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Graphical Abstract

Benzofuran-isatin-imine hybrids tethered *via* different length alkyl linkers: Design, synthesis and *in vitro* evaluation of anti-tubercular and anti-bacterial activities as well as cytotoxicity

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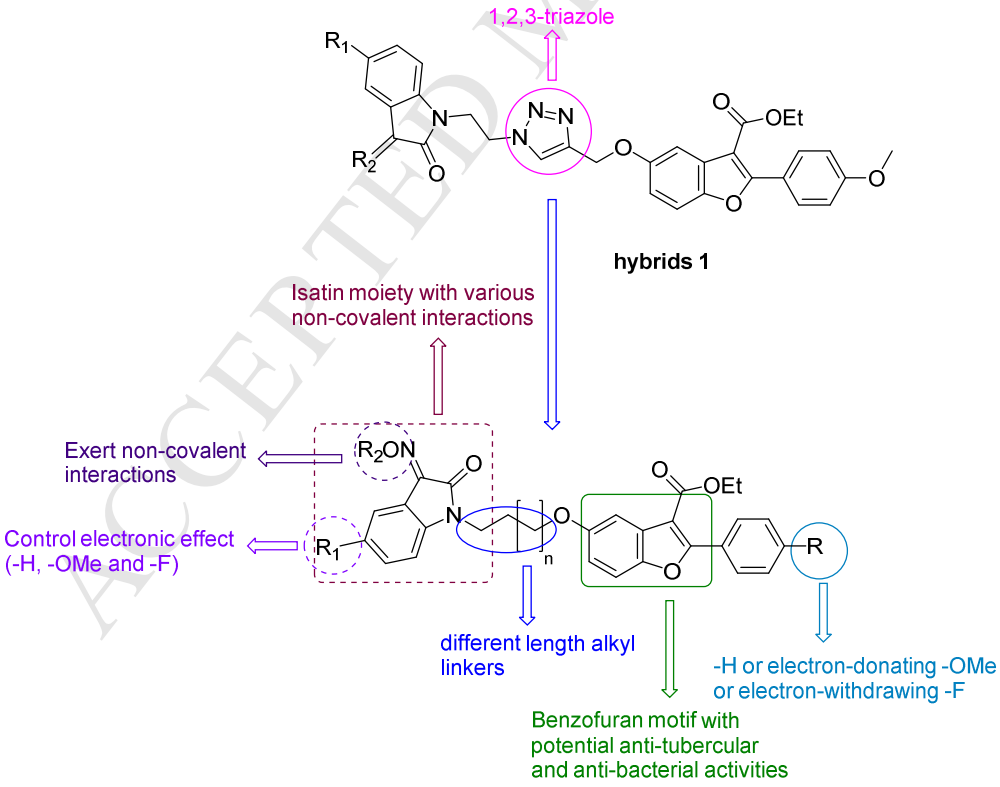
1 Academy of Advanced Interdisciplinary Studies, Qilu University of Technology (Shandong Academy of Sciences), Jinan, PR China;

2 School of Chemistry and Pharmaceutical Engineering, Qilu University of Technology (Shandong Academy of Sciences), Jinan, PR China;

3 Department of Medical Imaging, Jinling Hospital, Medical School of Nanjing University, Nanjing, PR China;

4 State Key Laboratory of Biobased Material and Green Papermaking (LBMP), Qilu University of Technology (Shandong Academy of Sciences), Jinan, PR China;

5 Key Laboratory of Hubei Province for Coal Conversion and New Carbon Materials, Wuhan University of Science and Technology, Wuhan, P R China.



All benzofuran-isatin-imine hybrids **7a-v** exhibited considerable *in vitro* anti-TB and anti-bacterial

activities, as well as acceptable cytotoxicity towards VERO. The most active hybrid **7j** (MIC: <0.016, 0.062 and 0.16 μg/mL, respectively) was >4.8 and ≥48 folds more potent than the first line anti-TB agents **RIF** and **INH** against both drug-sensitive MTB $H_{37}Rv$ and MDR-TB isolates, respectively. Moreover, hybrid **7j** also demonstrated promising anti-bacterial activities with MIC values of ≤1 μg/mL against the majority of the tested Gram-negative and Gram-positive pathogens, which was comparable to vancomycin (MIC: 0.5-4 μg/mL) and **CPFX** (MIC: 0.125-8 μg/mL) against Gram-positive bacteria, but slightly less potent than **CPFX** (MIC: ≤0.03-0.5 μg/mL) against Gram-negative bacteria. The results indicated that benzofuran-isatin-imine hybrids could act as candidates for the development of anti-TB and anti-bacterial agents.

Benzofuran-isatin-imine hybrids tethered *via* different length alkyl linkers: Design, synthesis and *in vitro* evaluation of anti-tubercular and anti-bacterial activities as well as cytotoxicity

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Abstract: Herein we report the design and synthesis of twenty-two novel benzofuran-isatin-imine hybrids **7a-v** tethered through propylene, butylene, pentylene and hexylene, and for the evaluation of their *in vitro* anti-tubercular and anti-bacterial activities as well as cytotoxicity. All benzofuran-isatin-imine hybrids exhibited considerable *in vitro* anti-TB (MIC: <0.016-0.218 μg/mL and 0.062-14.15 μg/mL against drug-sensitive and MDR MTB, respectively) and anti-bacterial (MIC: 0.25-64 μg/mL and 0.06-16 μg/mL against Gram-positive and Gram-negative strains, respectively) activities. All of them also showed acceptable cytotoxicity towards VERO (CC_{50}: 8-128 μg/mL). The most active hybrid **7j** (MIC: <0.016, 0.062 and 0.16 μg/mL, respectively) was >4.8 and ≥48 folds more potent than the first line anti-TB agents **RIF** and **INH** against both drug-sensitive MTB $H_{37}Rv$ and MDR-TB isolates, respectively. Moreover, hybrid **7j** also demonstrated promising anti-bacterial activities with MIC values of ≤1 μg/mL against the majority of the tested Gram-negative and Gram-positive pathogens, which was comparable to vancomycin (MIC: 0.5-4 μg/mL) and **CPFX** (MIC: 0.125-8 μg/mL) against Gram-positive bacteria, but slightly less potent than **CPFX** (MIC: ≤0.03-0.5 μg/mL) against Gram-negative bacteria. The

*Corresponding author: rggaofeng@hotmail.com (Feng Gao); jiaqixiao@qlu.edu.cn (Jiaqi Xiao)

results indicated that benzofuran-isatin-imine hybrids could act as candidates for the development of anti-TB and anti-bacterial agents.

Keywords: benzofuran; isatin; imine; hybrid compounds; anti-tubercular; anti-bacterial; multi-drug resistant; structure-activity relationship

1. Introduction

Infections, caused by Gram-positive and Gram-negative bacteria, have already put a heavy burden on the global health system [1,2]. Antibiotics are the most important weapons for human to fight against bacterial infection, but the overuse and misuse of antibiotics have already triggered increased drug resistance [3]. Approximately 700,000 drug-resistant pathogens caused deaths annually throughout the world and the number may increase to 10 million in the year 2050 if current trends continue.

Tuberculosis (TB), mainly caused by the bacterium *Mycobacterium tuberculosis* (MTB), is the leading cause from a single infectious agent (above HIV/AIDS) [4]. The World Health Organization (WHO) report estimated that that around 10 million people developed TB disease and around 1.3 million deaths happened in 2017 [4]. Drug-resistant TB (DR-TB), especially multidrug-resistant TB (DMR-TB), is one of the major reasons for the incremental prevalence of TB [5]. Obviously, novel anti-TB agents which are effective against both drug-susceptible TB and DR-TB especially MDR-TB are needed to control and eradication of this plague.

There are several anti-TB and anti-bacterial candidates which are under different stages of clinical trials. The efficiency of the candidates rely on the structure. Heterocyclic compounds play a dominate role in the development of new drugs as evidenced by the fact that 80% of top-selling drugs contain heterocycles [6]. Heterocycles can serve as useful tools to manipulate lipophilicity, polarity, and hydrogen bonding capacity of molecules, which may lead to improved pharmacological, pharmacokinetic, toxicological, and physicochemical properties of drug candidates and ultimately drugs [7].

