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Preliminary communication

A facile synthesis and antimycobacterial evaluation of novel spiro-pyrido-pyrrolizines and pyrrolidines

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ABSTRACT

An efficient synthesis of 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones was achieved by the reaction of 1-methyl-4-piperidone and aromatic aldehydes in the presence of pyrrolidine under solvent-free microwave irradiation. These dipolarophiles upon cycloaddition with nitrile oxide and azomethine ylides afford stereoselectively novel spiro-isoxazolines, pyrrolizines and pyrrolidines respectively in excellent yields. The spiro compounds were screened for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB), multi-drug resistant *M. tuberculosis* (MDR-TB) and *Mycobacterium smegmatis* (MC^2) using agar dilution method. Among the synthesized compounds, 1-methyl-4-(2,4-dichlorophenyl)pyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one was found to be the most active with a minimum inhibitory concentration (MIC) of 1.76 and 0.88 μM against MTB and MDR-TB respectively.

1. Introduction

1,3-Dipolar cycloaddition provides an efficient approach for the synthesis of five-membered ring heterocycles [1]. 1,3-Dipolar cycloaddition of nitrile oxide to olefins assumes importance since the resulting isoxazolines are versatile intermediates for the synthesis of bifunctional [2] and naturally occurring compounds [3], besides finding medicinal and agricultural applications [4]. The cycloaddition of nitrile oxide to exocyclic olefins results in the formation of spiro-isoxazolines [5], which are useful precursors for many synthetic intermediates [6] and also display important biological activities [7]. Azomethine ylides are reactive and versatile 1,3-dipoles, which readily react with diverse dipolarophiles affording pyrrolizines, pyrrolidines and pyrazolidines [8,9]. The 1,3-dipolar cycloaddition of azomethine ylides to dipolarophiles with exocyclic double bonds affords spiro-heterocycles [10], which display important biological activities [11]. The spiro-oxindoles are present in several natural products [12], and act as potent non-peptide inhibitor of the p53–MDM2 interaction [13].

Spiro compounds are also known for their antimycobacterial properties [14]. Our recent studies on the synthesis and screening of novel spiro-heterocycles disclosed various antimycobacterial leads [15]. In a previous study, we reported that spiro-pyrido-pyrrolizines and pyrrolidines **7**–**9** (Scheme 1) displayed good *in vitro* antimycobacterial activity against MTB, MDR-TB and MC^2 [15a]. The present work reports the preliminary studies on the antimycobacterial activity of spiro-pyrido-pyrrolizines and pyrrolidines **4**–**6** which are chemically modified compounds of **7**–**9**. Compounds **4**–**6** were synthesized via 1,3-dipolar cycloaddition of azomethine ylides from isatin and α-amino acids (proline and sarcosine) or isatin and benzylamine to 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **2**. The present work also discloses the 1,3-dipolar cycloaddition of nitrile oxide generated *in situ* from the dehydrohalogenation of 4-chlorobenzohydroximoyl chloride. It is to be noted that this is the first report on the cycloaddition of **2**.

2. Chemistry

The dipolarophiles **2** employed in the present work were synthesized, more efficiently than the literature methods, from the reaction of 1-methyl-4-piperidone **1** and aromatic aldehydes in the presence of pyrrolidine in good yields (50–76%) under solvent-free

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microwave irradiation (Scheme 2). Previously, McElvain et al. [16] reported the synthesis of **2** from the reaction of **1** and benzaldehyde in 60% alcoholic KOH, but later the product of this reaction was shown to be a dimer of **2** [17]. The mass spectral data and X-ray crystallographic studies of these dimers were reported by Lyle et al. [18]. Gyorgy et al. [19] prepared **2** from 1-methyl-4-morpholino-1,2,3,6-tetrahydropyridine and benzaldehyde in 40% yield, while Bell et al. [20] reported 14% yield of **2** from the same reaction. The above literature methods suffer from longer reaction time and lower yields.

All the dipolarophiles **2a–e** reported in this work are new and their structural elucidation was done with the help of NMR spectroscopic data. The HMBC correlations as well as ^{1}H and ^{13}C NMR chemical shifts for a representative case **2c** are shown in Fig. 1. The structure of **2** deduced from NMR spectroscopic studies is in good agreement with that determined from single crystal X-ray studies of **2b** [21a] and **2e** [21b] (Fig. 2). The structures in Fig. 2 reveal (i) half-chair conformation for the piperidone ring and (ii) (*E*)-configuration for the C=C bond of the arylidene functionality.

The 1,3-dipolar cycloaddition of nitrile oxide, generated *in situ* from 4-chlorobenzohydroximoyl chloride and triethylamine to **2a–e** (Scheme 3) affords novel 3-(4-chlorophenyl)-7-methyl-4-aryl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-ones (**3a–e**) in good yields (55–73%). This reaction is (i) regioselective, as the oxygen of the nitrile oxide adds to the α-carbon of **2** furnishing exclusively the spiro-isoxazolines **3**, (ii) chemoselective, as the nitrile oxide prefers to react with C=C and not with C=O bond of **2** and (iii) stereoselective as only one diastereomer of **3** is formed. The structure of the spiro-isoxazolines **3** was determined by ^{1}H, ^{13}C and two-dimensional NMR spectroscopic techniques. The HMBC correlations and the NMR chemical shifts for **3a** are shown in Fig. 3. The structure of **3** determined from NMR spectroscopic studies and single crystal X-ray crystallographic study (Fig. 4) is in good agreement with each other. The ORTEP diagrams of **3a** [22] (Fig. 4) show that the piperidin-4-one and the isoxazoline ring adopt a chair and an envelope conformation respectively with one carbon atom lying out of plane in the latter. It is also seen that the addition of nitrile oxide has occurred from the bottom side of **2** accounting for the facial selectivity.

The 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of isatin with (i) proline, (ii) sarcosine and (iii) benzylamine to **2a–e** afforded respectively spiro[2.3″]oxindolespiro[3.3′]-1′-methyltetrahydro-4′(1*H*)-pyridinone-4-arylhexahydro-1*H*-pyrrolizines **4a–e**, 1-methyl-4-arylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-ones **5a–e** and 4-aryl-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-ones **6a–e** in excellent yields in a regio- and stereoselective manner (Scheme 4). All these reactions were effected by refluxing an equimolar ratio of the reactants in methanol on a water bath. After completion of the reactions (TLC), the reaction mixtures were poured into water to get pure **4–6** as solids. The compounds **4a–e** are obtained in racemic form, although the amino acid precursor proline is chiral. This is ascribable to the fact that

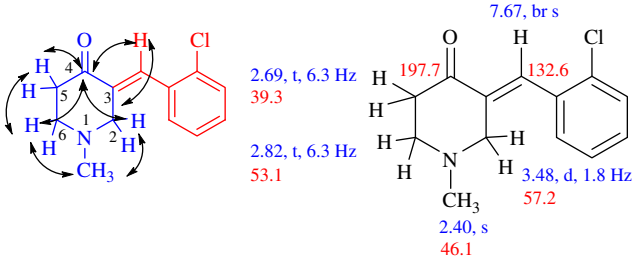


Fig. 1. HMBC correlations and ^{1}H and ^{13}C NMR chemical shifts of **2c**.

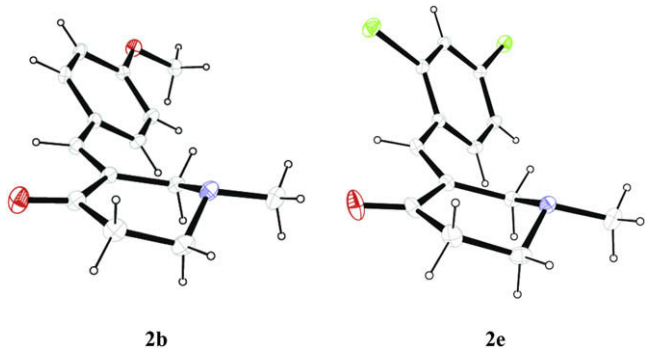


Fig. 2. ORTEP diagrams of **2b** and **2e**.

the intermediate involved in the cycloaddition, *viz.* the azomethine ylide generated from the amino acid is achiral.

