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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL TRISUBSTITUTED QUINAZOLINE 1, 2, 4 TRI AZOLE DERIVATIVES BEARING CIS-SUBSTITUTED PYRROLIDINE AND SULPHONE MOIETIES.

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ABSTRACT

Quinazoline moiety associated with different heterocycle scaffolds gives rise to a new class of hybrid heterocycles possessing improved activity. Heterocycles containing sulphur and nitrogen atoms in the core structure, shows number of pharmacologically and biologically active compounds. So, various Quinazoline derivatives were studied in the past decade and were found to possess remarkable pharmacological properties. The present Researsch Investigation provides a broad view of the biological and medicinal properties expressed by compounds having Quinazoline nucleus.

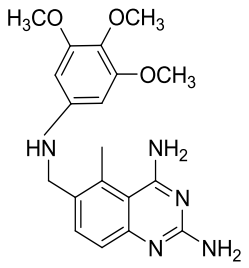
KEYWORDS: Heterocycles, Tri azoles, Sulphones, Biological, Pharmacological Significance, Anti microbial.

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 Quinazoline alkaloid, possessing anti-malarial potential from the Chinese plant aseru (Dichroa febrifuga Lour), which served as animpetus 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. Heterocycles have a central position in medicinal as well as in organic chemistry[1-3] and considerable attention has been focused on their syntheses. Nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities[4-6] due in part to the similarities with many natural and synthetic molecules with known biological activity[7] Moreover, quinazolines are of the most extensively studied classes of heterocyclic compounds, and have received much attention from synthetic organic as well as medicinal chemists, because of the diverse range of their biological activities[8,9] and their applications in several areas as materials in electronics, in electrochemistry as anticorrosive agents, as polymers or optical materials and fluorescent tags in DNA sequencing.[10-12] In general, quinazoline compounds have been well-recognized for their pharmacological properties, such as anti-inflammatory[13,14], antihypertensive[15], anti-HIV[16], bronco-dilatory[17], antiallergic[18], anti-cancer[19-21], anticonvulsant[22,23], antihelmintic[24], analgesic[25], antimalarial[26] and antimicrobial[27] activities.

The quinazoline skeleton is present in a variety of biologically active compounds, among these are several marketed drugs such as Trimetrexate glucuronate[1] (dihydrofolate reductase inhibitor), Bunazosin hydrochloride[2] and Trimazosin Hydrochloride[3] (hypotensive properties).



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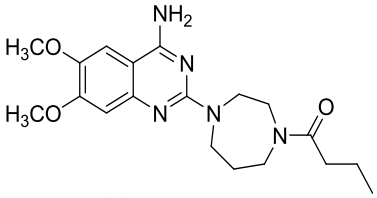

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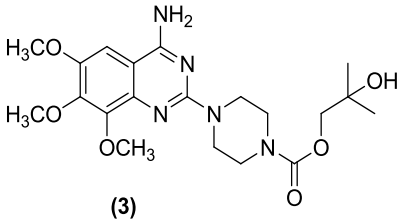


(3)

Sulphones have a variety of biological activities such as antibacterial[28-30], insulin releasing[31], carbonic anhydrase inhibitory[32,33], anti- inflammatory[34] andantitumor[35] activities. These findings encouraged us to explore the synthesis of sulfones containing Quinazolines moieties and to examine their antibacterial and antifungal properties.

The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic

organic compound[36]. The pyrrolidine ring system is found in a vast variety of compounds displaying an impressive range of biological activities. Thus, the incorporation of different substitution patterns and motives into the basic heterocyclic substance common to such activities has potential in the discovery of new substances with useful pharmacological properties[37]. Review of literature revealed that pyrrolidines are well known for their versatile pharmacological activities such as antimicrobial[38,39,40], antitumor[41], antiHIV-1[42], anticonvulsant[43,44], sphingosine-1-phosphate (S1P) receptor ragonists[45,46], malic enzyme inhibitors[47], ketoamide-based cathepsin K inhibitors[48], human melanocortin-4 receptor agonists[49], etc.

The therapeutic effects of compounds containing 1,2,4-triazole rings have been well studied for a number of pathological conditions including inflammation[50,51], pain[52-54] or hypertension.[55] Moreover, synthesis of thiadiazoles and triazoles has attracted widespread attention due to their diverse applications as antibacterial[56], antimycobacterial[57, 58], antimycotic[59,60], antifungal[61, 62] and antidepressant agents.[63] Meanwhile, N-acylated aminoacids are known for their hepatoprotective and antimicrobial effects.[64, 65]

