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ISSN: 2231 – 3087(print)
ISSN: 2230 – 9632 (Online)
Coden HLEEAI
Vol. 5: (2), 2015, 295-310

SYNTHESIS,CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL TRISUBSTITUTED QUINAZOLINE-1,3,4 OXADIAZOLE DERIVATIVES BEARING CIS-SUBSTITUTED THIOMORPHOLINE AND THIAZOLIDIN-4-ONE MOIETIES

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ABSTRACT:
Heterocyclic Chemistry comprises at least half of all organic chemistry research worldwide. Quinazoline and its derivatives constitute an important class of heterocyclic compounds .The chemistry of quinazoline compounds has more than centuries old history, however the intense search for biologically active substances in quinazoline series began only in the last few cascades. In this present communication an attempt is made to cover the medicinally active compounds, along with the recent synthesis, which were reported to possess antimicrobial and antifungal activity.

Key words: 1,3,4 Oxadiazoles ,Anti microbial activity, Thiazolidinones, Quinazolines,Thio morpholines, Heterocyclic

Introduction

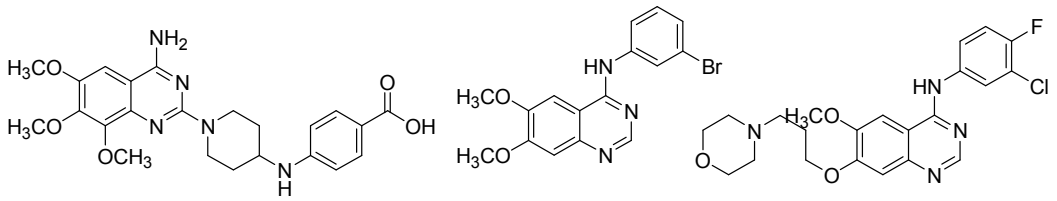
Quinazoline is the main six-membered heterocyclic ring system reported for their biological activities, compounds with multiple pharmacophores, which bring together knowledge of a target with understanding of the molecule types that might interact with the target family.

Quinazoline derivatives, which belong to the nitrogen-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of Quinazoline derivatives, including anti cancer[1-4], antiinflammation[5-6],antibacterial[7-10],antivirus[11],anti cytotoxin[12],antispasm[13],anti tuberculosis[14],anti oxidation[15],anti malarial[16],anti hypertension[17],anti obesity[18],antipsychotic[19],anti diabetes[20],etc.

Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities.

Thiazolidinone and their derivatives are an important class of heterocyclic compounds containing sulphur and nitrogen in a five membered ring. The 4-Thiazolidinone ring system also a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, anti-cancer[21], anti-HIV[22], antimicrobial[23-25], antioxidant[26], analgesic[27], local anesthetic, anti-inflammatory activities[28,29], anti-tubercular[30], anthelmintic activity[31] etc.

2-Amino quinazolines such as (1) have been shown to act as antibacterial agents in several assays. An improved broad-spectrum antibacterial activity against a variety of bacterial strains was found. 4-Amino quinazolines PD 153035 (2) and ZD 1839 (Iressa) (3)have been found to be specific inhibitors of the EpidermalGrowthFactorTyrosineKinase,which is thought to be a key enzyme in respect to the development and progression of tumours in humans.



(1) (2) (3)

Among the five member heterocyclic compounds, 1,3,4-oxadizoles has become an important synthon for the development new therapeutic agents. 1,3,4-oxadiazoles belong to the group of heterocyclic compounds that have been attracting attention for last two decades due to their wide range of biological interactions. 1,3,4-oxadiazole there is a large amount of compounds exhibiting anti-inflammatory activity [32-34]. 1,3,4-Oxadiazoles are an important class of heterocyclic compound with broad spectrum of biological activities in addition to anti-inflammatory activity such as hypoglycemic [35], antimicrobial [36,37], antimycobacterial [38], anticonvulsant [39],anticancer [40], antimalarial [41] etc.

