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Design of novel dispirooxindolopyrrolidine and dispirooxindolopyrrolothiazole derivatives as potential antitubercular agents

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ABSTRACT

With the aim to develop new potent antitubercular agents, a series of novel dispirooxindolopyrrolidines and dispirooxindolopyrrolothiazoles have been synthesized via a three-component 1,3-dipolar cycloaddition of (*Z*)-3-arylidenebenzofuran-2-ones, substituted isatin derivatives and α-aminoacids. The stereochemistry of the spiroadducts has been confirmed by an X-ray diffraction analysis. All the target heterocycles were evaluated for in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain and the most active compounds were subjected to cytotoxicity studies against (RAW 264.7) cell lines. Among them, twelve compounds showed potent anti-tubercular activity with MIC ranging from 1.56 to 6.25 μg/mL. In particular dispirooxindolopyrrolothiazole derivatives **5c** and **5f** were found to be the most active (MIC of 1.56 μg/mL) with a good safety profile (27.53% and 20.74% at 50 μM, respectively). This is the first report demonstrating the benzofuranone oxindole hybrids as potential antimycobacterial agents.

Tuberculosis (TB), an airborne infectious disease caused by pathogen *Mycobacterium tuberculosis* (MTB), represents the second-leading cause in mortality with 1.4 million of deaths every year and 8.6 million incident cases across the world statistics of 2012.[1,2] The current treatment for susceptible strains prescribed under Directly Observed Treatment Short Course (DOTS) requires the combination of four first-line drugs: isoniazid, rifampicin, pyrazinamide and ethambutol for a period of at least 6 months.[3] Despite extensive research over the last four decades, no new anti-TB drugs have been introduced into clinical practice for the treatment of TB. In addition, the multi-drug resistant tuberculosis (MDR-TB) strains are responsive to current treatment and require a second-line therapy with an increased current drug regimen as well as increased toxicity.[4–7] Therefore, there is a critical need to develop alternative potent antitubercular drugs with low toxicity profiles that would work via novel mechanisms to combat the spread of TB and to shorten the lengthy of therapy. *N*-heterocyclic compounds have been much exploited in drug discovery development owing to their wide biological spectrum. Notably spirooxindole and its derivatives have attracted considerable attention due to their highly pronounced biological activities such as antimicrobial,[8] antidiabetic,[9] antiproliferative[10] and anti-inflammatory behavior.[11] Among those spirooxindoles-derived compounds, spirooxindolopyrrolidines and spirooxindolopyrrolothiazoles are recognized for their antimycobacterial properties and some of them have shown comparable or even better activities than some of the currently employed first-line TB drugs (Fig. 1).[12]

In our previous research work, we showed that some spirooxindolepyrrolidine and dispiropyrrolothiazole derivatives incorporating the pyrrolidine-2,5-dione structure possess antibacterial, antifungal, antimalarial and antimycobacterial activities.[13]

On the other hand, benzofuran-2-one derivatives are significant core moieties featured in a variety of natural products with widespread biological applications.[14] They are well known for their antioxidant,[15] anti-HIV[16] and antibacterial activities[17] (Fig. 2).

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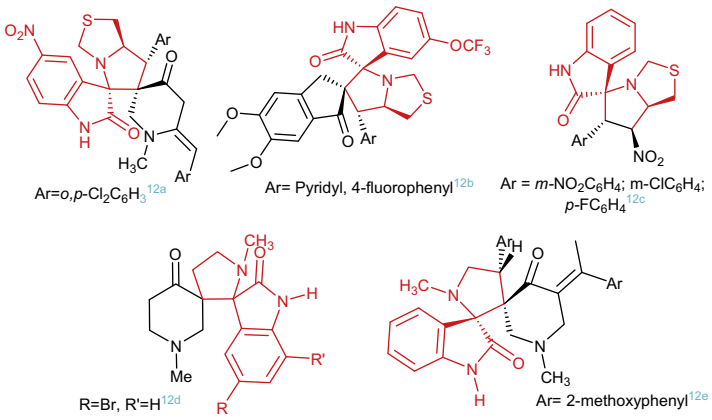


Figure 1. Representative antitubercular agents derived from spirooxindolopyrrolidines and spirooxindolopyrrolothiazoles.

