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Der Pharma Chemica, 2013, 5(5):205-212
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

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

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ABSTRACT

4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazet-idin-1-yl)benzamide were prepared by reflux the ethyl 2-(4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzamido)-4-oxoazetidin-2-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate and hydrazine hydrate afford corresponding 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl) phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxo azetidin-1-yl)benzamide. This was subjected to in phosporyl chloride reaction with benzoic acid to give corresponding 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl) phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxo azetidin-1-yl)benzamide in excellent yields. The structure of these newly synthesized compounds were characterized by 1HNMR,Mass, IR& Elemental analysis.

Key words: 1,3,4-Oxadiazole, pyrazolones ,2-Azetidinone ,Antibactirial and antifungal activity.

INTRODUCTION

Heterocyclic compounds represents an important class of biologically active molecules specifially, those containing the pyrazolone nucleus have been shown to posses high biological actives 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]. Some substituted pyrazolines and their derivatives such as 2-oxo-azetidine ring shows various biological activities such as antimicrobial activity[8-10] antifungal (13-17), antibacterial (18-23), antitubercular (24-26), anticonvulsant(27), analgesic, anti-inflammatory (28), synthetic precursor for amino acids (29), and antiviral (30).

MATERIALS AND METHODS

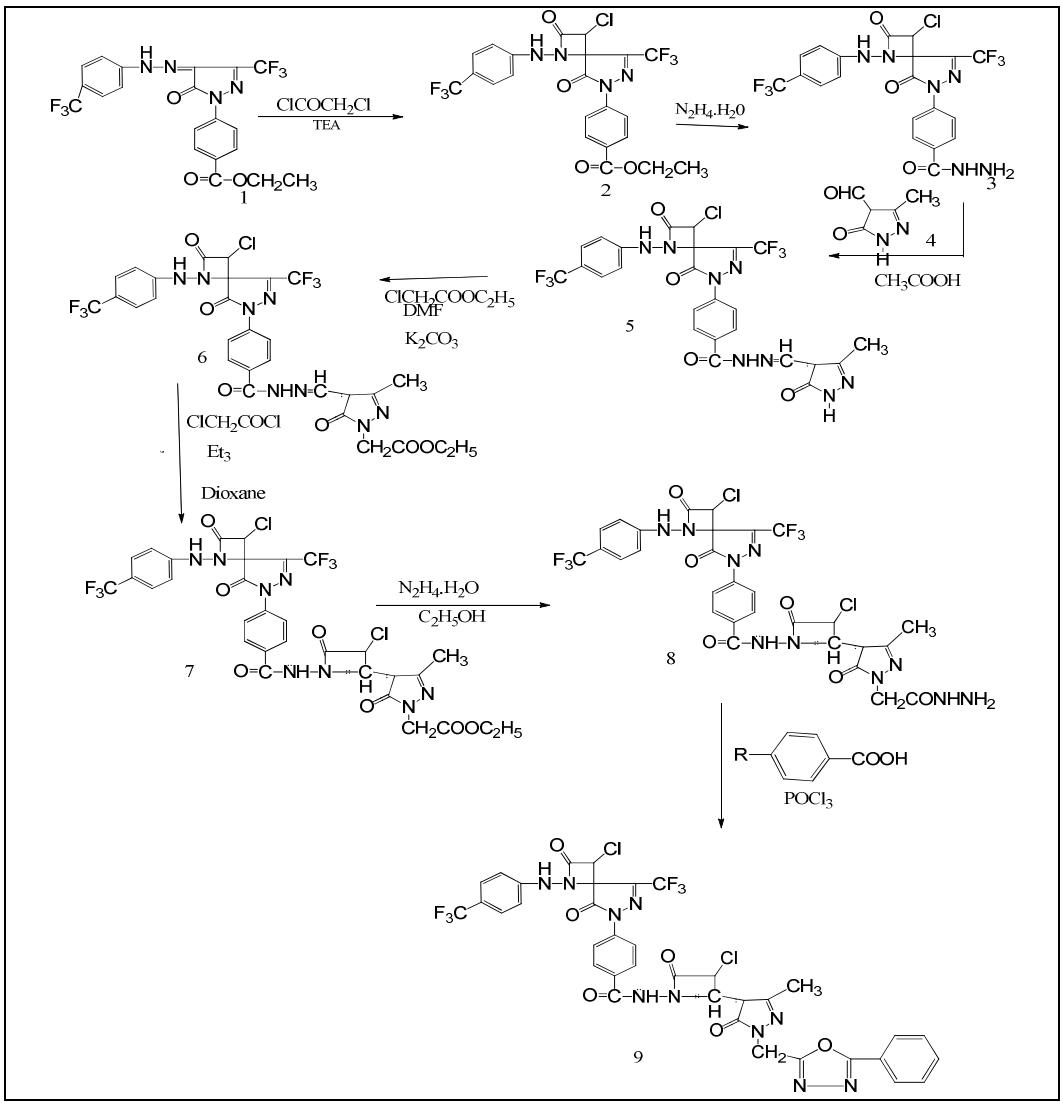
Melting points were taken in open capillaries and are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates using MeOH: $CHCl_3$ system (1:9). The spot was visualized by exposing the dry plate to iodine vapours chamber. IR spectra were recorded in KBr disc on a Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 MHz using TMS as an internal standard. All chemical shifts were reported on δ scales. The FAB mass spectra were recorded on a Jeol SX-102 mass spectrometer. Elemental analyses were performed on a Carlo Erba-1108 analyzer. Microwave irradiation was carried out in an open glass vessel. Modified microwave oven (800 W) was

