DESIGN, SYNTHESIS AND *IN VITRO* ANTI-BACTERIAL ACTIVITIES OF BENZOFURAN-ISATIN HYBRIDS

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A series of novel benzofuran-isatin hybrids **6a-x** tethered through propylene, butylene, pentylene and hexylene were designed, synthesized and evaluated for their *in vitro* anti-bacterial activities against a panel of clinically important Gram-positive and Gram-negative pathogens including drug-resistant bacteria. All hybrids exhibited decent *in vitro* anti-bacterial activities, and the most active hybrid **6l** was not only comparable to vancomycin against the majority of the tested Gram-positive strains, but also highly active against Gram-negative bacteria. Based on the above results, hybrid **6l** could act as a lead for further investigation. Moreover, the enriched structure-activity relationship may pave the way for further optimization

INTRODUCTION

Bacterial infections are responsible for the majority of both hospital-acquired and community-acquired infections.^{1,2} *Staphylococcus aureus*/*S. aureus*, *Staphylococcus epidermidis*/*S. epidermidis*, *Streptococcus pneumoniae*/*S. pneumoniae*, *Enterococcus faecalis*/*E. faecalis* and *Enterococcus faecium*/*E. faecium* are clinically important Gram-positive pathogens, and *Escherichia coli*/*E. coli* and *Pseudomonas aeruginosa*/*P. aeruginosa* are the common Gram-negative bacteria. Drug-resistant organisms which generate due to the long-term, broad, inappropriate use and even abuse of antibiotics poses an ever-growing health concern, and around 700,000 deaths occurred annually due to the drug-resistant pathogens.^{3,4}

The benzofuran and isatin motifs are ubiquitous in nature, and their derivatives possess a variety of

pharmacological properties such as anti-cancer,^{5,6} anti-viral,⁷ anti-Alzheimer's disease,⁸ anti-tubercular^{9,10} and anti-bacterial^{11,12} activities. Moreover, some of isatin and benzofuran based compounds such as sunitinib, nintedanib, benzbromarone and amiodarone have already used in clinics or under clinical trials for the treatment various diseases, so benzofuran and isatin derivatives play a pivotal role in the development of new drugs.

Molecular hybridization, has the potential to overcome cross resistance, improvement of affinity and efficacy compared to the parent drugs, represents a promising strategy in the development of new drugs.^{13,14} The benzofuran and isatin derivatives have the anti-bacterial potential, so it's reasonable to evaluate the anti-bacterial activity of benzofuran-isatin hybrids.

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Fig. 1 – Design strategy for benzofuran-isatin hybrids tethered *via* different linkers.

Based on the facts stated above and as a continuous program to develop novel anti-bacterial candidates, a series of novel benzofuran-isatin hybrids **6a-x** tethered *via* different length alkyl linkers were designed, synthesized and evaluated for their *in vitro* anti-bacterial activities against a panel of clinically important Gram-positive and Gram-negative pathogens including drug-resistant bacteria in this study. The design strategy was depicted in Figure 1.

RESULTS AND DISCUSSION

Synthesis

All of the desired benzofuran-isatin hybrids **6a-x** can be achieved by the synthetic route depicted in Scheme 1. 5-Methoxyisatin/5-fluoroisatin/isatin **1a-c** were alkylated with 1,3-dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane and 1,6-dibromohexane **2a-d** provided *N*-(3-bromopropyl/4-bromobutyl/5-bromopentyl/6-bromohexyl)isatin derivatives **3a-i** with yields 62-76%.¹⁵ The benzofuran intermediate **5a-c** was obtained by cyclization of ethyl 3-(4-substituted phenyl)-3-oxopropionate **4a-c** and benzoquinone with copper (II) triflate ($\text{Cu}(\text{OTf})_2$) as catalyst.¹⁶ Treatment of isatin derivatives **3a-i** and benzofuran intermediates **5a-c** with potassium carbonate as base generated the desired benzofuran-isatin hybrids **6a-m** (58-83%). Finally, condensations of **6a-m** with the corresponding amine hydrochlorides in the presence of sodium bicarbonate gave the rest benzofuran-isatin hybrids **6i-x** (18-73%). The chemical structures of targets **6a-x** were listed in Table 1.