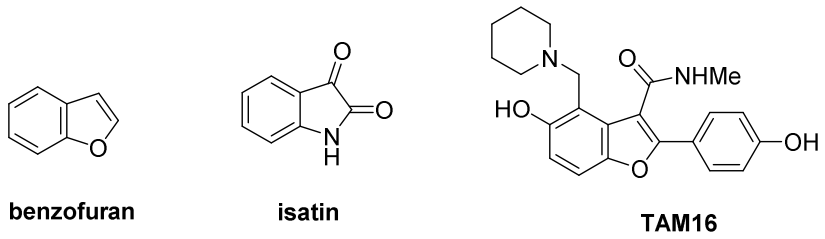


Figure 1 Chemical structures of benzofuran, isatin and **TAM16**

Benzofuran (constituted by fused benzene and furan rings) and isatin (1*H*-indole-2,3-dione, **Figure 1**), are fundamental structure units in a variety of biologically active natural products [8,9]. Benzofuran and isatin have the ability to exert several noncovalent interactions such as Van der Waals force and hydrogen bonds [10,11], and their derivatives possess various biological properties such as anti-cancer [12,13], anti-viral [14,15], anti-bacterial [16,17] and anti-tubercular [18,19] activities. Many benzofuran- or isatin-based derivatives have already been used for the treatment various diseases, so benzofuran and isatin derivatives occupy an important position in the development of new drugs.

Molecular hybridization, a method to form the novel compounds which has the potential to overcome cross resistance and improve efficacy compared to the parent drugs, represents a promising strategy in the development of new drugs [20,21]. Benzofuran derivative **TAM16** (**Figure 1**) not only showed broad-spectrum *in vitro* anti-bacterial activities, but also exhibited excellent *in vivo* physiochemical, toxicological and pharmacological properties [22,23]. Our previous results indicated that benzofuran-isatin hybrids **1** exhibited promising *in vitro* anti-TB activities against both drug-susceptible and MDR-TB strains, demonstrating that benzofuran-isatin hybrids could act as potential anti-TB candidates [24-31]. The structure-activity relationship (SAR) for isatin-containing hybrids indicated that the linker between the isatin and the other pharmacophores and imines at C-3 position of isatin moiety played a pivotal role in exertion of the anti-TB and anti-bacterial activities [32-36].

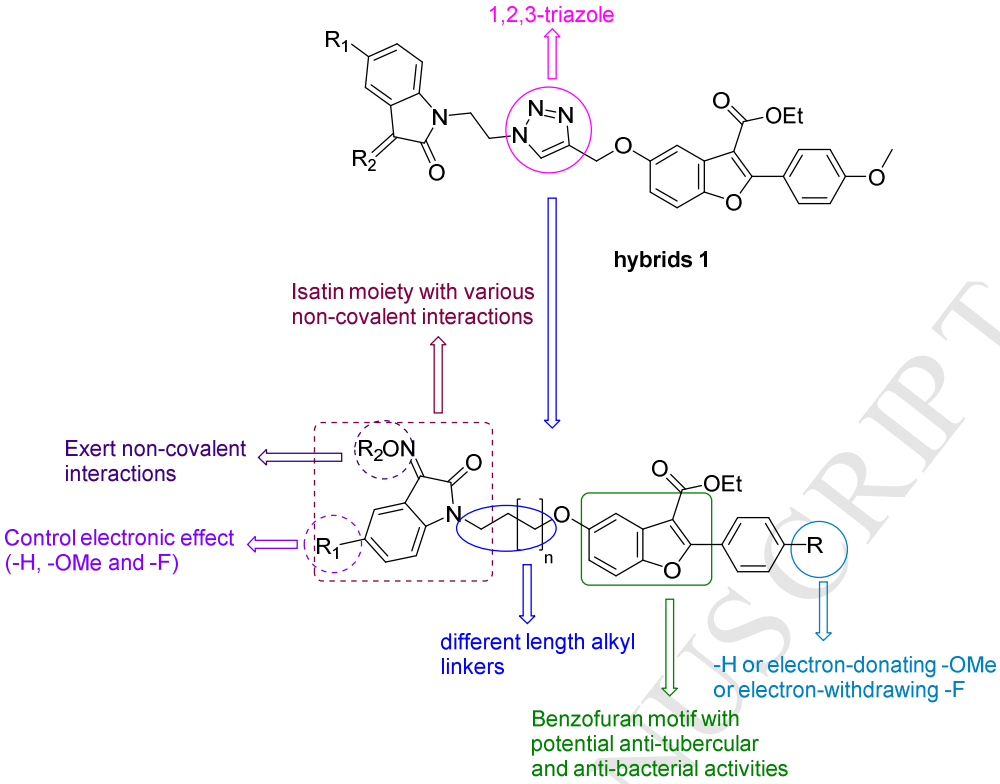


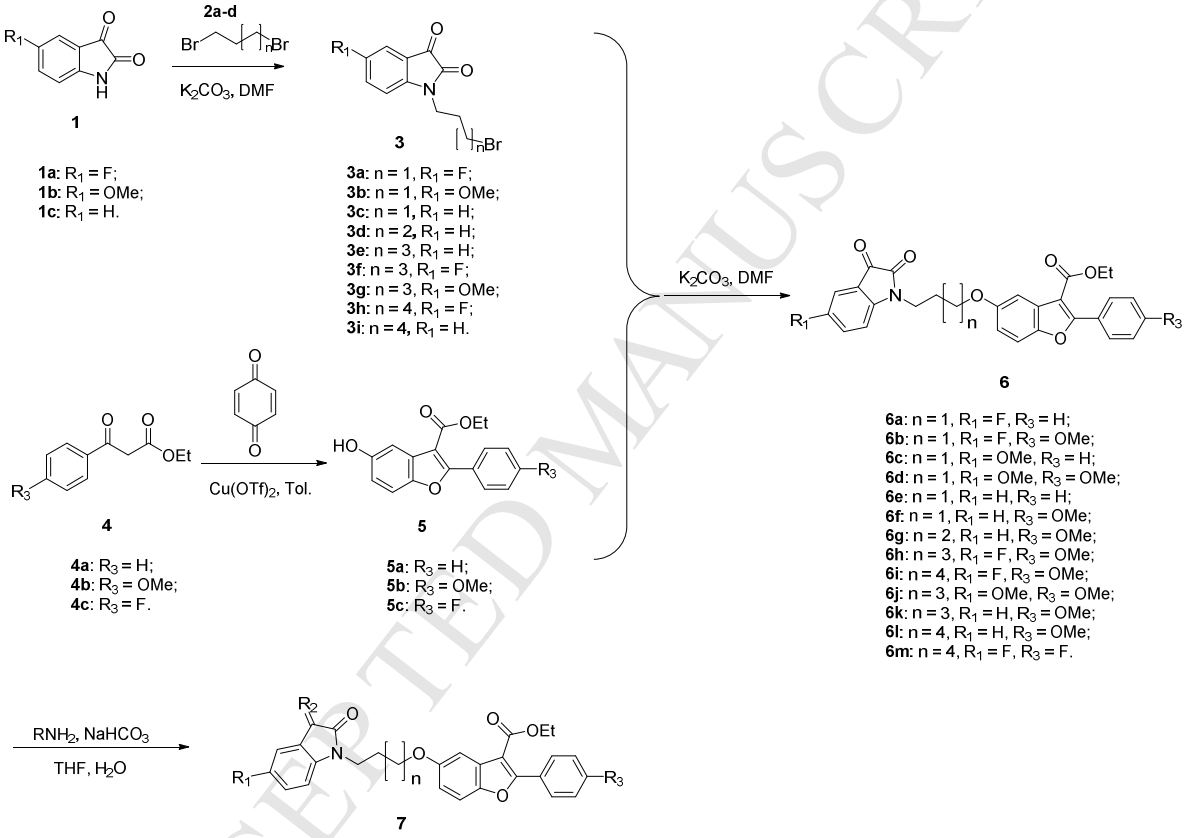
Figure 2 Design strategies for benzofuran-isatin-imine hybrids tethered *via* different length alkyl linkers

Based on the facts stated above and as a continuous program to develop novel anti-TB and anti-bacterial candidates, a series of novel benzofuran-isatin-imine hybrids **7a-v** tethered *via* different length alkyl linkers were designed and synthesized. *In vitro* anti-mycobacterial and anti-bacterial activities, together with cytotoxicity of the hybrids in VERO cells were also investigated. The design strategy was depicted in **Figure 2**.

