Indian Journal of Chemistry
Vol. 57B, November 2018, pp. 1391-1408

Synthesis of novel spiropiperidine derivatives and their antimicrobial and antioxidant activities

Rajagopalan Srinivasan[a,b], Badiadka Narayana*[a], Balladka Kunhanna Sarojini[c] & Channa Govindaraju Darshan Raj[d]

[a] Department of Studies in Chemistry, Mangalore University, Mangalagangotri 574 199, India
[b] Aurigene Discovery Technologies Limited, Electronics city, Phase-II, Bangalore 560 100, India
[c] Department of Industrial Chemistry, Mangalore University, Mangalagangothri, Mangalore University 574 199, India
[d] Research Department of Chemistry, P. A College of Engineering, Nadupadavu, Mangalore 574 153, India

E-mail: nbadiadka@yahoo.co.uk

Received 19 June 2017; accepted (revised) 10 September 2018

A series of novel spiro-piperidinyl pyrazolones are synthesized by the reaction of *N*-Boc protected ethyl nipecotate with heteroaryl and alkyl aldehydes in presence of lithium diisopropyl amide (LDA) to yield corresponding β-hydroxy ester, followed by MnO_2 oxidation to give *β*-keto ester. Further reaction of *β*-keto ester with hydrazine hydrate results in the formation of spiro-piperidinyl pyrazolone scaffold **5a-d** which upon N-benzylation followed by deprotection yields compounds **7a-s**. The pyrazolone-NH group has been alkylated in compound **5a** with ethyl chloroacetate followed by hydrolysis and amide coupling to afford compounds **9a-d**. The furan ring in compound **5a** is oxidized to carboxylic acid with $KMnO_4$ and coupled with amines to prepare amide derivatives **11a-c**. All the synthesized compounds are evaluated for their *in vitro* antibacterial and antioxidant activity. Compounds **7a-d** and **7g-s** are found to possess high antibacterial activity and compounds **7a**,**7b**, **9a**, **9b**, **11a** and **11c** are found to be potent antioxidants.

Keywords: Spiro piperidines, pyrazolones, antimicrobial, antioxidant

Spiro compounds, the bicyclic ring system in which the rings are connected through an atom represent an important class of naturally occurring substances characterized by highly pronounced biological properties[1]. The spiro skeleton is very common in natural products and appears in a number of alkaloids. Histrionicotoxins (HTX) (I)(a spiro-piperidine)are a group of related toxins found in the skin of poison frogs from the Dendrobatidae family. HTX has very similar special arrangements to the neurotransmitter acetyl choline. The histrionicotoxins have been shown to be potent nicotinic non-competitive antagonists. Spirocyclics and spiro-piperidine skeleton in particular is present in some of the marketed drugs and different methods of synthesis of the spiro skeleton is very well reported in the literature[2,3]. Spiro piperidines have been used as high affinity, selective sigma ligands[4]. They have been also used as inhibitors for the modulation of the dynamics of the M2 proton channel from influenza A virus[5]. Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. Literature review shows that many spiro compounds have been evaluated for their antimicrobial activity. *β*-Lactam grafted spiropyrrolidines and pyrrolizidines[6], spiro oxindole[7], spirothiazoline piperidine[8], and spiroazetidineindoline diones[9] have been synthesized and studied for their antimicrobial activity.

Pyrazolone skeleton exhibits wide variety of applications as analgesic, antipyretic, antiarthritic, uricosuric and ant-inflammatory agents[10,11,12,13]. *N*-Aryl pyrazolone compounds like metamizole, antipyrine, amino pyrine and propyphenazone are well known drugs with analgesic and antipyretic activities.

Antioxidants are vital because of their importance as prophylactic and therapeutic agents in many ailments. Free radicals are being constantly formed in the body and higher levels can cause damage to lipids, proteins, enzymes and DNA resulting in the development of cancer[14,15]. Piperidine derivatives have been prepared as antioxidants for preventing the fading of artificial hair dye[16]. Some spiroindolinones have been reported to have antioxidant activity[17].

The above mentioned biological importance of both spiropiperidines and pyrazolones led us to synthesize novel spiropiperidinylpyrazolones incorporating these

functionalities. Also the evolution of Moxifloxacin, a broad spectrum antibiotic from its earlier compounds prompted us to do the substitutions at other positions keeping the piperidine NH unsubstituted (Figure 1). The newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, DEPT-135 NMR and mass spectral data and evaluated for their *in vitro* antibacterial and antioxidant activity and the results are presented in this paper. Some of the compounds emerged as very potent compounds in both antimicrobial and antioxidant studies.

Results and Discussion

In continuation to our work on spiro piperidines[18,19,20,21], we herein report the synthesis of novel spiropiperidines containing thiophene and furan ring systems. These compounds were synthesized starting from ethyl nipecotate which is a commercially available starting material. The *N*-Boc protected ethyl nipecotate **2** (Ref 22,23) was reacted with freshly prepared LDA and the resultant anion was reacted with various aldehydes to get the *β*-hydroxy ester intermediate **3**. The MnO_2 oxidation[24,25] of the β -hydroxy ester[26,27] then afforded the β-keto ester **4** (Ref 28) which upon reaction with hydrazine hydrate resulted in the formation of spiropyrazolone **5** (Ref 29). The spiro-piperidinyl pyrazolones **5a-d** were *N*-alkylated[30,31] using sodium hydride and corresponding substituted benzyl bromides after deprotection of Boc group to afford various *N*-benzyl derivatives **7a-s** (Scheme I, Table I). Similarly, they were *N*-alkylated[32] with ethylchloroacetate followed by lithium hydroxide hydrolysis[33] and amide coupling followed by deprotection of Boc group to afford the final compounds **9a-d** (Scheme I, Table II). On the other hand, furan ring of the spiropyrazolone was oxidized with potassium permanganate[34] to afford the carboxylic acid, which was reacted with various amines using the HATU[35,36] coupling method followed by deprotection of the Boc group to afford amides**11a-c** (Scheme I, Table III).

All the synthesized compounds **7a-s**, **9a-d** and **11a-c** were racemic mixtures and no attempt was made to separate the mixture by resolution or chiral prep HPLC separation. All the compounds were characterized by LCMS, ^{1}H NMR, ^{13}C NMR, DEPT-135 NMR and FT-IR. LCMS spectrum of all compounds showed the mass corresponding to the free base as the HCl in the parent compound gets dissociated under LCMS conditions. The LCMS spectra of compound **7a** showed a peak at 344.0, which underwent fragmentation[37,38] with the extrusion of ethylene to give the fragment peak at 314.7 due to the stable tertiary alkyl radical. Subsequent fragmentation yielded the fragment peak at 300.9 (Scheme II). This trend of fragmentation was seen in all the compounds recorded in API-2000 mass spectrometer, whereas only the molecular ion peak was seen in LCMS spectra recorded in Agilent technologies mass spectrometer. This could be due to the fact that API-2000 is a triple quadrupole machine and Agilent technologies machine is a single quadrupole machine. This fragmentation pattern supported the formation of the compound **7a**.

In the ^{1}H NMR spectra of the compounds, all the 8 protons of the piperidine ring resonated in the region δ 1.8-3.8 ppm as multiplets due to the non-equivalence of these protons. The –OCH_3 group in **9a, 9b, 11a** and **11c** appeared as a singlet in the range δ 3.7-3.8 ppm. Both the protons of the CH_2 group attached to the pyrazolone nitrogen are diastereotopic and they both give doublets. Because of the close differences in chemical shift both doublets overlap to give quartet like peaks in **7b, 7d, 7e, 7i, 7j, 7l, 7n, 7o, 7q, 7r** and **9a-d** whereas in other examples they

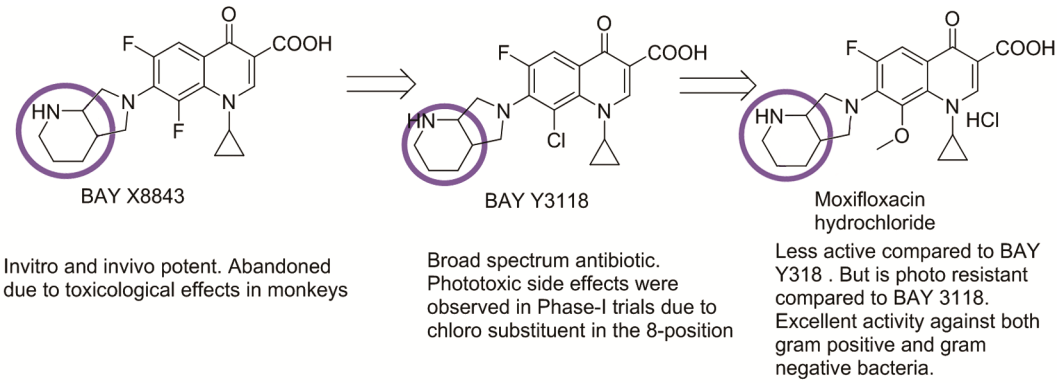
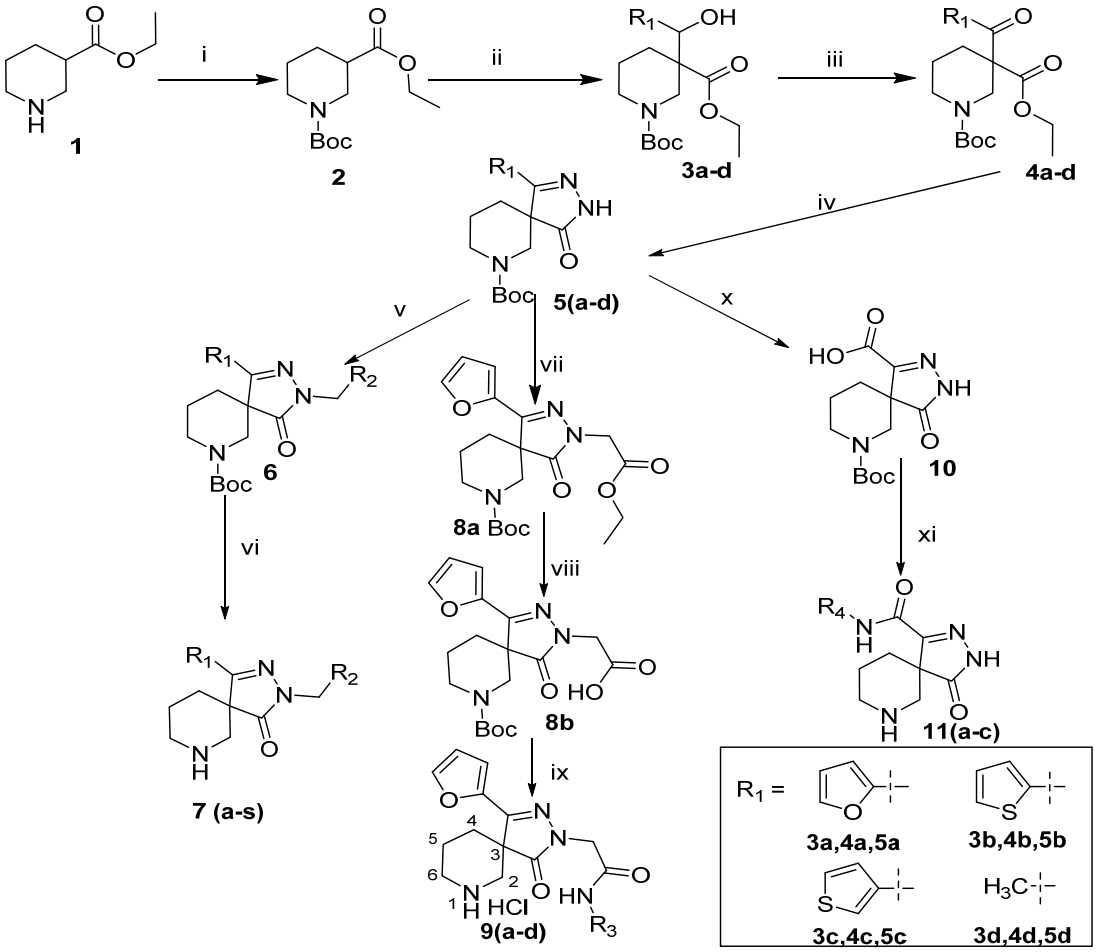


Figure 1 — Evolution of Moxifloxacin hydrochloride



Scheme I — Conditions: (i) Boc_2O, DCM, TEA, 2 h; (ii) LDA, R_1CHO, −78°C, 30 min; (iii) MnO_2, DCM, RT, 4 h; (iv) $NH_2.NH_2.H_2O$, EtOH, AcOH, 3-4 h ; (v) NaH, DMF, R_2CH_2Br; (vi) HCl in 1,4-Dioxane, 2 h; (vii) **5a**, K_2CO_3/DMF, $ClCH_2COOEt$, 60°C, 3 h; (viii) LiOH/THF/MeOH/H_2O; (ix) R_3NH_2, DMF, DIPEA, HATU, HCl in 1,4-Dioxane; (x) **5a**, $KMnO_4$, acetone, water, 60°C, 4 h; (xi) R_4NH_2, DMF, DIPEA, HATU; HCl in 1,4-Dioxane.

appear as singlet. The aromatic protons resonated in the region δ 7.8-8.4. The methyl group in compounds **7e** and **7f** appeared as a singlet around δ 2.0 ppm. The HCl proton appeared as a D_2O exchangeable broad peak at around δ 7.8 in all the compounds. In compounds **7e** and **7f** where there are no aromatic protons this broad peak can be clearly seen. The piperidine NH appeared as a D_2O exchangeable broad singlet at δ 9.9.

^{13}C NMR spectra of all the compounds gave peaks corresponding to the no. of carbons present. The peak at δ 179.3 in the ^{13}C NMR spectrum of compound **7a** was attributed ~~due~~ to the –C=O group of the amide. The peak at δ 167.9 was due to the –C=N carbon.

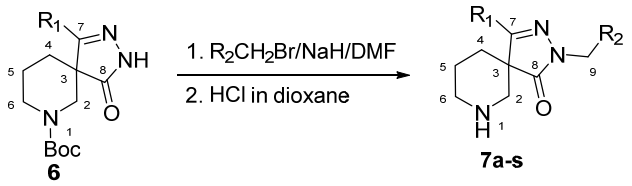
DEPT-135 spectra showed the presence of four piperidine methylene groups and the benzylic CH_2 as negative peaks in the region δ 17 to 48. In compound **7a** they appear as negative signals at δ 19.7, 30.69, 46.64, 48.16 and 50.41 ppm. In compounds **7e** and **7f** positive peaks were observed at δ 13.32 and 11.86 ppm respectively confirming the presence of CH_3 groups. In compound **9a**, two positive peaks were observed at δ 56.34 and 56.66 respectively confirming the presence of two $–OCH_3$ groups in the molecule. The aromatic carbons (Ar-H) appeared as positive peaks in the region δ 102 – 150 ppm.