Scheme 1 – Synthesis of benzofuran-isatin hybrids **6a-x**.

Table 1

Chemical structures of benzofuran-isatin hybrids **6a-x**

6a-x

Compounds	n	R ₁	R ₂	R ₃
6a	2	F	OMe	O
6b	2	F	F	O
6c	2	OMe	H	O

Table 1 (continued)

6d	2	OMe	F	O
6e	2	H	F	O
6f	2	H	OMe	O
6g	3	OMe	OMe	O
6h	3	H	OMe	O
6i	4	F	OMe	O
6j	4	OMe	F	O
6k	5	F	OMe	O
6l	5	F	F	O
6m	5	H	OMe	O
6n	2	H	NOH	OMe
6o	3	H	NOH	OMe
6p	4	H	NOH	OMe
6q	2	H	NOH	F
6r	2	H	NNHCSNH ₂	OMe
6s	3	H	NNHCSNH ₂	OMe
6t	4	H	NNHCSNH ₂	OMe
6u	2	F	NOH	H
6v	2	F	NOH	F
6w	2	OMe	NOH	H
6x	2	OMe	NOH	F

Table 2

In vitro antibacterial activity of benzofuran-isatin hybrids **6a-x** against Gram-positive strains

Compd.	MSSE	MRSE	MIC ($\mu\text{g/mL}$)		E.fa.	E.fm.
			MSSA	MRSA		
6a	0.5	2	2	1	8	32
6b	1	1	2	2	4	8
6c	1	2	2	1	2	16
6d	2	2	8	4	8	32
6e	4	1	2	2	1	8
6f	1	2	1	1	1	16
6g	0.5	2	2	2	8	64
6h	2	4	8	4	4	16
6i	1	8	2	2	4	64
6j	2	4	8	4	8	16
6k	1	8	2	2	2	16
6l	0.25	4	1	1	2	8
6m	1	4	1	2	2	16
6n	2	8	4	8	16	32
6o	2	4	4	4	8	16
6p	1	2	2	2	4	32
6q	2	2	8	4	8	32
6r	8	8	16	8	16	64
6s	16	8	8	8	16	32
6t	8	16	16	32	64	128
6u	4	8	4	2	8	16
6v	2	8	2	4	8	32
6w	1	2	4	4	4	64
6x	4	8	4	2	8	32
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.

Anti-bacterial activity

All benzofuran-isatin hybrids **6a-x** were evaluated for their *in vitro* antibacterial activities against a panel of Gram-positive and Gram-

negative pathogens.^{17,18} 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 Tables 2 and 3, respectively.

Table 3

In vitro antibacterial activity of benzofuran-isatin hybrids **6a-x** against Gram-negative strains

Compd.	MIC ($\mu\text{g/mL}$)							
	<i>E.co.</i>	<i>K.p.</i>	<i>P.a.</i>	<i>A.c.</i>	<i>E.c.</i>	<i>E.a.</i>	<i>P.m.</i>	<i>C.f.</i>
6a	0.5	1	8	4	2	2	0.5	1
6b	0.25	2	4	4	1	1	2	0.25
6c	0.5	1	8	8	0.5	1	2	2
6d	1	4	8	2	1	4	8	4
6e	0.25	2	1	2	4	2	0.5	1
6f	0.5	4	4	1	2	1	1	2
6g	1	8	1	4	2	0.5	2	2
6h	0.5	1	1	1	0.25	1	0.5	1
6i	0.25	2	8	8	1	1	0.25	1
6j	0.25	0.5	2	1	0.5	0.25	0.125	0.5
6k	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
6n	2	4	8	4	2	4	8	16
6o	4	8	8	16	4	2	4	8
6p	4	4	8	4	2	8	4	16
6q	2	4	4	8	4	8	4	8
6r	4	16	8	32	16	16	32	64
6s	8	4	16	16	32	32	64	64
6t	4	16	16	32	64	32	64	64
6u	2	4	4	8	2	4	8	8
6v	1	8	4	2	4	2	4	8
6w	4	2	8	4	8	1	8	16
6x	2	4	8	8	2	2	16	4
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.*, *Acinetobacteral coacetious*; *E.c.*, *Enterobacter cloacae*; *E.a.*, *Enterobacter aerogenes*; *P.m.*, *Proteus mirabilis*; *C.f.*, *Citrobacter freundii*; CPFX, ciprofloxacin.

