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A facile 1,3-dipolar cycloaddition of azomethine ylides to 2-arylidene-1,3-indanediones: Synthesis of dispiro-oxindolylpyrrolothiazoles and their antimycobacterial evaluation

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ABSTRACT

A facile 1,3-dipolar cycloaddition of azomethine ylide generated in situ from the reaction of 1,3-thiazolane-4-carboxylic acid and isatin to 2-arylidene-1,3-indanediones furnished novel dispiro-oxindolylpyrrolothiazoles regio- and stereo-selectively in moderate to good yields (60–92%). In vitro antitubercular screening of 27 compounds against *Mycobacterium tuberculosis* H37Rv (MTB) disclosed that spiro[5.3′]-5′-nitrooxindolespiro-[6.3″]-1*H*-inden-1″,3″(2*H*)-dione-7-(4-bromophenyl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole has the maximum potency with a minimum inhibitory concentration (MIC) of 1.4 μM against MTB, being 3.4 and 5.4 times more potent than ciprofloxacin and ethambutol, respectively.

1,3-Dipolar cycloaddition reactions constitute a highly versatile and powerful tool for the construction of pharmacologically important five-membered ring heterocycles.[1] Spiro-oxindolyl nucleus represents an important part of many naturally occurring alkaloids,[2] such as coerulescine,[3] pteropodine,[4] formosanine,[5] rychnophyilline,[5] strychnofoline,[6] and alstonisine[7] with highly pronounced pharmacological properties (Fig. 1). Many spiro-oxindoles display a wide spectrum of biological activities such as antimicrobial,[8] inhibition of human NK-1 receptor[9] and potent non-peptide inhibition of the p53–MDM2 interaction.[10] Oxindole derivatives are also found to be potent aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol,[11] enzyme inhibitors or as ligands of G-protein coupled receptors,[12] HIV-1 protease inhibitors,[13] orally active non-peptide arginine-vasopressin receptor antagonists (SSR-149415), growth hormone secretagogue (ghrelin) receptor agonists[14] and AG-041R, a potent gastrin/CCK-B receptor antagonist.[15] 1,3-Indanediones display anti-inflammatory and anti-blood coagulation activities,[16] while pyrrolothiazoles show diverse biological activities, enabling their use as hepatoprotective,[17] antibiotic,[18] antidiabetic,[19] anticonvulsant,[20] anti-inflammatory,[21] antileukemic agents,[22] and in treatment for Alzheimer disease.[23]

The above biological importance led us recently to (i) synthesise hybrid spiro-heterocycles comprising oxindole, pyrrolidine, pyrrolothiazole, acenaphthylenone, piperidinone, indanone, and pyrrolizine[24] and (ii) disclose the antimycobacterial activities of many of these compounds, which are comparable to or even greater than some of the currently employed drugs for TB. This has provided the impetus for the present work on the synthesis and screening of a series of novel dispiro-oxindolylpyrrolothiazoles comprising indanedione, isatin and pyrrolothiazole rings (Scheme 1) in a bid to spot compounds with high antimycobacterial activity and report the results in this Letter. Incidentally, this study forms a part of our research programme initiated on the construction of novel heterocycles via domino and cycloaddition reactions[25] and to discover new lead molecules with antimycobacterial activities.[26]

This study derives importance as tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis* (MTB), has become a serious worldwide problem, infecting in synergy with human immunodeficiency virus (HIV) infection.[27] It is estimated that, about one third of the world's population is infected with this disease.[28] According to World Health Organization (WHO), approximately 8 million people are believed to have contracted TB annually with almost 2 million deaths.[29] In India alone, one person