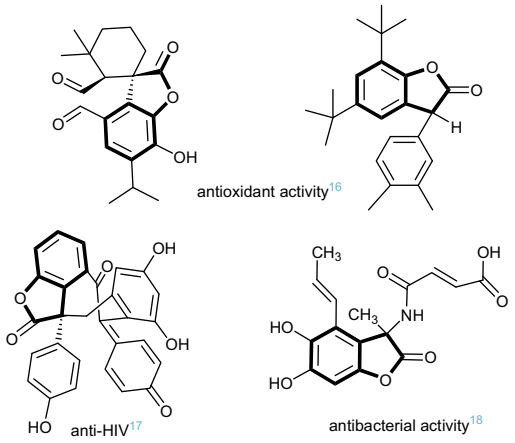


Figure 2. Examples of benzofuran-2-one derivatives exhibiting biological activity.

However, till date, there are no reports on benzofuran-2-one derivatives as anti-TB agents.

In continuation of our interests in the construction of spirocyclic scaffolds through cycloaddition reactions,[13,18] and inspired by the broad range of biological activities of spirooxindole and benzofuran-2-one derivatives, we developed a synthetic path to incorporate these two pharmacophores into a single framework to evaluate their antimycobacterial activity. In this context, a literature survey revealed that there are no reports available on the combination of a benzofuranone–oxindole framework with antituberculosis properties.

The target molecules were efficiently synthesized through a multicomponent sequential reaction of (*Z*)-3-arylidenebenzofuran-2-ones **1** with azomethine ylides generated in situ from isatin **2** and 1,3-thiazolane-4-carboxylic acid **3** or sarcosine **4** (Scheme 1).

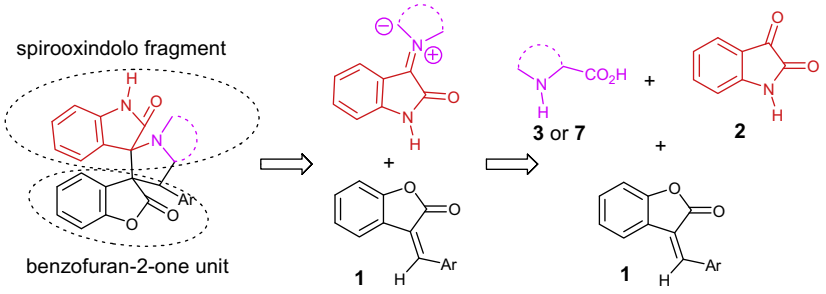
This methodology has already been employed as a strategy for the synthesis of a variety of spirooxindolopyrrolidines and spirooxindolopyrrolothiazoles using isatin **2**, amino acid **3** or **4** and various alkenes.[19] However, to the best of our knowledge, this is the first report describing the use of lactones bearing exocyclic double bond as the reaction partner with azomethine ylides. Finally, very encouraging activities of some of the synthesized heterocyclic compound against *M. tuberculosis* $H_{37}Rv$ growth are finally reported justifying our approach.

Initially, we carried out the reaction of (*Z*)-3-arylidenebenzofuran-2-ones **1** with non-stabilized azomethine ylides,[20] generated in situ by the decarboxylative condensation of various substituted isatin derivatives **2** with 1,3-thiazolane-4-carboxylic acid **3** in refluxing methanol (Scheme 2). The reaction proceeded smoothly with high regio- and stereoselectivity to give the expected functionalized dispirooxindolopyrrolothiazole derivatives **5**–**7** in good yields (Table 1). We found no spectroscopic evidence for a competing formation of regioisomeric compounds **5′**–**7′** (Scheme 2).

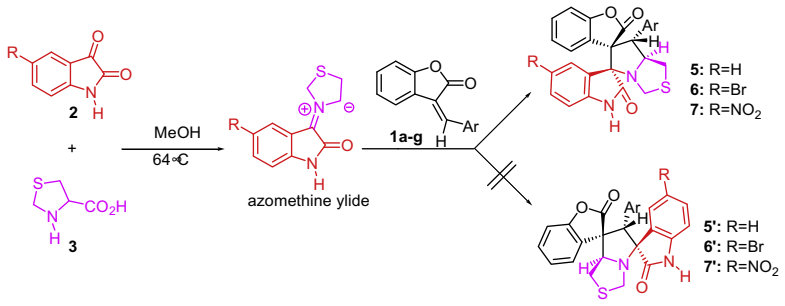
It seems that neither the regiochemistry nor the reaction yields are much influenced by the electronic properties of the *p*-substituent on the aryl group (H, CH_3, OCH_3, SCH_3, Cl, Br and NO_2) of dipolarophile **1** (Table 1).

