Design, Synthesis, and Antibacterial Evaluation of Propylene-tethered 8-Methoxyl Ciprofloxacin-isatin Hybrids

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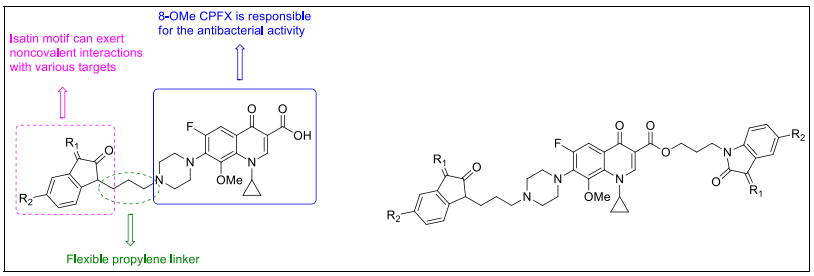

A series of 8-methoxyl ciprofloxacin (8-OMe CPFX)-isatin hybrids **3a–f** and **4a–f** tethered through propylene were designed, synthesized, and examined for their *in vitro* antibacterial activities against a panel of Gram-positive and Gram-negative pathogens including drug-resistant bacteria. All the synthesized hybrids (minimum inhibitory concentration: ≤0.03–64 μg/mL) exhibited considerable activities against the tested strains, especially against the Gram-negative pathogens. Among them, hybrid **3b** was no inferior to the parent 8-OMe CPFX that could act as a starting point for further optimization.

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INTRODUCTION

Gram-positive and Gram-negative bacteria, which are the most common pathogens in hospital and community settings, are capable of causing various serious and even fatal infections [1,2]. Antibiotics are the key weapons in the fight against bacterial infection, but the overuse and misuse of antibiotics have triggered increased drug resistance [3]. Currently, antimicrobial resistance constitutes a global health problem. To combat antibiotic resistance, the paucity of new antibacterial drugs is evident [4].

The current arsenal of broad spectrum antibiotics is dominated by only four major scaffolds: cephalosporins, penicillins, macrolides, and quinolones [5,6]. Among them, quinolones as the second largest antibiotics are used widely in the treatment of various bacterial infections caused by both Gram-positive and Gram-negative pathogens [7–9]. Moreover, besides typical antibacterial activity, quinolone motif as a multivalent scaffold exhibited diverse biological properties [10] such as antitubercular [11], antimalarial [12,13], and anticancer [14] activities, which play a pivotal role in drug development. Unfortunately, like other antibiotics, bacteria have already developed resistance to quinolone antibiotics, making them more and more ineffective [15–17]. Thus, it is of paramount importance to develop new quinolone antibiotics to overcome drug resistance.

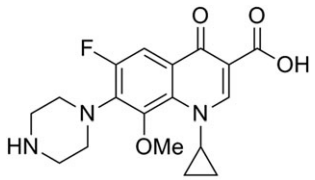
The structure–activity relationship indicated that the introduction of the methoxyl group on the C-8 position of the quinolone moiety could enhancement of the activity against Gram-positive organisms and anaerobes while maintaining excellent potency against Gram-negative bacteria [18]. It is worth to notice that some of the 8-methoxyl ciprofloxacin (8-OMe CPFX, Fig. 1) derivatives exhibit considerable antibacterial activity [19,20]. Obviously, 8-OMe CPFX is a reasonable choice used to develop new antibacterial agents.

Isatin is an endogenous compound identified in many organisms and has the ability to exert several noncovalent interactions such as Van der Waals force and hydrogen bonds [21,22]. Isatin derivatives endow with a variety of biological properties including antibacterial activity, and some isatin-based compounds have been approved for clinical use [23,24]. Thus, isatin is a useful chemical protype to exploit new drugs.

Based on the aforementioned research results and as an ongoing program to develop novel antibacterial agents, a series of 8-OMe CPFX-isatin hybrids **3a–f** and **4a–f** tethered through propylene were designed, synthesized, and examined for their *in vitro* antibacterial activities against clinically important Gram-positive and Gram-negative pathogens including drug-resistant bacteria. The design strategy is illustrated in Figure 2.