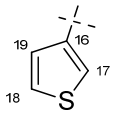
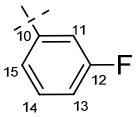
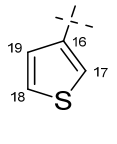
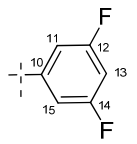
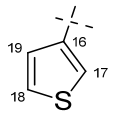
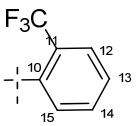
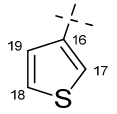
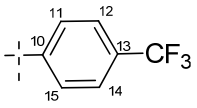
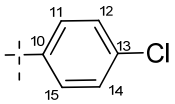
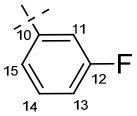
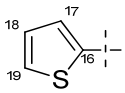
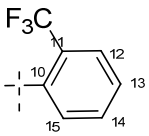
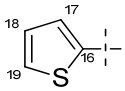
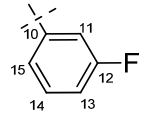
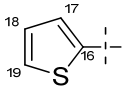
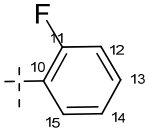
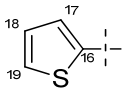
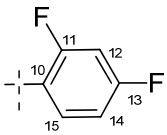
The IR spectrum of all the compounds showed broad peak in the region 3400-3200 cm^{-1} for the piperidine-NH and sharp peaks at 1700-1650 cm^{-1} for the C=O groups of the pyrazolone group.

Antibacterial activity

The newly synthesized compounds were evaluated for their antimicrobial activity (Table IV) against four bacterial strains, *Staphylococcus aureus, Escherichia coli, Pseudomonas aeroginosa* and *Klebsiella*

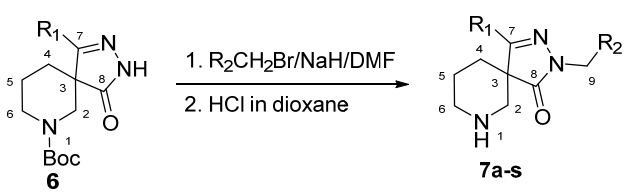
Table I — Chemical structures of substituted spiropiperidines **7a-s**

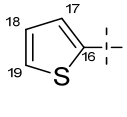
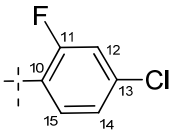
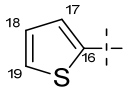
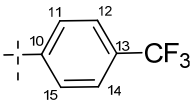
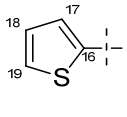
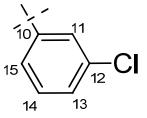
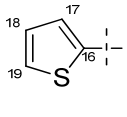
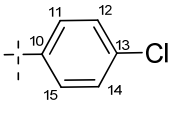
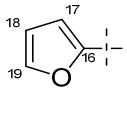
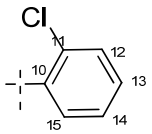
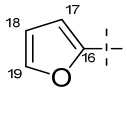
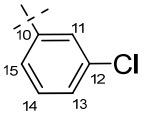
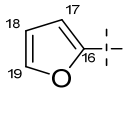
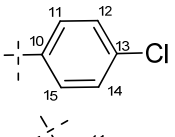
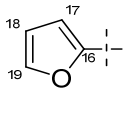
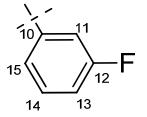
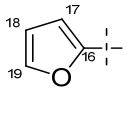
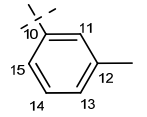


Compd	R_1	R_2	m.p. (°C)	Yield (%)
7a			223-25	61
7b			210-13	69
7c			234-35	74
7d			190-92	62
7e	CH_3		225-30	81
7f	CH_3		225-28	70
7g			215-20	54
7h			165-69	88
7i			154-57	60
7j			193-95	40

(*Contd*.)

Table I — Chemical structures of substituted spiropiperidines **7a-s**

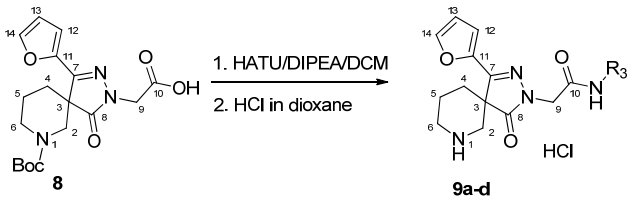


Compd	R_1	R_2	m.p. (°C)	Yield (%)
7k			210-13	34
7l			135-40	47
7m			176-79	55
7n			195-98	64
7o			185-92	43
7p			156-60	56
7q			204-207	49
7r			143-48	42
7s			154-58	53

pneumoniae strains by disc diffusion method and compared with the known antibacterial drug, nitrofurazone. The minimum inhibitory concentration (MIC, μgmL^{-1}) was determined for each compound in triplicate experiments. The values are presented in Table IV. In general **7a-7s** series were very potent against all four bacterial strains except compounds **7e**

and **7f**. This indicated that smaller methyl group is detrimental to the antimicrobial activity as compared to the larger 2-thienyl, 3-thienyl and 2-furyl group in other examples. In the series **9a-9d**, all the compounds were inactive. The presence of two electron donating methoxy substituents decrease the activity to a considerable extent in **9a** and **9b**., The compounds **9c** and **9d** were also inactive showing that the amide linkage is not tolerated unlike in the series **7** where the pyrazolone NH group is linked to a substituted benzyl group. Compounds **7a**, **7b**,**7c**, **7d**, **7g**, **7i** and **7q** were more active for gram positive

Table II — Chemical structures of substituted spiropiperidines **9a-d**



8 **9a-d**

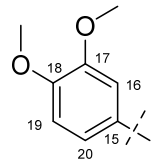
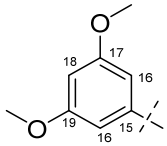
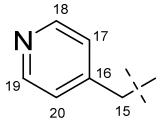
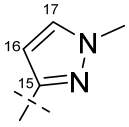
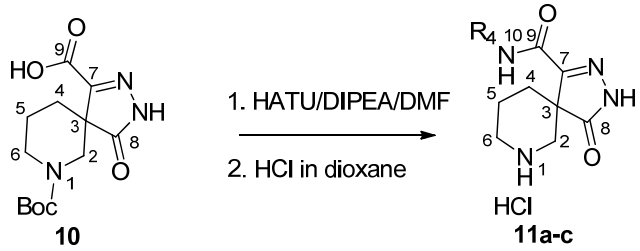
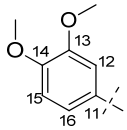
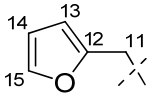
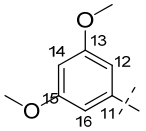
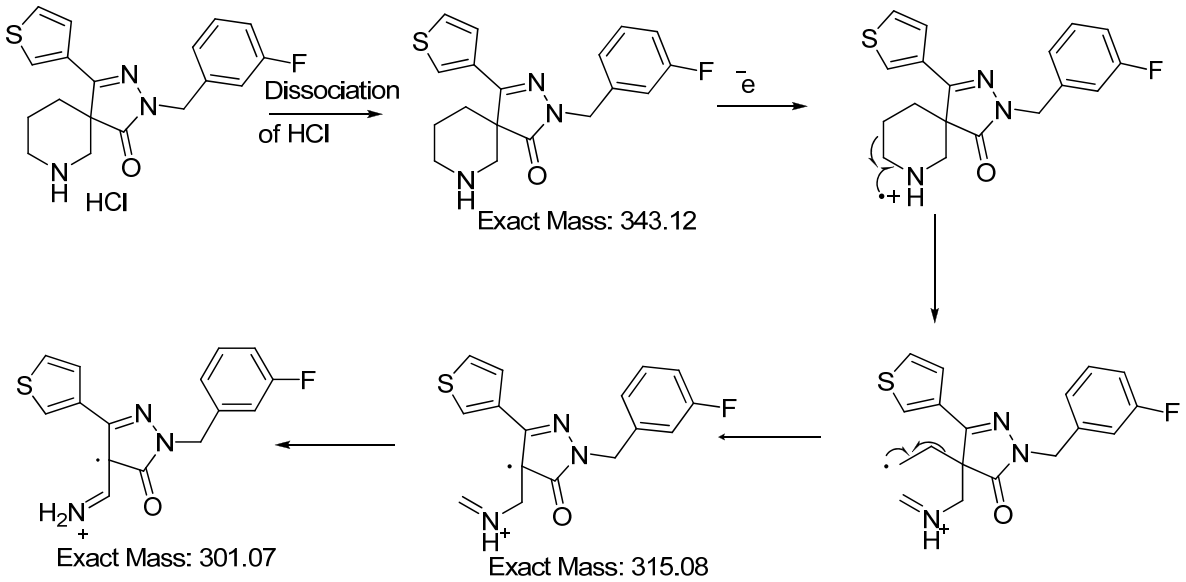
Compd	R_3	m.p. (°C)	Yield (%)
9a		208-10	55
9b		243-47	50
9c		210-14	49
9d		205-209	40

Table III — Chemical structures of substituted spiropiperidines **11a-c**



10 **11a-c**

Compd	R_4	m.p. (°C)	Yield (%)
11a		207-13	54
11b		201-207	15
11c		230-35	45



Scheme II — Mass fragmentation pattern of compound **7a**

Table IV — Antibacterial activity of the spiropiperidines

Compd	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeroginosa*	*Klebsiella pneumoniae*
7a	6.25 (35±1.52)	12.5 (34±2.32)	6.25 (24±2.65)	6.25(18±2.17)
7b	6.25 (26±1.35)	6.25 (26±1.34)	6.25 (20±1.66)	12.5 (14±2.33)
7c	6.25 (32±0.0)	6.25 (31±1.21)	6.25 (26±2.54)	12.5(18±2.33)
7d	6.25 (33±2.5)	6.25 (22±1.67)	12.5 (31±1.87)	12.5 (21±2.87)
7e	25 (25±1.6)	12.5 (13±2.81)	25 (30±1.98)	25 (23±2.12)
7f	50 (23±1.44)	25 (28±3.67)	25 (22±2.77)	25 (19±2.89)
7g	6.25 (26±1.45)	6.25 (25±1.89)	12.5 (24±1.9)	6.25 (21±3.78)
7h	12.5 (32±1.56)	12.5 (25±2.56)	12.5 (26±2.89)	12.5 (22±0.0)
7i	6.25 (25±2.65)	12.5 (25±1.00)	12.5 (31±0.0)	12.5 (23±2.98)
7j	6.25 (26±2.31)	12.5 (27±2.89)	6.25 (25±2.23)	12.5 (21±1.98)
7k	6.25 (32±1.55)	12.5 (25±1.56)	12.5 (28±2.78)	12.5 (25±2.45)
7l	6.25 (26±1.20)	12.5 (28±1.2)	12.5 (31±3.00)	12.5 (26±2.18)
7m	6.25 (27±0.0)	12.5 (29±2.5	12.5 (28±1.87)	12.5 (27±2.56)
7n	6.25 (23±1.8)	12.5 (29±2.55)	12.5 (29±1.98)	12.5 (25±1.00)
7o	6.25 (27±1.39)	12.5 (22±1.77)	12.5 (30±3.55)	12.5 (26±2.87)
7p	6.25 (31±1.56)	6.25 (19±2.67)	6.25 (22±2.45)	12.5 (20±2.67)
7q	6.25 (34±1.45)	12.5 (27±1.25)	12.5 (26±1.76)	12.5 (21±1.76)
7r	12.5 (29±1.21)	12.5 (18±0.98)	6.25 (25±1.55)	6.25 (17±1.67)
7s	12.5 (29±1.21)	12.5 (26±2.45)	12.5 (28±0.0)	12.5 (23±1.67)
9a	100 (26±2.00)	50 (25±2.78)	50 (19±1.87)	50 (20±1.76)
9b	50 (24±3.10)	25 (18±2.33)	25 (25±2.45)	25 (16±1.32)
9c	25 (23±1.77)	25 (24±2.55)	25 (21±1.78)	25 (13±2.66)
9d	50 (19±1.67)	25 (20±1.98)	25 (21±2.78)	25 (20±2.67)
11a	50 (17±1.82)	50 (25±1.23)	12.5 (09±1.78)	100 (20±1.44)
11b	50 (12±1.00)	25 (17±2.00)	50(11±1.09)	25 (19±0.00)
11c	50 (13±1.08)	50 (15±3.14)	50 (18±1.04)	50 (13±2.09)
Nitrofurazone Standard Drug	<6.25 (32±1.22)	<6.25 (30±1.00)	<6.25 (36±2.09)	<6.25 (32±1.08)
DMSO(2%) Solvent control	00	00	00	00

Zone of inhibition in mm is given in parenthesis; MIC is expressed in μg mL^{-1} (MIC for the standard drug, nitrofurazone, is reported earlier[39]); standard drug used: nitrofurazone;
solvent control: 1% DMSO. M±SD indicates Mean ± Standard deviation

(*Staphylococcus aureus*) bacterial strains compared to the gram negative (*Escherichia coli*, *Pseudomonas aeroginosa* and *Klebsiella pneumonia*) bacterial strains. In the series **11a-c**, all the tested compounds were inactive towards all four bacterial strains indicating that the direct attachment of the hetero aryl group is required for antibacterial activity. An analysis of the structure activity relationship of all the compounds indicated that the pyrazolone ring has to be attached to a heteroaryl group and the pyrazolone NH group has to be substituted with a substituted benzyl group to show broad spectrum of antibacterial activity.

Antioxidant activity

All the synthesized compounds were screened for their *in vitro* antioxidant activity (Table V). A rapid, simple and inexpensive method to measure antioxidant capacity of substances involves the use of the free radical, 2,2-diphenyl-1-picrylhydrazyl (DPPH). DPPH is widely used to test the ability of compounds to act as free radical scavengers or hydrogen donors. Antioxidants tested on DPPH are also found extremely effective in cell systems. This simple test further provides information on the ability of a compound to donate electrons during antioxidant action. The radical scavenging mechanism is based on the transfer of acidic H-atom from the compound to DPPH radical to form DPPH-H. Compounds **7a** and **7b** show very good antioxidant activity. These two compounds have a 3-thienyl group attached to the pyrazolone moiety of the spiro compound and the fluoro benzyl group attached to the pyrazolone –NH group. Compounds **7c** and **7d** which also has a 3-thienyl group but has a trifluoromethyl phenyl group instead of a fluoro phenyl is only moderately active. The compounds **9a**, **9b**, **11a** and **11c** also showed very good antioxidant activity attributed to the presence of

Table V — Antioxidant activity of the spiropiperidines

Compd	% Inhibition
7a	78.21±2.97
7b	81.32±1.55
7c	68.12±2.78
7d	62.34±0.67
7e	71.54±2.31
7f	68.66±1.22
7g	64.38±1.08
7h	70.33±2.00
7i	72.47±2.41
7j	65.91±1.55
7k	61.38±1.07
7l	65.66±2,09
7m	67.20±0,06
7n	72.30±1.04
7o	70.34±1.11
7p	70.14±1.45
7q	71.44±1.87
7r	72.92±1.22
7s	63.80±0.62
9a	80.54±0.00
9b	79.45±0.16
9c	54.80±0.67
9d	55.70±1.29
11a	81.75±0.56
11b	56.43±1.33
11c	81.92±1.89
Ascorbic Acid	82.33±0.28

two electron donating methoxy groups in these four compounds which enhanced the antioxidant activity. The overall antioxidant activity of these compounds could be due to the presence of piperidines unsubstituted at the –NH portion which does efficient radical scavenging.

