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A regio- and stereoselective 1,3-dipolar cycloaddition for the synthesis of new-fangled dispiropyrrolothiazoles as antimycobacterial agents

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ABSTRACT

A series of dispiropyrrolothiazoles compounds were synthesized using 1,3-dipolar cycloaddition and were screened for antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ and INH resistant *M. tuberculosis* strains. Two of them were showing good activity with MIC of less than 1 μM. Compound (**5f**) was found to be the most active with MIC of 0.210 and 8.312 μM respectively.

Over the last century, tuberculosis (TB) has killed more than 100 million people and this has continued relatively unchanged over the last 50 years, despite the development of effective antituberculous drugs. TB disproportionally affecting the world's poorest populations, and remains one of the major public health problems in the 21st century.[1] TB drug development has made substantial progress in the past decade.[2] TB continues to affect the young and the middle-aged adults faster than any other disease apart from AIDS. In 2007, about 13.7 million prevalent cases of with 1.3 million deaths were reported and 0.5 million cases of multidrug-resistant (MDR-TB) among HIV negative incident cases of TB were reported. Today, TB remains one of the leading infectious disease around the world. the emerging drug-resistant strains of the disease are presenting a new challenge in the ever changing battle to control and prevent TB.[2] The spread of Multidrug-resistant tuberculosis (MDR-TB) and the appearance of extensively drug-resistant tuberculosis (XDR-TB) pose new challenges for the control of fatal tuberculosis. So it is vital that new, reasonable and nontoxic drugs to be developed, which act by different mechanism from those of existing drugs. Such drugs would greatly tackle resistance emergency.[3]

The next threat for tuberculosis is the emergence of drug resistant strains of *Mycobacterium tuberculosis*. The antituberculosis drugs that are currently utilized in the treatment are associated with severe toxicity and adverse effects. In spite of toxicity on repeated dosing of isoniazid (INH) is still considered to be a first line drug in the chemotherapy of tuberculosis.[4]

Spiro compounds especially are known for their antimycobacterial properties and many of them have shown comparable or even better activities than some of the first-line TB drugs.[5,6] Hence, our group has synthesized and evaluated a series of novel five and six-membered heterocyles using various technique in the purpose to obtain novel and more potent antimycobacterial agents.[7–13] As part of the ongoing our research program to synthesis the novel five-membered heterocyclic derivatives and were screened for antimycobacterial activity against *Mycobacterium tuberculosis H37Rv* (MTB) and INH resistant *Mycobacterium tuberculosis* (INHR-MTB) (Schemes 1 and 2).

Herein we report the synthesis of indanone substituted dispiropyrrolothiazoles through [3+2]-cycloaddition reaction of azomethine ylide generated in situ from 1-morpholinoindoline-2, 3-dione and thiazoline-4-carboxylic acid to arylmethylideneindanones. The synthesized compounds were screened for their antimycobacterial activity and the results are presented in this Letter.