used for the synthesis of the compounds. A thermocouple was used to monitor the temperature inside the vessel of the microwave. 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 reagent grade chemicals were purchased from the commercial sources and further purified before use.

RESULTS AND DISCUSSION

The IR spectrum of 9a revealed the appearance of bands characteristics of 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3038(Ar-H str),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),1148(C-O-C),1132(N-N),831(C-Cl). In [1] H-NMR ((CD)2SO) the compounds (9a) shown δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,13H, two C_6H_4 group and one C_6H_5 group). The ^{13}C-NMR spectrum of (CDCl3) shown δ:154.3-C_1, 113.5-C_2&C_6, 125.7-C_3&C_5, 121.4-C_4, 163.5-C_7, 57.8-C_8, 52.0-C_9, 155.6-C_{10}, 114.1-C_{11} ,173.1- C_{12}, 143.8- C_{13},121.8-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 164.9-C_{19}, 163.2-C_{20},58.9-C_{21}, 50.9-C_{22}, 41.2-C_{23} ,155.6-C_{24}, 22.4-C_{25}, ,175.0-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.

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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triaza spiro[3,4]oct-7-en-6-yl)benzoate(2).

To a solution of (1) in 1,4-dioxane,chloro acetyl chloride and, triethyl amine 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 oxo azetidin ring),1682(C=O group of ester group),1652(C=O group of pyrazoline-2-one ring). ^{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**$\underline{CH_3}$**), 5.44(s,1H,-CH of azetidin attached to –Cl), 6.81-7.88 (m, 8H, for C_6H_4 and C_6H_4 of two phenyl group;

Synthesis of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)benzohydrazide (3)

A solution of 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)(0.01 M) and hydrazine hydrate (0.015M) in ethanol 20mL was refluxed for 5 hours.The progress of the reaction was monitored byTLC using ethyl acetate:acetone (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 aqueous dimethyl formamide to afforded 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)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 oxoazetidin ring),1652(>C=O group of pyrazoline-2-ring),1620(>C=N 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), 5.44(s,1H,-CH of azetidin attached to –Cl), 6.80-7.40(m, 8H, for C_6H_4 and C_6H_4 of two phenyl groups.

Synthesis of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N'-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methylene)benzohydrazide (5)

Equimolar quantities of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)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 byTLC using ethyl acetate:acetone (9:1). After standing for 24h at room temperature, the product was dried and recrystallized from warm aqueous dimethyl formamide to afford compound 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4] oct-7-en-6-yl)-N'-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)methylene)benzohydrazide (5) obtained. 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,1H,CONH), 5.16(d,H, J=7.6Hz CH group attatched to pyrazolone ring) 3.4(d,H,J=7.6Hz CH of pyrazoline ring), 7.3(s,H,CONH of pyrazoline ring), 5.44(s,1H,-CH of azetidin attached to –Cl),1.92(s,3H,CH_3 of pyrazolone ring), 6.80-7.40 (m, 8H, for two C_6 H_4 groups).

