological activities such as cardiotonic, fungicidal, sedative, anesthetic, bactericidal and anti-inflamatory. The synthesis of thiazole derivatives is important of their wide range of pharmaceutical and biological properties. The most straight forward procedure reported by Hantzch in 1887 involves condensation of haloketones and thiourea or thioamides in refluxing alcohol. This method is long reaction time (24-25 h), harsh reaction conditions. Thiazole or 1,3-thiazole is a heterocyclic organic compound which has a five-membered ring containing three carbon, one sulfur, and one nitrogen atoms. Thiazoles are members of the azole heterocycles that include imidazoles and oxazoles. They are isomeric with the 1,2azoles and the nitrogen and sulfur containing compounds called isothiazole.

Thiazoles and pyrazoles have been reported to show pharmacological activities. Some of them are used as medicines**[27]**. According to literature survey, thiazoles were reported to possess antimicrobial**[28-31]**, analgesic**[32]**, anti- inflammatory[**33]**, anticonvulsant**[34]**,cardiotonic**[35]**,anticancer**[36,37]**, antitubercular**[38]** and anthelmintic**[39]** activities. Antimicrobial activities of some substituted thiazoles are well established because it posses (S-C=N) toxophoric unit. Thiazoles have enhanced lipid solubility with hydrophilicity. Thiazoles are easily metabolized by routine biochemical reactions and are non-carcinogenic in nature **[40].**

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. ^{1}H 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.

All reactions were carried out under argon inoven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^1H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane 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 CDCl3-*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).

Scheme I:

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

Reagents and Reaction conditions:

(a)*Dry THF0^{0}c*

(b)1,4 Di Oxane,$PdCl_2(PPh_3)_2$, K_2CO_3

(c)*Hydrazine hydrate, Ethanol, reflux*

(d) *KSCN,Conc.HCl,ethanol*

(e)*Ethanol,$NaHCO_3$*

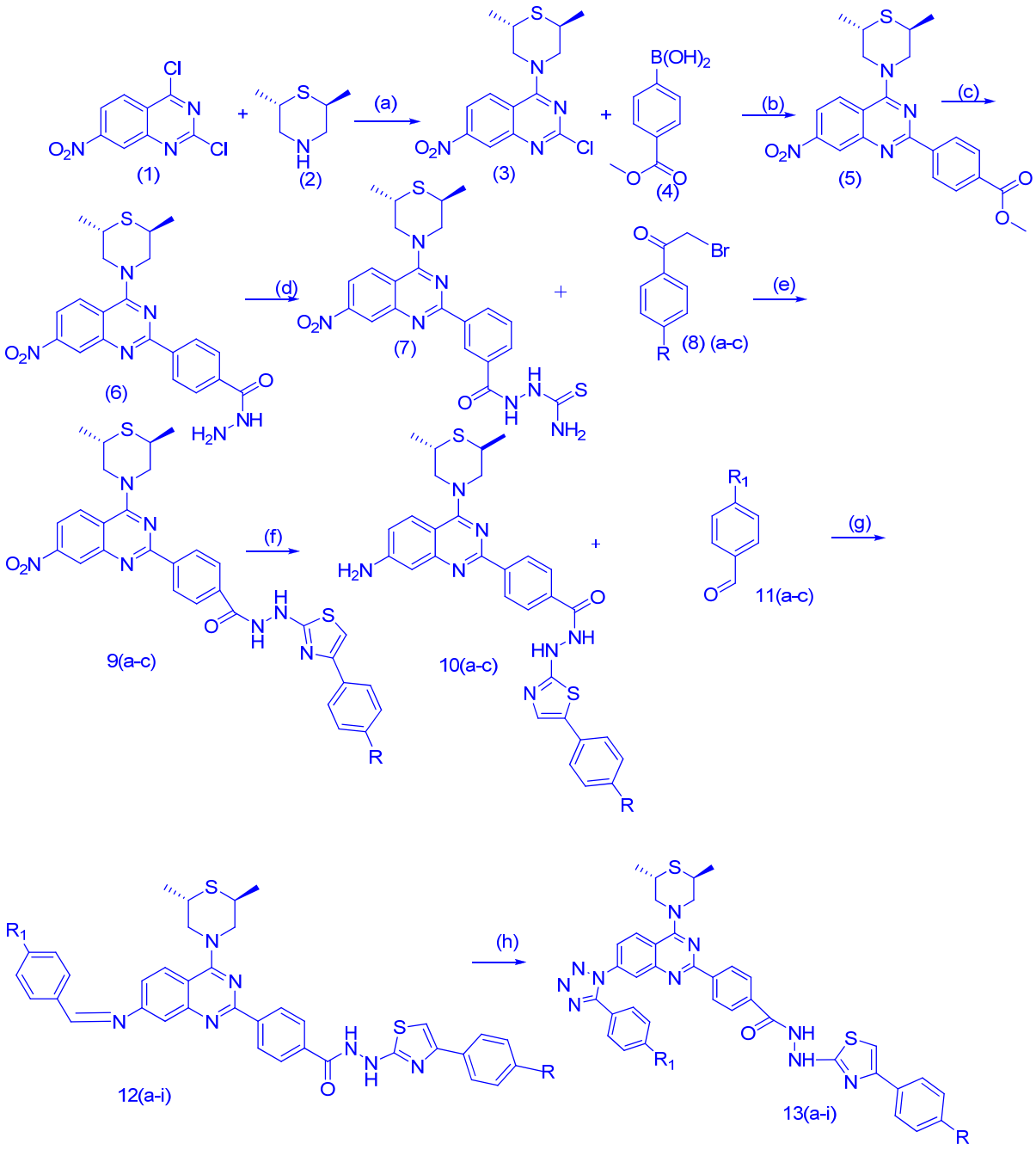
(f)*FePowder,NH_4Cl,Ethanol,reflux*

(g)*Ethanol, AceticAcid*

*(**h**)PCl_3,100^{0}c,NaN_3,$ZnCl_2$,Sodium acetate.*

Compound	***13(a)***	***13(b)***	***13(c)***	***13(d)***	***13(e)***	***13(f)***	***13(g)***	***13(h)***	***13(i)***
R	*-CH_3*	*-CH_3*	*-CH_3*	*-NO_2*	*-NO_2*	*-NO_2*	*-H*	*-H*	*-H*
R$_1$	*-CF_3*	*OCH_3*	*-NO_2*	*-CF_3*	*OCH_3*	*-NO_2*	*-CF_3*	*OCH_3*	*-NO_2*

Synthetic Scheme:



Experimental Setup

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were

dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (60–120 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^1H, for ^{13}C, respectively, in CDCl3 solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents.

Synthesis of (2S,6S)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylthiomorpholine (Compound 3):

To a cooled (0° C.) suspension of 2,4-dichloro-7-nitroquinazoline(1) (0.1 m. mol) in ethanol (5 ml), which was stirred under an inert atmosphere, was added triethylamine (0. 5 m.mol) and then Trans 2,6,di methyl Thio morpholine (0.2 m.mol). The mixture was maintained at this temperature for 3 hours, the reaction mixture diluted with NaOH (10 ml, 1M) and extracted with EtOAc (3.x.20 ml). The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated in vacuo to give a colorless liquid. The crude residue was purified by using column chromatography using EtOAc/Hexanes(3:7) to give the title compound (90percent) as a colorless liquid. This ^1H NMR (400 MHz, $CDCl_3$): 8.9 (d, J=2.4 Hz, 1H), 8.5 (dd, J=9.2, 2.5 Hz, 1H), 8.10 (d, J=9.2 Hz, 1H),1.3(6H,d,J=8HZ,2× CH_3),3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2)

Synthesis of methyl 2-(4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)phenyl)acetate (compound 5):

A mixture of compound(3) (0.61 mmol), 4-(2-methoxy-2-oxoethyl)phenylboronic acid (0.1m.mol),K_2CO_3(1m.mol) and $(PPh3)_2PdCl_2$(5 mol%),in 5 ml solvent(DME/Water/Ethanol 7:3:2)was placed in a sealed vial and heated to 120^0c for 2 hrs, The reaction mixture was diluted with water, Extracted with ethyl acetate, dried over Na_2SO_4,filtered,and evaporated to dryness. The crude product was purified by column chromatography to afford product 5 with 70% yield as a white solid. Melting point 122.4^0c-124^0c Yield:70% melting point: 142-144^0c

