Design, Synthesis and *in vitro* Antimycobacterial Activities of Isatin-1,2,3-triazole-moxifloxacin Hybrids

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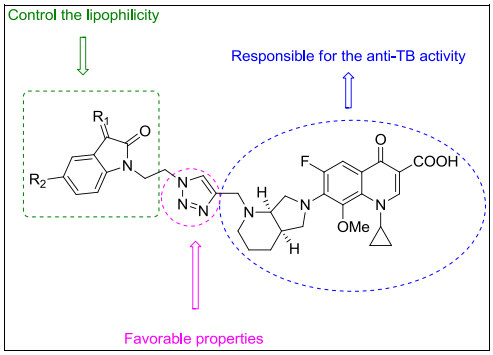


A new class of isatin-1,2,3-triazole-moxifloxacin (**MXFX**) hybrids **5a–j** was designed, synthesized, and screened for their *in vitro* antimycobacterial activities against *Mycobacterium tuberculosis* $H_{37}Rv$ and MDR-TB. All the synthesized hybrids (MIC: 0.10–0.78 μg/mL) exhibited excellent activities against MTB $H_{37}Rv$ and MDR-TB, in spite of none of them were more potent than the parent **MXFX** (MIC: 0.10 and 0.12 μg/mL). Against MTB $H_{37}Rv$, the most active **5f** (MIC: 0.10 μg/mL) was comparable with **MXFX** and 4 times more potent than **RIF** (MIC: 0.39 μg/mL). Against MDR-TB, all hybrids were more active than **RIF** (MIC: 32 μg/mL) and **INH** (MIC: >128 μg/mL). In particular, hybrid **5e** (MIC: 0.10 μg/mL) was comparable with **MXFX** and 256 and >1,024 times more potent than **RIF** and **INH**. Both conjugates **5e** and **5f** warrant further investigations.

INTRODUCTION

Tuberculosis (TB) causes predominately by *Mycobacterium tuberculosis* (MTB), threats human being for thousands of years. According to the World Health Organization (WHO) 2016 report, TB resulted in 1.4 million deaths and 10.4 million newly clinical cases in a single year of 2015 [1]. The wide spread of drug-resistant TB (DR-TB), multidrug-resistant TB (MDR-TB), and coinfection with HIV, as well as the emergence of extensively drug-resistant TB (XDR-TB), and totally drug resistant TB (TDR-TB) has already alarming the serious problem in TB control [2–5]. Thus, the serious situation is creating an urgent need to develop new anti-TB drugs.

Fluoroquinolones (FQs) are the second widest used antibiotics in clinical with extensive indications for infections, act by binding two type II bacterial topoisomerase enzymes, DNA gyrase, and topoisomerase IV, thereby inhibiting DNA replication and transcription [5,6]. Moreover, some of them are currently recommended as the second-line agents by the WHO to treat primarily in cases involving resistance or intolerance to first-line anti-TB therapy [7]. However, the emergence of MTB strains resistant to FQs has already caused great concern throughout the world. The fourth generation FQs moxifloxacin (**MXFX**) demonstrated promising *in vitro* and *in vivo* activities against MTB including MDR-TB [8–10] and is under phase III clinical trial for the treatment of TB. It is worth to notice that **MXFX** also retains activity against MTB strains with various levels of FQs resistance [9].

Several series of FQs-isatin hybrids have been screened for their *in vitro* and *in vivo* anti-TB activities, and the results suggested that the anti-TB activity was greatly influenced by the linkers between FQs and isatin [11–17]. Our previous study demonstrated that introduction of 1*H*-1,2,3-triazole linker between FQs and isatin could increase the activity of these hybrids against MTB $H_{37}Rv$ and MDR-TB strains, which was exemplified by GTFX-isatin hybrid **1** [18]. Chemical structures of isatin, **MXFX**, and GTFX-isatin hybrid **1** are shown in Figure 1.