Synthesis of ethyl 2-(4-((2-(4-(3-chloro-2,5-dioxo-8-(trifluoromethyl) phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzoyl)hydrazono)methyl)-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 byTLC using ethyl acetate:acetone (9:1). The reaction mixture was diluted with ice cold water. The separated solid was identified as ethyl 2-(4-((2-(4-(3-chloro-2,5-dioxo-8-(trifluoromethyl) phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzoyl)hydrazono) methyl)-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 oxoazetidin ring),1682(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1610(>C=N group). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 1.82(s, 3H, CH_3), 5.16(d,1H,J=7.6Hz -CH attached to pyrazoline-2-one ring), 3.4(d,1H,J=7.6Hz CH of pyrazoline ring, 4.16(s,2H,CH_2),4.29 (q, 2H,J=6.5HzCOO**$\underline{CH_2}$**CH_3), 1.30 (t, 3H, J=6.5Hz $COOCH_2$**$\underline{CH_3}$**), 8.03(s, H, CONH), 10.65(s, 1H, Ar-NH-N=), 6.80-7.40(m, 8H, for two C_6H_4groups.

Synthesis of ethyl 2-(4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzamido)-4-oxoazetidin-2-yl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl) acetate(7)

Monochloroacetyl chloride (0.01mol) was added drop wise to ethyl 2-(4-((2-(4-(3-chloro-2,5-dioxo-8-(trifluoromethyl) phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzoyl)hydrazono)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate (6) (0.01mol) and triethyl amine (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). 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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)benzamido)-4-oxoazetidin-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 oxoazetidin ring),1682(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1610(>C=N group) .^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 1.82(s, 3H, CH_3), 5.16(d,1H,J=7.6Hz -CH of azetidin attached to pyrazole ring), 3.4(d,H,J=7.6Hz CH of pyrazoline ring, 5.44(d,2H,-CH of azetidin attached to –Cl), 4.16(s,2H,CH_2),4.29 (q, 2H,J=6.5HzCOO**$\underline{CH_2}$**CH_3), 1.30 (t, 3H, J=6.5Hz $COOCH_2$**$\underline{CH_3}$**), 8.03(s, H, CONH), 10.65(s, 1H, Ar-NH-N=), 6.80-7.40(m, 8H, for two C_6H_4groups.

Synthesis of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-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 eluent. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystalised from ethanol to afford **4**-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-(2-hydrazinyl-2-oxoethyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(8). IR (KBr): 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) ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 2.10(s, 2H, -NH_2), 5.16(m,1H -CH of azetidin attached to pyrazole ring), 3.4(d,H,J=5.6Hz CH of pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl), 4.09(s,2H,CH_2),1.92(s,3H,-CH_3) , 8.03(s, 2H, CONH), 10.65(s, 1H, Ar-NH-N=), 6.80-7.40(m, 8H, for two C_6H_4groups.

Synthesis of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9)

A mixture of benzoic acid (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 with cold water, dried in vacuum and recrystallized from absolute ethanol to afford N-(3-chloro-5-(1-((5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)methyl)-5-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-oxopyrrolidin-1-yl)-4-(5-thioxo-3-(trifluoromethyl)-4-(2-(4(trifluoromethyl)phenyl)hydrazono)-4,5-dihydro-1H-pyrazol-1-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9a)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3038(Ar-H str),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),1148(C-O-C),1132(N-N),831(C-Cl) . ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,13H, two C_6H_4 group and one C_6H_5 group). 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, 163.5-C_7, 57.8-C_8, 52.0-C_9, 155.6-C_{10}, 114.1-C_{11} ,173.1- C_{12}, 143.8-C_{13},121.8-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 164.9-C_{19}, 163.2-C_{20},58.9-C_{21}, 50.9-C_{22}, 41.2-C_{23} ,155.6-C_{24}, 22.4-C_{25}, ,175.0-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-methyl phenyl)-1,3,4-oxadiazol-2-yl)methyl) -3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9b)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3039(Ar-H str),1706(>C=O group of oxoazetidin ring),1682(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1611(>C=N group),1149(C-O-C),1133(N-N),832(C-Cl). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,12H, two C_6H_4 groups). 13C NMR (75 MHz, CDCl3,TMS) δ: 154.3-C_1, 113.5-C_2&C_6, 125.8-C_3&C_5, 121.4-C_4, 163.5-C_7, 57.8-C_8, 52.0-C_9, 155.6-C_{10}, 114.1-C_{11} ,173.1- C_{12}, 143.8- C_{13},121.8-C_{14} &C_{18},127.7-C_{15} & C_{17},129.8-C_{16} , 164.9-C_{19}, 163.2-C_{20},58.9-C_{21}, 50.9-C_{22}, 41.2-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}, 124.3-C_{36},124.2- C_{37}

