Design, Synthesis, and *in vitro* Anti-mycobacterial Evaluation of Propylene-1*H*-1,2,3-triazole-4-methylene-tethered (Thio)semicarbazone-isatin-moxifloxacin Hybrids

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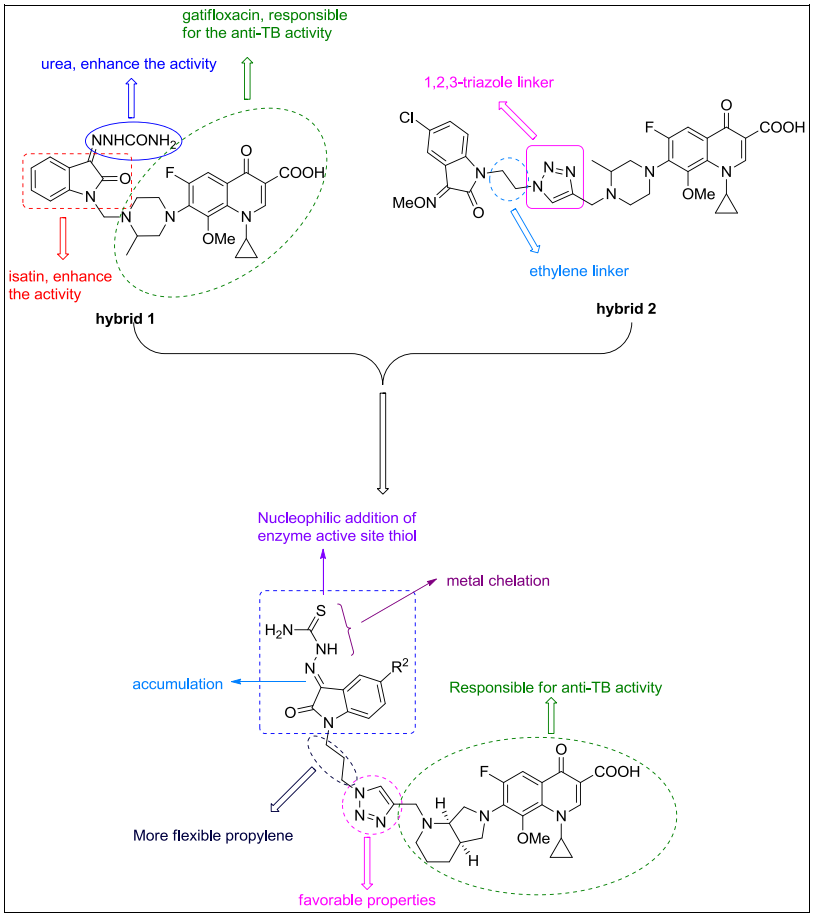

A new class of propylene-1*H*-1,2,3-triazole-4-methylene-tethered (thio)semicarbazone-isatin-moxifloxacin hybrids **6a**–**h** was designed, synthesized, and screened for their in vitro anti-mycobacterial activities against *Mycobacterium tuberculosis* (MTB) $H_{37}Rv$ and MDR-TB as well as cytotoxicity in VERO cell line. All the synthesized hybrids (MIC: 0.05–2.0 μg/mL) exhibited excellent activities against *M. tuberculosis* $H_{37}Rv$ and MDR-TB; in particular, conjugate **6c** (MIC: 0.05 and 0.12 μg/mL) was no inferior to the three references **MXFX** (MIC: 0.10 and 0.12 μg/mL), **RIF** (MIC: 0.39 and 32 μg/mL), and **INH** (MIC: 0.05 and >128 μg/mL) against the tested two strains. All hybrids (CC_{50}: 2–8 μg/mL) were much more cytotoxic than the parent **MXFX** (CC_{50}: 128 μg/mL) should be further optimized.

