ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2019, *64*(2), 199-204
Doi: 10.33224/rrch.2019.64.2.10

TETRAETHYLENE GLYCOL TETHERED HOMONUCLEAR AND HETERONUCLEAR ISATIN DIMERS AND THEIR *IN VITRO* ANTI-MYCOBACTERIAL ACTIVITIES

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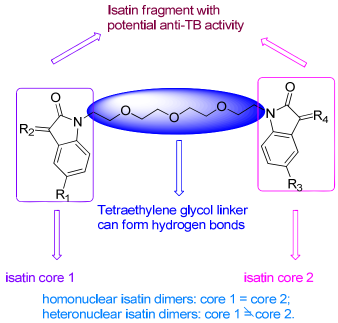
Received May 31, 2018

A series of novel homonuclear and heteronuclear isatin dimers tethered *via* tetraethylene glycol were synthesized and assessed for their *in vitro* anti-mycobacterial activities against MTB H37Rv and MDR-TB as well as cytotoxicity in VERO cells. The preliminary results showed that all dimers had potential anti-mycobacterial activities and acceptable cytotoxicity. Amongst them, the heteronuclear isatin dimer **10f** (MIC: 32 and 32 μg/mL) was found to be most active against MTB H37Rv and MDR-TB strains, which was as potent as or better than the first-line anti-tubercular agents rifampicin (MIC: 32 μg/mL) and isoniazid (MIC: >128 μg/mL) against MDR-TB, also demonstrated excellent cytotoxicity profile (CC_{50}: 250 μg/mL).



INTRODUCTION

Tuberculosis (TB) is a highly infectious deadliest disease caused predominately by *Mycobacterium tuberculosis* (MTB), and affects mainly the lungs (pulmonary TB).[1,2] The World Health Organization (WHO) has estimated that roughly 2 billion people harbor latent MTB infection globally, and around 10.4 million people fell ill and 1.67 million deaths in 2016.[1]

The first-line anti-TB agents such as isoniazid (**INH**), rifampicin (**RIF**), pyrazinamide (**PZA**) and ethambutol (**EMB**) play a pivotal role in the treatment of drug-susceptible MTB infected patients.[1] However, the reemergence of TB infection is complicated by the evolution of MTB new virulent forms including drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), extremely drug-resistant TB (XDR-TB) and totally drug resistant TB (TDR-TB).[3-5] Only a handful of candidates have entered human trials after the discovery of **RIF**, and the number is obviously insufficient.[4] All the above facts necessitated an urgent need to develop new anti-TB agents which are effective against both drug-susceptible and drug-resistant TB.

Isatins possess diverse biological and pharmacological properties such as antibacterial,[6,7] anticancer,[8] antimalarial[9] and anti-TB activities,[10-14] and isatin dimers also showed considerable anti-TB activity.[15-17] The structure-activity relationship (SAR) of isatin dimers revealed that the linker between the two isatins is crucial for their anti-TB

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activity,[18,19] so it's reasonable to optimize the linker. Tetraethylene glycol fragment has the potential to form hydrogen bonds that facilitate binding with active site,[20] so introduction of tetraethylene glycol as linker may enhance the anti-TB activity.

Based on the above research results, a series of novel tetraethylene glycol tethered homonuclear and heteronuclear isatin dimers were designed and synthesized in this study. These isatin dimers were also evaluated for their *in vitro* anti-TB activity against MTB $H_{37}Rv$ and MDR-TB, as well as cytotoxicity in VERO cell line. The illustration of the design strategy is depicted in Figure 1.

