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1*H*-1,2,3-Triazole-Tethered Isatin–Ferrocene and Isatin–Ferrocenylchalcone Conjugates: Synthesis and in Vitro Antitubercular Evaluation

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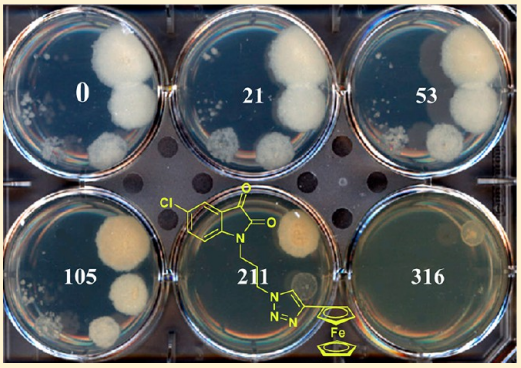
Supporting Information

ABSTRACT: A Cu-mediated azide–alkyne cycloaddition protocol has been employed for the synthesis of 16 different triazoles to probe the antitubercular structure–activity relationships within the isatin–ferrocene–triazole conjugate family. The antitubercular evaluation studies revealed a marked improvement in activity with the introduction of ferrocene nucleus among precursors *N*-alkylazido isatins with a prefernce for halogen (F, Cl) substituent at C-5 position of isatin as well as propyl chain length as a spacer. The induction of a chalcone nucleus resulted in the enhanced antimycobacterial efficacy irrespective of the subtituent and alkyl chain length as evidenced by the isatin–ferrocenylchalcone hybrids. The described protocol is the first successful attempt of the amalgamation of ferrocene–isatin nuclei tethered via a triazole linker.



Tuberculosis (TB) is more prevalent now than at any other time in human history.[1] It disproportionately burdens developing countries of the world and is one of their leading causes of death. *Mycobacterium tuberculosis*, the causative agent of TB, has infected approximately 2 billion people globally with 8 million new active cases per year.[2] It results in 2 million deaths each year, with the majority of these in developing countries.[2] One-third of the world's population asymptomatically still harbors a dormant or latent form of *M. tuberculosis* with a lifelong risk of disease reactivation.[3] Co-infection with human immunodeficiency virus (HIV) leads to an exacerbation of the disease and contributes to higher mortality in HIV patients. There are 0.7 million HIV-positive people infected with TB, contributing to 0.2 million deaths per year.[4−6] The development of multidrug resistant TB (MDR-TB) with the extensive and inadequate use of chemotherapeutics requires administration of more expensive, second line antibiotics.[7] A recent study by Dalton et al. revealed a more than 4-fold increase in the development of extensively drug resistant TB (XDR-TB) following previous treatment with second line antitubercular drugs.[8] Different mechanisms have been put forward for the acquisition of resistance in *M. tuberculosis* such as membrane impermeability, expression of drug efflux systems and drug inactivation by enzymes viz. β-lactamases, amino-glycosides acyl transferases and chromosomal mutations.[9] The slow moving pipeline of antitubercular agents and the threat posed by the emergence of MDR- and XDR-TB calls for intensified research efforts, not only for the development of new molecular scaffolds but also for the re-engineering and repositioning of some old drug families.

In the past few years, the medicinal applications of organometallics have come to the fore using the structural diversity and chemical tunability of organometallic complexes.[10,11] In addition to the simplest organometallic therapeutic agents, a diverse range of scaffolds with a metal carbon single bond such as organoarsenes have been evaluated for their antitumor and antibacterial profiles.[12] Among metallocenes, ferrocene is the most attractive pharmacophore for drug design and drug discovery, as it is a neutral, chemically stable and nontoxic molecule.[10]

Indeed, a few ferrocene derivatives have been designed and synthesized in order to increase the biological response of the purely organic drugs as depicted in Figure 1. For example,

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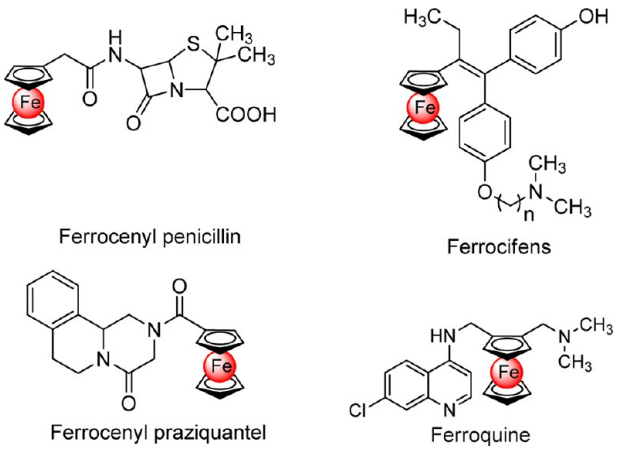


Figure 1. Chemical structures of representative bioactive ferrocenyl analogues.

