European Journal of Medicinal Chemistry 45 (2010) 411–422

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Preliminary communication

Novel three-component domino reactions of ketones, isatin and amino acids: Synthesis and discovery of antimycobacterial activity of highly functionalised novel dispiropyrrolidines

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ARTICLE INFO

Article history:
Received 26 August 2009
Received in revised form
22 September 2009
Accepted 28 September 2009
Available online 2 October 2009

Keywords:
Cascade reactions
Isatin
Sarcosine
Phenylglycine
Spiropyrrolidines
Anti-tubercular activity

ABSTRACT

One-pot three-component domino reactions of cyclic mono ketones, isatin and sarcosine/phenylglycine furnishing highly functionalised dispiropyrrolidines in moderate yields are described. The reaction when performed with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. These compounds have been screened for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) using agar dilution method. Among thirty eight compounds screened, 1-methyl-pyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]-1″-nitrosotetrahydro-4″(1*H*)-pyridinone (**4t**) was found to be the most active with MIC of 1.98 μM against MTB and was 3.86 and 25.64 times more potent than the standard first line TB drugs, ethambutol and pyrazinamide respectively.

1. Introduction

Domino multi-component reactions offer a rapid access to highly functionalised complex molecules in a single procedural step [1,2]. The development of new methods for the synthesis of *N*-heterocycles with structural diversity is one of the major interests of modern synthetic organic chemists [3]. Indole fragment prevails in a variety of pharmacologically and biologically active compounds [4]. Oxindole derivatives are known to possess a variety of biological activities [5] such as (i) potent inhibition of monoamine oxidase (MAO) in human urine and rat tissues [6], (ii) inhibition of several enzymes such as acetylcholinestrease (AChE) [7] and atrial natriuretic peptide-stimulated guanylate cyclase and (iii) potent antagonist of *in vitro* receptor binding by atrial natriuretic peptide [8], besides possessing a wide range of central nervous system activities [9]. Schiff bases and Mannich bases of isatin were reported to possess antibacterial [10], antifungal [11], antiviral [12], anti-HIV [13], antiprotozoal [14], and antihelminthic [15] activities.

The derivatives of spirooxindole ring systems are useful as antimicrobial, antitumour agents and as inhibitors of the human NKI receptor, besides being found in a number of alkaloids like horsifiline, spirotryprostatin and (+)-elacomine [16]. Highly functionalised pyrrolidines constitute the main structural element of many alkaloids and pharmacologically active compounds [17].

Tuberculosis is an infection caused by *Mycobacterium tuberculosis* and is the leading cause of infectious disease mortality in the world [18]. Around 1.86 billion people, that is, 32% of the world's population is infected [19] with *M. tuberculosis* (MTB). World health organization estimates about 8 million new active cases of tuberculosis (TB) per year and nearly 2 million deaths each year [19,20], that is, 5000 people every day [21]. HIV positive patients are more susceptible to MTB with a 50-fold risk increase over HIV negative patients [22,23]. Similarly, the rate of progression of latent TB to active disease in HIV positive patients is higher than non-HIV infected individuals. It is pertinent to note that no new drug against tuberculosis has been developed in the last 30 years. Increasing incidence of MTB strains resistant to one or more first line TB drugs such as isoniazid [24], pyrazinamide [25] and rifampicin [26] has recently intensified the need to develop new and more efficient drugs for the treatment of mycobacterial

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doi:10.1016/j.ejmech.2009.09.044

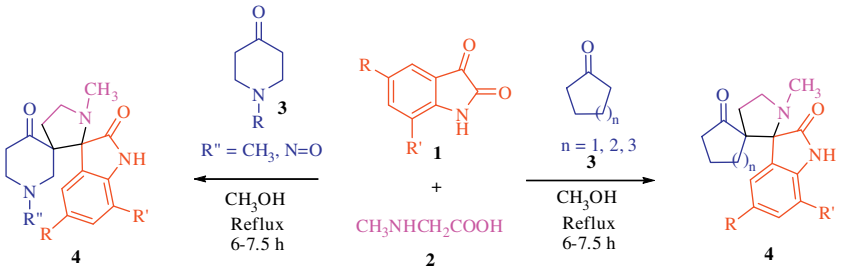
infections and this is the subject of numerous recent studies [27,28].

Recently, [29] we have communicated our preliminary results on the synthesis of dispiropyrrolidines from the novel domino reactions of isatin, sarcosine and cyclic mono ketones. This manuscript presents the results of detailed investigations on the synthetic potential of the domino protocol in the construction of (i) more dispiroheterocycles of the previously reported series [29] and (ii) novel spiroheterocycles from the reactions of isatin and cyclic mono ketones with phenylglycine. The reaction with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. The synthesized compounds were subjected to preliminary antitubercular screening against *M. tuberculosis* H37Rv (MTB) and these results are also presented in this paper.

2. Chemistry

Our previous study [29] reported the synthesis of dispiropyrrolidines **4** in moderate yields from the domino reactions of cyclic mono ketones, isatin and sarcosine in a molar ratio of 1:1:2. In the present work, this reaction has been investigated further with four more substituted isatins (Scheme 1) and amino acids, phenylglycine, proline, thiaproline and pipecolic acid. The three-component reaction of cyclic mono ketones, isatin and phenylglycine **5** in a 1:1:2 molar ratio in methanol:water (2:1) at reflux for 24 h (Scheme 2) also furnished novel dispiropyrrolidines **6** in moderate yields (32–45%) as in the case of reaction with sarcosine. After completion of the reaction (TLC), the dispiropyrrolidines **6** in pure form was obtained by column chromatographic purification.

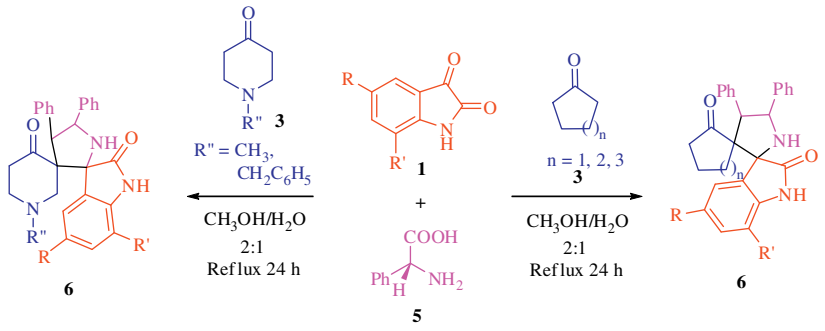
The structure of dispiropyrrolidines **4** and **6** are in accord with their 1D and 2D NMR spectroscopic data (Figs. 1 and 2). The ^{1}H NMR spectrum of **6e** has two doublets at 4.59 and 5.37 ppm ($J = 11.3$ Hz) related by a H,H-COSY correlation assignable to H-4 and H-5 respectively. This is also supported by the HMBC correlation (Fig. 2) of the signal at 4.59 ppm with the carbonyl carbon at 207.2 ppm, besides correlating with (i) C-5 at 62.9 ppm, (ii) spiro carbon C-3 at 68.5 ppm and (iii) C-2′ at 58.9 ppm. H-4 and H-5 are *trans* to each other. The C,H-COSY correlation of H-4 assigns the



4 **3** **1** + **2** **3** **4**

Comp 3 and 4	n	R	R′	R″	Reaction time (h)	Yield of 4 (%)
a	1	H	$CH(CH_3)_2$	-	7	40
b	2	H	$CH(CH_3)_2$	-	6.5	45
c	3	H	$CH(CH_3)_2$	-	7	39
d	-	H	$CH(CH_3)_2$	CH_3	6	43
e	-	H	$CH(CH_3)_2$	N=O	10	38
f	1	CH_3	H	-	7	42
g	2	CH_3	H	-	6	40
h	3	CH_3	H	-	7.5	38
i	-	CH_3	H	CH_3	6	44
j	-	CH_3	H	N=O	10	40
k	1	Cl	H	-	7	39
l	2	Cl	H	-	7	42
m	3	Cl	H	-	6.5	38
n	-	Cl	H	CH_3	6	52
o	-	Cl	H	NO	10	40
p	1	Br	H	-	7.5	41
q	2	Br	H	-	6.5	43
r	3	Br	H	-	7	37
s	-	Br	H	CH_3	6	49
t	-	Br	H	NO	10	38

Scheme 1. Synthesis of dispiropyrrolidines.



Comp 3 and 6	n	R	R′	R″	Yield of 6 (%)
a	1	H	H	-	35
b	2	H	H	-	38
c	3	H	H	-	32
d	-	H	H	CH_3	36
e	-	H	H	$CH_2C_6H_5$	41
f	1	H	$CH(CH_3)_2$	-	39
g	2	H	$CH(CH_3)_2$	-	37
h	-	H	$CH(CH_3)_2$	CH_3	40
i	-	H	$CH(CH_3)_2$	$CH_2C_6H_5$	42
j	2	CH_3	H	-	36
k	-	CH_3	H	CH_3	41
l	-	CH_3	H	$CH_2C_6H_5$	40
m	2	Cl	H	-	38
n	-	Cl	H	CH_3	40
o	-	Cl	H	$CH_2C_6H_5$	41
p	2	Br	H	-	36
q	-	Br	H	CH_3	39
r	-	Br	H	$CH_2C_6H_5$	40

Scheme 2. Synthesis of dispiropyrrolidines **6**.

signal at 54.8 ppm to C-4. The other spiro carbon at 69.8 ppm is assigned to C-2 as it shows HMBC correlations with (i) the lactum NH proton at 8.70 ppm, (ii) the aromatic proton of the oxindole ring and (iii) one of the 2′-CH_2 protons appearing as a multiplet at 1.66–1.80 ppm. The other 2′-CH_2 proton appears as a doublet of doublets at 3.93 ppm ($J = 12.3$ and 2.4 Hz). The carbon signal at 50.1 ppm is assigned to C-6′ as it shows HMBC correlations with the 2′-CH_2 protons and the N–CH_2 protons giving doublets at 3.01 and 3.79 ppm ($J = 13.2$ Hz). The C,H-COSY correlation of C-6′ assigns the multiplets at 1.66–1.80 and 2.51–2.56 ppm to 6′-CH_2. The multiplets centering at 1.44 and 1.99 ppm are due to 5′-CH_2. The aromatic protons appear in the region of 6.88–7.50 ppm, the NH proton of the pyrrolidine ring appears as a singlet at 2.32 ppm and the oxindole carbonyl appears at 181.9 ppm. The structure of other spiropyrrolidines was also assigned similarly. X-ray crystallographic study of a single crystal of **6e** (Fig. 3) [30] confirms the structure deduced from NMR spectroscopic studies.