Inspired by the above research results and as a continuous program for seeking for new anti-TB drugs, a set of 1*H*-1,2,3-triazole-tethered isatin-**MXFX** hybrids was evaluated in this study. Illustration of the design

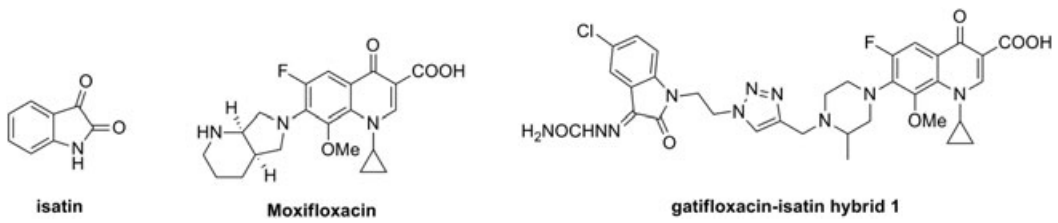


Figure 1. Chemical structures of isatin, moxifloxacin, and 1*H*-1,2,3-triazole-tethered GTFX-isatin hybrid **1**.

strategy for 1*H*-1,2,3-triazole-tethered isatin-**MXFX** hybrids is depicted in Figure 2.

RESULTS AND DISCUSSION

Detailed synthetic route of 1*H*-1,2,3-triazole-tethered isatin-**MXFX** hybrids **5a–l** is described in Scheme 1. Isatin, 5-bromoisatin, and **MXFX** were alkylated with 1,2-dibromoethane and propargyl bromide, respectively, in the presence of anhydrous potassium carbonate to provide the corresponding *N*-(2-bromoethyl)isatins **2a,b** (yield: 56% and 62%) and propargyl **MXFX 4** (yield: 69%) via literature methods [18–22]. Treatment of *N*-(2-bromoethyl)isatins **2a,b** with sodium azide at 60°C yielded the desired azido precursors **3a,b**, which was used together with **4** for the synthesis of desired 1,2,3-triazole-tethered hybrids **5a**,**b** (yield: 46% and 48%) in the presence of $Cu(OAc)_2$ in DMF [18]. Subsequent condensations of conjugates **5a**,**b** with requisite substituted amine hydrochlorides in the presence of sodium bicarbonate formed other hybrids **5c–j** (42–65%) [10].

Compared with the parent **MXFX** (Log *P*: 1.68), all hybrids **5a–j** (Log *P*: 1.84–4.30) showed greater lipophilicity that may improve their permeation properties toward mycobacterial cell membrane. The hybrids **5a–j** were screened for their *in vitro* antimycobacterial activities against MTB $H_{37}Rv$ and MDR-TB strains by rapid direct susceptibility test technique [18]. The MDR-TB strain was resistant to **INH**, **RIF**, and ethambutol. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give 90% inhibition of bacterial growth and MICs of the targets were reported in Table 1.

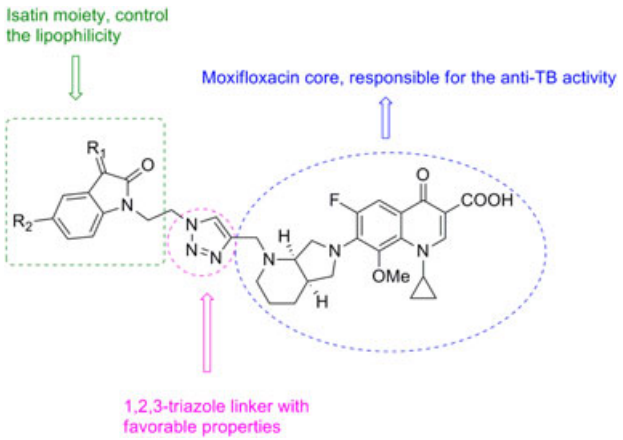


Figure 2. Illustration of the design strategy for 1*H*-1,2,3-triazole-tethered moxifloxacin-isatin hybrids. [Color figure can be viewed at wileyonlinelibrary.com]

All the synthesized hybrids (MIC: 0.10–0.78 μg/mL) exhibited promising activities against MTB $H_{37}Rv$, but none of them were more active than the parent **MXFX** (MIC: 0.10 μg/mL). Conjugate **5f** (MIC: 0.10 μg/mL) was comparable with **MXFX** and fourfolds more active than the reference **RIF** (MIC: 0.39 μg/mL). Against MDR-TB, all hybrids showed excellent activities with MIC ranging from 0.12 to 0.5 μg/mL, far more potent than the references **RIF** (MIC: 32 μg/mL) and **INH** (MIC: >128 μg/mL). In particular, hybrid **55** (MIC: 0.12 μg/mL) was comparable with **MXFX** and 256 and >1,024 times more potent than the parent **MXFX** (MIC: 0.12 μg/mL) and **RIF** and **INH**.

