Design, Synthesis, and *In Vitro* Anti-mycobacterial Activities of Propylene Tethered Benzofuran–Isatin Hybrids

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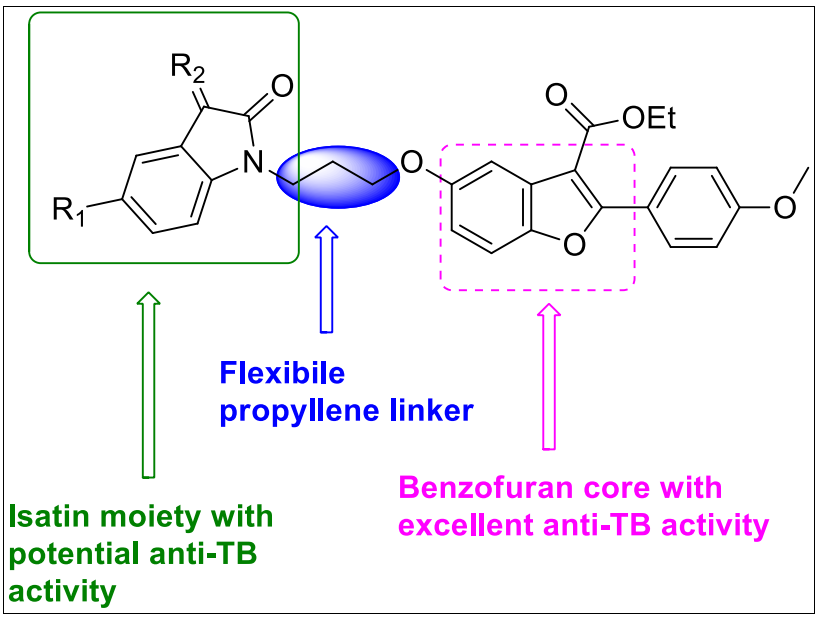


A series of novel propylene tethered benzofuran–isatin hybrids **5a–j** were designed, synthesized, and assessed for their *in vitro* anti-mycobacterial activity against *Mycobacterium tuberculosis* (MTB) $H_{37}Rv$ and multidrug-resistant (MDR)-MTB strains. All hybrids exhibited promising anti-mycobacterial activities against the tested two pathogens with minimum inhibitory concentration (MIC) ranging from 2 to 32 μg/mL, and the resistance index for a significant part of the hybrids was ≤1, indicating their potential for the treatment of drug-resistant tuberculosis. Hybrid **5g** (MIC: 2 and 4 μg/mL) was found to be the most active against MTB $H_{37}Rv$ and MDR-MTB, which was eightfold and >32-fold more active than the first-line anti-tuberculosis drugs rifampicin (MIC: 32 μg/mL) and isoniazid (MIC: >128 μg/mL) against MDR-MTB, and it could act as a starting point for further optimization.

INTRODUCTION

Tuberculosis (TB), which is an infectious disease usually caused by *Mycobacterium tuberculosis* (MTB), generally affects the lungs but can also affect other parts of the body [1,2]. TB is one of the most deadly infectious diseases, and 10.4 million people fell ill in 2016, resulted in 1.67 million deaths [3]. The drug-susceptible TB can be cured by the first-line anti-TB agents such as isoniazid (**INH**), rifampicin (**RIF**), pyrazinamide, streptomycin, and ethambutol, but the emergency and widely spread of drug-resistant TB, multidrug-resistant TB (MDR-TB), and extremely drug-resistant TB create an urgent need to develop novel, fast-acting, and high-effective anti-TB drugs against both drug-susceptible and drug-resistant strains of MTB to prevent the spread of TB [4–6].