Edwards et al.[13] synthesized ferrocenyl−penicillin and ferrocenyl−cephalosporin conjugates, which were tested against penicillin-resistant bacteria. Ferrocenyl−tamoxifen hybrids called ferrocifens were prepared by the group of Jaouen.[14] These compounds showed antiproliferative effects against both hormone-dependent and hormone-independent breast cancer cells. Ferrocenyl derivatives of the anthelmintic praziquantel were also synthesized by the group of Gasser.[15] A similar approach lead to the design of ferroquine, a ferrocenyl analogue of chloroquine. Ferroquine is equally effective on both chloroquine-susceptible and chloroquine-resistant strains of *Plasmodium falciparum* and is currently in the phase II Sanofi portfolio.[16]

A previous report from our laboratory has described the synthesis of quinoline-ferrocene hybrids and the assessment of their antitubercular profiles showing significant activity with MIC values ranging from 2.5 to 5 μg mL^{-1}.[17] In an independent study, Pélinski et al. reported the antimycobacterial profiles of a range of ferrocenyl derivatives viz. ferrocenyl amides derived from nicotinamide and pyrazinamide, ferrocenyl pyridinyl, quinolyl and acridinylhydrazones.[18]

The isatin (1*H*-indole-2,3-dione) moiety is a privileged scaffold for chemical modification and is responsible for a broad spectrum of biological properties in many synthetically versatile molecules.[19] Schiff bases of nalidixic acid carbohydrazide and isatin derivatives have also shown potential activity against different mycobacterial species. One of the compounds showed a potent anti-TB activity with MIC 0.625 μg mL^{-1}, which is 20 times greater than the reference drug isoniazid, which is used against these species.[20] Previous works have also reported the inhibitory activity of isatin-β-thiosemicarbazones on HIV replication,[21] which was extended toward the synthesis of diverse *N*-Mannich base derivatives of 3-(*N*-hydroxy/methoxy thiosemicarbazones) of 5-substituted isatins as potential non-nucleoside reverse transcriptase inhibitors (NNRTI). These compounds have also been shown to inhibit the isocitrate lyase of *M. tuberculosis*, thereby tackling the issue of dormant TB, which often presents itself as an opportunistic infection in patients afflicted with AIDS.

Chalcones, or 1,3-diaryl-2-propen-1-ones, are prominent secondary metabolite precursors of flavonoids and isoflavonoids in plants. Chemically, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon-α,β-unsaturated carbonyl system. The wide variety of pharmacological activities reported for these compounds includes anticancer, anti-inflammatory, immunomodulatory, antibacterial, antimicrobial and immunosuppressive, as well as antiprotozoan including trypanocidal, leishmanicidal, and antimalarial activities.[22] Recent reports by Marrapu and coworkers have shown that the aryloxy azolyl chalcones exhibit potent activity against *M. tuberculosis* $H_{37}Rv$.[23]

The incorporation of 1,2,3-triazoles as attractive linker units between two pharmacophores to generate innovative bifunctional drugs has become increasingly useful and important in constructing bioactive molecules.[24] The introduction of "click chemistry" for the synthesis of 1,2,3-triazole rings as well as the favorable properties like a moderate dipole character, hydrogen bonding capability, rigidity and stability under in vivo conditions are evidently responsible for their extensive use in the design of structural chimeras.[25]

Recent disclosure from our laboratory has shown the successful and unprecedented inclusion of a ferrocene nucleus in the β-lactam family of therapeutics, linked via the 1*H*-1,2,3-triazole ring, along with their antitubercular evaluations.[26] The methodology was further extended toward the synthesis of mono- and bis-1*H*-1,2,3-triazole tethered β-lactam-ferrocene and β-lactam-ferrocenylchalcone hybrids along with the evaluation of their antitubercular profiles.[27] In continuation with our efforts to synthesize novel molecular frameworks utilizing click chemistry approaches,[28] the present manuscript entails the synthesis of novel 1*H*-1,2,3-triazole-tethered isatin−ferrocene and isatin−ferrocenylchalcone conjugates as shown in Figure 2 along with their anti-TB evaluations.

