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A highly atom economic, chemo-, regio- and stereoselective synthesis and evaluation of spiro-pyrrolothiazoles as antitubercular agents

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ABSTRACT

The 1,3-dipolar cycloaddition of azomethine ylides derived from substituted isatins and 1,3-thiazolane-4-carboxylic acid to a series of 1-methyl-3,5-bis[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones afforded novel spiro-pyrrolothiazoles chemo-, regio- and stereoselectively in quantitative yields. These compounds were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB) using agar dilution method. Among the synthesized compounds, spiro[5.3′′]-5′′-nitrooxindole-spiro-[6.3′]-1′-methyl-5′-(2,4-di-chlorophenylmethylidene)-tetrahydro-4′(1*H*)-pyridinone-7-(2,4-dichlorophenyl)tetra-hydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazole (**9k**) was found to be the most active with a minimum inhibitory concentration (MIC) of 0.6 μM against MTB and MDR-TB.

Tuberculosis (TB) is mainly an illness of the respiratory system caused by *Mycobacterium tuberculosis* (MTB). About one-third of the world's population is infected with TB, among which annually about 8 million new cases and 3.1 million deaths are reported.[1–7] Since 1985 and particularly in the 1990s, a search for new antituberculosis substances has ranked among the priority areas of chemotherapeutic research[8] as (i) the current frontline therapy consists of administering three drugs (isoniazid, rifampin, and pyrazinamide) during an extended period of time[9] and (ii) the multi-drug resistant tuberculosis (MDR-TB) aggravates the problems. Further, HIV-infected patients have an elevated risk of primary or reactivated tuberculosis, and such active infectious process may enhance HIV replication and increase the risk of death. The World Health Organization (WHO) has estimated that, if the present trend continues, TB could claim more than 30 million lives between 2000 and 2020.[10] Thus, there is an urgent need for the development of potent new antituberculosis agents, having a unique mechanism of action different from that of the currently used antitubercular drugs, effective against both drug-susceptible and drug resistant strains of *M. tuberculosis* with low toxicity profiles and shortened therapy duration.[11]

Spiro compounds represent an important class of naturally occurring substances with highly pronounced biological properties.[12] 1,3-Dipolar cycloaddition, both inter- or intramolecular, of nonstabilised azomethine ylides to the olefinic dipolarophiles having an exocyclic bond provides a facile route for the synthesis of many spiroheterocycles comprising five membered nitrogen heterocycles.[13] Pyrrolo[2,1-*b*]thiazole is an unusual ring system with biological activity, viz. antineoplastic,[14] hypoglycemic,[15] modulators of dopaminergic neurotransmission in CNS in vivo[16] and as γ-lactam analogues of the penems.[17] Further, polyhydropyrrolo[2,1-*b*]thiazoles have interesting pharmacological properties and have been successfully employed as intermediates in the synthesis of pyrrolidines, such as racemic R-allokainic[18] and kainic acids[19] or 2*S*,4*R*-4-methylpyrrolidine-2,4-dicarboxylate.[20] Retrosynthetic analysis of polyhydropyrrolo[2,1-*b*]thiazoles shows the 1,3-dipolar addition of thiazolium ylides to alkenes as the most direct route for their preparation.

In our ongoing effort to discover novel antitubercular lead candidates,[21] we have recently reported the synthesis and antimicobacterial activity of spiro-pyrrolidines and pyrrolizines **3**–**5**[22] through 1,3-dipolar cycloaddition of azomethine ylides generated in situ from isatin **2** and α-amino acids viz. proline, phenylglycine, and sarcosine to a series of 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **1** (Fig. 1). These compounds **3**–**5** displayed excellent in vitro antimycobacterial activity against

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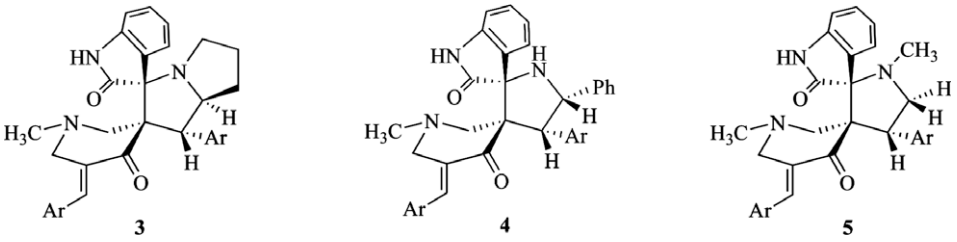


Figure 1.