Materials and Methods

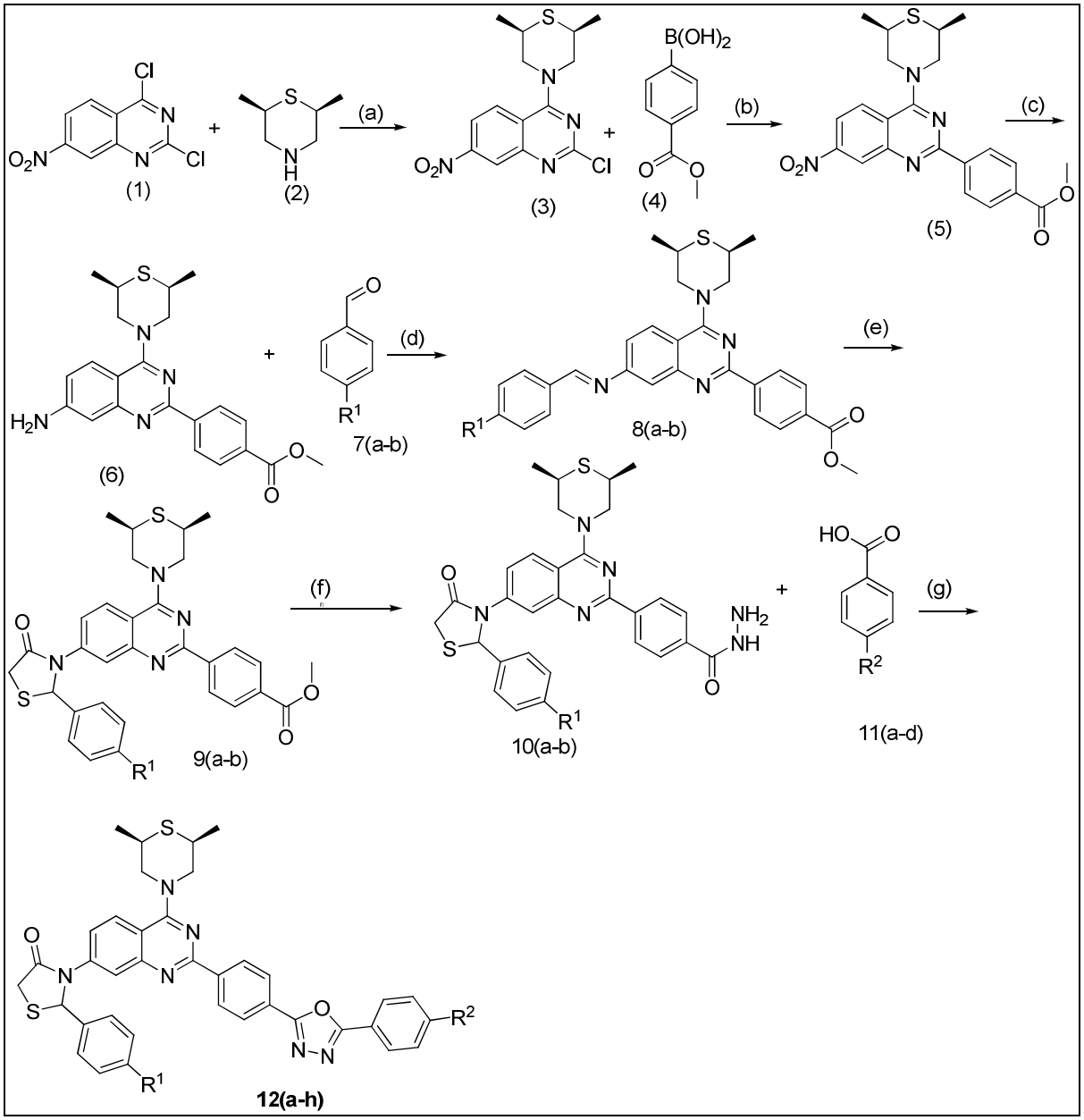
Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. ^{1}H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer using TMS as internal standard. The mass 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 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 fitted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz 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 Reaction conditions: **(a)**Ethanol,0^0C-RT **(b)**DME,Water,Ethanol, $(PPh3)_2PdCl_2$,K_2CO_3**(c)**$SnCl_2$,Conc.HCl**(d)**Toluene,Reflux**(e)**Thio-AceticAcid, $ZnCl_2$,1,4dioxane,Reflux**(f)**Hydrazine hydrate,Ethanol,Reflux**, (g)**$POCl_3$,Reflux

compound	12(a)	12(b)	12(c)	12(d)	12(e)	12(f)	12(g)	12(h)
R^1	$-CF_3$	$-CF_3$	$-CF_3$	$-CF_3$	$-NO_2$	$-NO_2$	$-NO_2$	$-NO_2$
R^2	-H	$-CF_3$	-OMe	$-NO_2$	-H	$-CF_3$	-OMe	$-NO_2$