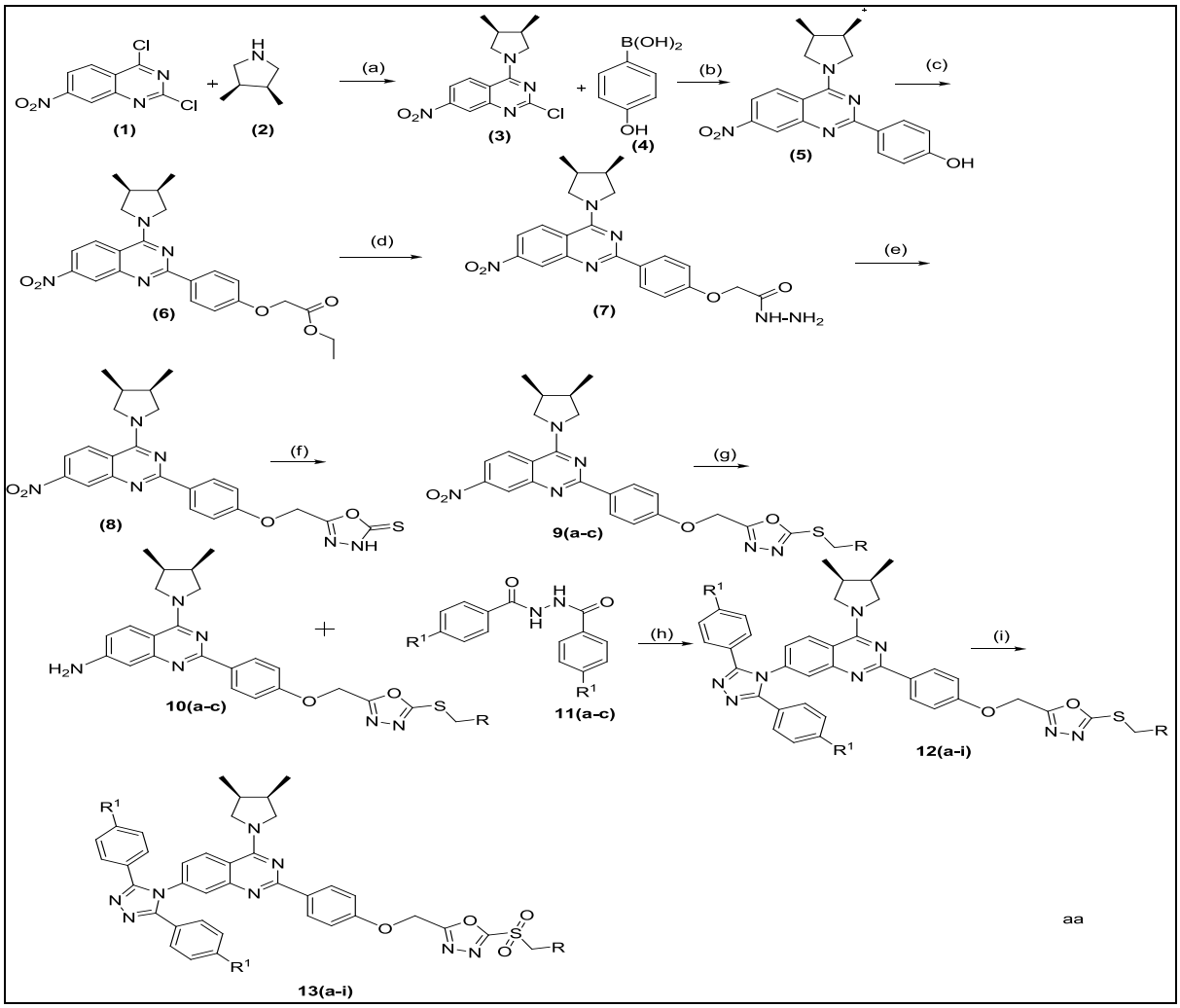
MATERIALS AND METHODS

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 ^{1}H 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 (^{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 (^{1}H 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.



Reagents and conditions: (a) Dry THF, 0 °C (b) 1,4 Di Oxane, $PdCl_2(PPh_3)_2$, CS_2CO_3 (c) Chloro ethyl Acetate, K_2CO_3, Ethanol (d) Hydrazine hydrate, Ethanol, Reflux (e) KOH, CS_2, Ethanol (f) substituted Pyrazole/Iso Oxazole/IsoThiazole Methyl chlorides (g) Fe Powder, NH_4Cl (h) PCl_3, 1,2dichlorobenzene, Reflux, 3hrs (i) MCPBA

S.NO	Compound	R	R^1
01	13a	1H-pyrazole	$-CF_3$
02	13b	1H-pyrazole	-F
03	13c	1H-pyrazole	-NO2

04	13d	Iso Oxazole	$-CF_3$
05	13e	Iso Oxazole	-F
06	13f	Iso Oxazole	$-NO_2$
07	13g	Iso thiazole	$-CF_3$
08	13h	Iso thiazole	-F
09	13i	Iso thiazole	$-NO_2$

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

EXPERIMENTAL Section

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a 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 ^{1}H, 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.

Synthesis of 2-chloro-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazoline (Compound 3)

To a cooled (0°C.) suspension of 2,4-dichloro-7-nitroquinazoline(1) (0.1 m mol) in dry THF (5 ml), which was stirred under an inert atmosphere, was added tri ethylamine (0. 5 m.mol) and then Cis 3,4-dimethylpyrrolidine (0.1 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 (3x20 ml). The organic extracts were combined, dried with 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 colourless liquid.

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=9.2 Hz, 1H), 2.8(4H,d,J=8HZ), 1.2(2H,m), 0.96(6H,d,J=7 HZ)

Synthesis of(3R,4S)-1-(2-(4-hydroxyphenyl)-7-nitroquinazolin-4-yl)-4-methylpyrrolidin-3-yl)methylium (Compound 5)

A mixture of compound(3) (0.1 m.mol), 4-hydroxyphenylboronic acid(4)(0.2 m.mol),K_2CO_3(2 m.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 pale yellow solid.

Melting point 144^0c-146^0c

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), 2.8(4H,d,J=8HZ), 1.6(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 6.9(2H,d,J=8HZ), 5.5(1H,broad singlet)

Synthesis of ethyl 2-(4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)acetate (Compound 6)

To a mixture of compound 5 (0.1 m.mol), anhydrous K_2CO_3 (0.5m. moles) in anhydrous acetone (10v) was added ethyl 2-chloroacetate (0.2m moles) and refluxed for 12 hours. Reaction progress was monitored by TLC. After completion of Starting material, Acetone was distilled and water (15 ml) was added. Crude product was filtered, dried, and re crystallized from a mixture of Ethyl acetate:Hexane (1:5) to give pure Compound 72.5percent Yield as a white fluffy powder. M.p: 97-98.4°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),2.8(4H,d,J=8HZ), 1.6(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5(2H,S), 4.2(2H,q,J=7HZ), 1.3(3H,t,J=7HZ)

Synthesis of 2-(4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl) phenoxy)acetohydrazide (Compound 7)