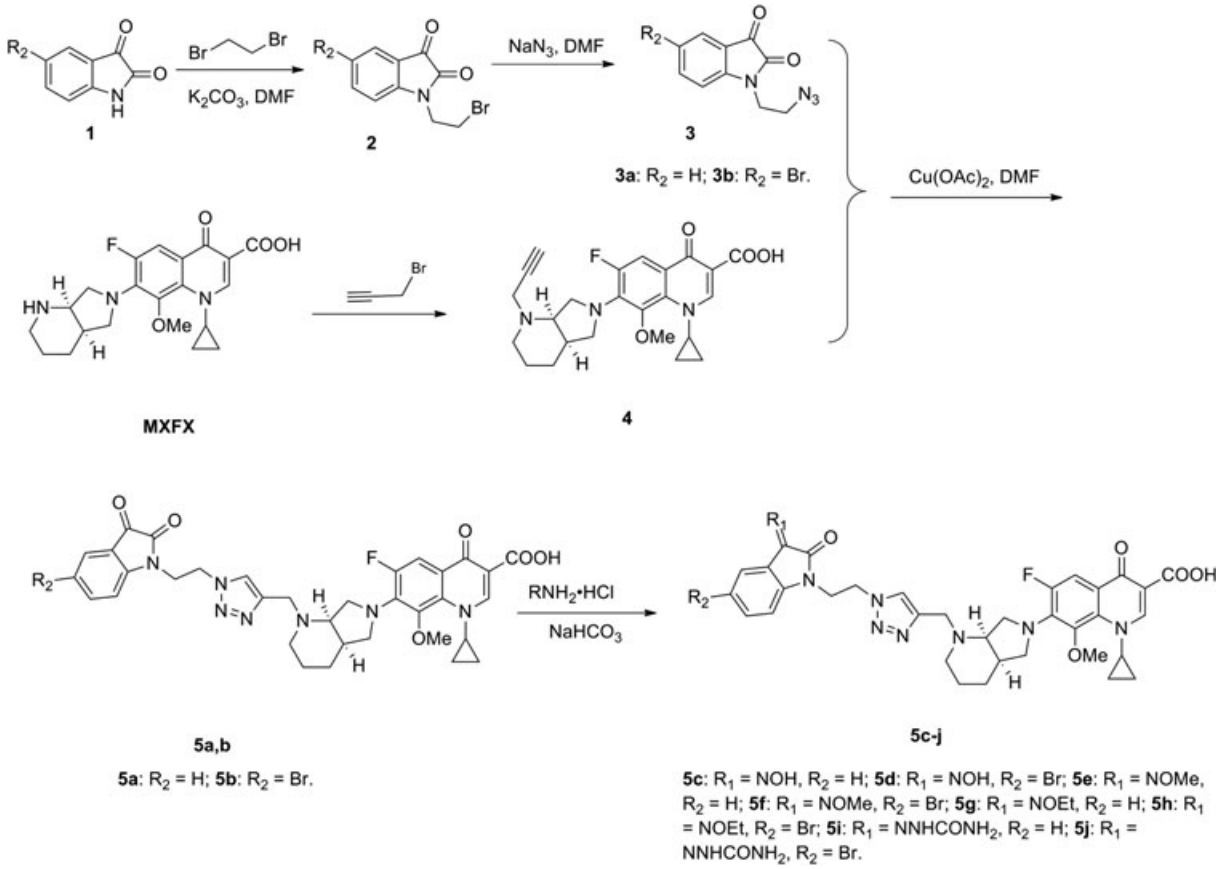
The resistance index (RI: $MIC_{MDR\text{-}TB}$: $MIC_{MTB\ H37Rv}$) for the majority targets was around 1, indicating this kind of hybrids could reduce the cross-resistant to some extent.

In summary, a series of novel 1*H*-1,2,3-triazole-tethered isatin-**MXFX** hybrids were designed, synthesized, and evaluated for their *in vitro* antimycobacterial activities against MTB $H_{37}Rv$ and MDR-TB strains. All the synthesized hybrids exhibited excellent activities against MTB $H_{37}Rv$ and MDR-TB. Against MTB $H_{37}Rv$, the most active **5f** was 4 times more potent than **RIF**. Against MDR-TB, hybrid **5e** was 256 and >1,024 times more potent than **RIF** and **INH**. Both conjugates **5e** and **5f** warrant further investigations.