Presumably, the regio- and stereoselective formation of the dispiropyrrolidines **6** occurs via domino reactions (Scheme 3) as postulated for the reaction of sarcosine [29]. Isatin and phenylglycine afford the iminium carboxylic acid **7** which undergoes (i) decarboxylation to provide the azomethine ylide **13** and (ii) nucleophilic substitution to afford phenylglycolic acid **9**. The latter **9** reacts with isatin to afford benzaldehyde, which reacts with azomethine ylide **13** to afford the iminium alcohol **14**. Then, **14** reacts with enol **3** to furnish **15**, which cyclises to afford the dispiropyrrolidines **6**.

It is found that when this domino protocol was applied to the reaction of ketone, isatin and cyclic amino acid, (*L*)-proline **17** (Scheme 4) instead of phenylglycine/sarcosine, no spiroheterocycle could be obtained, instead a dimer **18** of azomethine ylide (Scheme 5) was isolated in 32–38% yield, besides a non characterisable polar mixture. The reaction of isatin (1 mmol) and (*L*)-proline (1 mmol) in methanol also afforded the dimer **18** only. In case of entries 5–7 involving thiaproline or pipecolic acid (Scheme 4), no reaction occurred. Presumably, the absence of formation of the spiroheterocycles from cyclic amino acids may be ascribed to their instability arising from enhanced steric interactions. Probably, the puckered six membered ring of the pipecolic acid could increase the steric interactions in the dimer rendering its formation difficult.

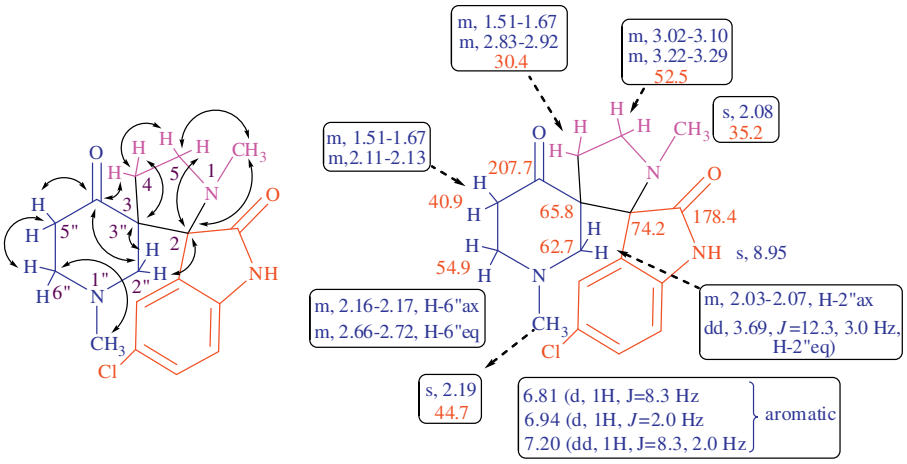


Fig. 1. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **4n**.

In the case of thiaproline, the sulfur of the azomethine ylide could conjugate with the anionic centre of the dipole, which could diminish its reactivity towards further reactions.

Structural elucidation of the dimer **18** was accomplished using 1D and 2D NMR spectroscopic data. The ^{1}H NMR spectrum of **18b**, a representative example, shows a singlet at 2.24 ppm due to the CH_3 linked to the aromatic ring, which shows HMBC correlations (Fig. 4) with C-4′ at 127.0 ppm and C-6′ at 129.3 ppm. The C,H-COSY correlation assigns the doublet at 6.86 ppm ($J = 7.8$ Hz) to H-6′ and the singlet at 7.30 ppm to H-4′. The doublet at 6.39 ppm ($J = 7.8$ Hz) is assigned to H-7′ from its H,H-COSY correlation with H-6′. Further, H-6′ shows HMBC correlation with C-7′a at 138.1 ppm. From the HMBC correlation of H-4′, the signal at 68.6 ppm is assigned to the spiro carbon C-5. A triplet of doublets at 2.62 ppm ($J = 8.7$ and 2.7 Hz) and a multiplet at 2.12–2.20 ppm are assigned to 3-CH_2 protons. From the C,H-COSY correlation, the signal at 47.6 ppm is assigned to C-3. The 1-CH_2 and 2-CH_2 protons appear as multiplets centering at 1.60 and 1.79 ppm. The multiplet at 3.61 ppm is due to H-10a and the C,H-COSY assigns C-10a to 59.1 ppm. The NH proton of the indolinone ring occurs as a singlet at 7.40 ppm and the carbonyl appears at 176.0 ppm. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **18b** are shown in Fig. 4.

This domino protocol is more advantageous for the synthesis of spiropyrrolidines which would otherwise require (i) conversion of the cyclic mono ketones to α-methylene/arylideneketones and (ii) the dipolar cycloaddition of the α-methylene/arylidene ketones with azomethine ylides.

3. Biological results and discussion

The compounds were screened for their *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv by agar dilution method for the determination of MIC in triplicates. The MIC is defined as the minimum concentration of compound required to inhibit 99% of bacterial growth, and the MIC values of the synthesized compounds along with the standard drugs for comparison are presented in Table 1. All the thirty eight compounds screened in the present study against MTB had MICs ranging from 1.98–160.05 μM and ten compounds inhibited MTB with MIC less than 10 μM. In the first series (**4a–t**), all the compounds showed moderate to good activity, except **4a** and **4c**, with MICs 1.98–41.89 μM and were more potent than the first-line anti-TB drug pyrazinamide (MIC of 50.77 μM). Seven compounds (**4e**, **4j**, **4o–r**, and **4t**) showed good activity with MICs less than 10 μM. Five compounds (**4j**, **4o**, **4q**, **4r** and **4t**) with MICs ranging from 1.98–4.75 μM are more potent than the standard drug ethambutol with MIC of 7.64 μM and the compound 1-methylpyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]-1″-nitrosotetrahydro-4″(1*H*)-pyridinone (**4t**) was found to be most active with MIC of 1.98 μM. In the second series, **6a–b**, **6f–r** inhibited MTB with MICs ranging from 6.24–118.34 μM and twelve compounds are more potent than pyrazinamide. Compounds **6p** and **6q** showed good activity with MIC of 6.24 and 6.06 μM respectively, being more potent than ethambutol. Among dimers **18a–d**, the MIC ranged from 5.61–124.85 μM and compound **18d** was found to be the most active with MIC of 5.61 μM showing more activity than ethambutol and pyrazinamide.

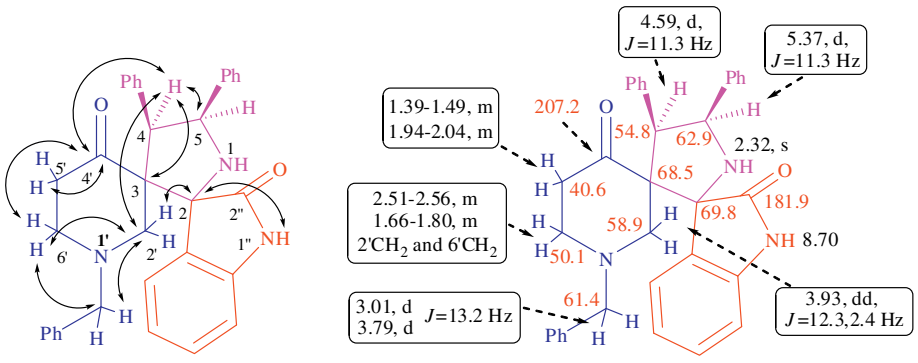


Fig. 2. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **6e**.

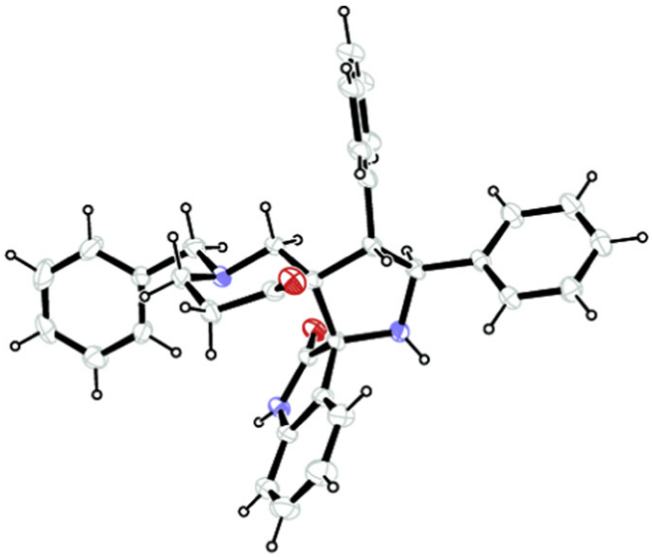


Fig. 3. ORTEP diagram of **6e**.

With respect to the structure-MTB activity, introduction of substituent in the 5-position of isatin enhances the activity particularly, bromo substitution showed enhanced activity. In general, the *N*-nitroso compounds **4e**, **4j**, **4o** and **4t** showed better activity than the N-Me compounds belonging to **4**. Among thirty eight compounds, 1-methylpyrrolo-(spiro[2.3′]-5-bromooxindole) spiro[3.2″]-1″nitrosotetrahydro-4″(1*H*)-pyridinone **4t** is found to possess the maximum activity with MIC of 1.98 μM against MTB displaying higher activity than the standard drugs, ethambutol and pyrazinamide.

4. Conclusions

The present investigation describes a facile access to highly functionalised dispiropyrrolidines via one-pot three-component domino reactions of cyclic mono ketones, isatin and sarcosine/phenylglycine. The reaction with cyclic amino acid, proline resulted in the dimerization of azomethine ylides. Many of the compounds synthesized in the present work show good to excellent activity and those with *N*-nitroso functionality are found to be more promising against *M. tuberculosis*.

5. Experimental

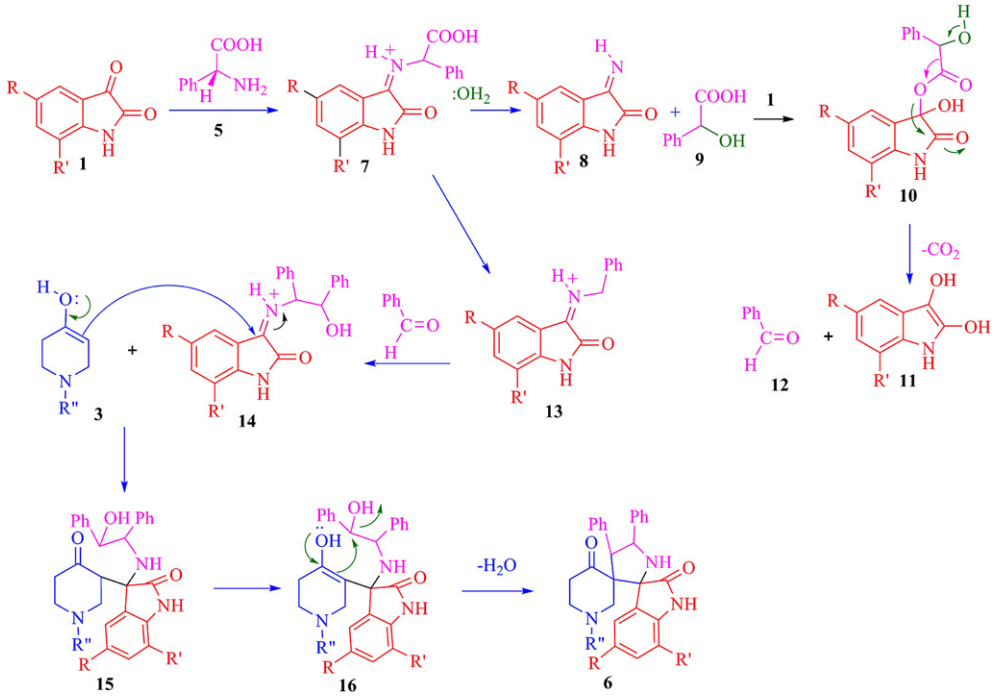
Melting points were taken using open capillary tubes and are uncorrected. ^{1}H, ^{13}C and two-dimensional NMR spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in case of solids and $CHCl_3$ in case of liquids). Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyser. Column chromatography was performed on silica gel (230–400 mesh) using petroleum ether–ethyl acetate as eluent.