The structure of **4–6** was elucidated with the help of one and two-dimensional NMR spectroscopic data as illustrated for **4a**. The HMBC correlations useful in the signal assignments of **4a** are shown in Fig. 5. In the ^{1}H NMR spectrum of **4a**, the doublet at 4.08 ppm ($J = 11.7$ Hz) is assigned to H-4 on the basis of its multiplicity. From the H,H-COSY correlation of H-4, the doublet of triplets at 4.48 ppm ($J = 11.7$ and 6.6 Hz) is readily assigned to H-4a. Further, from H,H-COSY correlations, it is evident that 5-CH_2 protons appear as multiplets at 1.51–1.58 ppm and 2.00–2.07 ppm, while 6-CH_2 protons occur as a multiplet in the range 1.88–1.99 ppm. The multiplets at 2.54–2.60 and 2.82–2.90 ppm are due to 7-CH_2 protons. The H-2′ax and H-2′eq appear as a doublet and doublet of doublets at 1.63 ($J = 12.3$ Hz) and 3.75 ppm ($J = 12.3$ and 2.7 Hz) respectively. The *J* value of 2.7 Hz is due to the long range coupling of H-2′eq with H-6′eq (inferred from H,H-COSY correlation) which overlaps with 7-CH_2 signals at 2.54–2.60 ppm. The H-6′ax and one of the 5′-CH_2 protons overlap with the 6-CH_2 protons, whereas the other 5′-CH_2 proton overlaps with that of 5-CH_2. The aromatic protons appear as a multiplet at 6.85–7.27 ppm and the NH and N–CH_3 protons appear as singlets at 8.40 and 2.14 ppm respectively.

The structure of **4a** determined from NMR spectroscopic studies was further confirmed from a single crystal X-ray crystallographic study (Fig. 6) [23]. The ORTEP diagram of **4a** shows that (i) the piperidin-4-one ring adopts a chair conformation, (ii) H-4 and H-4a are *trans* and (iii) the two carbonyls linked to C-2 and C-3 of **4a** are in *trans*, which is explicable by the fact that the corresponding transition state (A) would require less free energy of activation than the transition state (B) leading to **4′** as the latter would result in electrostatic repulsion between the *cis* carbonyls increasing the free energy of activation (Scheme 5). Further, the chemical shifts of H-2′eq (3.75 ppm) and H-2′ax (1.63 ppm) of **4a** differ significantly (2.12 ppm) suggesting that presumably, H-2′eq is proximate to the carbonyl of spiro-oxindole ring shifting it downfield, while H-2′ax lies in the shielding zone of the spiro-oxindole ring placing it upfield.

Similarly, by straightforward considerations, the ^{1}H and ^{13}C chemical shifts of **5** and **6** were also assigned, the HMBC correlations of representative examples **5e** and **6e** are furnished in Figs. 7 and 9 respectively. The structure deduced from NMR spectroscopic data and X-ray crystallographic study for **5e** [23] (Fig. 8) agrees well.

3. Biological results and discussion

The spiro compounds **4–6** were screened for their *in vitro* antimycobacterial activity against MTB, MDR-TB and MC^2 by agar dilution method for the determination of MIC in triplicates. The MDR-TB clinical isolate was resistant to isoniazid (INH), rifampicin,

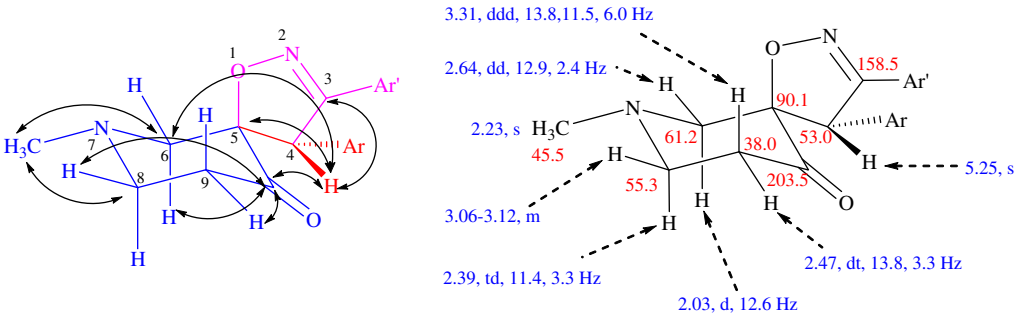


Fig. 3. HMBC correlations and ^{1}H and ^{13}C NMR chemical shifts of **3a**.

ethambutol and ciprofloxacin. The MICs of **4**–**6** along with the standard drugs for comparison are reported in Table 1. In the first phase of screening against MTB, the newer compounds showed good activity with MICs ranging from 1.76 to 30.83 μM. Three compounds **4c**, **4e**, and **5e** showed excellent activity with MIC of less than 4.0 μM. When compared to ethambutol (MIC of 7.64 μM), six compounds *viz.*, **4a**, **4c**, **4d**, **4e**, **5e** and **6d** were more potent with MICs of 7.53, 3.58, 7.46, 3.32, 1.76 and 6.87 μM respectively and compound **5c** was equally active. All the compounds were more potent than first-line anti-TB drug pyrazinamide (MIC of 50.77 μM). The synthesized compounds were less active than isoniazid. Among the fifteen compounds screened, **5e** was found to be the most potent anti-tubercular agent.

Subsequently, those compounds which showed good activity with MTB were screened against MDR-TB. All the three compounds **4c**, **4e** and **5e** inhibited MDR-TB with MIC ranging from 0.88 to 3.58 μM. These compounds were more potent than standard anti-TB drugs like isoniazid, ethambutol and pyrazinamide. Compound **5e** was found to be the most potent being 13.0, 69.5, 461.5 times more potent than isoniazid, ethambutol and pyrazinamide respectively. All the compounds **4**–**6** inhibited non-tubercular mycobacteria MC^2 with MICs ranging from 15.04 to 110.72 μM and five compounds (**4a**, **4c**, **4d**, **5a**, **5c**) were found to be more active than isoniazid.

4. Conclusions

In conclusion, an efficient synthesis of 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**2**) in higher yields than the literature methods is described. The 1,3-dipolar cycloaddition of azomethine ylides to **2** proceeds regio- and stereoselectively affording novel spiro-cycloadducts comprising piperidone, oxindole and pyrrolidine or pyrrolizine rings in excellent yields under mild conditions. The products in the azomethine ylide cycloadditions are obtained in a pure form without employing column chromatography. Three of the spiro compounds synthesized show better activity against MDR-TB than the standard drugs and some compounds display either enhanced or comparable activity with reference to the standard anti-TB drugs.

5. Experimental

The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and $CDCl_3$ as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz. An IFB Microwave oven (Model: Electron) operating at 230 V and 50 Hz with consumption of 1000 W with microwave power maximum level of 600 W and microwave frequency of 2450 MHz was employed for the irradiation done in this work. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer.

5.1. General procedure for the synthesis of 1-methyl-3-[(E)-arylmethylidene]tetrahydro-4(1H)-pyridinones (*2a*–*e*)

A mixture of 1-methyl-4-piperidone **1** (1 mmol) and pyrrolidine (1.2 mmol) was taken in a glass tube, mixed well and kept aside for 5 min at ambient temperature. To this mixture, aromatic aldehyde (1 mmol) was added, mixed thoroughly and the tube containing the mixture was partially immersed in a silica bath placed in a microwave oven and irradiated at 4 power level (480 W) for the appropriate time interval (Scheme 1). The progress of the reaction was monitored after every 1 min of irradiation by TLC with petroleum ether:ethyl acetate (1:2 v/v mixture) as eluent. After each

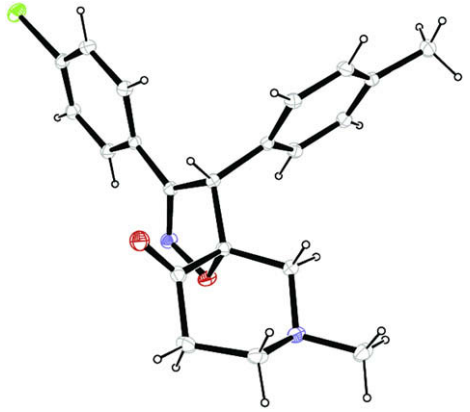


Fig. 4. ORTEP diagram of **3a**.