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INTRODUCTION

Tuberculosis (TB), caused predominately by the pathogen *Mycobacterium tuberculosis* (MTB), resulted in around 10 million newly clinical cases and 1 million deaths annually according to the World Health Organization (WHO) report [1]. In spite of the first-line drugs, isoniazid (**INH**), rifampicin (**RIF**), pyrazinamide

(**PZA**), and ethambutol (**EMB**) are crucial therapeutics for the treatment of TB; these drugs are becoming less and less effective because of the increasing prevalence of drug-resistant TB, multidrug-resistant TB (MDR-TB), extremely drug-resistant TB, and totally drug-resistant TB [2–5]. Therefore, it is imperative to develop new agents for efficient treatment.

Fluoroquinolones exhibit considerable anti-TB activities, although some of them such as ciprofloxacin, ofloxacin, and levofloacin are presently recommended as second-line anti-TB agents by WHO [6]; these drugs such as moxifloxacin (**MXFX**) are potential first-line agents and are under study for this indication [7]. In general, MTB isolates expressing resistance to both **INH** and **RIF** are susceptible to fluoroquinolones, while **MXFX** retains activity against MTB strains with various levels of fluoroquinolones resistance [8].

Numerous of fluoroquinolone derivatives were synthesized for searching more potent anti-TB agents, among them, fluoroquinolone-isatin hybrids caused great interests attribute to their promising in vitro and in vivo activities [9–26]. The previous work demonstrated that the linkers between fluoroquinolones and isatin have great influence on the anti-TB activity of these hybrids, that is, methylene-linked gatifloxacin-isatin hybrid **1** (Fig. 1) exhibited higher in vitro and in vivo potency than the parent gatifloxacin [9]. Our work showed that hybrids with 1,2,3-triazole linker could boost up the activity against MTB $H_{37}Rv$ and MDR-TB strains, and as the most emblematic example, the 1,2,3-triazole-tethered gatifloxacin-isatin hybrid **2** was 4≥512 times more potent in vitro than the three references gatifloxacin, **RIF**, and **INH** against the tested two strains [25–27].