RESULTS AND DISCUSSION

The synthetic pathway for the desired hybrids **3a–f** and **4a–f** is described in Scheme 1. C-5 substituted isatins **1a**,**b**



8-OMe CPFX

Figure 1. Chemical structure of 8-OMe CPFX.

were alkylated with 1,3-dibromopropane to afford *N*-(3-bromopropyl) isatins **2a**,**b**, which were then incorporated into 8-OMe CPFX moiety to give the desired targets **3a**,**b** and **4a**,**b**. Subsequently, condensation of hybrids **3a**,**b** or **4a**,**b** with the corresponding alkoxyamine yielded other conjugates **3c**–**f** and **4c**–**f** [25].

All 8-OMe CPFX-isatin hybrids **3a**–**f** and **4a**–**f** were evaluated for their *in vitro* antibacterial activities against a panel of Gram-positive and Gram-negative pathogens [26]. 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 1 and 2, respectively.

From Table 1, it can be concluded that all 8-OMe CPFX hybrids **3a**–**f** bearing mono-isatin motif exhibited considerable antibacterial activities against all of the tested Gram-positive strains with MIC in a range of 0.25 to 64 μg/mL, but less active than the parent 8-OMe CPFX and CPFX. The structure–activity relationship indicated that introduction of imine at C-3 position of isatin moiety seems did not increase the activity greatly; mono-isatin hybrids were far more potent than the corresponding bis-isatin hybrids.

As it can be seen from Table 2, all 8-OMe CPFX hybrids **3a**–**f** exhibited promising antibacterial activities against all of the tested Gram-negative strains with MIC ranging from ≤0.03 to 8 μg/mL. Further analysis revealed that the MICs of hybrids **3a**–**f** were < 1 μg/mL against the majority of the tested pathogens. In general, introduction of imine at C-3 position of isatin moiety was detrimental to the activity. Similar as their anti-Gram-positive bacteria activity, mono-isatin hybrids were more active than the corresponding bis-isatin hybrids against Gram-negative pathogens, which may attribute to the fact that carboxylic acid on quinolone motif is essential for gyrase binding and bacterial membrane transport. In particular, the most active hybrid **3b** was comparable to or better than the parent 8-OMe CPFX and was far more potent than VAN against Gram-negative organisms, which could act as a lead for further optimization.

EXPERIMENTAL SECTION

Synthesis. ***General procedure for the preparation of 3a,b and 4a,b.*** *N*-(3-bromopropyl) isatins **2a**,**b** were prepared by literature reported method [25]. A mixture of *N*-(3-bromopropyl) isatins **2a**,**b** (1.4 mmol), 8-OMe CPFX (1 mmol) and K_2CO_3 (3 mmol) in DMF (10 mL) was stirred at room temperature for 5 days. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by MPLC to provide the desired targets **3a**,**b** and **4a**,**b**.

*1-Cyclopropyl-7-(4-(3-(2,3-dioxoindolin-1-yl)propyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**3a**).* Brown solid, yield: 11%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14–1.28 (4H, m, 2 × cyclopropyl-CH_2), 2.02 (2H, t, –CH_2–), 2.96 (4H, s, piperazine-4H), 3.18 (4H, s, piperazine-4H), 3.84 (2H, t, –CH_2–), 3.87 (3H, s, OCH_3), 3.98–4.00 (1H, m, cyclopropyl-CH), 4.27 (2H, t, –CH_2–), 7.06–8.42 (6H, m, Ar-H). ESI-MS *m/z*: 549 $[M + H]^+$. Elemental *Anal.* Calcd (%) for $C_{29}H_{29}FN_4O_6$: C, 63.50; H, 5.33; N, 10.21; Found: C, 63.27; H, 5.14; N, 10.03.