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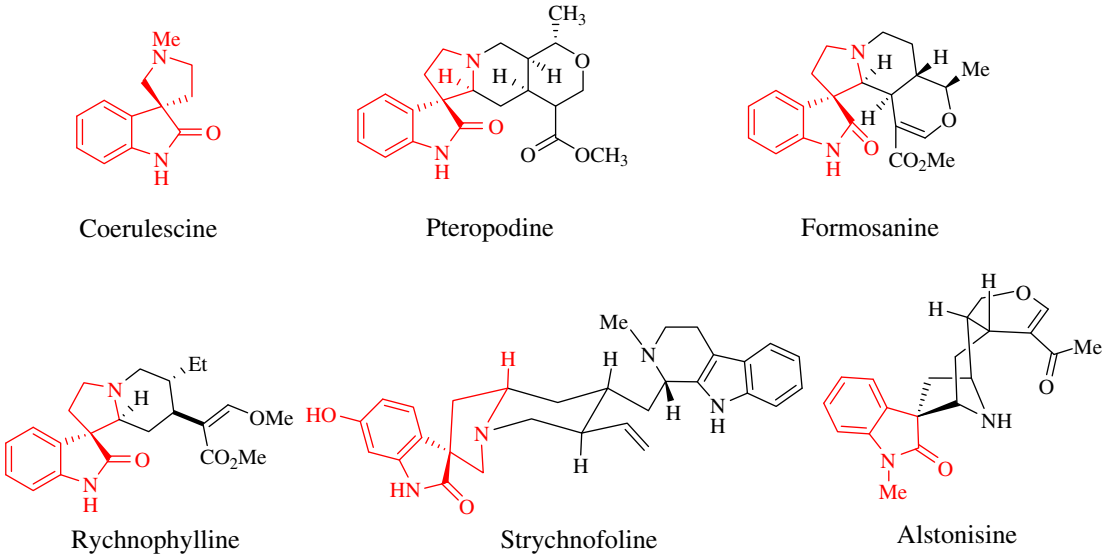
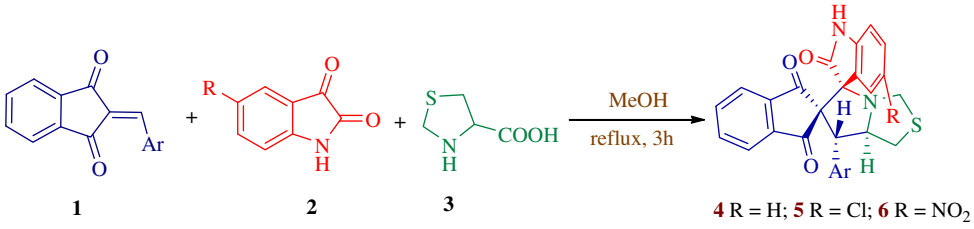


Figure 1. Representative naturally occurring spiro[pyrrolidine-3,3′-oxindole] alkaloids.



Scheme 1. Synthesis of dispiro-oxindolylpyrrolothiazoles **4**–**6**.

dies of TB every minute.[28] Currently, the recommended standard chemotherapeutic regimen for TB treatment prescribed under Directly Observed Treatment Short Course (DOTS) involves an initial 2 months treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol followed by treatment lasting 4 months with isoniazid and rifampicin.[30,31] Poor patient compliance, in general, promotes the emergence of drug resistance, and this is particularly true in TB chemotherapy.[31,32] The emergence of strains resistant to either of these drugs causes a major impediment in TB treatment, as it leaves only drugs that are far less effective and have more toxic side effects resulting in higher death rates, especially among HIV-infected persons. Serial selection of drug resistance, thus, is the predominant mechanism for the development of MDR strains; the patients with MDR strains constitute a pool of chronic infections, which propagate primary MDR resistance. Besides the accumulation of mutations in the individual drug target genes, the permeability barrier imposed by the MTB cell wall could also contribute to the development of low-level drug resistance.[32,33] Consequently, it is imperative to develop highly effective, fast acting and affordable anti-TB drugs possessing new mechanisms of action against both actively growing and latent infections with low toxicity profiles.[34]

In the present investigation, 2-arylidene-1,3-indanediones **1** readily reacted with non-stabilized ylides generated in situ by the decarboxylative condensation of isatin **2** with amino acid, 1,3-thiazolane-4-carboxylic acid **3**, to afford dispiro-oxindolylpyrrolothiazoles **4**–**6** (Scheme 1). Typically, an equimolar mixture of 2-arylidene-1,3-indanediones **1**, isatin **2** and 1,3-thiazolane-4-carboxylic acid **3** in methanol was heated under reflux for 3 h. After completion of the reaction (TLC) and workup, the product was obtained by column chromatographic purification to afford pure