A solution of hydrazine hydrate (0.5 m.mol) in 10 volumes of EtOH was added dropwise to the compound 6 (0.1 m.mol). The mixture was refluxed for 5 h and filtered, and the corresponding acid hydrazide 7 was obtained by washing the residue with ice water. and Re crystalised from Ethanol to give pure compound(compound 7)

Yield 80%, Melting point: 80-82^0c

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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5(2H,S), 4.7(2H,broad singlet), 8(1H,S,-NH), 8(2H,broad singlet,-NH_2)

Synthesis of 5-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole-2(3H)-thione (Compound 8)

Compound 7(2 m.mol) and KOH(3 m.mol) were dissolved in Ethanol(6v).CS_2 (3m.mol) was added drop wise. The mixture was refluxed for 12 hr, Then distilled under reduced pressure. The residue was added into distilled water and the solid was formed was filtered.The filtrate was acidified and set to P^H =1 With 2N. HCl solution and turned to slurry,The product was obtained by filtration and dissolved in Ethyl acetate.The solution dried with Na_2SO_4 and evaporated by vaccum.The compound was obtained with 90% yield. White solid, Melting Point: 199-201^{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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 4(2H,S),7(1H,S,-NH)

Synthesis of 2-((1H-pyrazol-5-yl)methylthio)-5-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole(9a), 2-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-5-(isoxazol-5-ylmethylthio)-1,3,4-oxadiazole(9b), 2-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-5-(isothiazol-5-ylmethylthio)-1,3,4-oxadiazole(9c)

To a solution of Heterocyclic methyl halide (0.1 m.mol) in acetonitrile (6v) cooled at 0^0 c in a two necked Round bottom flask , was added anhydrous triethyl ammine (1 m.mol) followed by the drop wise addition of thi ophenol (compound 8 0.1 m.mol) over a period of 10 min and the reaction mixture was stirred further for a period of 20 min under a nitrogen atmosphere. The reaction mixture was diluted with CH_2Cl_2, washed with water, brine and dried over Na_2SO_4 and filtered. The organic layer was evaporated under reduced pressure to furnish the crude product which was purified by flash column chromatography using 5% EtOAc/hexane (v/v) to afforded 9(a-c) as a brown colour oil (95-97% yield). TLC (SiO2): Rf = 0.2 (ethyl acetate: hexanes, 0.5:9.5).

Compound 9a

yield:93% Melting Point: 170-172^{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),2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.2(2H,S,-O-CH_2), 4.19(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ).

Compound 9b

yield:92% Melting Point: 158-160^{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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 5.9(1H,d,J=7HZ).

Compound 9c

yield:95% Melting Point: 186-188^{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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.2(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ)

Synthesis of 2-(4-((5-((1H-pyrazol-5-yl)methylthio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-7-amine(10a), 4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-2-(4-((5-(isoxazol-5-ylmethylthio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)quinazolin-7-amine(10b), 4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-2-(4-((5-(isothiazol-5-ylmethylthio)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)quinazolin-7-amine(10c)

Compound 9(a-c) (1 m.mol) and iron(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 alkalinised 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)

Compound 10a

yield:85% Melting Point: 120-122^{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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 6.3(2H,S,-NH_2)

Compound 10b

yield:92% Melting Point: 158-160^{0}c

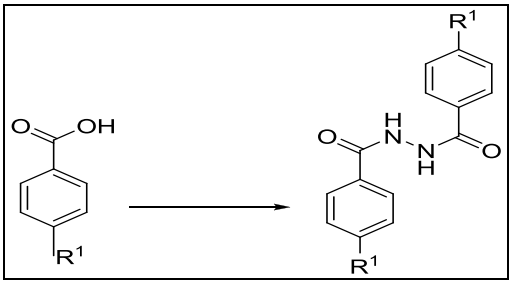
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.2 (d, J=2.4 Hz, 1H), 6.8 (dd, J=9.2, 2.5 Hz, 1H), 7.6 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 6(1H,d,J=7HZ), 6.3(2H,S,-NH_2)

Compound 10c

yield:94% Melting Point: 136-138^{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),2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 4(2H,S), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 6.3(2H,S,-NH_2)

Synthesis of intermediate 11(a-c) was prepared by the following procedure (Scheme:2)



Scheme:2

R^1=-CF_3,-F,-$N0_2$ ***Reagents & Reaction Conditions****: $SOCl_2$ & Hydrazine hydrate*

Experimental procedure for preparation of The Intermediate 11(a-c)

A solution of Para substituted benzoic acid(0.1 m.mol) and thionyl chloride (10 v) in chloroform was heated to reflux and stirred for 4 h. The solvent and excess reagents were removed under vacuum. Dry toluene (20 ml) was added and then evaporated under vacuum. The light yellow oil was dissolved in dry THF and the solution added drop wise to a solution of hydrazine (2 m.mol) and tri ethylamine (2 m.mol) in THF cooled in an ice/water bath. The reaction mixture was allowed to warm to room temperature and stirred overnight. Potassium carbonate solution was added to the reaction mixture. The resulting suspension was stirred for 2 h and then filtered. The collected solid was washed with water and dried under vacuum, affording 11(a-c) as a white solid in 68% yield.

Synthesis of 2-((1H-pyrazol-5-yl)methylthio)-5-((4-(7-(3,5-bis(4-(trifluoromethyl/ Fluoro/Nitro)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole(12 a-c), 2-((4-(7-(3,5-bis(4-(trifluoromethyl/Fluoro/Nitro))phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-5-(isoxazol-5-ylmethylthio)-1,3,4-oxadiazole(12d-f), 2-((4-(7-(3,5-bis(4-(trifluoromethy Fluoro/Nitro)l/)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-5-(isothiazol-5-ylmethylthio)-1,3,4-oxadiazole(12g-i)

Into a 25 ml three necked round-bottomed flask equipped with a reflux condenser, compound 10(a-c) (0.1 m.mol) and O-di chloro benzene (2 ml) were charged. Under nitrogen atmosphere, phosphorus tri chloride PCl_3 (1m.mol) dissolved in o-dichlorobenzene (2 ml) was then added slowly to the flask through a dropping funnel. Subsequently, compound 11(a-c) (0.3m.mol) dissolved in o-dichlorobenzene (2 ml) was added to the mixture and allowed to reflux for 3 h and then cooled to room temperature. The reaction mixture was poured into cold water in an ice bath to yield an orange precipitate, which was then purified by flash column chromatography with silica gel(100-200 mesh size). After evaporation in a rotary vacuum evaporator, a white solid was obtained (yield 55 %).