*11-Cyclopropyl-6-fluoro-8-methoxy-7-(4-(3-(5-methyl-2,3-dioxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**3b**).* Brown solid, yield: 26%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12–1.26 (4H, m,

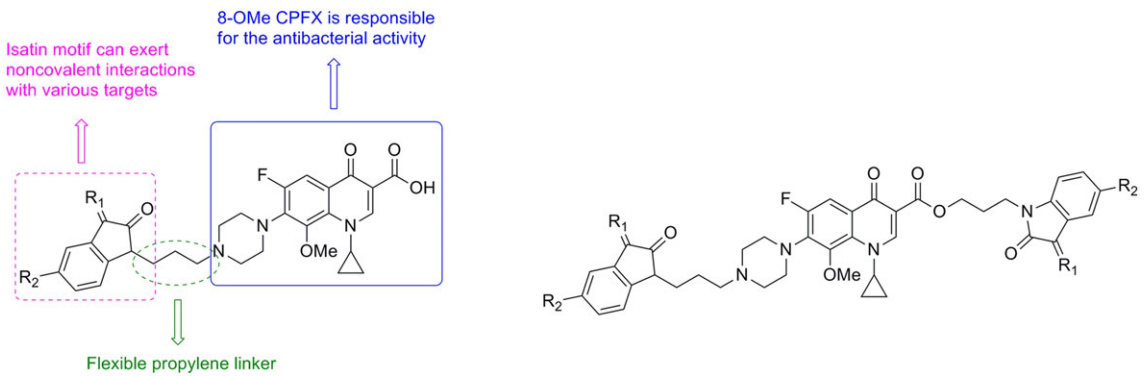


Figure 2. The design strategy of 8-OMe CPFX-isatin hybrids. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthetic route of hybrids 3a-f and 4a-f.