Table 1
Yield, mp and antimycobacterial activity of dispiro-oxindolylpyrrolothiazoles **4**–**6**

Compd	Ar	R	Yield (%)[a]	Mp (°C)	MTB (MIC) (μM)
4a	C_6H_5	H	60	189	>55.2
4b	4-ClC_6H_4	H	62	210	25.7
4c	4-$Pr^iC_6H_4$	H	65	199	25.3
4d	4-$MeOC_6H_4$	H	88	192	>51.8
4e	2-MeC_6H_4	H	61	213	53.6
4f	2-ClC_6H_4	H	68	184	25.7
4g	2-BrC_6H_4	H	63	201	11.8
4h	3-$O_2NC_6H_4$	H	62	200	25.1
4i	3,4-$(MeO)_2C_6H_3$	H	70	178	>48.8
4j	3,4,5-$(MeO)_3C_6H_2$	H	75	185	>46.1
5a	C_6H_5	Cl	61	205	25.7
5b	4-ClC_6H_4	Cl	71	204	2.99
5c	4-$Pr^iC_6H_4$	Cl	62	196	11.8
5d	4-$MeOC_6H_4$	Cl	92	193	24.2
5e	2-ClC_6H_4	Cl	62	205	6.0
5f	2-BrC_6H_4	Cl	69	212	2.8
5g	3,4-$(MeO)_2C_6H_3$	Cl	82	191	22.9
5h	3,4,5-$(MeO)_3C_6H_2$	Cl	86	198	21.7
6a	C_6H_5	NO_2	61	213	12.6
6b	4-ClC_6H_4	NO_2	65	216	2.9
6c	4-BrC_6H_4	NO_2	69	208	1.4
6d	4-$MeOC_6H_4$	NO_2	74	194	11.9
6e	2-ClC_6H_4	NO_2	63	209	5.9
6f	3-FC_6H_4	NO_2	66	206	3.0
6g	3-BrC_6H_4	NO_2	63	207	2.7
6h	3,4-$(MeO)_2C_6H_3$	NO_2	85	213	11.2
6i	3,4,5-$(MeO)_3C_6H_2$	NO_2	72	208	10.6
Isoniazid					0.4
Rifampicin					0.1
Ciprofloxacin					4.7
Ethambutol					7.6

[a] Isolated yield after purification by column chromatography.

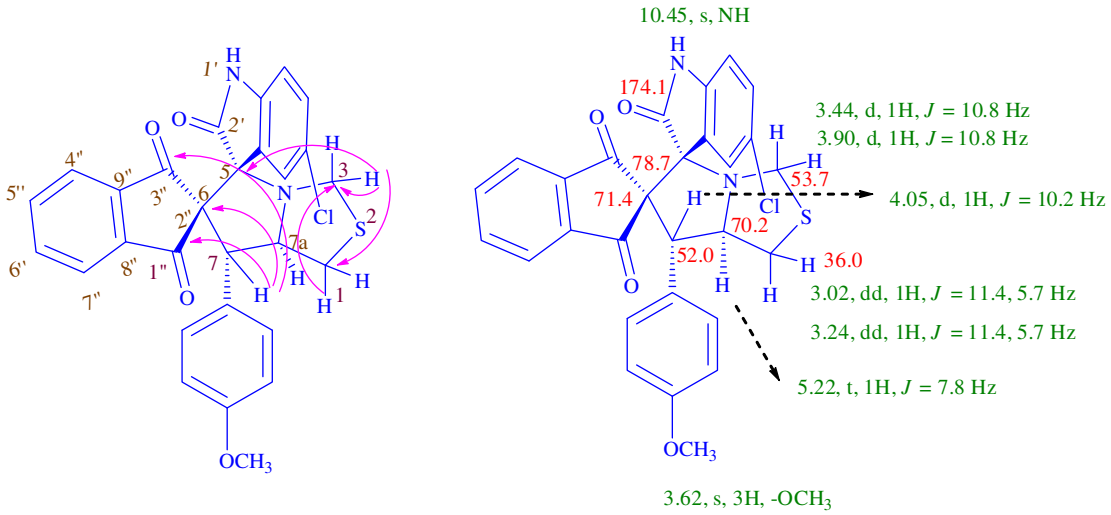


Figure 2. HMBCs and key NMR assignments in compound **5d**.