Compound 12a

yield:55% Melting Point: 140-142^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8.6 (dd, J=9.2, 2.5 Hz, 1H), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ),

7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8.6(2H,d,J=8.3HZ), 7.7(2H,d,J=8.3HZ)

Compound 12b

yield:53% Melting Point: 134-136^{0}c

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 7.8(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ)

Compound 12c

yield:52% Melting Point: 184-186^{0}c

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ)

Compound 12d

yield:55% Melting Point: 188-190^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8.6(2H,d,J=8.3HZ), 7.7(2H,d,J=8.3HZ)

Compound 12e

yield:53% Melting Point: 160-163^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 6(1H,d,J=7HZ), 7.8(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ)

Compound 12f

yield:53% Melting Point: 145-147^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ)

Compound 12g

yield:55% Melting Point: 128-130^{0}c

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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 8.6(2H,d,J=8.3HZ), 7.7(2H,d,J=8.3HZ)

Compound 12h

yield:54% Melting Point: 146-148^{0}c

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), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 7.3(2H,d,J=8.3HZ), 7.7(2H,d,J=8.3HZ)

Compound 12i

yield:53% Melting Point: 155-158^{0}c

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ)

Synthesis of 2-((1H-pyrazol-5-yl)methylsulfonyl)-5-((4-(7-(3,5-bis(4-(trifluoromethyl/Fluoro/Nitro)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole(13 a-c), 2-((4-(7-(3,5-bis(4-(trifluoromethyl/Fluoro/Nitro)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-5-(isoxazol-5-ylmethylsulfonyl)-1,3,4-oxadiazole(13d-f), 2-((4-(7-(3,5-bis(4-(trifluoromethyl Fluoro/Nitro/)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-

yl)quinazolin-2-yl)phenoxy)methyl)-5-(isothiazol-5-ylmethylsulfonyl)-1,3,4-oxadiazole(13 g-i)

Compounds 12(a-i) (0.1 m.mol) were dissolved in chloroform (2 ml), and thereto is added m-chloroperbenzoic acid (75 percent, 0.5 m.mol) under ice-cooling. The mixture is stirred at room temperature for one hour, added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate, and the mixture is separated. The organic layer is washed with a saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue is purified by column chromatography (hexane : ethyl acetate = 7: 3- to give Title compounds(13(a-i).

Compound 13a

yield:65% Melting point:164-166^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1200(C-F Stret), 1143 and 1340(S=O Stretching in sulfones)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8.6 (dd, J=9.2, 2.5 Hz, 1H), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.7(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8.6(2H,d,J=8.3HZ), 7.7(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$): 130, 135, 128, 125, 172, 123, 152, 161, 127, 130, 115, 160, 163, 165, 145, 138, 103, 125, 126, 153, 137 (Aromatic Carbons), 124(-CF_3 Carbon), 15.6, 44, 61, 72, 60(Aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 901 (M+1 100%) and Anal. calculated for Chemical Formula $C_{43}H_{34}F_6N_{10}O_4S$ (in %) C, 57.33; H, 3.80; N, 15.55 Found: C, 57.31; H, 3.78; N, 15.53.

Compound 13b

yield:68% Melting point:184-186^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1200(C-F Stret),1150 and 1350(S=O Stretching in sulfones)

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.7(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 7.8(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,145,138,103,125,126,153,137 (Aromatic Carbons),15.6, 44,61,72,60(Aliphatic carbons) The EIMS m/z values and corresponding percentage were as follows: 802 (M+1 100%) and Anal. calculated for Chemical Formula $C_{41}H_{34}F_2N_{10}O_4S$ (in %) C, 61.49; H, 4.28; N, 17.49;Found: C, 61.47; H, 4.26; N, 17.46;

Compound 13c

yield:62% Melting Point:148-150^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1320 and 1510(Nitro symmetric and asymmetric stretching),1150 and 1350(S=O Stretching in sulfones)

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 13.8(1H,S,-NH), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,145,138,103,125,127,153,140, 148(Aromatic Carbons),15.6,44,61,72,60(Aliphatic carbons). The EIMS m/z values and corresponding percentage were as follows: 856 (M+1 100%) and Anal. calculated for Chemical Formula $C_{41}H_{34}N_{12}O_8S$ (in %) C, 57.61; H, 4.01; N, 19.66; Found: C, 57.60; H, 4.01; N, 19.64;

Compound 13d

yield:55% Melting Point: 188-190^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1200(C-F Stret), 1143 and 1340(S=O Stretching in sulfones)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.2(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8.6(2H,d,J=8.3HZ), 7.7(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,158,150,103,125,126,153,137 (Aromatic Carbons),124(-CF3 Carbon),15.6, 44,61,72,60(Aliphatic carbons). The EIMS m/z values and corresponding percentage were as follows: 902(M+1 100%) and Anal. calculated for Chemical Formula $C_{43}H_{33}F_6N_9O_5S$ (in %) C, 57.27; H, 3.69; N, 13.98; Found: C, 57.25; H, 3.67; N, 13.96;

Compound 13e

yield:67.8% Melting point:184-186^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1200(C-F Stret),1150 and 1350(S=O Stretching in sulfones)

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.7(2H,S,-S-CH_2), 8(1H,d,J=7HZ), 6(1H,d,J=7HZ), 7.8(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,158,150,103,153,130,129,116,162 (Aromatic Carbons),15.6, 44,61,72,60(Aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 803 (M+1 100%) and Anal. calculated for Chemical Formula C41H33F2N9O5S (in %) C, 61.42; H, 4.15;; N, 15.72; Found C, 61.40; H, 4.13; N, 15.70;

Compound 13f

yield:61% Melting Point:152-154^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1320 and 1510(Nitro symmetric and asymmetric stretching),1150 and 1350(S=O Stretching in sulfones)

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.9(2H,S,-S-CH_2), 7.5(1H,d,J=7HZ), 6(1H,d,J=7HZ), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,145,150,103,125,127,153,140, 148(Aromatic Carbons),15.6,44,61,72,60(Aliphatic carbons).