Benzofuran and isatin derivatives occupy an important position in medicinal chemistry, which is attributed to their fascinating array of pharmacological properties [7–9]. Some benzofuran and isatin derivatives exhibited excellent anti-TB activity [10–12], and the most representative example is **TAM16** (Fig. 1). **TAM16** is an inhibitor of polyketide synthase 13 with highly *in vivo* anti-TB efficacy, which was comparable with the first-line TB agent **INH**, both as a monotherapy and in combination with **RIF**, and the frequency of resistance for **TAM16** was around 100-fold lower than **INH** [13]. Thus, hybridization of the benzofuran and isatin pharmacophores into one single molecule may provide more effective candidates.

Our previous research results demonstrated that the linker between the two pharmacophores has significant influence on the anti-TB activity [14–19], and some hybrids tethered by propylene exhibited excellent

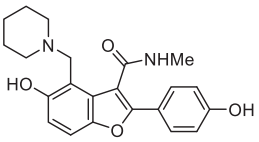


Figure 1. Chemical structure of **TAM16**.

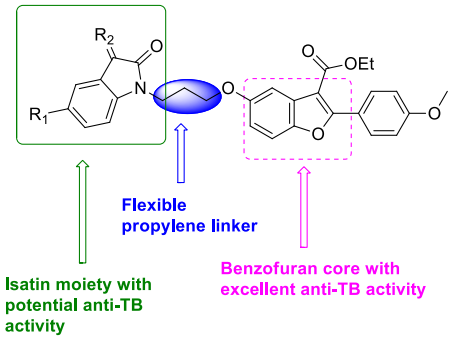


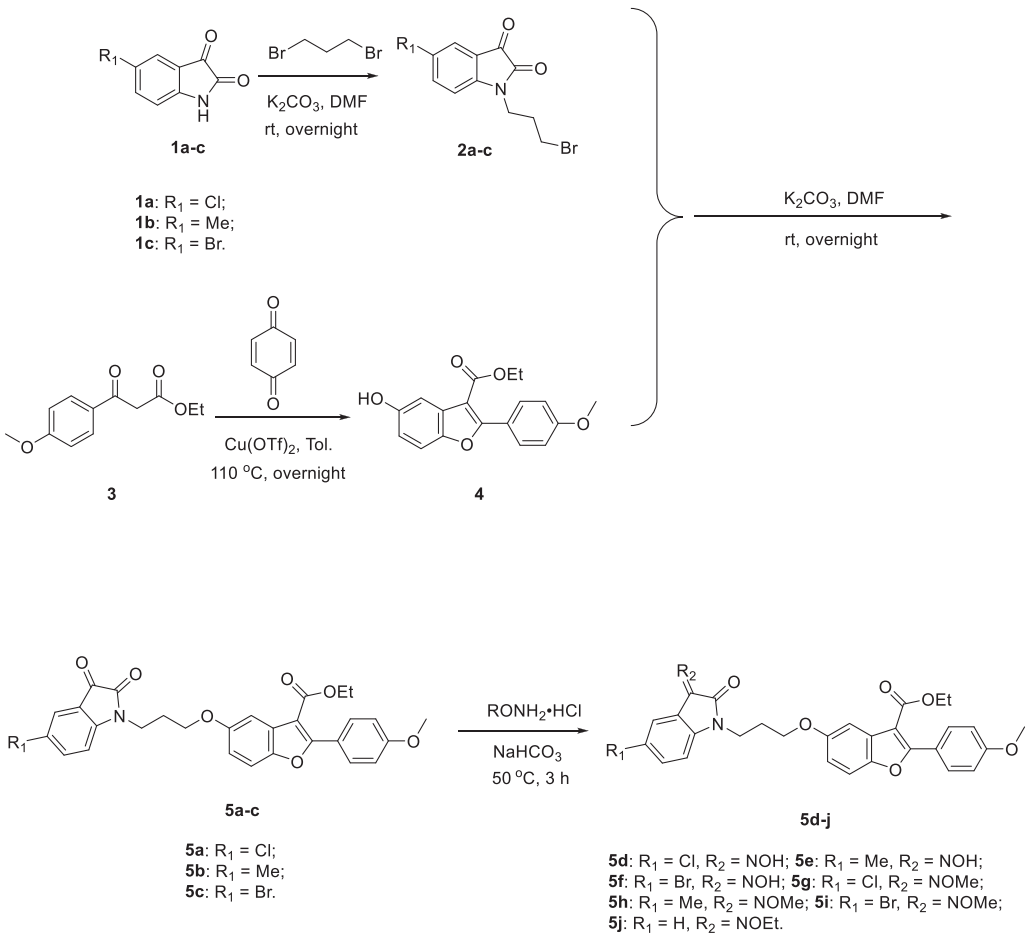
Figure 2. Illustration of the design strategy for propylene tethered benzofuran–isatin hybrids. TB, tuberculosis. [Color figure can be viewed at wileyonlinelibrary.com]