dispiro-oxindolylpyrrolothiazoles **4**–**6** in 60–92% yields[35] (Table 1). Neither starting materials nor any other characterizable product could be obtained from this reaction. A series of 27 dispiro-oxindolylpyrrolothiazoles has been synthesized by this protocol. This cycloaddition is regioselective with the electron rich carbon of the dipole adding to the β-carbon of the α,β-unsaturated moiety of **1** and stereoselective affording only one diastereomer exclusively, despite the presence of four stereocentres in the product as found in many similar cycloaddition studies.[24c,24f,26d]

The structure of dispiro-oxindolylpyrrolothiazoles **4**–**6** was elucidated using ^{1}H, ^{13}C and 2D NMR spectroscopic data as described for one example, **5d**. In the ^{1}H NMR spectrum of **5d**, the 1-CH_2 hydrogens appear as doublets of doublets at 3.02 and 3.24 ppm (J = 11.4 and 5.7 Hz) which are related by a H,H-COSY correlation. These hydrogens show a HMBC with C-3 at 53.7 ppm. The doublets at 3.44 and 3.90 ppm (J = 10.8 Hz), related by a H,H-COSY correlation and assignable to 3-CH_2 hydrogens, show HMBCs with C-1 at 36.0 ppm and C-5 at 78.7 ppm. The doublet at 4.05 ppm (J = 10.2 Hz) due to H-7 shows HMBCs (Fig. 2) with C-1 at 36.0 ppm, C-6 at 71.4 ppm and the carbonyl carbons, C-1″ and C-3″ at 194.5 and 194.9 ppm. The H-7a appears as a triplet at 5.22 ppm (J = 10.2 Hz), while the NH hydrogen gives a singlet at 10.5 ppm. The signals of proton bearing carbons, viz. C-1, C-3, C-7 and C-7a were assigned using the proton chemical shifts and C,H-COSY correlations. The structure of dispiro-oxindolylpyrrolothiazoles determined from X-ray crystallographic study[36] of single crystals of **4b** and **4d** confirm the structure deduced from NMR spectroscopic studies, besides unearthing the complete stereochemistry of the compounds. Thus the ORTEP diagrams of **4b** and **4d** (Figs. 3 and 4) show that both the aryl at C-7 and 1-CH_2 are in a *trans* relationship with respect to C7–C7a bond, probably in a bid to minimize steric interaction.

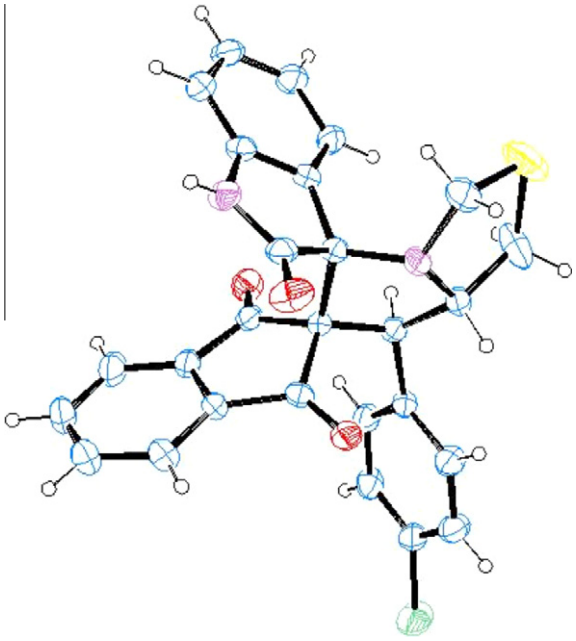


Figure 3. ORTEP diagram of **4b**.