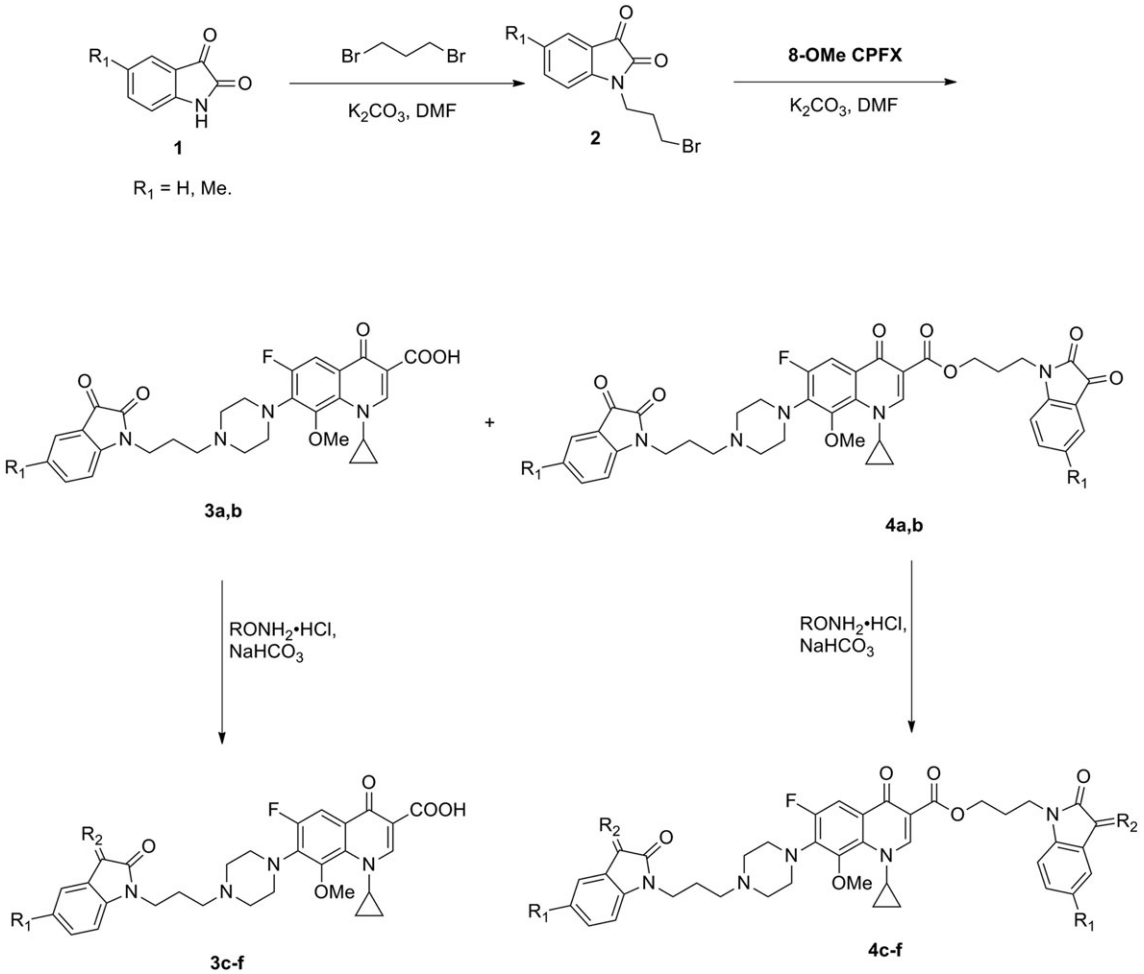


Table 1

In vitro antibacterial activity of hybrids **3a–f** and **4a–f** against Gram-positive strains.

	MIC (μg/mL)					
Compd.	MSSE	MRSE	MSSA	MRSA	E.fa.	E.fm.
3a	0.5	4	1	1	4	16
3b	0.5	8	1	1	4	8
3c	0.25	8	2	2	2	64
3d	0.5	8	4	1	2	16
3e	0.5	4	4	2	4	16
3f	2	8	4	2	2	16
4a	64	>128	64	32	128	>128
4b	64	>128	32	>128	>128	>128
4c	32	>128	>128	>128	>128	>128
4d	16	>128	128	>128	>128	>128
4e	64	>128	128	>128	128	>128
4f	64	>128	>128	>128	>128	>128
CPFX	0.125	4	0.25	0.25	0.5	8
8-OMeCPFX	0.125	2	0.125	0.25	1	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; 8-OMe CPFX, 8-methoxy ciprofloxacin; VAN, vancomycin.

Table 2

In vitro antibacterial activity of hybrids **3a–f** and **4a–f** against Gram-negative strains.

	MIC											
Compd.	E.co.	K.p.	P.a.	A.c.	E.c.	E.a.	S.m.	M.m.	P.r.	P.v.	P.m.	C.f.
3a	0.06	1	0.5	4	0.125	0.06	0.06	≤0.03	≤0.03	0.06	≤0.03	0.06
3b	0.06	0.5	0.5	4	0.06	0.25	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
3c	0.25	0.5	1	8	0.125	0.125	0.125	0.06	0.06	≤0.03	0.125	0.06
3d	0.5	0.5	2	8	0.125	0.25	0.25	≤0.03	≤0.03	0.125	0.25	0.06
3e	0.25	1	1	4	0.06	0.06	0.25	≤0.06	≤0.03	0.06	≤0.03	≤0.03
3f	0.125	1	0.5	4	0.25	0.125	0.25	0.125	0.125	0.125	≤0.03	0.06
4a	32	32	64	16	64	128	32	16	8	16	32	32
4b	64	32	32	128	32	16	32	32	16	8	16	16
4c	64	16	32	32	64	16	64	16	16	16	32	32
4d	128	64	128	128	32	32	>128	8	32	32	16	32
4e	128	64	32	64	128	64	128	64	32	32	64	64
4f	128	128	>128	64	64	32	64	>128	64	64	32	64
CPFX	0.06	0.5	0.25	0.5	≤0.03	≤0.03	0.06	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
8-OMeCPFX	0.125	1	2	0.5	≤0.03	0.125	0.25	≤0.03	0.06	≤0.03	0.125	0.06
VAN	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128

Abbreviations: E.co., *Escherichia coli*; K.p., *Klebsiella pneumoniae*; P.a., *Pseudomonas aeruginosa* ATCC 27853; A.c., *Acinetobactercal coacetious*; E.c., *Enterobacter cloacae*; E.a., *Enterobacter aerogenes*; S.m., Serratia marcescens; M.m., *Morganella morganii*; P.r., *Providentia rettgeri*; P.v., *Proteus vulgaris*; P.m., *Proteus mirabilis*; C.f., *Citrobacter freundii*; CPFX, ciprofloxacin; 8-OMe CPFX, 8-methoxy ciprofloxacin; VAN, vancomycin.