5.1. Synthesis of spiropyrrolidines *4*

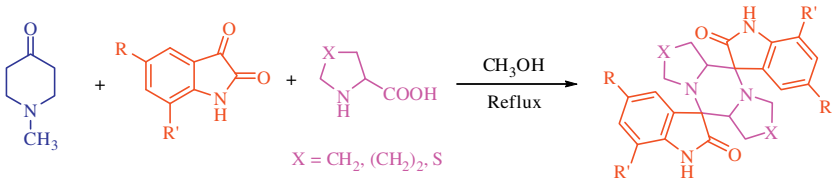
5.1.1. General procedure

A mixture of isatin (0.350 g, 2.38 mmol), sarcosine (0.424 g, 4.76 mmol) and ketone (0.200 g, 2.38 mmol) in methanol (20 mL) was refluxed on a water bath for 6–7.5 h. After completion of the reaction (TLC), the excess solvent was removed under vacuum and the residue was subjected to flash column chromatography using petroleum ether:ethyl acetate mixture (4:1 v/v) as eluent.

*5.1.1.1. 1-Methylpyrrolo(spiro[2.3′]-8-isopropyloxindole)spiro[3.2″] cyclopentanone (**4a**).* Pale yellow solid; (0.295 g, 40%); mp 181–182 °C; Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97; Found: C, 73.09; H, 7.81; N, 8.92. IR (KBr): 1692, 1725, 3296 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.22–1.38 (m, 6H, CH($\underline{CH_3}$)$_2$), 1.55–1.69 (m, 1H, H-4), 1.82–2.08 (m, 4H, cyclopentanone ring protons), 2.16 (s, 3H, CH_3), 2.21–2.36 (m, 3H, H-4 and cyclopentanone ring



Scheme 3. Mechanism for the formation of dispiropyrrolidines.



3 1 17 18

Entry	Comp 1 and 18	R	R′	X	Yield of 18 (%)
1	a	H	H	CH_2	36
2	b	CH_3	H	CH_2	38
3	c	Cl	H	CH_2	36
4	d	Br	H	CH_2	32
5	e	H	$CH(CH_3)_2$	CH_2	-[a]
6	f	H	H	$(CH_2)_2$	-[a]
7	g	H	H	S	-[a]

[a]Product not obtained

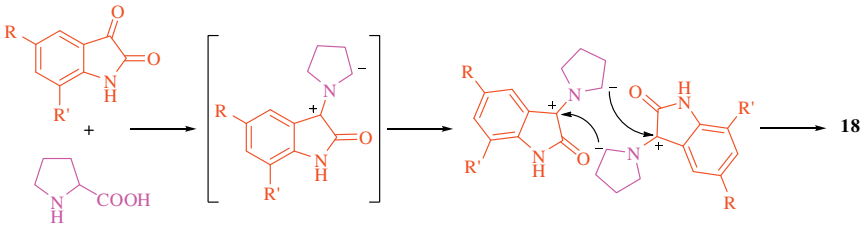
Scheme 4. Synthesis of azomethine ylide dimers.

protons), 2.98–3.07 (m, 1H, CH), 3.30–3.38 (m, 1H, H-5), 3.44–3.51 (m, 1H, H-5), 6.95–7.03 (m, 2H, aromatic), 7.16–7.19 (m, 1H, aromatic), 9.69 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.1, 22.4, 22.7, 28.4, 31.6, 33.7, 35.7, 39.0, 51.5, 60.3, 77.2, 123.0, 123.4, 125.4, 126.1, 129.9, 139.5, 179.9.

*5.1.1.2. 1-Methylpyrrolo(spiro[2.3′]-8-isopropyloxindole)spiro[3.2″] cyclohexanone (**4b**).* White solid; (0.300 g, 45%); mp 147–148 °C; Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58; Found: C, 73.65; H, 8.10; N, 8.54. IR (KBr): 1689, 1721, 3287 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.29 (d, 3H, J = 4.5 Hz, $(\underline{CH_3})_2$), 1.31 (d, 3H, J = 4.5 Hz, $(\underline{CH_3})_2$), 1.42–2.01 (m, 7H, H-4 and cyclohexanone ring protons), 2.09 (s, 3H, CH_3), 2.17–2.18 (m, 1H, cyclohexanone ring proton), 2.41–2.52 (m, 1H, cyclohexanone ring proton), 2.63–2.71 (m, 1H, H-4), 2.99–3.01 (m, 1H, CH), 3.21–3.34 (m, 2H, H-5), 6.87 (d, 1H, J = 7.2 Hz, aromatic), 6.96–7.01 (m, 1H, aromatic), 7.17 (d, 1H, J = 7.5 Hz, aromatic), 9.55 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.3, 22.2, 22.9, 25.2, 28.4, 33.9, 35.5, 35.6, 41.2, 51.8, 62.4, 77.1, 122.7, 124.0, 125.9, 126.8, 130.2, 139.1, 180.0, 212.5.

*5.1.1.3. 1-Methylpyrrolo(spiro[2.3′]-8-isopropyloxindole)spiro[3.2″] cycloheptanone (**4c**).* Pale yellow solid; (0.235 g, 39%); mp 185–186 °C; Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23; Found: C, 74.13; H, 8.35; N, 8.17. IR (KBr): 1623, 1720, 3215 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98–1.17 (m, 2H, cycloheptanone ring protons), δ_H 1.29 (d, 3H, J = 6.9 Hz, $(\underline{CH_3})_2$), 1.33 (d, 3H, J = 6.9 Hz, $(\underline{CH_3})_2$), 1.50–2.06 (m, 7H, H-4 and cycloheptanone ring protons), 2.11 (s, 1H, CH_3), 2.13–2.19 (m, 2H, cycloheptanone ring protons), 2.57–2.66 (m, 1H, H-4), 2.97–3.06 (m, 1H, CH), 3.26–3.34 (m, 1H, H-5), 3.42–3.49 (m, 1H, H-5), 6.81 (d, 1H, J = 7.5 Hz, aromatic), 6.94–6.99 (m, 1H, aromatic), 7.18 (d, 1H, J = 7.8 Hz, aromatic), 9.43 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 22.7, 25.2, 27.5, 28.4, 29.8, 32.2, 32.8, 35.6, 43.8, 52.1, 64.1, 78.7, 122.5, 123.4, 124.8, 126.0, 130.1, 139.4, 180.0, 216.0.

*5.1.1.4. 1-Methylpyrrolo(spiro[2.3′]-8-isopropyloxindole)spiro[3.2″]-1′-methylpiperidin-4-one (**4d**).* Yellow solid; (0.260 g, 43%); mp 128–129 °C; Anal. Calcd. for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31; Found: C, 70.41; H, 7.94; N, 12.37. IR (KBr): 1706, 1733, 3210 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.27–1.32 (m, 6H, $CH(\underline{CH_3})_2$), 1.51–1.62 (m, 2H, H-4 and H-5″), 1.97–2.01 (m, 1H, H-5″), 2.05 (d, 1H, J = 12.3 Hz, H-2″ax), 2.09 (s, 3H, 1-N–CH_3), 2.12-2.18 (m, 1H, H-6″ax), 2.19 (s, 3H, 1″-N–CH_3), 2.60–2.66 (m, 1H, H-6″eq), 2.84–2.93 (m, 1H, H-4), 3.01–3.14 (m, 2H, CH and H-5), 3.25–3.32 (m, 1H, H-5), 3.70 (dd, 1H, 12.3, 2.4 Hz, H-2″eq), 6.28 (d, 1H, J = 7.2 Hz, aromatic), 6.90–6.95 (m, 1H, aromatic), 7.14 (d, 1H, J = 7.5 Hz, aromatic), 9.33



Scheme 5. Formation of dimer **18**.

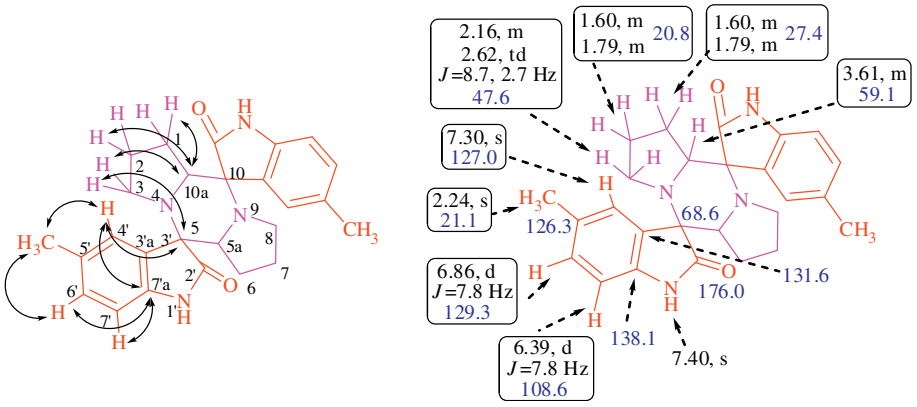


Fig. 4. Selected HMBC correlations and ^{1}H and ^{13}C chemical shifts of **18b**.

(s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.1, 22.8, 28.4, 30.3, 35.2, 40.6, 44.8, 52.2, 55.0, 62.9, 65.1, 74.6, 122.1, 123.9, 125.3, 127.2, 129.6, 139.1, 179.0, 208.4.