It can be concluded from Tables 2 and 3 that benzofuran-isatin hybrids **6a-x** possess broad-spectrum anti-bacterial activities, and MIC values were 0.25-128 $\mu\text{g/mL}$ and 0.06-64 $\mu\text{g/mL}$ against Gram-positive and Gram-negative pathogens, respectively. It is worth to notice that the activity of benzofuran-isatin hybrids **6a-x** against MRSA and MRSE was equal to that of against MSSA and MSSE, indicating that these hybrids could be used to treat infections caused by drug-resistant bacteria. The SAR results suggested that introduction of hydroxylimine and thiosemicarbazide at C-3 position of isatin moiety was detrimental to the anti-bacterial activity, and the relative contribution order was ketone > hydroxylimine > thiosemicarbazide. The length of the linker has great influence on the activity, and the longer linker was more favorable than the shorter one especially against Gram-negative pathogens.

Among them, hybrids **6b,l** (MIC: 0.25-8 $\mu\text{g/mL}$) were comparable to vancomycin against the majority of the tested Gram-positive strains, and four hybrids **6j-m** (MIC: 0.06-4 $\mu\text{g/mL}$) were highly active against Gram-negative bacteria especially against *Escherichia coli*, *Enterobacter*

cloacae, *Enterobacter aerogenes*, *Proteus mirabilis*, and *Citrobacter freundii*.

EXPERIMENTAL

N-(3-bromopropyl/4-bromobutyl/5-bromopentyl)isatin derivatives **3a-f** (yield: 63-81%) and ethyl 2-(4-substituted phenyl)-5-(prop-2-yn-1-yloxy)benzofuran-3-carboxylate **5a-c** were synthesized *via* literature methods.

A mixture of *N*-(3-bromopropyl/4-bromobutyl/5-bromopentyl)isatin derivatives **3a-f** (1.0 mmol), ethyl 2-(4-substituted phenyl)-5-(prop-2-yn-1-yloxy)benzofuran-3-carboxylate **5a-c** (1.0 mmol) and K_2CO_3 (3.0 mmol) in DMF (20 mL) was stirred at room temperature for 48h. After filtration, 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-h**.

The mixture of **6a-h** (1 mmol), sodium bicarbonate (2 mmol), and hydroxylamine hydrochloride or thiosemicarbazide hydrochloride (1.5 mmol) dissolving in water (10 mL) and tetrahydrofuran (THF, 30 mL) was stirred at 60 °C for 12 h. After cooling to room temperature, the mixture was extracted with EA (20 mL $\times$ 3). The combined organic layers were washed with water (50 mL $\times$ 2) and brine (50 mL), and then dried over Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to give a residue, which was further purified by silica gel chromatography eluted with PE: EA=1:8 to give the desired benzofuran-isatin-hydroxylimine-/thiosemicarbazide hybrids **7a-l**.

5-(3-(5-fluoro-2,3-dioxindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6a)

Yellow solid, yield: 69%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.33 (3H, t, $J = 4.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.11 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 3.85 (3H, s, OCH_3), 3.89 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.12 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.33 (2H, q, $J = 4.0$ Hz,

$\text{CO}_2\text{CH}_2\text{CH}_3$), 6.94 (1H, dd, $J = 4.0$ Hz, Ar-H), 7.09 (2H, d, $J = 4.0$ Hz, Ar-H), 7.25-7.28 (1H, m, Ar-H), 7.39 (1H, d, $J = 4.0$ Hz, Ar-H), 7.45-7.50 (2H, m, Ar-H), 7.57 (1H, d, $J = 8.0$ Hz, Ar-H), 7.94-7.97 (2H, m, Ar-H). ESI-MS m/z : 540 $[\text{M}+\text{Na}]^+$.