RESULTS AND DISCUSSION

Detailed synthetic route for tetraethylene glycol tethered homonuclear isatin dimers **5a-d** and heteronuclear dimers **10a-f** were depicted in Scheme 1 and 2, respectively. Intermediate **2** was obtained by treatment of tetraethylene glycol **1** with tosyl chloride (3 eq) in presence of triethylamine. C-5 substituted isatin **3** was alkylated with intermediate **2** in presence of K_2CO_3 to provide the desired targets **4a,b**, which were consequently condensation with semicarbazide or thiosemicarbazide hydrochloride in the presence of $NaHCO_3$ provided targets **5a-d**.[21,22]

5-Methylisatin **6** was reacted with the requested amine hydrochloride with potassium carbonate as base yielded the intermediates **7**. Intermediate **9** was obtained by treatment of 5-fluoroisatin **8** with intermediate **2**, and intermediate **9** was consequently utilized for the synthesis of desired tetraethylene glycol tethered heteronuclear isatin dimers **10a,b** with potassium carbonate as base. Finally, condensations of targets **10a,b** with hydroxylamine or methoxyamine or ethoxyamine hydrochloride in the presence of sodium bicarbonate provided targets **10c-f** (43~68%).[21]

All tetraethylene glycol tethered homonuclear isatin dimers **5a-d** and heteronuclear dimers **10a-f** were screened for their *in vitro* anti-mycobacterial activities against MTB H37Rv and MDR-TB strains as well as cytotoxicity in VERO cell line, and the results were listed in **Table 1**. The MDR-TB strain was resistant to **INH**, **RIF** and **EMB**. The minimum inhibitory concentration (MIC) is defined as the lowest concentration that inhibits the visible bacterial growth.

The preliminary results indicated that all isatin dimers displayed considerable anti-mycobacterial activities against the tested strains with MIC in a range of 32 to 512 μg/mL, and the potential activity may be partly attributed to their hydrogen bonding capacity. The structure-activity relationship (SAR) revealed that the anti-mycobacterial activity was greatly influenced by the substituents at C-3 and C-5 positions of isatin moiety: for C-3 position, the relative contribution order of the substituents to the activity was as follows: -NOMe > -NOEt > -O > -NOH and –$NNHCSNH_2$ > -$NNHCONH_2$; introduction of electron-withdrawing group -F at C-5 position of isatin motif favored the activity. In particular, the isatin dimer **10f** (MIC: 32 and 32 μg/mL) was found to be most active against MTB $H_{37}Rv$ and MDR-TB strains, which was comparable to or better than the first-line anti-TB agents **RIF** (MIC: 32 μg/mL) and **INH** (MIC: >128 μg/mL) against MDR-TB, could act as a lead for further optimization.