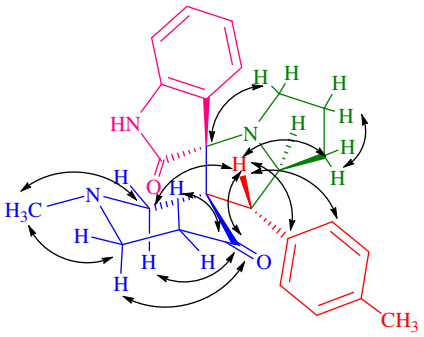


Fig. 5. HMBC correlations of **4a**.

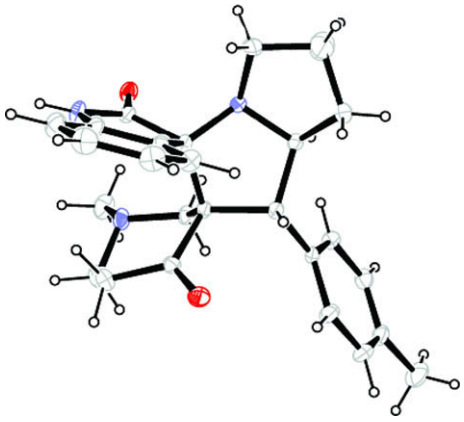


Fig. 6. ORTEP diagram of **4a**.

irradiation, the reaction mixture was cooled to room temperature and mixed well. The maximum temperature of the silica bath, measured immediately after each irradiation was over by stirring the silica bath with the thermometer, was found to be 65 °C. The product **2** was purified by column chromatography using petroleum ether:ethyl acetate (7:2 v/v) mixture.

*5.1.1. 1-Methyl-3-[(*E*)-(4-methylphenyl)methylidene]tetrahydro-4(1*H*)-pyridinone (**2a**)*

Yellow viscous paste; Yield: 1.45 g, 76% (Found: C, 78.17; H, 7.90; N, 6.47. $C_{14}H_{17}NO$ requires C, 78.10; H, 7.96; N, 6.51); υ_{max} ($CHCl_3$) 1670 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (1H, br s, C═CH), 7.26 (2H, d, $J = 8.4$ Hz, Ar–H), 7.21 (2H, d, $J = 8.1$ Hz, Ar–H), 3.66 (2H, d, $J = 1.8$ Hz, 2-CH_2), 2.81 (2H, t, $J = 6.0$ Hz, 6-CH_2), 2.67 (2H, t, $J = 6.0$ Hz, 5-CH_2), 2.45 (3H, s, N–CH_3), 2.38 (3H, s, Ar–CH_3); δ_C (75 MHz, $CDCl_3$) 197.7, 139.4, 136.1, 132.0, 131.9, 130.5, 129.2, 57.8, 52.7, 46.2, 39.0, 21.4.

*5.1.2. 3-[(*E*)-(4-Methoxyphenyl)methylidene]-1-methyltetrahydro-4(1*H*)-pyridinone (**2b**)*

Yellow solid; Yield: 1.04 g, 51%; m.p. 64–65 °C (Found: C, 72.63; H, 7.49; N, 6.14. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06); υ_{max} (KBr) 1673 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.54 (1H, s, C═CH), 7.32 (2H, d, $J = 8.7$ Hz, Ar–H), 6.92 (2H, d, $J = 8.7$ Hz, Ar–H), 3.82 (3H, s, Ar–OCH_3), 3.65 (2H, s, 2-CH_2), 2.79 (2H, t, $J = 6.0$ Hz, 6-CH_2), 2.64 (2H, t, $J = 6.3$ Hz, 5-CH_2), 2.45 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 198.0, 160.7, 136.4, 132.9, 131.2, 127.9, 114.5, 58.3, 55.7, 53.1, 46.7, 39.4.

*5.1.3. 3-[(*E*)-(2-Chlorophenyl)methylidene]-1-methyltetrahydro-4(1*H*)-pyridinone (**2c**)*

Yellow solid; Yield: 1.12 g, 54%; m.p. 70–71 °C (Found: C, 66.33; H, 6.05; N, 6.01. $C_{13}H_{14}ClNO$ requires C, 66.24; H, 5.99; N, 5.94); υ_{max} (KBr) 1670 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (1H, br s, C═CH), 7.17–7.45 (4H, m, Ar–H), 3.48 (2H, d, $J = 1.8$ Hz, 2-CH_2), 2.82 (2H, t, $J = 6.0$ Hz, 6-CH_2), 2.69 (2H, t, $J = 6.3$ Hz, 5-CH_2), 2.40 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 197.7, 135.0, 134.6, 133.3, 132.6, 130.3, 130.0, 129.8, 126.3, 57.2, 53.1, 46.1, 39.3.

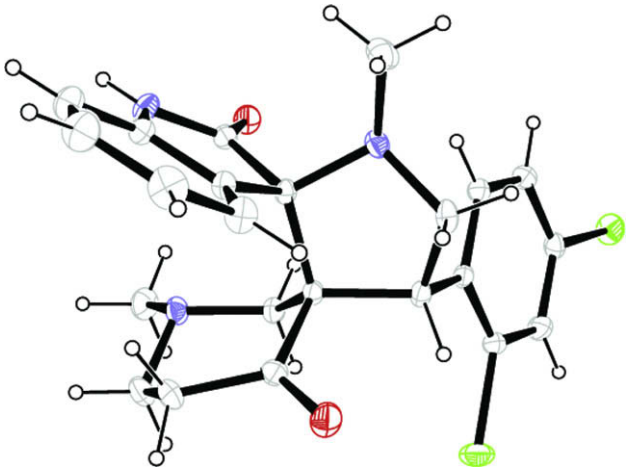


Fig. 8. ORTEP diagram of **5e**.

*5.1.4. 3-[(*E*)-(3-Fluorophenyl)methylidene]-1-methyltetrahydro-4(1*H*)-pyridinone (**2d**)*

Yellow viscous paste; Yield: 1.22 g, 63% (Found: C, 71.29; H, 6.51; N, 6.32. $C_{13}H_{14}FNO$ requires C, 71.21; H, 6.44; N, 6.39); υ_{max} ($CHCl_3$) 1675 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48 (1H, br s, C═CH), 6.97–7.39 (4H, m, Ar–H), 3.60 (2H, d, $J = 2.1$ Hz, 2-CH_2), 2.80 (2H, t, $J = 6.0$ Hz, 6-CH_2), 2.66 (2H, t, $J = 6.0$ Hz, 5-CH_2), 2.43 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 197.5, 162.4, 136.80, 134.3, 133.8, 130.0, 126.15, 116.6, 115.9, 57.4, 52.6, 46.1, 39.0.

*5.1.5. 3-[(*E*)-(2,4-Dichlorophenyl)methylidene]-1-methyltetrahydro-4(1*H*)-pyridinone (**2e**)*

Yellow solid; Yield: 1.19 g, 50%; m.p. 79–80 °C (Found: C, 66.33; H, 6.05; N, 6.01. $C_{13}H_{13}Cl_2NO$ requires C, 57.80; H, 4.85; N, 5.18); υ_{max} (KBr) 1670 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, br s, C═CH), 7.10–7.45 (4H, m, Ar–H), 3.45 (2H, d, $J = 1.8$ Hz, 2-CH_2), 2.81 (2H, t, $J = 6.3$ Hz, 6-CH_2), 2.68 (2H, t, $J = 6.0$ Hz, 5-CH_2), 2.40 (3H, s, N–CH_3); δ_C (75 MHz, $CDCl_3$) 197.4, 135.8, 135.1, 134.9, 131.7, 131.3, 130.9, 129.7, 126.7, 57.1, 52.9, 46.0, 39.2.

