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Research Article

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Synthesis, characterization and anti microbial evaluation of novel 1,3,4-oxadiazole containing pyrazolones and 2-thiazolidinone ring systems

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ABSTRACT

4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide were prepared by reflux the ethyl 2-(4-(3-(4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)benzamido)-4-oxothiazolidin-2-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate and hydrazine hydrate afford corresponding 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide.This was subjected to in phosporyl chloride reaction with benzoic acid to give corresponding 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide in excellent yields. The structure of these newly synthesized compounds were characterized by [1]HNMR, Mass, IR & Elemental analysis.

Key words: 1,3,4-oxadiazole, pyrazolones, 2-thiazolidinone, antibactirial and antifungal activity.

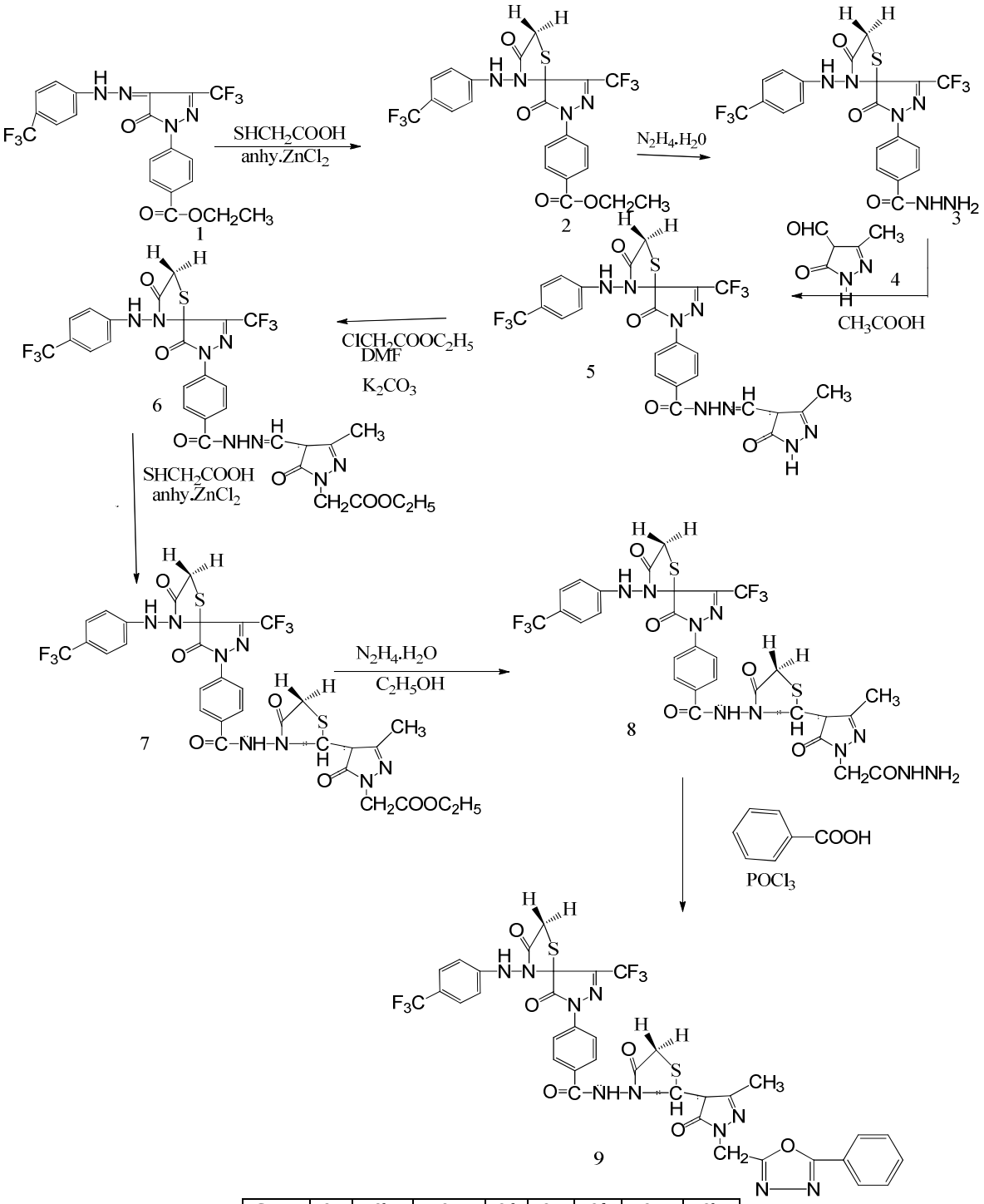
INTRODUCTION

Heterocyclic compounds represents an important class of biologically active molecules specifically, those containing the pyrazolone nucleus have been shown to posses high biological activities such as tranquillizing, muscle relaxant, psycho analeptic, anticonvulsant, antihypertensive, antidepressant activities. The derivatives of pyrazolone are important class of antipyretic and analgesic compounds[1-7]. Thiazolidines have been shown to possess various remarkable biological activities such as analgesic[12], amoebicidal[13], nematocidal[14], anaesthetic[15], mosquito-repellent[16], Anti-HIV, anticancer[17], antibacterial[18-23], antifungal[24-25], antiinflammatory[27-30], antitubercular[31-33], egfr and her-2 kinase Inhibitor[34] and antiproliferative[35-36].

EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. The progress of the reactions was monitored on silica gel-G coated TLC plates using cyclohexane: ethyl acetate (9:1). The spot was visualized by exposing the dry plate to iodine vapour. The IR spectra were recorded in KBr discs on a Shimadzu 8201 PC, FTIR spectrophotometer (vmax in cm-1) and the ^{1}H- NMR spectra was measured on a Bruker DRX-400 spectrometer in DMSO-d_6 at 400 while ^{13}C-nmr spectra was recorded in $CDCl_3$ at 75MHz, using TMS as an internal standard. All chemical shifts are reported on δ scales. The FAB mass spectra were recorded on a Jeol SX–102 mass spectrometer. Elemental analyses were realized on a Carlo Erba-1108 analyzer. The analytical data of all the compounds were highly satisfactory. For column chromatographic purification of the products, Merck silica Gel 60 (230–400 Mesh) was used. The employed reagent grade chemicals were purchased from commercial sources and further purified before use.

Scheme-I



Comp	9a	9b	9c	9d	9e	9f	9g	9h
R	-H	$-CH_3$	$-OCH_3$	-F	-Cl	-Br	$-NO_2$	$-CF_3$

Synthesis of ethyl 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro [4,4]non-8-en-7yl)benzoate(2).

To a solution of (1) in 1,4-dioxane, mercaptoacetic acid and anhydrous $ZnCl_2$ was added drop wise with constant stirring. The reaction mixture was then refluxed on water bath for 2 hours .The progress of the reaction was monitered by using ethyl acetate and acetone as an elutent(9:1).After the completion of the reaction the excess of dioxane was distilled out and resulting mixture was poured in ice cold HCl, filtered, dried and recrystallized from aqueous dimethyl formamide to give the desired product Ethyl 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzoate(2). IR (KBr): 3120 (Ar–NH-group), 1705(C=O group of oxothiozolidine ring),1682(C=O group of ester group), 1652(C=O group of pyrazoline-2-one

ring), 1615(C=N group) &1188 (C-S group). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 10.56(s, H, Ar-NH-N), 4.29 (q, 2H, **$\underline{CH_2}CH_3$**), 1.30 (t, 3H, CH_2**$\underline{CH_3}$**), 3.28(s,H_a of-CH_2 of Thiazolidinone), 3.38(s,H_b of CH_2 of Thiazolidinone), 6.81-7.88 (m, 8H, for C_6H_4 and C_6H_4 of two phenyl group;

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl) benzohydrazide (3)