M. tuberculosis (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB), wherein **4e** with *p*-F phenyl rings was found to be the most active in vitro with a MIC of 0.07 μM against MTB and were 5.1 and 67.2 times more potent than isoniazid and ciprofloxacin, respectively. The excellent antimycobacterial activity of spiro-pyrrolidines/pyrrolizines in conjunction with the biological potential of spiro-pyrrolothiazoles prompted us to undertake the synthesis of the spiro-pyrrolothiazoles with different substituents on the isatin nucleus and screen them for antimycobacterial activity with a view to discerning the structural dependence of antimycobacterial activity and report the results in this Letter.

Consequently, in the present work, azomethine ylides were generated in situ from the reaction of differently substituted isatins **2** with 1,3-thiazolane-4-carboxylic acid **6**, which underwent 1,3-dipolar cycloaddition with 1-methyl-3,5-bis[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones **1** to afford spiro-[5.3″]-oxindole-spiro-[6.3′]-1′-methyl-5′-arylmethylidene-tetrahydro-4′(1*H*)-pyridinone-7-aryltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]thiazoles **7–9** (Scheme 1).

These reactions were performed by heating an equimolar mixture of 1-methyl-3,5-bis[(*E*)-arylmethylidene]-tetrahydro-4(1*H*)-pyridinones **1**, substituted isatins **2** and 1,3-thiazolane-4-carboxylic acid **6** to reflux in methanol for one hour. After completion of the reaction (tlc), the reaction mixture was poured into ice-water, the resulting solid filtered and washed with water to afford pure spiro-pyrrolothiazoles **7–9**. These reactions afford solely the spiro-pyrrolothiazoles in near quantitative yields (Table 1) and hence neither crystallization nor column chromatographic purification is necessary. A total of thirty eight spiro-pyrrolothiazoles have been synthesized from this cycloaddition.

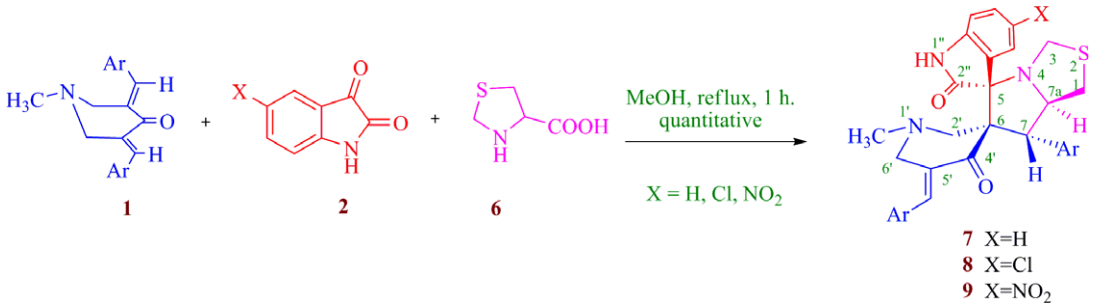
All the reactions proceed chemoselectively as the cycloaddition involves only one C=C bond of **1** furnishing exclusively the mono spiro-cycloadducts **7–9**. This reaction is regioselective with the addition of the electron rich carbon of the dipole to the β carbon of **1** and stereoselective affording only one diastereomer in excellent yields, *albeit* four stereocentres are present in these cycloadducts. The atom economy of the reaction is also very high, viz. 89–90% as water and carbon dioxide alone are generated as waste.

Table 1
Yield and mp of spiro-pyrrolothiazoles **7–9**

Entry	Compd **7–9**	Ar	Yield (%)			mp (°C)		
			7	**8**	**9**	**7**	**8**	**9**
1	**a**	C_6H_5	95	96	98	216	222	236
2	**b**	4-ClC_6H_4	97	98	97	161	235	229
3	**c**	4-MeC_6H_4	98	97	96	219	231	225
4	**d**	4-$MeOC_6H_4$	96	96	95	202	203	219
5	**e**	4-FC_6H_4	97	97	97	129	228	234
6	**f**	4-BrC_6H_4	96	95	96	207	238	222
7	**g**	4-$Pr^iC_6H_4$	96	98	—[a]	223	214	—
8	**h**	2-ClC_6H_4	95	98	97	219	223	207
9	**i**	2-MeC_6H_4	96	97	98	227	221	215
10	**j**	2-$MeOC_6H_4$	97	96	98	205	199	231
11	**k**	2,4-$Cl_2C_6H_3$	98	96	96	223	225	218
12	**l**	2,4-$(MeO)_2C_6H_3$	95	95	96	197	209	221
13	**m**	2-Thienyl	95	96	96	210	231	219

[a] Reaction failed to occur.