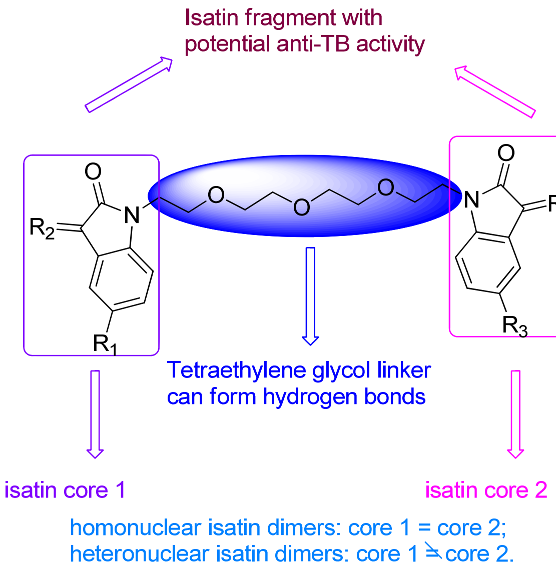
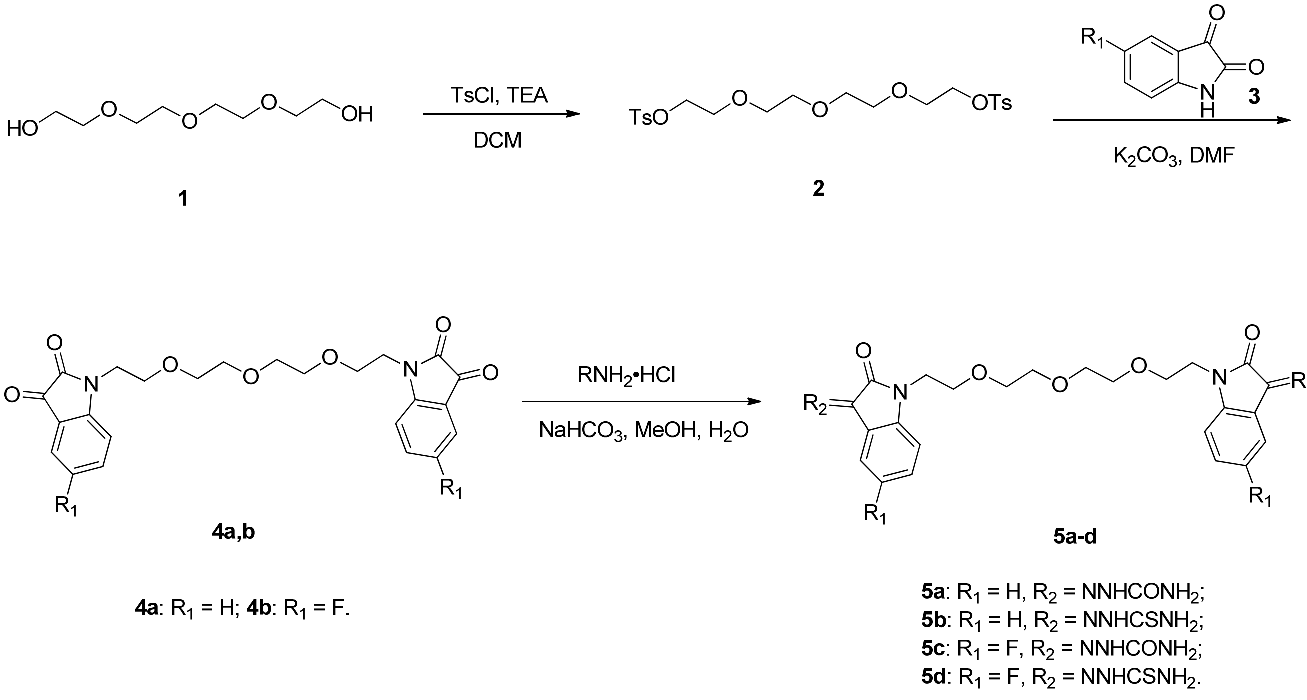