potency. Based on the aforementioned results and as a part of an ongoing program to optimize benzofuran–isatin hybrids as anti-TB agents, a series of propylene tethered benzofuran–isatin hybrids were designed, synthesized, and evaluated for their *in vitro* anti-TB activity against MTB $H_{37}Rv$ and MDR-MTB in this study. Illustration of the design strategy is depicted in Figure 2.

RESULTS AND DISCUSSION

The benzofuran–isatin hybrids **5a–j** were achieved by the synthetic route depicted in Scheme 1. C-5 substituted isatins were alkylated with 1,3-dibromopropane in presence of potassium carbonate in DMF at room temperature to provide the intermediates N-(2-bromopropyl)isatins **2a–c**. Cyclization of ethyl 3-(4-methoxyphenyl)-3-oxopropanoate **3** and benzoquinone catalysized by copper(II) triflate afforded the benzofuran intermediate **4** [13]. Phenolic hydroxyl of benzofuran **4** was alkylated with intermediates **2a–c** with potassium carbonate as base to give benzofuran–isatin hybrids **5a–c**. Finally,

Scheme 1. Synthesis of propylene tethered benzofuran–isatin hybrids **5a–j**.



condensations of targets **5a–c** with the requested amine hydrochlorides yielded targets **5d–j**.

The synthesized hybrids were screened for their *in vitro* anti-mycobacterial activities against MTB $H_{37}Rv$ and MDR-MTB strains. The minimum inhibitory concentration (MIC) is defined as the lowest concentration that inhibits the visible bacterial growth. The MIC values of the compounds along with **TAM16**, **INH**, and **RIF** for comparison were presented in μg/mL in Table 1.

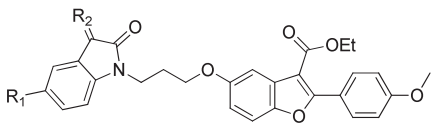
The data revealed that all hybrids exhibited promising activity with MIC in a range of 2 to 32 μg/mL against MTB $H_{37}Rv$ and MDR-MTB but were far less potent than **TAM16** (MIC: <0.06 μg/mL). The structure–activity relationship indicated that substituents on C-3 and C-5 positions of isatin motif have great influence on the anti-mycobacterial activity, which was in accordance with previous studies [14–17]: incorporation of alkyloxyamines on C-3 position could enhance the activity, while hydroxyimino was detrimental to the activity, which may be attributed to hydroxyimino that decreased the lipophilicity; introduction of halogen atoms —Cl and —Br was favorable to the activity, but electron-donating —Me disfavored the activity.

Notably, the resistance index for a great part of benzofuran–isatin hybrids was around 1, suggesting that their action mechanism may differ with the first-line anti-TB agents.

Among the synthesized benzofuran–isatin hybrids, the hybrid **5g** (MIC: 2 and 4 μg/mL) was found to be the most active against MTB $H_{37}Rv$ and MDR-MTB strains, which was eightfold and >32-fold more potent than the first-line anti-TB agents **RIF** (MIC: 32 μg/mL) and **INH** (MIC: >128 μg/mL) against MDR-MTB, warranting further investigation.