2 Results and discussion

Benzofuran-isatin-imine hybrids **7a-k** were prepared following the synthetic route described in **Scheme 1**. Alkylation of 5-methoxyisatin/5-fluoroisatin/isatin **1a-c** with 1,3-dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane and 1,6-dibromohextane **2a-d** provided *N*-(3-bromopropyl/4-bromobutyl/5-bromopentyl/6-bromohexyl)isatin derivatives **3a-i** with yields 62-76% [15,16]. The reaction of ethyl 3-(4-substituted

phenyl)-3-oxopropanoates **4a-c** with benzoquinone in the presence of copper (II) triflate ($Cu(OTf)_2$) as catalyst yielded benzofuran intermediates **5a-c** [13]. Treatment of isatin derivatives **3a-i** and benzofuran intermediate **5a-c** with potassium carbonate as base afforded the key intermediates **6a-m** (51-68%). Finally, condensations of **6a-m** with the corresponding amine hydrochlorides in the presence of sodium bicarbonate gave benzofuran-isatin-imine hybrids **7a-v** (18-73%). The chemical structures and yields of target compounds **7a-v** were listed in **Table 1**.



1a: R_1 = F;
1b: R_1 = OMe;
1c: R_1 = H.

3a: n = 1, R_1 = F;
3b: n = 1, R_1 = OMe;
3c: n = 1, R_1 = H;
3d: n = 2, R_1 = H;
3e: n = 3, R_1 = H;
3f: n = 3, R_1 = F;
3g: n = 3, R_1 = OMe;
3h: n = 4, R_1 = F;
3i: n = 4, R_1 = H.

4a: R_3 = H;
4b: R_3 = OMe;
4c: R_3 = F.

5a: R_3 = H;
5b: R_3 = OMe;
5c: R_3 = F.

6a: n = 1, R_1 = F, R_3 = H;
6b: n = 1, R_1 = F, R_3 = OMe;
6c: n = 1, R_1 = OMe, R_3 = H;
6d: n = 1, R_1 = OMe, R_3 = OMe;
6e: n = 1, R_1 = H, R_3 = H;
6f: n = 1, R_1 = H, R_3 = OMe;
6g: n = 2, R_1 = H, R_3 = OMe;
6h: n = 3, R_1 = F, R_3 = OMe;
6i: n = 4, R_1 = F, R_3 = OMe;
6j: n = 3, R_1 = OMe, R_3 = OMe;
6k: n = 3, R_1 = H, R_3 = OMe;
6l: n = 4, R_1 = H, R_3 = OMe;
6m: n = 4, R_1 = F, R_3 = F.

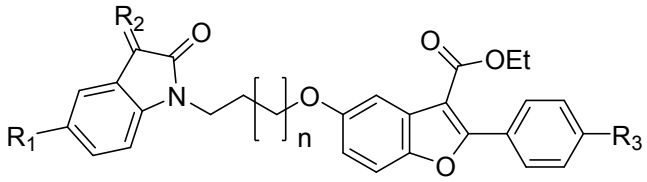
7a: n = 1, R_1 = F, R_2 = NOMe, R_3 = H;
7b: n = 1, R_1 = F, R_2 = NOMe, R_3 = OMe;
7c: n = 1, R_1 = F, R_2 = NOEt, R_3 = OMe;
7d: n = 1, R_1 = OMe, R_2 = NOMe, R_3 = H;
7e: n = 1, R_1 = OMe, R_2 = NOMe, R_3 = OMe;
7f: n = 1, R_1 = OMe, R_2 = NOEt, R_3 = OMe;
7g: n = 1, R_1 = H, R_2 = NOMe, R_3 = H;
7h: n = 1, R_1 = H, R_2 = NOMe, R_3 = OMe;
7i: n = 1, R_1 = H, R_2 = NOEt, R_3 = OMe;
7j: n = 2, R_1 = H, R_2 = NOMe, R_3 = OMe;
7k: n = 2, R_1 = H, R_2 = NOEt, R_3 = OMe;
7l: n = 3, R_1 = F, R_2 = NOMe, R_3 = OMe;
7m: n = 3, R_1 = F, R_2 = NOEt, R_3 = OMe;
7n: n = 4, R_1 = F, R_2 = NOMe, R_3 = OMe;
7o: n = 4, R_1 = F, R_2 = $NNHCSNH_2$, R_3 = OMe;
7p: n = 4, R_1 = F, R_2 = NOMe, R_3 = F;
7q: n = 3, R_1 = OMe, R_2 = NOMe, R_3 = OMe;
7r: n = 3, R_1 = H, R_2 = NOH, R_3 = OMe;
7s: n = 3, R_1 = H, R_2 = NOMe, R_3 = OMe;
7t: n = 4, R_1 = H, R_2 = NOMe, R_3 = OMe;
7u: n = 4, R_1 = H, R_2 = NOEt, R_3 = OMe;
7v: n = 4, R_1 = H, R_2 = $NNHCSNH_2$, R_3 = OMe.

Scheme 1 Synthesis of benzofuran-isatin-imine hybrids **7a-v**

The anti-mycobacterial activity of benzofuran-isatin-imine hybrids **7a-v**, their precursors **6h,i** and **6l,m**, together with the references **TAM16**, ciprofloxacin (**CPFX**),

rifampicin (**RIF**) and isoniazid (**INH**) against MTB $H_{37}Rv$ strains and the cytotoxicity towards VREO cells were studied and the results were presented in **Table 2**.

Table 1. Chemical structures and yields of benzofuran-isatin-imine hybrids **7a-v**



7

Compounds	n	R_1	R_2	R_3	Yield (%)
7a	1	F	NOMe	H	59
7b	1	F	NOMe	OMe	79
7c	1	F	NOEt	OMe	49
7d	1	OMe	NOMe	H	83
7e	1	OMe	NOMe	OMe	58
7f	1	OMe	NOEt	OMe	46
7g	1	H	NOMe	H	45
7h	1	H	NOMe	OMe	68
7i	1	H	NOEt	OMe	51
7j	2	H	NOMe	OMe	69
7k	2	H	NOEt	OMe	53
7l	3	F	NOMe	OMe	67

7m	3	F	NOEt	OMe	43
7n	4	F	NOMe	OMe	42
7o	4	F	$NNHCSNH_2$	OMe	18
7p	4	F	NOMe	F	49
7q	3	OMe	NOMe	OMe	36
7r	3	H	NOH	OMe	73
7s	3	H	NOMe	OMe	39
7t	4	H	NOMe	OMe	71
7u	4	H	NOEt	OMe	62
7v	4	H	$NNHCSNH_2$	OMe	27

All benzofuran-isatin-imine hybrids **7a-v** and their precursors **6h,i** and **6l,m** exhibited excellent *in vitro* anti-mycobacterial activities against MTB $H_{37}Rv$, and MIC values ranging from < 0.016 to 0.218 μg/mL were found. All hybrids were more active than the reference **CPFX** (MIC: 0.291 μg/mL), and the majority of them were also more potent than the first-line anti-TB agents **INH** and **RIF** (MIC: 0.078 μg/mL). In particular, among all the hybrids, sixteen compounds **6i**, **6m**, **7d-l**, **7n**, **7o** and **7t-v** (MIC: < 0.016 μg/mL), held comparable activities to **TAM16** (MIC: < 0.016 μg/mL) against MTB $H_{37}Rv$.