This ^1H NMR (400 MHz, $CDCl_3$): 8.9 (d, J=2.4 Hz, 1H), 8.5 (dd, J=9.2, 2.5 Hz, 1H), 8.10 (d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ ,N-CH_2), 8(2H,d,J=8.3HZ), 8.1(2H,d,J=8.3HZ),3.8(3H,S,-OCH_3)

Synthesis of 2 - (4 - (4 - ((2S, 6S) - 2, 6 – dimethylthio morpholino) - 7 - nitroquinazolin – 2 -yl) phenyl) acetohydrazide (compound 6): A mixture of compound 5 (0.1m. mol) and hydrazine hydrate (0.3 m.mol) was refluxed for 6 h using ethanol as a solvent. The formed product was isolated and re crystallized from Ethanol to yield white needle like crystals of pure compound.

Yield:70% melting point: 122-124^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.9 (d, J=2.4 Hz, 1H), 8.5 (dd, J=9.2, 2.5 Hz, 1H), 8.10(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 7.3 (2H,d,J=8.3HZ), 8.5(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 2(2H,-NH_2,broad singlet)

Synthesis of 2-(3-(4-((2S,6S)-2,6-Dimethylthiomorpholino)-7-Nitroquinazolin-2-Yl) Benzoyl) Hydrazinecarbothioamide (Compound7):

A mixture of (compound 6) (0.1 m.mol), 0.2 m.mol. Of potassium thiocyanate, 1.5 ml of hydrochloric acid, and 20 ml of water was heated with stirring for 4 h at 95°C. The reaction mixture was left for a day at room temperature. The solution was alkalinized to pH = 6–7, the precipitate formed was filtered off. The re crystallization from ethanol gave 84% of compound 7 MP 217–218°C.

Synthesis of 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)-N'-(4-phenylthiazol-2-yl)benzohydrazide (9a) and 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)-N'-(4-p-tolyl/Nitro thiazol-2-yl)benzohydrazide (compound 9 b-c):

A mixture of compound(7) (0.1 m.mol) and phenacyl bromide/ 4-methyl/Nitro phenacyl bromide (0.2m.mol) in methanol (5 ml) in presence of fused sodium acetate (0.3 m.mol) was heated under reflux for 6hr. the reaction mixture was cooled and poured into water. The resulting solid was filtered off, washed with hot water, dried and purified by Ethanol solvent to give compounds9(a-c). Yield 62-65%; as brown crystals .

Compound 9a: Yield:64%, Melting Point: 210^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 9(d, J=2.4 Hz, 1H), 8.5 (dd, J=9.2, 2.5 Hz, 1H), 8.10(d,J=9.2Hz,1H),1.3(6H,d,J=8HZ,2×CH_3),3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2),8.0(2H,d,J=8.3HZ),7.96(2H,d,J=8.3HZ),8(1H.-NH,broad singlet),4(1H,broad singlet,_NH linked with thiazole ring),7.3(1H,S,thiazole ring proton),7.5-7.8(5H,m)

Compound 9b: Yield:62%, Melting Point: 180-182^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 9(d, J=2.4 Hz, 1H), 8.5 (dd, J=9.2, 2.5 Hz, 1H), 8.10(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**),3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.25(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring).

Compound 9c: Yield:66%, Melting Point: 230-232^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 9(d, J=2.4 Hz, 1H), 8.5 (dd, J=9.2, 2.5 Hz, 1H), 8.10(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.25(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ).