The structure of the spiroadducts was elucidated on the basis of their spectroscopic data and an X-ray structure analysis as exemplified for cycloadduct **6g**. The IR spectrum of **6g** exhibits absorptions at 1706, 1796 and 3184 cm^{-1} due to C=O oxindole, C=O benzofuranone and N–H stretching vibrations, respectively. Selected ^1H and ^{13}C chemical shifts assignment of **6g** are shown in Figure 3.

The ^1H NMR spectrum of the compound **6g** exhibits a doublet of doublets at δ 2.99 and δ 3.21 ppm (J = 10.8 and 5.4 Hz) corresponding to the 1-CH_2 group, as well as two mutually coupled doublets at δ 3.77 and δ 3.98 ppm (J = 8.4 Hz) assigned to the 3-CH2 group. Furthermore, H-7 and H-7a give rise to a doublet at δ 4.05 ppm



Scheme 1. Design strategy to achieve target compounds.



Scheme 2. Reaction of (*Z*)-3-arylidenebenzofuran-2-ones **1** with isatin **2** and 1,3-thiazolane-4-carboxylic acid **3**.

Table 1
Synthesis of dispirooxindolopyrrolothiazole derivatives **5**–**7**[a]

Compound	Ar	R	Yield (%)[b]
5a	C_6H_5	H	85
5b	*p*-$CH_3C_6H_4$	H	84
5c	*p*-$CH_3OC_6H_4$	H	87
5d	*p*-$CH_3SC_6H_4$	H	81
5e	*p*-ClC_6H_4	H	88
5f	*p*-$NO_2C_6H_4$	H	85
5g	*p*-BrC_6H_4	H	86
6a	C_6H_5	Br	89
6b	*p*-$CH_3C_6H_4$	Br	83
6c	*p*-$CH_3OC_6H_4$	Br	81
6d	*p*-$CH_3SC_6H_4$	Br	84
6e	*p*-ClC_6H_4	Br	81
6f	*p*-$NO_2C_6H_4$	Br	89
6g	*p*-BrC_6H_4	Br	88
7a	C_6H_5	NO_2	82
7b	*p*-$CH_3C_6H_4$	NO_2	88
7c	*p*-$CH_3OC_6H_4$	NO_2	84
7d	*p*-$CH_3SC_6H_4$	NO_2	87
7e	*p*-ClC_6H_4	NO_2	85
7f	*p*-$NO_2C_6H_4$	NO_2	82
7g	*p*-BrC_6H_4	NO_2	85

[a] The reactions were carried out with **1** (0.5 mmol), **2** (0.5 mmol) and **3** (0.6 mmol) in methanol (5 mL) at 60 °C for 1 h.
[b] Isolated yield after purification by column chromatography.

(J = 9.9 Hz) and a multiplet at δ 5.08–5.11 ppm, respectively. This excludes the presence of the hypothetical inverse regioisomer **6′g** (Scheme 2), for which the ^{1}H NMR spectrum should exhibit a singlet and doublet of doublet pattern for the pyrrolizidinyl protons H-7 and H-7a, respectively. The NH proton of the oxindole ring appears as a broad singlet at δ 7.8 ppm. The ^{13}C NMR spectrum of **6g** displays two peaks at δ 34.7 and 50.5 ppm indicating the presence of two methylene groups. The peaks at δ 56.3 and 70.2 ppm are assigned to the pyrrolizidinyl carbons C-7 and C-7a, respectively. The two spirocarbons C-6 and C-5 resonate at δ 67.5 and 76.3 ppm, respectively. In addition, two carbonyl carbons are recognized at δ 173.7 and 175.3 ppm and are assigned to the benzofuran-2-one and oxindole carbonyl groups, respectively.

The regio- and stereochemical outcome of the cycloaddition was furthermore ascertained by a single-crystal X-ray diffraction study.[21] The crystal structure of this cycloadduct depicted in Figure 4 reveals that **6g** was formed through an *exo*-approach between (*Z*)-3-arylidenebenzofuran-2-one **1** and a *W*-shaped ylide, in accord with many similar cycloaddition studies.[13b,22,23]

Noteworthy is also the occurrence of intermolecular hydrogen bonds between the N–H function and the carbonyl oxygen atoms of the amides group of neighbored molecules, thus forming a six-membered centrosymmetric cyclic dimer with N2–H2···O1 distances of 2.13(3) Å and a N2–H2–O1 angle of 168.0(3)° (Fig. S57 in the Supporting information).