Table 2 *In vitro* anti-mycobacterial activity and cytotoxicity of benzofuran-isatin-imine hybrids **7a-v** and their precursors **6h,i** and **6l,m**

Compounds	MIC (μg/mL)	CC_{50} (μg/mL)	SI
6h	0.064	512	8,000

6i	<0.016	1,024	>64,000
6l	0.062	256	4,129
6m	<0.016	512	>32,000
7a	0.062	64	516
7b	0.031	32	1,032
7c	0.156	32	410
7d	<0.016	64	>4,000
7e	<0.016	128	>8,000
7f	<0.016	32	>4,000
7g	<0.016	64	>2,000
7h	<0.016	128	>1,000
7i	<0.016	16	>8,000
7j	<0.016	32	>2,000
7k	<0.016	64	>4,000
7l	<0.016	32	>2,000
7m	0.031	32	1,032
7n	<0.016	16	>1,000
7o	<0.016	8	>500
7p	0.218	16	73
7q	0.156	16	102

7r	0.062	64	1,032
7s	0.049	32	1,032
7t	<0.016	32	>2,000
7u	<0.016	16	>1,000
7v	<0.016	8	>500
TAM16	<0.016	>1,024	>64,000
CPFX	0.291	512	1,759
INH	0.078	256	3,282
RIF	0.078	512	6,564

[a]SI: selectivity index, $CC_{50}/MIC_{MTB\ H37Rv}$

All hybrids **7a-v** also displayed acceptable toxicological profiles with CC_{50} values ranging from 8 to 128 μg/mL. The structure-cytotoxicity relationship study indicated that introduction of imines at C-3 position of isatin motif increased the cytotoxicity greatly, and the relative contribution order was -O > -NOH > -NOMe ≈ -NOEt > $NNHCSNH_2$. Introduction of -F at *para*-position of phenyl position resulted in the increment of cytotoxicity. In general, hybrids with longer linkers displayed higher cytotoxicity.

In order to test the selectivity of these hybrids, the selectivity index (SI) values from the ratio of $CC_{50}/MIC_{MTB\ H37Rv}$ were calculated (**Table 2)**. All hybrids possessed high SI values (SI: ≥73), and some of them were much greater than references **CPFX**, **INH** and **RIF** (SI: 1,759, 3,282 and 6,564, respectively), suggesting that this kind of hybrids hold excellent selectivity properties.

Encouraged by their strong potency against the drug sensitive MTB $H_{37}Rv$ strain, the most active hybrids **6i**, **6m**, **7d-l**, **7n**, **7o** and **7t-v** were selected for further evaluation about *in vitro* activity against two clinical MDR-TB isolates (resistant to **INH** and

RIF). The *in vitro* activity of the selected hybrids against MDR-TB isolates was listed in **Table 3**.

Table 3. *In vitro* activity of selected hybrids against MDR-TB isolates

Compounds	MIC (μg/mL)	
	MDR-TB-1	MDR-TB-2
6i	14.15	12.94
6m	5.89	2.98
7d	0.21	0.27
7e	0.49	0.29
7f	2.24	2.12
7g	0.94	0.91
7h	0.16	0.21
7i	4.25	5.88
7j	0.062	0.16
7k	3.23	3.42
7l	3.46	4.24
7n	2.85	3.56
7o	0.95	0.90
7t	1.73	1.87
7u	2.69	3.86
7v	0.47	0.48

TAM16	<0.016	<0.016
CPFX	0.39	0.27
INH	>40	>40
RIF	>40	>40

All of the selected hybrids **6i**, **6m**, **7d-l**, **7n**, **7o** and **7t-v** showed promising activity against the tested two clinical MDR-TB isolates with MIC values in the range of 0.062 to 14.15 μg/mL. All of these hybrids were more potent than **RIF** and **INH** (MIC: >40 μg/mL), and three of them **7d** (MIC: 0.21 and 0.27 μg/mL), **7h** (MIC: 0.16 and 0.21 μg/mL) and **7j** (MIC: 0.062 and 0.16 μg/mL) were more potent than **CPFX** (MIC: 0.39 and 0.27 μg/mL). However, all of these hybrids were less active than **TAM16** (MIC: <0.016 μg/mL) against the two clinical MDR-TB isolates.

The SAR indicated that hybrids with shorter propylene and butylene linkers were more potent than the corresponding analogs with longer hexylene and pentylene linkers against both drug-sensitive and MDR MTB strains generally. Introduction of imines could enhance the anti-mycobacterial activity, and the relative contribution was -NNHCSNH$_2$ > -NOMe > -NOEt > -O > -NOH. Introduction of -F at the *para*-position of phenyl position (R_3) was detrimental to the activity generally. Hybrid **7j** (MIC: 0.062 and 0.16 μg/mL) was found to be the most active compound against the two clinical MDR-TB isolates used in this study. The result displayed that hybrid **7j** was ≥48 folds more potent than first-line anti-TB agents **RIF** (MIC: >40 and >40 μg/mL) and **INH** (MIC: 2.98 and >40 μg/mL), and also superior to **CPFX** (MIC: 0.39 and 0.27 μg/mL).

In vitro antibacterial activities of all benzofuran-isatin-imine hybrids **7a-v** and their precursors **6h,i** and **6l,m** against a panel of Gram-positive and Gram-negative pathogens were evaluated [37]. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give 90% inhibition of bacterial growth. The results were listed in **Table 4** and **5**, respectively.

Table 4 *In vitro* antibacterial activity of benzofuran-isatin-imine hybrids **7a-v** and their precursors **6h,i** and **6l,m** against Gram-positive strains

Compd.	MIC (μg/mL)					
	MSSE	MRSE	MSSA	MRSA	E.fa.	E.fm.
6h	1	8	2	2	4	64
6i	1	8	2	2	2	16
6l	0.25	4	1	1	2	8
6m	1	4	1	2	2	16
7a	0.25	1	1	2	2	8
7b	0.50	2	1	4	2	16
7c	1	16	8	4	4	32
7d	0.5	0.5	1	4	1	16
7e	0.25	2	4	2	1	8
7f	1	8	4	8	8	64
7g	0.125	0.5	8	2	1	8
7h	0.5	1	4	4	4	32
7i	1	8	8	4	4	16
7j	0.125	0.5	1	1	1	8
7k	0.5	2	1	1	4	64
7l	0.5	4	4	2	1	16
7m	1	4	8	4	4	32
7n	0.5	16	4	4	2	16
7o	0.5	2	1	1	1	32
7p	0.25	8	2	1	1	8
7q	1	4	1	1	1	16

7r	0.25	4	2	2	2	8
7s	0.5	4	2	4	4	32
7t	0.5	8	2	2	4	16
7u	1	8	1	1	2	32
7v	1	4	1	0.5	1	64
CPFX	0.125	4	0.25	0.25	0.5	8
VAN	1	1	0.5	1	4	1

Abbreviations: MSSE, methicillin-sensitive Staphylococcus epidermidis; MRSE, methicillin-resistant Staphylococcus epidermidis; MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; E.fa., Enterococcus faecalis ATCC; E.fm., Enterococcus faecium; CPFX, ciprofloxacin; VAN, vancomycin.

Table 5 *In vitro* antibacterial activity of benzofuran-isatin-imine hybrids **7a-v** and their precursors **6h,i** and **6l,m** against Gram-positive strains against Gram-negative strains

Compd.	MIC (μg/mL)							
	E.co.	*K.p.*	*P.a.*	*A.c.*	*E.c.*	*E.a.*	*P.m.*	*C.f.*
6h	0.25	2	8	8	1	1	0.25	1
6i	0.125	1	4	4	0.5	0.25	0.125	1
6l	0.06	0.5	4	2	0.125	0.5	0.125	0.25
6m	0.25	1	2	4	0.5	0.125	0.06	0.06
7a	0.125	0.25	0.5	1	1	0.125	0.25	0.25
7b	0.25	2	8	4	0.5	0.5	0.25	0.25
7c	0.5	2	8	8	0.25	0.5	0.25	0.5
7d	0.125	0.5	1	2	0.5	2	2	0.5

7e	0.25	1	1	4	0.25	0.125	0.25	0.5
7f	0.5	2	4	4	1	2	4	2
7g	0.25	0.5	1	1	2	0.25	0.5	0.5
7h	0.25	1	2	1	0.5	1	0.5	1
7i	0.5	1	4	2	4	1	2	2
7j	0.5	0.25	4	1	0.25	0.06	0.125	0.25
7k	1	2	2	0.5	1	2	2	2
7l	0.125	0.5	1	1	2	0.125	0.06	0.125
7m	0.125	4	4	8	0.25	0.5	0.25	0.125
7n	0.25	2	8	4	0.5	0.5	0.125	0.5
7o	0.125	1	4	16	0.5	2	1	0.25
7p	0.5	2	2	4	0.25	0.25	0.125	0.125
7q	0.125	2	2	2	0.06	0.125	0.06	0.125
7r	0.25	1	4	2	1	0.5	0.25	0.5
7s	0.25	2	1	1	0.25	1	0.5	1
7t	0.125	4	2	4	0.125	0.25	0.125	0.125
7u	0.5	1	1	2	0.5	0.25	0.25	1
7v	1	8	4	4	1	2	1	2
CPFX	0.06	0.5	0.25	0.5	0.06	0.06	≤0.03	0.03

Abbreviations: E.co., Escherichia coli; K.p., Klebsiellapneumoniae; P.a., Pseudomonas aeruginosa ATCC 27853; A.c., Acinetobactercal coacetious; E.c., Enterobacter cloacae; E.a., Enterobacter aerogenes; P.m., Proteus mirabilis; C.f., Citrobacter freundii; CPFX, ciprofloxacin.