A solution of ethyl 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro [4,4]non-8-en-7yl)benzoate(2) (0.01 M) and hydrazine hydrate (0.015M) in ethanol 20mL was refluxed for 5 hours.The progress of the reaction was monitored by TLC using ethyl acetate:acetone solvent mixture (9:1).The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afforded 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoro methyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl) benzohydrazide(3).IR (KBr): 3420& 3380(-NH_2 group), 3232(NH of -CONH group), 3208(NH of ArNH-N-group), 1705(>C=O group of oxothiozolidine ring), 1682(>C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1620(>C=N group), &1188 (C-S group). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 2.0 (S, 2H, NH_2), 8.03(s, H, CONH), 10.56(s, H, Ar-NH-N), 3.28(d,H_a of-CH_2 of Thiazolidinone), 3.38(s,H_b of CH_2 of Thiazolidinone), 6.80-7.40(m, 8H, for C_6H_4 and C_6H_4 of two phenyl groups.

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N'-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methylene)benzohydrazide (5)

Equimolar quantity of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triaza spiro [4,4] non-8-en-7yl) benzohydrazide(3) and 4,5-dihydro-3-methyl-5-oxo-1H-pyrazole-4-carbaldehyde(4) were dissolved in absolute alcohol, to this one drop of acetic acid was added then heated on a steam bath for 5-6h at 100 ^{0}C. The progress of the reaction was monitored by TLC using ethyl acetate: acetone (9:1) solvent mixture. After standing for 24h at room temperature, the product was dried and recrystallized from warm aqueous dimethyl formamide to afford compound 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N'-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methylene)benzohydrazide (5). IR (KBr): 3248(-NH of pyrazoline-2-one ring), 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group), 1705(>C=O group of oxoazetidin ring),1682(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1610(>C=N group) respectively. ^{1}HNMR (400 MHz, DMSO–d_6) δ ppm; 10.58(s, H, Ar-NH-N-), 8.03(s,2H,CONH), 6.44(d,1H,J=6.4Hz,CH group attatched to pyrazolone ring), 7.3(s, H, CONH of pyrazoline ring), 3.8(d,H,J=6.4Hz CH of pyrazoline ring), 1.92(s, 3H, CH_3), 3.28(d,H_a of-CH_2 of Thiazolidinone), 3.38(s,H_b of CH_2 of Thiazolidinone), 6.80-7.40 (m, 8H, for two C_6 H_4 groups).

Synthesis of ethyl 2-(4-((2-(4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7ylbenzoyl)hydrazono)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate (6)

A mixture of **(5)**, anhydrous K_2CO_3, Chloro ethyl acetate and DMF were stirred at room temperature for 8 hours. The progress of the reaction was monitored by TLC using ethylacetate : acetone (9:1) as an eluent. The reaction mixture was diluted with ice cold water. The separated solid was identified as ethyl 2-(4-((2-(4-(3,6-dioxo-9-(trifluoro methyl)-4-((4-(trifluoro methyl)phenyl)amino)-1-thia-4,7,8-triaza spiro[4,4]non-8-en-7-ylbenzoyl) hydrazono)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate **(6).** IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),1705(>C=O group of oxothiozolidine ring), 1682(C=O of exocyclic –CONH group), 1652(>C=O group of pyrazoline-2-ring),1610(>C=N group), &1188 (C-S group). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm;1.92(s, 3H, CH_3), 3.28(d, H_a of-CH_2 of Thiazolidinone), 3.38(s, H_b of CH_2 of Thiazolidinone), 4.16(s,2H,,-N-CH_2-C=O group) 6.44 (d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazole ring), 8.03(s, 1H, CONH), 10.65(s, 1H, Ar-NH-N=), 6.80-7.50(m, 8H, for two C_6 H_4 groups,and 3.8(d,H,J=6.4Hz CH of pyrazoline ring).