Synthesis of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-methoxy phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9c)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3039(Ar-H str),1706(>C=O group of oxoazetidin ring),1683(C=O of exocyclic –CONH group),1652(>C=O group of pyrazoline-2-ring),1611(>C=N group),1149(C-O-C),1134(N-N),832(C-Cl). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,12H, two C_6H_4 groups). 13C NMR (75 MHz, CDCl3,TMS) δ: 154.4-C_1, 113.6-C_2&C_6, 125.8-C_3&C_5, 121.5-C_4, 163.6-C_7, 57.8-C_8, 52.1-C_9, 155.7-C_{10}, 114.2-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}, 163.3-C_{20},59.0-C_{21}, 50.9-C_{22}, 41.3-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-fluoro phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9d)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3040(Ar-H str),1707(>C=O group of oxoazetidin ring),1683(C=O of exocyclic –CONH group),1653(>C=O group of pyrazoline-2-ring),1613(>C=N group),1150(C-O-C),1135(N-N),833(C-Cl) . ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,12H, two C_6H_4 groups).13C NMR (75 MHz, CDCl3,TMS) δ: 154.4-C_1, 113.6-C_2&C_6, 125.9-C_3&C_5, 121.5-C_4, 163.6-C_7, 57.9-C_8, 52.2-C_9, 155.6-C_{10}, 114.2-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}, 163.3-C_{20},59.0-C_{21}, 51.0-C_{22}, 41.3-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-chloro phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9e)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3041(Ar-H str),1713(>C=O group of oxoazetidin ring),1681(C=O of exocyclic –CONH group),1653(>C=O group of pyrazoline-2-ring),1616(>C=N group),1155(C-O-C),1137(N-N),838(C-Cl). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,12H, two C_6H_4 groups). 13C NMR (75 MHz, CDCl3,TMS) δ: 154.5-C_1, 113.7-C_2&C_6, 125.8-C_3&C_5, 121.6-C_4, 163.7-C_7, 57.9-C_8, 52.3-C_9, 155.7-C_{10}, 114.3-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}, 163.4-C_{20},59.1-C_{21}, 51.1-C_{22}, 41.4-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-bromo phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9f)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3040(Ar-H str),1711(>C=O group of oxoazetidin ring),1679(C=O of exocyclic –CONH group),1655(>C=O group of pyrazoline-2-ring),1611(>C=N group),1158(C-O-C),1141(N-N),836(C-Cl). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring)

and 6.59-7.93(m,12H, two C_6H_4 groups). 13C NMR (75 MHz, CDCl3,TMS) δ: 154.4-C_1, 113.6-C_2&C_6, 125.9-C_3&C_5, 121.5-C_4, 163.6-C_7, 57.8-C_8, 52.3-C_9, 155.8-C_{10}, 114.4-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}, 163.4-C_{20},59.1-C_{21}, 51.1-C_{22}, 41.3-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-nitro phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9g)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3042(Ar-H str),1707(>C=O group of oxoazetidin ring),1687(C=O of exocyclic –CONH group),1657(>C=O group of pyrazoline-2-ring),1616(>C=N group),1156(C-O-C),1135(N-N),832(C-Cl). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,12H, two C_6H_4 groups). 13C NMR (75 MHz, CDCl3,TMS) δ: 154.5-C_1, 113.7-C_2&C_6, 125.9-C_3&C_5, 121.6-C_4, 163.7-C_7, 57.9-C_8, 52.2-C_9, 155.7-C_{10}, 114.3-C_{11} ,173.2- 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}, 163.5-C_{20},59.1-C_{21}, 51.2-C_{22}, 41.4-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro [3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-trifluoromethyl phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9h)