As shown in **Table 4** and **5**, all benzofuran-isatin-imine hybrids **7a-v** and their precursors **6h,i** and **6l,m** exhibited considerable antibacterial activities against all the tested pathogens including drug-resistant MRSA and MRSE with MIC ranging from 0.06 to 64 μg/mL. In general, the hybrids were more potent against Gram-negative pathogens than Gram-positive strains. Substitution of the ketone at C-3 position of isatin motif could improve the anti-bacterial activity against both Gram-positive and Gram-negative organisms. In particular, the most active anti-TB hybrid **7j** demonstrated promising anti-bacterial activities with MIC values of ≤1 μg/mL against the majority of the tested Gram-negative and Gram-positive pathogens, which further suggested that *in vitro* activity of hybrid **7j** was comparable to vancomycin (MIC: 0.5-4 μg/mL) and **CPFX** (MIC: 0.125-8 μg/mL) against Gram-positive bacteria, and slightly less potent than **CPFX** (MIC: ≤0.03-0.5 μg/mL) against Gram-negative bacteria.

Table 6 The metabolic stability and *in vivo* pharmacokinetic values of hybrid **7j**, **TAM16** and **CPFX** in mice

Compd.	metabolic stability ($t_{1/2}$, min)	Pharmacokinetics (p.o.)			
		C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng•h/mL)
7j	19.2	927	3.33	1.65	3,024
TAM16[24]	>60	5,064	9.88	3.46	39,329
CPFX[17]	>60	3,129	5.2	1.8	17,835

$t_{1/2}$: half-life;

C_{max}: the peak concentration;

T_{max}: the time to reach peak concentration;

AUC: the area under the curve.

With the promising anti-TB and anti-bacterial activities, hybrid **7j** was selected for the further investigation of metabolic stability and *in vivo* pharmacokinetics in mice (25 mg/kg, single oral administration) [24]. The results were listed in **Table 6**. Comparing to **TAM16** ($t_{1/2}$: >60 min) and **CPFX** ($t_{1/2}$: >60 min), hybrid **7j** showed much lower

metabolic stability ($t_{1/2}$: 19.2 min). Pharmacokinetic study showed that hybrid **7j** was also inferior to **TAM16 and CPFX** in terms of C_{max} (927 ng/mL *vs* 5,064 and 3,129 ng/mL), $t_{1/2}$ (3.33 h *vs* 9.88 and 5.2 h), T_{max} (1.65 h *vs* 3.46 and 1.8 h) and $AUC_{0\text{-inf}}$ (3,024 ng•h/mL *vs* 39,329 and 17,835 ng•h/mL).

3 Conclusions

In conclusion, a series of novel benzofuran-isatin-imine hybrids tethered by different length alkyl linkers propylene, butylenes, pentylene and hexylene were designed and synthesized. The evaluation of all the hybrids about the *in vitro* anti-TB activities against both drug-sensitive MTB $H_{37}Rv$ and MDR-TB isolates, anti-bacterial activities against a panel of Gram-positive and Gram-negative pathogens as well as cytotoxicity towards VERO were performed. All benzofuran-isatin-imine hybrids not only exhibited considerable *in vitro* anti-TB and anti-bacterial activities, but also showed acceptable cytotoxicity. The most active hybrid **7j** was >4.8 and ≥48 folds more potent than the first line anti-TB agents **RIF** and **INH** against both drug-sensitive MTB $H_{37}Rv$ and MDR-TB isolates, respectively. Moreover, hybrid **7j** also demonstrated promising anti-bacterial activities which was comparable to vancomycin and **CPFX** against Gram-positive bacteria, but slightly less potent than **CPFX** against Gram-negative bacteria. The results suggested the potential utility of benzofuran-isatin-imine hybrids as anti-TB and anti-bacterial agents.

4. Synthesis methods

N-(3-bromopropyl/4-bromobutyl/5-bromopentyl/6-bromohexyl)isatin derivatives **3a-i** (yield: 62-76%) and ethyl 2-(4-substituted phenyl)-5-(prop-2-yn-1-yloxy)benzofuran-3-carboxylate **5-c** were synthesized *via* literature methods [13,15].

A mixture of *N*-(3-bromopropyl/4-bromobutyl/5-bromopentyl/6-bromohexyl)isatin derivatives **3a-i** (1 mmol), ethyl 2-(4-substituted phenyl)-5-(prop-2-yn-1-yloxy)benzofuran-3-carboxylate **5a-c** (1 mmol) and K_2CO_3 (3 mmol) in DMF (20 mL) was stirred at room temperature for 48 h. Then the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography with PE:EA=1:1 to give the precursors **6a-m** (51-68%).

Precursors **6a-m** (1 mmol), sodium bicarbonate (2 mmol), and the corresponding amine hydrochlorides (1.5 mmol) were dissolved in water (10 mL) and tetrahydrofuran (THF, 30 mL), and the mixturewas stirred at 60 ^{o}C for 12 h. After cooling to room temperature, the mixture was extracted with EA (20 mL×3). The combined organic phases were washed with water (50 mL×2) and brine (50 mL), and then dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a residue, which was further purified by silica gel chromatography with PE: EA=1:8 as eluant to give the desired benzofuran-isatin-imine hybrids **7a-v** (18-79%).

4.1. ethyl 5-((5-(5-fluoro-2,3-dioxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**6h**)

Yellow solid, yield: 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.51-1.54 (2H, m, -CH_2-), 1.66-1.70 (2H, m, -CH_2-), 1.78-1.82 (2H, m, -CH_2-), 3.68 (2H, t, J = 8.0 Hz, -CH_2-), 3.85 (3H, s, OCH_3), 4.01 (2H, t, J = 8.0 Hz, -CH_2-), 4.32 (2H, q, J = 4.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.96 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.09 (2H, d, J = 8.0 Hz, Ar-H), 7.41-7.45 (2H, m, Ar-H), 7.49-7.57 (2H, m, Ar-H), 7.57 (1H, d, J = 8.0 Hz, Ar-H), 7.95 (2H, d, J = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 183.40, 163.64, 161.43, 161.22, 158.61, 157.69, 156.25, 148.25, 147.42, 131.41, 127.97, 124.35, 121.73, 118.89, 118.82, 114.45, 114.16, 112.62, 112.55, 112.29, 112.03, 111.79, 107.69, 105.67, 68.35, 60.81, 55.87, 28.83, 26.89, 23.31, 14.47. ESI-MS m/z: 568 $[M+Na]^+$.