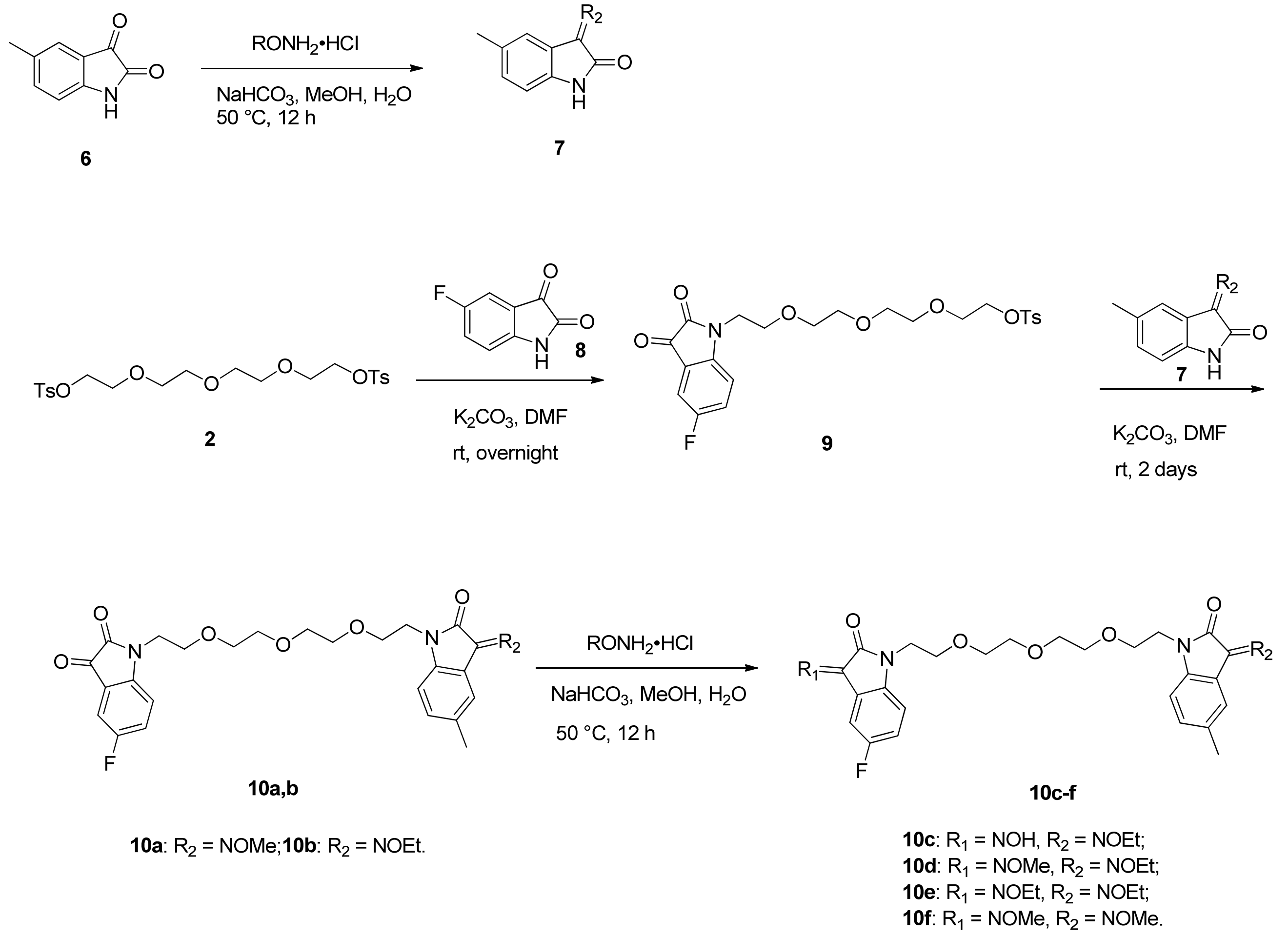
Fig. 1 – Design strategy of tetraethylene glycol tethered homonuclear and heteronuclear isatin dimers.



4a: R_1 = H; **4b**: R_1 = F.

5a: R_1 = H, R_2 = $NNHCONH_2$;
5b: R_1 = H, R_2 = $NNHCSNH_2$;
5c: R_1 = F, R_2 = $NNHCONH_2$;
5d: R_1 = F, R_2 = $NNHCSNH_2$.

Scheme 1 – Synthesis of tetraethylene glycol tethered homonuclear isatin dimers **5a-d**.



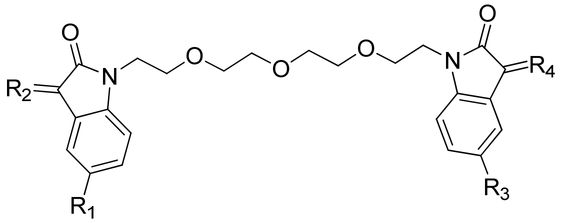
10a: R_2 = NOMe;**10b**: R_2 = NOEt.

10c: R_1 = NOH, R_2 = NOEt;
10d: R_1 = NOMe, R_2 = NOEt;
10e: R_1 = NOEt, R_2 = NOEt;
10f: R_1 = NOMe, R_2 = NOMe.

Scheme 2 – Synthesis of heteronuclear isatin dimers **10a-f**.