*5.1.1.5. 1-Methylpyrrolo(spiro[2.3′]-8-isopropyloxindole)spiro[3.2″]-1′-nitrosopiperidin-4-one (**4e**).* White solid; (0.210 g, 38%); mp 112–113 °C; Anal. Calcd. for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72; Found: C, 64.10; H, 6.84; N, 15.66. IR (KBr): 1618, 1709, 3294 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.22 (d, 3H, $J = 6.9$ Hz, $(CH_3)_2$), 1.28 (d, 3H, $J = 7.2$ Hz, $(CH_3)_2$), 2.13 (s, 1H, CH_3), 2.16–2.23 (m, 2H, H-4 and H-6″), 2.43–2.54 (m, 2H, H-4 and H-5″), 2.58–2.71 (m, 1H, H-5″), 2.79–2.88 (m, 1H, CH), 3.38–3.50 (m, 3H, H-5 and H-6″), 4.24 (d, 1H, $J = 14.7$ Hz, H-2″), 5.21 (d, 1H, $J = 14.7$ Hz, H-2″), 6.80 (d, 1H, $J = 7.5$ Hz, aromatic), 6.94–6.99 (m, 1H, aromatic), 7.16 (d, 1H, $J = 7.2$ Hz, aromatic), 9.12 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.6, 22.7, 28.3, 30.2, 34.9, 36.3, 39.5, 51.2, 51.9, 61.0, 76.3, 122.5, 123.0, 123.7, 126.9, 130.3, 139.0, 177.1, 207.7.

*5.1.1.6. 1-Methylpyrrolo(spiro[2.3′]-5-methyloxindole)spiro[3.2″]cyclopentanone (**4f**).* White solid; (0.282 g, 42%); mp 176–177 °C; Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85; Found: C, 71.87; H, 7.16; N, 9.81. IR (KBr): 1692, 1728, 3292 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.26–1.41 (m, 1H, cyclopentanone ring proton), 1.59–1.68 (m, 1H, H-4), 1.83–2.06 (m, 3H, cyclopentanone ring protons), 2.15 (s, 3H, CH_3), 2.19–2.24 (m, 1H, cyclopentanone ring proton), 2.27 (s, 3H, CH_3), 2.31–2.41 (m, 2H, H-4 and cyclopentanone ring proton), 3.28–3.56 (m, 1H, H-5), 3.43–3.49 (m, 1H, H-5), 6.74 (d, 1H, $J = 7.8$ Hz, aromatic), 6.99 (s, 1H, aromatic), 7.04 (d, 1H, $J = 7.8$ Hz, aromatic), 9.19 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.1, 21.0, 31.6, 33.6, 35.7, 39.0, 51.5, 60.3, 76.9, 109.5, 125.8, 126.8, 129.7, 132.4, 139.6, 178.9.

Table 1
MIC values of the dispiropyrrolidines, **4** and **6** and dimers, **18**

Comp	(MTB)[a]	Comp.	(MTB)[a]
4a	160.05	**6a**	61.20
4b	38.29	**6b**	118.34
4c	73.43	**6c–6e**	–[b]
4d	36.60	**6f**	27.74
4e	**8.78**	**6g**	13.45
4f	–[b]	**6h**	26.06
4g	41.89	**6i**	22.49
4h	40.01	**6j**	114.54
4i	19.94	**6k**	55.36
4j	**4.75**	**6l**	23.69
4k	41.01	**6m**	13.68
4l	39.20	**6n**	26.48
4m	18.78	**6o**	22.81
4n	37.45	**6p**	**6.24**
4o	**4.47**	**6q**	**6.06**
4p	**8.96**	**6r**	10.55
4q	**4.29**	**18a**	124.85
4r	**4.13**	**18b**	29.17
4s	33.05	**18c**	26.63
4t	**1.98**	**18d**	**5.61**
Isoniazid		0.36	
Ciprofloxacin		4.71	
Ethambutol		7.64	
Pyrazinamide		50.77	

[a] Minimum inhibitory concentrations (μM) against *M. tuberculosis* H37Rv and the MICs of the compounds with higher activity are given in bold.
[b] Not tested.

*5.1.1.7. 1-Methylpyrrolo(spiro[2.3′]-5-methyloxindole)spiro[3.2″]cyclohexanone (**4g**).* Yellow solid; (0.240 g, 40%); mp 150–151 °C; Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%; Found: C, 72.51; H, 7.50; N, 9.34. IR (KBr): 1689, 1721, 3286 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.26–1.88 (m, 6H, cyclohexanone ring protons), 1.90–2.01 (m, 1H, H-4), 2.07 (s, 3H, CH_3), 2.27 (s, 3H, N–CH_3), 2.30–2.51 (m, 2H, cyclohexanone ring protons), 2.62–2.76 (m, 1H, H-4), 3.19–3.34 (m, 2H, H-5), 6.80 (d, 1H, $J = 7.6$ Hz, aromatic), 6.86 (s, 1H, aromatic), 7.04 (d, 1H, $J = 7.6$ Hz, aromatic), 8.94 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.0, 21.5, 25.3, 33.9, 35.5, 35.6, 41.2, 51.9, 62.6, 76.6, 109.7, 127.1, 127.4, 129.6, 132.0, 139.1, 179.2, 212.1.

*5.1.1.8. 1-Methylpyrrolo(spiro[2.3′]-5-methyloxindole)spiro[3.2″]cycloheptanone (**4h**).* Pale yellow solid; (0.210 g, 38%); mp 198–199 °C; Anal. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97; Found: C, 73.12; H, 7.80; N, 8.91. IR (KBr): 1617, 1720, 3215 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97–1.60 (m, 4H, cycloheptanone ring protons), 1.70–2.06 (m, 5H, H-4 and cycloheptanone ring protons), 2.11 (s, 3H, CH_3), 2.14–2.17 (m, 2H, cycloheptanone ring protons), 2.26 (s, 3H, CH_3), 2.58–2.66 (m, 1H, H-4), 3.26–3.34 (m, 1H, H-5), 3.42 (td, 1H, $J = 8.7$, 4.8 Hz, H-5), 6.79–7.82 (m, 2H, aromatic), 7.05 (d, 1H, $J = 7.8$ Hz, aromatic), 8.70 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 25.2, 27.5, 29.8, 32.2, 32.8, 35.6, 43.8, 52.2, 64.2, 78.3, 109.6, 125.2, 126.8, 129.6, 131.8, 139.4, 179.0, 216.5.

*5.1.1.9. 1-Methylpyrrolo(spiro[2.3′]-5-methyloxindole)spiro[3.2″]-1′-methylpiperidin-4-one (**4i**).* Pale yellow solid; (0.240 g, 44%); mp 166–167 °C; Anal. Calcd. for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41; Found: C, 68.92; H, 7.46; N, 13.35. IR (KBr): 1708, 1739, 3205 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.51–1.68 (m, 2H, H-4 and H-5″), 1.98–2.01 (m, 1H, H-5″), 2.03 (d, 1H, $J = 12.0$ Hz, H-2″ax), 2.08 (s, 3H, CH_3), 2.13–2.18 (m, 1H, H-6″ax), 2.19 (s, 3H, 1-N–CH_3), 2.26 (s, 3H, 1″-N–CH_3), 2.62–2.73 (m, 1H, H-6″eq), 2.86–2.94 (m, 1H, H-4), 3.04–3.12 (m, 1H, H-5), 3.23–3.30 (m, 1H, H-5), 3.77 (dd, 1H, 12.0,

2.4 Hz, H-2″eq), 6.76 (s, 1H, aromatic), 6.79 (d, 1H, $J = 7.8$ Hz, aromatic), 7.01 (d, 1H, $J = 7.8$ Hz, aromatic), 9.60 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.0, 30.4, 35.2, 40.9, 44.6, 52.6, 54.9, 62.9, 65.5, 74.0, 109.5, 127.2, 127.5, 129.3, 131.3, 139.1, 179.1, 208.2.

*5.1.1.10. 1-Methylpyrrolo(spiro[2.3′]-5-methyloxindole)spiro[3.2″]-1′-nitrosopiperidin-4-one (**4j**).* White solid, (0.204 g, 40%), mp 117–118 °C; Anal. Calcd. for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06; Found: C, 62.24; H, 6.09; N, 17.13. IR (KBr): 1622, 1703, 3206 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.86–1.00 (m, 1H, H-4), 2.02–2.08 (m, 1H, H-5″), 2.17 (s, 3H, CH_3), 2.31 (s, 3H, N–CH_3), 2.35–2.54 (m, 2H, H-4 and H-6″), 2.63–2.76 (m, 1H, H-5″), 3.38–3.52 (m, 3H, H-5 and H-6″), 4.26 (d, 1H, $J = 14.7$ Hz, H-2″), 5.20 (d, 1H, $J = 14.7$ Hz, H-2″), 6.71 (d, 1H, $J = 7.5$ Hz, aromatic), 6.78 (s, 1H, aromatic), 7.03 (d, 1H, $J = 7.5$ Hz, aromatic), 8.82 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.0, 30.1, 34.9, 36.2, 39.8, 51.2, 52.0, 61.0, 76.1, 110.7, 123.9, 125.6, 130.5, 132.4, 139.3, 176.3, 207.6.

*5.1.1.11. 1-Methylpyrrolo(spiro[2.3′]-5-chlorooxindole)spiro[3.2″]cyclopentanone (**4k**).* White solid; (0.420 g, 39%); mp 169–170 °C; Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19; Found: C, 63.10; H, 5.56; N, 9.12. IR (KBr): 1692, 1726, 3291 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.31–1.48 (m, 1H, H-4), 1.60–1.74 (m, 1H, H-5″), 1.84–1.88 (m, 1H, H-5″), 1.91–1.99 (m, 3H, H-4″and H-3″), 2.16 (s, 3H, CH_3), 2.20–2.25 (m, 1H, H-4″), 2.27–2.36 (m, 1H, H-4), 3.29 (td, 1H, $J = 9.2$, 4.8 Hz, H-5), 3.46 (td, 1H, $J = 9.2$, 4.8 Hz, H-5), 6.81 (d, 1H, $J = 8.1$, aromatic), 7.19–7.28 (m, 2H, aromatic), 8.47 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.2, 31.7, 33.5, 35.8, 39.0, 51.5, 60.5, 76.8, 110.7, 126.8, 127.8, 128.5, 129.5, 140.5, 178.4, 212.4.

*5.1.1.12. 1-Methylpyrrolo(spiro[2.3′]-5-chlorooxindole)spiro[3.2″]cyclohexanone (**4l**).* Pale yellow solid; (0.410 g, 42%); mp 197–198 °C; Anal. Calcd. for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79; Found: C, 64.12; H, 6.08; N, 8.85. IR (KBr): 1685, 1723, 3287 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.32–1.92 (m, 6H, cyclohexanone ring protons), 1.95–2.05 (m, 1H, H-4), 2.08 (s, 1H, N–CH_3), 2.31–2.36 (m, 2H, cyclohexanone ring protons), 2.59–2.67 (m, 1H, H-4), 3.22–3.29 (m, 2H, H-5), 6.86 (d, 1H, $J = 8.1$, aromatic), 7.09 (s, 1H, aromatic), 7.22–7.28 (m, 1H, aromatic), 8.96 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.5, 25.2, 33.8, 35.1, 35.6, 41.0, 51.8, 62.8, 76.6, 111.0, 127.2, 128.1, 129.0, 129.4, 140.1, 178.8, 211.4.