The title compounds 12(a-h) were synthesised in seven sequential steps using different reagents and reaction conditions, the 12(a-h) were obtained in moderate yields. The structures of 12(a-h) 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 (2S,6R)-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 mmol) and then Cis 2,6,dimethylthiomorpholine (0.2 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 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),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 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)benzoate (compound 5):

A mixture of compound(3) (0.61 mmol), 4-(methoxycarbonyl)phenylboronicacid(4) (0.90mmol), K_2CO_3(3.2mmol) and $(PPh3)_2PdCl_2$ (0.033mmol), 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

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), 8(2H,d,J=8.3HZ),8.1(2H,d,J=8.3HZ),3.9(3H,S,-OCH_3)

Synthesis of methyl 4-(7-amino-4-((2S,6R)-2,6-dimethylthiomorpholino)quinazolin-2-yl)benzoate (compound 6):

$SnCl_2$ (1 g) dissolved in 2.5 mL of conc. HCl was added to the solution of methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)benzoate (compound 5) in 42.5 ml of 6N HCl at 0^oC The reaction mixture was neutralized with KOH 10 minutes later and then extracted with diethylether(Et_2O) and dried with sodium sulphate.The product methyl 4-(7-amino-4-((2S,6R)-2,6-dimethylthiomorpholino)quinazolin-2-yl)benzoate (compound 6) was obtained 75% yield as a liquid form.

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),6.3(2H,S,broad singlet,-N**H**$_2$), 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),3.9(3H,S,-OCH_3)

Synthesis of methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(-4- Tri fluoro methyl /Nitro)benzylideneamino)quinazolin-2-yl)benzoate (compound 8 a-b):

To a solution of the quinazoline amine(compound 6) (10 mmol) in toluene(5v) was added arylaldehyde (7 a-b) (12 mmol) and the reaction mixture was refluxed overnight using a Dean-stark water separator (monitored by TLC) when the reaction was over ,Toluene was evaporated under reduced pressure , and the crude product was used as such for the next reaction.

Compound 8a:

This ^{1}H NMR (400 MHz, $CDCl_3$): 8.2 (d, J=2.4 Hz, 1H), 7.9 (dd, J=9.2, 2.5 Hz, 1H), 7.8 (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), 7.9(2H,d,J=8.3HZ),8.0(2H,d,J=8.3HZ),3.9(3H,S,-OCH_3),7.8(2H,d.J=8.2HZ), 7.7(2H,d,J=8.2HZ), 8.6(1H,S,**H**C=N)

Compound 8b:

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), 7.9(2H,d,J=8.3HZ),8.0(2H,d,J=8.3HZ),3.9(3H,S,-OCH_3),8(2H,d.J=8.2 HZ), 8.4(2H,d,J=8.2HZ), 8.7(1H,S,**H**C=N)

Synthesis of methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(4-oxo-2-(4(trifluoro -methyl/Nitro) phenyl)thiazolidin-3-yl)quinazolin-2-yl)benzoate (compound 9a-b):

An oven-dried Round bottom Flask was charged with a magnetic stir bar, analogs 8a–b (0.01mol), thioglycolic acid (0.02 mol), anhydrous zinc chloride(0.001 mol) and 1,4-dioxane (5v). The flask was placed in a oil bath at refluxed temperature and the reaction slurry was stirred vigorously for 12–14h. After the completion of the reaction, the reaction mass was poured in crushed ice and the resulting precipitate was filtered, washed with water, dried and crystallized with a suitable solvent to obtain 9(a-b). The progress of the reaction was monitored by Thin Layer Chromatography (20percent EA in Hex)

Compound 9a:

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(2H,d,J=8.3HZ),8.0(2H,d,J=8.3HZ),3.9(3H,S,-OCH_3),7.2(2H,d.J=8.2 HZ),7.5(2H,d,J=8.2HZ),6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13HZ

Compound 9b:

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(2H,d,J=8.3HZ),8.0(2H,d,J=8.3HZ),3.9(3H,S,-OCH_3),7.5(2H,d.J=8.2 HZ),8.2(2H,d,J=8.2HZ),6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13HZ

Synthesis of 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(4-oxo-2-(4-(trifluoromethyl/ Nitro)phenyl)thiazolidin-3-yl)quinazolin-2-yl)benzohydrazide (Compound10a-b):

A mixture of compound 9(a-b) (0.01 mol) and hydrazine hydrate (0.03 mol) was refluxed for 6 h using ethanol as a solvent. The formed product was isolated and recrystallized from Ethanol to yield white needle like crystals of pure compound.