The EIMS m/z values and corresponding percentage were as follows: 857 (M+1 100%) and Anal. calculated for Chemical Formula $C_{41}H33N_{11}O_9S$ (in %) C, 57.54; H, 3.89; N, 18.00; Found: C, 57.52; H, 3.86; N, 18.00;

Compound 13g

yield:60% Melting Point:195-197^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1320 and 1200(C-F Stret),1150 and 1350(S=O Stretching in sulfones)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.7(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 7.7(2H,d,J=8.3HZ), 8.6(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,148,158,123,155,137,125,126, (Aromatic Carbons),124(-CF_3 Carbon)15.6,44,61,72,60(Aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 918 (M+1 100%) and Anal. calculated for Chemical Formula $C_{43}H_{33}F_6N_9O_4S_2$ (in %) C, 56.27; H, 3.62; N, 13.73; Found: C, 56.25; H, 3.60; N, 13.72;

Compound 13h

yield:64% Melting Point:167-169^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1320 and 1200(C-F Stret),1150 and 1350(S=O Stretching in sulfones)

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), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.7(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 7.8(2H,d,J=8.3HZ), 7.3(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,148,158,123,155,130,129,116, 163 (Aromatic Carbons),124(-CF_3 Carbon)15.6,44,61,72,60(Aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 819 (M+1 100%) and Anal. calculated for Chemical Formula $C_{41}H_{33}F_2N_9O_4S_2$ (in %) C, 60.21; H, 4.07; N, 15.41; Found: C, 60.20; H, 4.05; N, 15.40;

Compound 13i

yield:61% Melting Point:135-137^{0}c

IR(KBr,cm-^{1}):1050(C-O-C stret),2900(SP^3 C-H stret),1550(C=C Stret),3370(-NH Stret),1240(C-N Stretch),1600(-NH bending),3058(Ar-H),2957(C-H),1590(C=N),1320 and 1510(Nitro symmetric and asymmetric stretching),1150 and 1350(S=O Stretching in sulfones)

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.3 (d, J=2.4 Hz, 1H), 8 (dd, J=9.2, 2.5 Hz, 1H), 8.1 (d, J=9.2Hz,1H), 2.8(4H,d,J=8HZ), 1.8(2H,m), 0.96(6H,d,J=7HZ), 8(2H,d,J=8HZ), 7(2H,d,J=8HZ), 5.4(2H,S,-O-CH_2), 4.7(2H,S,-S-CH_2), 8.6(1H,d,J=7HZ), 7.3(1H,d,J=7HZ), 8(2H,d,J=8.3HZ), 8.3(2H,d,J=8.3HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$)

130,135,128,125,172,123,152,161,127,130,115,160,163,165,148,158,123,155,127,124,140, 148(Aromatic Carbons), 15.6, 44,61,72,60(Aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 873 (M+1 100%) and Anal. calculated for Chemical Formula $C_{41}H_{33}N_{11}O_8S_2$ (in %) C, 56.48; H, 3.81; N, 17.67; Found: C, 56.46; H, 3.80; N, 17.65

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 added5 to a sterile sabouraud dextrose agar at 45ºC. 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 37ºC 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 Quinazoline derivates containing Iso thiazole with Trifluoromethyl (13g) and Iso thiazole with Fluoro(13h) showed more activity than other substituent's the order of activity was **13g>13d>13a>13h>13e>13b>13i>13f>13c**

Table 1: Antimicrobial activity of 2-((1H-pyrazol-5-yl)methylsulfonyl)-5-((4-(7-(3,5-bis(4-(trifluoromethyl/Fluoro/Nitro)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole(13 a-c), 2-((4-(7-(3,5-bis(4-(trifluoromethyl/Fluoro/Nitro)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-5-(isoxazol-5-ylmethylsulfonyl)-1,3,4-oxadiazole(13d-f), 2-((4-(7-(3,5-bis(4-(trifluoromethyl Fluoro/Nitro/)phenyl)-4H-1,2,4-triazol-4-yl)-4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)quinazolin-2-yl)phenoxy)methyl)-5-(isothiazol-5-ylmethylsulfonyl)-1,3,4-oxadiazole(13 g-i);