Table 1

Structures, anti-mycobacterial activities and cytotoxicity of homonuclear isatin dimers **5a-d** and heteronuclear dimers **10a-f**



Compd.	R_1	R_2	R_3	R_4	MIC (μg/mL)		^{b}CC$_{50}$ (μg/mL)
					^{a}MTB	MDR-TB	
5a	H	NNHCONH$_2$	H	NNHCONH$_2$	128	256	62.5
5b	H	NNHCSNH$_2$	H	NNHCSNH$_2$	128	128	31.2
5c	F	NNHCONH$_2$	F	NNHCONH$_2$	64	128	31.2
5d	F	NNHCSNH$_2$	F	NNHCSNH$_2$	64	32	15.6
10a	F	O	Me	NOMe	128	128	62.5
10b	F	O	Me	NOEt	128	256	62.5
10c	F	NOH	Me	NOEt	256	512	125
10d	F	NOMe	Me	NOEt	64	64	31.2
10e	F	NOEt	Me	NOEt	128	64	125
10f	F	NOMe	Me	NOMe	32	32	250
INH					0.05	>128	125
RIF					0.39	32	500

[a] MTB: MTB H37Rv
[b] CC$_{50}$: The 50% cytotoxic concentration in a mammalian VERO cell line.

Interestingly, the resistance index (RI) for a significant part of tetraethylene glycol tethered isatin dimers was around 1, suggesting they may bear a novel action mechanism.

The isatin dimers were subsequently examined for toxicity (the 50% cytotoxic concentration/CC$_{50}$, causing visible morphological changes in 50% of the cells with respect to cell control, determined with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide cell viability assay) in a mammalian VERO cell line.[21] After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into a formazan product and the results were reported in **Table 1**. The results showed that all isatin dimers showed acceptable cytotoxicity against VERO cell line with CC$_{50}$ of 15.6-250 μg/mL. The most active isatin dimer **10f** (CC$_{50}$: 250 μg/mL) showed the lowest cytotoxicity, which was comparable to **RIF** (MIC: 500 μg/mL) and **INH** (MIC: 125 μg/mL), warrant further investigation.

EXPERIMENTAL

The general procedure for preparing targets 5a-d and 10a-f

A mixture of tetraethylene glycol **1** (10 mmol), tosyl chloride (30 mmol) and triethylamine (50 mmol) in DCM (100 mL) was stirred at room temperature overnight, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with PE:EA=1:2 to give the intermediate **2**.

The mixture of intermediate **2** (1 mmol), potassium carbonate (10 mmol) and isatins **3** (0.5 mmol) in DMF (10 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 PE:EA=1:2 to give the key intermediates **4a,b**. To a mixture of intermediates **4a,b** (1 mmol) in water (10 mL) and THF (50 mL), the requested amine hydrochloride (5 mmol) was added. The mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the mixture was extracted with EA (100 mL*2). The combined organic layers were washed with H_2O (100 mL*2) and brine (100 mL) in sequence, and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel chromatography eluted with PE:EA=1:2 to give the homonuclear isatin dimers **5a-d**.

A mixture of 5-methylisatin **6** (1 mmol), potassium carbonate (5 mmol) and methoxyamine or ethoxyamine hydrochloride (1.2 mmol) in a mixture of water (5 mL) and THF (30 mL) was stirred at 50 °C for 12 h. After cooling to room temperature, the mixture was extracted with EA (30 mL*2). The combined organic layers were washed with H_2O (20 mL*2) and brine (20 mL) in sequence, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. The crude intermediates **7** were obtained as a yellow solid which were used directly without further purification.

The mixture of intermediate **2** (2 mmol), potassium carbonate (10 mmol) and 5-fuloroisatin **8** (1 mmol) in DMF (10 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 PE:EA=1:2 to give the intermediates **9**. A mixture of intermediate **9** (1 mmol), intermediate **7** (1 mmol) and potassium carbonate (10 mmol) in DMF (10 mL) was stirred at room temperature for 2 days. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with PE:EA=1:2 to give the desired heteronuclear isatin dimers **10a,b**.