Synthesis of 4-(7-amino-4-((2S,6S)-2,6-dimethylthiomorpholino)quinazolin-2-yl)-N'-(5-phenylthiazol-2-yl)benzohydrazide(compound 10a) and 4-(7-amino-4-((2S,6S)-2,6-dimethylthiomorpholino)quinazolin-2-yl)-N'-(5-p-tolyl/Nitrothiazol-2-yl)benzohydrazide(compound 10 b-c):

Compound 9(a-c) (1 m.mol) and iron powder(7 m.mol) and acetic acid(14 m.mol) were suspended in aqueous ethanol(8:2 Ethanol: water) and heated at reflux about 70-80^{0}c for 5-6 hrs. Mean time this mixture would be stirred for 1 minute every half hour with a glass rod and the yellow solution become reddish brown slowly. The reaction mixture was cooled to room temperature and alkalinized by addition of concentrated ammonia, insoluble material was removed by filtration through celite and the filtrate was evaporated under reduced pressure. The resulting solid was extracted with Ethyl acetate for column chromatography. Column chromatography was performed using silica gel(200-300 mesh) eluting with ethyl acetate and petroleum ether(3:1 v/v) to give amine 10(a-c)

Compound10a: Yield:74%, Melting Point: 110-112^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.2(d, J=2.4 Hz, 1H), 6.8 (dd, J=9.2, 2.5 Hz, 1H), 7.6(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.0(1H,S,thiazole ring proton), 7.5-7.8(5H,m), 6.3(2H,broad singlet,-NH_2)

Compound 10b: Yield:72%, Melting Point: 130-132^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.2(d, J=2.4 Hz, 1H), 6.8 (dd, J=9.2, 2.5 Hz, 1H), 7.6(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.09(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 6.3(2H,broad singlet,-NH_2)

Compound 10c: Yield:76%, Melting Point: 146-147.4^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.2(d, J=2.4 Hz, 1H), 6.8 (dd, J=9.2, 2.5 Hz, 1H), 7.6(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.09(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 6.3(2H,broad singlet,-NH_2)

Synthesis of 4-(4-((2S,6S)-2,6-Dimethylthiomorpholino)-7-((-4-(Trifluoromethyl/ Methoxy /Nitro) Benzylideneamino) Quinazolin-2-Yl)-N'- (4-P-Tolyl/Nitro Thiazol-2-Yl) Benzohydrazide (Compound 12 A-I):

To a solution of the Para substituted aryl aldehyde(11 a-c) (1 m.mol) in dry toluene was added Quinazoline amine(compound10 a-c,1m.mol),and the mixture was refluxed overnight using a Dean-Stark water separator, Reaction progress was monitored by TLC when the reaction is over, toluene was evaporated under reduced pressure, the crude product was used as such for the next reaction.

Compound 12a: Yield:86% appearance: colorless liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.7(2H,d,J=8.3HZ)

Compound 12b: Yield:84% appearance: yellow liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.1(2H,d,J=8.3HZ), 3.9(3H,S,-OCH_3)

Compound 12c: Yield:82% appearance: light yellow liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 8.7(1H,S,**H**C=N), 8(2H,d,J=8.4HZ), 8.3(2H,d,J=8.3HZ).

Compound 12d: Yield:80% appearance: pale yellow liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.7(2H,d,J=8.3HZ).

Compound 12e: Yield:80% appearance: yellow liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.07(2H,d,J=8.3HZ), 3.9(3H,S,-OCH_3 Attached to Benzene ring)

Compound 12f: Yield:85% appearance: colorless liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet),4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 8.7(1H,S,**H**C=N), 8(2H,d,J=8.4HZ), 8.33(2H,d,J=8.3HZ),

Compound 12g: Yield:83% appearance: pale yellow liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.4-7.8(5H,m),8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.7(2H,d,J=8.3HZ)

Compound 12h: Yield:80% appearance: yellow liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.4-7.8(5H,m), 8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.7(2H,d,J=8.3HZ)

Compound 12i: Yield:84% appearance: colorless liquid

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.4-7.8(5H,m), 8.7(1H,S,**H**C=N), 7.8(2H,d,J=8.4HZ), 7.1(2H,d,J=8.3HZ), 3.9(3H,S,-OCH_3 attached to benzene ring)

Synthesis of 4-(4-((2S,6S)-2,6-Dimethylthiomorpholino)-7-(5-(4-(Trifluoromethyl /Methoxy /Nitro) Phenyl) -1H-Tetrazol-1-Yl) Quinazolin-2-Yl) -N'- (4-P-Tolyl /Nitro Thiazol-2-Yl) Benzohydrazide (Compound 13 A-I):

