Design, Synthesis, and Antimycobacterial Activities of Diethylene Glycol Tethered Moxifloxacin–Isatin Hybrids

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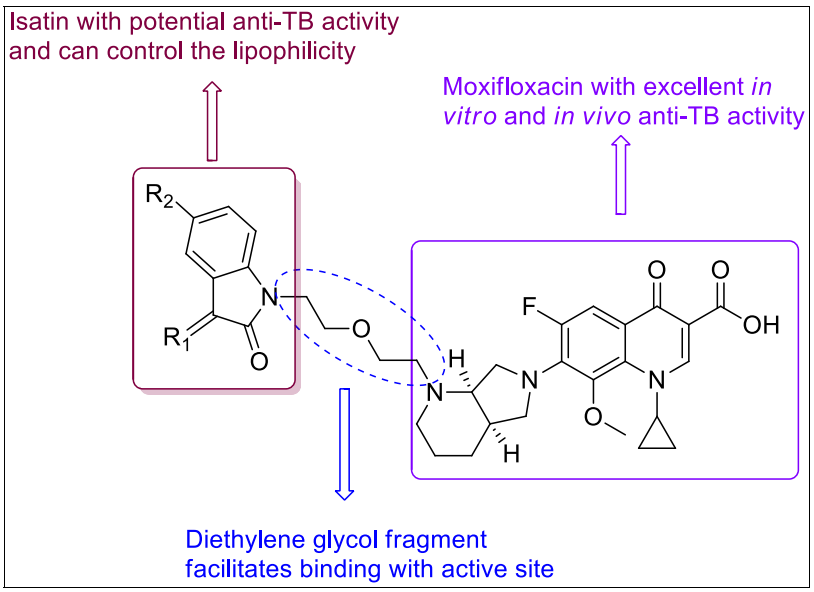


A new class of diethylene glycol tethered moxifloxacin–isatin hybrids **5a–l** was designed, synthesized, and evaluated for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* (MTB) H37Rv and multidrug-resistant tuberculosis (MDR-TB) strains. Our results showed that all hybrids with higher lipophilicity than the parent moxifloxacin exhibited promising activity against the tested strains with minimum inhibitory concentration (MIC) in a range of 0.2–16 μg/mL. In particular, hybrid **5h** (MIC: 0.20 and 0.5 μg/mL), which was found to be most active against MTB H37Rv and MDR-TB, was twofold more potent than isoniazid (MIC: 0.39 μg/mL) against MTB H37Rv and ≥64-fold more active than isoniazid and rifampicin (MIC: >128 and 32 μg/mL, respectively) against MDR-TB.

INTRODUCTION

Tuberculosis (TB) is a highly infectious deadliest disease caused predominately by *Mycobacterium tuberculosis* (MTB) and kills around 5000 people every day [1]. The first-line anti-TB agents such as isoniazid (**INH**), rifampicin (**RIF**), pyrazinamide, and ethambutol are used widely in clinical practice for the treatment of MTB-infected patients [2]. However, the emergency and widely spread of MTB new virulent forms such as drug-resistant TB, multidrug-resistant TB (MDR-TB), and extremely drug-resistant TB as well as MTB coinfection with HIV [3,4], creating an urgent need to develop anti-TB drugs with novel mechanisms of action and that are active against MDR-TB and extremely drug-resistant TB.

Some fluoroquinolones possess excellent *in vitro* and *in vivo* anti-TB activity, and DNA gyrase is known to be the only type II topoisomerase present in MTB and is thus the only target for fluoroquinolones action [3,4]. More importantly, MTB isolates expressing resistance to both **INH** and **RIF** are still sensitive to fluoroquinlones generally [5,6], so fluoroquinolones have the potential to treat MDR-TB-infected patients. Indeed, some early fluoroquinlones have been already recommended as the second-line anti-TB agents by the World Health Organization for the treatment of TB mainly in cases involving resistance or intolerance to first-line anti-TB

therapy [2]. Thus, fluoroquinolones have caused continuous interests in the discovery of new anti-TB agents.