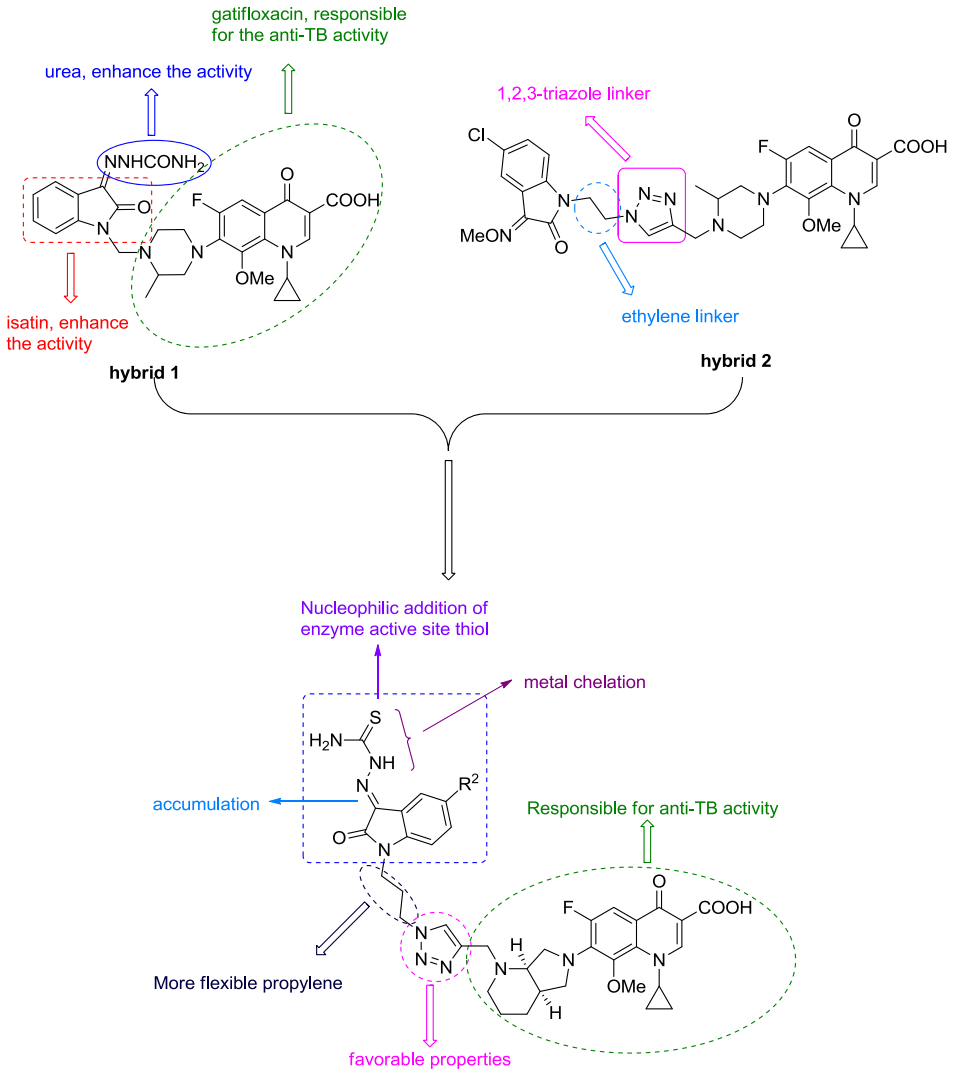


Figure 1. Illustration of the design strategy for propylene-1*H*-1,2,3-triazole-4-methylene-tethered (thio)semicarbazone-isatin-MXFX hybrids. [Color figure can be viewed at wileyonlinelibrary.com]

Currently, **MXFX** is under phase III clinical trial for the treatment of TB, and compared with the standard regimen, **MXFX** exhibited equivalent or even slightly better efficacy in the clinical trial [28]. Thus, incorporation of isatin into **MXFX** with propylene-1*H*-1,2,3-triazole-4-methylene as linker may provide more effective candidates.

Based on the aforementioned considerations, series of propylene-1*H*-1,2,3-triazole-4-methylene-tethered (thio) semicarbazone-isatin-MXFX hybrids were designed, synthesized, and screened for their in vitro anti-mycobacterial activities against MTB $H_{37}Rv$ and MDR-TB as well as cytotoxicity in VERO cell line in this study. Illustration of the design strategy is depicted in Figure 1.

RESULTS AND DISCUSSION

Detailed pathways for synthesis of propylene-1*H*-1,2,3-triazole-4-methylene-tethered (thio)semicarbazone-isatin-MXFX hybrids **6a**–**h** are depicted in Scheme 1. Alkylation of C-5 substituted isatins and **MXFX** with 1,3-dibromopropane and propargyl bromide respectively yielded the desired *N*-(3-bromoproyl)isatins **2a**–**d** (yield: 33–59%) and propargyl **MXFX 4** (yield: 69%) via literature methods [25,26]. Introduction of azido by treatment of C-5 substituted *N*-(3-bromoproyl)isatins **2a**–**d** with sodium azide at 60°C to provide *N*-(3-azidoproyl) isatins **3a**–**d**, which was utilized together with propargyl **MXFX 4** for the synthesis of the precursors **5a**–**d** (yield: 41–63%) via Cu-promoted azide-alkyne cycloaddition reaction in the presence of $Cu(OAc)_2$ in DMF [25]. Finally, condensations of conjugates **5a**–**d** with semicarbazide or thiosemicarbazide hydrochlorides in the presence of sodium bicarbonate formed other hybrids (16–33%) [26].

All the synthesized propylene-1*H*-1,2,3-triazole-4-methylene-tethered (thio)semicarbazone-isatin-MXFX hybrids **6a**–**h** were screened for their in vitro anti-mycobacterial activities against MTB $H_{37}Rv$ and MDR-TB strains by rapid direct susceptibility test technique [25]. The MDR-TB strain was resistant to **INH**, **RIF**, and ethambutol (**EMB**). 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.