On the basis of our experimental results and previous studies on the reaction mechanism,[13b] we propose in Scheme 3 a mechanistic pathway rationalizing the regio- and stereoselective spirooxindole formation. The azomethine ylides are generated in situ by the decarboxylative condensation of isatin **2** with 1,3-thiazolane-4-carboxylic acid **3**. Presumably, the *W*-shaped ylide, which is slightly more stable than the *S*-shaped form,[13b,22a] undergoes then a 1,3-dipolar cycloaddition reaction with the dipolarophile **1** in a regioselective manner (*path A*). The formation of the regioisomer **5**–**7** via *path A* is more favorable due to the presence of a secondary orbital interaction (SOI)[24] occurring between the

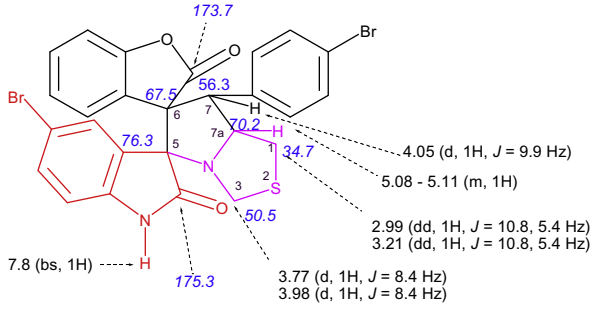


Figure 3. Selected ^{1}H and ^{13}C NMR chemical shifts of **6g**.

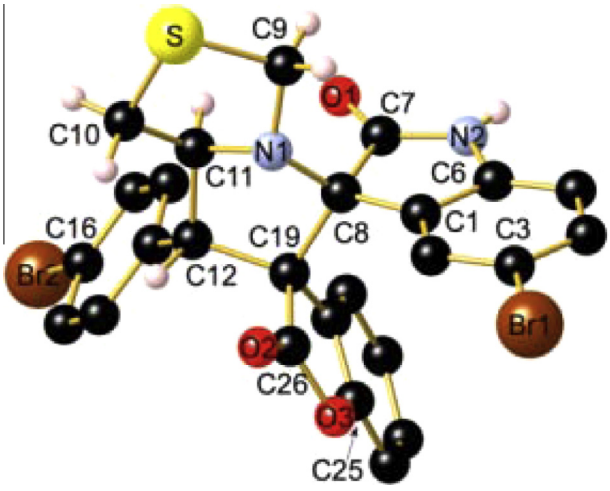
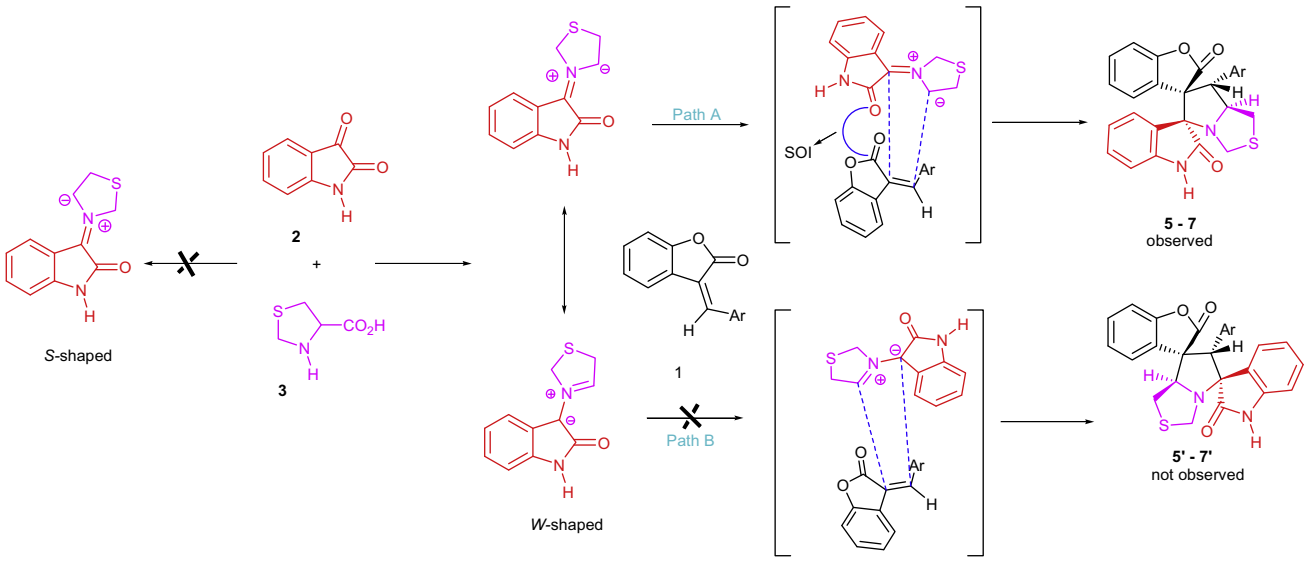