To a mixture of heteronuclear isatin dimers **10a,b** (1 mmol) in water (10 mL) and THF (50 mL), methoxyamine or ethoxyamine hydrochloride (1.4 mmol) was added. The mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the mixture was extracted with EA (100 mL*2). The combined organic layers were washed with H_2O (100 mL*2) and brine (100 mL) in sequence, and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a residue which was purified by silica gel chromatography eluted with PE:EA=1:2 to give the desired products **10c-f**.

1.1. *1,1'-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(3-(ethoxyimino)indolin-2-one)* (**5a**)
Yellow solid, yield: 52%. ^1H NMR (400 MHz, DMSO-d_6) 1.38 (6H, t, $2\times NOCH_2\underline{CH_3}$), 3.38 (4H, t, $-CH_2CH_2-$), 3.44 (4H, t, $-CH_2CH_2-$), 3.62 (4H, t, $-CH_2CH_2-$), 3.86 (4H, t, $-CH_2CH_2-$), 4.48 (4H, q, $2\times NO\underline{CH_2}CH_3$), 7.06 (2H, t, Ar-H), 7.15 (2H, d, Ar-H), 7.44 (2H, t, Ar-H), 7.88 (2H, d, Ar-H). ESI-MS m/z: 539 $[M+H]^+$, 561 $[M+Na]^+$.

1.2. *2,2'-(1,1'-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(2-oxoindoline-1-yl-3-ylidene))bis(hydrazinecarboxamide)* (**5b**)
Yellow solid, yield: 17%. ^1H NMR (400 MHz, DMSO-d_6) 3.38 (4H, t, $-CH_2CH_2-$), 3.45 (4H, t, $-CH_2CH_2-$), 3.66 (4H, t, $-CH_2CH_2-$), 3.92 (4H, t, $-CH_2CH_2-$), 7.12-7.20 (8H, m, $2\times NNHCO\underline{NH_2}$ and Ar-H), 7.38 (2H, t, Ar-H), 7.65 (2H, d, Ar-H), 11.70 (2H, s, $2\times N\underline{NH}CONH_2$). ESI-MS m/z: 589 $[M+Na]^+$.

1.3. *2,2'-(1,1'-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(5-fluoro-2-oxoindoline-1-yl-3-ylidene))bis(hydrazinecarboxamide)* (**5c**)
Yellow solid, yield: 27%. ^1H NMR (400 MHz, DMSO-d_6) δ 3.39 (4H, t, $-CH_2CH_2-$), 3.47 (4H, t, $-CH_2CH_2-$), 3.65 (4H, t, $-CH_2CH_2-$), 3.92 (4H, t, $-CH_2CH_2-$), 7.21-7.26 (8H, m, Ar-H and $2\times NNHCO\underline{NH_2}$), 7.50 (2H, d, Ar-H), 11.62 (2H, s, $2\times N\underline{NH}CONH_2$). ESI-MS m/z: 625 $[M+Na]^+$.

1.4. *2,2'-(1,1'-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(5-fluoro-2-oxoindoline-1-yl-3-ylidene))bis(hydrazinecarbothioamide)* (**5d**)
Yellow solid, yield: 19%. ^1H NMR (400 MHz, DMSO-d_6) δ 3.40 (4H, t, $-CH_2CH_2-$), 3.48 (4H, t, $-CH_2CH_2-$), 3.67 (4H, t, $-CH_2CH_2-$), 3.92 (4H, t, $-CH_2CH_2-$), 7.24 (4H, s, Ar-H), 7.56 (2H, d, Ar-H), 8.82, 9.18 (4H, s, $2\times NNHCS\underline{NH_2}$), 12.32 (2H, s, $2\times N\underline{NH}CSNH_2$). ESI-MS m/z: 635 $[M+H]^+$.