Experimental Section

Material and methods

Melting points were recorded on a Stuart Scientific melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer IR spectrophotometer using KBr disc of the sample.The ^{1}H,^{13}C NMR and DEPT-135 spectra were recorded in a DMSO-d_6 solution at 400 MHz on a Varion spectrometer and Mass spectra were recorded on a API-2000 mass spectrometer operating at 70eV. Routine monitoring of the reactions was made using thin layer chromatography (TLC) on silica gel F_{254} plates (0.2mm, Fluka) and spots were visualized under UV light (254 and 366nm). For anhydrous reactions, glasswares used were thoroughly dried in a hot air-oven, cooled and assembled under a stream of nitrogen. The organic extracts of crude products were dried over anhyd. Na_2SO_4 and purified by column chromatography using silica gel (60-120 mesh) and gradient (0-50%) ethyl acetate in hexane as the eluent system. The starting materials ethyl nipecotate, 2-furaldehyde, thiophene-2-carbaldehyde, thiophene-3-carbaldehyde, ethylchloro acetate and manganese dioxide were purchased from Aldrich chemical company and used as such. Lithium diisopropyl amide(LDA) used was purchased from Aldrich and used within a period of one month.

Preparation of *N*-Boc Piperidine-4-carboxylic acid ethyl ester, 2

To a cooled solution (0-5^{o}C) of ethyl nipecotate (5g, 31.8mmol, 1eq) in DCM (50mL) was added TEA (6.7mL, 47.7mmol, 1.5eq), followed by BOC-anhydride (7.7mL,33.39mmol, 1.05eq), stirring continued at RT for 2h. After checking the completion of reaction by TLC, water was added to the reaction mixture and extracted with DCM (100mLx3). The organic layer was washed with brine solution and dried over anhyd. $Na_2SO_4$and concentrated to afford the title product (8g, 98%yield).

General method for the preparation of 1-(*tert*-butyl) 3-ethyl 3-(heteroaryl/alkyl-2-yl(hydroxy)methyl)piperidine-1,3-dicarboxylate, 3a-d

THF (70mL) was taken in a RB flask in an Argon atmosphere and cooled to -78^{o}C, LDA (1.8M in THF/heptane/ethyl benzene) (89.63mmol) was added and compound **2** (38.8mmol) in THF (100mL) was added drop-wise from a dropping funnel. Stirring continued at -78^{o}C for 30min.The corresponding aldehyde in THF (25 mL) (41.63mmol) was added drop wise and the reaction temperature was gradually raised to 0^{o}C. After checking the completion of reaction by TLC, the reaction was quenched by the addition of ice cold water, followed by addition of ethyl acetate. The aqueouslayer was extracted twice with ethyl acetate (2*100mL). Ethyl acetate layers were combined and concentrated and the crude material was purified by column chromatography using 20% ethyl acetate in hexane to afford the desired product.

1-(*tert*-Butyl) 3-ethyl 3-(hydroxy(furan-2-yl)methyl)piperidine-1,3-dicarboxylate, 3a: Yellow brown gummy mass, Yield: 9.1 g (66 %).^{1}H-NMR (400 MHz, DMSO-d_6+D_2O, 80^{o}C): δ ppm, 1.13-1.17 (m, 3H, -ester CH_3), 1.39-1.45 (m, 9H, Boc), 1.49-1.60 (m, 2H, pip. CH_2), 2.02-2.05 (m, 1H,

pip.CH_2), 2.55-2.62 (m, 1H, pip. CH_2), 2.74-2.78 (d, J = 13.2 Hz,1H, pip. CH_2), 3.79-3.82 (m, 1H, pip. CH_2), 4.0 (m, 2H, ester CH_2), 4.29-4.36 (m, 1H, pip. CH_2), 4.65-4.69 (m, 1H, **CH**-OH), 6.22-6.25 (m, 1H, furyl-H), 6.35-6.38 (m, 1H, furyl-H), 7.48-7.50 (m, 1H, furyl-H). LCMS *m/z*: 354.1 $[M+H]^+$

1-(*tert*-Butyl) 3-ethyl 3-(hydroxy(thiophen-2-yl)methyl)piperidine-1,3-dicarboxylate, 3b: Yellow brown gummy mass, Yield: 7.1 g (49 %). ^{1}HNMR (400 MHz, DMSO-d_6, 90^{o}C): δ ppm, 1.13-1.17 (m, 3H, -ester CH_3), 1.39-1.43 (m, 9H, Boc), 1.53-1.66 (m, 3H, pip. CH_2), 2.04-2.08 (m, 1H, pip.CH_2), 2.56-2.63 (m,1H, pip. CH_2), 2.78-2.81 (d, J =13.2 Hz, 1H, pip. CH_2), 3.82-3.85 (m, 1H, pip.CH_2), 3.99-4.05 (m, 2H, ester CH_2), 4.36-4.4 (m, 1H, pip.CH_2), 4.93-4.99 (m, 1H, **CH**-OH), 6.86-6.90 (m, 1H, thiophene-H), 6.94-6.98 (m, 1H, thiophene-H), 7.35-7.39 (m, 1H, thiophene-H). LCMS *m/z*: 392.2 $[M+Na]^+$.

1-(*tert*-Butyl) 3-ethyl 3-(hydroxy(thiophen-3-yl)methyl)piperidine-1,3-dicarboxylate, 3c: Pale yellow gummy mass, Yield: 7.8 g (54 %). ^{1}HNMR (400 MHz, DMSO-d_6+D_2O, 80^{o}C): δ ppm, 1.06-1.15 (m, 3H, -ester CH_3), 1.26-1.34 (m, 9H, Boc), 1.34-1.57 (m, 2H, pip. CH_2), 1.85-1.99 (m, 1H, pip. CH_2), 2.68-2.72 (d, J = 13.6 Hz, 1H, pip. CH_2), 3.77-3.81 (m, 1H, pip. CH_2), 3.96 (q, J = 6.8 Hz, 2H, ester CH_2), 4.25-4.34 (m, 1H, pip. CH_2), 4.71-4.76 (m, 1H, **CH**-OH), 6.93 (d, J = 4.4 Hz, 1H, thiophene-H), 7.15-7.17 (m, 1H, thiophene-H), 7.34-7.37 (m, 1H, thiophene-H). LCMS *m/z*: 392.2 $[M+Na]^+$.

1-(*tert*-Butyl) 3-ethyl 3-(1-hydroxyethyl)piperidine-1,3-dicarboxylate, 3d: Off-white sticky mass, Yield: 4.5 g (38 %) ^{1}HNMR (400 MHz, DMSO-d_6+D_2O, 80^{o}C): δ ppm, 1.00-1.06 (m, 3H, CH_3), 1.16 (m, 3H, ester CH_3), 1.35-1.42 (m, 9H, Boc), 1.46-1.54 (m, 2H, pip. CH_2),1.94-1.97 (m, 1H, pip. CH_2), 2.67-2.96 (m, 2H, pip.CH_2), 3.62-3.76 (m, 2H, pip.CH_2), 4.03-4.13 (m, 3H, ester $CH_2$and pip. CH_2), 4.31-4.33 (m, 1H, **CH**-OH), LCMS *m/z*: 302.1 $[M+H]^+$.

General method for the preparation of 1-(*tert*-butyl) 3-ethyl 3-(heteroaryl-2/3-carbonyl/acetyl)piperidine-1,3-dicarboxylate, 4a-d

To a solution of **3a-d** (25.46mmol) in DCM(150mL), MnO_2(828mmol) was added and stirring continued at RT for 3-4h. After checking the completion of reaction by TLC, the reaction mixture was filtered through a Celite® bed and the filtrate was concentrated to afford the desired product.

1-(*tert*-Butyl) 3-ethyl 3-(furan-2-carbonyl)piperidine-1,3-dicarboxylate, 4a: Off-white solid, Yield: 8.1g (90% yield); ^{1}HNMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.04 (t, J = 7.2 Hz, 3H, ester CH_3), 1.3 (s, 9H, Boc), 1.71-1.76 (m, 2H, pip. CH_2, H-4), 2.05 (t, J = 5.6 Hz, 2H, pip. CH_2, H-5), 3.30-3.36 (m, 2H, pip. CH_2, H-6), 3.9 (m, 1H, pip. CH_2, H-2), 4.05-4.11 (m, 3H, ester CH_2 and H-6'), 6.68 (dd, J = 3.2 Hz, 1H, 1.6, furyl-H), 7.25 (d, J = 4 Hz, 1H, furyl-H), 7.90-7.91 (m, 1H, furyl-H); LCMS *m/z*: 352.1 $[M+H]^+$.

1-(*tert*-Butyl) 3-ethyl 3-(furan-2-carbonyl)piperidine-1,3-dicarboxylate, 4b: Off-white solid, Yield: 6.5g (69 % yield); ^{1}H NMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.07 (t, J = 7.2 Hz, 3H, ester CH_3),1.3 (s, 9H, Boc-H's), 1.68-1.77 (m, 2H, pip.CH_2, H-4), 2.04-2.09 (m, 1H, pip.CH_2, H-5), 2.16-2.22 (m, 1H, pip.CH_2, H-5'), 3.22-3.28 (m, 1H, pip.CH_2, H-6), 3.39-3.42 (m, 1H, pip.CH_2, H-6'), 3.9-3.93 (m, 1H, pip. CH_2, H-2), 4.07-4.15 (m, 3H, ester CH_2 and H-2'), 7.21 (t, J = 4.8 Hz, 1H, thiophene-H), 7.67 (d, J = 4.0 Hz, 1H, thiophene-H), 7.96 (d, J =4.8 Hz, 1H, thiophene-H); LCMS *m/z*: 368.1 $[M+H]^+$.

1-(*tert*-Butyl) 3-ethyl 3-(furan-3-carbonyl)piperidine-1,3-dicarboxylate, 4c: Off-white solid, Yield: 6.2 g (66 % yield); ^{1}H NMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.06 (t, J = 7.2 Hz, 3H, CH_3, ester), 1.29 (s, 9H, Boc-H's), 1.68-1.76 (m, 2H, pip.CH_2, H-4), 2.01-2.03 (m, 1H, pip.CH_2, H-5), 2.15-2.17 (m, 1H, pip.CH_2, H-5), 3.24-3.26 (m, 1H, pip.CH_2, H-6), 3.39-3.40 (m, 1H, pip.CH_2, H-6'), 3.82-3.9 (m, 1H, pip. CH_2, H-2), 4.08-4.14 (m, 3H, CH_2 ester and pip.CH_2, H-2'),7.39-7.40 (m, 1H, thiophene-H, H-14), 7.59-7.61 (m, 1H, thiophene-H), 8.17-8.18 (m, 1H, thiophene-H). LCMS *m/z*: 368.1 $[M+H]^+$.

1-(*tert*-Butyl) 3-ethyl 3-acetylpiperidine-1,3-dicarboxylate, 4d: Off-white solid, Yield: 5.8 g (76 % yield); ^{1}H NMR (400MHz, DMSO-d_6,80^{o}C): δ ppm, 1.19 (t, J = 6.8 Hz, 3H, ester CH_3), 1.4 (s, 9H, Boc-H's), 1.53-1.6 (m, 2H, pip. CH_2, H-4), 1.87-1.93 (m, 1H, pip.CH_2, H-5), 1.99-2.04 (m, 1H, pip. CH_2, H-5'), 2.15 (s, 3H, CH_3), 3.15-3.2 (m, 1H, pip. CH_2, H-6), 3.35-3.41 (m, 1H, pip. CH_2, H-6'), 3.68 (d, J = 13.6 Hz, 1H, pip. CH_2, H-2), 3.89 (d, J = 14 Hz, 1H, pip. CH_2, H-2'), 4.11-4.17 (m, 2H, ester CH_2); LCMS *m/z*: 300.1 $[M+H]^+$.

General method for the preparation of *tert*-butyl 4-oxo-1-(heteroaryl/methyl)-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate, 5a-d

To a solution of **4a-d** (10.78mmol) in ethanol (20 mL), hydrazine hydrate(100mmol) and acetic acid

(0.3 mL)was added. Stirring was continued at RT for 3-4h. A thick solid is precipitated which was filtered and dried under vacuum to afford the desired product[18].

***tert*-Butyl 4-oxo-1-(furan-2-yl)-2,3,7-triazaspiro[4.5] dec-1-ene-7-carboxylate, 5a**: Off-white solid, Yield: 3.1 g (90.1% yield); ^{1}H NMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.36 (s, 9H, Boc-H's), 1.50-1.54 (m, 1H, pip. CH_2, H-4*)*, 1.79 (d, *J* = 13.2 Hz, 1H, H-4'), 2.10 (dt, *J* = 13.2, 3.6 Hz, 1H, pip. CH_2, H-5), 2.15-2.18 (m, 1H, pip. CH_2, H-5'), 3.10-3.18 (m, 1H, pip. CH_2, H-6), 3.47 (d, *J* = 13.6 Hz, 1H, pip. CH_2, H-6'), 3.80 (d, *J* = 13.6 Hz, 1H, pip. CH_2, H-2), 3.91 (d, *J* = 13.2 Hz, 1H, pip.CH_2, H-2'), 6.60-6.61 (m, 1H, furyl-H), 6.94 (d, *J* = 3.6 Hz, 1H, furyl-H), 7.76 (d, *J* = 1.6 Hz, 1H, furyl-H), 11.32 (s, 1H, -CONH); LCMS *m/z*: 220.1 [M-Boc+H]$^+$.

***tert*-Butyl 4-oxo-1-(thiophen-2-yl)-2,3, 7-triazas piro[4.5]dec-1-ene-7-carboxylate, 5b**: Off-white solid,Yield: 2.8 g (78 % yield); ^{1}H NMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.37 (s, 9H, Boc-H's), 1.48-1.55 (m, 1H, pip.CH_2, H-4*)*, 1.80 (d, *J* = 13.2 Hz, 1H, pip. CH_2, H-4'), 2.11-2.26 (m, 2H, pip.CH_2, H-5), 3.08-3.14 (m, 1H, pip. CH_2, H-6), 3.51 (d, *J* = 13.6 Hz, 1H, pip.CH_2, H-6'), 3.82-3.86 (m, *J* = 13.6 Hz, 1H, pip. CH_2, H-2), 3.94 (d, *J* = 13.2 Hz, 1H, pip. CH_2, H-2'), 7.10-7.12 (m, 1H, thiophene-H), 7.52 (d, *J* = 3.2 Hz, 1H, thiophene-H), 7.59 (d, *J* = 4.8 Hz, 1H, thiophene-H), 11.28 (s, 1H, -CONH); LCMS *m/z*: 236.0 [M-Boc+H]$^+$.

***tert*-Butyl 4-oxo-1-(thiophen-3-yl)-2,3,7-triazaspiro-[4.5]dec-1-ene-7-carboxylate, 5c**: Off-white solid, Yield: 2.1 g (68 % yield);^{1}H NMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.37 (s, 9H, Boc-H's), 1.51 (td, *J* = 16.4 Hz, 4.0 Hz, 1H, pip.CH_2, H-4*)*, 1.74-1.78 (m, 1H, H-4'), 2.13-2.29 (m, 2H, pip.CH_2, H-5), 3.12-3.15 (m, 1H, pip. CH_2, H-6), 3.54 (d, *J* = 13.2 Hz, 1H, pip. CH_2, H-6'), 3.83 (d, *J* = 13.6 Hz, 1H, pip. CH_2, H-2), 3.96 (d, *J* = 13.2 Hz, 1H, pip. CH_2, H-2'), 7.50 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H, thiophene-H), 7.60 (dd, 1H, *J* = 5.2, 2.8 Hz, thiophene-H), 7.97 (d, 1H, *J* = 1.6 Hz, thiophene-H), 11.22 (s, 1H, -CONH).