4.2. ethyl 5-((6-(5-fluoro-2,3-dioxoindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**6i**)

Yellow solid, yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.35-1.49 (4H, m, 2×-CH_2-), 1.59-1.66 (2H, m, -CH_2-), 1.70-1.77 (2H, m, -CH_2-), 3.66 (2H, t, J = 8.0 Hz, -CH_2-), 3.85 (3H, s, OCH_3), 4.00 (2H, t, J = 8.0 Hz, -CH_2-), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, dd, J = 4.0, 8.0 Hz, Ar-H),

7.07 (2H, d, *J* = 8.0 Hz, Ar-H), 7.19-7.22 (1H, m, Ar-H), 7.40-7.43 (2H, m, Ar-H), 7.49-7.54 (2H, m, Ar-H), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 183.38, 163.62, 161.40, 161.17, 160.07, 158.53, 157.67, 156.23, 148.22, 147.42, 131.37, 127.97, 124.56, 124.32, 121.73, 118.85, 114.43, 114.11, 112.54, 112.47, 112.21, 111.99, 107.66, 105.64, 68.40, 60.78, 55.83, 49.07, 29.08, 27.13, 26.45, 25.73, 14.44. ESI-MS m/z: 582 $[M+Na]^+$.

4.3. ethyl 5-((6-(2,3-dioxoindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**6l**)

Yellow solid, yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.48-1.56 (4H, m, 2×-CH_2-), 1.76-1.87 (4H, m, 2×-CH_2-), 3.76 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.88 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.43 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.91-6.94 (2H, m, Ar-H), 7.02 (2H, d, *J* = 8.0 Hz, Ar-H), 7.12 (1H, t, *J* = 4.0 Hz, Ar-H), 7.40 (1H, d, *J* = 8.0 Hz, Ar-H), 7.53 (1H, d, *J* = 4.0 Hz, Ar-H), 7.57-7.63 (2H, m, Ar-H), 8.00 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 565 $[M+Na]^+$.

4.4. ethyl ethyl 5-((6-(5-fluoro-2,3-dioxoindolin-1-yl)hexyl)oxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (**6m**)

Yellow solid, yield: 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.39-1.51 (4H, m, 2×-CH_2-), 1.62-1.65 (2H, m, -CH_2-), 1.73-1.77 (2H, m, -CH_2-), 3.68 (2H, t, *J* = 4.0 Hz, -CH_2-), 4.03 (2H, t, *J* = 4.0 Hz, -CH_2-), 4.32 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 7.00 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.21-7.24 (2H, m, Ar-H), 7.36-7.54 (5H, m, Ar-H), 7.58 (1H, d, *J* = 8.0 Hz, Ar-H), 8.00 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 183.39, 163.39, 162.41, 160.00, 158.57, 157.68, 156.36, 148.51, 147.45, 13.36, 13.27, 127.65, 126.04, 124.58, 124.34, 115.90, 115.68, 115.06, 112.58, 112.51, 108.94, 105.63, 68.45, 60.96, 29.05, 27.13, 26.44, 25.73, 14.29. ESI-MS m/z: 570 $[M+Na]^+$.

4.5 ethyl 5-(4-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl)butoxy)-2-phenylbenzofuran-3-carboxylate (**7a**)

Yellow solid, yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, J = 4.0 Hz, -CH_2-), 3.92 (2H, t, J = 4.0 Hz, -CH_2-), 4.08 (2H, t, J = 4.0 Hz, -CH_2-), 4.21 (3H, s, $NOCH_3$), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.18-7.21 (1H, m, Ar-H), 7.30-7.32 (1H, m, Ar-H), 7.38 (1H, d, J = 4.0 Hz, Ar-H), 7.53-7.61 (4H, m, Ar-H), 7.68 (1H, d, J = 4.0 Hz, Ar-H), 7.93-7.96 (2H, m, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 163.41, 162.70, 160.96, 159.54, 157.17, 156.07, 148.64, 143.50, 140.62, 130.95, 129.70, 129.45, 128.67, 127.68, 119.63, 119.42, 116.02, 114.96, 114.71, 112.49, 110.97, 108.98, 105.70, 66.35, 65.12, 60.93, 37.40, 27.21, 14.40. ESI-MS m/z: 553 $[M+Na]^+$.

4.6. ethyl 5-(4-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7b**)

Yellow solid, yield: 79%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, J = 4.0 Hz, -CH_2-), 3.86 (3H, s, OCH_3), 3.92 (2H, t, J = 4.0 Hz, -CH_2-), 4.08 (2H, t, J = 4.0 Hz, -CH_2-), 4.22 (3H, s, $NOCH_3$), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.91 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.10 (2H, d, J = 4.0 Hz, Ar-H), 7.20-7.23 (1H, m, Ar-H), 7.32-7.37 (2H, m, Ar-H), 7.58 (1H, d, J = 8.0 Hz, Ar-H), 7.70 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.95-7.97 (2H, m, Ar-H). ESI-MS m/z: 583 $[M+Na]^+$.

4.7. ethyl 5-(4-(5-fluoro-3-(ethoxyimino)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7c**)

Yellow solid, yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29-1.39 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.10 (2H, t, J = 4.0 Hz, -CH_2-), 3.85 (3H, s, OCH_3), 3.92 (2H, t, J = 4.0 Hz, -CH_2-), 4.08 (2H, t, J = 4.0 Hz, -CH_2-), 4.32 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.48 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.91 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.10 (2H, d, J = 4.0 Hz, Ar-H), 7.20-7.23 (1H, m, Ar-H), 7.32-7.37 (2H, m, Ar-H), 7.58 (1H, d, J = 8.0 Hz, Ar-H), 7.70 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.95-7.97 (2H, m, Ar-H). ESI-MS m/z: 597 $[M+Na]^+$.

4.8. ethyl 5-(3-(5-methoxy-3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxylate (**7d**)

Yellow solid, yield: 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.10 (2H, dd, J = 4.0, 8.0 Hz, -CH_2-), 3.74 (3H, s, OCH_3), 3.90 (2H, t, J = 8.0 Hz, -CH_2-), 4.08 (2H, t, J = 4.0 Hz, -CH_2-), 4.20 (3H, s, $NOCH_3$), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.98 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 6.99-7.13 (2H, m, Ar-H), 7.39 (1H, d, J = 4.0 Hz, Ar-H), 7.48 (1H, d, J = 4.0 Hz, Ar-H), 7.54-7.58 (3H, m, Ar-H), 7.62 (1H, d, J = 8.0 Hz, Ar-H), 7.94-7.97 (2H, m, Ar-H). ESI-MS m/z: 551 $[M+Na]^+$.

4.9. ethyl 5-(3-(5-methoxy-3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7e**)

Yellow solid, yield: 59%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.09 (2H, dd, J = 4.0, 8.0 Hz, -CH_2-), 3.75 (3H, s, OCH_3), 3.86-3.91 (5H, m, -CH_2- and OCH_3), 4.05-4.20 (5H, m, -CH_2- and $NOCH_3$), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.01-7.11 (4H, m, Ar-H), 7.48 (1H, d, J = 4.0 Hz, Ar-H), 7.56 (1H, d, J = 4.0 Hz, Ar-H), 7.62 (1H, d, J = 8.0 Hz, Ar-H), 7.95-7.97 (2H, m, Ar-H). ESI-MS m/z: 581 $[M+Na]^+$.

4.10. ethyl 5-(3-(5-methoxy-3-(ethoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)b enzofuran-3-carboxylate (**7f**)

Yellow solid, yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, J = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, J = 4.0 Hz, -CH_2-), 3.93 (2H, t, J = 4.0 Hz, -CH_2-), 4.03 (2H, t, J = 4.0 Hz, -CH_2-), 4.34 (2H, q, J = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.45 (2H, q, J = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.90-7.09 (5H, m, Ar-H), 7.36-7.56 (3H, m, Ar-H), 7.93-7.96 (2H, m, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 163.61, 162.74, 161.22, 156.01, 155.54, 148.31, 143.96, 137.73, 131.38, 127.91, 121.71, 118.52, 117.73, 116.12, 114.48, 112.23, 110.33, 107.69, 105.78, 72.78, 66.30, 60.80, 56.11, 55.85, 37.21, 27.36, 14.90, 14.38. ESI-MS m/z: 595 $[M+Na]^+$.

4.11. ethyl 5-(3-(3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxyla te (**7g**)

Yellow solid, yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29-1.38 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.08 (2H, dd, *J* = 4.0, 8.0 Hz, $-CH_2-$), 3.75 (3H, s, OCH_3), 3.83-3.89 (5H, m, $-CH_2-$ and OCH_3), 4.06 (2H, t, *J* = 4.0 Hz, $-CH_2-$), 4.20 (3H, s, $NOCH_3$), 4.32 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.45 (2H, q, *J* = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.98-7.20 (3H, m, Ar-H), 7.40-7.62 (4H, m, Ar-H), 7.89-7.97 (3H, m, Ar-H). ESI-MS m/z: 521 $[M+Na]^+$.