IR (KBr): 3232(exocyclic NH of -CONH group), 3208(NH of ArNH-N= group),3040(Ar-H str),1707(>C=O group of oxoazetidin ring),1692(C=O of exocyclic –CONH group),1659(>C=O group of pyrazoline-2-ring),1613(>C=N group),1158(C-O-C),1137(N-N),835(C-Cl). ^{1}HNMR (400 MHz, DMSO – d_6) δ ppm; 4.21(s,2H,-CH_2), 5.16(m,1H,-CH of azetidin attached to pyrazoline-2-one ring), 5.44(d,1H,J=6.4Hz -CH of azetidin attached to –Cl),1.92 (s,3H,-CH_3 attatched to pyrazoline ring),8.03 (s,H,CONH), 10.56(s,H,Ar-NH-N=),3.4(d,H, J=5.6Hz CH of pyrazoline ring) and 6.59-7.93(m,12H, two C_6H_4 groups). 13C NMR (75 MHz, CDCl3,TMS) δ: 154.5-C_1, 113.7-C_2&C_6, 125.9-C_3&C_5, 121.7-C_4, 163.7-C_7, 57.9-C_8, 52.4-C_9, 155.8-C_{10}, 114.4-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}, 163.5-C_{20},59.2-C_{21}, 51.2-C_{22}, 41.4-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	190-3	76	$C_{36}H_{24}Cl_2F_6N_{10}O_6$	49.27	49.23	2.76	2.72	15.96	15.91
9b	CH_3	192-4	78	$C_{37}H_{26}Cl_2F_6N_{10}O_6$	49.84	49.78	2.94	2.86	15.71	15.65
9c	OCH_3	194-4	76	$C_{37}H_{26}Cl_2F_6N_{10}O_7$	48.97	48.91	2.89	2.81	15.43	15.35
9d	F	186-5	70	$C_{36}H_{23}Cl_2F_7N_{10}O_6$	48.28	48.21	2.59	2.53	15.64	15.57
9e	Cl	195-3	74	$C_{36}H_{23}Cl_3F_6N_{10}O_6$	47.41	47.34	2.54	2.51	15.36	15.30
9f	Br	198-3	76	$C_{36}H_{23}BrCl_2F_6N_{10}O_6$	45.21	45.12	2.42	2.38	14.64	14.50
9g	NO_2	210-5	75	$C_{36}H_{23}Cl_2F_6N_{11}O_8$	46.87	46.79	2.51	2.48	16.70	16.65
9h	CF_3	190-6	71	$C_{37}H_{23}Cl_2F_9N_{10}O_6$	47.00	46.95	2.45	2.40	14.81	14.74

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 synyhesized compounds were used at the concentration of 250µ/ml DMF as a solvent[12]

Anti- Bacterial Activity:

The antibacterial activity of 4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9a-h) were screened against Aspergillus niger, Candida

albicans[13-17]. 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-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9a)	_	10	_	09	_	08	_	12	_	11
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-methyl phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9b)	_	09	_	11	_	10	_	13	_	10
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-methoxy phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9c)	_	11	_	11	_	12	_	13	_	11
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-fluoro phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9d)	13	17	13	18	12	16	10	15	11	16
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-chloro phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9e)	11	15	11	16	10	14	08	13	09	14
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-bromo phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9f)	10	13	11	15	09	13	07	12	08	13
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-nitro phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9g)	14	17	14	18	13	16	13	16	12	15
4-(3-chloro-2,5-dioxo-8-(trifluoromethyl)-1-((4-(trifluoromethyl)phenyl)amino)-1,6.7-triazaspiro[3,4]oct-7-en-6-yl)-N-(3-chloro-2-(1-((5-(4-trifluoromethyl phenyl)-1,3,4-oxadiazol-2-yl)methyl)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-4-oxoazetidin-1-yl)benzamide(9h)	16	20	15	22	14	20	14	18	13	17
Chloromphenicol(5)	_	28	_	29	_	25	_	_	_	_
Ketocanazole(50)	_	_	_	_	_	_	_	21	_	19

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