2 × cyclopropyl-CH_2), 2.01 (2H, t, –CH_2–), 2.22 (3H, s, CH_3), 2.98 (4H, s, piperazine-4H), 3.21 (4H, s, piperazine-4H), 3.84 (2H, t, –CH_2–), 3.87 (3H, s, OCH_3), 3.99–4.00 (1H, m, cyclopropyl-CH), 4.24 (2H, t, –CH_2–), 7.08–8.44 (5H, m, Ar-H). ESI-MS *m/z*: 563 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{31}FN_4O_6$: C, 64.05; H, 5.55; N, 9.96; Found: C, 63.88; H, 5.34; N, 9.72.

*3-(2,3-Dioxoindolin-1-yl) propyl 1-cyclopropyl-7-(4-(3-(2,3-dioxoindolin-1-yl)propyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4a**).* Brown solid, yield: 17%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10–1.28 (4H, m, 2 × cyclopropyl-CH_2), 1.85 (2H, t, –CH_2–), 2.04 (2H, t, –CH_2–), 2.48 (2H, t, –CH_2–), 3.01 (4H, s, piperazine-4H), 3.32 (4H, s, piperazine-4H), 3.74–3.90 (7H, m, 2 × –CH_2– and OCH_3), 3.99–4.01 (1H, m, cyclopropyl-CH), 4.24 (2H, t, –CH_2–), 7.05–8.46 (10H, m, Ar-H). ESI-MS *m/z*: 736 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{40}H_{38}FN_5O_8$: C, 65.30; H, 5.21; N, 9.52; Found: C, 65.09; H, 5.04; N, 9.37.

*3-(5-Methyl-2,3-dioxoindolin-1-yl) propyl 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-(3-(5-methyl-2,3-dioxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4b**).* Brown solid, yield: 14%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20–1.37 (4H, m, 2 × cyclopropyl-CH_2), 2.02 (2H, t, –CH_2–), 2.20 (2H, t, –CH_2–), 2.24 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.54 (2H, t, –CH_2–), 2.82 (4H, s, piperazine-4H), 3.30 (4H, s, piperazine-4H), 3.74–3.89 (5H, m, –CH_2– and OCH_3), 3.98–4.03 (3H, m, –CH_2– and cyclopropyl-CH), 4.36 (2H, t, –CH_2–), 7.01–8.47 (8H, m, Ar-H). ESI-MS *m/z*: 764 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{42}H_{42}FN_5O_8$: C, 66.04; H, 5.54; N, 9.17; Found: C, 65.79; H, 5.28; N, 9.02.

The general procedure for preparing targets 3c–f and 4c–f. A mixture of methoxylamine or ethoxylamine hydrochloride (8 mmol), sodium bicarbonate (15 mmol), and **3a**,**b** or **4a**,**b** (5 mmol) in a mixture of water (10 mL) and methanol (10 mL) was stirred at room temperature for 24 h. After removal of the solvent, the residue was diluted with water (10 mL) and filtered. The solid crude product was purified by silica gel chromatography eluted with DCM to *v* (DCM):*v* (MeOH) = 10:1 to give the title hybrids **3c–f** and **4c–f**.

*1-Cyclopropyl-6-fluoro-8-methoxy-7-(4-(3-(3-(methoxyimino)-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**3c**).* Yellow solid, yield: 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12–1.26 (4H, m, 2 × cyclopropyl-CH_2), 2.02 (2H, t, –CH_2–), 2.88 (4H, s, piperazine-4H), 3.22 (4H, s, piperazine-4H), 3.86 (3H, s, OCH_3), 3.90 (2H, t, –CH_2–), 3.99–4.00 (1H, m, cyclopropyl-CH), 4.16–4.22 (5H, m, –CH_2– and $NOCH_3$), 7.04–8.42 (6H, m, Ar-H). ESI-MS *m/z*: 578 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{30}H_{32}FN_5O_6$: C, 62.38; H, 5.58; N, 12.12; Found: C, 62.22; H, 5.37; N, 12.03.