EXPERIMENTAL SECTION

Synthesis. ***General Procedure for thereparation of 5a,b.*** *N*-(2-azidoethyl)isatins **3a,b** and propargyl **MXFX 4** (yield: 39%) were prepared via literature methods [18]. To a mixture of *N*-(2-azidoethyl)isatins **3a,b** (1.0 mmol) and propargyl **MXFX 4** (1.0 mmol) in DMF (50 mL), $Cu(OAc)_2$ (100 mg) was added under N_2 atmosphere. The mixture was allowed to react for 48 h at room

Scheme 1. Synthesis of 1*H*-1,2,3-triazole-tethered isatin-moxifloxacin hybrids **5a–j**.



temperature. After removal of the solvent *in vacuo*, the residue was purified by silica gel column chromatography eluted with DCM to *v*(DCM):*v*(MeOH) = 10:1. After removal of the solvent by evaporation, targets **5a,b** (46% and 48%) were obtained.

1-cyclopropyl-7-((4aR,7aR)-1-((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)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: 46%. Mp: 168–170°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00–1.61 (m, 9H), 2.05–2.07 (m, 1H), 2.32–2.34 (m, 1H), 2.60–2.62 (m, 1H), 2.76–2.79 (m, 1H), 3.55–3.80 (m, 8H), 4.10–4.14 (m, 3H), 4.61–4.62 (m, 2H), 6.87–8.67 (7H, m, Ar-H), 15.22 (1H, brs, COOH). ESI-MS *m*/*z*: 656 $[M + H]^+$. Elemental *Anal.* Calcd (%) for $C_{34}H_{34}FN_7O_6$: C, 62.28; H, 5.23; N, 14.95; found: C, 62.11; H, 5.08; N, 14.87.

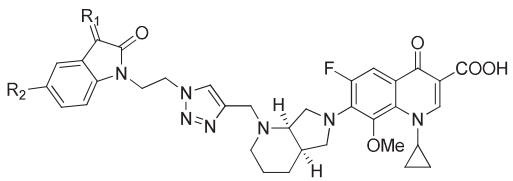
7-((4aR,7aR)-1-((1-(2-(5-bromo-2,3-dioxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5b). Light yellow solid, yield: 48%. Mp: 154–155°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98–1.59 (m, 9H), 2.06–2.07 (m, 1H), 2.31–2.33 (m, 1H), 2.57–2.59 (m, 1H), 2.80–2.81 (m, 1H), 3.57–3.83 (m, 8H), 4.09–4.14 (m, 3H), 4.61–4.63 (m, 2H), 6.96–8.65 (6H, m, Ar-H), 15.28 (1H, brs, COOH). ESI-MS *m*/*z*: 734 $[M + H]^+$, 736 $[M + 2 + H]^+$. Elemental *Anal.* Calcd (%) for $C_{34}H_{33}FBrN_7O_6$: C, 55.59; H, 4.53; N, 13.35; found: C, 55.47; H, 4.52; N, 13.28.

The general procedure for preparing other targets. 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 **5a,b**. The reaction mixture was stirred at room temperature for 24 h. After removal of the solvent *in vacuo*, 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) = 10:1. After removal of the solvent by evaporation, targets **5c–l** (42–65%) were obtained.

1-cyclopropyl-6-fluoro-7-((4aR,7aR)-1-((1-(2-(3-(hydroxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5c). Yellow solid, yield: 65%. Mp: 203–205°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99–1.65 (m, 9H), 2.06–2.07 (m, 1H), 2.30–2.32 (m, 1H), 2.61–2.62 (m, 1H), 2.78–2.80 (m, 1H), 3.57–3.84 (m, 8H), 4.11–4.14

Table 1

Structures, lipophilicity, and antimycobacterial activity of compounds **5a–j**.



Compd.	R1	R2	Log P a	MIC (μg/mL)	
				MTB H37Rv	MDR-TBb
5a	O	H	2.48	0.39	0.25
5b	O	Br	3.31	0.78	0.50
5c	NOH	H	2.87	0.78	0.25
5d	NOH	Br	3.70	0.78	0.5
5e	NOMe	H	3.14	0.20	0.12
5f	NOMe	Br	3.96	0.10	0.25
5g	NOEt	H	3.47	0.39	0.25
5h	NOEt	Br	4.30	0.78	0.25
5i	NNHCONH2	H	1.84	0.78	0.5
5j	NNHCONH2	Br	2.67	0.78	0.5
MXFX			1.68	0.10	0.12
INH			−0.67	0.05	>128
RIF			3.71	0.39	32

MXFX, moxifloxacin; MTB, *Mycobacterium tuberculosis*; MIC, minimum inhibitory concentration; MDR-TB, multidrug-resistant TB.
[a]The Log *P* is calculated with ChemOffice 2014 software.
[b]MDR-TB: resistant to INH, RIF, and EMB.