Compound 10a:

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(2H,d,J=8.3HZ),8.0(2H,d,J=8.3HZ),8(1H,broad singlet),2(2H,broadsinglet), 7.2(2H,d.J=8.2HZ),7.5(2H,d,J=8.2HZ),6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13HZ)

Compound 10b:

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(2H,d,J=8.3HZ),8.0(2H,d,J=8.3HZ),8(1H,broad singlet,-NH),2(2H,broadsinglet,-NH2),7.5(2H,d.J=8.2HZ), 8.2(2H,d,J=8.2HZ),6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13HZ)

Synthesis of 3-(4-((2S,6R)-2,6-dimethylthiomorpholino)-2-(4-(5-(4-Trifluoro methyl/ methoxy/Nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)quinazolin-7-yl)-2-(4-(trifluoro-methyl/ Nitro)phenyl)thiazolidin-4-one(12a-h):

Acid hydrazide 10(a-b) (3.65 mmol), aromatic acid 11(a-d) (3.65 mmol), Phosphorous oxychloride (5.36 mmol) was added to this mixture and then reaction mixture refluxed for 6 hrs. After completion of the reaction, the mixture was then poured into ice-cold water. The precipitate was filtered and washed with 10 % solution of $NaHCO_3$, and then purified by column chromatography using ethylacetate as an eluent to afford Title compounds(12a-h) 2,5disubstituted-1,3,4-oxadiazoles as slightly yellowish solids.

Compound 12a:

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),7.2(2H,d.J=8.2HZ),7.5(2H,d,J=8.2HZ),6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13 HZ),7.4-8(5H,m)

This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole), 135,126,127,128,130,145,129,125,124(-CF_3 carbon),165(carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)

The EIMS m/z values and corresponding percentage were as follows: 726 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{31}F3N6O_2S_2$ C, 62.97; H, 4.31; N, 11.59; Found: C, 62.95; H, 4.30; N, 11.57

Compound 12b:

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.

This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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),7.9(4H,S), 8.0(2H,d,J=8.3HZ), 7.5(2H,d.J=8.2HZ),7.2(2H,d,J=8.2HZ),6.5(1H,S),

3.9(1H,d,J=13HZ),4(1H,d,J=13HZ),7.7(1H,d,J=8HZ),8(2H,d,J=8HZ)
This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole), 149,128,126,130,124(-CF_3 carbon), 142,130,125,130,165 (carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)
The EIMS m/z values and corresponding percentage were as follows: 794 (M+1 100%) and Anal. calculated for Chemical Formula $C_{39}H_{30}F_6N_6O_2S_2$ C, 59.08; H, 3.81; N, 10.60;
Found: C, 59.06; H, 3.80; N, 10.58

Compound 12c:

yield: 76%

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret),2935(-OCH3 Stretching vibration), 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),8.0(2H,d,J=8.3HZ), 7.00(2H,d.J=8.3HZ), 6.5(1H,S),3.9(1H,d,J=13HZ), 4(1H,d,J=13HZ),7.5(1H,d,J=8HZ),7.2(2H,d,J=8HZ),3.9(3H,S,-OCH_3)
This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole), 129,115,116,160,124(-CF_3 carbon),142,130,125,130,165 (carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons),55(methoxy carbon)
The EIMS m/z values and corresponding percentage were as follows: 756 (M+1 100%) and Anal. calculated for Chemical Formula $C_{39}H_{33}F_3N_6O_3S_2$ C, 62.05; H, 4.41; N, 11.13;
Found: C, 62.03; H, 4.40; N, 11.11

Compound 12d:

yield: 74%

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric), 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),8.3(2H,d,J=8.3HZ),8.4(2H,d.J=8.3HZ), 6.5(1H,S),3.9(1H,d,J=13HZ), 4(1H,d,J=13HZ),7.2(1H,d,J=8HZ),7.5(2H,d,J=8HZ)
This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole),132,130,128,150,124(-CF_3 carbon),142,130,125,130,165(carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)
The EIMS m/z values and corresponding percentage were as follows: 771 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{30}F_3N_7O_4S_2$ C, 59.29; H, 3.93; N, 12.74;
Found: C, 59.29; H, 3.91; N, 12.72