Table 1

Structures and anti-mycobacterial activity of propylene tethered benzofuran–isatin hybrids **5a–j**.



Compd.	R_1	R_2	MIC (μg/mL) MTB $H_{37}Rv$	MIC (μg/mL) MDR-MTB[a]
5a	Cl	O	8	8
5b	Me	O	16	16
5c	Br	O	8	16
5d	Cl	NOH	16	8
5e	Me	NOH	32	32
5f	Br	NOH	16	32
5g	Cl	NOMe	2	4
5h	Me	NOMe	4	8
5i	Br	NOMe	4	4
5j	H	NOEt	8	8
TAM16	—	—	<0.06	<0.06
INH	—	—	0.12	>128
RIF	—	—	0.5	32

INH, isoniazid; MDR-MTB, multidrug-resistant *Mycobacterium tuberculosis*; MIC, minimum inhibitory concentration; **RIF**, rifampicin.
[a]Resistant to ethambutol, **INH**, and **RIF**.

CONCLUSIONS

A new class of propylene tethered benzofuran–isatin hybrids **5a–j** was designed, synthesized, and evaluated for their *in vitro* anti-mycobacterial activity in this paper. All hybrids showed considerable activity, and some of them were more potent than the first-line anti-TB agents against MDR-MTB. The structure–activity relationship was enriched, which may pave the way for further optimization.

EXPERIMENTAL SECTION

General procedure for the preparation of 5a–j. The mixture of C-5 substituted isatins (10 mmol), 1,3-dibromopropane (20 mmol), and potassium carbonate (40 mmol) in DMF (50 mL) was stirred at room temperature overnight. After filtration, the filtrate was concentrated under reduced pressure. The reside was purified by silica gel chromatography eluted with petroleum ether:EtOAc = 3:1 to give N-(3-bromopropyl) isatin derivatives **2a–c** as red solids.

To a mixture of 3-(4-methoxyphenyl)-3-oxopropanoate **3** (10 mmol) and Cu $(OTf)_2$ (5 mol%, 0.11 g) in anhydrous toluene (35 mL) was added dropwise a solution of benzoquinone (7 mmol) dissolved in toluene (5 mL) under N_2 atmosphere. After addition, the mixture was stirred at 110°C overnight. After cooling to room temperature, the mixture was quenched with sat. NH_4Cl (20 mL) and then extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with petroleum ether: EtOAc = 10:1 to give benzofuran **4** as a brown solid.

The mixture of compounds **2a–c** (5 mmol), **4** (4 mmol), and potassium carbonate (12 mmol) in DMF (50 mL) was stirred at room temperature overnight. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with petroleum ether:EtOAc to give benzofuran–isatin hybrids **5a–c**.

The mixture of **5a–c** (1 mmol), sodium bicarbonate (2 mmol), and hydroxylamine or methoxyamine or ethoxyamine hydrochloride (1.2 mmol) in a mixture of water (10 mL) and THF (30 mL) was stirred at 50°C for 3 h. After cooling to room temperature, the mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (50 mL) and then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with petroleum ether:EtOAc = 3:1 to give the rest benzofuran–isatin hybrids **5d–j**.

Ethyl 5-(3-(5-chloro-2,3-dioxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5a). Yield: 47%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, —CH_2—), 3.85 (3H, s, OCH_3), 3.89 (2H, t, —CH_2—), 4.12 (2H, t, —CH_2—), 4.36 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.91 (1H, d, Ar–H), 7.05–7.16 (4H, m, Ar–H), 7.35 (1H, t, Ar–H), 7.54 (1H, s, Ar–H), 7.60 (1H, d, Ar–H), 7.96 (2H, d, Ar–H). ESI-MS *m/z*: 534 $[M + H]^+$, 536 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{24}ClNO_7$: C, 65.23; H, 4.53; N, 2.62; found: C, 65.08; H, 4.31; N, 2.39.