*5.1.1.13. 1-Methylpyrrolo(spiro[2.3′]-5-chlorooxindole)spiro[3.2″]cycloheptanone (**4m**).* Solid; (0.336 g, 38%); mp 167–168 °C; Anal. Calcd. for $C_{18}H_{21}ClN_2O_2$: C, 64.96; H, 6.36; N, 8.42; Found: C, 64.90; H, 6.42; N, 8.49. IR (KBr): 1617, 1722, 3312 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.98–1.59 (m, 5H, cycloheptanone ring protons), 1.72–2.05 (m, 4H, H-4 and cycloheptanone ring protons), 2.11 (s, 1H, CH_3), 2.16–2.22 (m, 2H, cycloheptanone ring protons), 2.57–2.66 (m, 1H, H-4), 3.21–3.31 (m, 1H, H-5), 3.40–3.47 (m, 1H, H-5), 6.80 (d, 1H, $J = 8.3$ Hz, aromatic), 6.97 (d, 1H, $J = 1.8$ Hz, aromatic), 7.24 (dd, 1H, $J = 8.3$, 1.8 Hz, aromatic), 8.80 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.2, 27.5, 29.8, 32.3, 32.8, 35.6, 43.8, 52.2, 64.5, 78.3, 111.0, 126.4, 127.2, 128.1, 129.4, 140.3, 178.8, 214.5.

*5.1.1.14. 1-Methylpyrrolo(spiro[2.3′]-5-chlorooxindole)spiro[3.2″]-1″-methyltetrahydro-4″(1H)-pyridinone (**4n**).* Colorless crystals; (0.460 g, 52%); mp 201–202 °C; Anal. Calcd. for $C_{17}H_{20}ClN_3O_2$: C, 61.17; H, 6.04; N, 12.59; Found: C, 61.12; H, 6.10; N, 12.53. IR (KBr): 1702, 1734, 3205 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.51–1.67 (m, 2H, H-4 and H-5″), 2.03–2.07 (m, 1H, H-2″ax), 2.08 (s, 3H, 1-N–CH_3), 2.11–2.13 (m, 1H, H-5″), 2.16–2.17 (m, 1H, H-6″ax), 2.19 (s, 3H, 1″-N–CH_3), 2.66–2.72 (m, 1H, H-6″eq), 2.83–2.92 (m, 1H, H-4), 3.02–3.10 (m, 1H, H-5), 3.22–3.29 (m, 1H, H-5), 3.69 (dd, 1H, 12.3, 3.0 Hz, H-2″eq), 6.81 (d, 1H, $J = 8.3$ Hz, aromatic), 6.94 (d, 1H, $J = 2.0$ Hz, aromatic), 7.20 (dd, 1H, $J = 8.3$, 2.0 Hz, aromatic), 8.95 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.4, 35.2, 40.9, 44.7, 52.5, 54.9, 62.7, 65.8, 74.2, 110.5, 127.1, 127.5, 129.1, 129.3, 139.9, 178.4, 207.7 (Fig. 1).

*5.1.1.15. 1-Methylpyrrolo(spiro[2.3′]-5-chlorooxindole)spiro[3.2″]-1″ nitrosotetrahydro-4″(1H)-pyridinone (**4o**).* White solid; (0.325 g, 40%); mp 172–173 °C; Anal. Calcd. for $C_{16}H_{17}ClN_4O_3$: C, 55.10; H, 4.91; N, 16.06; Found: C, 55.16; H, 4.85; N, 16.12. IR (KBr): 1618, 1702, 3209 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.12 (s, 1H, CH_3), 2.14–2.20 (m, 1H, H-4), 2.28–2.47 (m, 2H, H-4 and H-6″), 2.55–2.78 (m, 2H, H-5″), 3.36–3.50 (m, 3H, H-5 and H-6″), 4.24 (d, 1H, $J = 14.7$ Hz, H-2″), 5.21 (d, 1H, $J = 14.7$ Hz, H-2″), 6.73 (d, 1H, $J = 8.4$ Hz, aromatic), 6.95 (d, 1H, $J = 2.0$ Hz, aromatic), 7.21 (dd, 1H, $J = 8.4$, 2.0 Hz, aromatic), 8.34 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.2, 34.9, 36.2, 39.5, 51.2, 51.9, 61.5, 76.0, 110.7, 125.6, 126.1, 128.2, 130.2, 140.1, 176.1, 207.0.

*5.1.1.16. 1-Methylpyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]cyclopentanone (**4p**).* White solid; (0.510 g, 41%); mp 177–178 °C; Anal. Calcd. for $C_{16}H_{17}BrN_2O_2$: C, 55.03; H, 4.91; N, 8.02; Found: C, 55.10; H, 4.85; N, 8.07. IR (KBr): 1686, 1725, 3298 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.32–1.47 (m, 1H, H-4), 1.60–1.79 (m, 2H, H-5″), 1.88–1.99 (m, 3H, H-4″and H-3″), 2.16 (s, 3H, CH_3), 2.18–2.36 (m, 2H, H-4″and H-4), 3.28 (td, 1H, $J = 9.5$, 5.0 Hz, H-5), 3.45 (td, 1H, $J = 9.0$, 5.0 Hz, H-5), 6.75 (d, 1H, $J = 8.3$ Hz, aromatic), 7.33 (d, 1H, $J = 2.1$ Hz, aromatic), 7.38 (dd, 1H, $J = 8.3$, 2.1 Hz, aromatic), 8.35 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.2, 31.7, 33.5, 35.8, 39.0, 51.5, 60.5, 76.8, 111.2, 115.8, 128.1, 129.6, 132.4, 141.0, 178.2, 212.3.

*5.1.1.17. 1-Methylpyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]cyclohexanone (**4q**).* Solid; (0.475 g, 43%), mp 164–166 °C; Anal. Calcd. for $C_{17}H_{19}BrN_2O_2$: C, 56.21; H, 5.27; N, 7.71; Found: C, 56.25; H, 5.34; N, 7.76. IR (KBr): 1685, 1721, 3286 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.32–1.58 (m, 3H, cyclohexanone ring protons), 1.62–2.06 (m, 5H, H-3″, H-4 and cyclohexanone ring protons), 2.09 (s, 1H, N–CH_3), 2.29–2.40 (m, 1H, H-3″), 2.58–2.68 (m, 1H, H-4), 3.22–3.25 (m, 2H, H-5), 6.79 (d, 1H, $J = 8.3$ Hz, aromatic), 7.23 (s, 1H, aromatic), 7.39 (d, 1H, $J = 8.3$ Hz, aromatic), 8.86 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.5, 25.2, 33.8, 35.1, 35.7, 41.0, 51.8, 62.8, 76.6, 111.4, 115.4, 129.4, 130.0, 132.2, 140.6, 178.7, 211.4.

*5.1.1.18. 1-Methylpyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]cycloheptanone (**4r**).* Solid, (0.375 g, 37%), mp 179–180 °C; Anal. Calcd. for $C_{18}H_{21}BrN_2O_2$: C, 57.30; H, 5.61; N, 7.43; Found: C, 57.38; H, 5.56; N, 7.48. IR (KBr): 1620, 1722, 3315 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98–1.58 (m, 5H, cycloheptanone ring protons), 1.73–2.07 (m, 4H, H-4 and cycloheptanone ring protons), 2.11 (s, 1H, CH_3), 2.14–2.22 (m, 2H, cycloheptanone ring protons), 2.56–2.66 (m, 1H, H-4), 3.23–3.31 (m, 1H, H-5), 3.40–3.47 (m, 1H, H-5), 6.79 (d, 1H, $J = 8.1$ Hz, aromatic), 7.11 (s, 1H, aromatic), 7.36–7.40 (m, 1H, aromatic), 8.76 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2, 27.5, 29.8, 32.3, 32.8, 35.6, 43.8, 52.2, 64.5, 78.2, 111.4, 115.3, 127.6, 129.2, 132.3, 140.8, 178.7, 214.5.

*5.1.1.19. 1-Methylpyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]-1″-methyltetrahydro-4″(1H)-pyridinone (**4s**).* White solid; (0.490 g, 49%); mp 164–165 °C; Anal. Calcd. for $C_{17}H_{20}BrN_3O_2$: C, 53.98; H, 5.33; N, 11.11; Found: C, 53.92; H, 5.26; N, 11.18. IR (KBr): 1698, 1734, 3204 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.50–1.66 (m, 2H, H-4 and H-5″), 2.02–2.04 (m, 1H, H-2″ax), 2.07 (s, 3H, 1-N–CH_3), 2.10–2.14 (m, 1H, H-5″), 2.18 (s, 3H, 1″-N–CH_3), 2.22–2.26 (m, 1H, H-6″ax), 2.65–2.71 (m, 1H, H-6″eq), 2.82–2.91 (m, 1H, H-4), 3.01–3.09 (m, 1H, H-5), 3.21–3.28 (m, 1H, H-5), 3.68 (dd, 1H, 12.3, 2.7 Hz, H-2″eq), 6.76 (d, 1H, $J = 8.4$ Hz, aromatic), 7.07 (d, 1H, $J = 1.7$ Hz,

aromatic), 7.35 (dd, 1H, $J = 8.4$, 1.7 Hz, aromatic), 8.91 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.4, 35.2, 40.9, 44.7, 52.5, 54.9, 62.7, 65.8, 74.2, 111.1, 114.7, 129.7, 129.8, 132.0, 140.4, 178.3, 207.6.

*5.1.1.20. 1-Methylpyrrolo(spiro[2.3′]-5-bromooxindole)spiro[3.2″]-1″ nitrosotetrahydro-4″(1H)-pyridinone (**4t**).* Solid; (0.350 g, 38%); mp 195–196 °C; Anal. Calcd. for $C_{16}H_{17}BrN_4O_3$: C, 48.87; H, 4.36; N, 14.25; Found: C, 48.81; H, 4.29; N, 14.30. IR (KBr): 1617, 1703, 3210 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.11 (s, 1H, CH_3), 2.16–2.32 (m, 2H, H-4 and H-6″), 2.35–2.47 (m, 1H, H-4), 2.54–2.79 (m, 2H, H-5″), 3.35–3.50 (m, 3H, H-5 and H-6″), 4.24 (d, 1H, $J = 14.7$ Hz, H-2″), 5.20 (d, 1H, $J = 14.7$ Hz, H-2″), 6.69 (d, 1H, $J = 8.3$ Hz, aromatic), 7.07 (d, 1H, $J = 1.8$ Hz, aromatic), 7.35 (dd, 1H, $J = 8.3$, 1.8 Hz, aromatic), 8.81 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.1, 34.9, 36.1, 39.8, 51.2, 51.9, 61.4, 76.0, 112.4, 115.9, 126.3, 128.3, 133.1, 140.7, 175.8, 207.0.