Moxifloxacin (**MXF**, Fig. 1), the fourth generation fluoroquinolone, exhibits notable *in vitro* and *in vivo* anti-TB activity against MTB including strains with various levels of fluoroquinolones resistance. Furthermore, **MXF** was no inferior to the standard regimen in clinical trials and is under phase III clinical trial as potential first-line agent for the treatment of TB currently [7]. Obviously, **MXF** is a promising prototype for the development of new anti-TB candidates. Several studies revealed that the lipophilicity of fluoroquinlones plays an important role in the penetration of these compounds into bacterial cells, and introduction of isatin in to C-7 position of fluoroquinolones could improve the lipophilic character and consequently boost up the anti-TB activity [8–11]. Moreover, the activity–structure relationship indicated that the linker between the fluoroquinolones and isatin influenced the anti-TB activity significantly and the linker that could exert noncovalent bind interactions was preferred [12].

As a part of an ongoing program to develop new anti-TB candidates, various fluoroquinlone–isatin hybrids with different linkers including methylene, ethylene, acetyl, and 1,2,3-triazole were synthesized and screened for their *in vitro* activity against MTB H37Rv and MDR-TB by our group in recent years, and some of them exhibited considerable inhibitory activity against the tested strains [13–18]. Inspired by the aforementioned research results, a series of MXF–isatin hybrids tethered *via* diethylene glycol were designed, synthesized, and evaluated for their *in vitro* antimycobacterial activity in this paper because diethylene glycol fragment has the potential to exert various noncovalent interactions, which may facilitate binding with active site. Our primary objective was to identify optimized linker between **MXF** and isatin to facilitate the further development. The illustration of the design strategy is depicted in Figure 2.

RESULTS AND DISCUSSION

The synthetic route for diethylene glycol tethered MXF–isatin hybrids **5a–l** was depicted in Scheme 1. Oxybis(ethane-2,1-diyl)bis(4-methylbenzenesulfonate) **2**

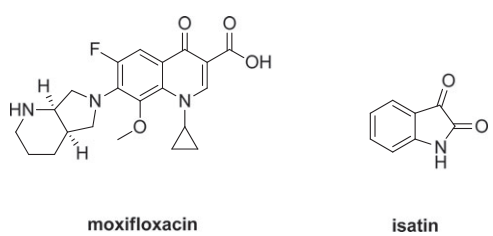


Figure 1. Chemical structures of moxifloxacin and isatin.

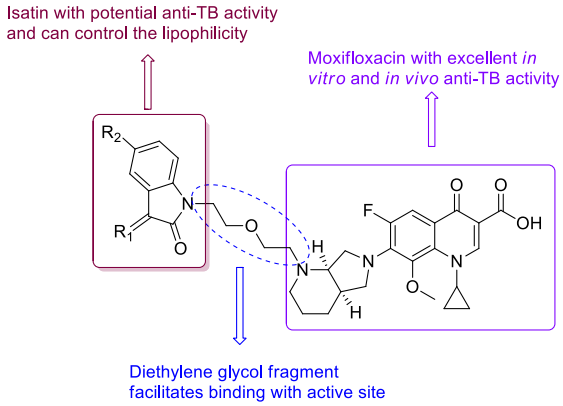


Figure 2. The design strategy of diethylene glycol tethered moxifloxacin–isatin hybrids. TB, tuberculosis. [Color figure can be viewed at wileyonlinelibrary.com]

was obtained by treatment of diethylene glycol **1** with tosyl chloride in presence of triethylamine, and then alkylation of **2** with C-5 substituted isatins **3** yielded the key intermediates **4a–c**. Introduction of **4a–c** into **MXF** provided the desired MXF–isatin hybrids **5a–c**, which was consequently condensation with the corresponding amine hydrochlorides gave the other hybrids **5d–l**.