1.5. *5-fluoro-1-(2-(2-(2-(2-(3-(methoxyimino)-5-methyl-2-oxoindolin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indoline-2,3-dione* (**10a**)
Yellow solid, yield: 83%. ^1H NMR (400 MHz, DMSO-d_6) δ 2.29 (3H, s, $-CH_3$), 3.42 (4H, t, $-CH_2CH_2-$), 3.48 (4H, t, $-CH_2CH_2-$), 3.67 (4H, t, $-CH_2CH_2-$), 3.84 (4H, t, $-CH_2CH_2-$), 4.21 (3H, s, NOMe), 7.06 (1H, d, Ar-H), 7.24-7.27 (2H, m, Ar-H), 7.44 (1H, d, Ar-H), 7.50 (1H, t, Ar-H), 7.70 (1H, s, Ar-H). ESI-MS m/z: 536 $[M+Na]^+$.

1.6. *1-(2-(2-(2-(2-(3-(ethoxyimino)-5-methyl-2-oxoindolin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-fluoroindoline-2,3-dione* (**10b**)
Yellow solid, yield: 72%. ^1H NMR (400 MHz, DMSO-d_6) δ 1.40 (3H, t, $NOCH_2\underline{CH_3}$), 2.29 (3H, s, $-CH_3$), 3.41 (4H, t, $-CH_2CH_2-$), 3.48 (4H, t, $-CH_2CH_2-$), 3.62 (4H, t, $-CH_2CH_2-$), 3.84 (4H, t, $-CH_2CH_2-$), 4.47 (4H, q, $2\times NO\underline{CH_2}CH_3$), 7.05 (1H, t, Ar-H), 7.17-7.31 (3H, m, Ar-H), 7.43-7.50 (1H, m, Ar-H), 7.65-7.71 (1H, m, Ar-H). ESI-MS m/z: 550 $[M+Na]^+$.

1.7. *1-(2-(2-(2-(2-(2-(ethoxyimino)-5-methyl-3-oxoindolin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-fluoro-3-(hydroxyimino)indolin-2-one* (**10c**)
Yellow solid, yield: 51%. ^1H NMR (400 MHz, DMSO-d_6) 1.40 (3H, t, $NOCH_2\underline{CH_3}$), 2.31 (3H, s, $-CH_3$), 3.42 (4H, t, $-CH_2CH_2-$), 3.49 (4H, t, $-CH_2CH_2-$), 3.64 (4H, t, $-CH_2CH_2-$), 3.87 (4H, t, $-CH_2CH_2-$), 4.49 (4H, q, $2\times NO\underline{CH_2}CH_3$), 7.07 (1H, d, Ar-H), 7.20 (1H, d, Ar-H), 7.27-7.30 (2H, m, Ar-H), 7.73-7.78 (2H, m, Ar-H), 13.73 (1H, s, NOH). ESI-MS m/z: 565 $[M+Na]^+$.

1.8. *1-(2-(2-(2-(2-(2-(ethoxyimino)-5-methyl-3-oxoindolin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-fluoro-3-(methoxyimino)indolin-2-one* (**10d**)
Yellow solid, yield: 61%. ^1H NMR (400 MHz, DMSO-d_6) 1.40 (3H, t, $NOCH_2\underline{CH_3}$), 2.28 (3H, s, $-CH_3$), 3.40 (4H, t, $-CH_2CH_2-$), 3.46 (4H, t, $-CH_2CH_2-$), 3.61 (4H, t, $-CH_2CH_2-$), 3.83 (4H, t, $-CH_2CH_2-$), 4.24-4.50 (5H, m, NOMe and $NO\underline{CH_2}CH_3$), 7.03-7.30 (4H, m, Ar-H), 7.64 (1H, d, Ar-H), 7.69 (1H, d, Ar-H). ESI-MS m/z: 579 $[M+Na]^+$.

