



Design, synthesis and *in vitro* anti-mycobacterial activities of homonuclear and heteronuclear bis-isatin derivatives



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ABSTRACT

A series of novel homonuclear and heteronuclear bis-isatin derivatives tethered through ethylene were designed, synthesized and evaluated for their *in vitro* anti-mycobacterial activities against MTB H37Rv and MDR-TB. All hybrids exhibited potential anti-mycobacterial activities against MTB H37Rv and MDR-TB with MIC ranging from 16 to 256 µg/mL. In particular, the heteronuclear bis-isatin **4i** (MIC: 25 and 16 µg/mL) was most active against MTB H37Rv and MDR-TB strains, and could act as a lead for further optimization.

1. Introduction

According to the latest World Health Organization (WHO) report, tuberculosis (TB) is the ninth leading cause of death throughout the world and the leading cause from a single infectious agent, ranking above HIV/AIDS [1]. There was around 10.4 million people fell ill with TB in the year 2016, resulting 1.67 million deaths. The new virulent forms of *Mycobacterium tuberculosis* (MTB) such as drug-resistant TB (DR-TB) and multidrug-resistant TB (MDR-TB) has already increased up to alarming level in the recent decades [2,3]. In 2016, there were 600,000 new cases with resistance to rifampicin (RIF), of which 490,000 had MDR-TB [1]. Although several drugs such as ciprofloxacin, amikacin, cycloserine and ethionamide have been approved as the second-line anti-TB agents for the treatment of TB infected patients, these agents are less effective and more toxic generally [4,5]. Therefore, it's imperative to develop novel anti-TB agents.

Isatin (1*H*-indole-2,3-dione, Fig. 1), found in many plants, such as *Isatis tinctoria*, *Calanthe discolor* and in *Couroupita guianensis*, is a versatile structure for chemical modification. Its derivatives exhibited a varied of biological properties such as antibacterial [6,7], anticancer [8], antimalarial [9] and anti-TB activities [10–14]. Moreover, some isatin-based drugs such as sunitinib and nintedanib have been approved for clinical use for the treatment of various diseases. The broad spectrum of biological activities combined with a wide range of structural modifications makes isatin an important prototype in drug development.

Dimer means a chemical structure formed from two similar or the

same sub-units, and dimers have caused great interests in medicinal chemistry since they usually exhibited some unique properties such as enhanced biological activities when compared with the corresponding monomeric compounds [15]. It is worth to notice that some dimers such as dicoumarol (Fig. 1) has already used in clinical practice, demonstrating their potential in the development of new drugs [16].

Isatin dimers demonstrated endow with diverse biological profiles including anti-TB activity [17–19]. Our previous demonstrated that some propylene-tethered homonuclear isatin dimers displayed considerable anti-TB activity against both MTB H37Rv and MDR-TB, and the linkers of the two isatin motifs were crucial for the anti-TB activity of isatin derivatives [19]. Besides, our results also indicated that the ethylene linker is better than propylene linker [20–23].

Based on the above research results and as a continuous research program, a set of novel homonuclear and heteronuclear bis-isatin derivatives tethered through ethylene was designed, synthesized and assessed for their *in vitro* anti-mycobacterial activities against MTB H37Rv and MDR-TB in this study. To the best of our knowledge, this is the first attempt in making heteronuclear bis-isatin derivatives as potential anti-TB agents.

2. Results and discussion

Detailed synthetic route for homonuclear and heteronuclear bis-isatin derivatives **4a–i** was depicted in Scheme 1. Isatin was alkylated with 1,2-dibromoethane in the presence of potassium carbonate to provide the corresponding *N*-(2-bromoethyl)isatin **2** (yield: 49%) by