*5.2. General procedure for the synthesis of 3-(4-chlorophenyl)-7-methyl-4-aryl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-ones (**3a–e**)*

To a well-stirred mixture of 1-methyl-3-[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones (**2**, 1 mmol) and benzohydroximinoyl

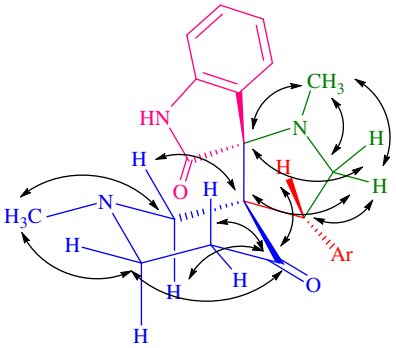


Fig. 7. HMBC correlations of **5e**.

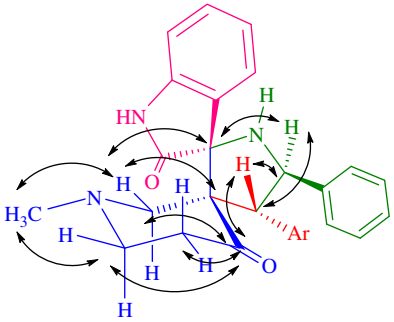


Fig. 9. HMBC correlations of **6e**.

Table 1
Minimum inhibitory concentrations of **4–6** against mycobacterial species.

Comp.	MIC (μM)		
	MTB	MDR-TB	MC^2
4a	7.53	NT	15.04
4b	14.48	NT	57.94
4c	3.58	3.58	28.68
4d	7.46	NT	29.79
4e	3.32	1.66	53.15
5a	16.05	NT	32.09
5b	30.83	NT	61.65
5c	7.64	NT	30.49
5d	7.95	NT	63.53
5e	1.76	0.88	56.26
6a	27.68	NT	110.72
6b	26.73	NT	53.46
6c	13.24	NT	52.97
6d	6.87	NT	54.88
6e	12.34	NT	98.74
Isoniazid	0.39	11.38	45.57
Ethambutol	7.64	61.18	122.36
Pyrazinamide	50.77	406.13	406.13

MTB: *M. tuberculosis*; MDR-TB: Multi-drug resistant *M. tuberculosis*; MC^2: *M. smegmatis*; NT: Not tested.

chloride (3 mmol) in benzene (15 mL), triethylamine (3 mmol) was added drop-wise over a period of 10 min and stirring continued for 5 h at ambient temperature. The triethylamine hydrochloride was filtered off, solvent evaporated *in vacuo* and the product **3** was purified by column chromatography using petroleum ether:ethyl acetate (4:1 v/v) mixture.

*5.2.1. 3-(4-Chlorophenyl)-7-methyl-4-(4-methylphenyl)-1-oxa-2,7-diazaspiro[4.5]-dec-2-en-10-one (**3a**)*

White solid; Yield: 0.25 g, 73%; m.p. 135–136 °C (Found: C, 68.31; H, 5.79; N, 7.67. $C_{21}H_{21}ClN_2O_2$ requires C, 68.38; H, 5.74; N, 7.59); δ_H (300 MHz, $CDCl_3$); 7.03–7.52 (8H, m, Ar–H), 5.25 (1H, s, 4-CH), 3.31 (1H, ddd, $J = 13.8$, 11.5, 6.0 Hz, H-9ax), 3.06–3.12 (1H, m, H-8eq), 2.64 (1H, dd, $J = 12.9$, 2.4 Hz, H-6eq), 2.47 (1H, dt, $J = 13.8$, 3.3 Hz, H-9eq), 2.39 (1H, td, $J = 11.4$, 3.3 Hz, H-8ax), 2.31 (3H, s, Ar–CH_3), 2.23 (3H, s, N–CH_3), 2.03 (1H, d, $J = 12.6$ Hz, H-6ax); δ_C (75 MHz, $CDCl_3$) 203.5, 158.5, 138.1, 136.0, 129.8, 129.3, 128.8, 128.7, 126.8, 90.1, 61.2, 55.3, 53.0, 45.5, 38.0, 21.1.

*5.2.2. 3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-7-methyl-1-oxa-2,7-diazaspiro[4.5]-dec-2-en-10-one (**3b**)*

White solid; Yield: 0.21 g, 63%; m.p. 127–128 °C (Found: C, 65.50; H, 5.56; N, 7.21. $C_{21}H_{21}ClN_2O_3$ requires C, 65.54; H, 5.50; N, 7.28); δ_H (300 MHz, $CDCl_3$); 6.98–7.67 (8H, m, Ar–H), 5.38 (1H, s, 4-CH), 3.93 (3H, s, Ar–OCH_3), 3.44 (1H, ddd, $J = 13.8$, 11.4, 6.3 Hz, H-9ax), 3.19–3.26 (1H, m, H-8eq), 2.78 (1H, dd, $J = 12.9$, 2.4 Hz, H-6eq), 2.64 (1H, dt, $J = 13.8$, 3.3 Hz, H-9eq), 2.54 (1H, td, $J = 11.4$, 3.3 Hz, H-8ax), 2.38 (3H, s, N–CH_3), 2.18 (1H, d, $J = 12.9$ Hz, H-6ax); δ_C (75 MHz, $CDCl_3$) 204.0, 159.9, 159.0, 136.4, 130.6, 129.2, 129.1, 127.3, 124.7, 114.9, 90.5, 61.7, 55.7, 55.6, 53.2, 46.0, 38.5.

*5.2.3. 4-(2-Chlorophenyl)-3-(4-chlorophenyl)-7-methyl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (**3c**)*

White solid; Yield: 0.23 g, 70%; m.p. 105–106 °C (Found: C, 61.79; H, 4.73; N, 7.27. $C_{20}H_{18}Cl_2N_2O_2$ requires C, 61.71; H, 4.66; N, 7.20); δ_H (300 MHz, $CDCl_3$); 6.97–7.49 (8H, m, Ar–H), 5.92 (1H, s, 4-CH), 3.29 (1H, ddd, $J = 14.1$, 11.7, 6.3 Hz, H-9ax), 3.05–3.12 (1H, m, H-8eq), 2.52–2.63 (2H, m, H-6eq and H-9eq), 2.41 (1H, td, $J = 11.4$, 3.3 Hz, H-8ax), 2.22 (3H, s, N–CH_3), 2.16 (1H, d, $J = 12.9$ Hz, H-6ax); δ_C (75 MHz, $CDCl_3$) 202.1, 158.4, 136.3, 133.8, 130.7, 130.5, 130.1, 129.6, 128.9, 128.6, 127.5, 126.2, 89.8, 60.4, 55.0, 49.6, 45.4, 37.8.

*5.2.4. 3-(4-Chlorophenyl)-4-(3-fluorophenyl)-7-methyl-1-oxa-2,7-diazaspiro[4.5]dec-2-en-10-one (**3d**)*

Viscous paste; Yield: 0.19 g, 55% (Found: C, 64.49; H, 4.81; N, 7.59. $C_{20}H_{18}ClFN_2O_2$ requires C, 64.43; H, 4.87; N, 7.51); δ_H (300 MHz, $CDCl_3$); 6.92–8.00 (8H, m, Ar–H), 4.45 (1H, s, 4-CH), 3.59 (1H, d, $J = 13.2$, Hz, H-9ax), 3.54 (1H, d, $J = 13.2$, Hz, H-9eq), 3.04–3.07 (2H, t, 5.7 Hz, 8-CH_2), 2.47 (3H, s, N–CH_3), 2.33–2.40 (2H, m, 6-CH_2); δ_C (75 MHz, $CDCl_3$) 203.3, 157.4, 137.9, 131.2, 129.9, 129.1, 128.5, 128.0, 124.6, 112.8, 90.2, 51.9, 44.2, 34.2.