5.2. Synthesis of spiropyrrolidines **6**

5.2.1. General procedure

A mixture of ketone (0.200 g, 1.78 mmol), isatin (0.262 g, 1.78 mmol) and phenylglycine (0.540 g, 3.56 mmol) in methanol:-water (2:1 v/v; 30 mL) was refluxed in a water bath for 24 h. After completion of the reaction as monitored by tlc, the excess solvent was removed under vacuum and the residue subjected to flash column chromatography using petroleum ether:ethyl acetate mixture (8:2 v/v) as eluent.

*5.2.1.1. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)spiro[3.2′]cyclopentanone (**6a**).* White solid; (0.340 g, 3), mp 140–141 °C; Anal. Calcd for $C_{27}H_{24}N_2O_2$: C, 79.39; H, 5.92; N, 6.86; Found: C, 79.45; H, 5.87; N, 6.81. IR (KBr): 1620, 1703, 3324 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.21–1.45 (m, 3H, 3′CH_2, 4′CH_2 and 5′CH_2), 1.64–1.74 (m, 1H, 5′CH_2), 1.84–1.96 (m, 1H, 4′CH_2), 2.14–2.17 (m, 1H, 3′CH_2), 2.53 (s, 1H, NH), 4.03 (d, 1H, $J = 9.6$ Hz, H-4), 5.49 (d, 1H, $J = 9.6$ Hz, H-5), 6.87 (d, 1H, $J = 7.8$ Hz, aromatic), 7.02–7.06 (m, 1H, aromatic), 7.18–7.31 (m, 8H, aromatic), 7.42 (d, 2H, $J = 6.9$ Hz, aromatic), 7.48 (d, 1H, $J = 7.2$ Hz, aromatic), 8.43 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.7, 33.0, 37.5, 60.5, 66.4, 67.2, 73.0, 109.7, 123.0, 126.6, 126.8, 127.4, 127.5, 127.8, 128.2, 128.3, 129.6, 130.4, 138.6, 141.1, 141.5, 180.4, 219.0.

*5.2.1.2. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)spiro[3.2′]cyclohexanone (**6b**).* White solid; (0.325 g, 38%), mp 144–145 °C; Anal. Calcd for $C_{28}H_{26}N_2O_2$: C, 79.59; H, 6.20; N, 6.63; Found: C, 79.54; H, 6.15; N, 6.67. IR (KBr): 1618, 1700, 3325 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.05–1.70 (m, 6H, 3′CH_2, 4′CH_2, 5′CH_2 and 6′CH_2), 2.14(d, 1H, $J = 13.8$ Hz, 6′CH_2), 2.46 (s, 1H, NH), 2.66 (d, 1H, $J = 14.1$ Hz, 3′CH_2), 4.69 (d, 1H, $J = 11.0$ Hz, H-4), 5.30 (d, 1H, $J = 11.0$ Hz, H-5), 6.89 (d, 1H, $J = 7.8$ Hz, aromatic), 7.04–7.09 (m, 1H, aromatic), 7.16–7.26 (m, 8H, aromatic), 7.36 (d, 2H, $J = 7.2$ Hz, aromatic), 7.48 (d, 1H, $J = 7.2$ Hz, aromatic), 8.32 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.9, 25.2, 32.0, 41.8, 57.3, 63.7, 67.1, 71.0, 109.9, 123.2, 126.2, 126.6, 127.5, 127.6, 128.0, 128.2, 129.4, 130.2, 130.5, 137.5, 140.2, 140.7, 181.1, 210.2.

*5.2.1.3. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)spiro[3.2′]cycloheptanone (**6c**).* White solid; (0.248 g, 32%), mp 137–138 °C; Anal. Calcd for $C_{29}H_{28}N_2O_2$: C, 79.79; H, 6.46; N, 6.42; Found: C, 79.85; H, 6.40; N, 6.48. IR (KBr): 1623, 1706, 3329 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.94–2.68 (m, 11H, 3′CH_2, 4′CH_2, 5′CH_2, 6′CH_2, 7′CH_2 and NH), 4.63 (d, 1H, $J = 10.0$ Hz, H-4), 5.39 (d, 1H, $J = 10.0$ Hz, H-5), 6.86 (d, 1H, $J = 7.5$ Hz, aromatic), 6.99–7.48 (m, 13H, aromatic), 8.14 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 24.5, 27.5, 30.0, 31.0, 43.1, 56.5, 66.1, 68.8, 73.6, 109.8, 122.8, 126.3, 126.6, 127.4, 127.5, 127.8, 128.1, 128.2, 128.4, 129.4, 137.9, 140.8, 141.4, 181.4, 212.8.

*5.2.1.4. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4-one (**6d**).* Yellow solid; (0.275 g, 36%), mp 168–169 °C; Anal. Calcd for $C_{28}H_{27}N_3O_2$: C, 76.86; H, 6.22; N, 9.60; Found: C, 76.91; H, 6.16; N, 9.55. IR (KBr): 1620, 1699, 3335 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.42–1.47 (m, 1H, 5′CH_2), 1.51 (d, 1H, $J = 12.3$ Hz, 2′CH_2), 1.92–2.05 (m, 2H, 5′CH_2 and 6′CH_2), 2.15 (s, 1H, CH_3), 2.35 (s, 1H, NH), 2.55–2.61 (m, 1H, 6′CH_2), 3.72 (dd, 1H, $J = 12.3$, 2.4 Hz, 2′CH_2), 4.54 (d, 1H, $J = 11.6$ Hz, H-4), 5.28 (d, 1H, $J = 11.6$ Hz, H-5), 6.82 (d, 1H, $J = 7.8$ Hz, aromatic), 6.99–7.24 (m, 9H, aromatic), 7.32 (d, 2H, $J = 7.5$ Hz, aromatic), 7.46 (d, 2H, $J = 7.2$ Hz, aromatic), 7.65 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.5, 44.7, 54.0, 54.5, 58.8, 62.9, 68.5, 69.7, 109.6, 122.4, 125.9, 126.6, 127.5, 127.6, 128.0, 128.2, 129.2, 129.8, 130.9, 136.6, 140.2, 140.9, 182.2, 206.8.

*5.2.1.5. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-benzylpiperidin-4-one (**6e**).* White solid; (0.220 g, 41%), mp 173–174 °C; Anal. Calcd for $C_{34}H_{31}N_3O_2$: C, 79.51; H, 6.08; N, 8.18; Found: C, 79.45; H, 6.12; N, 8.12. IR (KBr): 1618, 1699, 3334 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.39–1.49 (m, 1H, 5′CH_2), 1.66–1.80 (m, 2H, 2′CH_2 and 6′CH_2), 1.94–2.04 (m, 1H, 5′CH_2), 2.32 (s, 1H, NH), 2.51–2.56 (m, 1H, 6′CH_2), 3.01 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 3.79 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 3.93 (dd, 1H, $J = 12.3$,2.4 Hz, 2′CH_2), 4.59 (d, 1H, $J = 11.3$ Hz, H-4), 5.37 (d, 1H, $J = 11.3$ Hz, H-5), 6.90 (d, 1H, $J = 7.5$ Hz, aromatic), 6.97–7.10 (m, 3H, aromatic), 7.17–7.26 (m, 12H, aromatic), 7.37 (d, 2H, $J = 7.2$ Hz, aromatic), 7.49 (d, 1H, $J = 6.9$ Hz, aromatic), 8.70 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.6, 50.1, 54.8, 58.9, 61.4, 62.9, 68.5, 69.8, 109.5, 122.7, 126.0, 126.7, 126.9, 127.5, 127.6, 128.1, 128.2, 128.8, 129.2, 129.9, 130.8, 136.7, 138.0, 140.5, 140.7, 181.9, 207.2.

*5.2.1.6. 4,5-Diphenylpyrrolo(spiro[2.3″]-8-isopropyloxindole)spiro[3.2′]cyclopeantanone (**6f**).* White solid; (0.415 g, 39%), mp 191–192 °C; Anal. Calcd for $C_{30}H_{30}N_2O_2$: C, 79.97; H, 6.71; N, 6.22; Found: C, 79.92; H, 6.78; N, 6.26. IR (KBr): 1619, 1698, 3280 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.16–1.35 (m, 3H, 3′CH_2, 4′CH_2 and 5′CH_2), 1.38–1.42 (m, 6H, CH($\underline{CH_3}$)$_2$), 1.63–1.80 (m, 1H, 5′CH_2), 1.84–1.98 (m, 1H, 4′CH_2), 2.21–2.32 (m, 1H, 3′CH_2), 2.55 (s, 1H, NH), 3.20–3.29 (m, 1H, CH), 4.09 (d, 1H, $J = 9.5$ Hz, H-4), 5.51 (d, 1H, $J = 9.5$ Hz, H-5), 6.96–7.48 (m, 13H, aromatic), 10.22 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.7, 22.6, 22.7, 28.8, 33.3, 37.5, 60.3, 66.4, 67.4, 73.5, 123.3, 123.7, 126.3, 126.8, 127.3, 127.4, 127.5, 128.3, 130.2, 130.3, 138.8, 138.9, 141.3, 181.8.

*5.2.1.7. 4,5-Diphenylpyrrolo(spiro[2.3″]-8-isopropyloxindole)spiro[3.2′]cyclohexanone (**6g**).* White solid; (0.350 g, 37%), mp 95–96 °C; Anal. Calcd for $C_{31}H_{32}N_2O_2$: C, 80.14; H, 6.94; N, 6.03; Found: C, 80.20; H, 6.89; N, 6.08. IR (KBr): 1621, 1702, 3327 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.83–1.17 (m, 6H, 3′CH_2, 4′CH_2, 5′CH_2 and 6′CH_2), 1.34–1.45 (m, 6H, CH($\underline{CH_3}$)$_2$), 2.14 (d, 1H, $J = 12.6$ Hz, 6′CH_2), 2.35 (s, 1H, NH), 2.65 (d, 1H, $J = 14.1$ Hz, 3′CH_2), 3.12–3.24 (m, 1H, CH), 4.73 (d, 1H, $J = 10.8$ Hz, H-4), 5.37 (d, 1H, $J = 10.8$ Hz, H-5), 7.01–7.49 (m, 13H, aromatic), 10.11 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.5, 22.7, 25.1, 26.8, 28.7, 32.4, 41.7, 57.7, 64.1, 66.7, 72.0, 123.2, 123.3, 126.1, 126.6, 127.5, 128.0, 128.2, 129.5, 130.4, 130.5, 130.6, 137.9, 138.2, 140.8, 182.1, 210.7.