Schiff base(0.1m.mol) and PCl_5 (0.1m.mol) was heated at 100^0c for 1h. When the evolution of fumes of HCl ceased, excess of PCl_3 was removed under reduced pressure and the residual imidoyl chloride was treated with an ice-cold solution of sodium azide(0.5m. mol) and excess of sodium acetate in water (5ml) and acetone (7ml) with stirring[41]. Stirring was continued for overnight, thereafter acetone was removed under reduced pressure. The remaining aqueous portion was extracted with chloroform was dried. The yield was 55% -65%

Compound 13a: Yield:86% appearance: off white solid Melting point: 120-123^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),1150(C-F Stret),3100(aromatic C-H stret), 691(C-S of Thiazole), 1150(C-F Stret), 1157 (Tetrazole).

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 7.8(2H,d,J=8.4HZ), 8.6(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,160,128,130,132,165(carbonyl carbon in hydrazide), 173,105,150,130,125,130,132,165,134,126,126,131(aromatic carbons),124(-CF_3 carbon), 23(methyl gp attached to benzene ring), 23,40,70(aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 780 (M+1 100%) and Anal. calculated for Chemical Formula $C_{39}H_{33}F_3N_{10}OS_2$ C, 59.08; H, 3.81; N, 17.98;

Found: C, 59.06; H, 3.80; N, 17.96

Compound 13b: Yield:84% appearance: white solid Melting point: 160-163^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),1150(C-F Stret),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole).

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet),4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 7.8(2H,d,J=8.4HZ), 7(2H,d,J=8.3HZ), 3.9(3H,S,-OCH_3 attached to benzene ring)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,160,128,130,132,165(carbonyl carbon in hydrazide), 173,105,150,130,125,130,132,165,123,130,116,161(aromatic carbons),55(-OCH_3 carbon), 23(methyl gp attached to benzene ring), 23,40,70(aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 742 (M+1 100%) and Anal. calculated for Chemical Formula $C_{39}H_{36}N_{10}O_2S_2$ C, 63.22; H, 4.90; N, 18.91; Found: C, 63.20; H, 4.89; N, 18.90;

Compound 13c: Yield:84% appearance: pale yellow solid Melting point: 140-142^{0}c

IR(KBr,cm^{-1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric Stretching)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.7(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ), 2.3(3H,S,-CH_3 attached with benzene ring), 8(2H,d,J=8.4HZ), 8.4(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,160,128,130,132,165(carbonyl carbon in hydrazide), 173,105,150,130,125,130,132,165,123,136,27,125,150(aromatic carbons), 23(methyl gp attached to benzene ring), 23,40,70(aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 757 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{33}N_{11}O_3S_2$ C, 60.38; H, 4.40; N, 20.38;

Found: C, 60.36; H, 4.40; N, 20.36;

Compound 13d: Yield:83% appearance: yellow solid Melting point: 110-112^{0}c

IR(KBr,cm^{-1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric Stretching) ,

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 8.5(2H,d,J=8.4HZ), 7.7(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,160,128,130,132,165(carbonyl carbon in hydrazide), 173,105,150,139,127,125,148,165,133,126,27,125,131(aromatic carbons),124(-CF_3 Carbon), 23,40,70(aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 811 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{30}F_3N_{11}O_3S_2$ C, 56.36; H, 3.73; N, 19.03 Found: C, 56.34; H, 3.71; N, 19.01

Compound 13e: Yield:86% appearance: yellow solid Melting point: 134-136^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric Stretching)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 8.0(2H,d,J=8.4HZ), 8.3(2H,d,J=8.3HZ),3.9(3H,S)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,160,128,130,132,165(carbonyl carbon in hydrazide), 173,105,150,139,127,125,148,165,123,130,115,160(aromatic carbons), 23,40,70 (aliphatic carbons), 55(Methoxy Carbon)

The EIMS m/z values and corresponding percentage were as follows: 773 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{33}N_{11}O_4S_2$ C, 59.13; H, 4.31; N, 19.96; Found: C, 59.12; H, 4.30; N, 19.94;

Compound 13f: Yield:83% appearance: yellow solid Melting point: 110-112^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric Stretching)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet),4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ), 8.0(2H,d,J=8.4HZ), 8.3(2H,d,J=8.3HZ).