4.12. ethyl 5-(3-(3-(methoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran -3-carboxylate (**7h**)

Yellow solid, yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (3H, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 2.25 (2H, t, *J* = 4.0 Hz, $-CH_2-$), 3.90 (3H, s, OCH_3), 4.02 (2H, t, *J* = 4.0 Hz, $-CH_2-$), 4.12 (2H, t, *J* = 4.0 Hz, $-CH_2-$), 4.31 (3H, s, $NOCH_3$), 4.43 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.92-6.97 (2H, m, Ar-H), 7.01-7.07 (3H, m, Ar-H), 7.28-7.33 (1H, m, Ar-H), 7.42 (1H, d, *J* = 8.0 Hz, Ar-H), 7.52 (1H, d, *J* = 4.0 Hz, Ar-H), 7.96 (1H, d, *J* = 8.0 Hz, Ar-H), 8.02 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, CD_3OD) δ 164.20, 163.66, 161.75, 161.19, 155.67, 148.69, 143.99, 143.69, 132.55, 131.14, 128.15, 127.97, 122.89, 122.17, 115.81, 113.97, 113.52, 111.50, 108.70, 107.83, 106.05, 65.69, 64.77, 60.53, 55.40, 37.13, 27.70, 14.36. ESI-MS m/z: 551 $[M+Na]^+$.

4.13. ethyl 5-(3-(3-(ethoxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3 -carboxylate (**7i**)

Yellow solid, yield: 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.39 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 2.11 (2H, t, *J* = 8.0 Hz, $-CH_2-$), 3.86 (3H, s, OCH_3), 3.93 (2H, t, *J* = 8.0 Hz, $-CH_2-$), 4.08 (2H, t, *J* = 4.0 Hz, $-CH_2-$), 4.32 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.46 (2H, q, *J* = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.92 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.07-7.11 (3H, m, Ar-H), 7.18 (1H, d, *J* = 8.0 Hz, Ar-H), 7.38-7.43 (2H, m, Ar-H), 7.56 (1H, d, *J* = 8.0 Hz, Ar-H), 7.92 (1H, d, *J* = 8.0 Hz, Ar-H), 7.97 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 565 $[M+Na]^+$.

4.14. ethyl 5-(4-(3-(methoxyimino)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7j**)

Yellow solid, yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.74-1.78 (4H, m, 2×-CH_2-), 3.78 (2H, t, *J* = 4.0 Hz, -CH_2-), 3.85 (3H, s, OCH_3), 4.04 (2H, t, *J* = 4.0 Hz, -CH_2-), 4.19 (3H, s, $NOCH_3$), 4.32 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.93 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.06-7.09 (3H, m, Ar-H), 7.16 (1H, d, *J* = 8.0 Hz, Ar-H), 7.37-7.42 (2H, m, Ar-H), 7.52 (1H, d, *J* = 12.0 Hz, Ar-H), 7.86 (1H, d, *J* = 8.0 Hz, Ar-H), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 163.62, 162.74, 161.41, 161.20, 156.08, 148.26, 144.13, 143.75, 133.38, 131.38, 127.94, 127.83, 123.12, 122.85, 121.73, 115.40, 114.47, 112.24, 109.91, 107.69, 105.79, 67.96, 64.89, 60.75, 55.85, 26.48, 24.12, 14.45. ESI-MS m/z: 565 $[M+Na]^+$.

4.15. ethyl 5-(4-(3-(ethoxyimino)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7k**)

Yellow solid, yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.39 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 1.78-1.81 (4H, m, 2×-CH_2-), 3.79 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.85 (3H, s, OCH_3), 4.06 (2H, t, *J* = 4.0 Hz, -CH_2-), 4.33 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.46 (2H, q, *J* = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.95 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.08-7.11 (3H, m, Ar-H), 7.18 (1H, d, *J* = 8.0 Hz, Ar-H), 7.38-7.41 (2H, m, Ar-H), 7.56 (1H, d, *J* = 8.0 Hz, Ar-H), 7.90 (1H, d, *J* = 8.0 Hz, Ar-H), 7.97 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, DMSO-d_6) δ 163.63, 162.86, 161.43, 161.22, 156.11, 148.27, 144.06, 143.66, 133.29, 131.39, 127.94, 127.74, 123.12, 121.73, 115.47, 114.16, 112.27, 109.90, 107.70, 105.80, 72.78, 67.98, 60.80, 55.86, 26.49, 24.14, 14.94, 14.47. ESI-MS m/z: 579 $[M+Na]^+$.

4.16. ethyl 5-((5-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7l**)

Yellow solid, yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.46-1.49 (2H, m, -CH_2-), 1.66-1.69 (2H, m, -CH_2-), 1.77-1.80 (2H, m, -CH_2-), 3.72 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.86 (3H, s, OCH_3), 4.00 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.22 (3H, s, $NOCH_3$), 4.32 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.96 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.09 (2H, d, *J* = 8.0 Hz, Ar-H), 7.17-7.21 (1H, m, Ar-H), 7.31-7.37 (1H, m, Ar-H), 7.40 (1H, d, *J* = 4.0 Hz, Ar-H), 7.56 (1H, d, *J* = 8.0 Hz, Ar-H), 7.68

(1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 597 $[M+Na]^+$.

4.17. ethyl 5-((5-(3-(ethoxyimino)-5-fluoro-2-oxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl) benzofuran-3-carboxylate (**7m**)

Yellow solid, yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.44 (3H, t, *J* = 8.0 Hz, $NOCH_2\underline{CH_3}$), 1.59-1.65 (2H, m, $-CH_2-$), 1.76-1.82 (2H, m, $-CH_2-$), 3.72 (2H, t, *J* = 8.0 Hz, $-CH_2-$), 3.82 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, $-CH_2-$), 4.43 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.58 (2H, q, *J* = 4.0 Hz, $NO\underline{CH_2}CH_3$), 6.80 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 6.92 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.02 (2H, d, *J* = 8.0 Hz, Ar-H), 7.11 (1H, t, *J* = 4.0 Hz, Ar-H), 7.38 (1H, d, *J* = 12.0 Hz, Ar-H), 7.52 (1H, d, *J* = 4.0 Hz, Ar-H), 7.74 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 8.02 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, CD_3OD) δ 164.27, 163.41, 161.65, 161.15, 156.08, 148.55, 143.08, 139.82, 131.14, 128.10, 122.24, 118.56, 118.32, 116.50, 115.58, 115.33, 114.09, 113.50, 111.43, 109.12, 109.05, 107.83, 105.77, 73.37, 68.29, 60.48, 55.40, 39.96, 29.00, 27.25, 23.54, 14.71, 14.36. ESI-MS m/z: 611 $[M+Na]^+$.

4.18. ethyl 5-((6-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7n**)

Yellow solid, yield: 52%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30-1.38 (5H, m, $-CH_2-$ and $CO_2CH_2\underline{CH_3}$), 1.46-1.49 (2H, m, $-CH_2-$), 1.62-1.64 (2H, m, $-CH_2-$), 1.72-1.75 (2H, m, $-CH_2-$), 3.71 (2H, t, *J* = 8.0 Hz, $-CH_2-$), 3.85 (3H, s, OCH_3), 3.99 (2H, t, *J* = 8.0 Hz, $-CH_2-$), 4.22 (3H, s, $NOCH_3$), 4.33 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.95 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.08 (2H, d, *J* = 8.0 Hz, Ar-H), 7.15-7.18 (1H, m, Ar-H), 7.32-7.34 (1H, m, Ar-H), 7.40 (1H, d, *J* = 4.0 Hz, Ar-H), 7.56 (1H, d, *J* = 8.0 Hz, Ar-H), 7.66 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 611 $[M+Na]^+$.