***tert*-Butyl 4-oxo-1-methyl-2,3,7-triazaspiro[4.5]-dec-1-ene-7-carboxylate, 5d**: Off-white solid, Yield: 2.5g (81 % yield); ^{1}H NMR (400MHz, DMSO-d_6, 80^{o}C): δ ppm, 1.4 (s, 9H, Boc-H's), 1.57-1.61 (m, 1H, pip. CH_2, H-4*)*, 1.67-1.72 (m, 2H, pip. CH_2, H-4' and H-5), 1.91-1.96 (m, 4H, CH_3 and H-5'), 3.25-3.29 (d, *J* = 13.6 Hz, 1H, pip. CH_2, H-6), 3.37-3.38 (m, 1H, pip.CH_2, H-6'), 3.47-3.50 (m, 2H, pip. CH_2, H-2), 10.9 (s, 1H, pyrazolone NH), LCMS *m/z*: 268.0 [M +H]$^+$.

General procedure for the synthesis of *N*-alkyl spiropyrazolones, 7a-s

To a solution of the sprio-pyrazolones**5a-d** (1eqt) in DMF, cooled to 0^{o}C, sodium hydride (2 eqt), was added and the corresponding benzyl bromide (1.2-1.4eqt) was added and the temperature was gradually raised to the ambient and stirred for 30min. After checking the completion of reaction by TLC, the reaction mixture was quenched with crushed ice and extracted with ethyl acetate. The ethyl acetate layer was dried over anhyd. Na_2SO_4 and concentrated to afford the crude product which was purified by column chromatography using 20-30% ethyl acetate in hexane. The resultant *N*-Boc substituted spiropyrazolones were treated with 4M HCl in 1,4-dioxane to afford the title compound as hydrochloride salt.

2-(3-Fluorobenzyl)-4-(thiophen-3-yl)-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride, 7a: Yield: 138 mg (61 %); IR (KBr) ν_{max}/cm^{-1}: 3435 (NH), 3063, 2933, 1694 (C=O), 1447, 1286, 935; ^{1}H NMR (400MHz-DMSO-d_6): δ 1.8 (d, 1H, *J* = 10.0 Hz, pip.CH_2, H-4), 1.89 (d, 1H, *J* = 10.2 Hz, pip.CH_2, H-4'), 2.36 (d, 2H, *J* = 10.8 Hz, pip.CH_2, H-5), 3.54-3.57 (m, 2H, pip. CH_2, H-6), 3.68 (d, 1H, *J* = 12.8 Hz, pip. CH_2, H-2), 4.9 (s, 2H, CH_2, H-9), 7.15-7.2 (m, 3H, Ar-H, H-11, H-13, H-15), 7.39-7.45 (m, 1H, Ar-H, H-14), 7.54 (dd, 1H, *J* = 5.2, 1.2 Hz, thiophene-H, H-19), 7.71 (dd, 1H, *J* = 5.2, 2.8 Hz, thiophene-H, H-17), 7.74-7.82 (brs, 1H, HCl), 8.44 (dd, 1H, *J* = 2.8, 1.2 Hz, thiophene-H, H-18), 9.7-9.8 (brs, 1H, Pip. NH); ^{13}C NMR (100 MHz, CD_3OD): 19.7 (pip. C, C-4), 30.69 (pip.C, C-5), 46.66 (pip.C, C-6), 48.18 (pip. C, C-2), 51.66 (CH_2, C-9), 117.92, 126.8, 128.83, 129.58, 130.17, 133.63, 134.11, 142.35, 157.56 (C=N, C-7), 165.15 (C-F, C-12), 167.59 (C-F, C-12), 179.3 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ,19.7 (CH_2), 30.69 (CH_2), 46.64 (CH_2), 48.16 (CH_2), 50.41 (CH_2), 117.91, 126.82, 126.85, 128.83, 129.55, 133.72 (aryl and thiophene C-H); LCMS: *m/z*: 344 [M+H]$^+$; C H N analysis; Calculated for $C_{18}H_{19}ClFN_3OS$, C, 56.91%; H, 5.04%; N, 11.06%; Found: C, 56.98%; H, 5.07%; N, 11.01%.

2-(3,5-Difluoro-benzyl)-4-thiophen-3-yl-2,3,7-triaza-spiro[4.5]dec-3-en-1-one hydrochloride, 7b: Yield: 164 mg (69%); IR (KBr) ν_{max}/cm^{-1}: 3460 (NH), 3051, 1695 (C=), 1600, 1309, 1122, 991, 870, 796,

631; ^{1}HNMR (400 MHz-DMSO-d_6): δ 1.81 (d, 1H, J = 8.4 Hz, pip. CH_2, H-4), 1.93 (d, 1H, J = 9.6 Hz, pip. CH_2, H-4'), 2.34 (d, 1H, J = 10.4 Hz, pip.CH_2, H-5), 3.57 (m, 2H, pip.CH_2, H-6), 3.72 (d, 1H, J = 13.2 Hz, pip.CH_2, H-2), 4.96 (s, 2H, CH_2, H-9), 7.10 (d, 2H, J = 6.8 Hz, Ar-H, H-11, H-15), 7.20 (t, 1H, J = 9.2 Hz, Ar-H, H-13), 7.54 (d, 1H, J = 5.4 Hz, thiophene-H, H-19), 7.7-7.72 (m, 1H, thiophene-H, H-17), 7.72-7.82 (brs, 1H, HCl), 8.46 (m, 1H, thiophene-H, H-18), 9.7 (brs, 1H, pip.NH, H-1); ^{13}C NMR (150 MHz, CD_3OD): δ 17.72 (pip.C, C-4), 28.72 (pip.C, C-5), 44.65 (pip.C, C-6), 46.15 (pip.C, C-2), 48.16 (pip.C, CH_2, C-9), 68.16, 104.09, 112.05, 126.84, 127.74, 128.21, 132.07, 141.94 (Aryl and thiophene C's), 155.75 (C=N, C-7), 163.87 (C-F, C-12, C-14), 165.52 (C-F, C-12, C-14), 177.34 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ,17.72 (CH_2), 28.72 (CH_2), 44.64 (CH_2), 46.14 (CH_2), 48.15 (CH_2), 104.1, 112.11, 126.83, 127.7, 128.22 (aryl and thiophene C-H); LCMS *m/z*: 362 $[M+H]^+$; C H N analysis; Calculated for $C_{18}H_{18}ClF_2N_3OS$, C, 54.34%; H, 4.56%; N, 10.56%; Found: C, 54.39%; H, 4.51%; N, 10.49%.

4-Thiophen-3-yl-2-(2-trifluoromethyl-benzyl)-2,3,7-triaza-spiro[4.5]dec-3-en-1-one hydrochloride, 7c: Yield: 190 mg (74%); IR (KBr) ν_{max}/cm^{-1}: 3395 (NH), 3066 (aromatic C-H), 2703, 1702 (C=O) 1544, 1313, 1163, 1127, 773; ^{1}H NMR (400 MHz-CD_3OD) : δ 1.97-2.14 (m, 2H, pip. CH_2, H-4), 2.45-2.63 (m, 2H, pip.CH_2, H-5), 3.4 (m, 1H, pip.CH_2, H-6), 3.5-3.52 (m, 1H, pip.CH_2, H-6'), 3.64-3.77 (m, 2H, pip.CH_2, H-2), 5.1 (d, 2H, CH_2, H-9), 5.26 (d, 1H, CH_2, H-9'), 7.44-7.56 (m, 3H), 7.6-7.64 (m, 1H), 7.74 (d, 1H), 8.11 (m, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.29 (pip.C, C-4), 26.63 (pip.C, C-5), 41.99 (pip.C, C-6), 43.56 (pip.C, C-2), 47.27 (CH_2, C-9), 122.94, 125.56, 126.1, 126.51, 127.3,127.66, 128.19, 129.19, 130.46, 133.1, 134.35 (Aryl and thiophene C's), 154.17 (C=N, C-7), 175.73 (pyrazolone C=O, C-8); LCMS *m/z*: 393.8 $[M+H]^+$; C H N analysis; Calculated for $C_{19}H_{19}ClF_3N_3OS$, C, 53.08%; H, 4.45%; N, 9.77%; Found: C, 53.24%; H, 4.39%; N, 9.71%.

4-(Thiophen-3-yl)-2-(4-(trifluoromethyl)benzyl)-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride, 7d: Yield: 158 mg (62%);IR (KBr) ν_{max}/cm^{-1}: 3429 (NH), 3069 (aromatic C-H), 2935 (aliphatic C-H), 2706, 1698 (C=O), 1619, 1540, 1329, 1106, 821; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80-1.81 (d, 1H, J = 6.8 Hz, pip. CH_2, H-4), 1.88-1.91 (d, 1H, J = 9.2 Hz, pip. CH_2, H-4'), 2.32-2.38 (m, 2H, pip. CH_2, H-5), 3.54-3.57 (m, 2H, pip.CH_2, H-6), 3.65-3.68 (d, 1H, J = 12.8 Hz, pip. CH_2, H-2), 4.98-5.08 (m, 2H, CH_2, H-9), 7.52-7.57 (m. 3H, Ar-H's H-11, H-15 and thiophene-H H-19), 7.69-7.74 (m, 4H, Ar-H's H-12, H-14, thiophene-H, H-17 and HCl H), 8.46-8.47 (m, 1H, thiophene-H, H-18), 9.9-10.05 (brs, 1H, pip. NH, H-1, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): δ 17.72 (pip.C, C-4), 28.69 (pip.C, C-5), 44.66 (pip.C, C-6), 46.17 (pip.C, C-2), 48.44 (CH_2, C-9), 124.74, 126.54, 126.73, 126.85, 127.63, 128.18, 129.59, 130.94, 131.15, 132.12 (aryl and thiophene C's), 142.1 (C=N, C-7), 177.38 (pyrazolone C=O, C-8) ; DEPT-135 (100 MHz, CD_3OD): δ 17.72 (CH_2), 28.68 (CH_2), 44.64 (CH_2), 46.17 (CH_2), 48.42 (CH_2), 126.68, 126.72, 126.83, 127.6, 128.16, 129.57 (aryl and thiophene C-H); LCMS *m/z*: 393.8 $[M+H]^+$; C H N analysis; Calculated for $C_{19}H_{19}ClF_3N_3OS$, C, 53.08%; H, 4.45%; N, 9.77%; Found: C, 53.24%; H, 4.39%; N, 9.71%

2-(4-Chloro-benzyl)-4-methyl-2,3,7-triaza-spiro-[4.5]dec-3-en-1-one hydrochloride, 7e: Yield: 184 mg (81 %); IR (KBr) ν_{max}/cm^{-1}: 3505 (NH), 2923, 2820, 2713, 1693 (C=O), 1537, 1494, 1385, 1287, 1085, 799, 670, 482; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.64 (d, 1H, J = 13.6 Hz, pip. CH_2, H-4), 1.74 (d, 1H, J = 13.2 Hz, pip. CH_2, H-4'), 1.95 (s, 3H, CH_3), 2.05 (m, 2H, pip. CH_2, H-5), 2.92-3.2 (m, 1H, pip. CH_2, H-6), 3.23-3.34 (m, 3H, pip.CH_2, H-6', H-2), 4.73-4.75 (m, 2H, CH_2, H-9), 7.25 (d, 2H, J = 8.4 Hz, Ar-H, H-11, H-15), 7.4 (d, 2H, J = 8.4 Hz, Ar-H, H-12, H-14), 7.8-8.0 (brs, 1H, pip.NH, D_2O exch.), 9.7 (brs, HCl, D_2O exch.); ^{13}C NMR (100MHz, CD_3OD); δ 13.32 (CH_3), 17.55 (pip.C, C-4), 27.37 (pip.C, C-5), 44.75 (pip.C, C-6), 45.35 (pip.C, C-2), 47.86 (CH_2, C-9), 129.83, 130.71, 134.68, 136.58 (aryl C's), 161.42 (C=N, C-7), 177.41 (pyrazolone C=O, C-8); DEPT-135 (400MHz, CD_3OD); δ 13.32 (CH_3), 17.41 (CH_2), 27.23 (CH_2), 44.61 (CH_2), 45.21 (CH_2), 47.72 (CH_2), 129.68, 130.55, (aryl C-H);LCMS *m/z*: 292.1[M+H]+; C H N analysis; Calculated for $C_{15}H_{19}Cl_2N_3O$, C, 54.89%; H, 5.83%; N, 12.80%; Found: C, 54.81%; H, 5.89%; N, 12.88%.

2-(3-Fluoro-benzyl)-4-methyl-2,3,7-triaza-spiro [4.5]dec-3-en-1-one hydrochloride, 7f: Yield: 162 mg (70 %); IR (KBr) ν_{max}/cm^{-1}: 3435 (NH), 2945, 2816, 1693 (C=O), 1385, 1247, 1070, 940, 784, 565 ;^{1}H NMR (400MHz-DMSO-d_6); δ 1.64 (d, 1H, J = 13.2 Hz, pip. CH_2, H-4), 1.77-1.74 (m, 1H, pip. CH_2, H-4'), 2.08 (s, 3H, -CH_3), 2.23-2.27 (m, 2H, pip. CH_2, H-5), 3.0 (m,

1H, pip.CH_2, H-6), 3.22-3.35 (m, 3H, pip. CH_2, H-6', H-2), 4.79 (s, 2H, -CH_2 , H-9), 7.09-7.15 (m, 3H, Ar-H), 7.37-7.42 (m, 1H, Ar-H), 7.8-7.9 (brs, 1H, HCl, D_2O exch.), 9.6-9.7 (brs, 1H, pip NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD); δ 11.86 (CH_3), 16.08 (pip.C, C-4), 25.93 (pip.C, C-5), 43.27 (pip.C, C-6), 43.88 (pip.C, C-2), 46.48 (CH_2, C-9), 114.24, 123.39, 130.15, 139.06 (Aryl C's), 160 (C=N, C-7), 162.07 (C-F, C-12), 163.69 (C-F, C-12), 175.98 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD); δ,11.86 (CH_3), 15.71 (CH_2), 25.83 (CH_2), 43.71 (CH_2), 43.83 (CH_2), 46.46 (CH_2), 113.92, 123.27, 130.09 (aryl C-H);LCMS *m/z*:276.4 $[M+H]^+$; C H N analysis; Calculated for $C_{15}H_{19}ClFN_3O$, C, 57.78%; H, 6.14%; N, 13.48%; Found: C, 57.71%; H, 6.19%; N, 13.43%.