5-(3-(5-fluoro-2,3-dioxindolin-1-yl)propoxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (6b)

Yellow solid, yield: 77%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.12 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 3.89 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.12 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$),

4.32 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.98 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.24-7.28 (1H, m, Ar-H), 7.36-7.41 (2H, m, Ar-H), 7.44-7.42 (2H, m, Ar-H), 7.60 (1H, d, $J = 12.0$ Hz, Ar-H), 8.01-8.04 (2H, m, Ar-H). ESI-MS m/z : 528 $[\text{M}+\text{Na}]^+$.

5-((5-(5-fluoro-2,3-dioxindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6c)

Yellow solid, yield: 58%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.32 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.51–1.54 (2H, m, $-\text{CH}_2-$), 1.66–1.70 (2H, m, $-\text{CH}_2-$), 1.78–1.82 (2H, m, $-\text{CH}_2-$), 3.68 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.85 (3H, s, OCH_3), 4.01 (2H,

t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 4.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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), 7.94–7.97 (2H, m, Ar-H). ESI-MS m/z : 568 $[\text{M}+\text{Na}]^+$.

5-((6-(5-fluoro-2,3-dioxindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6d)

Yellow solid, yield: 62%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.32 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.35–1.49 (4H, m, $2 \times -\text{CH}_2-$), 1.59–1.66 (2H, m, $-\text{CH}_2-$), 1.70–1.77 (2H, m, $-\text{CH}_2-$), 3.66 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.85 (3H, s, OCH_3), 4.00 (2H,

t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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), 7.93–7.96 (2H, m, Ar-H). ESI-MS m/z : 582 $[\text{M}+\text{Na}]^+$.

Ethyl ethyl 5-((6-(5-fluoro-2,3-dioxindolin-1-yl)hexyl)oxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (6e)

Yellow solid, yield: 62%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.39-1.51 (4H, m, $2 \times -\text{CH}_2-$), 1.62-1.65 (2H, m, $-\text{CH}_2-$), 1.73-1.77 (2H, m, $-\text{CH}_2-$),

3.68 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.03 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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), 8.01-8.05 (2H, m, Ar-H). ESI-MS m/z : 570 $[\text{M}+\text{Na}]^+$.

5-(3-(5-methoxy-2,3-dioxindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxylate (6f)

Yellow solid, yield: 59%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.42 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.24-2.27 (2H, m, $-\text{CH}_2-$), 3.85 (3H, s, OCH_3), 4.00 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$),

4.13 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.42 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.90 (1H, dd, $J = 4.0$, 8.0 Hz, Ar-H), 6.99-7.02 (3H, m, Ar-H), 7.07-7.11 (1H, m, Ar-H), 7.38 (1H, d, $J = 12.0$ Hz, Ar-H), 7.50-7.55 (2H, m, Ar-H), 7.59-7.61 (1H, m, Ar-H), 8.00-8.02 (2H, m, Ar-H). ESI-MS m/z : 522 $[\text{M}+\text{Na}]^+$.

5-((5-(5-fluoro-2,3-dioxindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6g)
 Yellow solid, yield: 76%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.12 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 3.76 (3H, s, OCH_3), 3.87 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$),

4.12 (2H, t, $J = 2.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.98 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.14-7.20 (3H, m, Ar-H), 7.37-7.42 (3H, m, Ar-H), 7.60 (1H, d, $J = 12.0$ Hz, Ar-H), 8.01-8.05 (2H, m, Ar-H). ESI-MS m/z : 540 $[\text{M}+\text{Na}]^+$.