The structure of spiro-pyrrolothiazoles **7–9** was elucidated with the help of ^1H, ^{13}C and 2D NMR spectroscopic data as illustrated for **7b**. In the ^1H NMR spectrum of **7b** (Fig. 2) the H-7 appears as a doublet at 4.40 ppm (J = 10.2 Hz) which has a *H,H*-COSY correlation with a multiplet (H-7a) at 4.60–4.68 ppm. Further, H-7 shows HMBCs (Fig. 3) with the carbonyl carbon, C-4′ at 197.2 ppm, spiro carbon, C-6 at 71.5 ppm and C-1 at 33.5 ppm. The 1-CH_2 hydrogens appear as doublets of doublets at 2.78 ppm (J = 10.0, 6.9 Hz) and 3.00 ppm (J = 10.0, 5.6 Hz), respectively. The 3-CH_2 hydrogens appear as a 1H multiplet at 3.45–3.55 ppm and 1H doublet at 3.70 ppm (J = 6.9 Hz) and they show HMBCs with C-7a and oxindole spiro carbon, C-5 at 68.8 and 72.3 ppm, respectively. The doublet at 1.76 ppm (J = 12.3 Hz) and the multiplet at 3.45–3.55 ppm are assigned to 2′-CH_2 hydrogens, while the doublet at 3.37 ppm (J = 14.1 Hz) and the doublet of doublets at 2.86 ppm (J = 14.1, 2.7 Hz) are assigned to the 6′-CH_2 hydrogens on the basis of HMBCs. The singlets at 8.31 and 2.07 ppm are due to the NH of oxindole ring and the N–CH_3 hydrogens. The structure determined from an X-ray crystallographic study of the single crystal of **7b** is in accord with the structure deduced from NMR spectroscopic data (Figs. 4 and 5).[23]



Scheme 1. Synthesis of spiro-pyrrolothiazoles.

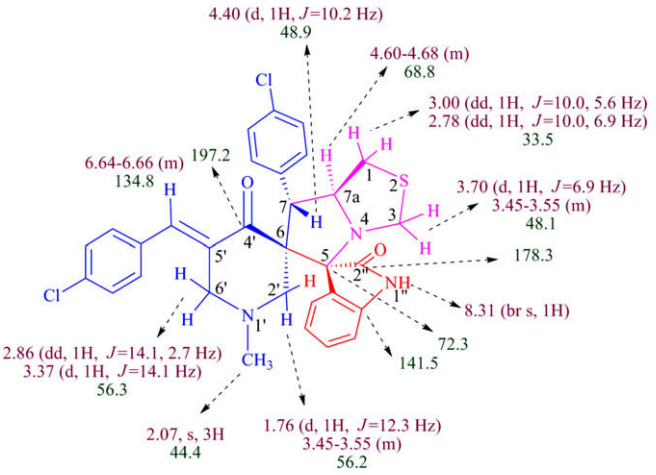


Figure 2. Selected ^{1}H and ^{13}C NMR chemical shifts of **7b**.

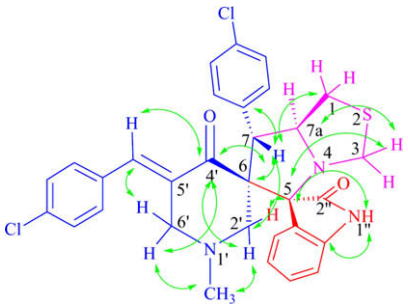


Figure 3. Selected HMBCs in **7b**.

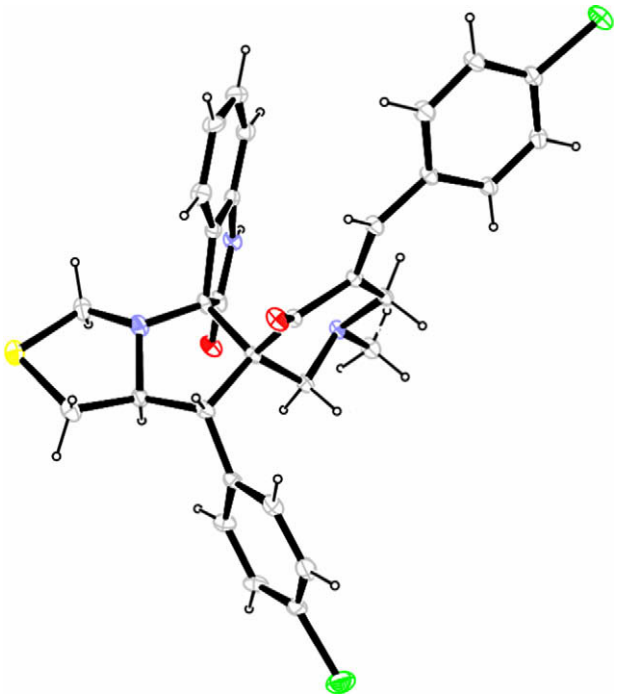


Figure 4. X-ray structure of **7b**.