Synthesis of ethyl 2-(4-(3-(4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)benzamido)-4-oxothiazolidin-2-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) acetate (7)

Mercapto acetic acid (0.01mol) was added drop wise to the reaction mixture of ethyl 2-(4-((2-(4-(3,6-dioxo-9-(trifluoro methyl)-4-((4-(trifluoro methyl) phenyl)amino)-1-thia-4,7,8-triaza spiro[4,4]non-8-en-7-ylbenzoyl) hydrazono)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate (0.01mol,6) and anhydrous $ZnCl_2$ (0.02mol) in dioxane (25ml) at room temperature. The reaction mixture was stirred for 8h and left at room temperature for 3 days. The progress of the reaction was monitored by TLC using ethyl acetate:acetone (9:1) solvent mixture. After the reaction is completed, the contents of the reaction mixture was poured on crushed ice. The product thus formed was filtered and washed with sodium bicarbonate solution. The dried product was recrystalised with absolute alcohol to afford ethyl 2-(4-(3-(4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl) amino)-1-thia-4,7,8-triaza spiro[4,4]non-8-en-7yl)benz amido)-4-oxothia zolidin-2-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) acetate (7).IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N- group), 1705(>C=O group of

oxothiozolidine ring),1682(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1610(>C=N group), &1188 (C-S group) .^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 1.94(d, 3H, CH_3), 3.28(d, H_a, of CH_2 of Thiazolidinone), 3.38(s, H_b,of CH_2 of Thiazolidinone), 6.44 (d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazole ring), 4.16(s,2H, s,2H,,-N-CH_2-C=O group),4.29 (q, 2H, COO**CH$_2$**CH_3), 1.30 (t, 3H, $COOCH_2$**CH$_3$**) 8.03(s, H, CONH), 10.65(s, 1H, Ar-NH-N-), 6.85-7.80(m, 8H, for two C_6 H_4 groups and 3.8(d,H,J=6.4 Hz CH of pyrazoline ring)

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (8)

A solution of (7) and hydrazine hydrate in ethanol was refluxed for 5 hours. The progress of the reaction was monitored by TLC using ethylacetate : acetone (9:1) as an eluent. The reaction mixture was cooled and poured on to ice (50g) with stirring. The separated solid was filtered, washed with water and recrystalised from aqueous dimethyl formamide to afford 4-(3,6-dioxo-9-(trifluoro methyl)-4-((4-(trifluoro methyl) phenyl) amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (8). IR (KBr): 3420& 3380(-NH_2 group), 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N- group),1705(>C=O group of oxothiozolidine ring), 1682(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1610(>C=N group) , &1188 (C-S group) respectively. ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 2.05(s,2H,-NH_2), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 4.09(s,2H ,-N-CH_2-C=O group), 8.03(s, 2H, two CONH), 10.65(s, 1H, Ar-NH-N-), 6.85-7.80(m, 8H, for two C_6H_4 groups, 3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 1.94(s,3H,CH_3).

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide(9)

A mixture of benzoic acids (0.01mol) with compound (8) (0.01mol) in phosphoryl chloride (15ml) was refluxed over a steam bath for 5-6 h. The progress of the reaction was monitored by TLC using ethylacetate : acetone (9:1) as an eluent. The reaction mixture was cooled and poured on to crushed ice (~200g) with continuous stirring. The solid mass separated was neutralized with sodium bicarbonate Solution (10% w/v). The resulting solid thus obtained was collected by filtration, washed well within vacuum and recrystallized from absolute ethanol (95%) to afford 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl) methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothia zolidin-3-yl)benzamide(9a). By adopting the similar procedure, other compounds of the series (9b-h) were prepared using benzoic acid,4-methyl benzoic acid,4-methoxy benzoic acid,4-fluoro benzoic acid, 4-Chloro benzoicacid, 4-Bromo benzoicacid,4-Nitro benzoicacid,4-Trifluoromethyl benzoicacid.. The structures of these newly synthesized compounds **(9a-h)** were characterized by their elemental analysis and spectral data (^{1}H-NMR, ^{13}C-NMR, IR, and Mass).The analytical data of 9a-h was shown in the table I

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9a)