5-(4-(5-methoxy-2,3-dioxindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6h)
 Yellow solid, yield: 62%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.32 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.80-1.84 (4H, m, $2 \times -\text{CH}_2-$), 3.71-3.76 (5H, m, $-\text{CH}_2-$ and OCH_3), 3.85 (3H, s,

OCH_3), 4.06 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.33 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.96 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08-7.16 (4H, m, Ar-H), 7.22-7.25 (1H, m, Ar-H), 7.42 (1H, d, $J = 4.0$ Hz, Ar-H), 7.55 (1H, d, $J = 8.0$ Hz, Ar-H), 7.94-7.97 (2H, m, Ar-H). ESI-MS m/z : 566 $[\text{M}+\text{Na}]^+$.

2-(4-fluorophenyl)-5-((5-(5-methoxy-2,3-dioxindolin-1-yl)pentyl)oxy)benzofuran-3-carboxylate (6i)

Yellow solid, yield: 66%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.32 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.50-1.55 (2H, m, $-\text{CH}_2-$), 1.65-1.71 (2H, m, $-\text{CH}_2-$), 1.76-1.82 (2H, m, $-\text{CH}_2-$), 4.68 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.85 (3H, s, OCH_3), 4.01 (2H,

t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.96 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08-7.11 (2H, m, Ar-H), 7.22-7.25 (1H, m, Ar-H), 7.41-7.45 (2H, m, Ar-H), 7.49-7.57 (2H, m, Ar-H), 7.94-7.97 (2H, m, Ar-H). ESI-MS m/z : 568 $[\text{M}+\text{Na}]^+$.

5-(3-(2,3-dioxindolin-1-yl)propoxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (6j)

Yellow solid, yield: 83%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.13 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.89 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.12 (2H, t, $J = 4.0$

Hz, $-\text{CH}_2-$), 4.33 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.98 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.11 (1H, t, $J = 4.0$ Hz, Ar-H), 7.24 (1H, d, $J = 8.0$ Hz, Ar-H), 7.37-7.42 (3H, m, Ar-H), 7.54-7.64 (3H, m, Ar-H), 8.01-8.05 (2H, d, $J = 8.0$ Hz, Ar-H). ESI-MS m/z : 510 $[\text{M}+\text{Na}]^+$.

5-(3-(2,3-dioxindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6k)

Yellow solid, yield: 77%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.33 (3H, t, $J = 4.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.13 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 3.86 (3H, s, OCH_3), 3.88 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$),

4.12 (2H, t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.34 (2H, q, $J = 4.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.96 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08–7.13 (3H, m, Ar-H), 7.24 (1H, d, $J = 8.0$ Hz, Ar-H), 7.40 (1H, d, $J = 8.0$ Hz, Ar-H), 7.54–7.63 (3H, m, Ar-H), 7.96 (2H, d, $J = 8.0$ Hz, Ar-H). ESI-MS m/z : 522 $[\text{M}+\text{Na}]^+$.

5-(4-(2,3-dioxindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6l)

Yellow solid, yield: 68%. ^1H NMR (400 MHz, CDCl_3) δ 1.39 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.86–1.94 (4H, m, $2\times-\text{CH}_2-$), 3.78 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.84 (3H, s, OCH_3), 4.04 (2H,

t, $J = 4.0$ Hz, $-\text{CH}_2-$), 4.38 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.85–6.91 (2H, m, Ar-H), 6.94–6.89 (2H, m, Ar-H), 7.06 (1H, t, $J = 8.0$ Hz, Ar-H), 7.34 (1H, d, $J = 12.0$ Hz, Ar-H), 7.48 (1H, d, $J = 4.0$ Hz, Ar-H), 7.50–7.53 (1H, m, Ar-H), 7.95–7.99 (2H, m, Ar-H). ESI-MS m/z : 536 $[\text{M}+\text{Na}]^+$.

ethyl 5-((6-(2,3-dioxindolin-1-yl)hexyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6m)

Yellow solid, yield: 59%. ^1H NMR (400 MHz, CDCl_3) δ 1.43 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.48-1.56 (4H, m, $2\times\text{-CH}_2\text{-}$), 1.76-1.87 (4H, m, $2\times\text{-CH}_2\text{-}$), 3.76 (2H, t, $J = 8.0$ Hz, $\text{-CH}_2\text{-}$), 3.88 (3H, s, OCH_3), 4.05 (2H, t, $J = 8.0$ Hz, $\text{-CH}_2\text{-}$), 4.43 (2H,

q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 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), 7.99-8.02 (2H, m, Ar-H). ESI-MS m/z : 565 $[\text{M}+\text{Na}]^+$.