*5.2.5. 3-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-7-methyl-1-oxa-2,7-diazaspiro[4.5]-dec-2-en-10-one (**3e**)*

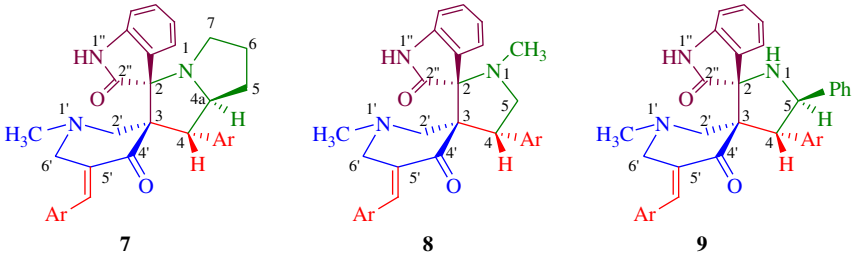
White solid; Yield 0.21 g, 67%; m.p. 146–147 °C (Found: C, 56.62; H, 4.12; N, 6.69. $C_{20}H_{17}Cl_3N_2O_2$ requires C, 56.69; H, 4.04; N, 6.61); δ_H (300 MHz, $CDCl_3$); 6.90–7.50 (7H, m, Ar–H), 5.86 (1H, s, 4-CH), 3.28 (1H, ddd, $J = 13.8$, 11.4, 6.0 Hz, H-9ax), 3.05–3.13 (1H, m, H-8eq), 2.60 (1H, dd, $J = 12.9$, 2.4 Hz, H-6eq), 2.55 (1H, dt, $J = 13.8$, 3.0 Hz, H-9eq), 2.49 (1H, td, $J = 11.4$, 3.3 Hz, H-8ax), 2.15 (3H, s, N–CH_3), 2.18 (1H, d, $J = 12.6$ Hz, H-6ax); δ_C (75 MHz, $CDCl_3$) 202.0, 158.2, 136.5, 135.0, 134.5, 131.4, 130.0, 129.5, 129.1, 128.5, 128.0, 126.0, 89.8, 60.4, 55.1, 49.2, 45.5, 37.8.

*5.3. General procedure for the synthesis of spiro[2.3″]oxindolespiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone-4-arylhexahydro-1H-pyrrolizine (**4a–e**)*

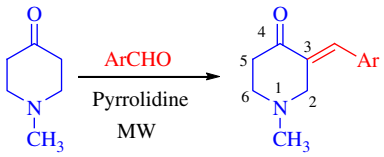
A mixture of 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone (**2**, 1 mmol), isatin (1 mmol) and proline (1 mmol) in methanol (15 mL) was refluxed for 10–15 min. After completion of the reaction (TLC), the mixture was poured into water (30 mL) and the precipitated **4** was filtered off and washed with water.

*5.3.1. Spiro[2.3″]oxindolespiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone-4-(4-methylphenyl)hexahydro-1H-pyrrolizine (**4a**)*

White solid; Yield: 0.18 g, 93%; m.p. 178–179 °C (Found: C, 75.10; H, 7.09; N, 10.17. $C_{26}H_{29}N_3O_2$ requires C, 75.15; H, 7.03; N, 10.11); δ_H



Scheme 1. Structure of compounds investigated for antimycobacterial activities previously.



1 2

Comp **2**	Ar	Irradiation time (min)	Yield (%)
a	*p*-MeC_6H_4	4	76
b	*p*-$MeOC_6H_4$	8	51
c	*o*-ClC_6H_4	6	54
d	*m*-FC_6H_4	5	63
e	*o,p*-$Cl_2C_6H_3$	7	50

Scheme 2. Synthesis of tetrahydro-4(1*H*)-pyridinones **2**.

(300 MHz, $CDCl_3$) 8.40 (1H, s, NH), 6.85–7.27 (8H, m, Ar), 4.48 (1H, dt, $J = 11.7$, 6.6 Hz, 4a-CH), 4.08 (1H, d, $J = 11.7$ Hz, 4-CH), 3.75 (1H, dd, $J = 12.3$, 2.7 Hz, H-2′eq), 2.82–2.90 (1H, m, 7-CH_2), 2.54–2.60 (2H, m, H-6′eq and 7-CH_2), 2.33 (3H, s, Ar–CH_3), 2.14 (3H, s, N–CH_3), 2.00–2.07 (1H, m, 5-CH_2), 1.88–1.99 (4H, m, 6-CH_2, 5′-CH_2 and H-6′ax), 1.63 (1H, d, 12.3 Hz, H-2′ax), 1.51–1.58 (2H, m, 5′-CH_2 and 5-CH_2); δ_C (75 MHz, $CDCl_3$) 207.2, 180.4, 141.3, 136.3, 134.1, 129.7, 129.2, 128.9, 127.8, 127.0, 121.6, 109.7, 73.5, 72.4, 65.9, 58.0, 54.0, 51.5, 47.6, 44.7, 40.9, 29.1, 26.3, 21.0.

*5.3.2. Spiro[2.3″]oxindolespiro-[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone-4-(4-methoxyphenyl)hexahydro-1H-pyrrolizine (**4b**)*

White solid; Yield: 0.17 g, 91%; m.p. 163–164 °C (Found: C, 72.31; H, 6.72; N, 9.79. $C_{26}H_{29}N_3O_3$ requires C, 72.37; H, 6.77; N, 9.74); δ_H (300 MHz, $CDCl_3$) 9.10 (1H, s, NH), 6.97–7.42 (8H, m, Ar), 4.61 (1H, dt, $J = 11.7$, 6.6 Hz, 4a-CH), 4.21 (1H, d, $J = 11.4$ Hz, 4-CH), 3.95 (3H, s, Ar–OCH_3), 3.90 (1H, dd, $J = 12.3$, 2.4 Hz, H-2′eq), 2.96–3.04 (1H, m, 7-CH_2), 2.68–2.76 (2H, m, H-6′eq and 7-CH_2), 2.28 (3H, s, N–CH_3), 2.14–2.24 (1H, m, 5-CH_2), 2.05–2.11 (4H, m, 6-CH_2, 5′-CH_2 and H-6′ax), 1.79 (1H, d, 12.3 Hz, H-2′ax), 1.64–1.73 (2H, m, 5′-CH_2 and 5-CH_2); δ_C (75 MHz, $CDCl_3$) 207.6, 181.4, 158.7, 141.9, 131.2, 129.7, 129.5, 128.2, 127.0, 122.0, 113.9, 110.3, 74.1, 72.8, 66.4, 58.3, 55.6, 54.5, 51.7, 48.2, 45.1, 41.4, 29.8, 26.8.

*5.3.3. Spiro[2.3″]oxindolespiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone-4-(2-chlorophenyl)hexahydro-1H-pyrrolizine (**4c**)*

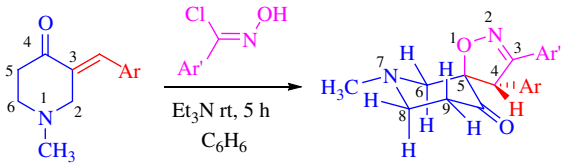
White solid; Yield: 0.16 g, 86%; m.p. 120–122 °C (Found: C, 68.82; H, 6.09; N, 9.57. $C_{25}H_{26}ClN_3O_2$ requires C, 68.88; H, 6.01; N, 9.64); δ_H (300 MHz, $CDCl_3$) 8.93 (1H, s, NH), 7.02–7.90 (8H, m, Ar), 4.85 (1H, d, $J = 10.2$ Hz, 4-CH), 4.65–4.73 (1H, m, 4a-CH), 3.73 (1H, d, $J = 12.1$ Hz, H-2′eq), 3.23–3.28 (1H, m, 7-CH_2), 2.55–2.74 (2H, m, H-6′eq and 7-CH_2), 2.18 (3H, s, N–CH_3), 1.91–2.23 (7H, m, 5-CH_2, 6, CH_2, 5′-CH_2, and H-6′ax) 1.85 (1H, d, 12.1 Hz, H-2′ax), 1.64–1.73 (2H, m, 5′-CH_2 and 5-CH_2); δ_C (75 MHz, $CDCl_3$) 207.5, 179.4, 141.7, 136.0, 135.7, 130.9, 129.9, 129.2, 127.8, 126.7, 126.2, 121.8, 109.9, 74.6, 70.4, 68.2, 59.7, 53.8, 49.3, 47.8, 45.2, 40.1, 28.6, 25.4.