Figure 4. Molecular structure of spiro compound **6g**. Only the non-aromatic H atoms are shown. Selected bond lengths (Å) and angles(°): C1–C6 1.398(4), C6–N2 1.404(3), C7–N2 1.347(4), C7–O1 1.277(3), C7–C8 1.570(3), C8–N1 1.449(3), C9–N1 1.450(3), C9–S 1.839(3), C10–S 1.834(3), C10–C11 1.521(4), C11–N1 1.457(3), C26–O2 1.194(3), C26–O3 1.365(3); C8–N1–C9 121.2(12), N1–C8–C19 100.05(19), N1–C9–S 103.05(19), C9–S–C10 93.16(13), S–C10–C11 103.68(19), C11–N1–C9 108.9(12), N1–C8–C7 114.1(2), C7–N2–C6 112.2(2), O2–C26–O3 120.9(2).



Scheme 3. Plausible mechanism for the regio- and stereoselective spirooxindole formation.

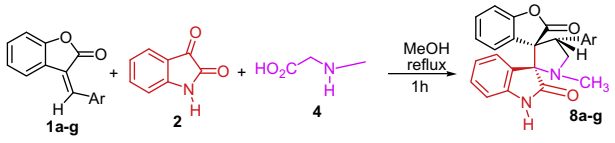
carbon atom of the carbonyl of the dipolarophile **1** and the oxygen atom of the carbonyl of the isatin as shown in Scheme 3. This kind of SOI is not possible in *path B*.

To expand the scope of the regio- and stereoselective cycloaddition of azomethine ylides towards dipolarophiles **1**, also *N*-methylglycine (sarcosine) **4** was used as reagent instead of 1,3-thiazolane-4-carboxylic acid **3**. Under identical reaction conditions, the resulting dispirooxindolopyrrolidine series **8** was obtained in good yields (Scheme 4 and Table 2) using refluxing methanol as solvent.

The structural and stereochemical features of all spiroadducts **8** are fully supported by the IR and NMR spectroscopic data, as exemplified for cycloadduct **8c**. The ^{1}H and ^{13}C spectroscopic data of **8c** are illustrated in Figure 5.

The ^{1}H NMR spectrum of compound **8c** shows the characteristic singlets at δ 2.28, 3.68 and 7.14 ppm corresponding to the $-NCH_3$, $-OCH_3$ and –NH protons of the oxindole cycle, respectively. The presence of these resonances proves the incorporation of both oxindole and dipolarophile **1c**. The multiplet between δ 4.38 and 4.39 ppm and a triplet at 3.66 ppm (J = 10.8 Hz) are assigned to the two geminal $-CH_2$ protons of the spiropyrrolidine ring and H-4 proton, respectively. The occurrence of these signals clearly proves the regiochemistry of the cycloaddition reaction. In the ^{13}C NMR spectrum of **8c**, the signals at δ 63.8 and 78.9 ppm are attributed to the two spiro-carbons C-3 and C-2, respectively. The resonance at 158.6 and 178.4 ppm are characteristic of the presence of two carbonyl groups belonging to the oxindole and benzofuran-2-one, respectively.

All synthesized heterocycles were screened for their in vitro antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the agar dilution method[25] for the determination of the Minimum Inhibitory Concentration (MIC) in triplicate. The (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values



Scheme 4. Synthesis of dispirooxindolopyrrolidines **8**.