Ethyl 5-(3-(3-(hydroxyimino)-2-oxindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6l)

Yellow solid, yield: 51%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.32 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.10 (2H, t, $J = 8.0$ Hz, $\text{-CH}_2\text{-}$), 3.85 (3H, s, OCH_3), 3.93 (2H, t, $J = 8.0$ Hz, $\text{-CH}_2\text{-}$), 4.08 (2H, t, $J = 8.0$ Hz, $\text{-CH}_2\text{-}$), 4.32 (2H, q, $J = 8.0$ Hz,

$\text{CO}_2\text{CH}_2\text{CH}_3$), 6.93 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.07-7.10 (3H, m, Ar-H), 7.16 (1H, d, $J = 8.0$ Hz, Ar-H), 7.40-7.42 (2H, m, Ar-H), 7.56 (1H, d, $J = 8.0$ Hz, Ar-H), 7.96 (2H, d, $J = 8.0$ Hz, Ar-H), 8.00 (1H, d, $J = 4.0$ Hz, Ar-H), 13.41 (1H, s, NOH). ESI-MS m/z : 537 $[\text{M}+\text{Na}]^+$.

Ethyl 5-(4-(3-(hydroxyimino)-2-oxindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6n**)**

Yellow solid, yield: 38%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.32 (3H, t, *J* = 8.0 Hz, CO₂CH₂CH₃), 1.79-1.82 (4H, m, 2×-CH₂-), 3.80-3.86 (5H, m, OCH₃ and -CH₂-), 4.07 (2H, t, *J* = 8.0 Hz, -CH₂-), 4.34 (2H, q, *J* = 8.0 Hz, CO₂CH₂CH₃),

6.97 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.06-7.11 (3H, m, Ar-H), 7.16 (1H, d, *J* = 8.0 Hz, Ar-H), 7.41-7.44 (2H, m, Ar-H), 7.56 (1H, d, *J* = 8.0 Hz, Ar-H), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H), 8.00 (1H, d, *J* = 8.0 Hz, Ar-H), 13.42 (1H, s, NOH). ESI-MS *m/z*: 551 [M+Na]⁺.

Ethyl 5-((5-(3-(hydroxyimino)-2-oxindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (60)

Yellow solid, yield: 33%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.48 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 1.67 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 1.79 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.74 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.85 (3H, s,

OCH_3), 4.00 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.96 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.07–7.10 (3H, m, Ar-H), 7.12 (1H, d, $J = 8.0$ Hz, Ar-H), 7.40–7.42 (2H, m, Ar-H), 7.56 (1H, d, $J = 8.0$ Hz, Ar-H), 7.96 (2H, d, $J = 8.0$ Hz, Ar-H), 8.00 (1H, d, $J = 8.0$ Hz, Ar-H), 13.44 (1H, s, NOH). ESI-MS m/z : 565 $[\text{M}+\text{Na}]^+$.

Ethyl 2-(4-fluorophenyl)-5-(3-(3-(hydroxyimino)-2-oxindolin-1-yl)propoxy)benzofuran-3-carboxylate (**6p**)

Yellow solid, yield: 54%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.30 (3H, t, *J* = 8.0 Hz, CO₂CH₂CH₃), 2.21 (2H, t, *J* = 8.0 Hz, -CH₂-), 3.93 (2H, t, *J* = 8.0 Hz, -CH₂-), 4.09 (2H, t, *J* = 8.0 Hz,

-CH₂-), 4.34 (2H, q, *J* = 8.0 Hz, CO₂CH₂CH₃), 6.98 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 7.08 (1H, t, *J* = 8.0 Hz, Ar-H), 7.16 (1H, d, *J* = 8.0 Hz, Ar-H), 7.39–7.43 (4H, m, Ar-H), 7.60 (1H, d, *J* = 12.0 Hz, Ar-H), 7.99–8.06 (3H, m, Ar-H), 13.44 (1H, s, NOH). ESI-MS *m/z*: 525 [M+Na]⁺.