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,160,128,130,132,165(carbonyl carbon in hydrazide), 173,105,150,139,127,125,148,165,136,125,127,150(aromatic carbons), 23,40,70 (aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 787 (M+1 100%) and Anal. calculated for Chemical Formula $C_{37}H_{30}N_{12}O_5S_2$ C, 56.48; H, 3.84; N, 21.36 Found: C, 56.46; H, 3.82; N, 21.34

Compound 13g: Yield:80% appearance: pale yellow solid Melting point: 130-132^{0}c

IR(KBr,cm^{-1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole), 1150(C-F Stret)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet),4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.4-7.8(5H,m), 8.6(2H,d,J=8.4HZ), 7.7(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,127,130,132,165(carbonyl carbon in hydrazide), 173,105,150,133,127,129,128,165,136,125,131,124(aromatic carbons),23,40,70(aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 787 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{31}F_3N_{10}OS_2$ C, 59.67; H, 4.09;; N, 18.31; Found: C, 59.65; H, 4.07; N, 18.30;

Compound 13h: Yield:84% appearance yellow solid Melting point: 160-162^{0}c

IR(KBr,cm^{-1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole),

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet),4(1H,broad singlet,_NH linked with thiazole ring), 7.28(1H,S,thiazole ring proton), 7.4-7.8(5H,m), 8.0(2H,d,J=8.4HZ), 7.0(2H,d,J=8.3HZ), 3.9(3H,S,.-O**CH_3**)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130,135,127,124,123,170,151,138,127,130,132,165(carbonyl carbon in hydrazide), 173,105,150,133,127,129,128,165,136,125,131,124(aromatic carbons),23,40,70(aliphatic Carbons),55(methoxy carbon)

The EIMS m/z values and corresponding percentage were as follows: 728 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{34}N_{10}O_2S_2$ C, 62.79; H, 4.71; N, 19.27; Found: C, 62.77; H, 4.70; N, 19.25;

Compound 13i: Yield:86% appearance yellow solid Melting point: 187-189^{0}c

IR(KBr,cm^{-1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret), 1680 (CO of hydrazide), 1624(C=N Stretch),691(C-S of Thiazole),3100(aromatic C-H stret), 691(C-S of Thiazole), 1157 (Tetrazole), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric Stretching)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2(d, J=2.4 Hz, 1H), 7.8 (dd, J=9.2, 2.5 Hz, 1H), 8(d,J=9.2Hz,1H), 1.3(6H,d,J=8HZ,2×CH_3), 3(2H,m,S-C**H**), 3.6(4H,d,J=8HZ,N-CH_2), 8.0(2H,d,J=8.3HZ), 7.96(2H,d,J=8.3HZ), 8(1H.-NH,broad singlet), 4(1H,broad singlet,_NH linked with thiazole ring),7.28(1H,S,thiazole ring proton), 7.4-7.8(5H,m), 8.1(2H,d,J=8.4HZ), 8.3(2H,d,J=8.3HZ)

This ^{13}CNMR(100MHz,$CDCl_3$): 130,135,127,124,123,170,151,138,127,130,132,165 (carbonyl carbon in hydrazide), 173,105,150,136,127,129,128,165,136,125,124,147(aromatic carbons),23,40,70(aliphatic Carbons) the EIMS m/z values and corresponding percentage were as follows: 743 (M+1 100%) and Anal. calculated for Chemical Formula $C_{37}H_{31}N_{11}O_3S_2$ C, 59.90; H, 4.21; N, 20.77. Found: C, 59.90; H, 4.21; N, 20.77

Biological Activity:

The newly synthesized compounds 13(a-i) were screened for antibacterial (Staphylo- cocas aurous, Escherichia coli, Pseudoonas aerug- inosa at 37^{0}C) and antifungal (Candida albicans, Asperigillus flavus, Asperigillus fumigatus at 25^{0}C) activities, using nutrient agar and Sabouraudís agar media, respectively, by disk diffusion method at a concentration of 2 mg per ml using DMF as a solvent. The results were recorded in duplicate using ampicillin 1 mg/ml and fluconazole 2.5 mg/ml as standards were given in Table 1.