Scheme 1. Synthesis of propylene-1*H*-1,2,3-triazole-4-methylene-tethered (thio)semicarbazone-isatin-MXFX hybrids **6a**–**h**.

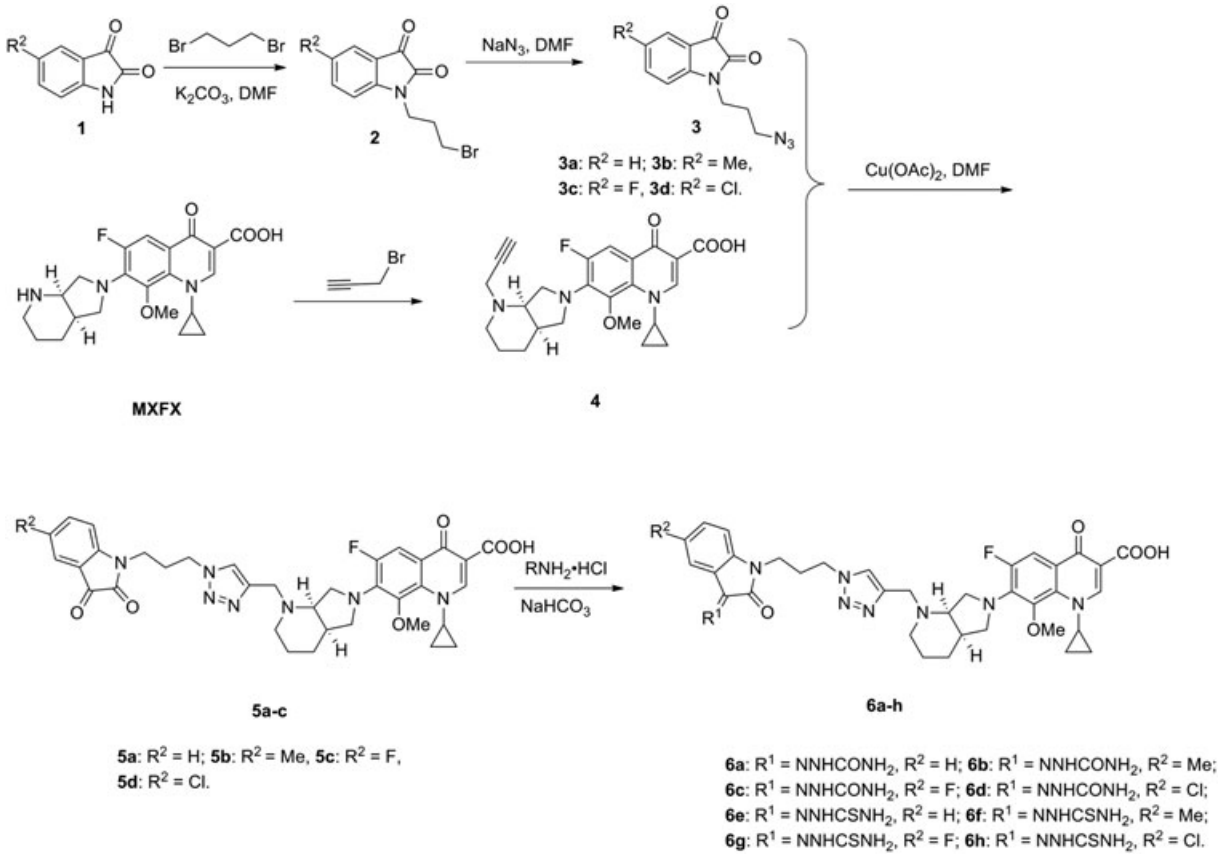
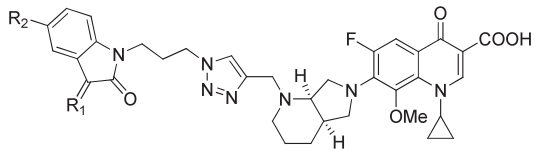