*5.2.1.8. 4,5-Diphenylpyrrolo(spiro[2.3″]-8-isopropyloxindole)spiro[3.3′]-1′methylpiperidin-4-one (**6h**).* Yellow solid; (0.336 g, 40%), mp 104–105 °C; Anal. Calcd for $C_{31}H_{33}N_3O_2$: C, 77.63; H, 6.94; N, 8.76; Found: C, 77.58; H, 6.99; N, 8.70. IR (KBr): 1619, 1697, 3328 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.06 (d, 3H, $J = 6.6$ Hz, CH($\underline{CH_3}$)$_2$), 1.22 (d, 3H, $J = 6.6$ Hz, CH($\underline{CH_3}$)$_2$), 1.32–1.42 (m, 1H, 5′CH_2), 1.81 (d, 1H, $J = 12.3$ Hz, 2′CH_2), 2.12 (s, 1H, CH_3), 2.35–2.40 (m, 1H, 5′CH_2), 2.46 (s, 1H, CH_3), 2.88–2.98 (m, 2H, CH and 6′CH_2), 3.38 (d, 1H,

$J = 14.7$ Hz, 6′CH_2), 3.48 (d, 1H, $J = 12.3$ Hz, 2′CH_2), 4.73 (d, 1H, $J = 10.8$ Hz, H-4), 5.44 (d, 1H, $J = 10.8$ Hz, H-5), 6.99–7.54 (m, 13H, aromatic), 8.94 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.0, 22.5, 28.7, 44.7, 55.5, 56.6, 56.9, 63.7, 67.4, 71.8, 122.0, 124.1, 125.5, 126.7, 127.7, 128.1, 128.2, 128.3, 129.0, 129.6, 129.7, 133.5, 135.0, 137.2, 137.3, 138.9, 140.6, 181.6, 198.8.

*5.2.1.9. 4,5-Diphenylpyrrolo(spiro[2.3″]-8-isopropyloxindole)spiro[3.3′]-1′-benzylpiperidin-4-one (**6i**).* White solid; (0.245 g, 42%), mp 182–183 °C; Anal. Calcd for $C_{37}H_{37}N_3O_2$: C, 79.97; H, 6.71; N, 7.56; Found: C, 79.91; H, 6.78; N, 7.52. IR (KBr): 1620, 1696, 3331 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.36 (d, 3H, $J = 6.9$ Hz, CH($\underline{CH_3}$)$_2$), 1.39 (d, 3H, $J = 6.9$ Hz, CH($\underline{CH_3}$)$_2$), 1.43–1.48 (m, 1H, 5′CH_2), 1.64–1.72 (m, 2H, 2′CH_2 and 6′CH_2), 1.99 (dd, 1H, $J = 15.6$, 2.4 Hz, 5′CH_2), 2.44–2.53 (m, 2H, NH and 6′CH_2), 2.91 (d, 1H, $J = 12.9$ Hz, CH_2Ph), 3.08–3.17 (m, 1H, CH), 3.75 (d, 1H, $J = 12.9$ Hz, CH_2Ph), 3.96 (dd, 1H, $J = 12.6$, 2.4 Hz, 2′CH_2), 4.63 (d, 1H, $J = 11.4$ Hz, H-4), 5.40 (d, 1H, $J =$ 11.4 Hz, H-5), 6.98–7.38 (m, 11H, aromatic), 7.47 (d, 2H, $J = 6.9$ Hz, aromatic), 9.23 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.1, 22.6, 40.5, 50.3, 54.5, 59.5, 61.5, 62.8, 68.2, 70.2, 122.9, 123.2, 125.9, 126.7, 126.9, 127.5, 127.6, 128.0, 128.1, 128.2, 128.7, 129.7, 129.8, 130.4, 137.0, 138.2, 138.3, 140.4, 182.0, 207.4.

*5.2.1.10. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-methyloxindole)spiro[3.2′]cyclohexanone (**6j**).* White solid; (0.320 g, 36%), mp 154–155 °C; Anal. Calcd for $C_{29}H_{28}N_2O_2$: C, 79.79; H, 6.46; N, 6.42; Found: C, 79.85; H, 6.39; N, 6.46. IR (KBr): 1615, 1703, 3326 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.85–1.62 (m, 6H, 3′CH_2, 4′CH_2, 5′CH_2 and 6′CH_2), 2.14 (d, 1H, $J = 17.4$ Hz, 6′CH_2), 2.32 (s, 3H, CH_3), 2.40 (s, 1H, NH), 2.67 (d, 1H, $J = 16.8$ Hz, 3′CH_2), 4.68 (d, 1H, $J = 10.8$ Hz, H-4), 5.30 (d, 1H, $J = 10.8$ Hz, H-5), 6.79 (d, 1H, $J = 7.5$ Hz, aromatic), 7.02-7.25 (m, 8H, aromatic), 7.36 (d, 2H, $J = 6.9$ Hz, aromatic), 7.48 (d, 2H, $J = 6.9$ Hz, aromatic), 8.78 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.1, 21.9, 25.3, 32.1, 41.8, 57.4, 63.7, 67.0, 71.1, 109.7, 126.6, 126.7, 127.5, 127.6, 128.0, 128.2, 129.8, 130.2, 130.5, 132.7, 137.6, 137.8, 140.7, 181.3, 210.3.

*5.2.1.11. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-methyloxindole)spiro[3.3′]-1′-methylpiperidin-4-one (**6k**).* White solid; (0.325 g, 41%), mp 125–126 °C; Anal. Calcd for $C_{29}H_{29}N_3O_2$: C, 77.13; H, 6.47; N, 9.31; Found: C, 77.19; H, 6.42; N, 9.38. IR (KBr): 1621, 1702, 3324 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.41–1.52 (m, 2H, 2′CH_2 and 5′CH_2), 1.92–2.08 (m, 2H, 5′CH_2 and 6′CH_2), 2.13 (s, 3H, CH_3), 2.32 (s, 3H, N–CH_3), 2.37 (s, 1H, NH), 2.50–2.60 (m, 1H, 6′CH_2), 3.74 (dd, 1H, $J = 12.3$, 2.4 Hz, 2′CH_2), 4.54 (d, 1H, $J = 11.5$ Hz, H-4), 5.27 (d, 1H, $J = 11.5$ Hz, H-5), 6.74 (d, 1H, $J = 7.8$ Hz, aromatic), 6.97–7.48 (m, 12H, aromatic), 8.27 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.1, 40.6, 44.8, 54.1, 54.4, 58.9, 62.9, 68.4, 69.6, 109.2, 126.5, 126.6, 127.6, 127.7, 128.0, 128.2, 129.6, 129.8, 130.9, 132.0, 136.6, 138.3, 140.2, 181.8, 206.9.

*5.2.1.12. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-methyloxindole)spiro[3.3′]-1′-benzylpiperidin-4-one (**6l**).* Pale yellow solid; (0.220 g, 40%), mp 156–157 °C; Anal. Calcd for $C_{35}H_{33}N_3O_2$: C, 79.67; H, 6.30; N, 7.96; Found: C, 79.62; H, 6.26; N, 7.99. IR (KBr): 1619, 1698, 3330 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.42–1.53 (m, 1H, 5′CH_2), 1.65–1.79 (m, 2H, 2′CH_2 and 6′CH_2), 1.95–2.01 (m, 1H, 5′CH_2), 2.27 (s, 1H, NH), 2.31 (s, 3H, CH_3), 2.49–2.60 (m, 1H, 6′CH_2), 3.01 (d, 1H, $J = 13.0$ Hz, CH_2Ph), 3.80 (d, 1H, $J = 13.0$ Hz, CH_2Ph), 3.96 (dd, 1H, $J =$ 12.3,2.4 Hz, 2′CH_2), 4.59 (d, 1H, $J = 11.4$ Hz, H-4), 5.36 (d, 1H, $J = 11.4$ Hz, H-5), 6.78 (d, 1H, $J = 8.1$ Hz, aromatic), 6.98–7.38 (m, 15H, aromatic), 7.45 (d, 2H, $J = 6.9$ Hz, aromatic), 8.39 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.1, 40.6, 50.1, 54.7, 58.9, 61.4, 62.9, 68.5, 69.9, 109.2, 126.6, 126.7, 126.9, 127.6, 127.7, 128.0, 128.2, 128.8, 129.0, 129.6, 130.0, 130.9, 132.2, 136.8, 138.0, 138.3, 140.5, 181.8, 207.3.

*5.2.1.13. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-chlorooxindole)spiro[3.2′]cyclohexanone (**6m**).* Solid; (0.280 g, 38%), mp 189–190 °C; Anal. Calcd for $C_{28}H_{25}ClN_2O_2$: C, 73.59; H, 5.51; N, 6.13; Found: C, 73.65; H, 5.58; N, 6.07. IR (KBr): 1621, 1697, 3323 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.09–1.73 (m, 6H, 3′CH_2, 4′CH_2, 5′CH_2 and 6′CH_2), 2.24(d, 1H, $J = 14.4$ Hz, 6′CH_2), 2.47 (s, 1H, NH), 2.63 (d, 1H, $J = 13.8$ Hz, 3′CH_2), 4.65 (d, 1H, $J = 11.0$ Hz, H-4), 5.29 (d, 1H, $J = 11.0$ Hz, H-5), 6.84 (d, 1H, $J = 8.1$ Hz, aromatic), 7.11–7.85 (m, 12H, aromatic), 8.29 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.8, 25.0, 31.8, 41.8, 57.5, 63.5, 67.0, 71.2, 111.5, 115.2, 126.2, 126.7, 127.6, 127.8, 128.1, 128.3, 128.6, 130.6, 130.8, 137.7, 140.2, 140.8, 181.3, 210.4.

*5.2.1.14. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-chlorooxindole)spiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone (**6n**).* Pale yellow solid; (0.498 g, 40%); mp 206–207 °C; Anal. Calcd for $C_{28}H_{26}ClN_3O_2$: C, 71.25; H, 5.55; N, 8.90; Found: C, 71.30; H, 5.48; N, 8.96. IR (KBr): 1621, 1696, 3331 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.42–1.47 (m, 1H, 5′CH_2), 1.52 (d, 1H, $J = 12.6$ Hz, 2′CH_2), 1.90–2.09 (m, 2H, 5′CH_2 and 6′CH_2), 2.11 (s, 1H, CH_3), 2.34 (s, 1H, NH), 2.53–2.61 (m, 1H, 6′CH_2), 3.70 (d, 1H, $J = 12.6$ Hz, 2′CH_2), 4.72 (d, 1H, $J = 11.3$ Hz, H-4), 5.25 (d, 1H, $J = 11.3$ Hz, H-5), 6.79 (d, 1H, $J = 8.4$ Hz, aromatic), 7.12–7.46 (m, 12H, aromatic), 8.63 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.6, 44.7, 53.9, 54.5, 58.7, 62.8, 68.5, 69.6, 110.6, 126.7, 127.2, 127.6, 127.7, 128.1, 128.3, 129.0, 129.2, 129.9, 132.7, 136.3, 139.4, 140.1, 181.8, 206.3.