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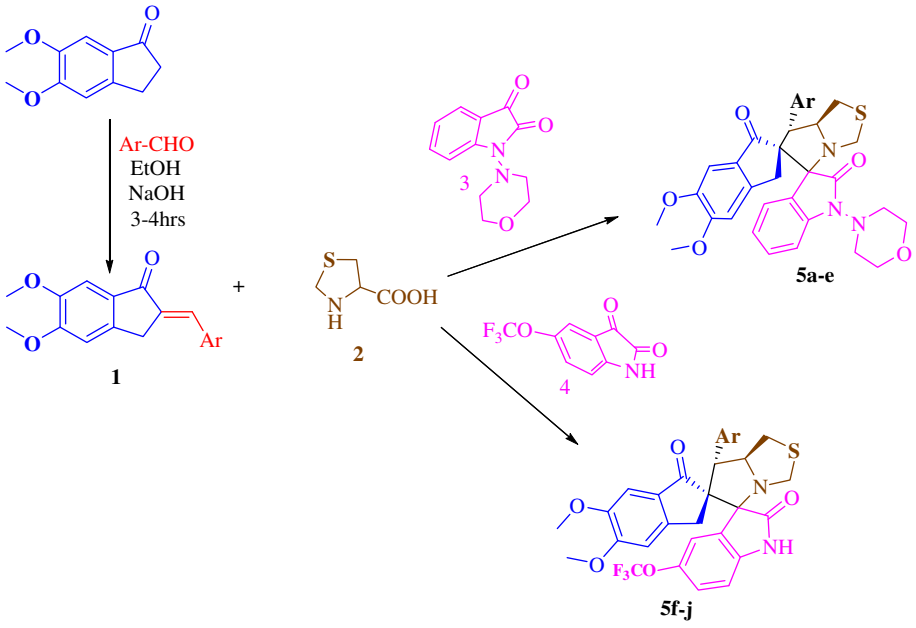
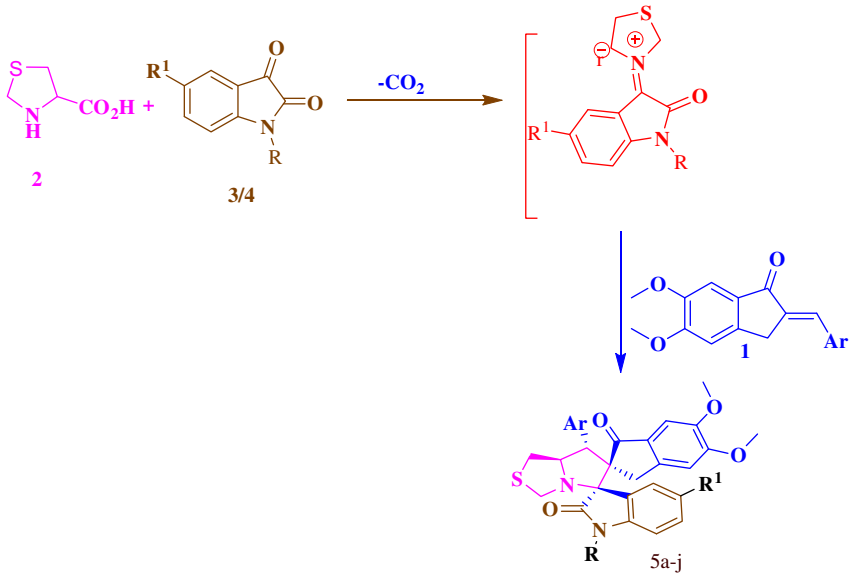


Scheme 1. Protocol for synthesis of titled compounds.

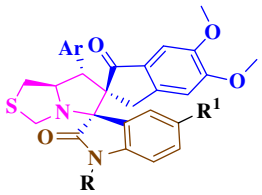


Scheme 2. Plausible mechanism for the regioselective formation of compounds **5a–j**.

The reactions were initially performed by heating an equimolar mixture of the starting materials under reflux in methanol and were subsequently investigated under microwave irradiation in a focused microwave synthesizer, as this technique has evolved as a valuable alternative to conventional heating for the introduction of energy into reactions and has clear benefits in many chemical transformations, including cycloadditions, in terms of rate accelerations and yield enhancements. As in the case of the thermal reactions, an equimolar mixture of the starting materials **1**–**3/4** in methanol was subjected to microwave irradiation[14–26] for 4–8 min until completion of the reaction (TLC) and the pyrrolothiazole derivatives purified by crystallization. The results obtained for both methods are summarized in (Table 1), and they clearly show that microwave irradiation lead to an enhancement in the yield of the product (88–92%) over the conventional thermal method (66–72%). This cycloaddition proceeds regioselectively with the electron rich carbon of the dipole adding to the β-carbon of the α,β-unsaturated moiety of **1** and stereoselectively affording only one diastereomer exclusively, despite the presence of four stereocentres in the product.

The structure of the newly synthesized dispiropyrrolothiazoles were elucidated using NMR, CHN and mass spectrometry. All the analytical and spectral data showed that the synthesized compounds were in full agreement with the proposed structures. In the ^{1}H NMR spectrum, the signals of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. ^{1}H NMR spectrum of **5e** showed a multiplet in the region δ 0.85–0.91 ppm corresponding to morpholino CH_2 groups; a doublets at 2.98, 3.03 ppm with (J = 11.4 Hz, 3.6 Hz) is due to H-3 protons. The doublets 3.20, 3.28 ppm (J = 6.6, 6.9 Hz) is due to each H-1 protons and the doublet at 3.75, 3.93 ppm (J = 21.3 Hz, 1.2) is due

Table 1
Comparison of the reaction time, yields for thermal and microwave-assisted [3+2]-cycloaddition reactions and antimycobacterial activity of pyrrolidine derivatives **5a–j**