4-(Thiophen-2-yl)-2-(2-(trifluoromethyl)benzyl)-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride, 7g: Yield: 137 mg (54%); IR (KBr) ν_{max}/cm^{-1}: 3418 (NH), 3070 (aromatic C-H), 2936 (aliphatic C-H), 1703 (C=O), 1552, 1314, 1164, 1125, 993, 775; ^{1}H NMR (400 MHz-DMSO-d_6); δ 1.72-1.84 (m, 1H, pip. CH_2, H-4), 1.92 (d, 1H, *J* = 10.4 Hz, pip. CH_2, H-4'), 2.32-2.35 (m, 2H, H-5), 3.5-3.62 (m, 2H, pip. CH_2, H-6), 3.72 (d, 1H, *J* = 10.2 Hz, pip. CH_2, H-2), 4.93 (s, 2H, CH_2, H-9), 7.22 (t, 1H, *J* = 4.4 Hz, thiophene-H), 7.27 (d, 1H, *J* = 6.4 Hz, thiophene-H), 7.39-7.43 (m, 3H, Ar-H), 7.77 (d, 1H, *J* = 5.2 Hz, thiophene-H), 7.93-7.94 (d, 1H, *J* = 3.6 Hz, Ar-H), 9.8 (brs, 1H, pip. NH, D_2O exch.); ^{13}CNMR (150 MHz-CD_3OD): δ 17.74 (pip.C, C-4), 28.99 (pip.C, C-5), 44.73 (pip.C, C-6), 45.59 (pip. C, C-2), 46.3 (CH_2, C-9), 123.11, 124.92, 126.73, 127.28, 128.65, 129.28, 130.66, 133.79, 135.6 (aryl and thiophene C's), 155.03 (C=N, C-7), 177.25 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.74 (CH_2), 28.9 (CH_2), 44.71 (CH_2), 45.56 (CH_2), 46.28 (CH_2), 127.23, 129.24, 129.31, 130.47, 130.64, 133.79 (aryl and thiopheneC-H); LCMS: *m/z*: 394.1 $[M+H]^+$; C H N analysis; Calculated for $C_{19}H_{19}ClF_3N_3OS$, C, 53.08%; H, 4.45%; N, 9.77%; Found: C, 53.02%; H, 4.49%; N, 9.74%.

2-(3-Fluorobenzyl)-4-(thiophen-2-yl)-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride, 7h: Yield: 198 mg (88%); IR (KBr) ν_{max}/cm^{-1}:3435 (NH), 3069 (aromatic C-H), 2932 (aliphatic C-H), 1694 (C=O), 1594, 1397, 1127, 692; ^{1}HNMR (400MHz-DMSO-d_6): δ 1.80 (d, 1H, *J* = 7.6 Hz, pip.CH_2, H-4), 1.94 (d, 1H, *J* = 9.6 Hz, pip.CH_2, H-4'), 2.34 (d, 2H, *J* = 10 Hz, pip.CH_2, H-5), 3.51-3.54 (m, 2H, pip. CH_2, H-6), 3.71 (d, 1H, *J* = 12.8 Hz, pip. CH_2, H-2), 4.93 (s, 2H, CH_2, H-9), 7.15-7.23 (m, 4H, Ar-H,), 7.40-7.46 (m, 1H, thiophene-H, H-18), 7.76 (d, 1H, *J* = 5.2 Hz, thiophene-H, H-17), 7.95 (d, 1H, *J* = 3.6 Hz, thiophene-H, H-19), 10 (brs, 1H, pip.NH, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.25 (pip.C, C-4), 26.98 (pip.C, C-5),42.05 (pip.C, C-6), 43.7 (pip. C, C-2), 46.52 (CH_2, C-9), 47.51, 114.09, 123.35, 128.39, 129.22, 129.64, 130.66, 132.51, 139.17 (aryl and thiophene C's), 153.33 (C=N, C-7), 161.02 (C-F, C-12), 163.44 (C-F, C-12), 175.32 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.45 (CH_2), 28.71 (CH_2), 44.42 (CH_2), 45.98 (CH_2), 48.16 (CH_2), 115.35, 115.57, 124.60, 129.06, 129.58, 130.31, 131.38, (aryl and thiophene C-H); LCMS *m/z*: 344.1$[M+H]^+$; C H N analysis; Calculated for $C_{18}H_{19}ClFN_3OS$, C, 56.91%; H, 5.04%; N, 11.06%; Found: C, 56.85%; H, 5.07%; N, 11.01%.

2-(2-Fluorobenzyl)-4-(thiophen-2-yl)-2,3,7-triaz aspiro[4.5]dec-3-en-1-one hydrochloride, 7i: Yield: 129 mg (60 %); IR (KBr) ν_{max}/cm^{-1}: 3431 (NH), 3096 (aromatic C-H), 2934 (aliphatic C-H), 2627, 1691 (C=O), 1443, 1396, 1129, 1070, 937, 753, 674; ^{1}H NMR (400MHz-DMSO-d_6): δ 1.80 (d, 1H, *J* = 8.8 Hz, pip. CH_2, H-4), 1.88 (d, 1H, *J* = 2 Hz, pip. CH_2, H-4'), 2.33 (d, 2H, *J* = 8 Hz, pip.CH_2, H-5), 3.53 (d, *J* =12.8 Hz, 2H, pip. CH_2, H-6), 3.66 (d, 1H, *J* = 12.8, pip. CH_2, H-2), 4.90 (d,1H, *J* = 16 Hz, CH_2, H-9), 5.00 (d, 1H, *J* = 16 Hz, CH_2,H-9'), 7.2-7.26 (m, 3H), 7.38 (t, 2H), 7.75 (d, 1H), 7.93 (d, 1H), 7.98 (brs,1H, Pip. NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): δ 17.73 (pip. C, C-4) , 29 (pip. C, C-5), 42.86 (pip.C, C-6), 44.74 (pip. C, C-2), 46.32 (CH_2, C-9), 116.58, 124.16, 124.26, 125.65, 129.25, 129.75, 130.52, 131.15, 134.07 (aryl and thiophene C's), 154.74 (C=N, C-7), 161.39 (C-F, C-11), 163.01 (C-F, C-11), 176.9 (pyrazolone C=O); LCMS *m/z*: 344.1$[M+H]^+$; C H N analysis; Calculated for $C_{18}H_{19}ClFN_3OS$, C, 56.91%; H, 5.04%; N, 11.06%; Found: C, 56.97%; H, 4.98%; N, 11.01%.

2-(2,4-Difluoro-benzyl)-4-thiophen-2-yl-2,3,7-triaza-spiro[4.5]dec-3-en-1-one hydrochloride, 7j: Yield: 94 mg (40%); IR (KBr) ν_{max}/cm^{-1}: 3420 (NH), 3047 (aromatic C-H), 1699 (C=O), 1627, 1121, 993, 850; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.79 (d, 1H, *J* = 8 Hz, pip. CH_2, H-4), 2.0 (d, 1H, *J* = 9.6 Hz, pip. CH_2, H-4'), 2.34 (d, 2H, *J* = 9.6 Hz, H-5), 3.49-3.55 (m, 2H, pip. CH_2, H-6), 3.75 (d, 1H, *J* = 12.8 Hz, H-2), 4.95 (s, 2H, CH_2, H-9), 7.1 (d, 2H, *J* = 6.8 Hz, Ar-H and thiophene-H), 7.18-7.23 (m, 2H, Ar-H), 7.7 (brs, 1H, HCl), 7.77 (d, 1H, *J* = 4.8 Hz, thiophene-H), 7.95 (d, 1H, *J* = 3.6 Hz, thiophene-H), 10.0 (brs, 1H, pip. NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): δ 18.15 (pip.C, C-4), 29.42 (pip.C, C-5), 45.12 (pip.C,

C-6), 46.66 (pip. C, C-2), 48.6 (CH_2, C-9), 104.55, 112.29, 129.77, 130.38, 131.08, 134.37, 142.28, (aromatic and thiophene C's), 155.44 (C=N, C-7), 163.89 (C-F), 166.35 (C-F), 177.49 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 18.14 (CH_2), 29.41 (CH_2), 45.11 (CH_2), 46.65 (CH_2), 48.58 (CH_2), 104.56, 112.3, 129.76, 130.37, 131.09, 135.47 (aryl and thiophene C-H); LCMS *m/z*: 362.1 $[M+H]^+$; C H N analysis; Calculated for $C_{18}H_{18}ClF_2N_3OS$, C, 54.34%; H, 4.56%; N, 10.56%; Found: C, 54.38%; H, 4.50%; N, 10.52%.

2-(4-Chloro-2-fluoro-benzyl)-4-thiophen-2-yl-2,3,7-triaza-spiro[4.5]dec-3-en-1-one hydrochloride, 7k: Yield: 83 mg (34%); IR (KBr) ν_{max}/cm^{-1}: 3447 (NH), 3073 (aromatic C-H), 2820, 2709, 1700 (C=O), 1552, 1492, 1352, 1237, 939, 724; ^{1}H NMR (400MHz-DMSO-d_6): δ 1.79 (d, 1H, *J* = 4 Hz, pip. CH_2, H-4), 1.9 (d, 1H, *J* = 9.6 Hz, pip. CH_2, H-4'), 2.33 (m, 2H, pip.CH_2, H-5), 3.51 (d, 1H, *J* = 12.8 Hz, H-6), 3.7 (d, 1H, *J* = 13.2 Hz, pip. CH_2,H-6'), 4.1 (brs, 2H, H-2), 4.90 (d, 1H, *J* = 15.6 Hz, CH_2, H-9), 4.98 (d, 1H, *J* = 15.6 Hz, CH_2, H-9') 7.2-7.23 (t, 1H, *J* = 3.2 Hz, thiophene-H, H-18), 7.29-7.34 (t, 1H, *J* = 9.2 Hz, Ar-H, H-15), 7.46-7.51 (m, 2H, Ar-H, H-12, H-14), 7.76 (d, 1H, *J* = 4.8 Hz, thiophene-H, H-17), 7.93 (d, 1H, *J* = 3.2 Hz, thiophene-H, H-19), 10 (br, 1H, pip. NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): δ 17.74 (pip.C, C-4), 29.06 (pip.C, C-5), 42.69 (pip.C, C-6), 44.75 (pip.C, C-2), 46.31 (CH_2, C-9), 118.22, 126.25, 129.31, 130.55, 130.62, 131.08, 133.96 (aromatic and thiophene C's), 154.93, (C=N, C-7), 160.01(C-F, C-11), 161.64 (C-F, C-11), 176.88 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.45 (CH_2), 28.77 (CH_2), 42.37 (CH_2), 44.46 (CH_2), 46.01 (CH_2), 117.87, 129.04, 129.62, 130.37, 130.75, 131.22 (aryl and thiophene C-H); LCMS *m/z*: 378 $[M+1]^+$; C H N analysis; Calculated for $C_{18}H_{18}Cl_2FN_3OS$, C, 52.18%; H, 4.38%; N, 10.14%; Found: C, 52.11%; H, 4.32%; N, 10.19%.

4-(Thiophen-2-yl)-2-(4-(trifluoromethyl)benzyl)-2,3,7-triazaspiro[4.5]dec-3-en-1-one hydrochloride, 7l: Yield: 121 mg (47%); IR (KBr) ν_{max}/cm^{-1}: 3447 (NH), 3021, 1642 (C=O), 1402, 1216; ^{1}H NMR (400MHz-DMSO-d_6): δ 1.80 (d, 1H, *J* = 7.2 Hz, pip. CH_2, H-4), 1.95 (d, 1H, *J* = 8.8 Hz, pip. CH_2, H-4'), 2.34-2.36 (d, 2H, *J* = 8.8 Hz,pip. CH_2, H-5), 3.4 (m, 2H, pip. CH_2, H-6), 3.52 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-2), 3.71 (d, 1H, *J* = 12.8 Hz, pip. CH_2, H-2'), 4.97-5.03 (m, 2H, *J* = 6.4 Hz, CH_2, H-9),7.21 (t, 1H, *J* = 4 Hz, thiophene-H, H-18), 7.55 (d, 2H, *J* = 8 Hz, Ar-H's, H-11, H-15), 7.72-7.77 (m, 3H, Ar-H's H-12, 14 and thiophene-H, H-17), 7.95 (d, 1H, thiophene-H, H-19), 10.1 (brs, 1H, pip. NH, D_2O exch.); ^{13}CNMR (75 MHz, CD_3OD): δ 16.33 (pip.C, C-4), 27.63 (pip.C, C-5), 43.51 (pip.C, C-6), 45.08 (pip.C, C-2), 125.26, 127.88, 128.22, 128.42, 129.18, 129.55, 132.45, 140.43, 153.56 (C=N, C-7), 173.74 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 16.3 (CH_2), 27.54 (CH_2), 43.30 (CH_2), 44.84 (CH_2), 47.42 (CH_2), 125.29, 127.85, 128.16, 128.39, 129.18, (aryl and thienyl C-H); LCMS *m/z*: 394.3 $[M+H]^+$; C H N analysis; Calculated for $C_{19}H_{19}ClF_3N_3OS$, C, 53.09%; H, 4.46%; N, 9.77%; Found: C, 53.02%; H, 4.41%; N, 9.72%.

2-(3-Chlorobenzyl)-4-(thiophen-2-yl)-2,3,7-triaz aspiro[4.5]dec-3-en-1-one hydrochloride, 7m: Yield: 128 mg (55%); IR (KBr) ν_{max}/cm^{-1}: 3439 (NH), 2926, 1697 (C=O), 1549, 1396, 940, 711; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.80 (d, 1H, *J* = 7.2 Hz, pip. CH_2, H-4), 1.95 (d, 1H, *J* = 8.8 Hz, pip. CH_2, H-4'), 2.35 (d, 2H, *J* = 8.8 Hz, pip. CH_2, H-5), 3.4 (m, 2H, H-6), 3.52 (d, 1H, *J* = 13.2 Hz, H-2), 3.71 (d, 1H, *J* = 12.8 Hz, H-2'), 5.02 (d, 2H, *J* = 6.4 Hz, H-9),7.21 (t, 1H, *J* = 4 Hz, thiophene-H, H-18), 7.55 (d, 2H, *J* = 8 Hz, Ar-H's, H-11, H-15), 7.72-7.77 (m, 3H, Ar-H's H-12, 14 and thiophene-H, H-17), 7.95 (d, 1H, thiophene-H, H-19), 10.1 (brs, 1H, pip. NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD) 17.74 (pip.C,C-4), 29.0 (pip.C, C-5), 44.71 (pip. C, C-6), 46.28 (pip. C-2), 48.45, (pip. C, C-9), 127.54, 129.13, 129.35, 129.84, 130.6, 131.44, 134.03, 135.59, 139.78 (aromatic and thiophene C's), 154.86 (C=N, C-7), 177.01 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ,17.73 (CH_2), 29.00 (CH_2), 44.70 (CH_2), 46.27 (CH_2), 48.44 (CH_2), 127.55, 129.13, 129.22, 129.31, 129.80, 130.62, 131.45 (aryl and thiophene C-H); LCMS *m/z*: 360.1 $[M+H]^+$; C H N analysis; Calculated for $C_{18}H_{19}Cl_2N_3OS$, C, 54.55%; H, 4.83%; N, 10.60%; Found: C, 54.59%; H, 4.89%; N, 10.68%.