IR (KBr): 3050(Ar-H), 1709(>C=O group of thiazolidine ring), 1685(C=O of exocyclic –CONH group), 1651(>C=O group of pyrazoline-2-ring),1614(>C=N group),1190(C-S),1158(C-O-C),1142(N-N). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 6.80-7.80(m,13H, two C_6H_4 groups and C_6H_5).. 13C NMR (75 MHz, CDCl3,TMS) δ: 154.3-C_1, 113.5-C_2&C_6, 125.7-C_3&C_5, 121.4-C_4, 168.8-C_7, 33.3-C_8, 50.9-C_9, 155.6-C_{10}, 113.5-C_{11} ,173- C_{12}, 143.8- C_{13},121.7-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 164.9-C_{19}, 168.5-C_{20},35.4-C_{21}, 45.8-C_{22}, 48.3-C_{23} ,155.6-C_{24}, 21.7-C_{25}, ,170-C_{26}, ,48.8-C_{27},164.5-C_{28} &C_{29},126.2- C_{30}, 127.5-C_{31}& C_{35}, 129.3-C_{32}& C_{34},, 128.8-C_{33}, 124.2-C_{36}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(p-tolyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9b)

IR (KBr): 3049(Ar-H), 1708(>C=O group of thiazolidine ring),1685(C=O of exocyclic –CONH group),1651(>C=O group of pyrazoline-2-ring),1615(>C=N group) ,1189(C-S),1159(C-O-C),1143(N-N). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and

6.85-7.80(m,12H, three C_6H_4 groups).. 13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.3-C_1, 113.5-C_2&C_6, 125.8-C_3&C_5, 121.4-C_4, 168.8-C_7, 33.3-C_8, 51.0-C_9, 155.6-C_{10}, 113.5-C_{11} ,173.1- C_{12}, 143.8- C_{13},121.7-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 164.9-C_{19}, 168.5-C_{20},35.4-C_{21}, 45.8-C_{22}, 48.3-C_{23} ,155.6-C_{24}, 22.4-C_{25}, ,175.0-C_{26}, ,48.8-C_{27},164.5-C_{28} &C_{29},123.2- C_{30}, 127.4-C_{31}& C_{35}, 129.6-C_{32}& C_{34},, 138.4-C_{33}, 24.3-C_{36} , 124.2-C_{37}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-methoxyphenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9c)

IR (KBr): 3049(Ar-H), 1706(>C=O group of thiazolidine ring),1686(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1615(>C=N group) ,1188(C-S),1159(C-O-C),1144(N-N).^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 6.90-7.70(m,12H, three C_6H_4 groups). 13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.4-C_1, 113.6-C_2&C_6, 125.8-C_3&C_5, 121.5-C_4, 168.9-C_7, 33.4-C_8, 51.1-C_9, 155.7-C_{10}, 113.6-C_{11} ,173.2- C_{12}, 143.8- C_{13},121.8-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 165.0-C_{19}, 168.6-C_{20},35.5-C_{21}, 45.9-C_{22}, 48.4-C_{23} ,155.7-C_{24}, 22.5-C_{25}, ,175.1-C_{26}, ,48.9-C_{27},164.6-C_{28} &C_{29},118.5- C_{30}, 128.5-C_{31}& C_{35}, 114.8-C_{32}& C_{34},, 160.7-C_{33}, 55.9-C_{36} , 124.2-C_{37}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-fluorophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol -4-yl)-4-oxothiazolidin-3-yl)benzamide (9d)

IR (KBr): 3048(Ar-H), 1705(>C=O group of thiazolidine ring),1686(C=O of exocyclic –CONH group),1653(>C=O group of pyrazoline-2-ring),1613(>C=N group) ,1188(C-S),1160(C-O-C),1145(N-N).. ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 7-7.80(m,12H, three C_6H_4 groups).13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.4-C_1, 113.6-C_2&C_6, 125.9-C_3&C_5, 121.5-C_4, 168.9-C_7, 33.5-C_8, 51.2-C_9, 155.6-C_{10}, 113.7-C_{11} ,173.2- C_{12}, 143.9- C_{13},121.8-C_{14} &C_{18},127.7-C_{15} & C_{17},129.9-C_{16} , 165.0-C_{19}, 168.7-C_{20},35.6-C_{21}, 46.0-C_{22}, 48.5-C_{23} ,155.7-C_{24}, 22.6-C_{25}, ,175.1-C_{26}, ,48.9-C_{27},164.6-C_{28} &C_{29},121.8- C_{30}, 129.1-C_{31}& C_{35}, 116-C_{32}& C_{34},, 162.9-C_{33}, 124.2-C_{36}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-chlorophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol -4-yl)-4-oxothiazolidin-3-yl)benzamide (9e)