*5.3.4. Spiro[2.3″]oxindolespiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone-4-(3-fluorophenyl)hexahydro-1H-pyrrolizine (**4d**)*

White solid; Yield: 0.18 g, 94%; m.p. 169–170 °C (Found: C, 71.67; H, 6.17; N, 9.95. $C_{25}H_{26}FN_3O_2$ requires C, 71.58; H, 6.25; N, 10.02); δ_H (300 MHz, $CDCl_3$) 8.82 (1H, s, NH), 6.88–7.27 (8H, m, Ar), 4.48 (1H, dt, $J = 11.4$, 6.6 Hz, 4a-CH), 4.11 (1H, d, $J = 11.4$ Hz, 4-CH), 3.75 (1H, d, $J = 12.3$ Hz, H-2′eq), 2.82–2.90 (1H, m, 7-CH_2), 2.54–2.60 (2H, m, H-6′eq and 7-CH_2), 2.14 (3H, s, N–CH_3), 2.03–2.09 (1H, m, 5-CH_2), 1.91–1.99 (4H, m, 6-CH_2, 5′-CH_2 and H-6′ax), 1.57 (1H, d, 12.3 Hz, H-2′ax), 1.47–1.52 (2H, m, 5′-CH_2 and 5-CH_2); δ_C (75 MHz, $CDCl_3$) 206.1, 179.5, 140.4, 139.0, 128.5, 128.4, 126.7, 125.5, 124.5, 120.7, 115.7, 112.7, 108.9, 72.3, 71.4, 64.7, 57.0, 53.1, 50.4, 46.6, 43.6, 39.8, 28.0, 25.3.

*5.3.5. Spiro[2.3″]oxindolespiro[3.3′]-1′-methyltetrahydro-4′(1H)-pyridinone-4-(2,4-dichlorophenyl)hexahydro-1H-pyrrolizine (**4e**)*

White solid; Yield: 0.16 g, 92%; m.p. 110–112 °C (Found: C, 63.74; H, 5.27; N, 8.97. $C_{25}H_{26}FN_3O_2$ requires C, 63.83; H, 5.36; N, 8.93); δ_H (300 MHz, $CDCl_3$); 8.42 (1H, s, NH), 7.00–7.74 (7H, m, Ar), 4.79 (1H, d, $J = 11.2$ Hz, 4-CH), 4.62–4.69 (1H, m, 4a-CH), 3.66 (1H, dd, $J = 12.3$, 2.4 Hz, H-2′eq), 2.61–2.76 (2H, m, H-6′eq and 7-CH_2), 2.22–2.30 (1H, m, 7-CH_2), 2.19 (3H, s, N–CH_3), 2.06–2.15 (1H, m, 5-CH_2), 1.83–2.03 (4H, m, 6-CH_2, 5′-CH_2 and H-6′ax), 1.80 (1H, d, 12.3 Hz, H-2′ax), 1.70–1.75 (2H, m, 5′-CH_2 and 5-CH_2); δ_C (75 MHz, $CDCl_3$) 207.4, 178.8, 141.6, 136.6, 134.5, 132.9, 131.7, 129.5, 129.3, 127.7, 126.2, 121.9, 109.8, 74.4, 70.2, 68.2, 59.8, 53.8, 48.9, 47.7, 45.2, 40.0, 28.5, 25.4.



2 3

Comp **3**[a]	Ar	Yield (%)
a	*p*-MeC_6H_4	73
b	*p*-$MeOC_6H_4$	63
c	*o*-ClC_6H_4	70
d	*m*-FC_6H_4	55
e	*o,p*-$Cl_2C_6H_3$	67

[a] Ar′=*p*-ClC_6H_4 in all cases

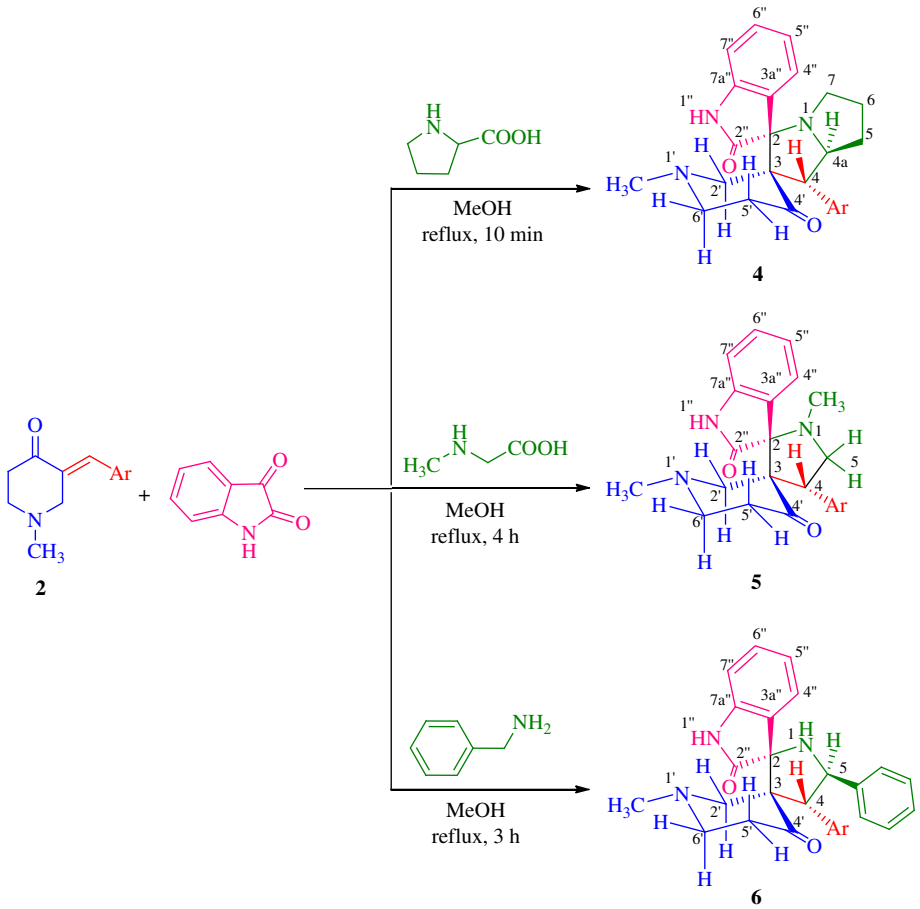
Scheme 3. Synthesis of spiro-isoxazolines **3**.

*5.4. General procedure for the synthesis of 1-methyl-4-arylpyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methylpiperidin-4′-ones (**5a–e**)*

A mixture of 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone (**2**, 1 mmol), isatin (1 mmol) and sarcosine (1 mmol) was refluxed in methanol (15 mL) for 4 h. After completion of the reaction (TLC), the mixture was poured into water (30 mL) and the precipitated **5** was filtered off and washed with water.