2-(4-Chlorobenzyl)-4-(thiophen-2-yl)-2,3,7-triaz aspiro[4.5]dec-3-en-1-one hydrochloride, 7n: Yield: 151 mg (64%); IR (KBr) ν_{max}/cm^{-1}: 3438 (NH), 3049 (aromatic C-H), 1694 (C=O), 1425, 1393, 840; ^{1}H NMR(400 MHz-DMSO-d_6): δ 1.75-1.82 (m, 1H, pip.CH_2, H-4), 1.9-1.94 (m, 1H, pip.CH_2, H-4'), 2.32-2.34 (m, 2H, pip.CH_2, H-5), 3.5 (m, 2H, pip.CH_2, H-6), 3.68 (d, 2H, H-2), 4.9-4.92 (m, 2H, CH_2, H-9), 7.21 (t, 1H, *J* = 4 Hz, thiophene-H, H-18), 7.35 (d, 2H, *J*= 8 Hz, Ar-H, H-11, H-15), 7.43 (d, 2H, *J* = 8.4 Hz, Ar-H, H-12, H-14), 7.76 (d, 1H, *J* = 5.2 Hz,

thiophene-H, H-17), 7.93 (d, 1H, *J* = 3.2 Hz, thiophene-H, H-19), 9.9 (br, 1H, pip. NH, D_2O exch.); ^{13}C NMR (100MHz, CD_3OD): δ 17.77 (pip.C, C-4), 29.0 (pip.C, C-5), 44.82 (pip.C, C-6), 46.36 (pip.C, C-2), 129.33, 129.81, 130.59, 130.76, 134.07, 134.84, 136.32 (aryl and thiophene C's), 154.8 (C=N, C-7), 177.02 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.77 (CH_2), 29.0 (CH_2), 44.82 (CH_2), 46.36 (CH_2), 48.31 (CH_2), 129.33, 129.85, 129.91, 130.58, 130.74 (aryl and thiophene C-H); LCMS *m/z*: 360.1 $[M+H]^+$ and C H N analysis; Calculated for $C_{18}H_{19}Cl_2N_3OS$, C, 54.55%; H, 4.83%; N, 10.60%; Found: C, 54.51%; H, 4.79%; N, 10.55%.

2-(2-Chloro-benzyl)-4-furan-2-yl-2,3,7-triaza-spiro[4.5]dec-3-en-1-one hydrochloride, 7o: Yield: 103 mg (43%); IR (KBr) ν_{max}/cm^{-1}: 3436 (NH), 3076 (aromatic C-H), 1691 (C=O), 1547, 1388, 1005, 752; ^1H NMR (100 MHz-DMSO-d_6): δ 1.78 (d, 1H, *J* = 13.6 Hz, pip. CH_2, H-4), 1.94 (d, 1H, *J* = 12 Hz, pip. CH_2, H-4'), 2.08-2.33 (m, 2H, pip.CH_2, H-5), 3.46 (d, 2H, *J* = 13.2 Hz, pip. CH_2, H-6), 3.69 (d, 1H, *J* = 14.4 Hz, pip. CH_2, H-2), 4.92 (d, 1H, *J* = 16 Hz, CH_2, H-9), 5.03 (d, 1H, *J* = 15.6 Hz, CH_2, H-9'), 6.73 (dd, 1H, *J* = 2 Hz, furyl-H, H-18), 7.36-7.4 (m, 4H, Ar-H, H-12, H-13, H-14, H-15), 7.5-7.52 (m, 1H, furyl-H, H-17), 7.91 (d, 1H, *J* = 1.2 H,furyl-H, H-19), 9.5-9.7 (brs, 1H, Pip.NH, D_2O exch.); ^{13}C (400 MHz, CD_3OD) δ 17.62 (pip.C, C-4), 28.73 (pip.C, C-5), 44.88 (pip.C, C-6), 46.11 (pip.C, C-2), 46.85 (CH_2, C-9), 113.41 (furyl-C, C-17), 113.67 (furyl-C, C-18), 128.45, 130.65, 131.23 (aromatic C's), 146.64 (furyl-C, C-16, C-19), 155 (C=N, C-7), 176 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.62 (CH_2), 28.72 (CH_2), 44.88 (CH_2), 46.09 (CH_2), 46.85 (CH_2), 113.42, 113.63, 128.45, 130.66, 130.81, 131.24, 146.64 (aryl and furyl C-H) LCMS *m/z*: 344 $[M+H]^+$; C H N analysis; Calculated for $C_{18}H_{19}Cl_2N_3O_2$, C, 56.85%; H, 5.04%; N, 11.05%; Found: C, 56.89%; H, 5.09%; N, 11.06%.

2-(3-Chloro-benzyl)-4-furan-2-yl-2,3,7-triaza-spiro[4.5]dec-3-en-1-one hydrochloride, 7p: Yield: 134 mg (56%); IR (KBr) ν_{max}/cm^{-1}: 3409 (NH), 3172 (aromatic C-H), 2921 (aliphatic C-H), 2337, 1713 (C=O), 1534, 1381, 1127, 888, 672; ^1H NMR (400 MHz-DMSO-d_6): δ 1.79 (d, 1H, *J* = 14 Hz, pip. CH_2, H-4), 1.91 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-4'), 2.2-2.35 (m, 2H, pip.CH_2 , H-5), 3.69 (d, 1H, *J* = 12.8 Hz, H-2), 4.9 (s, 2H, CH_2, H-9), 6.73 (dd, 1H, *J* = 3.6, 1.6 Hz, furyl-H, H-18), 7.28 (m, 1H, furyl-H, H-17), 7.38-7.43 (m, 4H, Ar-H, H-11, H-13, H-14, H-15), 7.8 (br, 1H, HCl, D_2O exch.), 7.9 (d, 1H, *J* = 1.6 Hz, furyl-H, H-19), 9.8 (s, 1H, pip. NH); ^{13}C NMR (75 MHz, CD_3OD): δ 17.6 (pip.C, C-4), 28.58 (pip.C, C-5), 45 (pip.C, C-6), 46.15 (pip.C, C-2), 68.13, 113.35 (furyl-C, C-17), 113.66 (furyl-C, C-18), 127.49, 129.1, 131.35, 135.62, 139.63, 146.8 (furyl-C, C-16, C-19), 151.28 (C=N, C-7), 176.5 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.6 (CH_2), 28.59 (CH_2), 44.83 (CH_2), 45.96 (CH_2), 48.50 (CH_2), 113.45, 113.83, 127.51, 129.12, 129.15, 131.46, 146.71 (aryl and furyl C-H) LCMS *m/z*: 344.0 $[M+1]^+$; C H N analysis; Calculated for $C_{18}H_{19}Cl_2N_3O_2$, C, 56.85%; H, 5.04%; N, 11.05%; Found: C, 56.89%; H, 5.09%; N, 11.01%.

2-(4-Chlorobenzyl)-4-(furan-2-yl)-2,3,7-triazas piro[4.5]dec-3-en-1-one hydrochloride, 7q: Yield: 117 mg (49%); IR (KBr) ν_{max}/cm^{-1}: 3456 (NH), 3087 (aromatic C-H), 2934 (aliphatic C-H), 2822, 1694 (C=O), 1382, 885, 672; ^1H NMR(400MHz-DMSO-d_6) : 1.77 (d, 1H, *J* = 13.6 Hz, pip. CH_2, H-4), 1.90 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-4'), 2.2-2.35 (m, 2H, pip. CH_2, H-5), 3.67 (d, 1H, *J* = 12.8 Hz, pip. CH_2, H-2), 4.86-4.95 (m, 2H,CH_2, H-9), 6.73 (dd, 1H, *J* = 3.2, 1.6 Hz, furyl-H, H-18), 7.34-7.44 (m, 5H, Ar-H's & furyl-H, H-17), 7.72-7.84 (brs, 1H, HCl, D_2O exch.), 7.91 (d, 1H, *J* = 1.6 Hz, furyl-H, H-19), 9.9 (brs, 1H, pip. NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): 17.62 (pip.C, C-4), 28.56 (pip.C, C-5), 44.86 (pip.C, C-6), 45.99 (pip.C, C-2), 48.38 (CH_2, C-9), 113.42 (furyl-C, C-17), 113.73 (furyl-C, C-18), 129.91, 130.74, 134.82, 136.3, 146.64 (furyl-C, C-16), 146.77 (furyl-C, C-19), 151.16 (C=N, C-7), 176.43 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.63 (CH_2), 28.56 (CH_2), 44.87 (CH_2), 46.0 (CH_2), 48.38 (CH_2), 113.43, 113.71, 129.92, 130.74, 146.66 (aryl and furyl C-H); LCMS *m/z*: 344 $[M+H]^+$;C H N analysis; Calculated for $C_{18}H_{19}Cl_2N_3O_2$, C, 56.85%; H, 5.04%; N, 11.05%; Found: C, 56.89%; H, 5.09%; N, 11.01%.

2-(3-Fluorobenzyl)-4-(furan-2-yl)-2,3,7-triazas piro[4.5]dec-3-en-1-one hydrochloride, 7r: Yield: 96 mg (42 %); IR (KBr) ν_{max}/cm^{-1}: 3440 (NH), 2938 (aromatic C-H), 1699 (C=O), 1613, 1515, 1407, 1234, 1131, 1025, 766; ^1H NMR (400 MHz-DMSO-d_6): δ 1.80 (d, 1H, *J* = 12.2 Hz, pip. CH_2, H-4), 1.93 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-4'), 2.0-2.3 (m, 2H, pip. CH_2, H-5), 3.71 (d, 1H, *J* = 12.8 Hz, pip. CH_2, H-2), 4.93 (s, 2H, CH_2, H-9), 6.73 (dd, 1H, *J* = 3.6, 2.0 Hz, furyl-H, H-18), 7.13-7.18 (m, 3H, Ar-H's and furyl-H, H-17), 7.4-7.45 (m, 2H, Ar-H), 7.72-7.84 (brs, 1H, HCl, D_2O exch.), 7.91 (d, 1H, *J* = 1.6 Hz,furyl-H, H-19), 9.7 (brs,

1H, pip.NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): 17.63 (pip.C, C-4), 28.59 (pip.C, C-5), 44.86 (pip.C, C-6), 46.6 (pip.C, C-2), 48.55 (CH_2, C-9), 113.44 (furyl-C, C-17), 113.71 (furyl-C, C-18), 115.8, 124.89, 131.71 (Ar-C's), 140.24 (furyl-C, C-16), 146.78 (furyl-C. C-19), 163.57 (C-F, C-12), 163.19 (C-F, C-12), 176.46 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.63 (CH_2), 28.60 (CH_2), 44.85 (CH_2), 45.99 (CH_2), 48.54 (CH_2), 113.43, 113.76, 115.64, 115.85, 124.86, 131.67, 146.69 (aryl and furyl C-H) LCMS *m/z*: 328 $[M+H]^+$;C H N analysis; Calculated for $C_{18}H_{19}CFN_3O_2$, C, 59.42%; H, 5.26%; N, 11.55%; Found: C, 59.48%; H, 5.21%; N, 11.59%.

4-(Furan-2-yl)-2-(3-methylbenzyl)-2,3,7-triazas piro[4.5]dec-3-en-1-one hydrochloride, 7s: Yield: 119 mg (53%); IR (KBr) ν_{max}/cm^{-1}: 3451 (NH), 3088 (aromatic C-H), 2932 (aliphatic C-H), 2716, 1693 (C=O), 1382, 1125, 1011, 886; ^1H NMR (400MHz-DMSO-d_6): δ 1.79 (d, 1H, *J* = 14.1 Hz, pip. CH_2, H-4), 1.88 (d, 1H, *J* = 13.4 Hz, pip.CH_2, H-4'), 2.18-2.25 (m, 1H, H-5), 2.3-2.36 (m, 5H, pip. CH_2, H-5', CH_3), 3.65 (d, 1H, *J* = 12.8 Hz, pip. CH_2, H-2), 4.81-4.85 (d, 1H, *J* = 15.6 Hz, H-9), 4.87-4.91 (d, 1H, *J* = 15.6 Hz, H-9') 6.72 (dd, 1H, *J* = 3.6, 1.6 Hz, furyl-H, H-18), 7.08-7.12 (m, 3H, Ar-H), 7.23-7.27 (m, 1H, Ar-H), 7.39 (d, 1H, *J* = 3.2 Hz, furyl-H, H-17), 7.79 (brs, 1H, HCl, D_2O exch.), 7.9 (d, 1H, *J* = 1.6 Hz, furyl-H, H-19), 9.9 (brs, 1H, pip.NH, D_2O exch.); ^{13}C NMR (150 MHz, CD_3OD): δ 17.56 (pip.C, C-4), 21.4 (CH_3), 28.51 (pip.C, C-5), 44.83 (pip.C, C-6), 45.98 (pip.C, C-2), 113.37 (furyl-C, C-17), 113.5 (furyl-C, C-18), 126.04, 129.65, 137.34, 140.14 (furyl-C, C-16), 146.55 (furyl-C, C-17), 150.95 (C=N, C-7), 176 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ 17.56 (CH_2), 21.38 (CH_3), 26.05 (CH_2), 28.49 (CH_2), 44.83 (CH_2), 45.99 (CH_2) 113.34, 113.42, 126.03, 129.61, 129.65, 146.51 (aryl and furyl C-H) LCMS *m/z*: 324 $[M+H]^+$; C H N analysis; Calculated for $C_{19}H_{22}ClN_3O_2$, C, 63.42%; H, 6.16%; N, 11.68%; Found: C, 63.49%; H, 6.19%; N, 11.61%.

Preparation of *tert*-butyl 3-(2-ethoxy-2-oxoethyl)-1-(furan-2-yl)-4-oxo-2,3,7-triazaspiro[4.5]dec-1-ene-7-carboxylate, 8a

To a solution of **5a**(1.36g, 4.26mmol, 1eqt) in DMF (25 mL), K_2CO_3 (1.3g, 9.4mmol, 2.2 eqt) was addedfollowed by 2-chloro ethyl acetate (0.6g, 4.89 mmol, 1.15mmol) and heated to 60°C on an oil bath for 3-4h. After checking the completion of reaction by TLC, ice cold water was added to the reaction mixture and extracted with ethyl acetate (2x50mL). The organic layers were combined, washed with brine solution and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by column chromatography using 20% ethyl acetate in hexane as eluent to afford the title product (1.54g, 89%). ^1H NMR (400MHz-DMSO-d_6-80°C): δ 1.22 (t, 1H, *J* = 7.2 Hz, ester CH_3), 1.35 (s, 9H, boc-H's), 1.54-1.57 (m, 1H, pip. CH_2, H-4), 1.82-1.84 (m, 1H, pip. CH_2, H-4'), 2.12-2.20 (m, 2H, pip. CH_2, H-5), 3.53 (d, 1H, *J* = 13.6 Hz, H-6), 3.89-3.99 (m, 2H, pip. CH_2, H-2), 4.13-4.21 (m, 2H, CH_2CO), 4.47 (m, 2H, ester CH_2), 6.65-6.66 (m, 1H, furyl-H, H-13), 7.06 (d, 1H, furyl-H, H-12), 7.82 (s, 1H, furyl-H, H-14); LCMS *m/z*: 428.1 $[M+Na]^+$.