Ethyl 5-(3-(3-(2-carbamothioylhydrazono)-2-oxoindolin-1-yl)propoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (**6q**)
 Yellow solid, yield: 36%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.32 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.15 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.86 (3H, s, OCH_3), 3.97 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.11 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.32 (2H, q, $J = 8.0$ Hz,

$\text{CO}_2\text{CH}_2\text{CH}_3$), 6.95 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08-7.14 (3H, m, Ar-H), 7.22 (1H, t, $J = 8.0$ Hz, Ar-H), 7.39-7.42 (2H, m, Ar-H), 7.55 (1H, d, $J = 12.0$ Hz, Ar-H), 7.71 (1H, d, $J = 8.0$ Hz, Ar-H), 7.96 (2H, d, $J = 8.0$ Hz, Ar-H), 8.71, 9.07 (2H, s, NNHCSNH_2), 12.38 (1H, s, NNHCSNH_2). ESI-MS m/z : 595 $[\text{M}+\text{Na}]^+$.

Ethyl 5-(4-(3-(2-carbamothioylhydrazono)-2-oxoindolin-1-yl)butoxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6r)

Yellow solid, yield: 24%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.38 (1H, s, NHCSNH₂), 9.07 (1H, s, NHCSNH₂), 8.71 (1H, s, NHCSNH₂), 7.96 (2H, d, *J* = 8.0 Hz, Ar-H), 7.70 (1H, d, *J* = 8.0 Hz, Ar-H), 7.41-7.43 (2H, m, Ar-H), 7.15 (1H, t, *J* = 8.0 Hz, Ar-H), 7.08 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 6.96 (1H, dd, *J* = 4.0, 8.0 Hz, Ar-H), 4.33 (2H, q, *J* = 8.0 Hz, CO₂CH₂CH₃), 3.82-3.86 (5H, m, -CH₂- and OCH₃), 1.79-1.82 (4H, m, 2×-CH₂-), 1.33 (3H, t, *J* = 8.0 Hz, CO₂CH₂CH₃).

ESI-MS *m/z*: 609 [M+Na]⁺.

Ethyl(E)-5-((5-(3-(2-carbamothioylhydrazono)-2-oxoindolin-1-yl)pentyl)oxy)-2-(4-methoxyphenyl)benzofuran-3-carboxylate (6s)

Yellow solid, yield: 19%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.32 (3H, t, J = 8.0 Hz, CO₂CH₂CH₃), 1.42-1.82 (6H, m, 3 $\times$ CH₂-), 3.80-3.86 (5H, m, -CH₂- and OCH₃), 4.02 (2H, t, J = 8.0 Hz, -CH₂-), 4.34 (2H, q, J = 8.0 Hz, CO₂CH₂CH₃),

6.96 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.08 (1H, dd, J = 4.0, 8.0 Hz, Ar-H), 7.15 (1H, t, J = 8.0 Hz, Ar-H), 7.22 (1H, d, J = 8.0 Hz, Ar-H), 7.41-7.43 (2H, m, Ar-H), 7.57 (1H, d, J = 12.0 Hz, Ar-H), 7.72 (1H, d, J = 8.0 Hz, Ar-H), 7.96 (2H, d, J = 8.0 Hz, Ar-H), 8.73, 9.08 (2H, s, NNHCSNH₂), 12.44 (1H, s, NNHCSNH₂). ESI-MS m/z : 623 [M+Na]⁺.