Compound 12e:

yield: 74%

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric Stretching), 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),7.4-8(5H,m), 6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13HZ), 7.5(1H,d,J=8HZ),8.2(2H,d,J=8HZ)
This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole),132,130,128,127,129,145,130,125,145,165(carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)
The EIMS m/z values and corresponding percentage were as follows: 703 (M+1 100%) and Anal. calculated for Chemical Formula $C_{37}H_{31}N_7O_4S_2$ C, 63.32; H, 4.45; N, 13.97
Found: C, 63.30; H, 4.43; N, 13.95

Compound 12f:

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric), 1150(C-F Stret) , 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),8(2H,d,J=8.3HZ),7.7(2H,d,J=8.3HZ), 6.5(1H,S),3.9(1H,d,J=13HZ), 4(1H,d,J=13HZ),7.5(1H,d,J=8HZ),8.2(2H,d,J=8HZ)
This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole),132,130,128,127,129,145,130,125,145,165(carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)
The EIMS m/z values and corresponding percentage were as follows: 771 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{30}F_3N_7O_4S_2$ C, 59.29; H, 3.93 N, 12.74;
Found: C, 59.29; H, 3.93 N, 12.74;

Compound 12g:

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), 1770 (CO of thiazolidinone), 1620(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric) , 2935(-OCH_3 Stretching vibration), 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),8(2H,d,J=8.3HZ),7.1(2H,d,J=8.3HZ),3.9(3H,S,OCH3)6.5(1H,S), 3.9(1H,d,J=13HZ), 4(1H,d,J=13HZ),7.5(1H,d,J=8HZ),8.2(2H,d,J=8HZ)

This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole),130,115,117,160,129,145,123,145,165(carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)
The EIMS m/z values and corresponding percentage were as follows: 733 (M+1 100%) and Anal. calculated for Chemical Formula $C_{38}H_{33}N_7O_5S_2$ C, 62.36; H, 4.54; N, 13.40;
Found: C, 62.34; H, 4.52; N, 13.38

Compound 12h:

yield: 77%

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), 1770 (CO of thiazolidinone), 1624(C=N Stretch),691(C-S of Thiazolidinone),1150(C-F Stret),3100(aromatic C-H stret), 1360 and 1570 cm^{-1}(Two bands for nitro group symmetric and asymmetric) , 1208 cm^{-1} corresponding to C-O-C Stretching, oxadiazole.
This ^{1}H NMR (400 MHz, $CDCl_3$): 7.9 (d, J=2.4 Hz, 1H), 7.5 (dd, J=9.2, 2.5 Hz, 1H), 7.9 (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), 7.9(4H,S),8.3(2H,d,J=8.3HZ),8.4(2H,d,J=8.3HZ),6.5(1H,S),3.9(1H,d,J=13HZ),4(1H,d,J=13 HZ),7.5(1H,d,J=8HZ),8.2(2H,d,J=8HZ)
This ^{13}CNMR (100 MHz, $CDCl_3$): 110,150,120,125,170,115,152,160,135,128,126,165(C_2 and C_5 of 1,3,4 oxa diazole),132,130,132,150,129,145,123,145,165(carbonyl carbon in Thiazolidinone ring),33 and 73(Thiazolidinone ring carbons),23,40,70(aliphatic carbons)
The EIMS m/z values and corresponding percentage were as follows: 748 (M+1 100%) and Anal. calculated for Chemical Formula $C_{37}H_{30}N_8O_6S_2$: C, 59.51; H, 4.05; N, 15.00;
Found: : C, 59.50; H, 4.03; N, 15.00;

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 activity1, 2 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 Trifluoromethyl (12b,12d) and

Nitro(12f,12h) showed more activity than other substituent's the order of activity was 12b>12d>12f>12h>12c>12a>12g>12e.