IR (KBr): 3045(Ar-H), 1702(>C=O group of thiazolidine ring),1684(C=O of exocyclic –CONH group),1653(>C=O group of pyrazoline-2-ring),1614(>C=N group),1265(C=S) ,1179(C-S),1164(C-O-C),1147(N-N).^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 6.90-7.7(m,12H, three C_6H_4 groups). 13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.5-C_1, 113.7-C_2&C_6, 125.8-C_3&C_5, 121.6-C_4, 169.0-C_7, 33.5-C_8, 51.3-C_9, 155.7-C_{10}, 113.7-C_{11} ,173.2- C_{12}, 143.9- C_{13},121.7-C_{14} &C_{18},127.7-C_{15} & C_{17},129.9-C_{16} , 165.0-C_{19}, 168.8-C_{20},35.6-C_{21}, 46.1-C_{22}, 48.5-C_{23} ,155.8-C_{24}, 22.6-C_{25}, ,175.2-C_{26}, ,49.0-C_{27},164.7-C_{28} &C_{29},124.3- C_{30}, 128.9-C_{31}& C_{35}, 129.4-C_{32}& C_{34},, 134.3-C_{33}, 124.2-C_{36}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-bromophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol -4-yl)-4-oxothiazolidin-3-yl)benzamide (9f)

IR (KBr): 3046(Ar-H), 1700(>C=O group of thiazolidine ring),1682(C=O of exocyclic –CONH group),1655(>C=O group of pyrazoline-2-ring),1619(>C=N group) ,1166(C-S),1162(C-O-C),1141(N-N).^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 6.80-7.6(m,12H, three C_6H_4 groups).13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.4-C_1, 113.6-C_2&C_6, 125.9-C_3&C_5, 121.5-C_4, 169.1-C_7, 33.6-C_8, 51.3-C_9, 155.8-C_{10}, 113.8-C_{11} ,173.3- C_{12}, 143.7- C_{13},121.9-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 165.1-C_{19}, 168.8-C_{20},35.7-C_{21}, 46.2-C_{22}, 48.6-C_{23} ,155.7-C_{24}, 22.7-C_{25}, ,175.2-C_{26}, ,49.1-C_{27},164.7-C_{28} &C_{29},125.2- C_{30}, 129.7-C_{31}& C_{35}, 132.2-C_{32}& C_{34},, 133.1-C_{33}, 124.3-C_{36}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-nitrophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9g)

IR (KBr): 3042(Ar-H), 1707(>C=O group of thiazolidine ring),1690(C=O of exocyclic –CONH group),1657(>C=O group of pyrazoline-2-ring),1612(>C=N group) ,1179(C-S),1158(C-O-C),1145(N-N).^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz,-CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S),. 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 7.0-8.0(m,12H, three C_6H_4 groups). 13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.5-C_1, 113.7-C_2&C_6, 125.9-C_3&C_5, 121.6-C_4, 169.1-C_7, 33.7-C_8, 51.2-C_9, 155.7-C_{10}, 113.8-C_{11} ,173.3- C_{12}, 143.8- C_{13},121.8-C_{14} &C_{18},127.7-C_{15} & C_{17},129.9-C_{16} , 165.1-C_{19}, 168.9-C_{20},35.8-C_{21}, 46.3-C_{22}, 48.7-C_{23} ,155.7-C_{24}, 22.7-C_{25}, ,175.3-C_{26}, ,49.2-C_{27},164.7-C_{28} &C_{29},129.5- C_{30}, 127.8-C_{31}& C_{35}, 135.7-C_{32}& C_{34},, 131.0-C_{33}, 124.2-C_{36}