Preparation of 2-(7-(tert-butoxycarbonyl)-4-(furan-2-yl)-1-oxo-2,3,7-triazaspiro[4.5]dec-3-en-2-yl)acetic acid, 8b

To the compound **8a**(1.5 g, 3.69 mmol), methanol(10mL) and THF(10ml) were added followed by lithium hydroxide monohydrate(356mg, 8.43mmol) in water(15mL), stirring continued at the ambient temperature for 2-3h. After checking the completion of reaction by TLC, the reaction mixture was evaporated under reduced pressure and to the residual mass dil.HCl was added till a pH of 4-5 is attained. The aqueouslayer was extracted with ethyl acetate (3x25ml). The organic layer was concentrated to afford the title product (1.14 g, 82%).^1H NMR (400MHz-DMSO-d_6-80°C): δ 1.4 (s, 9H), 1.35 (s, 9H, boc-H's), 1.53-1.57 (m, 1H, pip. CH_2, H-4), 1.81-1.84 (m, 1H, pip.CH_2, H-4'), 1.99-2.2 (m, 2H, pip. CH_2, H-5), 3.52 (d, 1H, *J* = 13.6 Hz, pip. CH_2, H-6), 3.88-3.99 (m, 2H, pip. CH_2, H-2), 4.36 (d, 1H, *J* = 17.6 Hz, H-9), 4.44 (d, 1H, *J* = 17.6 Hz, H-9'), 6.64-6.65 (m, furyl-H, H-13), 7.05 (d, 1H, furyl-H, H-12), 7.81 (d, 1H, furyl-H, H-14); LCMS *m/z*: 378.1 $[M+H]^+$.

General procedure for the synthesis of 2-(4-furan-2-yl-1-oxo-2,3,7-triaza-spiro[4.5]dec-3-en-2-yl)-*N*-aryl acetamides, 9a-d

To a solution of the acid **8**(1eqt), DMF was added followed by DIPEA(3eqt) and the corresponding amine. The reaction mixture was cooled to 0°C and HATU (1.2 eqt) was added. The reaction mixture was stirred at the ambient temperature for 4-5h. After checking the completion of reaction by TLC, water was added to the reaction mixture. The aqueous layer was extracted twice with ethyl acetate and the combined organic layer was dried over anhyd. $Na_2SO_4$and concentrated to give the crude product which was purified by column chromatography using

hexane/ ethyl acetate system to afford the product which was reacted with HCl in 1,4-dioxane to afford the title compound as hydrochloride salt.

***N*-(3,4-Dimethoxy-phenyl)-2-(4-furan-2-yl-1-oxo -2,3,7-triaza-spiro[4.5]dec-3-en-2-yl)-acetamide hydrochloride, 9a**: Yield: 164 mg (55%); IR (KBr) ν_{max}/cm^{-1}: 3440 (NH), 2938 (aromatic C-H), 1699 (C=O), 1613, 1515, 1407, 1234, 1131, 1025, 766; ^{1}H NMR (400 MHz-CD_3OD): δ 1.80 (d, 1H, *J* = 14.4 Hz, pip.CH_2, H-4), 1.92 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-4'), 2.0-2.3 (m, 2H, pip.CH_2, H-5), 3.25-3.29 (m, 1H, pip.CH_2, H-6), 3.56 (m, 1H, pip.CH_2, H-6'), 3.74-3.75 (m, 2H, pip. CH_2, H-2), 3.82 (s, 6H, OCH_3), 4.70 (m, 2H, CH_2, H-9), 6.75 (dd, 1H, *J* = 3.6, 1.6 Hz, furyl-H, H-13), 6.88 (d, 1H, *J* = 8.8 Hz, Ar-H, H-19), 7.05 (dd, 1H, *J* = 8.4, 2.4 Hz, Ar-H, H-20), 7.3 (d, 1H, *J* = 2.4 Hz, Ar-H, H-16), 7.4 (d, 1H, *J* = 3.6 Hz, furyl-H, H-12), 7.6-7.7 (brs, 1H, HCl, D_2O exch.), 7.9 (d, 1H, *J* 2 Hz, furyl-H, H-14), 9.7 (brs, 1H, pip. NH, D_2O exch.), 10.3 (s, 1H, amide NH); ^{13}C NMR (100 MHz, CD_3OD): δ 17.69 (pip.C, C-4), 28.44 (pip.C, C-5), 44.98 (pip.C, C-6), 46.23 (pip.C, C-2), 56.53 (OCH_3), 56.87 (OCH_3), 68.19, 106.77 (furyl.C, C-12, C-13), 113.45, 113.68, 133.05, 146.69 (aromatic C's), 146.9 (furyl-C, C-14), 147.73 (furyl-C, C-11), 150.66 (C-18), 151.13 (C-17), 166.85 (amide C=O, C-10), 177.65 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD); δ 17.59 (CH_2), 28.38 (CH_2), 44.82 (CH_2), 46.05 (CH_2), 48.30 (CH_2), 56.34 (OCH_3), 56.66 (OCH_3) 106.33, 113.13, 113.37, 113.41, 113.68, 146.62 (aryl and furyl C-H) LCMS *m/z*: 413 $[M+H]^+$; C H N analysis; Calculated for $C_{21}H_{25}ClN_4O_5$, C, 56.19 %; H, 5.61 %; N, 12.48 %; Found: C, 56.24 %; H, 5.58 %; N, 12.42 %.;

***N*-(3,5-Dimethoxy-phenyl)-2-(4-furan-2-yl-1-oxo -2,3,7-triaza-spiro[4.5]dec-3-en-2-yl)-acetamide hydrochloride, 9b**: Yield: 148 mg (50%); IR (KBr) ν_{max}/cm^{-}1: 3423 (NH), 3154 (aromatic C-H), 2937 (aliphatic C-H), 2526, 1685 (C=O), 1621, 1457, 1384, 1149, 839, 749, 638. ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.75-1.95 (m, 2H, pip. CH_2, H-4), 2.2-2.35 (m, 2H, H-5), 3.71 (s, 6H, OCH_3), 4.5 (m, 2H, CH_2, H-9), 6.2 (s, 1H, furyl-H, H-13), 6.8 (m, 3H, Ar-H), 7.4 (s, 1H, furyl-H, H-12), 7.8 (br, HCl, D_2O exch.), 7.9 (m, 1H, H-14), 9.6-9.8 (s, 1H, pip.NH, D_2O exch.), 10.4 (s, 1H, amide NH); ^{13}C NMR (150 MHz, CD_3OD): δ 17.94 (pip.C, C-4), 26.92 (pip.C, C-5), 43.7 (pip.C, C-6), 46.74 (pip.C, C-2), 53.2 (CH_2, H-9), 55.1 (OCH_3) 95.59, 97.44 (Ar-C's), 112.35 (furyl-C, C-13), 113.47 (furyl-C, C-14), 140.25 (Ar-C, C-11), 144.13 (furyl-C, C-11), 145.69 (furyl-C, C-14), 148.83 (C=N, C-7), 160.5 (Ar-C, C-17, C-19), 164.96 (amide C=O, C-10), 175.66 (pyrazolone C=O, C-8); DEPT-135 (100MHz, DMSO-d_6): δ 15.93 (CH_2), 26.7 (CH_2), 41.99 (CH_2), 43.47 (CH_2), 47.10 (CH_2), 53.21 (OCH_3), 54.97 (OCH_3), 95.37, 97.2, 112.13, 113.25, 145.47 (aryl and furyl C-H); LCMS *m/z*: 412.8 $[M+1]^+$;C H N analysis; Calculated for $C_{21}H_{25}ClN_4O_5$, C, 56.19 %; H, 5.61 %; N, 12.48 %; Found: C, 56.11 %; H, 5.68 %; N, 12.43 %.

2-(4-Furan-2-yl-1-oxo-2,3,7-triaza-spiro[4.5]dec-3-en-2-yl)-*N*-pyridin-4-ylmethyl-acetamide hydro chloride, 9c: Yield: 106 mg (49%); ^{1}H NMR (400 MHz-CD_3OD): δ 1.79 (d, 1H, *J* 14.4, H-4), 1.93 (d, 1H, *J* = 13.6, H-4'), 2.39-2.56 (m, 2H, H-5), 3.2-3.3 (m, 3H, pip.CH_2, H-6, H-2), 3.53 (d, 1H, *J* = 12 Hz, pip.CH_2, H-2'), 3.69-3.7 (m, 2H, CH_2, H-9), 4.45-4.47 (m, 2H. CH_2, H-15), 6.65 (m, 1H, furyl-H, H-13), 7.13- (d, 1H, *J* = 3.6 Hz, furyl-H, H-12), 7.65-7.68 (m, 1H, pyridyl-H, H-17), 7.7 (d, 1H, *J* = 1.6 Hz, furyl-H, H-14), 8.11 (d, 1H, *J* = 8 Hz, pyridyl-H, H-20), 8.5-8.54 (m, 2H, pyridyl-H, H-18, H-19); ^{13}C NMR (100 MHz, CD_3OD): δ 17.66 (pip. C, C-4), 28.50 (pip. C, C-5),43.74 (pip. C, C-6), 44.86 (pip. C, C-2), 46.04 (CH_2, C-15), 48.13 (CH_2, C-9), 113.48 (furyl-C, C-12), 114.0 (furyl-C, C-13), 126.60 (pyridyl C's, C-17, C-20), 142.56 (furyl-C, C-14), 146.6 (pyridyl C, C-16), 146.81 (pyridyl C's, C-18, C-19), 151.25 (furyl-C, C-11), 162.36 (C=N, C-7), 170.03 (amide C=O, C-10), 177.36 (pyrazolone C=O, C-8); DEPT-135 (100MHz, CD_3OD): δ,17.66 (CH_2), 28.5 (CH_2), 43.75 (CH_2), 44.86 (CH_2), 46.03 (CH_2), 48.13 (CH_2), 113.49, 114.01, 126.60, 142.57, 146.82 (aryl and pyridyl C-H); LCMS *m/z*: 368.2 $[M+H]^+$; C H N analysis; Calculated for $C_{19}H_{22}ClN_5O_3$, C, 56.51 %; H, 5.49 %; N, 17.34 %; Found: C, 56.58 %; H, 5.42 %; N, 17.39 %.

2-(4-Furan-2-yl-1-oxo-2,3,7-triaza-spiro[4.5]dec-3-en-2-yl)-*N*-(1-methyl-1H-pyrazol-3-yl)-acetamide hydrochloride, 9d: Yield: 84 mg (40%); IR (KBr) ν_{max}/cm^{-1}:3425 (NH), 3128 (aromatic C-H), 1686 (C=O), 1585, 1008, 746; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.78-1.82 (d, 1H, *J* = 13.2 Hz, pip.CH_2, H-4), 1.92 (d, 1H, *J* = 12 Hz, pip. CH_2, H-4'), 2.2-2.4 (m, 2H, pip.CH_2, H-5), 3.2-3.6 (m, 4H, pip.CH_2, H-6, H-2), 3.8 (s, 3H, N-CH_3), 4.51-4.62 (m, 2H, H-9), 6.39 (d, 1H, *J* = 2.0 Hz, pyrazole-H, H-16), 6.74-6.76 (m, 1H, furyl-H, H-13), 7.41 (d, 1H, *J* = 3.2 Hz, furyl-H, H-12), 7.57 (d, 1H, *J* = 2 Hz, pyrazole-H, H-17), 7.7-7.9 (br, 1H, HCl, D_2O exch.), 7.92 (d, 1H, *J* = 1.6

Hz, furyl-H, H-14), 10.1 (d, 1H, Pip. NH, D_2O exch.), 10.79 (s, 1H, amide NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.18 (pip.C, C-4), 26.94 (pip.C, C-5), 38.36 (pyr.N-CH_3), 42.28 (pip.C, C-2), 43.76 (pip. C, C-6), 46.74 (N-CH_2, C-9), 96.43 (pyrazole C, C-16), 112.36 (furyl C, C-12), 113.48 (furyl C, C-13), 131.15 (pyrazole C, C-17), 144.11 (furyl C, C-11), 145.7 (pyrazole C, C-15), 148.83 (C=N, C-7), 164.00 (amide C=O, C-10), 175.66 (pyrazolone C=O, C-8). DEPT-135 (100MHz, DMSO-d_6): δ 15.94 (CH_2), 26.71 (CH_2), 42.07 (CH_2), 43.52 (CH_2), 46.61 (CH_2), 96.20, 112.14, 113.26, 130.94, 145.49 (aryl and furyl C-H); LCMS *m/z*: 357.2 $[M+H]^+$; C H N analysis; Calculated for $C_{17}H_{21}ClN_6O_3$, C, 51.98 %; H, 5.39 %; N, 21.39 %; Found: C, 51.91 %; H, 5.35 %; N, 21.32 %.

Preparation of 4-oxo-2,3,7-triaza-spiro[4.5]dec-1-ene-1,7-dicarboxylic acid 7-*tert*-butyl ester, 10

To a solution of compound **5a**(0.5g, 1.56mmol) in acetone (30 mL) was added $KMnO_4$ (1.2g in 25 mL water) and heated to 60^{o}C on an oil bath. The reaction was maintained at the same temperature for 2h. After checking the completion of reaction by TLC, the reaction mixture was cooled to ambient temperature, IPA (5mL) was added and stirring continued at the ambient temperature for 30min. The reaction mass was filtered through a bed of celite. The alkaline aqueous layer was extracted with ether (2x25mL). The aq.layer was acidified with dil.HCl to pH 2-3. The aq. layer was extracted with ethyl acetate(4*25mL).The organic layers were combined and dried over anhyd.Na_2SO_4 to afford the title compound as a white solid (161mg, 35% yield). The acidic aqueous layer left after extraction was saturated with sodium chloride and extracted with ethyl acetate and concentrated to afford the 2nd crop material (87mg, 19% yield). ^{1}H NMR (400MHz-DMSO-d_6, 80^{o}C): δ 1.5 (s, 9H, Boc-H's), 1.52-1.56 (m, 1H, pip. CH_2, H-4), 1.68 (d, 1H, *J* = 12.4 Hz, pip. CH_2, H-4'), 2.07-2.22 (m, 2H, pip. CH_2, H-5), 2.92 (t, 1H, *J* = 10.8 Hz, H-6), 3.51 (d, 1H, *J* = 13.6 Hz, pip. CH_2, H-6'), 3.74 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-2),3.91 (d, 1H, *J* = 13.2 Hz, pip. CH_2, H-2'), 11.72 (s, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.63, 17.77, 26.79, 27.89, 28.09, 42.58, 43.71, 45.11, 46.24, 47.63, 47.83 (piperidine C's and CH_3 of Boc), 151.12 (C=N), 153.33, 153.65 (Boc C=O), 161.21 (acid C=O), 177.82, 177.98 (pyrazolone C=O, C-8). DEPT-135 (100MHz, CD_3OD): δ 17.63 (CH_2), 26.79 (CH_2), 27.89, 28.09 (CH_3), 42.58 (CH_2), 43.72 (CH_2), 45.12 (CH_2), 46.25 (CH_2); LCMS *m/z*: 198.0 $[M-Boc+H]^+$.

General procedure for the synthesis of 1-furan-2-yl-4-oxo-2,3,7-triaza-spiro[4.5]dec-1-ene-7-carboxamides, 11a-c

To a solution of the acid **10**(1eqt) in DMF, was added the corresponding amine(1.05eqt) followed by DIPEA(3 eqt), the reaction mixture was cooled to 0-5^{o}C and HATU(1.2eqt)was added. The reaction mixture was stirred at the ambient temperature for 4-5h. After checking the completion of reaction by TLC, the reaction mixture was concentrated, water and ethyl acetate were added and layer separated. The aqueous layer was extracted with ethyl acetate twice. Organic layers were combined and concentrated to afford the crude material which was purified by column chromatography using hexane/ethyl acetate system to get the pure product which was reacted with HCl in 1,4-Dioxane to afford the title compound.