*5.4.1. 1-Methyl-4-(4-methylphenyl)pyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methylpiperidin-4′-one (**5a**)*

White solid; Yield: 0.29 g, 80%; m.p. 132–133 °C (Found: C, 74.12; H, 6.90; N, 10.72. $C_{24}H_{27}N_3O_2$ requires C, 74.01; H, 6.99; N, 10.79); δ_H (300 MHz, $CDCl_3$) 8.31 (1H, s, NH), 6.81–7.27 (8H, m, Ar), 4.63 (1H, dd, $J = 10.8$, 6.3 Hz, 4-CH), 3.79 (1H, t, $J = 10.8$ Hz, 5-CH_2), 3.48 (1H, dd, $J = 12.6$, 2.4 Hz, H-2′eq), 3.20 (1H, t, $J = 8.4$ Hz, 5-CH_2), 2.49 (1H, t, $J = 6.0$ Hz, H-6′eq), 2.31 (3H, s, 1-N–CH_3), 2.17 (3H, s, Ar–CH_3), 2.05 (3H, s, 1′-N–CH_3), 1.90–1.98 (1H, m, H-6′ax), 1.85 (1H, br s, 5′-CH_2), 1.40–1.46 (1H, m, 5′-CH_2) 1.36 (1H, d, $J = 12.6$ Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 207.4, 177.7, 141.4, 136.2, 135.1, 130.1, 129.2,



Comp	Ar	Yield (%)		
		4	**5**	**6**
a	*p*-MeC_6H_4	93	80	85
b	*p*-$MeOC_6H_4$	91	85	81
c	*o*-ClC_6H_4	86	92	80
d	*m*-FC_6H_4	94	94	86
e	*o,p*-$Cl_2C_6H_3$	92	85	80

Scheme 4. Synthesis of spiro-cycloadducts **4**–**6**.

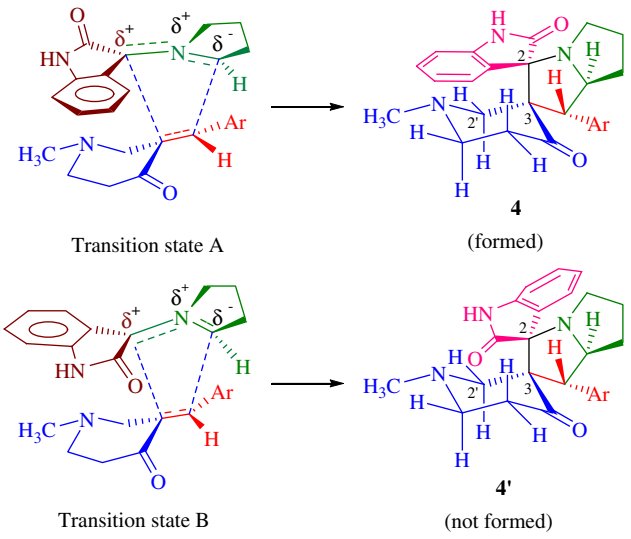
129.0, 128.8, 126.4, 122.4, 109.2, 74.2, 67.8, 59.4, 56.1, 54.3, 44.8, 44.1, 40.5, 34.9, 21.0.

*5.4.2. 1-Methyl-4-(4-methoxyphenyl)pyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methylpiperidin-4′-one (**5b**)*

White solid; Yield: 0.30 g, 85%; m.p. 139–141 °C (Found: C, 71.19; H, 6.80; N, 10.30. $C_{24}H_{27}N_3O_3$ requires C, 71.09; H, 6.71; N, 10.36); δ_H (300 MHz, $CDCl_3$) 8.35 (1H, s, NH), 6.96–7.42 (8H, m, Ar), 4.77 (1H, dd, $J = 11.1$, 6.6 Hz, 4-CH), 3.87–3.95 (4H, m, Ar–OCH_3 and 5-CH_2), 3.61 (1H, dd, $J = 12.6$, 2.4 Hz, H-2′eq), 3.35 (1H, dd, $J = 11.1$, 6.9 Hz, 5-CH_2), 2.64–2.70 (1H, m, H-6′eq), 2.32 (3H, s, 1-N–CH_3), 2.20 (3H, s, 1′-N–CH_3), 2.05–2.18 (1H, m, H-6′ax), 1.90 (1H, br s, 5′-CH_2), 1.55–1.63 (1H, m, 5′-CH_2), 1.49 (1H, d, $J = 12.6$ Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 207.9, 178.0, 158.7, 141.8, 130.7, 129.4, 126.8, 122.9, 113.9, 109.6, 74.6, 68.3, 59.9, 56.6, 55.6, 54.9, 45.3, 44.2, 41.0, 35.3.

*5.4.3. 1-Methyl-4-(2-chlorophenyl)pyrrolo(spiro[2.3″]oxindole)-spiro[3.3′]-1′-methylpiperidin-4′-one (**5c**)*

White solid; Yield: 0.32 g, 92%; m.p. 90–91 °C (Found: C, 67.33; H, 5.99; N, 10.20. $C_{23}H_{24}ClN_3O_2$ requires C, 67.39; H, 5.90; N, 10.25); δ_H (300 MHz, $CDCl_3$) 8.63 (1H, s, NH), 6.83–8.05 (8H, m, Ar), 5.04 (1H, dd, $J = 7.5$, 5.7 Hz, 4-CH), 3.54–3.59 (1H, m, 5-CH_2), 3.42–3.48 (1H, m, 5-CH_2), 3.10 (1H, dd, $J = 12.6$, 2.4 Hz, H-2′eq), 2.47–2.52 (1H, m, H-6′eq), 2.08 (3H, s, 1-N–CH_3), 2.00–2.05 (2H, m, 5′-CH_2 and



Scheme 5. Stereochemistry of cycloadducts differing in their relative configurations at C-2 and C-3.

H-6′ax), 1.94 (3H, s, 1′-N–CH_3), 1.46–1.66 (1H, m, 5′-CH_2), 1.44 (1H, d, J = 12.6 Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 206.7, 178.0, 141.5, 138.3, 135.2, 130.8, 129.7, 129.0, 127.8, 127.1, 126.9, 126.8, 122.1, 109.7, 75.4, 66.8, 60.0, 59.5, 53.9, 45.2, 40.9, 40.3, 35.2.

*5.4.4. 1-Methyl-4-(3-fluorophenyl)pyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**5d**)*

White solid; Yield: 0.34 g, 94%; m.p. 101–103 °C (Found: C, 70.30; H, 6.08; N, 10.62. $C_{23}H_{24}FN_3O_2$ requires C, 70.21; H, 6.15; N, 10.68); δ_H (300 MHz, $CDCl_3$) 8.25 (1H, s, NH), 6.82–7.28 (8H, m, Ar), 4.61 (1H, dd, J = 10.8, 6.6 Hz, 4-CH), 3.76 (1H, dd, J = 10.8, 9.0 Hz, 5-CH_2), 3.47 (1H, dd, J = 12.3, 2.7 Hz, H-2′eq), 3.22 (1H, dd, J = 8.7, 6.6 Hz, 5-CH_2), 2.49–2.59 (1H, m, H-6′eq), 2.17 (3H, s, 1-N–CH_3), 2.05 (3H, s, 1′-N–CH_3), 1.92–1.99 (1H, m, H-6′ax), 1.77 (1H, br s, 5′-CH_2), 1.41–1.49 (1H, m, 5′-CH_2), 1.32 (1H, d, J = 12.6 Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 207.2, 177.8, 141.2, 129.6, 129.4, 129.1, 128.7, 126.4, 125.0, 122.5, 116.1, 113.7, 109.3, 74.0, 67.8, 59.3, 55.8, 54.3, 44.8, 44.2, 40.4, 34.8.

*5.4.5. 1-Methyl-4-(2,4-dichlorophenyl)pyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**5e**)*

White solid; Yield: 0.28 g, 85%; m.p. 190–191 °C (Found: C, 62.10; H, 5.15; N, 9.56. $C_{23}H_{23}Cl_2N_3O_2$ requires C, 62.17; H, 5.22; N, 9.46); δ_H (300 MHz, $CDCl_3$) 8.78 (1H, s, NH), 6.85–8.08 (8H, m, Ar), 4.99 (1H, t, J = 6.3 Hz, 4-CH), 3.41–3.50 (2H, m, 5-CH_2), 3.10 (1H, dd, J = 12.3, 2.4 Hz, H-2′eq), 2.49–2.56 (1H, m, H-6′eq), 2.07 (3H, s, 1-N–CH_3), 2.02–2.14 (2H, m, 5′-CH_2 and H-6′ax), 1.98 (3H, s, 1′-N–CH_3), 1.56–1.64 (1H, m, 5′-CH_2), 1.43 (1H, d, J = 12.3 Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 206.9, 178.5, 141.8, 137.7, 136.2, 133.2, 132.2, 129.6, 129.1, 127.6, 127.5, 127.1, 122.6, 110.3, 75.6, 67.4, 60.5, 60.2, 54.4, 45.6, 40.9, 40.8, 35.6.