Table 1

Structures, anti-mycobacterial activity, and cytotoxicity of compounds **6a**–**h.**



			MIC (μg/mL)		
Compound	R_1	R_2	MTB $H_{37}Rv$	MDR-TB[a]	CC_{50} [b](μg/mL)
6a	$NNHCONH_2$	H	0.78	0.5	8
6b	$NNHCONH_2$	Me	0.78	1.0	8
6c	$NNHCONH_2$	F	0.05	0.12	2
6d	$NNHCONH_2$	Cl	0.39	0.25	4
6e	$NNHCSNH_2$	H	1.56	1.0	8
6f	$NNHCSNH_2$	Me	0.78	2.0	4
6g	$NNHCSNH_2$	F	0.39	0.5	2
6h	$NNHCSNH_2$	Cl	0.78	0.50	4
MXFX			0.10	0.12	128
INH			0.05	>128	128
RIF			0.39	32	512

[a]MDR-TB: resistant to INH, RIF and EMB.
[b]CC50: The 50% cytotoxic concentration in a mammalian VERO cell line.

All the synthesized hybrids (MIC: 0.05–2.0 μg/mL) exhibited considerable activities against both MTB $H_{37}Rv$ and MDR-TB strains, but the majority of them were less active than the parent **MXFX** (MIC: 0.10 and 0.12 μg/mL). The SAR indicated that introduction of halogen atoms –Cl and –F at C-5 position of isatin moiety favored the anti-TB activity, and hybrids with semicarbazone moiety at C-5 position of isatin motif were more active than the corresponding thiosemicarbazone analogs. In particular, conjugate **6c** (MIC: 0.05 and 0.12 μg/mL) was comparable with the parent **MXFX**, and 256≥1024 folds more potent than **RIF** (MIC: 32 μg/mL) and **INH** (MIC: >128 μg/mL) against MDR-TB, and was comparable with **INH** (MIC: 0.05 μg/mL) and twofold to eightfold more potent than **MXFX** and **INH** (MIC: 0.39 μg/mL) against MTB $H_{37}Rv$. Moreover, the resistance index (RI: $MIC_{MDR\text{-}TB}$: $MIC_{MTB\ H37Rv}$) of the most targets was around 1, suggesting this kind of hybrids could reduce the cross-resistant to some extent.

The conjugates **6a**–**h** were subsequently examined for toxicity (CC_{50}) in a mammalian VERO cell line [26]. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into a formazan product, and the results are reported in Table 1. All hybrids (CC_{50}: 2–8 μg/mL) were much more cytotoxic than the parent **MXFX** (CC_{50}: 128 μg/mL), and hybrids with halogen atoms at C-5 position of isatin motif showed highest cytotoxicity. Thus, reduce the cytotoxicity is the main direction for further modification.

CONCLUSION

In conclusion, a set of novel propylene-1H-1,2,3-triazole-4-methylene-tethered (thio)semicarbazone-isatin-MXFX hybrids was designed, synthesized, and evaluated for their in vitro anti-mycobacterial activities against MTB H37Rv and MDR-TB as well as cytotoxicity in VERO cell line. All hybrids exhibited excellent activities against the tested MTB H37Rv and MDR-TB, and the most active **6c**, which was no inferior to the three references **MXFX**, **RIF** and **INH** against the tested two strains, warrant further investigations. The SAR of 1H-1,2,3-triazole-tethered isatin-FQs hybrids was enriched, and the results warrant further development of the anti-TB properties of this kind of conjugates.