Compared with the parent **MXF** (Log *P*: 1.68), all diethylene glycol tethered MXF–isatin hybrids **5a–l** (Log *P*: 2.03–3.01) showed higher lipophilicity, and this character may improve their permeation properties toward mycobacterial cell membrane. All hybrids **5a–l** together with the references **MXF**, **INH**, and **RIF** were examined for their *in vitro* antimycobacterial activities against MTB H37Rv and MDR-TB (resistant to **INH**, **RIF**, and ethambutol) strains, and the results were presented in Table 1. The minimum inhibitory concentration (MIC) is defined as the lowest concentration that inhibits the visible bacterial growth.

From Table 1, it can be concluded that all synthesized diethylene glycol tethered MXF–isatin hybrids **5a–l** exhibited excellent activity against both drug-sensitive and MDR-MTB strains with MIC ranging from 0.20 to 16 μg/mL but were less active than the references **MXF** (MIC: 0.10 and 0.12 μg/mL, respectively) against MTB H37Rv and MDR-TB, suggesting that the lipophilicity was not the sole factor affected the antimycobacterial activity [8,9]. Installation of –NOMe or –NOEt into C-3 position of isatin moiety favored the activity, while –NOH decreased the activity, and the relative contribution of imines of the Schiff's bases to the activity was –NOMe > –NOEt > –O > –NOH; introduction of electron-donating –Me could improve the activity, while electron-withdrawing –F was detrimental to the activity. In particular, hybrid **5h** (MIC: 0.20 and 0.5 μg/mL), which was found to be most active against MTB H37Rv and MDR-TB, was twofold more potent than **RIF** (MIC: 0.39 μg/mL) against MTB H37Rv

Scheme 1. Synthetic route for diethylene glycol tethered moxifloxacin–isatin hybrids **5a–l**.

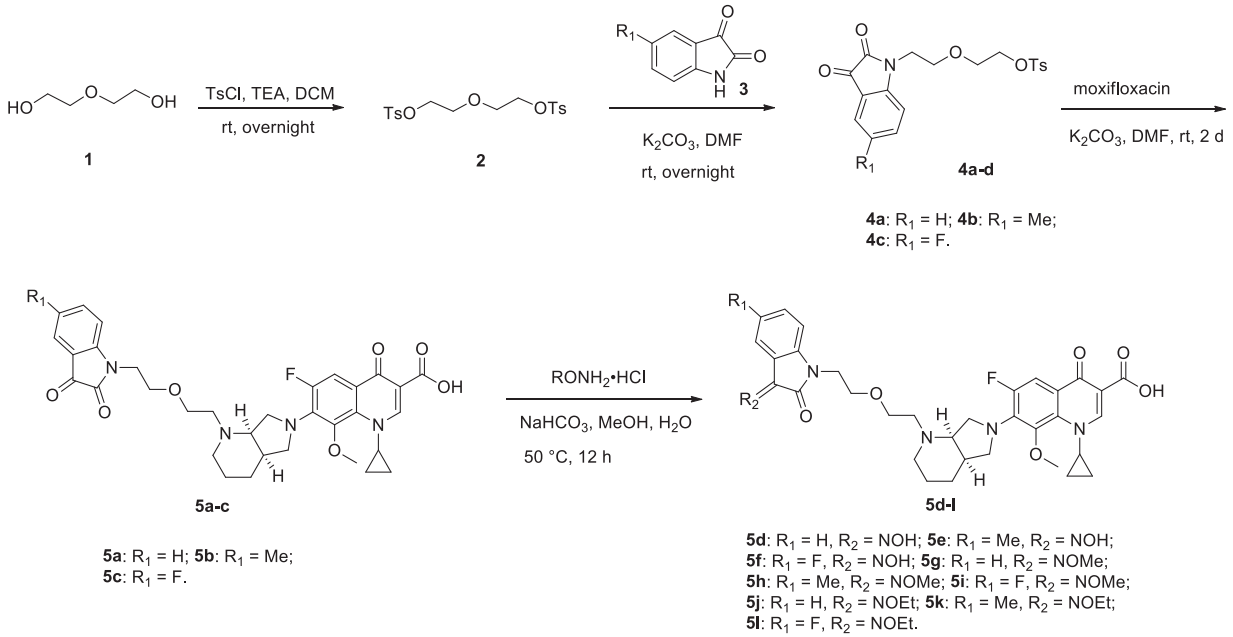
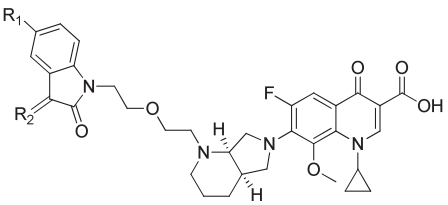