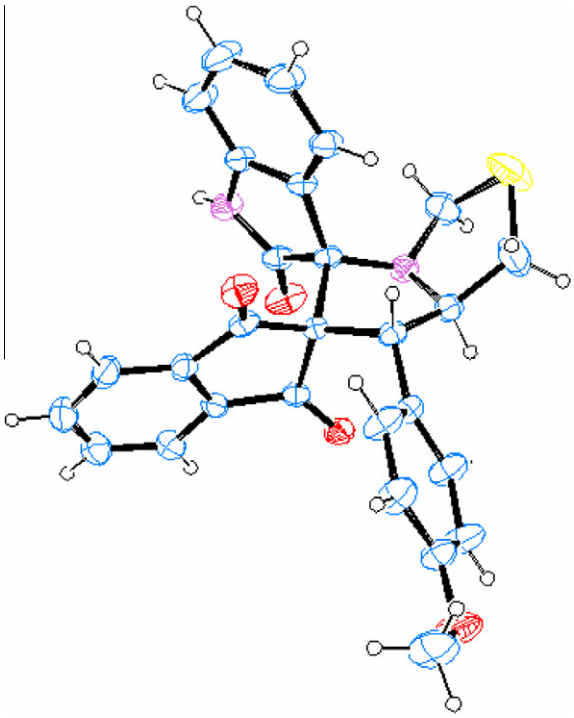


Figure 4. ORTEP diagram of **4d**.

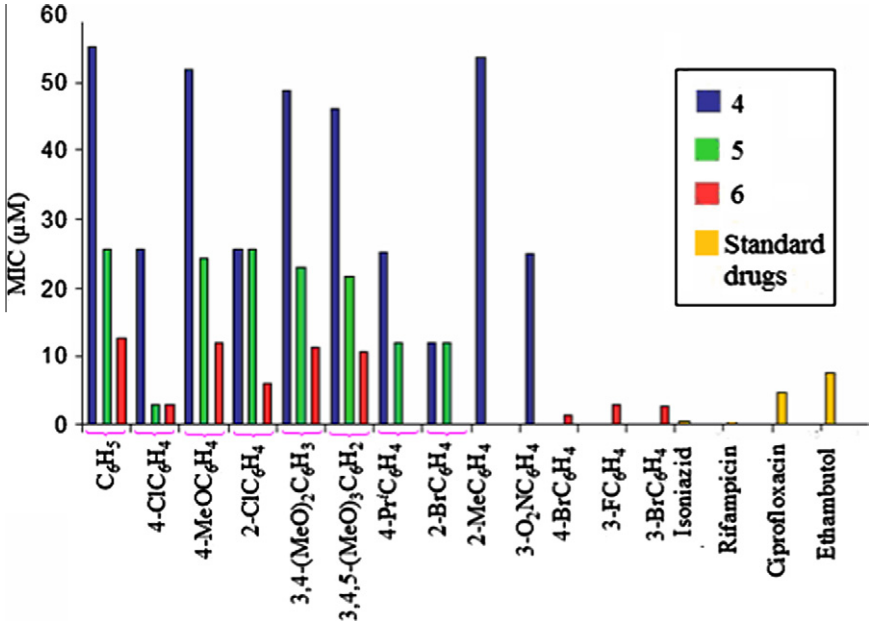


Figure 5. Comparison of MIC (μM) values of series **4**–**6** with standard drugs.

All the dispiro-oxindolylpyrrolothiazoles **4**–**6** synthesized in the present work have been screened for their in vitro activity against *M. tuberculosis* H37Rv (MTB) by agar dilution method for the determination of MIC in duplicate. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values of **4**–**6** along with the standard drugs for comparison are furnished in Table 1. The spiro heterocycles have MIC in the range of 1.4–55.2 μM (Table 1). Among them, eight compounds (**5b**, **5e**, **5f**, **6b**, **6c** and **6e**–**6g**) were more active against MTB than the first line anti-TB drug ethambutol (MIC 7.6 μM), whilst six of them **5b**, **5f**, **6b**, **6c**, **6f** and **6g** were more potent than ciprofloxacin (MIC 4.7 μM). All the compounds, however, were less potent than rifampicin and isoniazid. Spiro[5.3′]-5′-nitrooxindole-spiro-[6.3″]-1*H*-inden-1″,3″(2*H*)-dione-7-(4-bromo-phenyl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole (**6c**) displayed the maximum potency with MIC of 1.4 μM being 3.4 and 5.4 times more potent than ciprofloxacin and ethambutol respectively. It is pertinent to note that **6c** is twice active when compared to the activity of the most potent compound in a similar series of hybrid heterocycles comprising isatin, pyrrolothiazole and an indane ring with one carbonyl, viz. spiro[5.3′]-5′-nitrooxindolespiro-[6.3″]-2,3-dihydro-1*H*-inden-1″-one-7-(2,3-dichlorophenyl)-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole (MIC: 2.8 μM).[24f]