Synthesis of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro [4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-(trifluoromethyl)phenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9h)

IR (KBr): 3040(Ar-H), 1705(>C=O group of thiazolidine ring),1695(C=O of exocyclic –CONH group),1659(>C=O group of pyrazoline-2-ring),1610(>C=N group) ,1168(C-S),1168(C-O-C),1147(N-N). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.09(s,2H ,-N-CH_2-C=O group), 6.44(d,1H,J=6.4Hz ,CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, H_a of CH_2 of Thiazolidin attached to –S), 3.38(s, H_b,of CH_2 of Thiazolidinone), 1.94 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N-),3.8(d,H,J=6.4Hz CH of pyrazoline ring) and 7.10-8.2(m,12H, three C_6H_4 groups).13C NMR (75 MHz, $CDCl_3$,TMS) δ: 154.5-C_1, 113.7-C_2&C_6, 125.9-C_3&C_5, 121.7-C_4, 169.2-C_7, 33.8-C_8, 51.4-C_9, 155.8-C_{10}, 113.9-C_{11} ,173.3- C_{12}, 143.9- C_{13},121.9-C_{14} &C_{18},127.7-C_{15} & C_{17},129.9-C_{16} , 165.2-C_{19}, 168.9-C_{20},35.9-C_{21}, 46.3-C_{22}, 48.8-C_{23} ,155.8-C_{24}, 22.8-C_{25}, ,175.3-C_{26}, ,49.2-C_{27},164.8-C_{28} &C_{29},129.5- C_{30}, 127.8-C_{31}& C_{35}, 135.7-C_{32}& C_{34},, 131.0-C_{33}, 124.2-C_{36}

Table I. Analytical data of the compounds

Comp	R	M.P. °C	Yield %	Mol. formula	%Analysis					
					C		H		N	
					Cald	Found	Cald	Found	Cald	Found
9a	H	175-3	70	$C_{36}H_{26}F_6N_{10}O_6S_2$	49.54	49.47	3.00	2.92	16.05	15.96
9b	CH_3	177-4	70	$C_{37}H_{28}F_6N_{10}O_6S_2$	50.11	50.02	3.18	3.06	15.79	15.68
9c	OCH_3	179-4	65	$C_{37}H_{28}F_6N_{10}O_7S_2$	49.22	49.11	3.13	3.01	15.51	15.42
9d	F	171-5	72	$C_{36}H_{25}F_7N_{10}O_6S_2$	48.54	48.45	2.83	2.73	15.72	15.67
9e	Cl	180-3	70	$C_{36}H_{25}ClF_6N_{10}O_6S_2$	47.66	47.54	2.78	2.66	15.44	15.35
9f	Br	183-3	75	$C_{36}H_{25}BrF_6N_{10}O_6S_2$	45.43	45.34	2.65	2.58	14.72	14.60
9g	NO_2	195-5	75	$C_{36}H_{25}F_6N_{11}O_8S_2$	47.11	47.01	2.75	2.68	16.79	16.69
9h	CF_3	175-6	74	$C_{37}H_{25}F_9N_{10}O_6S_2$	47.24	47.13	2.68	2.56	14.89	14.79

Biological activity

The antimicrobial activity [8-10] of these newly synthesized compounds was performed according to disc diffusion method, as recommended by the national committee of clinical laboratory[11]. The synthesized compounds were used at the concentration of 250µ/ml DMF as a solvent[12]

Anti- Bacterial Activity:

The antibacterial activity of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triaza spiro[4,4] non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9a-h) were screened against the staphylococcus aures (gram positive) and Escherichia coli (gram negative) organisms. Most of the compounds exhibited moderate antibacterial activity against both bacteria. The presence of chloro, bromo, and nitro in the structure has shown increased effect on their antibacterial activity [18-23] in the following table II.