Compd	Ar	R	R^1	Conventional method (MeOH, reflux)		Microwave irradiation (100 °C,100 W)		(MIC) μM MTB[a]	(MIC) μM MTB[b]	Cytotoxicity (μg/mL)
				Time (h) Yield (%)	Yield (%)	Time (min)	Yield (%)			
5a	Pyridyl–	Morpholino	H	6	72	5	91	2.419	26.219	>62.5
5b	4-Fluorophenyl–	Morpholino	H	4.5	66	7	92	8.121	35.121	>62.5
5c	3,4-Dimethoxyphenyl–	Morpholino	H	4.5	70	6	90	21.195	24.195	>62.5
5d	Phenyl–	Morpholino	H	3.5	72	5	87	>6.25	>6.25	>62.5
5e	2-Chlorophenyl–	Morpholino	H	2.5	68	8	88	6.295	18.295	>62.5
5f	Pyridyl–	H	OCF_3	4.0	67	4	92	0.210	8.312	>62.5
5g	4-Fluorophenyl–	H	OCF_3	3.0	68	5	88	0.720	16.638	>62.5
5h	3,4-Dimethoxyphenyl–	H	OCF_3	3.5	72	5	86	12.21	22.214	>62.5
5i	Phenyl–	H	OCF_3	2.5	70	4	92	>6.25	>6.25	>62.5
5j	2-Chlorophenyl–	H	OCF_3	4.0	66	4.5	90	11.415	36.415	>62.5
Isoniazid	—	—	—	—	—	—	—	0.730	11.23	>62.5

[a] *Mycobacterium tuberculosis* $H_{37}R_v$.
[b] INH resistant *Mycobacterium tuberculosis*.

one proton each of H-3″CH_2 proton, singlet at 3.84, 3.86 ppm due to OCH_3 proton, while the other protons of multiplet at 4.81 ppm H-7a proton, doublets at 4.01 ppm due to H-7 proton respectively. The aromatic protons appear doublets at around 6.6, 6.8 and 7.9 (J = 5.7 Hz, J = 3.3 Hz and 7.5 Hz) and muliplets at 7.11–7.35 ppm.

The synthesized compounds **5a–j** was tested for their antimycobacterial activity in vitro against *Mycobacterium tuberculosis* (MTB-$H_{37}Rv$) and INHR-MTB using agar dilution method[27] for the determination of minimum inhibitory concentration (MIC). The MIC was defined as the minimum concentration of compound required to inhibit 90% of bacterial growth and MIC's of the compounds were reported in (Table 1) with standard drug INH for comparison. Among the ten newly synthesized compounds, compound **5f** produced highest worth and exhibited >90% inhibition against MTB at a concentration of 0.210 μM and against INHR-MTB 8.312 μM, followed by **5g**, **5a**, and **5e** showing moderate inhibitory activity at 0.720, 2.419, 6.295 μM, against INHR-MTB 13.638, 15.121 and 18.295 μM and respectively. The pyridine group substitution (**5f**) derivatives displayed relatively higher inhibitory activity in general. However the electron rich group such as chloro, flouro substituted analogues produced potent inhibitory against both tested strains. On the other hand the analogue dimethoxy substituted phenyl (**5c**), (**5h**) and phenyl substituted groups (**5d**) and (**5i**) showed relatively moderate to low antitubercular activity. These reports clearly showed 4-trifluorometoxy substituted analogue with pyridyl substitution causes remarkable improvement in antimycobacterial activity higher inhibitory activity against both tested organisms instead of N-substituted morpholino analogues.

All the compounds were tested for cytotoxicity (IC_{50}) in VERO cells at concentrations of 62.5 μg/mL or 10 times. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation method. Most of the active compounds were found to be nontoxic till 62.5 μg/mL.

In conclusion, we have synthesised successfully a series of indanone substituted dispiropyrrolothiazole derivatives in good yield under microwave irradiation, as this method was found to be synthetically useful in achieving high yields of the products with reduced reaction time compared to conventional heating. Among the newer derivatives, compounds **5f** exhibited good activity against MTB and INHR-MTB. It is conceivable that derivatives showing antimycobacterial activity can be further modified to exhibit better potency than standard drugs. Further studies to acquire more information about quantitative structure–activity relationships (QSAR) are in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.059.

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