(m, 3H), 4.61–4.62 (m, 2H), 6.84–8.65 (7H, m, Ar-H), 13.52 (1H, brs, NOH), 15.26 (1H, brs, COOH). ESI-MS *m*/*z*: 671 $[M + H]^+$. Elemental *Anal.* Calcd (%) for $C_{34}H_{35}FN_8O_6$: C, 60.89; H, 5.26; N, 16.71; found: C, 60.72; H, 5.21; N, 16.63.

7-((4aR,7aR)-1-((1-(2-(5-bromo-3-(hydroxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5d).
Light yellow solid, yield: 57%. Mp: 183–185°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00–1.61 (m, 9H), 2.04–2.05 (m, 1H), 2.30–2.31 (m, 1H), 2.57–2.58 (m, 1H), 2.79–2.80 (m, 1H), 3.56–3.79 (m, 8H), 4.12–4.14 (m, 3H), 4.60–4.61 (m, 2H), 6.87–8.67 (6H, m, Ar-H), 13.50 (1H, brs, NOH), 15.30 (1H, brs, COOH). ESI-MS *m*/*z*: 749 $[M + H]^+$, 751 $[M + 2 + H]^+$. Elemental *Anal.* Calcd (%) for $C_{34}H_{34}FBrN_8O_6$: C, 54.48; H, 4.57; N, 14.95; found: C, 54.42; H, 4.53; N, 14.78.

1-cyclopropyl-6-fluoro-8-methoxy-7-((4aR,7aR)-1-((1-(2-(3-(methoxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5e). Light yellow solid, yield: 59%. Mp: 150–151°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98–1.58 (m, 9H), 2.05–2.06 (m, 1H), 2.33–2.34 (m, 1H), 2.78–2.79 (m, 1H), 2.81–2.82 (m, 1H), 3.54–3.76 (m, 8H), 4.10–4.12 (m, 3H), 4.25 (s, 3H, $NOCH_3$), 4.62–4.63 (m, 2H), 6.71–8.65 (7H, m, Ar-H), 15.24 (1H, brs, COOH). ESI-MS *m*/*z*: 685 $[M + H]^+$. Elemental *Anal.* Calcd (%) for $C_{35}H_{37}FN_8O_6$: C, 61.39; H, 5.45; N, 16.36; found: C, 61.21; H, 5.37; N, 16.31.

7-((4aR,7aR)-1-((1-(2-(5-bromo-3-(methoxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5f).
Light yellow solid, yield: 51%. Mp: 138–140°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99–1.59 (m, 9H), 2.04–2.06 (m, 1H), 2.30–2.32 (m, 1H), 2.60–2.61 (m, 1H), 2.80–2.82 (m, 1H), 3.55–3.81 (m, 8H), 4.12–4.13 (m, 3H), 4.26 (s, 3H, $NOCH_3$), 4.61–4.62 (m, 2H), 6.89–8.65 (6H, m, Ar-H), 15.22 (1H, brs, COOH). ESI-MS *m*/*z*: 763 $[M + H]^+$, 765 $[M + 2 + H]^+$. Elemental *Anal.* Calcd (%) for $C_{35}H_{36}FBrN_8O_6$: C, 55.05; H, 4.75; N, 14.67; found: C, 54.91; H, 4.57; N, 14.49.

1-cyclopropyl-7-((4aR,7aR)-1-((1-(2-(3-(ethoxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5g). Light yellow solid, yield: 52%. Mp: 156–158°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00–1.60 (m, 12H), 2.03–2.04 (m, 1H), 2.31–2.32 (m, 1H), 2.72–2.74 (m, 1H), 2.80–2.82 (m, 1H), 3.56–3.836 (m, 8H), 4.11–4.12 (m, 3H), 4.41 (q, 2H, $NOCH_2CH_3$), 4.61–4.63 (m, 2H), 6.73–8.65 (7H, m, Ar-H), 15.22 (1H, brs, COOH). ESI-MS *m*/*z*: 699 $[M + H]^+$.