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

RESULTS 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 nine steps. The first step involves coupling of 2,4-dichloro-7-nitroquinazoline(1) with Cis 3,4-dimethylpyrrolidine (2) in ethanol (95%) to give (2S,6R)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylthiomorpholine(Compound3) according to the reported procedure.[66] Compound(3) coupling with 4-hydroxyphenylboronic acid (4) under Suzuki reaction conditions yielded ((3R,4S)-1-(2-(4-hydroxyphenyl)-7-nitroquinazolin-4-yl)-4-methylpyrrolidin-3-yl)methylium (compound 5) as per the reported procedure.[67] compound (5) on reaction with ethyl 2-chloroacetate, K_2CO_3 IN dry Acetone furnished ethyl 2-(4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)acetate (Compound 6) as per the reported procedure.[68]Compound(6) reacts with Hydrazine hydrate to give 2-(4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)acetohydrazide (compound 7) as per the reported procedure.[69] Compound 7 reacts with CS_2,KOH IN Ethanol to afford 5-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole-2(3H)-thione (Compound 8) according to the reported procedure[70]. Compound 8 reacts with Hetero cyclic Methyl halides in Aceto nitrile to give 2-((1H-pyrazol-5-yl)methylthio)-5-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-1,3,4-oxadiazole(9a), 2-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-5-(isoxazol-5-ylmethylthio)-1,3,4-oxadiazole(9b), 2-((4-(4-((3R,4S)-3,4-dimethylpyrrolidin-1-yl)-7-nitroquinazolin-2-yl)phenoxy)methyl)-5-(isothiazol-5-ylmethylthio)-1,3,4-oxadiazole(9c) as per the reported procedure.[70] Compound 9(a-c) reacts with iron powder, ammonium chloride in ethanol to afford 10(a-c) According to the reported procedure.[71] Compound 10(a-c) reacts with compound 11(a-c) in 1,2 di chloro benzene in presence of PCl_3 to give compound (12 a-i) as per the reported procedure.[72] Compound (12 a-i) oxidation with MCPBA to give title compounds 13(a-i) as per the reported procedure.[73] The scheme of synthetic procedure for preparation of title compounds is given in **(Scheme I).**

Characterization

The IR spectrum of the title Compounds 13(a-i) has given stretching vibration at 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The strong Intensity absorption at 1680 cm^{-1} is due to The stretching vibration of C=O which is present

in amide linkage of thiazolidinone ring and 691 cm^{-1} is due to The stretching vibration of C-S of thiazolidinone. The weak Intensity absorption at 1620 cm^{-1} corresponds to a C=N Stretching vibration.1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.

Anti microbial screening

The results of antimicrobial 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 12b and 12d 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 13g, 13d showed excellent anti bacterial and antifungal activity.

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REFERENCES

1. Polshettiwar, V.; Varma, R. S.; *Curr. Opin. Drug Discovery Dev*., 2007; *10: 723.*
2. Padwa, A.; Bur, S. K.; *Tetrahedron.,* 2007; *63: 5341.*
3. D'Souza, D. M.; Muller, T. J.; *Chem. Soc. Rev.,* 2007; *36: 1095.*
4. Sahu, S. K.; Afzal Azam, Md.; Banerjee, M.; Acharrya, S.; Beheraa , C. C.; Si , S.; *J. Braz. Chem. Soc*., 2008; *19: 963.*
5. Saeed, A.; Abbas, N.; Florke, U.; *J. Braz. Chem. Soc*., 2007; *18: 559.*
6. Cerchiaro, G.; Ferreira, A. M. C.; *J. Braz. Chem. Soc*., 2006; *17: 1473.*

7. DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A.*; Comb. Chem. High Throughput Screen.*, 2004; *7*: *473.*
8. Zhang, Y.; Chen, Z.; Lou, Y.; Yu, Y.; Eur. *J. Med. Chem.*, 2009; *44: 448.*
9. Ishida, T.; Suzuki, T.; Hirashima, S.; Mizutani, K.; Yoshida, A.; Ando, I.; Ikeda, S.; Adachi, T.; Hashimoto, H.; *Bioorg. Med. Chem. Lett.*, 2006; *16: 1859.*
10. Herget, T.; Freitag, M.; Morbitzer, M.; Kupfer, R.; Stamminger, T.; Marschall, M.; *Antimicrob. Agents Chemother*., 2004; *48: 4154.*
11. Hranjec, M.; Karminski-Zamola G.; *Chemistry in Industry.*, 2008; *57: 299.*
12. Chan, K. P.; Yang, H.; Hay, A. S.; J. *Polymer Sci.*, 1996; *34: 1923.*
13. Kumar, A.; Rajput, C. S.; *Eur. J. Med. Chem*., 2009; *44: 83*.
14. Spasov, A. A.; Yozhitsa, I. N.; Bugaeva, L. I.; Anisimova, V. A.; *Pharm. Chem. J.*, 1999; *33: 232*.
15. Alexandre, F.; Berecibar, A.; Wrigglesworth, R.; Besson, T.; *Tetrahedron.*, 2003; *59: 1413.*
16. Alagarsamy, V.; Giridhar, R.; Yadav, M. R.; Revathi, R.; Ruckmani, K.; Clercq, E. D.; *Indian J. Pharm. Sci.*, 2006; *68: 532.*
17. Jindal, D. P.; Bhatti, R. S.; Ahlawat, S.; Gupta, R.; *Eur. J. Med. Chem*., 2002; *37: 419*.
18. Sircar, J. C.; Capiris, T.; Kesten, S. J.; Herzig, D. J.; *J. Med. Chem.*, 1981; *24: 735.*
19. Zhang, Y.; Chen, Z.; Lou, Y.; Yu, Y.; *Eur. J. Med. Chem*., 2009; *44: 448.*
20. Rashood, S. T. A.; Aboldahab, I. A.; Nagi, M. N.; Abouzeid, L. A.; Aziz, A. A. M. A.; Hamide, S. G. A.; Youssef, K. M.; Obaid, A. M. A.; Subbagh, H. I. E.; *Bioorg. Med. Chem*., 2006; *14: 8608*.
21. Hennequin, L. F.; Allen, J.; Breed, J.; Curwen, J.; Fennell, M.; Green, T. P.; Brempt, C. L.; Morgentin, R.; Norman, R. A.; Oliver, A.; Otterbein, L.; Ple, P. A.; Warin, N.; Costello, G.; *J. Med. Chem*., 2006; *49: 6465*.
22. Hori, M.; Iemura, R.; Hara, H.; Ozaki, A.; Sukamoto, T.; Ohtaka, H.; *Chem. Pharm. Bull.*, 1990; *38: 681.*
23. Vostrova, L. N.; Voronina, T. A.; Karaseva, T. L.; Gernega, S. A.; Ivanov, É. I.; Kirichenko, A. M.; Totrova, M. Yu.; *Pharm. Chem. J.*, 1986; *20: 404*.
24. Gupta, D. P.; Ahmad, S.; Kumar, A.; Shankar, K.; *Indian J. Chem.*, 1998; *27B: 1060*.
25. Alagarsamy, V.; Rajasolomon, V.; Meena, R.; Ramseshu, K.V.; *Biol. Pharm. Bull.*, 2005; *28: 1091*.
26. Guan, J.; Zhang, Q.; Neil, M.; Obaldia, N.; Ager, A.; Gerena, L.; Lin, A.; *Antimicrob. Agents Chemother.*, 2005; *49: 4928.*