4.19. ethyl 5-((6-(3-(2-carbamothioylhydrazono)-5-fluoro-2-oxoindolin-1-yl)hexyl)oxy)-2-(4-met hoxyphenyl)benzofuran-3-carboxylate (**7o**)

Yellow solid, yield: 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.41-1.59 (4H, m, 2×-CH_2-), 1.65-1.85 (4H, m, 2×-CH_2-), 3.78 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.90 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.43 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.86 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 6.93 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.00 (2H, d, *J* = 8.0 Hz, Ar-H), 7.11 (1H, t, *J* = 8.0 Hz, Ar-H), 7.30 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.40 (1H, d, *J* = 4.0 Hz, Ar-H), 6.68, 7.53 (3H, s, Ar-H and NNHCS$\underline{NH_2}$), 8.02 (2H, d, *J* = 8.0 Hz, Ar-H), 12.91 (1H, s, N$\underline{NH}$CSNH_2). ESI-MS m/z: 655 $[M+Na]^+$.

4.20. ethyl 5-((6-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl)hexyl)oxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (**7p**)

Yellow solid, yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.37-1.39 (2H, m, -CH_2-), 1.46-1.48 (2H, m, -CH_2-), 1.61-1.64 (2H, m, -CH_2-), 1.72-1.76 (2H, m, -CH_2-), 3.71 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.00 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.22 (3H, s, $NOCH_3$), 4.33 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.99 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.16-7.20 (1H, m, Ar-H), 7.32-7.44 (4H, m, Ar-H), 7.60 (1H, d, *J* = 8.0 Hz, Ar-H), 7.68 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 8.04 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 599 $[M+Na]^+$.

4.21. ethyl 5-((5-(5-methoxy-3-(methoxyimino)-2-oxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7q**)

Yellow solid, yield: 36%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.72-1.81 (6H, m, 3×-CH_2-), 3.67-3.74 (5H, m, -CH_2- and OCH_3), 3.86 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.21 (3H, s, $NOCH_3$), 4.33 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.94-7.10 (6H, m, Ar-H), 7.40-7.45 (2H, m, Ar-H), 7.54 (1H, d, *J* = 8.0 Hz, Ar-H), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 609 $[M+Na]^+$.

4.22. ethyl 5-((5-(3-(hydroxyimino)-2-oxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7r**)

Yellow solid, yield: 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.46-1.52 (2H, m, -CH_2-), 1.65-1.71 (2H, m, -CH_2-), 1.78-1.81 (2H, m,

-CH_2-), 3.74 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.85 (3H, s, OCH_3), 4.00 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.31 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.96 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.07-7.14 (4H, m, Ar-H), 7.28-7.32 (2H, m, Ar-H), 7.54 (1H, d, *J* = 8.0 Hz, Ar-H), 7.95 (2H, d, *J* = 8.0 Hz, Ar-H), 8.00 (1H, d, *J* = 8.0 Hz, Ar-H), 13.42 (1H, brs, NOH). ^{13}C NMR (101Hz, DMSO-d_6) δ 163.64, 163.57, 161.42, 161.20, 156.24, 148.25, 143.98, 143.46, 132.37, 131.40, 127.96, 127.28, 122.94, 121.74, 115.75, 114.47, 114.15, 112.27, 109.60, 107.71, 105.70, 68.37, 60.80, 55.86, 28.82, 27.29, 23.40, 14.46. ESI-MS m/z: 565 $[M+Na]^+$.

4.23. ethyl 5-((5-(3-(methoxyimino)-2-oxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7s**)

Yellow solid, yield: 39%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.59-1.65 (2H, m, -CH_2-), 1.77-1.93 (4H, m, 2×-CH_2-), 3.80 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.89 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.27 (3H, s, $NOCH_3$), 4.43 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.86 (1H, d, *J* = 8.0 Hz, Ar-H), 6.92 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.02 (2H, d, *J* = 8.0 Hz, Ar-H), 7.08 (1H, t, *J* = 8.0 Hz, Ar-H), 7.38 (1H, d, *J* = 8.0 Hz, Ar-H), 7.52 (1H, d, *J* = 4.0 Hz, Ar-H), 7.96 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 8.02 (2H, d, *J* = 8.0 Hz, Ar-H). ^{13}C NMR (101Hz, CD_3OD) δ 164.28, 163.52, 16.64, 161.14, 156.09, 148.5, 14.89, 14.65, 132.45,131.13, 128.07, 128.02, 122.84, 122.24, 115.86, 114.11, 113.50, 111.43, 108.66, 107.83, 105.80, 68.33, 64.75, 60.50, 55.39, 39.83, 29.02, 27.32, 23.55, 14.36. ESI-MS m/z: 579 $[M+Na]^+$.

4.24. ethyl 5-((6-(3-(methoxyimino)-2-oxoindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7t**)

Yellow solid, yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.45-1.60 (4H, m, 2×-CH_2-), 1.74-1.78 (2H, m, -CH_2-), 1.82-1.86 (2H, m, -CH_2-), 3.79 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.91 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.31 (3H, s, $NOCH_3$), 4.43 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 6.87 (1H, d, *J* = 8.0 Hz, Ar-H), 6.92 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.02 (2H, d, *J* = 4.0 Hz, Ar-H), 7.08 (1H, t, *J* = 8.0 Hz, Ar-H), 7.38-7.41 (2H, m, Ar-H), 7.52 (1H, d, *J* = 4.0 Hz, Ar-H),

7.98 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 8.02 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 593 $[M+Na]^+$.

4.25. ethyl 5-((6-(3-(ethoxyimino)-2-oxoindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7u**)

Yellow solid, yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.49 (6H, m, $NOCH_2\underline{CH_3}$ and $CO_2CH_2\underline{CH_3}$), 1.51-1.58 (4H, m, 2×-CH_2-), 1.74-1.78 (2H, m, -CH_2-), 1.82-1.86 (2H, m, -CH_2-), 3.79 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.90 (3H, s, OCH_3), 4.05 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.45 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.56 (2H, q, *J* = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.88 (1H, d, *J* = 8.0 Hz, Ar-H), 6.92 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.02 (2H, d, *J* = 4.0 Hz, Ar-H), 7.08 (1H, t, *J* = 4.0 Hz, Ar-H), 7.37-7.41 (2H, m, Ar-H), 7.53 (1H, d, *J* = 4.0 Hz, Ar-H), 8.00 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 8.02 (2H, d, *J* = 8.0 Hz, Ar-H). ESI-MS m/z: 607 $[M+Na]^+$.

4.26. ethyl 5-((6-(3-(2-carbamothioylhydrazono)-2-oxoindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**7v**)

Yellow solid, yield: 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, *J* = 8.0 Hz, $CO_2CH_2\underline{CH_3}$), 1.40-1.50 (4H, m, 2×-CH_2-), 1.66-1.77 (4H, m, 2×-CH_2-), 3.77 (2H, t, *J* = 8.0 Hz, -CH_2-), 3.86 (3H, s, OCH_3), 4.01 (2H, t, *J* = 8.0 Hz, -CH_2-), 4.45 (2H, q, *J* = 8.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.32 (2H, q, *J* = 8.0 Hz, $NO\underline{CH_2}CH_3$), 6.96 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.10 (2H, d, *J* = 4.0 Hz, Ar-H), 7.16 (1H, t, *J* = 4.0 Hz, Ar-H), 7.22 (1H, d, *J* = 8.0 Hz, Ar-H), 7.27-7.41 (2H, m, Ar-H), 7.57 (1H, d, *J* = 8.0 Hz, Ar-H), 7.72 (1H, d, *J* = 8.0 Hz, Ar-H), 7.96 (2H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 8.73, 9.08 (2H, s, $NNHCS\underline{NH_2}$), 12.44 (1H, s, $N\underline{NH}CSNH_2$). ESI-MS m/z: 637 $[M+Na]^+$.

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1. All the synthesized hybrids exhibited promising anti-TB and anti-bacterial activities
2. Hybrid **7j** was more potent than **RIF** and **INH** against both drug-sensitive MTB $H_{37}Rv$ and MDR-TB isolates, respectively.
3. Hybrid **7j** was comparable to vancomycin and **CPFX** against Gram-positive bacteria, but slightly less potent than **CPFX** against Gram-negative bacteria.