4-Oxo-2,3,7-triaza-spiro[4.5]dec-1-ene-1-carboxylic acid (3,4-dimethoxy-phenyl)-amide hydrochloride, 11a[19]: Yield: 134 mg (54%); IR (KBr) ν_{max}/cm^{-1}: 3378 (NH), 2998 (aromatic C-H), 1731 (C=O), 1660, 1519, 1231, 831; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.80-1.82 (m, 2H, pip.CH_2, H-4), 2.06-2.08 (m, 2H, pip.CH_2, H-5), 3.29-3.20 (m, 2H, H-6), 3.58-3.61 (m, 2H, H-2), 3.73 (s, 6H, 2xOCH_3), 6.93 (d, 1H, *J* = 8.8 Hz, H-15), 7.28 (dd, 1H, *J* = 8.8, 2 Hz, H-16), 7.44 (d, 1H, *J* = 2.8 Hz, H-12), 8.5-8.6 (brs, 1H, pip.NH, H-1), 10.5 (s,1H, amide-NH, H-10), 12.46 (s, 1H, pyrazolone NH); ^{13}C NMR (100 MHz, CD_3OD): δ 19.02 (pip. C, C-4), 29.49 (pip.C, C-5), 44.78 (pip.C, C-6), 45.87 (pip.C, C-2), 56.51 (OCH_3), 68.13 (spiro C, C-3), 107.34 (Ar-C, C-12), 113.17 (Ar-C, C-15),114.65 (Ar-C, C-16), 132.1 (Ar-C, C-11), 148.13 (C=N, C-7), 150.50 (Ar-C, C-13), 155.3 (Ar-C, C-14), 160.84 (amide C=O, C-9), 178.53 (pyrazolone C=O); DEPT-135 (100MHz, CD_3OD): δ 18.99 (CH_2), 29.45 (CH_2), 44.70 (CH_2), 45.79 (CH_2), 56.42 (OCH_3), 56.72 (OCH_3), 107.09, 112.92, 114.5 (aryl C-H) LCMS *m/z*: 333.2 (M+H); C H N analysis; Calculated for $C_{16}H_{21}ClN_4O_4$, C, 52.10 %; H, 5.74 %; N, 15.19 %; Found: C, 52.18 %; H, 5.79 %; N, 15.11 %.

4-Oxo-2,3,7-triaza-spiro[4.5]dec-1-ene-1-carboxylic acid (furan-2-ylmethyl)-amide hydrochloride, 11b: Yield: 32 mg (15 %); IR (KBr) ν_{max}/cm^{-1}: 3345 (NH), 2929 (aromatic C-H), 2795, 1725 (C=O), 1659 (C=O), 1534, 1206, 1103, 1009, 745; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.7-1.82 (m, 2H, pip. CH_2, H-4), 1.9-2.2 (m, 2H, pip. CH_2, H-5), 3.14-3.23 (m, 3H, pip. CH_2, H-6, H-2), 3.53 (d, 1H, pip. CH_2, H-2'), 4.33-4.4 (m, 2H, CH_2, H-11), 6.27 (d, 1H, *J* = 2.8 Hz, furyl-H,

H-13), 6.4 (m, 1H, furyl-H, H-14), 7.58 (s, 1H, furyl-H, H-15), 8.68 (br, 1H, HCl), 8.92 (br, 1H, pip. NH), 9.34 (t, 1H, *J* = 6.0 Hz, amide NH, H-10), 12.3 (s, 1H, -CONH pyrazolone); ^{13}C NMR (75 MHz, CD_3OD): δ 19.12 (pip.C, C-4), 29.67 (pip.C, C-5), 37.05 (CH_2, C-11), 44.79 (pip.C,C-6), 45.91 (pip.C, C-2), 108.53 (furyl-C, C-13) 111.41 (furyl-C, C-14), 143.44 (furyl-C, C-15), 152.41 (furyl-C, C-12), 155.01 (C=N, C-7), 163.0 (amide C=O), 178.24 (pyrazolone C=O) ; DEPT-135 (400MHz, CD_3OD): δ 19.12 (CH_2), 29.66 (CH_2), 36.94 (CH_2),44.68 (CH_2), 45.77 (CH_2), 108.53, 114.41, 143.44, (furyl C-H); LCMS *m/z*: 277[M+H]$^+$; C H N analysis; Calculated for $C_{13}H_{17}ClN_4O_3$, C, 49.93%; H, 5.48%; N, 17.91%; Found: C, 49.99%; H, 5.72%; N, 17.98%.

4-Oxo-2,3,7-triaza-spiro[4.5]dec-1-ene-1-carbo xylic acid (3,5-dimethoxy-phenyl)-amide hydro chloride, 11c: Yield: 112 mg (45%); IR (KBr) ν_{max}/cm^{-}1: 3391 (NH), 2928, 2850, 1791, 1676, 1550, 1205, 900; ^{1}H NMR (400 MHz-DMSO-d_6): δ 1.8 (d, 2H, pip.CH_2, *J* = 10 Hz, H-4), 2.1 (m, 2H, pip.CH_2, H-5), 3.17 (m, 2H, pip. CH_2, H-2), 3.6 (d, 2H, pip. CH_2, *J* = 13.6 Hz, H-6), 3.72 (s, 6H, 2-OCH_3), 6.31 (s, 1H, Ar-H, H-14), 7.07 (s, 2H, Ar-H, H-12, H-16), 8.4 (br, 1H, pip. NH), 8.79 (br, 1H, HCl), 10.5 (s, 1H, amide NH, C-9), 12.5 (s, 1H, pyrazolone NH); ^{13}C NMR (75 MHz, CD_3OD): δ 18.94 (pip.C, C-4), 29.42 (pip.C, C-5), 44.87 (pip.C, C-6), 45.96 (pip.C, C-2), 55.95 (OCH_3), 98.57 (Ar-C, C-14), 100.69 (Ar-C, C-12, C-16), 140 (Ar-C, C-11) 155.14 (C=N, C-7), 161.09 (Ar-C, C-13, C-15), 162.64 (amide C=O, C-9), 178.63 (pyrazolone C=O); DEPT-135 (100MHz, CD_3OD): δ 18.69 (CH_2), 29.14 (CH_2), 44.49 (CH_2), 45.55 (CH_2), 55.58 (OCH_3), 97.88, 100.02, (aryl C-H) LCMS *m/z*: 333.1[M+H]$^+$; C H N analysis; Calculated for $C_{16}H_{21}ClN_4O_4$, C, 52.11%; H, 5.74%; N, 15.19%; Found: C, 52.19%; H, 5.78%; N, 15.11%.

Biological assays

The bacterial strains were collected from patients with different infectious status who had not been administered any antibacterial drugs for at least two weeks with the suggestions of an authorized physician and authenticated by a microbiologist at Kiran Diagnostic Health Center, Chitradurga, Karnataka (India).

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus,Escherichia coli, Pseudomonas aeroginosa* and*Klebsiellapneumoniae* strains by disc diffusion method. The discs measuring 6.25 mm in diameter were punched from Whatman No. 1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140°C for an hour. The test compounds were preparedwith different concentrations using DMSO. One milliliter containing 100 times the amount of chemical required in each disc was added to each bottle which contained 100 discs.The discs of each concentration were placed in triplicate innutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37.8°C for 24 h. Theminimum inhibitory concentration (MIC) was noted. For comparison, nitrofurazone was used as a drug standard. Solvent and growth controls were kept. Antibacterial activity was determined by measuring the diameter of the inhibition zone. Zone of inhibition (inhibition halos) was calculated as average of three repeated experimental data. Compounds which inhibited bacteria growth (more than3 mm zone of inhibition) were considered as active. MICwas determined for compounds which showed positive activity. The minimum inhibitory concentration (MIC) for the nitrofurazone in 1% DMSO was more than 1.0 mg mL against the tested species. One percent DMSO was used as solvent control; the data is illustrated in Table IV.

$$\% \text{ of inhibitioon} = \frac{\text{I (Diameter of the inhibition zone in mm)}}{\text{90 (Diameter of the petri-plates in mm)}} \times 100$$

DPPH radical scavenging assay

Briefly, 1 mM solution of DPPH in ethanol was prepared and the solution (1 mL) was added to sample solutions 50 μg/mL in DMSO. The mixture was shaken vigorously and allowed to stand at room temperature for 20 min. Then the absorbance was measured at 517 nm in a spectrophotometer. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH scavenging effect (\%)} = (A_0 - A_1 / A_0) \times 100$$

Where, A_0 is the absorbance of the control reaction and A_1 is the absorbance in the presence of samples or standards. Each sample was assayed at 50 μg/mL and all experiments were carried out in triplicate.

Conclusions

In summary we have synthesized a series of potent spiropiperidinyl pyrazolones incorporating the furan

and thiophene ring systems. Compounds **7a-d** and compounds **7 g-s** showed potent antibacterial activities. The presence of heteroaryl group and the presence of benzyl substituents attached to the pyrazolone NH are crucial for the antibacterial activity. Compounds 7a, 7b, 9a, 9b, 11a and 11c showed very good antioxidant activity. Compounds **7a** and **7b** have 3-thiophene group attached to the pyrazolone ring and substituted by monofluoro and difluoro benzyl groups on the pyrazolone NH. Compounds **9a**, **9b**, **11a** and **11c** have two electron donating OCH_3 groups which enhanced the antioxidant activity.

Acknowledgements

Authors thank Aurigene Discovery Technologies and Mangalore University for research facilities and for procurement of chemicals required for the research work.

References

1 Zheng Y, Tice, C M & Singh S B, *Bioorg Med Chem Lett*, 24 (2014) 3673.
2 Pradhan R, Patra M, Behera A K, Mishra B K & Behera R K, *Tetrahedron*, 62 (2006) 779.
3 Sannigrahi M, *Tetrahedron*, 55 (1999) 9007.
4 Chambers M S, Baker R, Billington D C, Knight A K, Middlemiss D N & Wong E H F, *J Med Chem*, 35 (1992) 2033.
5 Wang J, Cady S D, Balannik V, Pinto L H, DeGrado W F & Hong M, *J Am Chem Soc*, 131 (2009) 8066.
6 Arumugam N, Periyasami G, Raghunathan R, Kamalraj S & Muthumary J, *Eur J Med Chem*, 46 (2011) 600.
7 Periyasami G, Raghunathan R, Surendiran G & Mathivanan N, *Bioorg Med Chem Lett*, 18 (2008) 2342.
8 Bhaskar G, Arun Y, Balachandran C, Saikumar C & Perumal P T, *Eur J Med Chem*, 51 (2012) 79.
9 Singh G S & Luntha P, *Eur J Med Chem*, 44 (2009) 2265.
10 Braña M F, Gradillas A, Ovalles A G, López B, Acero N, Llinares F & Mingarro D M, *Bioorg Med Chem*, 14 (2006) 9.
11 Uramaru N, Shigematsu H, Toda A, Eyanagi R, Kitamura S & Ohta, S, *J Med Chem*, 53 (2010) 8727.
12 Ragavan R V, Kumar K M, Vijayakumar V, Sarveswari S, Ramaiah S, Anbarasu A, Karthikeyan S, Giridharan P & Kumari N S, *Org Med Chem Lett*, 3 (2013) 6.
13 Chen T, Benmohamed R, Arvanites A C, Ranaivo H R, Morimoto R I, Ferrante R J, Watterson D M, Kirsch D R & Silverman R B, *Bioorg Med Chem*, 19 (2011) 613.
14 Valko M, Rhodes C J, Moncol J, Izakovic M & Mazur M, *Chemico-Biol Int*, 160 (2006) 1.
15 Dröge W, *Physiol Rev*, 82 (2002) 47.
16 Jachowicz J, Locke B C & Chaudhuri R K, *US Patent* 99/6008359 (1999).
17 Karali N, Güzel O, Özsoy N, Özbey S & Salman A, *Eur J Med Chem*, 45 (2010) 1068.
18 Srinivasan R, Narayana B, Samshuddin S & Sarojini B K, *Molbank*, M757 (2012).
19 Srinivasan R, Narayana B, Samshuddin S & Sarojini B K, *Molbank*, M769 (2012).
20 Srinivasan R, Narayana B, Samshuddin S & Sarojini B K, *Molbank*, M771 (2012).
21 Srinivasan R, Narayana B, Samshuddin S & Sarojini B K, *Molbank*, M773 (2012).
22 Rustum A M, *J Chromatography*, 696 (1995) 75.
23 Quandt, G, Höfner G & Wanner K T, *Bioorg Med Chem*, 21 (2013) 3363.
24 Lou J-D & Xu Z-N, Tet*rahedron Lett*, 43 (2002) 6149.
25 Matsuo J-I, Lida D, Yamanaka H & Mukaiyama T, *Tetrahedron*, 59 (2003) 6739.
26 Hinterding K & Jacobsen E N, *J Org Chem*, 64 (1999) 2164.
27 Huerta F F & Bäckvall J-E, *Org Lett*, 3 (2001) 1209.
28 Liao M & Wang J, *Tet Lett*, 47 (2006) 8859.
29 Burness D M, *J Org Chem*, 21 (1956) 97.
30 Betschart C, Hintermann S, Behnke D, Cotesta S, Fendt M, Gee C E, Jacobson L H, Laue G, Ofner S, Chaudhari V, Badiger S, Pandit C, Wagner J & Hoyer D, *J Med Chem*, 56 (2013) 7590.
31 Golden J E, Sanders S D, Muller K M & Bürli R W, *Tetrahedron Lett*, 49 (2008) 794.
32 Michael B, Heather B, Deborah C, Ian E, Janet F, Jennifer F, Methvin I, Fubeng M A, David N, Abdelmalik S, Gary S M, Guangri S, Babu S, Radhakrishnan U, Rebecca U & Sally, W, *PCT Int Appl* WO 2006/071730 A1 (2006).
33 Dayal B, Salen G, Toome B, Tint G S, Shefer S & Padia J, *Steroids*, 5 (1990) 233.
34 Pruitt J R, Pinto D J P, Galemmo R A ~~Jr~~, Alexander R S, Rossi K A, Wells B L, Drummond S, Bostrom L L, Burdick D, Bruckner R, Chen H, Smallwood A, Wong P C, Wright M R, Bai S, Luettgen J M, Knabb R M, Lam P Y S & Wexler R R, *J Med Chem*, 46 (2003) 5298.
35 Carpino L A, *J Am Chem Soc*, 115 (1993) 4397.
36 Carpino L A, El-Faham A & Albericio F, *Tetrahedron Lett*, 35 (1994) 2279.
37 Pavia D L, Lampman G M & Kriz G S, in *Introduction to Spectroscopy*, 3rd Edn (Thompson Brooks/Cole, South Melbourne, Australia) pp.435 (2001).
38 Silverstein R M, Webster F X & Kiemle D J, in *Spectrometric Identification of Organic Compounds*, 7th edn (John-Wiley and Sons) p.32 (2005).
39 Sarojini B K, Krishna B G, Darshanraj C G, Bharath B R & Manjunatha H, *Eur J Med Chem*, 45 (2010) 3490.