Table 1: **Antimicrobial activity of 3-(4-((2S,6R)-2,6-dimethylthiomorpholino)-2-(4-(5-(4-Trifluoro methyl/ methoxy/Nitrophenyl)-1,3,4-oxadiazol-2-yl)phenyl)quinazolin-7-yl)-2-(4-(trifluoro-methyl/ Nitro)phenyl)thiazolidin-4-one(12a-h):**

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

Results and discussion

Synthesis:

The present scaffold **12(a-h)** is a part of the synthesis of new chemical entities in the form of antimicrobial agents. The title compounds **12(a-h)** were synthesized in seven steps. The first step involves coupling of 2,4-dichloro-7-nitroquinazoline(1) with Cis 2,6-dimethylthio morpholine(2) in ethanol (95%) to give (2S,6R)-4-(2-chloro-7-nitroquinazolin-4-yl)-2,6-dimethylthiomorpholine(Compound3) according to the reported procedure[42].Compound(3) coupling with 4-(methoxycarbonyl)phenylboronic acid(4) under Suzuki reaction conditions yielded methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-nitroquinazolin-2-yl)benzoate (compound 5) as per the reported procedure[43]. compound (5) on reduction with tin chloride,Conc.HCl furnished 4-(7-amino-4-((2S,6R)-2,6-dimethylthiomorpholino)quinazolin-2-yl)benzoate (compound 6) as per the reported procedure[44].Compound(6) reacts with aryl aldehydes7(a-b) to give methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(-4- Tri fluoro methyl /Nitro)benzylideneamino)quinazolin-2-yl)benzoate (compound 8 a-b) as per the reported procedure[45]. Compound 8(a-b) reacts with thioglycolic acid in presence of Zinc Chloride in 1,4,di oxane furnished methyl 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(4-oxo-2-(4-(trifluoromethyl/Nitro)phenyl)thiazolidin-3-yl)quinazolin-2-yl)benzoate(compound 9 a-b) according to the reported procedure[46]. Compound 9(a-b) reacts with Hydrazine hydrate in ethanol to give 4-(4-((2S,6R)-2,6-dimethylthiomorpholino)-7-(4-oxo-2-(4-(trifluoromethyl/Nitro)phenyl)thiazolidin-3-yl)quinazolin-2-yl)benzohydrazide(Compound 10 a-b) as per the reported procedure[47]. Compound 10(a-b) reacts with different aromatic

acids 11(a-d) in $POCl_3$ to give as a Title compounds 12(a-h) as per the reported procedure[48].
The scheme of synthetic procedure for preparation of title compounds is given in **(Scheme I).**

Characterization:
The IR spectrum of the title Compounds 12(a-h) has given stretching vibration at 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2935 cm^{-1} is due to The stretching vibration corresponding to the methoxy gp.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.

It has been observed from chemical structure of compound 12(a-h) that different pair of protons. The protons of methoxy group appeared as a singlet at δ =3.8 ppm, The protons of methyl group appeared as a multiplet at δ =1.3 ppm,The proton appeared as a singlet at δ =8.6 ppm ,due to the influence of imine linkage. The protons appeared as a doublets(diastereotopic protons) at δ =3.9,4 ppm, due to one side attachment with sulphur and other side attachment with carbonyl group. The protons attached with carbons C_5,C_6,C_8 IN Quinazoline ring appeared between δ =7.5-7.9 ppm respectively.
The chemical shifts of the final compound carbon vary from δ = 175 to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field,eg:The carbonyl carbon which is present in amide linkage (which is present in Thiazolidinone ring) which is directly linked to nitrogen, has a chemical shift value of δ=165 ppm.The carbons which are present in 1,3,4 oxa di azole nucleus C_2,C_5 has a chemical shift value of δ= 165 ppm.The carbon chemical shift of the methoxy group at δ= 55ppm. The carbon chemicalshift of the Tri Fluoro methyl group at δ= 124ppm.

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 12(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 12b,12d showed excellent anti bacterial and antifungal activity.

Acknowledgement:
- The authors are Thankful to Department of Chemistry, Sri Krishna Devaraya University, Anantapuramu.

➢ My sincere thanks to UGC authorities for providing financial assistance to continue research in better manner
➢ I am very thankful to S.K. University authorities for providing such an environment for doing better research very much.
➢ It's my pleasure to express my thanks to Department of Chemistry for giving an opportunity to do research.
➢ I express my sincere thanks to my research Supervisor Dr. K. Sudhakar Babu.
➢ I express my sincere thanks to Prof L.K. Ravindranath, who is giving valuable guidance during my research.
➢ I express my sincere thanks to Prof J.Latha, who is giving valuable guidance during my research.

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Received on February 9, 2015.