The compounds were screened for their in vitro antimycobacterial activity against MTB and MDR-TB by agar dilution method for the determination of MIC in duplicates. The MDR-TB clinical isolate

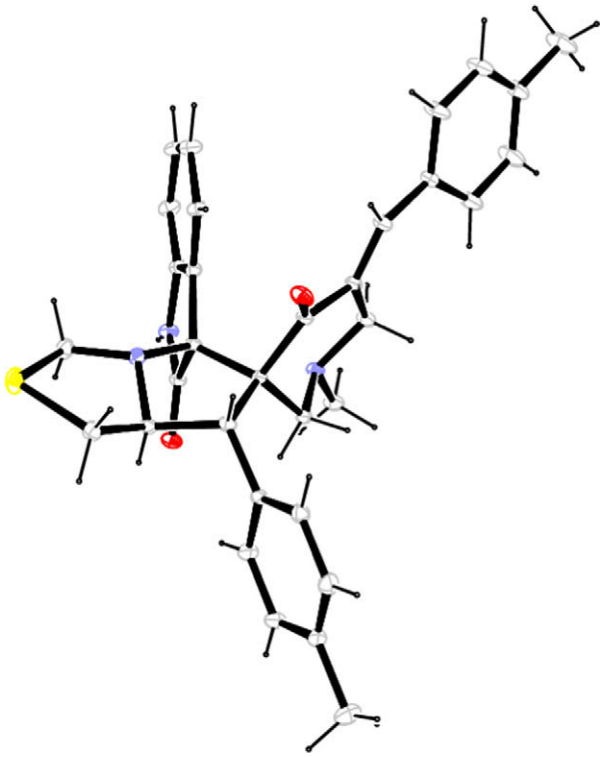


Figure 5. X-ray structure of **7c**.

was resistant to rifampicin (RIF), isoniazid (INH) ethambutol and pyrazinamide (PZA). The minimum inhibitory concentrations (MIC) of **7**–**9** and the first line standard drugs are reported in Table 2.

In the first phase of screening, all the compounds, except **7a**, showed excellent in vitro activity against MTB with a MIC of

Table 2
Minimum inhibitory concentrations (μM) of spiro-pyrrolothiazoles **7**–**9** against mycobacterial species[a]

Compd **7**–**9**	MIC (μM)				
	MTB			MDR-TB[b]	
	7	**8**	**9**	**8**	**9**
a	49.2	23.1	5.6	—	—
b	5.4	5.1	1.3	—	
c	23.3	11.0	5.3	—	—
d	22.0	20.8	10.3	—	—
e	5.7	2.8	1.4	2.8	1.4
f	4.7	4.4	1.1	—	2.3
g	10.6	10.1	—[c]	—	—[c]
h	10.9	5.1	2.6	—	2.6
i	23.3	11.0	5.3	—	—
j	22.0	20.8	5.1	—	—
k	4.7	1.2	0.6	2.4	0.6
l	19.9	18.9	9.4	—	—
m	12.1	11.4	5.5	—	—
Rifampicin	0.1			3.8	
Isoniazid	0.4			11.4	
Ethambutol	7.6			61.2	
Pyrazinamide	50.8			406.1	

[a] MTB: *Mycobacterium tuberculosis*; MDR-TB: multi-drug resistant *Mycobacterium tuberculosis*.
[b] Compounds **4** not screened against MDR-TB, as they showed lower activity against MTB.
[c] Reaction failed and the compound could not be synthesised.