Table 1

Structures, lipophilicity, and *in vitro* antimycobacterial activity of diethylene glycol tethered MXF–isatin hybrids **5a–l**.



Compd.	R_1	R_2	Log P[a]	MIC (μg/mL) MTB $H_{37}Rv$	MIC (μg/mL) MDR-TB	CC_{50}[b] (μg/mL)
5a	O	H	2.23	1.56	4	256
5b	O	Me	2.72	0.78	4	128
5c	O	F	2.39	6.25	8	128
5d	NOH	H	2.62	6.25	8	512
5e	NOH	Me	3.11	3.12	4	256
5f	NOH	F	2.78	12.5	16	512
5g	NOMe	H	2.88	0.78	2	128
5h	NOMe	Me	3.37	0.20	0.5	128
5i	NOMe	F	3.04	0.78	2	64
5j	NOEt	H	3.22	1.56	4	64
5k	NOEt	Me	3.71	1.56	2	128
5l	NOEt	F	3.38	6.25	8	64
MXF			1.68	0.10	0.12	128
INH			−0.67	0.05	>128	128
RIF			3.71	0.39	32	512

INH, isoniazid; MDR-TB, multidrug-resistant tuberculosis; MIC, minimum inhibitory concentration; MTB, *Mycobacterium tuberculosis*; **MXF**, moxifloxacin; **RIF**, rifampicin.
[a]The Log *P* is calculated with ChemOffice 2012 software.
[b]CC_{50}: The 50% cytotoxic concentration in a mammalian VERO cell line.

and ≥64-fold more active than **INH** and **RIF** (MIC: >128 and 32 μg/mL, respectively) against MDR-TB.

Besides, all MXF–isatin hybrids (CC_{50}: 64–512 μg/mL) showed excellent cytotoxic profiles, and the majority of them were less toxic than the parent **MXF** (CC_{50}: 128 μg/mL). The most active hybrid **5h** (CC_{50}: 128 μg/mL) also displayed acceptable cytotoxic profile, could act as a lead for further optimization.

CONCLUSIONS

In conclusion, a series of diethylene glycol tethered MXF–isatin hybrids were designed, synthesized, and evaluated for their *in vitro* antimycobacterial activity against both drug-sensitive and MDR-MTB strains as well as cytotoxicity in VERO cell line. All the synthesized hybrids exhibited promising activity against the tested MTB strains and low cytotoxicity in VERO cell line. In particular, hybrid **5h** not only showed great potency against the tested two strains (MIC: 0.20 and 0.5 μg/mL) but also displayed low cytotoxicity (CC_{50}: 128 μg/mL), worth to be further optimized.

EXPERIMENTAL SECTION

The general procedure for preparing hybrids 5a–c. To a mixture of diethylene glycol **1** (100 mmol) and triethylamine (500 mmol) in dichloromethane/DCM (1 L), tosyl chloride (300 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluted with petroleum ether:ethyl acetate = 1:1 to give the desired product **2**. The mixture of intermediate **2** (1.5 mmol), potassium carbonate (5 mmol), and isatins **3** (1 mmol) in dimethylformamide/DMF (30 mL) was stirred at room temperature overnight. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with petroleum ether:ethyl acetate = 1:1 to give the intermediates **4**. A mixture of **MXF** (1 mmol), intermediates **4** (1 mmol), and potassium carbonate (10 mmol) in DMF (10 mL) was stirred at room temperature for 2 days. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluted with DCM: methanol (MeOH) = 5:1 to give the desired diethylene glycol tethered MXF–isatin hybrids **5a–c**.