*5.5. General procedure for the synthesis of 4-aryl-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro [3.3′]-1′-methylpiperidin-4′-ones (**6a–e**)*

A mixture of 1-methyl-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**2**, 1 mmol), isatin (1 mmol) and benzylamine (1 mmol) was refluxed in methanol (15 mL) for 3 h. After completion of the reaction (TLC), the mixture was poured into water (30 mL) and the precipitated **6** was filtered off and washed with water.

*5.5.1. 4-(4-Methylphenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**6a**)*

White solid; Yield: 0.36 g, 85%; m.p. 105–107 °C (Found: C, 77.17; H, 6.42; N, 9.36. $C_{29}H_{29}N_3O_2$ requires C, 77.13; H, 6.47; N, 9.31); δ_H (300 MHz, $CDCl_3$) 8.33 (1H, s, NH), 6.99–7.48 (13H, m, Ar), 5.25 (1H, d, J = 11.7 Hz, 4-CH), 4.51 (1H, d, J = 11.7 Hz, 5-CH), 3.73 (1H, dd, J = 12.3, 2.7 Hz, H-2′eq), 2.55–2.60 (1H, m, H-6′eq), 2.26 (3H, s, Ar–CH_3), 2.15 (3H, s, N–CH_3), 1.93–2.06 (2H, m, H-6′ax and 5′-CH_2), 1.55 (1H, d, J = 12.3 Hz, H-2′ax), 1.38–1.50 (1H, m, 5′-CH_2); δ_C (75 MHz, $CDCl_3$) 206.9, 181.6, 140.7, 140.3, 136.1, 133.4, 130.9, 129.6, 129.1, 128.7, 128.2, 127.7, 125.9, 122.5, 109.4, 69.6, 68.5, 62.9, 58.8, 54.1, 54.0, 44.8, 40.6, 21.0.

*5.5.2. 4-(4-Methoxyphenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**6b**)*

White solid; Yield: 0.33 g, 81%; m.p. 96–98 °C (Found: C, 74.61; H, 6.13; N, 9.09. $C_{29}H_{29}N_3O_3$ requires C, 74.50; H, 6.25; N, 8.99); δ_H (300 MHz, $CDCl_3$) 8.17 (1H, s, NH), 6.73–7.46 (13H, m, Ar), 5.20 (1H, d, J = 11.7 Hz, 4-CH), 4.48 (1H, d, J = 11.7 Hz, 5-CH), 3.69–3.75 (4H, m, Ar–OCH_3 and H-2′eq), 2.54–2.59 (1H, m, H-6′eq), 2.14 (3H, s, N–CH_3), 1.92 2.02 (2H, m, H-6′ax and 5′-CH_2), 1.53 (1H, d, J = 12.3 Hz, H-2′ax), 1.38–1.49 (1H, m, 5′-CH_2); δ_C (75 MHz, $CDCl_3$) 207.0, 181.7, 158.2, 140.4, 130.9, 130.8, 129.8, 129.0, 128.4, 128.2, 127.7, 127.6, 125.9, 122.5, 113.4, 109.4, 69.5, 68.4, 63.0, 58.9, 55.0, 53.8, 44.8, 40.6.

*5.5.3. 4-(2-Chlorophenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**6c**)*

White solid; Yield: 0.32 g, 80%; m.p. 95–97 °C (Found: C, 71.33; H, 5.46; N, 8.99. $C_{28}H_{26}ClN_3O_2$ requires C, 71.25; H, 5.55; N, 8.90); δ_H (300 MHz, $CDCl_3$) 8.01 (1H, s, NH), 6.81–7.53 (13H, m, Ar), 5.46 (1H, d, J = 9.9 Hz, 5-CH), 5.10 (1H, d, J = 9.9 Hz, 4-CH), 3.23 (1H, d, J = 12.6 Hz, H-2′eq), 2.46–2.52 (1H, m, H-6′eq), 2.26 (1H, dd, J = 17.1, 4.8 Hz, 5′-CH_2), 2.09 (1H, td, J = 10.8, 5.1 Hz, H-6′ax), 1.99 (3H, s, N–CH_3), 1.77–1.89 (1H, m, 5′-CH_2), 1.65 (1H, d, J = 12.6 Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 207.7, 179.5, 141.3, 140.6, 136.0, 135.7, 130.8, 129.5, 129.2, 129.1, 128.4, 127.9, 127.7, 127.6, 126.5, 125.5, 122.6, 109.6, 72.8, 65.8, 65.3, 60.2, 53.8, 52.1, 45.8, 39.6.

*5.5.4. 4-(3-Fluorophenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**6d**)*

White solid; Yield: 0.36 g, 86%; m.p. 90–92 °C (Found: C, 73.91; H, 5.86; N, 9.29. $C_{28}H_{26}FN_3O_2$ requires C, 73.83; H, 5.75; N, 9.22); δ_H (300 MHz, $CDCl_3$) 8.12 (1H, s, NH), 6.82–7.48 (13H, m, Ar), 5.23 (1H, d, J = 11.6 Hz, 4-CH), 4.54 (1H, d, J = 11.6 Hz, 5-CH), 3.72 (1H, dd, J = 12.3, 2.7 Hz, H-2′eq), 2.56–2.62 (1H, m, H-6′eq), 2.15 (3H, s, N–CH_3), 1.92–2.06 (2H, m, H-6′ax and 5′-CH_2), 1.49 (1H, d, J = 12.3 Hz, H-2′ax), 1.39–1.46 (1H, m, 5′-CH_2); δ_C (75 MHz, $CDCl_3$) 206.7, 181.4, 140.6, 139.9, 139.2, 130.6, 129.5, 129.4, 129.3, 128.3, 127.8, 127.6, 125.9, 125.5, 122.6, 116.7, 113.7, 109.5, 69.4, 68.3, 62.8, 58.8, 54.1, 44.8, 40.5.

*5.5.5. 4-(2,4-Dichlorophenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (**6e**)*

White solid; Yield: 0.30 g, 80%; m.p. 124–125 °C (Found: C, 66.49; H, 4.89; N, 8.20. $C_{28}H_{25}Cl_2N_3O_2$ requires C, 66.41; H, 4.98; N, 8.30); δ_H (300 MHz, $CDCl_3$) 8.01 (1H, s, NH), 6.82–7.91 (12H, m, Ar), 5.39 (1H, d, J = 9.9 Hz, 5-CH), 5.06 (1H, d, J = 9.9 Hz,

4-CH), 3.21 (1H, dd, $J = 12.6$, 2.4 Hz, H-2′eq), 2.48–2.54 (1H, m, H-6′eq), 2.27 (1H, dd, $J = 16.8$, 4.5 Hz, 5′-CH_2), 2.11 (1H, td, $J = 10.8$, 4.8 Hz, H-6′ax), 2.00 (3H, s, N–CH_3), 1.79–1.91 (1H, m, 5′-CH_2), 1.64 (1H, d, $J = 12.6$ Hz, H-2′ax); δ_C (75 MHz, $CDCl_3$) 208.0, 179.8, 141.7, 140.8, 137.1, 134.9, 133.4, 132.1, 129.7, 129.3, 128.9, 128.3, 128.0, 127.2, 125.9, 123.1, 110.1, 73.2, 66.0, 65.8, 60.7, 54.2, 52.2, 46.2, 40.0.

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