EXPERIMENTAL

Synthesis. General Procedure for the Preparation of 6a–h. The key intermediates **5a**–**d** were prepared via the methods we previously reported [25–27]. To a solution of semicarbazide or thiosemicarbazide hydrochlorides (6 mmol) and sodium bicarbonate (6 mmol) dissolved in water (10 mL) and methanol (10 mL) was added **5a**–**d** (3 mmol). The reaction mixture was stirred at room temperature for 24 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) = 10:1 to give targets **6a**–**h** (16–33%).

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamoylhydrazono)-2-oxoindolin-1-yl)propyl)-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 (6a). Yellow solid, yield: 31%; mp: 191–193°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12–1.62 (8H, m), 2.12–2.33 (4H, m), 2.75–2.77 (1H, m), 2.99–3.00 (1H, m), 3.63–3.78 (11H, m), 4.11–4.13 (1H, m), 4.36–4.38 (2H, m), 6.76–7.28 (6H, m), 7.58 (1H, d), 8.06 (1H, s), 8.64 (1H, s), 11.50 (1H, brs), 15.20 (1H, brs). ESI-MS *m*/*z*: 727 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{39}FN_{10}O_6$: C, 59.50; H, 5.41; N, 19.27; found: C, 59.29; H, 5.33; N, 19.18.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamoylhydrazono)-5-methyl-2-oxoindolin-1-yl)propyl)-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 (6b). Light yellow solid, yield: 16%; mp: 173–174°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01–1.59 (m, 8H), 2.12–2.35 (m, 7H), 2.73–2.75 (m, 1H), 3.00–3.01 (m, 1H), 3.54–3.72 (m, 11H), 3.94–3.96 (m, 1H), 4.39–4.48 (m, 2H), 7.04–8.60 (7H, m), 8.68 (1H, s), 9.02 (1H, s), 11.52 (1H, brs), 15.16 (1H, brs). ESI-MS *m*/*z*: 741 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{37}H_{41}FN_{10}O_6$: C, 59.99; H, 5.58; N, 18.91; found: C, 59.78; H, 5.43; N, 18.82.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamoylhydrazono)-5-fluoro-2-oxoindolin-1-yl)propyl)-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 (6c). Light yellow solid, yield: 21%; mp: 201–203°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05–1.71 (8H, m), 2.11–2.37 (4H, m), 2.75–2.77 (1H, m), 2.99–3.01 (1H, m), 3.61–3.80 (11H, m), 4.11–4.12 (1H, m), 4.36–4.38 (2H, m), 7.00–8.62 (6H, m), 8.66 (1H, s), 9.01 (1H, s), 11.52 (1H, brs), 15.16 (1H, brs). ESI-MS *m*/*z*: 745 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{38}F_2N_{10}O_6$: C, 58.06; H, 5.14; N, 18.81; found: C, 57.95; H, 5.06; N, 18.72.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamoylhydrazono)-5-chloro-2-oxoindolin-1-yl)propyl)-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 (6d). Light yellow solid, yield: 18%; mp: 192–194°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08–1.66 (8H, m), 2.12–2.36 (4H, m), 2.76–2.77 (1H, m), 2.99–3.00 (1H, m), 3.58–3.77 (11H, m), 4.10–4.11 (1H, m), 4.36–4.38 (2H, m), 7.12–8.64 (6H, m), 8.70 (1H, s), 9.04 (1H, s), 11.64 (1H, brs), 15.18 (1H, brs). ESI-MS *m*/*z*: 761 $[M + H]^+$, 763 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{38}FClN_{10}O_6$: C, 56.80; H, 5.03; N, 18.40; found: C, 56.57; H, 4.81; N, 18.19.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamothioylhydrazono)-2-oxoindolin-1-yl)propyl)-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 (6e). Yellow solid, yield: 26%; mp: 183–185°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06–1.58 (8H, m), 2.12–2.32 (4H, m), 2.75–2.77 (1H, m), 2.99–3.01 (1H, m), 3.61–3.80 (11H, m), 4.11–4.13 (1H, m), 4.36–4.38 (2H, m), 7.06–8.64 (6H, m), 8.70 (1H, s), 9.12 (1H, s), 12.10 (1H, brs), 15.20 (1H, brs). ESI-MS *m*/*z*: 743 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{39}FN_{10}O_5S$: C, 58.21; H, 5.29; N, 18.86; found: C, 58.03; H, 5.11; N, 18.63.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamothioylhydrazono)-5-methyl-2-oxoindolin-1-yl)propyl)-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 (6f). Light yellow solid, yield: 33%; mp: 159–161°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08–1.61 (m, 8H), 2.11–2.34 (m, 7H), 2.71–2.73 (m, 1H), 3.00–3.01 (m, 1H), 3.60–3.78 (m, 11H), 4.01–4.02 (m, 1H), 4.38–4.42 (m, 2H), 7.00–8.62 (6H, m), 8.72 (1H, s), 9.10 (1H, s), 12.18 (1H, brs), 15.12 (1H, brs). ESI-MS *m*/*z*: 757 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{37}H_{41}FN_{10}O_5S$: C, 58.72; H, 5.46; N, 18.51; found: C, 58.59; H, 5.33; N, 18.37.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamothioylhydrazono)-5-fluoro-2-oxoindolin-1-yl)propyl)-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 (6g). Light yellow solid, yield: 27%; mp: 182–184°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.02–1.71 (8H, m), 2.13–2.38 (4H, m), 2.75–2.77 (1H, m), 3.00–3.01 (1H, m), 3.63–3.80 (11H, m), 4.11–4.13 (1H, m), 4.34–4.37 (2H, m), 7.12–7.64 (6H, m), 8.76 (1H, s), 9.10 (1H, s), 12.12 (1H, brs), 15.16 (1H, brs). ESI-MS *m*/*z*: 761 $[M + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{38}F_2N_{10}O_5S$: C, 56.83; H, 5.03; N, 18.41; found: C, 56.75; H, 4.92; N, 18.33.