1-Cyclopropyl-7-((4aR,7aR)-1-(2-(2-(2,3-dioxoindolin-1-yl) ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5a). Yellow solid, yield: 14%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98–1.54 (m, 8H), 2.12–2.41 (m, 2H), 2.73–2.76 (m, 1H), 2.98–3.00 (m, 1H), 3.16–3.28 (m, 3H), 3.56–3.80 (m, 8H), 3.86 (t, 2H), 4.11–4.12 (m, 1H), 4.21 (t, 2H), 7.11–7.14 (m, 2H, Ar–H), 7.52 (d, 1H, Ar–H), 7.62–7.66 (m, 2H, Ar–H), 8.66 (1H, s, C2-H), 14.96 (1H, brs, COOH). ESI-MS *m/z*: 619 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{33}H_{35}FN_4O_7$: C, 64.07; H, 5.70; N, 9.06; found: C, 63.83; H, 5.49; N, 8.87.

1-Cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-(2-(2-(5-methyl-2,3-dioxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5b). Light yellow solid, yield: 12%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86–1.56 (m, 8H), 2.12–2.41 (m, 5H), 2.74–2.76 (m, 1H), 2.99–3.01 (m, 1H), 3.15–3.27 (m, 3H), 3.48–3.82 (m, 8H), 3.88 (t, 2H), 4.11–4.12 (m, 1H), 4.20 (t, 2H), 7.01–7.05 (m, 1H, Ar–H), 7.30 (s, 1H, Ar–H), 7.37–7.40 (m, 1H, Ar–H), 7.94 (s, 1H, Ar–H), 8.44 (1H, s, C2-H). ESI-MS *m/z*: 633 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{34}H_{37}FN_4O_7$: C, 64.55; H, 5.89; N, 8.86; found: C, 64.27; H, 5.63; N, 8.59.

1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-1-(2-(2-(5-fluoro-2,3-dioxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5c). Light yellow solid, yield: 11%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99–1.62 (m, 8H), 2.11–2.32 (m, 2H), 2.74–2.77 (m, 1H), 2.99–3.01 (m, 1H), 3.17–3.29 (m, 3H), 3.51–3.84 (m, 8H), 3.88 (t, 2H), 4.11–4.12 (m, 1H), 4.21 (t, 2H), 7.17–7.21 (m, 1H, Ar–H), 7.44–7.52 (m, 2H, Ar–H), 7.63 (d, 1H, Ar–H), 8.64 (1H, s, C2-H). ESI-MS *m/z*: 637 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{33}H_{34}F_2N_4O_7$: C, 62.26; H, 5.38; N, 8.80; found: C, 62.01; H, 5.17; N, 8.59.

The general procedure for preparing targets 5d–l. To a solution of substituted amine hydrochlorides (6 mmol) and sodium bicarbonate (6 mmol) dissolved in water (10 mL) and methanol (10 mL) was added MXF–isatin hybrids **5a–c** (5 mmol). The reaction mixture was stirred at 50°C for 12 h. After removal of the solvent, the residue was diluted with water (20 mL) and stirred for 10 min and then filtered. The solid crude product was purified by column chromatography (silica gel) eluted with DCM to v_{DCM}: v_{MeOH} = 5:1 to give the title hybrids **5d–l**.