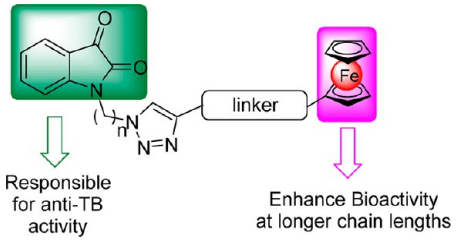
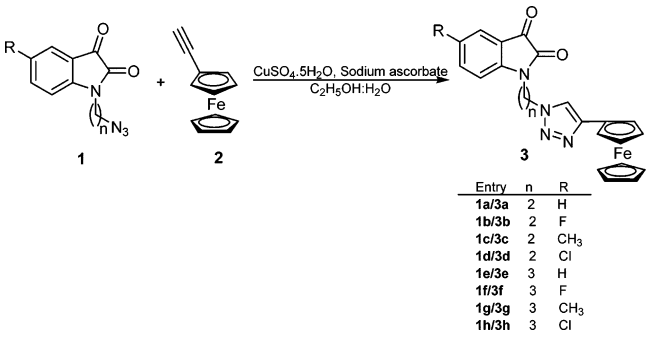


Figure 2. Designed isatin−ferrocene−triazole and isatin−ferrocenylchalcone−triazole hybrids.

The synthetic protocol for the synthesis of desired isatin−ferrocene hybrids **3a−h** involved the Cu-mediated click chemistry of *N*-alkyl azido isatin derivatives **1** with ethynyl ferrocene **2** (Scheme 1). The isatin derivatives **1** were prepared via a combination of literature methods[29] involving an initial base-assisted *N*-alkylation of substituted isatins with dibro-

Scheme 1. Synthesis of Isatin−Ferrocene-Based Hybrids



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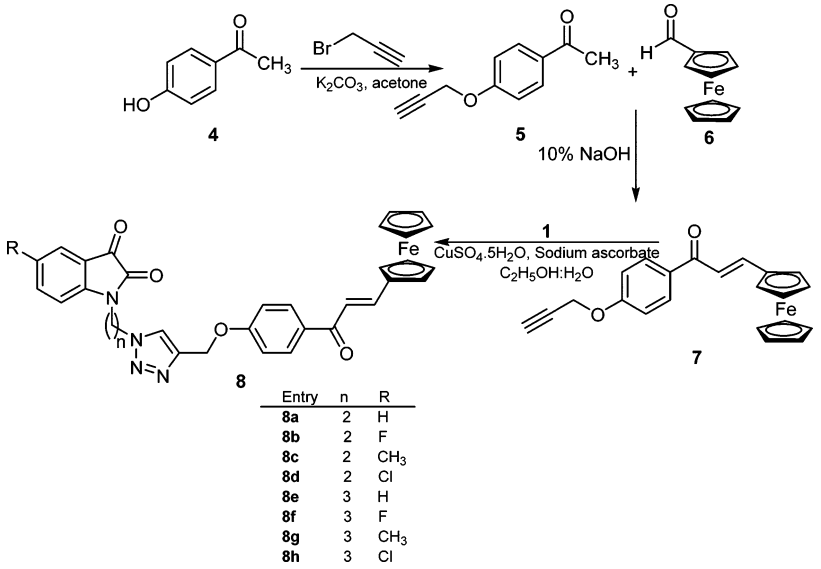
Scheme 2. Synthesis of Isatin−ferrocenylchalcone-Based Hybrids



moalkane to yield the corresponding *N*-alkyl bromo isatins, followed by subsequent reaction with sodium azide in DMF at 60 °C.