Table 2
Synthesis of spirooxindolopyrrolidine derivatives **8**[a]

Compound	Ar	Yield (%)[b]
8a	C_6H_5	76
8b	p-$CH_3C_6H_4$	71
8c	p-$CH_3OC_6H_4$	73
8d	p-$CH_3SC_6H_4$	78
8e	p-ClC_6H_4	77
8f	p-$NO_2C_6H_4$	87
8g	p-Br C_6H_4	76

[a] The reactions were carried out with 1 (0.5 mmol), 2 (0.5 mmol) and 7 (0.6 mmol) in methanol (5 mL) at 60 °C for 1 h.
[b] Isolated yield after purification by column chromatography.

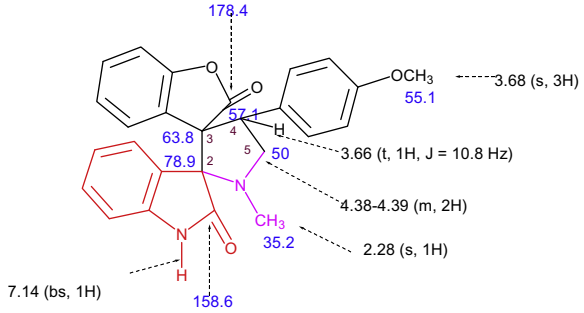


Figure 5. Selected ^{1}H and ^{13}C NMR chemical shifts of **8c**.

of the cycloadducts **5**–**8** along with the MIC's standard drugs for comparison are reported in Table 3.

The spiroheterocycles have their MIC in the range of 1.56–50 μg/mL. Among them, twelve compounds (**5c**, **5e**, **5f**, **5g**, **6d**, **6e**, **6f**, **6g**, **7a**, **8d**, **8e** and **8f**) were more active or at least equal to the first line anti-TB drug Pyrazinamide (MIC 6.25 μg/mL), whilst ten of them **5c**, **5e**, **5f**, **5g**, **6e**, **6f**, **6g**, **7a**, **8d** and **8f** were more potent than Ciprofloxacin (MIC 3.13 μg/mL). However, all the compounds were less potent than Isoniazid and Rifampicin. Between these compounds, the cycloadducts **5c** and **5f** displayed the same potency like the Ethambutol (MIC 1.56 μg/mL) and being two and four times more potent than Ciprofloxacin and Pyrazinamide, respectively. With respect to structure-activity relationship (SAR),

Table 3
Minimum inhibitory concentration (MIC) of cycloadducts **5**–**8** against mycobacterial species

Compound	Ar	R	MTB[a](MIC) μg/mL	(RAW 264.7 cells) %inhibition
5a	C_6H_5	H	25	NT
5b	*p*-$CH_3C_6H_4$	H	12.5	NT
5c	*p*-$CH_3OC_6H_4$	H	1.56	27.53
5d	*p*-$CH_3SC_6H_4$	H	12.5	NT
5e	*p*-ClC_6H_4	H	3.125	32.3
5f	*p*-$NO_2C_6H_4$	H	1.56	20.74
5g	*p*-BrC_6H_4	H	3.125	28.5
6a	C_6H_5	Br	25	NT
6b	*p*-$CH_3C_6H_4$	Br	12.5	NT
6c	*p*-$CH_3OC_6H_4$	Br	50	NT
6d	*p*-$CH_3SC_6H_4$	Br	6.25	28.14
6e	*p*-ClC_6H_4	Br	3.125	34.62
6f	*p*-$NO_2C_6H_4$	Br	3.125	43.1
6g	*p*-BrC_6H_4	Br	3.125	32.4
7a	C_6H_5	NO_2	3.125	35.23
7b	*p*-$CH_3C_6H_4$	NO_2	>25	NT
7c	*p*-$CH_3OC_6H_4$	NO_2	25	NT
7d	*p*-$CH_3SC_6H_4$	NO_2	12.5	NT
7e	*p*-ClC_6H_4	NO_2	NT	NT
7f	*p*-$NO_2C_6H_4$	NO_2	50	NT
7g	*p*-BrC_6H_4	NO_2	12.5	NT
8a	C_6H_5	H	12.5	NT
8b	*p*-$CH_3C_6H_4$	H	NT	NT
8c	*p*-$CH_3OC_6H_4$	H	12.5	NT
8d	*p*-$CH_3SC_6H_4$	H	3.125	28.74
8e	*p*-ClC_6H_4	H	6.25	30.15
8f	*p*-$NO_2C_6H_4$	H	3.125	29.5
8g	*p*-BrC_6H_4	H	NT	NT
Isoniazid			0.05	
Rifampicin			0.1	
Ethambutol			1.56	
Ciprofloxacin			3.13	
Pyrazinamide			6.25	