*1-Cyclopropyl-6-fluoro-8-methoxy-7-(4-(3-(3-(methoxyimino)-5-methyl-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**3d**).* Yellow solid, yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10–1.28 (4H, m, 2 × cyclopropyl-CH_2), 2.00 (2H, t, –CH_2–), 2.23 (3H, s, CH_3), 3.04 (4H, s, piperazine-4H), 3.32 (4H, s, piperazine-4H), 3.82–3.90 (5H, m, –CH_2– and OCH_3), 3.99–4.01 (1H, m, cyclopropyl-CH), 4.15–4.21 (5H, m, –CH_2– and $NOCH_3$), 7.10–8.41 (5H, m, Ar-H). ESI-MS *m/z*: 592 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{34}FN_5O_6$: C, 62.93; H, 5.79; N, 11.84; Found: C, 62.77; H, 5.57; N, 11.68.

*1-Cyclopropyl-7-(4-(3-(3-(ethoxyimino)-2-oxoindolin-1-yl) propyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**3e**).* Yellow solid, yield: 46%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10–1.28 (4H, m, 2 × cyclopropyl-CH_2), 1.36 (3H, t, $NOCH_2CH_3$), 2.03 (2H, t, –CH_2–), 2.96 (4H, s, piperazine-4H), 3.22 (4H, s, piperazine-4H), 3.85–3.92 (5H, m, –CH_2– and OCH_3), 3.98–3.99 (1H, m, cyclopropyl-CH), 4.20 (2H, t, –CH_2–), 4.37 (2H, q, $NOCH_2CH_3$), 7.06–8.46 (6H, s, Ar-H). ESI-MS *m/z*: 592 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{31}H_{34}FN_5O_6$: C, 62.93; H, 5.79; N, 11.84; Found: C, 62.69; H, 5.51; N, 11.59.

*3-(2,3-Dioxoindolin-1-yl) propyl 1-cyclopropyl-7-(4-(3-(2,3-dioxoindolin-1-yl)propyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**3f**).* Yellow solid, yield: 39%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09–1.26 (4H, m, 2 × cyclopropyl-CH_2), 1.36 (3H, t, $NOCH_2CH_3$), 2.00 (2H, t, –CH_2–), 2.24 (3H, s, CH_3), 3.00 (4H, s, piperazine-4H), 3.34 (4H, s, piperazine-4H), 3.86–3.92 (5H, m, –CH_2– and OCH_3), 3.99–4.02 (1H, m, cyclopropyl-CH), 4.16 (2H, t, –CH_2–), 4.36 (2H, q, $NOCH_2CH_3$), 7.08–8.48 (5H, m, Ar-H). ESI-MS *m/z*: 606 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{32}H_{36}FN_5O_6$: C, 63.46; H, 5.99; N, 11.56; Found: C, 63.18; H, 5.79; N, 11.38.

*3-(3-(Methoxyimino)-2-oxoindolin-1-yl) propyl 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-(3-(3-(methoxyimino)-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4c**).* Yellow solid, yield: 74%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12–1.26 (4H, m, 2 × cyclopropyl-CH_2), 1.85 (2H, t, –CH_2–), 2.02 (2H, t, –CH_2–), 2.56 (2H, t, –CH_2–), 2.98 (4H, s, piperazine-4H), 3.28 (4H, s, piperazine-4H), 3.72–3.88 (7H, m,

2 × $–CH_2–$ and OCH_3), 3.99–4.01 (1H, m, cyclopropyl-CH), 4.14–4.21 (8H, m, $–CH_2–$ and 2 × $NOCH_3$), 7.07–8.43 (10H, m, Ar-H). ESI-MS *m/z*: 794 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{42}H_{44}FN_7O_8$: C, 63.55; H, 5.59; N, 12.35; Found: C, 63.29; H, 5.37; N, 12.16.