27. Bedi, P. M. S.; Kumar, V.; Mahajan, M. P.*; Bioorg. Med. Chem. Lett*., 2004; *14: 5211.*
28. Gadad, A. K.; Mahajanshetti, C. S.; Nimbalkar, S.; Raichurkar, A. Eur . J. Med. Chem. 2000; *35(9): 853.*
29. Misra, V. S.; Saxena, V. K.; Srivastava, R. *J. Indian Chem. Soc*., 1982; *59: 781.*
30. Zani, F.; Vicini, P. *Arch. Pharm.,* 1998; *331: 219.*
31. Maren, T. H. *Ann. Rev. Pharmacol. Toxicol*., 1976; *16: 309.*
32. Supuran, C. T.; Scozzafava, A.; Jurca, B. C.; Iiies, M. A. *Eur. J. Med. Chem*., 1998*; 33: 83.*
33. Renzi, G.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.,* 2000; *10(7): 673.*
34. Li, J. J.; Anderson, D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H. C.; Isakson, P. C.; Koboldt, C. M.; Logusch, E. W.; Norton, M. B.; Perkins, W. E.; Reinhard, E. J.; Seibert, K.; Veenhuizem, A. W.; Zang, Y.; Reitz, D. B. *J. Med. Chem.,* 1995; *38: 4570.*
35. Yoshino, H.; Ueda, N.; Niijma, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Lijima, A.; Kitoh, K. *J. Med. Chem.,* 1992; *35: 2496*.
36. John HB, John MB. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry.11thed. Philadelphia: Lippincott Williams and Wilkins., 2004: p.1.
37. Katritzky Alan R, Nair Satheesh K, Witek Rachel M, Hutchins Steven M. *Arkivoc,* 2003*; (V): 9-18.*
38. Lokhande TN, Bobade AS, Khadse BG. *Indian Drugs, March.,* 2003; *40(3): 147-150.*
39. Hensler Mary E, Bernstein Gregory, Nizet Victor, Nefzi Adel. *Bioorg & Med Chem Lett.,* 2006; *16: 5073-5079.*
40. Dondas H Ali, Nural Yahya, Duran Nizami, Kilner Colin. *Turk J Chem.,* 2006; *30: 573-583.*
41. Li Xun, Li Yalin, Xu Wenfang. *Bioorg & Med Chem*., 2006; *14: 1287-1293.*
42. Imamura Shinichi, Ishihara Yuji, Hattori Taeko, Kurasawa Osamu, Matsushita Yoshihiro, Sugihara Yoshihiro et al. *Chem Pharm Bull.,* 2004; *52(1): 63-73.*
43. Obniska Jolanta, Zagorska Agnieszka.IL *Farmaco,* 2003; *58: 1227-1234.*
44. Malawska Barbara. *Current Topics In Medicinal Chemistry*, 2005; *5: 69-85.*
45. Colandrea Vincent J, Legiec Irene E, Huo Pei, Yan Lin, Hale Jeffery J, Mills Sander G et al. *Bioorg & Med Chem Lett.,* 2006; *16: 29052908*

46. Yan Lin, Budhu Richard, Huo Pei, Lynch Christopher L, Hale Jeffery J, Mills Sander G et al. *Bioorg & Med Chem Lett.,* 2006; *16: 3564-3568*
47. Zhang Y John, Wang Zhaolin, Sprous Dennis, Nabioullin Roustem. *Bioorg & Med Chem Lett.,* 2006; *16: 525-528.*
48. Barrett David G, Catalano John G, Deaton David N, Hassell Anne M, Long Stacey T, Miller Aaron B et al. *Bioorg & Med Chem Lett.,* 2006; *16: 1735-1739.*
49. Tran Joe A, Chen Caroline W, Jiang Wanlong, Tucci Fabio C, Fleck Beth A, Chen Chen et al. *Bioorg & Med Chem Lett.,* 2007; *17: 5165-5170*
50. Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altinok, G. Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3thiones. *Farmaco.,* 2002; *57: 101-107.*
51. Labanauskas, L.; Kalcas, V.; Udrenaite, E.; Gaidelis, P.; Brukstus, A.; Dauksas, V. Synthesis of 3(3,4-dimethoxyphenyl)-1 H-1,2,4-triazole-5-thiol and 2-amino-5-(3,4-dimethoxyphenyl)-1,3,4thiadiazole derivatives exhibiting anti-inflammatory activity. *Pharmazie.,* 2001; *56: 617-619.*
52. Onkol, T.; Cakir, B.; Sahin, M. F. Synthesis and Antinociceptive Activity of 2-[(2Oxobenzothiazolin-3-yl)methyl]-5-aminoalkyl / aryl-1,3,4-thiadiazole. *Turk. J. Chem.,* 2004; *28: 461-466.*
53. Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Filippeli, W.; Falcone, G.; Giordano, L.; Vitelli, M. R. 3-Arylsulphonyl-5-arylamino-1,3,4-thiadiazol-2(3H)ones as anti-inflammatory and analgesic agents. *Bioorg. Med. Chem*., 2001; *9: 2149-2153.*
54. Gokce. M.; Cakir, B.; Erol, K.; Sahin, M. F. Synthesis and antinociceptive activity of [(2oxobenzothiazolin-3-yl)methyl]-4-alkyl/aryl-1,2,4-triazoline-5-thiones. *Arch. Pharm,* 2001; *334: 279-283.*
55. Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Ponticello, G. S.; Atkinson, J. G.; Wasson, B. K.; Sweet, C. S.; Scriabine, A. Heterocyclic analogues of the antihypertensive beta-adrenergic blocking agents (S)-2-[3-(ter-butylamino)-2-hydroxypropoxy]-3-cyanopyridine. *J. Med. Chem*., 1980; *23: 65-70.*
56. (a) Varvaresou, A.; Tsantili-Kakoulidou, A.; Siatra-Papastasikoudi, T.; Tiligada, E. Synthesis and biological evaluation of indole containing derivatives of thiosemicarbazide and their cyclic 1,2,4triazole and 1,3,4-thiadiazole analogs. *Arzneimittelforschung.,* 2000, *50: 48-54;* (b) Varvaresou, A.; Siatra-Papastasikoudi, T.; Tsontinis, A.; Tsantili-Kakoulidou, A.; Vamvakides, A. Synthesis, lipophilicity and biological evaluation of