Ethyl 2-(4-methoxyphenyl)-5-(3-(5-methyl-2,3-dioxoindolin-1-yl)propoxy)benzofuran-3-carboxylate (5b). Yield: 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.13 (2H, t, —CH_2—), 2.29 (3H, s, —CH_3), 3.86 (3H, s, OCH_3), 3.92 (2H, t, —CH_2—), 4.12 (2H, t, —CH_2—), 4.34 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.91 (1H, d, Ar–H), 7.03 (1H, d, Ar–H), 7.08–7.16 (3H, m, Ar–H), 7.20 (1H, d, Ar–H), 7.57 (1H, d, Ar–H), 7.64 (1H, d, Ar–H), 7.96 (2H, d, Ar–H). ESI-MS *m/z*: 514 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{27}NO_7$: C, 70.16; H, 5.30; N, 2.73; found: C, 69.97; H, 5.13; N, 2.52.

Ethyl 5-(3-(5-bromo-2,3-dioxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5c). Yield: 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, —CH_2—), 3.85 (3H, s, OCH_3), 3.93 (2H, t, —CH_2—), 4.08 (2H, t, —CH_2—), 4.36 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.93 (1H, d, Ar–H), 7.08–7.22 (3H, m, Ar–H), 7.31 (1H, d, Ar–H), 7.60–7.68 (3H, m, Ar–H), 7.96 (2H, d, Ar–H). ESI-MS *m/z*: 578 $[M + H]^+$, 580 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{24}BrNO_7$: C, 60.22; H, 4.18; N, 2.42; found: C, 60.01; H, 4.07; N, 2.23.

Ethyl (Z)-5-(3-(5-chloro-3-(hydroxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5d). Yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, —CH_2—), 3.85 (3H, s, OCH_3), 3.89 (2H, t, —CH_2—), 4.12 (2H, t, —CH_2—), 4.36 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.90 (1H, d, Ar–H), 7.04–7.16 (3H, m, Ar–H), 7.28 (1H, t, Ar–H), 7.46 (1H, s, Ar–H), 7.57 (1H, d, Ar–H), 7.90 (1H, d, Ar–H), 8.02 (2H, d, Ar–H), 13.48 (1H, brs, NOH). ESI-MS *m/z*: 549 $[M + H]^+$, 551 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{25}ClN_2O_7$: C, 63.45; H, 4.59; N, 5.10; found: C, 63.33; H, 4.38; N, 4.96.

Ethyl 5-(3-(3-(hydroxyimino)-5-methyl-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5e). Yield: 64%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.12 (2H, t, —CH_2—), 3.89 (3H, s, OCH_3), 3.96 (2H, t, —CH_2—), 4.08 (2H, t, —CH_2—), 4.35 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, d, Ar–H), 7.04–7.18 (4H, m, Ar–H), 7.26 (1H, d, Ar–H), 7.58 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 8.04 (2H, d, Ar–H), 13.45 (1H, brs, NOH). ESI-MS *m/z*: 529 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{28}N_2O_7$: C, 68.17; H, 5.34; N, 5.30; found: C, 67.97; H, 5.15; N, 5.03.

Ethyl (Z)-5-(3-(5-bromo-3-(hydroxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5f). Yield: 63%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, —CH_2—), 3.87 (3H, s, OCH_3), 3.92 (2H, t, —CH_2—), 4.11 (2H, t, —CH_2—), 4.32 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.92 (1H, d, Ar–H), 7.08–7.30 (4H, m, Ar–H), 7.63–7.68 (3H, m, Ar–H), 8.01 (2H, d, Ar–H), 13.45 (1H, brs, NOH). ESI-MS *m/z*: 593 $[M + H]^+$, 595 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{29}H_{25}BrN_2O_7$: C, 58.70; H, 4.25; N, 4.72; found: C, 58.46; H, 4.06; N, 4.68.