1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-1-(2-(2-(3-(hydroxyimino)-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5d). Yellow solid, yield: 27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94–1.56 (m, 8H), 2.14–2.32 (m, 2H), 2.73–2.76 (m, 1H), 2.98–3.00 (m, 1H), 3.16–3.26 (m, 3H), 3.58–3.81 (m, 8H), 3.87 (t, 2H), 4.11–4.12 (m, 1H), 4.20 (t, 2H), 7.15–7.19 (m, 2H, Ar–H), 7.50 (d, 1H, Ar–H), 7.63–7.66 (m, 2H, Ar–H), 8.64 (1H, s, C2-H), 13.46 (1H, brs, NOH). ESI-MS *m/z*: 634 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{33}H_{36}FN_5O_7$: C, 62.55; H, 5.73; N, 11.05; found: C, 62.51; H, 5.66; N, 10.78.

1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-1-(2-(2-(3-(hydroxyimino)-5-methyl-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5e). Light yellow solid, yield: 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.94–1.56 (m, 8H), 2.12–2.35 (m, 5H), 2.74–2.76 (m, 1H), 2.99–3.00 (m, 1H), 3.15–3.30 (m, 3H), 3.48–3.80 (m, 8H), 3.88 (t, 2H), 4.11–4.12 (m, 1H), 4.20 (t, 2H), 7.04–7.07 (m, 1H, Ar–H), 7.33 (s, 1H, Ar–H), 7.39–7.41 (m, 1H, Ar–H), 7.94 (s, 1H, Ar–H), 8.62 (1H, s, C2-H), 13.48 (1H, brs, NOH). ESI-MS *m/z*: 648 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{34}H_{38}FN_5O_7$: C, 63.05; H, 5.91; N, 10.81; found: C, 62.83; H, 5.69; N, 10.57.

1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-1-(2-(2-(5-fluoro-3-(hydroxyimino)-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5f). Light yellow solid, yield: 15%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98–1.58 (m, 8H), 2.11–2.36 (m, 2H), 2.74–2.77 (m, 1H), 2.99–3.01 (m, 1H), 3.14–3.29 (m, 3H), 3.51–3.81 (m, 8H), 3.87 (t, 2H), 4.11–4.12 (m, 1H), 4.21 (t, 2H), 7.19–7.22 (m, 1H, Ar–H), 7.47–7.53 (m, 2H, Ar–H), 7.65 (d, 1H, Ar–H), 8.66 (1H, s, C2-H), 13.44 (1H, brs, NOH). ESI-MS *m/z*: 652 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{33}H_{35}F_2N_5O_7$: C, 60.82; H, 5.41; N, 10.75; found: C, 60.61; H, 5.19; N, 10.53.

1-Cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-(2-(2-(3-(methoxyimino)-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5g). Yellow solid, yield: 33%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96–1.58 (m, 8H), 2.14–2.34 (m, 2H), 2.75–2.77 (m, 1H), 2.99–3.00 (m, 1H), 3.18–3.30 (m, 3H), 3.54–3.80 (m, 8H), 3.86 (t, 2H), 4.11–4.16 (m, 4H), 4.20 (t, 2H), 7.12–7.16 (m, 2H, Ar–H), 7.48 (d, 1H, Ar–H), 7.63–7.65 (m, 2H, Ar–H), 8.64 (1H, s, C2-H). ESI-MS *m/z*: 648 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{34}H_{38}FN_5O_7$: C, 63.05; H, 5.91; N, 10.81; found: C, 62.80; H, 5.63; N, 10.58.

1-Cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-(2-(2-(3-(methoxyimino)-5-methyl-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5h). Light yellow solid, yield: 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96–1.58 (m, 8H), 2.12–2.36 (m, 5H), 2.74–2.76 (m, 1H), 2.97–3.00 (m, 1H), 3.15–3.33 (m, 3H), 3.42–3.81 (m, 8H), 3.88 (t, 2H), 4.11–4.17 (m, 4H), 4.20 (t, 2H), 7.03–7.06 (m, 1H, Ar–H), 7.35 (s, 1H, Ar–H), 7.40 (d, 1H, Ar–H), 7.91 (s, 1H, Ar–H), 8.60 (1H, s, C2-H). ESI-MS *m/z*: 662 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{35}H_{40}FN_5O_7$: C, 63.53; H, 6.09; N, 10.58; found: C, 63.31; H, 5.82; N, 10.29.