indole-containing derivatives of 1,3,4-thiadiazole and 1,2, 4-triazole. *Farmaco.,* 1998; *53: 320-326.*

57. Foroumadi, A.; Mirzaei, M.; Shafiee, A. Antituberculosis agents, I: Synthesis and antituberculosis activity of 2-aryl-1,3,4-thiadiazole derivatives. *Pharmazie.,* 2001; *56: 610-612*.
58. Mamolo, M. G.; Falagiani, V.; Zanpieir, D.; Vio, L.; Banfi, F. Synthesis and antimycobacterial activity of [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid arylidene-hydrazide derivatives. *Farmaco.,* 2001; *56: 587-592.*
59. Wujec, M.; Pitucha, M.; Dobosz, M.; Kosikowska, U.; Malm, A. Synthesis and potential antimycotic activity of 4-substituted-3-(thiophene-2-yl-methyl)-Delta2-1,2,4-triazoline-5-thiones. *Acta Pharm*., 2004; *54: 251-260.*
60. Zamani, K.; Faghifi, K.; Tefighi, I.; Sharlatzadeh, M. R. Synthesis and potential antimycotic activity of 4-substituted 3-(thiophene-2-yl-methyl)-Δ2-1,2,4-triazoline-5-thiones. *Turk. J. Chem.,* 2004; *28: 95-101*.
61. Chen, H.; Li, Z.; Han, Y. Synthesis and fungicidal activity against Rhizoctonia solani of 2-alkyl (Alkylthio)-5-pyrazolyl-1,3,4-oxadiazoles (Thiadiazoles). *J. Agric. Food Chem*., 2000; *48: 5312-5315.*
62. (a) Zou, X. J.; Jin, G. Y.; Zhang, Z. X. Synthesis, fungicidal activity, and QSAR of pyridazinonethiadiazoles. *J. Agric. Food Chem*., 2002; *50: 1461-1454*; (b) Zou, X. J.; Lai, L. H.; Jin, G. Y.; Zhang, Z. X. Synthesis, fungicidal activity, and 3D-QSAR of pyridazinone-substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles. *J. Agric. Food Chem*., 2002; *50*: *3757-3760.*
63. Clerici, F.; Pocar, D.; Guido, M.; Loche, A.; Perlini, V.; Brufani, M. Synthesis of 2-amino-5sulfanyl-1,3,4-thiadiazole derivatives and evaluation of their antidepressant and anxiolytic activity. *J. Med. Chem,* 2001; *44: 931-936.*
64. Sunel, V.; Lionte, C.; Popa, M.; Pintilie, O.; Mungiu, O.; Teleman, S. Synthesis of new methionine derivatives for the treatment of paracetamol-induced hepatic injury. *Eur. Chem. Tech. J.,* 2002; *4: 201-205.*
65. Rhee, S. G.; Chock, P.; Boon, W.; Sugiyama, Y. Subunit interaction in unadenylylated glutamine synthetase from Escherichia coli. Evidence from methionine sulfoximine. *J. Biol. Chem,* 1981; *256: 644-648*.
66. 7 TM PHARMA A/S Patent:*WO2006/10446A2*, 2006; Column *44-45.*
67. Henriksen,SigneTeuber;Sorensen,UlrikSvane *Tetrahedron Letters*, 2006; *47: 8251-8254.*

68. Wen, Huan; Zhou, Yayao;Lin, Chonglan; Ge, Hui; Ma, Lin; Wang, Zihou; Peng, Wenlie;Song,Huacan *Bioorganic and Medicinal Chemistry Letters*, 2007; *17(8): 2123-2125.*
69. Oezil, Musa; Canpolat, Mutlu *Polyhedron*, 2013; *51: 82- 89*
70. Kaplancikli, Zafer Asim; Altintop, Mehlika Dilek; Turan-Zitouni, Gulhan; Ozdemir, Ahmet; Ozic, Rasime; Akaliin, Guelsen *Journal of Enzyme Inhibition and Medicinal Chemistry*, 2012; *27: 51 – 57*
71. Zhang, Zaihui; Daynard, Timothy Scott; Sviridov, Serguei V.; Chafeev, Mikhail A.; Wang, Shisen Patent: US2003/60453 A1, 2003.
72. Feng, Xin Jiang; Wu, Po Lam; Li, King Fai; Wong, Man Shing; Cheah, Kok Wai Chemistry - A *European Journal*, 2011; *17: 2518 – 2526.*
73. Nirmal k.jana and john g.verkade *Org. Lett.*, 2003; *5(21): 3787–3790.*