1.9. *3-(ethoxyimino)-1-(2-(2-(2-(2-(2-(ethoxyimino)-5-methyl-3-oxoindolin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-5-fluoroindolin-2-one* (**10e**)
Yellow solid, yield: 45%. ^1H NMR (400 MHz, DMSO-d_6) 1.40 (6H, t, $2\times NOCH_2\underline{CH_3}$), 2.29 (3H, s, $-CH_3$), 3.40 (4H, t, $-CH_2CH_2-$), 3.46 (4H, t, $-CH_2CH_2-$), 3.62 (4H, t, $-CH_2CH_2-$), 3.85 (4H, t, $-CH_2CH_2-$), 4.50 (4H, q, $2\times NO\underline{CH_2}CH_3$), 7.05 (1H, d, Ar-H), 7.19 (1H, d, Ar-H), 7.24 (1H, d, Ar-H), 7.31 (1H, d, Ar-H), 7.64 (1H, d, Ar-H), 7.71 (1H, d, Ar-H). ESI-MS m/z: 593 $[M+Na]^+$.

1.10. *5-fluoro-3-(methoxyimino)-1-(2-(2-(2-(2-(2-(methoxyimino)-5-methyl-3-oxoindolin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)indolin-2-one* (**10f**)
Yellow solid, yield: 74%. ^1H NMR (400 MHz, DMSO-d_6) 2.29 (3H, s, $-CH_3$), 3.40 (4H, t, $-CH_2CH_2-$), 3.47 (4H, t, -

CH_2CH_2-), 3.62 (4H, t, -CH_2CH_2-), 3.85 (4H, t, -CH_2CH_2-), 4.28 (6H, s, 2×NOMe), 7.06 (1H, s, Ar-H), 7.19-7.33 (3H, m, Ar-H), 7.66-7.69 (2H, m, Ar-H). ESI-MS m/z: 565 $[M+Na]^+$.

MIC determination

The homonuclear isatin dimers **5a-d** and heteronuclear dimers **10a-f** along with the references **RIF** and **INH** were evaluated for their *in vitro* activities against MTB H37Rv and MDR-TB *via* rapid direct susceptibility test technique.[21,22] MTB H37Rv and MDR-TB strains were obtained from Chinese Center For Disease Control And Prevention. The wells of a sterile 48-well plate were filled with 100 mL two-fold diluted tested compounds and 100 mL MTB H37Rv or MDR-TB 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, then incubated at 37 °C in a wet box. The positive and negative control wells should 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.

Cytotoxicity

The synthesized homonuclear isatin dimers **5a-d** and heteronuclear dimers **10a-f** along with the references **RIF** and **INH** were further examined for toxicity (CC_{50}) determined with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide cell viability assay in a mammalian VERO cells (obtained from Chinese Center For Disease Control And Prevention).[21] The VERO cells were maintained in culture medium (Minimum Essential Medium with Earle's salt, supplemented with 10% fetal bovine serum) at 37 °C under 5% CO_2. Cells were seeded in 96-well plates at the plating density of 1×10^4 cells per well and allowed to recover for 24 h. Culture medium was replaced by assay medium containing the compound to be tested or drug-free. After 72 h of exposure, cells were harvested and cell viability was assessed by MTT assay. The CC_{50} values were calculated by Bliss analyses.

CONCLUSIONS

In summary, a series novel tetraethylene glycol tethered homonuclear and heteronuclear isatin dimers were designed, synthesized and examined for their *in vitro* anti-mycobacterial activities against MTB H37Rv and MDR-TB as well as cytotoxicity in this paper. All the synthesized homonuclear and heteronuclear isatin dimers exhibited promising activities against the tested strains and excellent cytotoxicity profile. The most active isatin dimer **10f** also showed the lowest cytotoxicity, and it could act as a starting point for further optimization.

Acknowledgements: This work was supported by the National Natural Science Foundation of China (Grant No. 51801068, 51701189), the Science and Technology Planning Project in Henan Province (Grant No. 132300410476) and Key Scientific Research projects of Colleges and Universities in Henan Province (Grant No. 19A430019).

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