Antimicrobial Evaluation of Novel Compounds 13(A-I):

Table1. Antimicrobial activity and antifungal activity of Synthesized Quinazoline derivative compounds 13(a-i):

Compound No	Zone of inhibition in mm					
	Antibacterial activity			Antifungal activity		
	S.aureus	E.coli	P.aeruginosa	C. albicans	A. flavus	A.fumigatus
13a	16	15	14	10	9	10
13b	15	14	12	9	9	10
13c	17	16	15	11	9	10
13d	23	22	22	18	9	10
13e	20	19	18	15	9	9
13f	22	21	20	17	10	10
13g	18	17	16	12	9	9
13h	13	12	11	9	9	10
13i	19	18	17	14	9	9
Ampicillin	20	21	22	21	-	-
Flucanazole	22	20	23	22	-	--

The Quinazoline derivates containing Thiazole (13f,13d) and Tetrazoles(13e,13i)showed more activity than other substituent's the order of activity was **13d>13f>13e>13i>13g>13c>13a>13b>13h.**

Result and Discussion

Synthesis:

The present scaffold **13(a-i)** is a part of the synthesis of new chemical entities in the form of antimicrobial agents. The title compounds **13(a-i)** were synthesized in Eight steps. The first step involves coupling of 2,4-dichloro-7-nitroquinazoline(1) with Trans 2,6,di methyl Thio morpholine(2) in ethanol (95%) to give 2S,6S)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylthiomorpholine(Compound3) according to the reported procedure**[41]**.Compound(3) coupling with 4-(methoxycarbonyl)phenylboronic acid(4) under Suzuki reaction conditions yielded methyl 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)benzoate (compound 5) as per the reported procedure**[42].** compound (5) on reaction with Hydrazine hydrate in Ethanol furnished 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)benzohydrazide (compound 6) as per the reported procedure**[43]**.Compound(6) reacts with potassium thiocyanate in aqueous HCl to give methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(-4- Tri fluoro methyl /Nitro)benzylideneamino)quinazolin-2-yl)benzoate (compound 7) as per the reported procedure**[44]**.

Compound 7 reacts with Para substituted Phenacyl bromides(8 a-c) in methanol in presence of fused sodium acetate furnished 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)-N'-(4-phenylthiazol-2-yl)benzohydrazide (9a) and 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)-N'-(4-p-tolyl/Nitro thiazol-2-yl)benzohydrazide(compound 9 b-c) according to the reported procedure**[45].** Compound 9(a-c) reacts with Fe Powder and Acetic acid to give 4-(7-amino-4-((2S,6S)-2,6-dimethylthiomorpholino)quinazolin-2-yl)-N'-(5-phenylthiazol-2-yl) benzohydrazide (compound 10a) and 4-(7-amino-4- ((2S,6S)-2, 6-dimethylthiomorpholino) quinazolin-2-yl) -N'-(5-p-tolyl /Nitrothiazol-2-yl) benzohydrazide (compound 10 b-c) as per the reported procedure**[46]**. Compound 10(a-c) reacts with different aromatic Aldehydes 11(a-c) in Toluene to give as a 4-(4-((2S,6S)-2,6-dimethylthiomorpholino)-7-((-4-(trifluoromethyl/Methoxy/Nitro)benzylideneamino)quinazolin-2-yl)-N'-(4-p-tolyl/Nitro thiazol-2-yl)benzohydrazide (compound 12 a-i) as per the reported procedure**[47].**Compound Reacts with PCl_5 and Sodium azide to give tetrazoles as a Title Compounds As per the Reported procedure**[48].** The scheme of synthetic procedure for preparation of title compounds is given in **(Scheme I).**

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 13d and 13f possess good activity.

Conclusions:

In conclusion a series of new quinazoline derivatives 13(a-i) 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 13d,13f showed excellent anti bacterial and antifungal activity.

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