Elemental *Anal.* Calcd (%) for $C_{36}H_{39}FN_8O_6$: C, 61.88; H, 5.63; N, 16.04; found: C, 61.83; H, 5.57; N, 15.93.

7-((4aR,7aR)-1-((1-(2-(5-bromo-3-(ethoxyimino)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5h). Light yellow solid, yield: 43%. Mp: 121–122°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02–1.68 (m, 12H), 2.05–2.06 (m, 1H), 2.31–2.32 (m, 1H), 2.71–2.73 (m, 1H), 2.81–2.82 (m, 1H), 3.56–3.79 (m, 8H), 4.11–4.13 (m, 3H), 4.43 (q, 2H, NO$\underline{CH_2}CH_3$), 4.60–4.62 (m, 2H), 6.80–8.67 (6H, m, Ar-H), 15.22 (1H, brs, COOH). ESI-MS *m*/*z*: 777 $[M + H]^+$, 779 $[M + 2 + H]^+$. Elemental *Anal.* Calcd (%) for $C_{36}H_{38}FBrN_8O_6$: C, 55.60; H, 4.93; N, 14.41; found: C, 55.47; H, 4.85; N, 14.37.

7-((4aR,7aR)-1-((1-(2-(3-(2-carbamoylhydrazono)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl)hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5i). Light yellow solid, yield: 42%. Mp: 133–134°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.00–1.61 (m, 9H), 2.07–2.08 (m, 1H), 2.35–2.36 (m, 1H), 2.68–2.69 (m, 1H), 2.77–2.79 (m, 1H), 3.58–3.81 (m, 8H), 4.11–4.13 (m, 3H), 4.61–4.62 (m, 2H), 6.88–8.67 (7H, m, Ar-H), 8.69, 9.00 (s, 2H, $CONH_2$), 12.16 (s, 1H, NNHCO), 15.24 (1H, brs, COOH). ESI-MS *m*/*z*: 747 $[M + H]^+$. Elemental *Anal.* Calcd (%) for $C_{35}H_{37}FN_{10}O_6$: C, 58.98; H, 5.23; N, 19.65; found: C, 58.79; H, 5.03; N, 19.47.

7-((4aR,7aR)-1-((1-(2-(5-bromo-3-(2-carbamoylhydrazono)-2-oxoindolin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methyl) hexahydro-1H-pyrrolo[3,4-b]pyridin-6(2H)-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5j). Light yellow solid, yield: 44%. Mp: 117–119°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98–1.59 (m, 9H), 2.05–2.06 (m, 1H), 2.37–2.38 (m, 1H), 2.72–2.74 (m, 1H), 2.80–2.82 (m, 1H), 3.56–3.84 (m, 8H), 4.10–4.13 (m, 3H), 4.60–4.62 (m, 2H), 6.86–8.65 (6H, m, Ar-H), 8.68, 9.01 (s, 2H, $CONH_2$), 12.14 (s, 1H, NNHCO), 15.24 (1H, brs, COOH). ESI-MS *m*/*z*: 791 $[M + H]^+$, 793 $[M + 2 + H]^+$. Elemental *Anal.* Calcd (%) for $C_{35}H_{36}FBrN_{10}O_6$: C, 53.10; H, 4.58; N, 17.69; found: C, 52.89; H, 4.43; N, 17.61.

MIC determination. Hybrids **5a–j** along with **MXFX**, **RIF**, and **INH** were evaluated *in vitro* activity against MTB $H_{37}Rv$ and MDR-TB via rapid direct susceptibility test technique [18]. The compounds together with the references **MXFX**, **RIF**, and **INH** were dissolved in dimethyl sulfoxide (DMSO) and twofold diluted at concentrations from 0.0125 to 200 μg/mL (for MTB $H_{37}Rv$) or 0.062 to 128 μg/mL (for MDR-MTB). The wells of a sterile 48-well plate were filled with 100 mL twofold diluted tested compounds and 100 mL MTB $H_{37}Rv$ or MDR-MTB suspension containing 4×10^{-3} mg cells. Pure medium replaced the diluted compounds in two wells as the positive control of growth and deionized water instead of the culture in other two wells as the negative control of growth in the plates. The plates were covered and sealed, and then incubated at 37°C in a wet box. The positive and negative control wells should show obvious difference after 3 days. The MIC was determined by observing the quantity and state of the cells in each test well by a continuous visual high magnification system and redetermined 7 days later. The MIC is defined as the concentration of the compound required to give complete inhibition of bacterial growth.

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