Antifungal Activity:

Antifungal activity of 4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triaza spiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9a-h) were screened against *Aspergillus niger, Candida albicans*[24-25]. The presence of chloro, bromo and nitro in the structure has shown increased effect on their antibacterial activity in the following table II.

Table II. Antibacterial activity and Anti fungal activity by the disc diffusion method

Entry	Bacteria								fungi	
	Staphylococcus aureus NCCS2079		*Bacillus Cereus NCCS2106*		*Escherichia Coli NCCS2065*		*Candida albicans NCCS2106*		*Aspergillus nigur NCCS 1196*	
	25	50	25	50	25	50	25	50	25	50
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoro methyl) phenyl) amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-phenyl-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9a)	_	15	_	14	_	13	_	17	_	16
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl) phenyl) amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(p-tolyl)-1,3,4-oxodiazol-2-yl) methyl) -4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl) benzamide (9b)	_	14	_	16	_	15	_	18	_	14
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl) phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-methoxyphenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9c)	_	16	_	16	_	17	_	18	_	15
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl) phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-fluorophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9d)	18	22	18	23	16	20	15	20	15	16
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-chlorophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9e)	16	20	16	21	16	19	13	18	12	16
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl) phenyl) amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-bromophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9f)	15	18	16	20	15	18	12	17	12	16
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl)phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-nitrophenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9g)	19	22	19	23	18	21	15	18	13	16
4-(3,6-dioxo-9-(trifluoromethyl)-4-((4-(trifluoromethyl) phenyl)amino)-1-thia-4,7,8-triazaspiro[4,4]non-8-en-7yl)-N-(-2-(3-methyl-5-oxo-1-((5-(4-(trifluoromethyl)phenyl)-1,3,4-oxodiazol-2-yl)methyl)-4,5-dihydro-1H-pyrazol-4-yl)-4-oxothiazolidin-3-yl)benzamide (9h)	20	23	20	25	19	22	19	18	15	17
Chloromphenicol(5)	-	28	-	29	-	25	-	-	-	-
Ketocanazole(50)	-	-	-	-	-	-	-	21	-	19

RESULTS AND DISCUSSION

The IR spectrum of 9a revealed the appearance of bands characteristics of 3050(Ar-H), 1709(>C=O group of thiazolidine ring), 1685(C=O of exocyclic –CONH group), 1651(>C=O group of pyrazoline-2-ring), 1614(>C=N group), 1190(C-S), 1158(C-O-C), 1142(N-N). In ^{1}H-NMR ($(CD)_2SO$) the compounds (9a) shown δ ppm; 4.21(s,2H $-CH_2$), 6.44(s, 1H, -CH of Thiazolidin attached to pyrazoline-5-one ring), 3.28(s, $2H_a$ of CH_2 of Thiazolidin attached to –S),. 3.38(s, $2H_b$, of CH_2 of Thiazolidinone), 1.94 (s, 3H, $-CH_3$ attatched to pyrazoline ring), 8.03 (s, H, CONH), 10.56(s, H, Ar-NH-N=), 3.4(d, H, CH of pyrazoline ring) and 6.80-7.80(m, 12H, three C_6H_4 groups). The ^{13}C-NMR spectrum of ($CDCl_3$) shown δ: 154.3-C_1, 113.5-C_2 & C_6, 125.7-C_3 & C_5, 121.4-C_4, 163.8-C_7, 33.3-C_8, 50.9-C_9, 155.6-C_{10}, 113.5-C_{11} ,173- C_{12}, 143.8- C_{13},121.7-C_{14} & C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 164.9-C_{19}, 168.5-C_{20}, 35.4-C_{21}, 45.8-C_{22}, 48.3-C_{23} ,155.6-C_{24}, 21.7-C_{25},170. -C_{26}, 48.8-C_{27}, 164.5-C_{28} &C_{29}, 126.2- C_{30}, 127.5-C_{31}& C_{35}, 129.3-C_{32} & C_{34}, 128.8-C_{33}, 124.2-C_{36} conformed the formation of compound 9a.

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