*3-(3-(Methoxyimino)-5-methyl-2-oxoindolin-1-yl) propyl 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-(3-(3-(methoxyimino)-5-methyl-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4d**).* Yellow solid, yield: 45%. ^1H NMR (400 MHz, DMSO-d_6) δ 1.10–1.26 (4H, m, 2 × cyclopropyl-CH_2), 1.86 (2H, t, $–CH_2–$), 2.02 (2H, t, $–CH_2–$), 2.23 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.44 (2H, t, $–CH_2–$), 2.69 (4H, s, piperazine-4H), 3.12 (4H, s, piperazine-4H), 3.74–3.89 (7H, m, 2 × $–CH_2–$ and OCH_3), 4.00–4.02 (1H, m, cyclopropyl-CH), 4.12–4.20 (8H, m, $–CH_2–$ and 2 × $NOCH_3$), 7.05–8.46 (8H, m, Ar-H). ESI-MS *m/z*: 822 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{44}H_{48}FN_7O_8$: C, 64.30; H, 5.89; N, 11.93; Found: C, 64.06; H, 5.77; N, 11.81.

*3-(3-(Ethoxyimino)-2-oxoindolin-1-yl) propyl 1-cyclopropyl-7-(4-(3-(3-(ethoxyimino)-2-oxoindolin-1-yl)propyl) piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4e**).* Yellow solid, yield: 36%. ^1H NMR (400 MHz, DMSO-d_6) δ 1.10–1.26 (4H, m, 2 × cyclopropyl-CH_2), 1.36 (6H, t, 2 × $NOCH_2CH_3$), 1.86 (2H, t, $–CH_2–$), 2.02 (2H, t, $–CH_2–$), 2.48 (2H, t, $–CH_2–$), 2.78 (4H, s, piperazine-4H), 3.16 (4H, s, piperazine-4H), 3.72–3.88 (7H, m, 2 × $–CH_2–$ and OCH_3), 3.98–4.00 (1H, m, cyclopropyl-CH), 4.16 (2H, t, $–CH_2–$), 4.42 (4H, q, 2 × $NOCH_2CH_3$), 7.06–8.41 (10H, m, Ar-H). ESI-MS *m/z*: 822 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{44}H_{48}FN_7O_8$: C, 64.30; H, 5.89; N, 11.93; Found: C, 64.17; H, 5.69; N, 11.73.

*3-(3-(Ethoxyimino)-5-methyl-2-oxoindolin-1-yl) propyl 1-cyclopropyl-7-(4-(3-(3-(ethoxyimino)-5-methyl-2-oxoindolin-1-yl)propyl)piperazin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylate (**4f**).* Yellow solid, yield: 46%. ^1H NMR (400 MHz, DMSO-d_6) δ 1.10–1.28 (4H, m, 2 × cyclopropyl-CH_2), 1.35 (6H, t, 2 × $NOCH_2CH_3$), 1.74 (2H, t, $–CH_2–$), 2.02 (2H, t, $–CH_2–$), 2.24 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.40 (2H, t, $–CH_2–$), 2.80 (4H, s, piperazine-4H), 3.24 (4H, s, piperazine-4H), 3.74–3.90 (7H, m, 2 × $–CH_2–$ and OCH_3), 3.99–4.01 (1H, m, cyclopropyl-CH), 4.18 (2H, t, $–CH_2–$), 4.44 (4H, q, 2 × $NOCH_2CH_3$), 7.07–8.44 (8H, m, Ar-H). ESI-MS *m/z*: 850 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{46}H_{54}FN_7O_8$: C, 65.00; H, 6.17; N, 11.54; Found: C, 64.83; H, 6.01; N, 11.32.

Antibacterial MIC determination. All hybrids were screened for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative strains, by means of standard twofold serial dilution method using agar media. Hybrids (10.0 mg) were dissolved in 0.1 N NaOH solution and water (10 mL). Further progressive twofolds serial dilution with melted Mueller–Hinton agar was performed to obtain the required concentrations of 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.06, and 0.03 μg/mL. Petri dishes were incubated with 10^4 colony-forming units and incubated at 35°C for 18–24 h.

CONCLUSION

In conclusion, a series of 8-OMe CPFX-isatin hybrids were designed, synthesized, and evaluated for their *in vitro* antibacterial activity against a panel of clinically important pathogens. The results showed that the hybrids bearing mono-isatin motif displayed excellent antibacterial activity especially against Gram-negative bacteria. Among them, hybrid **3b** was no inferior to the parent 8-OMe CPFX against the majority of the tested pathogens, worth to be further studied.

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