⩽23.3 μM and were more potent than the standard pyrazinamide (MIC: 50.8 μM). Nineteen compounds (**7b**–**9b**, **7e**–**9e**, **7f**–**9f**, **7k**–**9k**, **8h**, **9a**, **9c**, **9h**–**j** and **9m**) inhibited MTB with a MIC of less than 5.7 μM and were more active than the ethambutol (MIC: 7.6 μM). Among thirty eight compounds screened against MTB, spiro[5.3″]-5″-nitrooxindole-spiro-[6.3′]-1′-methyl-5′-(2,4-dichlorophenylmethyli-dene)-tetrahydro-4′(1*H*)-pyridinone-7-(2,4-dichlorophenyl)tetrahydro-1*H*-pyrrolo-[1,2-*c*][1,3]thiazole (**9k**) was found to be the most active in vitro with MIC of 0.6 μM against MTB, being 13 and 85 times more potent than ethambutol and pyrazinamide, respectively. All the compounds, however, showed lower activity than rifampicin and isoniazid (MIC: 0.1 μM and 0.4 μM, respectively).

Subsequently, six compounds (**8e**, **8k**, **9e**, **9f**, **9h** and **9k**) that displayed maximum activity against MTB were evaluated against MDR-TB. All these inhibited MDR-TB with MIC ranging from 0.6 to 2.8 μM and were found to be more active than all the currently available first line anti-TB drugs, viz. rifampicin (MIC: 3.8 μM), isoniazid (MIC: 11.4 μM), ethambutol (MIC: 61.2 μM) and pyrazinamide (MIC: 406.1 μM). The compound, spiro[5.3″]-5″-nitrooxindole-spiro-[6.3′]-1′-methyl-5′-(2,4-dichlorophenyl-methylidene)-tetrahydro-4′(1*H*)-pyridinone-7-(2,4-dichlorophenyl)tetrahydro-1*H*-pyrrolo-[1,2-*c*][1,3]-thiazole (**9k**) again emerged to be the most active one in vitro with a MIC of 0.6 μM against MDR-TB, as in the case of MTB, being more potent than the first line anti-TB drugs, rifampicin (6 times), isoniazid (19 times), ethambutol (102 times) and pyrazinamide (677 times).

With respect to structure-MTB activity relationship, the results demonstrated that the antimycobacterial activity of the spiro-pyrrolothiazoles diminish in the order: **9** > **8** > **7** as evident from the fact that ten compounds in series **9** (**9a**–**c**, **9e**, **9f**, **9h**–**k** and **9m**), five in series **8** (**8b**, **8e**, **8f**, **8h** and **8k**), and four in series **7** (**7b**, **7e**, **7f** and **7k**) were more active against MTB than ethambutol (Table 2). Among the compounds from the series **7**–**9**, compounds **7f** and **7k** (MIC: 4.7 μM), **8k** (MIC: 1.2 μM), and **9k** (MIC: 0.6 μM) were found to be the most active ones. These results demonstrate that the spiro-pyrrolothiazoles with chlorine at 5″-position of the isatin sub-structure is more active than the unsubstituted isatin nucleus, while the presence of a nitro group at 5″-position conferred maximum activity. Similarly, the presence of two chlorines in the phenyl rings also enhances the activity.

It is pertinent to note that spiro-pyrrolothiazoles of the present study having unsubstituted isatin sub-structure and aryl rings with chlorine at the *para* position (**7b**, 5.4 μM) and two chlorines at *ortho* and *para* positions (**7k**, 4.7 μM) showed better activity than the previously reported structurally analogous spiro-pyrrolizines[22] with *p*-Cl (**3b**, 22.73 μM) and *o*,*p*-Cl_2 (**3j**, 19.94 μM) substituents, which differ from the spiro-pyrrolothiazoles only by the absence of a sulfur atom. This clearly shows that the sulfur atom of the spiro-pyrrolothiazoles enhances the activity by about ∼4 times. Similarly, spiro-pyrrolothiazoles, **8** and **9**, respectively, with chloro- and nitro-substitutions in the isatin ring led to further enhancement of the activity relative to the compounds with unsubstituted isatin ring of spiro-pyrrolizines **3**, bearing similar substituents in the aryl rings.

In conclusion, the 1,3-dipolar cycloaddition of azomethine ylide generated in situ from substituted isatin and 1,3-thiazolane-4-carboxylic acid to 1-methyl-3,5-bis[(*E*)-arylmethyli-dene]tetrahydro-4(1*H*)-pyridinones afforded thirty eight spiro-pyrrolothiazoles **7**–**9** in near quantitative yields. These spiroheterocycles displayed good in vitro antimycobacterial activity against MTB and MDR-TB. The antimycobacterial potency of these spiro heterocycles renders them valid leads for synthesizing new heterocycles endowed with enhanced activity.

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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.2009.10.107.

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23. Crystallographic data (excluding structure factors) for spiro-pyrrolothiazoles **7b** and **7c** in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 697774 and 745157. 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].