Ethyl 5-(3-(5-chloro-3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5g). Yield: 54%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.09 (2H, t, —CH_2—), 3.86 (3H, s, OCH_3), 3.94 (2H, t, —CH_2—), 4.14 (2H, t, —CH_2—), 4.22 (3H, s, NOMe), 4.34 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.98 (1H, d, Ar–H), 7.03–7.20 (4H, m, Ar–H), 7.26 (1H, t, Ar–H), 7.58 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 8.02 (2H, d, Ar–H). ESI-MS *m/z*: 563 $[M + H]^+$, 565 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{27}ClN_2O_7$: C, 64.00; H, 4.83; N, 4.98; found: C, 63.79; H, 4.62; N, 4.87.

Ethyl 5-(3-(3-(methoxyimino)-5-methyl-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5h). Yield: 66%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, —CH_2—), 2.28 (3H, s, —CH_3), 3.86 (3H, s, OCH_3), 3.90 (2H, t, —CH_2—), 4.12 (2H, t, —CH_2—), 4.24 (3H, s, NOMe), 4.37 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.92 (1H, d, Ar–H), 7.04–7.16 (4H, m, Ar–H), 7.25 (1H, d, Ar–H), 7.62 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 8.01 (2H, d, Ar–H). ESI-MS *m/z*: 543 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{30}N_2O_7$: C, 68.62; H, 5.57; N, 5.16; found: C, 68.41; H, 5.39; N, 4.91.

Ethyl (Z)-5-(3-(5-bromo-3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5i). Yield: 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (3H, t, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, —CH_2—), 3.87 (3H, s, OCH_3), 3.93 (2H, t, —CH_2—), 4.16 (2H, t, —CH_2—), 4.24 (3H, s, NOMe), 4.37 (2H, q, $CO_2\underline{CH_2}CH_3$), 6.92 (1H, d, Ar–H), 7.06–7.28 (4H, m, Ar–H), 7.62–7.68 (3H, m, Ar–H), 7.98 (2H, d, Ar–H). ESI-MS *m/z*: 607

$[M + H]^+$, 609 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{27}BrN_2O_7$: C, 59.32; H, 4.48; N, 4.61; found: C, 59.14; H, 4.29; N, 4.54.

Ethyl 5-(3-(3-(ethoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (5j). Yield: 43%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36–1.41 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.13 (2H, t, $-CH_2-$), 3.87 (3H, s, OCH_3), 3.91 (2H, t, $-CH_2-$), 4.13 (2H, t, $-CH_2-$), 4.35–4.51 (4H, m, $NO\underline{CH_2}CH_3$ and $CO_2\underline{CH_2}CH_3$), 6.93 (1H, d, Ar–H), 7.06–7.19 (4H, m, Ar–H), 7.24 (1H, t, Ar–H), 7.56 (1H, d, Ar–H), 7.68 (1H, d, Ar–H), 7.99 (2H, d, Ar–H). ESI-MS *m/z*: 543 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{30}N_2O_7$: C, 68.62; H, 5.57; N, 5.16; found: C, 68.37; H, 5.31; N, 4.87.

Minimum inhibitory concentration determination. The hybrids **5a–j** together with the references **TAM16**, **RIF**, and **INH** were evaluated for their *in vitro* activities against MTB H37Rv and MDR-MTB *via* rapid direct susceptibility test technique [14,15]. The wells of a sterile 48-well plate were filled with 100-mL twofold diluted tested compounds and 100-mL MTB H37Rv or MDR-MTB suspension containing 4×10^{-3} mg cells. Pure medium replaced the diluted compounds in two wells as the positive control of growth and deionized water instead of the culture in other two wells as the negative control of growth in the plates. The plates were covered and sealed and then incubated at 37°C in a wet box. The positive and negative control wells show obvious difference after 3 days. The MIC was determined by observing the quantity and state of the cells in each test well by a continuous visual high magnification system and re-determined 7 days later. The MIC is defined as the concentration of the compound required to give complete inhibition of bacterial growth.

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