With respect to structure–MTB activity relationship, the data in Table 1 show that the substituents present in the isatin nucleus has a profound effect on the activity of dispiro-oxindolylpyrrolothiazoles, the order of activity, in general, being NO_2 > Cl > H (Fig. 5). Among the dispiro compounds bearing the nitro group (series **6**) and chlorine (series **5**) in the isatin nucleus, the presence of halogens, Br, F and Cl in the aryl ring enhanced the antimycobacterial activity as seen from the MIC values of **6c** (MIC: 1.4 μM), **6g** (MIC: 2.7 μM), **5f** (MIC: 2.8 μM), **6b** (MIC: 2.9 μM), **6f** (MIC: 3.0 μM) and **5b** (MIC: 3.0 μM) (Table 1).

In conclusion, the 1,3-dipolar cycloaddition of azomethine ylide generated in situ from substituted isatin and 1,3-thiazolane-4-carboxylic acid to 2-arylidene-1,3-indanediones afforded 27 new dispiro-oxindolylpyrrolothiazoles **4**–**6** regio- and stereoselectively in good yields. These dispiroheterocycles displayed good in vitro antimycobacterial activity against MTB.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.080.

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35. *General procedure for dispiro-oxindolylpyrrolothiazoles* (**4**–**6**):
A mixture of 2-arylidene-1,3-indanedione **1** (1 mmol), isatin **2** (1 mmol) and 1,3-thiazolane-4-carboxylic acid **3** (1 mmol) in methanol (10 mL) was heated under reflux on a water bath for 3 h. After completion of the reaction as evident from TLC, the mixture was poured into ice-water (50 mL) and the resulting solid was filtered off and purified by flash column chromatography on silica gel employing ethyl acetate/petroleum ether (1:1 v/v) as eluent to obtain pure product **4**–**6**. Spectroscopic data for compound **5d** is given below:
Spiro[5.3′]-5′-chlorooxindole-spiro-[6.3″]-1H-inden-1″,3″(2H)-dione-7-(4-methoxyphenyl)tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole (**5d**): Colorless solid; yield 92%; mp 193 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.02 (dd, 1H, J = 11.4, 5.7 Hz, H-1), 3.24 (dd, 1H, J = 11.4, 5.7 Hz, H-1), 3.44 (d, 1H, J = 10.8 Hz, H-3), 3.62 (s, 3H, OCH_3), 3.90 (d, 1H, J = 10.8 Hz, H-3), 4.05 (d, 1H, J = 10.2 Hz, H-7), 5.22 (t, 1H, J = 7.8 Hz, H-7a), 6.69 (d, 1H, J = 8.4 Hz, Ar-H), 6.76 (d, 2H, J = 8.7 Hz, Ar-H), 7.18 (d, 2H, J = 8.7 Hz, Ar-H), 7.33 (dd, 1H, J = 8.1, 2.1 Hz, Ar-H), 7.69 (d, 1H, J = 7.2 Hz, Ar-H), 7.76–7.89 (m, 3H, Ar-H), 7.97 (d, 1H, J = 1.8 Hz, Ar-H), 10.45 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 36.0, 52.0, 53.7, 54.8, 70.2, 71.4, 78.7, 111.0, 113.7, 122.7, 123.3, 124.5, 124.9, 126.0, 129.7, 130.1, 130.3, 136.0, 137.0, 140.3, 140.4, 142.2, 158.4, 174.1, 194.5, 194.9. Anal. Calcd for $C_{28}H_{21}ClN_2O_4S$: C, 65.05; H, 4.09; N, 5.42%. Found C, 65.12; H, 4.03; N, 5.49%.
36. Crystallographic data (excluding structure factors) for dispiro-oxindolylpyrrolo-thiazoles **4b** and **4d** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 783001 and 783000. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].