[a] Minimum inhibitory concentration against *M. tuberculosis*. NT: not tested.

the data in Table 3 show that the substituent present on the isatin has a profound effect on the activity of the dispirooxindolopyrrolothiazoles **5**–**8**, the order of the activity, in general, being H > Br > NO_2 was evidenced from the observation that four compounds in series **5** (**5c**, **5e**, **5f** and **5g**), four in series **6** (**6d**, **6e**, **6f**, and **6g**), and just one in series bearing the nitro group **7** (**7a**) were more active against MTB. As well as the presence of the H, Cl and NO_2 in the isatin, the substituents on the aryl rings enhanced the antimycobacterial activity as seen from the MIC values of **5e**, **6e** (MIC: 3.12), **5f**, **6f**, **8f** (MIC: 1.56–3.12) and **5g**, **6g** (MIC: 3.12)

In the series of spirooxindole derivatives, twelve compounds, showing potent anti-mycobacterial activity (MIC ⩽6.25 μg/mL) were selected for cytotoxicity studies against RAW 264.7 (Mouse monocyte macrophages) cells at 50 μM concentration using a (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) assay.[26,27] The percentages of cell inhibition are reported in Table 3. The most promising antitubercular agents **5c** and **5f** show 27.53% and 20.74% inhibition at 50 μM, respectively.

In conclusion, we have shown that a series of novel spirooxindolopyrrolidine and spirooxindolpyrrolothiazole can be synthesized in good yields via a three-component 1,3-dipolar cycloaddition of (*Z*)-3-arylidenebenzofuran-2-ones, substituted isatin derivatives and α-amino acids. The reaction proceeds with high regio- and stereoselectivity, regardless of the electronic propensities of the substituents at the *para*-position of the aryl groups. Screening all these derivatives against *Mycobacterium tuberculosis* H37Rv revealed that **5c** and **5f** are the most active antitubercular agents compared to the other evaluated compounds. Our results demonstrate the potential utility of benzofuranone–oxindole hybrids as antitubercular agents and the presented data will help global efforts for identification of new chemical entities as potent drugs like antimycobacterial agents. So, in a next step the use of enantiomeric pure compounds deserves to be investigated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.07.069.

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21. Crystal data for **6g** $C_{26}H_{18}Br_2N_2O_3S$: triclinic, *P-1*, $T = 173$ K; $a = 8.8270(3)$, $b = 11.2767(5)$, $c = 13.4672(6)$ Å, $\alpha = 68.871(4)°$, $\beta = 72.347(4)°$, $\gamma = 88.468(3)°$; $\lambda = 0.71073$ Å, $V = 1186.37(9)$ Å^3, $Z = 2$, $D_{calcd} = 1.675$ g/cm^3; $F(000)$ 596.0; 29423 reflections collected, 5182 independent reflections. Final agreement

factors: $R_1 = 0.0428$ (all observed) and 0.0330 with $I > 2s(I)$, $wR_2 = 0.0879$ (all observed) and 0.0833 with $I > 2\sigma(I)$. GOF = 1.43. Final residuals $\rho_{max} = 1.67$, $\rho_{min} = 0.70\,e\,Å^{-3}$. Further crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Center through www.ccdc.cam.ac.uk/data_request/cif: CCDC 1061548.

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25. *Antitubercular evaluation assay:* Twofold serial dilutions (50.0, 25.0, 12.5, 6.25, 3.13, 1.56, 0.78 and 0.4 μg/mL) of each test compounds **5a**–**v** and drugs were prepared and incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H37Rv ATCC 27294 was prepared from fresh Middlebrook 7H11 agar slants with OADC (oleic acid, albumin, dextrose and catalase; Difco) Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of $\sim 10^7$ cfu/mL. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.
26. *Evaluation of cytotoxicity:* Antitubercular active compounds with MIC $\leqslant$6.25 μg/mL were examined for their cytotoxicity against RAW 264.7 cell lines at the concentration of 50 μM. After 72 h of exposure, viability was assessed on the basis of cellular conversion of (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.
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