1-Cyclopropyl-6-fluoro-7-((4aR,7aR)-1-(2-(2-(5-fluoro-3-(methoxyimino)-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5i). Light yellow solid, yield: 15%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89–1.59 (m, 8H), 2.14–2.32 (m, 2H), 2.76–2.79 (m, 1H), 2.99–3.01 (m, 1H), 3.12–3.27 (m, 3H), 3.50–3.84 (m, 8H), 3.87 (t, 2H), 4.11–4.15 (m, 4H), 4.21 (t, 2H), 7.20 (t, 1H, Ar–H), 7.45–7.50 (m, 2H, Ar–H), 7.65 (d, 1H, Ar–H), 8.66 (1H, s, C2-H). ESI-MS *m/z*: 666 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{34}H_{37}F_2N_5O_7$: C, 61.35; H, 5.60; N, 10.52; found: C, 61.07; H, 5.33; N, 10.27.

1-Cyclopropyl-7-((4aR,7aR)-1-(2-(2-(3-(ethoxyimino)-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5j). Yellow solid, yield: 16%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96–1.56 (m, 11H), 2.15–2.31 (m, 2H), 2.71–2.76 (m, 1H), 2.98–3.00 (m, 1H), 3.14–3.26 (m, 3H), 3.56–3.82 (m, 8H), 3.87 (t, 2H), 4.11–4.12 (m, 1H), 4.20 (t, 2H), 4.40–4.44 (2H, m, NO$\underline{CH_2}CH_3$), 7.12–7.16 (m, 2H, Ar–H), 7.50 (d, 1H, Ar–H), 7.61–7.65 (m, 2H, Ar–H), 8.64 (1H, s, C2-H). ESI-MS *m/z*: 662 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{35}H_{40}FN_5O_7$: C, 63.53; H, 6.09; N, 10.58; found: C, 63.25; H, 5.81; N, 10.29.

1-Cyclopropyl-7-((4aR,7aR)-1-(2-(2-(3-(ethoxyimino)-5-methyl-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5k). Light yellow solid, yield: 23%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98–1.58 (m, 11H), 2.12–2.35 (m, 5H), 2.75–2.77 (m, 1H), 2.99–3.00 (m, 1H), 3.12–3.30 (m, 3H), 3.48–3.84 (m, 8H), 3.88 (t, 2H), 4.11–4.12 (m, 1H), 4.20 (t, 2H), 4.41–4.44 (2H, m, NO$\underline{CH_2}CH_3$), 7.03–7.05 (m, 1H, Ar–H), 7.35 (s, 1H, Ar–H), 7.34–7.37 (m, 1H, Ar–H), 7.92 (s, 1H, Ar–H), 8.63 (1H, s, C2-H). ESI-MS *m/z*: 676 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{42}FN_5O_7$: C, 63.99; H, 6.26; N, 10.36; found: C, 63.75; H, 5.99; N, 10.09.

1-Cyclopropyl-7-((4aR,7aR)-1-(2-(2-(3-(ethoxyimino)-5-fluoro-2-oxoindolin-1-yl)ethoxy)ethyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5l). Light yellow solid, yield: 19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92–1.62 (m, 11H), 2.14–2.36 (m, 2H), 2.77–2.79 (m, 1H), 2.99–3.01 (m, 1H), 3.13–3.28 (m, 3H), 3.50–3.82 (m, 8H), 3.88 (t, 2H), 4.11–4.15 (m, 1H), 4.21 (t, 2H), 4.42–4.46 (2H, m, NO$\underline{CH_2}CH_3$), 7.19 (t, 1H, Ar–H), 7.43–7.51 (m, 2H, Ar–H), 7.66 (d, 1H, Ar–H), 8.65 (1H, s, C2-H). ESI-MS *m/z*: 680 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{35}H_{39}F_2N_5O_7$: C, 61.85; H, 5.78; N, 10.30; found: C, 61.57; H, 5.49; N, 10.05.

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