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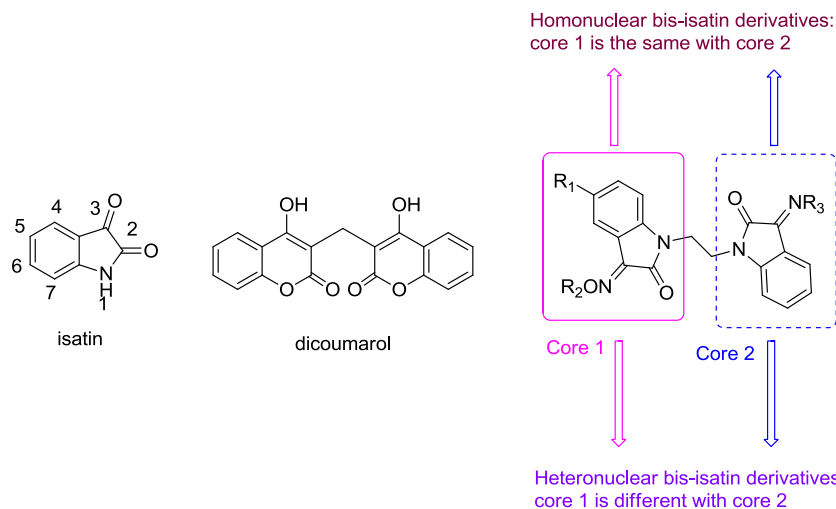
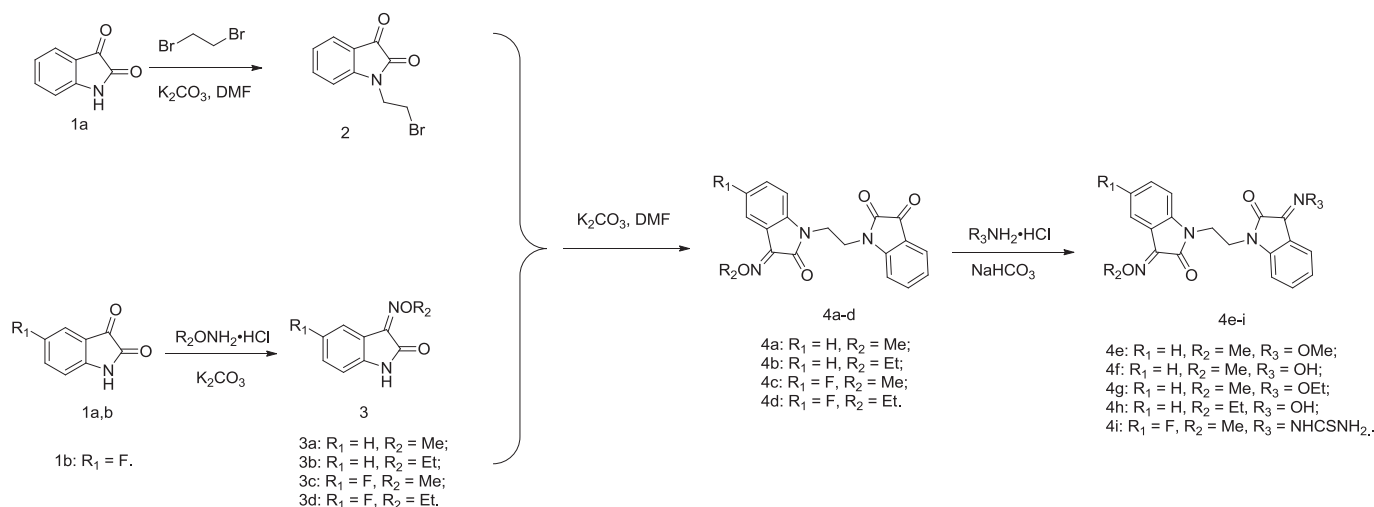


Fig. 1. Chemical structures of isatin, dicoumarol, homonuclear and heteronuclear bis-isatin derivatives.



Scheme 1. Synthesis of bis-isatin derivatives 4a-i.

literature methods [20,21]. The intermediates **3a-d** (yield: 57–69%) were obtained by reacting C-5 substituted isatins with methoxyamine or ethoxyamine hydrochloride in presence of potassium carbonate [22]. The precursors **2** and **3a-d** were utilized for the synthesis of desired heteronuclear bis-isatin derivatives **4a-d** (yield: 47–64%) with potassium carbonate as base [23]. Finally, condensations of targets **4a-c** with hydroxylamine or methoxyamine or ethoxyamine hydrochloride in the presence of sodium bicarbonate provided targets **4e-i** (23–79%) [19].

All homonuclear and heteronuclear bis-isatin derivatives **4a-i** were evaluated for their *in vitro* anti-mycobacterial activities against MTB H37Rv and MDR-TB strains (see Table 1). The MDR-TB strain was resistant to isoniazid (INH), rifampicin (RIF) and ethambutol (EMB). The minimum inhibitory concentration (MIC) is defined as the lowest concentration that inhibits the visible bacterial growth.

The results showed that all homonuclear and heteronuclear bis-isatin derivatives exhibited considerable anti-mycobacterial activities against MTB H37Rv and MDR-TB strains with MIC ranging from 16 to 256 µg/mL. The structure-activity relationship (SAR) revealed that substituents at C-3 and C-5 positions of isatin motifs have great influence on the activity: 1) for C-3 position, in general, the mono-substituted bis-isatin derivatives were more active than the bis-substituted and unsubstituted analogs, and the relative contribution of the substituents to the activity was as follows:

Table 1
Structures and anti-mycobacterial activities of hybrids 4a-i.

Compd.	R ₁	R ₂	R ₃	MIC (µg/mL)	
				MTB H ₃₇ Rv	MDR-TB
4a	H	NOMe	O	100	64
4b	H	NOEt	O	100	128
4c	F	NOMe	O	100	32
4d	F	NOEt	O	100	64
4e	H	NOMe	NOMe	100	128
4f	H	NOEt	NOH	200	256
4g	H	NOMe	NOEt	100	256
4h	H	NOEt	NOH	200	256
4i	F	NOMe	NNHCSNH ₂	25	16
INH	–	–	–	0.05	> 128
RIF	–	–	–	0.39	64

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