Ethyl 5-(3-(5-fluoro-3-(hydroxyimino)-2-oxindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxylate (6t)

Yellow solid, yield: 48%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.28 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.08 (2H, t, $J = 8.0$ Hz,

$-\text{CH}_2-$), 3.94 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.12 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.48 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.96–7.29 (3H, m, Ar-H), 7.39–7.96 (8H, m, Ar-H), 13.70 (1H, s, NOH). ESI-MS m/z : 525 $[\text{M}+\text{Na}]^+$.

Ethyl 5-(3-(5-fluoro-3-(hydroxyimino)-2-oxoindolin-1-yl)propoxy)-2-(4-fluorophenyl)benzofuran-3-carboxylate (6u)

Yellow solid, yield: 39%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.11 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.93 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.09 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$),

CH_2-), 4.34 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.96 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.18–7.31 (2H, m, Ar-H), 7.36–7.42 (3H, m, Ar-H), 7.60 (1H, d, $J = 12.0$ Hz, Ar-H), 7.76 (1H, d, $J = 8.0$ Hz, Ar-H), 8.01–8.05 (2H, m, Ar-H), 13.68 (1H, s, NOH). ESI-MS m/z : 543 $[\text{M}+\text{Na}]^+$.

Ethyl 5-(3-(3-(hydroxyimino)-5-methoxy-2-oxoindolin-1-yl)propoxy)-2-phenylbenzofuran-3-carboxylate (6v)

Yellow solid, yield: 46%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.24 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.15 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.74 (3H, s, OCH_3), 3.93 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$),

4.12 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.46 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.98 (1H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08-7.15 (2H, m, Ar-H), 7.54-7.70 (5H, m, Ar-H), 7.80-7.96 (3H, m, Ar-H), 13.46 (1H, s, NOH). ESI-MS m/z : 537 $[\text{M}+\text{Na}]^+$.

Ethyl 2-(4-fluorophenyl)-5-(3-(3-(hydroxyimino)-5-methoxy-2-oxoindolin-1-yl)propoxy)benzofuran-3-carboxylate (6w)

Yellow solid, yield: 43%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.10 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.74 (3H, s, OCH_3), 3.90 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$),

4.08 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.34 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.98 (2H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08 (1H, d, $J = 8.0$ Hz, Ar-H), 7.37-7.42 (3H, m, Ar-H), 7.61 (1H, d, $J = 4.0$ Hz, Ar-H), 8.02-8.06 (2H, m, Ar-H), 13.42 (1H, s, NOH). ESI-MS m/z : 555 $[\text{M}+\text{Na}]^+$.

Ethyl 2-(4-fluorophenyl)-5-(4-(3-(hydroxyimino)-5-methoxy-2-oxoindolin-1-yl)butoxy)benzofuran-3-carboxylate (6x)
 Yellow solid, yield: 28%. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.31 (3H, t, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.10 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 3.74 (3H, s, OCH_3), 3.90 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$),

4.08 (2H, t, $J = 8.0$ Hz, $-\text{CH}_2-$), 4.34 (2H, q, $J = 8.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.98 (2H, dd, $J = 4.0, 8.0$ Hz, Ar-H), 7.08 (1H, d, $J = 8.0$ Hz, Ar-H), 7.37-7.42 (3H, m, Ar-H), 7.61 (1H, d, $J = 4.0$ Hz, Ar-H), 8.02-8.06 (2H, m, Ar-H), 13.42 (1H, s, NOH). ESI-MS m/z : 569 $[\text{M}+\text{Na}]^+$.

CONCLUSION

In conclusion, twenty-four novel benzofuran-isatin hybrids **6a-x** tethered via different length alkyl linkers were designed, synthesized and evaluated for their *in vitro* anti-bacterial activities against a panel of clinically important pathogens. All hybrids displayed decent *in vitro* anti-bacterial activities against both drug-sensitive and drug-resistant Gram-positive and Gram-negative bacteria, have the potential to treat infections caused by various pathogens. In particular, the most active hybrid **6l** was not only comparable to vancomycin against the majority of the tested Gram-positive strains, but also highly active against Gram-negative bacteria. Based on the above results, hybrid **6l** could act as a lead for further optimization.

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