*5.2.1.15. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-chlorooxindole)spiro[3.3′]-1′-benzyltetrahydro-4′(1H)-pyridinone (**6o**).* White solid; (0.356 g, 41%), mp 170–172 °C; Anal. Calcd for $C_{34}H_{30}ClN_3O_2$: C, 74.51; H, 5.52; N, 7.67; Found: C, 74.56; H, 5.48; N, 7.73. IR (KBr): 1620, 1701, 3332 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.44–1.52 (m, 1H, 5′CH_2), 1.68–1.76 (m, 2H, 2′CH_2 and 6′CH_2), 1.96–2.10 (m, 1H, 5′CH_2), 2.27 (s, 1H, NH), 2.53–2.59 (m, 1H, 6′CH_2), 3.02 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 3.77 (d, 1H, $J = 13.2$ Hz, CH_2Ph), 3.92 (dd, 1H, $J = 12.3$,2.4 Hz, 2′CH_2), 4.54 (d, 1H, $J = 11.3$ Hz, H-4), 5.34 (d, 1H, $J =$ 11.3 Hz, H-5), 6.84 (d, 1H, $J = 8.4$ Hz, aromatic), 7.04–7.54 (m, 17H, aromatic), 8.96 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.6, 50.0, 54.6, 58.7, 61.4, 62.9, 68.6, 69.7, 110.5, 126.5, 126.9, 127.0, 127.6, 127.7, 128.0, 128.1, 128.3, 128.4, 128.7, 129.3, 130.0, 132.7, 136.4, 137.8, 139.3, 140.2, 182.0, 206.6.

*5.2.1.16. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-bromooxindole)spiro[3.2′]cyclohexanone (**6p**).* White solid; (0.290 g, 36%), mp 203–204 °C; Anal. Calcd for $C_{28}H_{25}BrN_2O_2$: C, 67.07; H, 5.03; N, 5.59; Found: C, 67.15; H, 5.10; N, 5.53. IR (KBr): 1618, 1702, 3324 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.88–1.75 (m, 6H, 3′CH_2, 4′CH_2, 5′CH_2 and 6′CH_2), 2.24 (d, 1H, $J = 14.1$ Hz, 6′CH_2), 2.38 (s, 1H, NH), 2.62 (d, 1H, $J = 13.8$ Hz, 3′CH_2), 4.65 (d, 1H, $J = 10.8$ Hz, H-4), 5.29 (d, 1H, $J = 10.8$ Hz, H-5), 6.83–7.90 (m, 13H, aromatic), 8.99 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.8, 25.0, 31.7, 41.8, 57.5, 63.7, 67.0, 71.0, 111.5, 115.7, 126.7, 127.1, 127.6, 128.0, 128.3, 128.6, 129.5, 130.5, 130.8, 132.4, 137.2, 140.4, 181.0, 209.9.

*5.2.1.17. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-bromooxindole)spiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone (**6q**).* Pale yellow solid; (0.532 g, 39%); mp 193–194 °C; Anal. Calcd for $C_{28}H_{26}BrN_3O_2$: C, 65.12; H, 5.07; N, 8.14; Found: C, 65.19; H, 5.13; N, 8.08. IR (KBr): 1622, 1697, 3336 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.42–1.48 (m, 1H, 5′CH_2), 1.53 (d, 1H, $J = 12.0$ Hz, 2′CH_2), 1.87–2.06 (m, 2H, 5′CH_2 and 6′CH_2), 2.11 (s, 1H, CH_3), 2.34 (s, 1H, NH), 2.51–2.65 (m, 1H, 6′CH_2), 3.70 (d, 1H, $J = 12.0$ Hz, 2′CH_2), 4.50 (d, 1H, $J = 11.9$ Hz, H-4), 5.26 (d, 1H, $J = 11.9$ Hz, H-5), 6.76 (d, 1H, $J = 8.1$ Hz, aromatic), 7.13–7.73 (m, 12H, aromatic), 8.77 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.6, 44.7, 53.9, 54.3, 58.7, 62.8, 68.6, 69.5, 111.1, 115.0, 126.8, 127.6, 128.1, 128.3, 129.2, 129.8, 130.5, 132.1, 133.1, 136.2, 139.8, 140.0, 181.8, 206.3.

*5.2.1.18. 4,5-Diphenylpyrrolo(spiro[2.3″]-5-bromooxindole)spiro[3.3′]-1′-benzyltetrahydro-4′(1H)-pyridinone (**6r**).* White solid; (0.375 g, 40%); mp 178–179 °C; Anal. Calcd for $C_{34}H_{30}BrN_3O_2$: C, 68.92; H, 5.10; N, 7.09; Found: C, 68.98; H, 5.15; N, 7.03. IR (KBr): 1618, 1698, 3332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.40–1.52 (m, 1H, 5′CH_2), 1.74 (d, 1H, $J = 12.3$ Hz, 2′CH_2), 1.98–2.12 (m, 2H, 5′CH_2), 2.35–2.62 (m, 2H, 6′CH_2 and NH), 3.03 (d, 1H, $J = 13.1$ Hz, CH_2Ph), 3.77 (d, 1H, $J = 13.1$ Hz, CH_2Ph), 3.92 (d, 1H, $J = 12.3$ Hz, 2′CH_2), 4.54 (d, 1H, $J = 11.3$ Hz, H-4), 5.33 (d, 1H, $J = 11.3$ Hz, H-5), 6.80 (d, 1H, $J = 8.1$ Hz, aromatic), 6.90–7.67 (m, 17H, aromatic) 8.85 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.6, 50.0, 54.6, 58.7, 61.4, 62.9, 68.6, 69.7, 111.0, 115.2, 126.8, 127.0, 127.6, 127.7, 128.1, 128.3, 128.7, 129.3, 130.0, 132.2, 133.1, 136.3, 137.8, 139.7, 140.2, 181.8, 206.6.

5.3. Synthesis of spiroheterocycles **18**

5.3.1. General procedure

A mixture of isatin (0.100 g, 0.68 mmol) and (*L*)-proline (0.078 g, 0.68 mmol) in methanol (15 mL) was refluxed on a water bath for 1 h. After completion of the reaction as monitored by TLC, the excess solvent was removed under vacuum and the residue subjected to flash column chromatography using petroleum ether:-ethyl acetate mixture (8:4) as eluent to afford the product.

*5.3.1.1. Spiro[3′,5]-bis(indolinone)perhydrodipyrrolo[1,2-a:1,2-d]-pyrazine (**18a**).* White solid; (0.098 g, 36%); mp 195–196 °C; Anal. Calcd for $C_{24}H_{24}N_4O_2$: C, 71.98; H, 6.04; N, 13.99; Found: C, 71.90; H, 6.11; N, 13.94. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.54–1.65 (m, 2H, H-1a and H-2a), 1.74–1.97 (m, 2H, H-1b and H-2b), 2.13–2.21 (m, 1H, H-3a), 2.63 (td, 1H, $J = 8.7$, 2.7 Hz, H-3b), 3.57–3.68 (m, 1H, H-10a), 6.51 (d, 1H, $J = 7.8$ Hz, aromatic), 6.87–6.93 (m, 1H, aromatic), 7.47 (d, 1H, $J = 7.5$ Hz, aromatic), 7.66 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.9, 27.4, 47.6, 59.1, 68.6, 108.9, 122.1, 126.2, 126.4, 129.1, 140.6, 176.1.

*5.3.1.2. Spiro[3′,5]-bis-(5-methylindolinone)perhydrodipyrrolo[1,2-a:1,2-d]-pyrazine (**18b**).* White solid; (0.100 g, 38%); mp 200–201 °C; Anal. Calcd for $C_{26}H_{28}N_4O_2$: C, 72.87; H, 6.59; N, 13.07; Found: C, 72.96; H, 6.67; N, 13.01. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.56–1.63 (m, 2H, H-1a and H-2a), 1.74–1.94 (m, 2H, H-1b and H-2b), 2.12–2.20 (m, 1H, H-3a), 2.24 (s, 1H, CH_3), 2.62 (td, 1H, $J = 8.7$, 2.7 Hz, H-3b), 3.56–3.66 (m, 1H, H-10a), 6.39 (d, 1H, $J = 7.8$ Hz, aromatic), 6.86 (d, 1H, $J = 7.8$ Hz, aromatic), 7.30 (s, 1H, aromatic), 7.40 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.8, 21.1, 27.4, 47.6, 59.1, 68.6, 108.6, 126.3, 127.0, 129.3, 131.6, 138.1, 176.0.

*5.3.1.3. Spiro[3′,5]-bis-(5-chloroindolinone)perhydrodipyrrolo[1,2-a:1,2-d]-pyrazine (**18c**).* White solid; (0.093 g, 36%); mp 232–234 °C; Anal. Calcd for $C_{24}H_{22}Cl_2N_4O_2$: C, 61.41; H, 4.72; N, 11.94; Found: C, 61.47; H, 4.66; N, 11.89. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.55–1.63 (m, 2H, H-1a and H-2a), 1.76–1.97 (m, 2H, H-1b and H-2b), 2.12–2.20 (m, 1H, H-3a), 2.61–2.66 (m, 1H, H-3b), 3.52–3.63 (m, 1H, H-10a), 6.49 (d, 1H, $J = 8.4$ Hz, aromatic), 7.07 (dd, 1H, $J = 8.4$, 2.1 Hz, aromatic), 7.45 (s, 1H, aromatic), 7.58 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.8, 27.3, 47.6, 59.0, 68.6, 110.2, 126.6, 127.7, 127.8, 129.3, 139.1, 175.3.

*5.3.1.4. Spiro[3′,5]-bis-(5-bromoindolinone)perhydrodipyrrolo[1,2-a:1,2-d]-pyrazine (**18d**).* White solid; (0.080 g, 32%); mp 236–237 °C; Anal. Calcd for $C_{24}H_{22}Br_2N_4O_2$: C, 51.63; H, 3.97; N, 10.04; Found: C, 51.68; H, 3.91; N, 10.13. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.54–1.72 (m, 2H, H-1a and H-2a), 1.77–1.96 (m, 2H, H-1b and H-2b), 2.13–2.18 (m, 1H, H-3a), 2.59–2.68 (m, 1H, H-3b), 3.53–3.64 (m, 1H, H-10a), 6.45 (d, 1H, $J = 8.3$ Hz, aromatic), 7.25 (d, 1H, $J = 8.3$ Hz, aromatic), 7.44 (s, 1H, aromatic), 7.59 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.9, 27.3, 47.7, 59.1, 68.0, 110.6, 115.1, 128.1, 129.4, 131.2, 139.6, 175.1.

Acknowledgements

S.P. thanks the Department of Science and Technology, New Delhi, for funding for a major research project (No. SR/S1/OC-70/2006) and for funds under (i) IRHPA program for funds for the purchase of a high resolution NMR spectrometer and (ii) FIST program and the University Grants Commission, New Delhi, for (i) funds under the DRS and ASIST programs and (ii) for funding for a major research project [F. No. 36-155/2008(SR)]. RSK thanks CSIR, New Delhi for Senior Research Fellowship and SMR thanks UGC, New Delhi for Junior Research Fellowship.

Appendix. Supplementary information

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2009.09.044.

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