7-((4aR,7aR)-1-((1-(3-(3-(2-carbamothioylhydrazono)-5-chloro-2-oxoindolin-1-yl)propyl)-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 (6h). Light yellow solid, yield: 16%; mp: 163–165°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.95–1.64 (m, 8H), 2.10–2.36 (m, 4H), 2.76–2.77 (m, 1H), 3.01–3.02 (m, 1H), 3.62–3.80 (m, 11H), 4.12 (s, 1H), 4.37–4.40 (m, 2H), 7.06–8.64 (6H, m), 8.78 (1H, s), 9.12 (1H, s), 12.10 (1H, brs), 15.12 (1H, brs). ESI-MS *m*/*z*: 777 $[M + H]^+$, 779 $[M + 2 + H]^+$. Elemental *Anal*. Calcd (%) for $C_{36}H_{38}FClN_{10}O_5S$: C, 55.63; H, 4.93; N, 18.02; found: C, 55.39; H, 4.77; N, 17.91.

MIC determination. Hybrids **6a**–**h** 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 [23]. 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, 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 re-determined 7 days later. The MIC is defined as the concentration of the compound required to give complete inhibition of bacterial growth.

Cytotoxicity. The synthesized hybrids **6a**–**h** along with the references **MXFX**, **RIF**, and **INH** were further examined for toxicity (CC_{50}) in a mammalian VERO cell line dissolved in DMSO at concentrations from 1024 to 1 μg/mL [26]. The VERO cells were maintained in culture medium (Minimum Essential Medium with Earle's salt, supplemented with 10% fetal bovine serum) at 37°C under 5% CO_2. Cells were seeded in 96-well plates at the plating density of 1×10^4 cells per well and allowed to recover for 24 h. Culture medium was replaced by assay medium containing the compound to be tested or drug free. After 72 h of exposure, cells were harvested, and cell viability was assessed by MTT assay. The CC_{50} values were calculated by Bliss analyses.

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