The structure assigned to the hybrids **3** was confirmed on the basis of spectral data and analytical evidence. Compound **3f**, for example, showed a molecular ion peak at *m*/*z* 458.0833 $[M]^+$ along with the characteristic signals in ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum exhibited a singlet at δ 4.08 corresponding to 5H (cyclopentadiene ring of ferrocene) along with singlets at δ 4.31 (2H) and δ 4.72 (2H) due to the ferrocene ring protons. The presence of a multiplet at δ 2.41 (2H) along with two triplets at δ 3.82 and 4.43 corresponds to the presence of the propyl chain, while the presence of a characteristic singlet at δ 7.63 corresponding to the triazole ring proton further ascertains the assigned structure, which was also corroborated with the number of carbon atoms in the ^{13}C NMR spectrum.

Ferrocenyl chalcones **7**, prepared by an initial propargylation of 4-hydroxyacetophenone followed by aldol condensation with ferrocene carboxaldehyde, were used as click chemistry precursors for azide−alkyne cyclization with variedly substituted *N*-alkyl azido isatins **1** in the presence of copper sulfate/sodium ascorbate in ethanol:water mixture (Scheme 2). The reaction resulted in the isolation of desired hybrids **8a−h** in good to excellent yields, the structure of which were assigned on the basis of spectral data and analytical evidence. Compound **8a**, for example, showed a molecular ion peak at *m*/*z* 586.5918 $[M]^+$, along with the appearance of characteristic signals in the ^{1}H NMR spectrum due to ferrocene ring protons as well as two singlets at δ 5.20, corresponding to $-OCH_2$, and δ 7.64, corresponding to the triazole ring proton. The presence of characteristic signals at 161.2 and 182.2 ppm, corresponding to the isatin ring carbonyls along with the requisite number of carbons in ^{13}C NMR spectrum, corroborated the structure assigned to isatin−ferrocenylchalcone hybrids.

The synthesized *N*-alkylazido isatins along with the chimeric scaffolds were then evaluated for their anti-TB profiles, and the results are summarized in Table 1. Cephalexin was included as a positive control, and found to exhibit a MIC value of 72−144 μM, consistent with previous findings.[30] The effect of cephalexin and three representative isatin−ferrocene hybrids, **3b**, **3f**, and **3h**, is depicted in Figure 3. As evident from the Table 1, the activity of the synthesized compounds show dependence on the C-5 substituent of isatin ring as well as the spacer length, with antimycobacterial efficacy enhancing considerably with the introduction of ferrocene nucleus. Comparing the effect of substituents among *N*-alkylazido-isatins attached via an ethyl linker (**1a−d**), the presence of fluoro-substituent at the C-5 position of the isatin ring improved the activity profiles, as evidenced by **1b**. A similar comparison among *N*-alkylazido-isatins with propyl linker (**1e−h**) revealed **1h** with chloro substituent having better activity profile among the series of test compounds. The introduction of ferrocene nucleus in the series (**3a−h**) have resulted in the improvement in antituberular efficacy with hybrids **3f** and **3h** having fluoro and chloro substituent, respectively at C-5 position as well as a propyl linker showing better activity among the isatin−ferrocene hybrids. Further, the induction of a chalcone nucleus in the isatin−ferrocene hybrids (**8a−h**) resulted in the enhanced antimycobacterial efficacy irrespective of the substituent at C-5 position of the isatin ring as well as the length of alkyl chain introduced as spacer.

Table 1. In Vitro Antimycobacterial Activity of Compounds 1a−h, 3a−h and 8a−h against *M. tuberculosis* mc^{2}7000

compound	MIC (μM)	compound	MIC (μM)	compound	MIC (μM)
1a	>463	**3a**	>234	**8a**	>167
1b	107−214	**3b**	224	**8b**	>162
1c	>435	**3c**	>226	**8c**	>163
1d	400	**3d**	>216	**8d**	>158
1e	>435	**3e**	>227	**8e**	>163
1f	>403	**3f**	109−218	**8f**	>159
1g	>410	**3g**	220	**8g**	>160
1h	189−377	**3h**	105−211	**8h**	>155

In conclusion, the present report describes the synthesis of isatin−ferrocene and isatin−ferrocenylchalcone hybrids using Cu-mediated azide−alkyne cycloaddition reactions and their anti-TB evaluations. Assaying their antimycobacterial property revealed the dependence of activity profile on the C-5 substituent of the isatin ring as well as the length of alkyl chain, with a preference for halogen substituents (F, Cl) along

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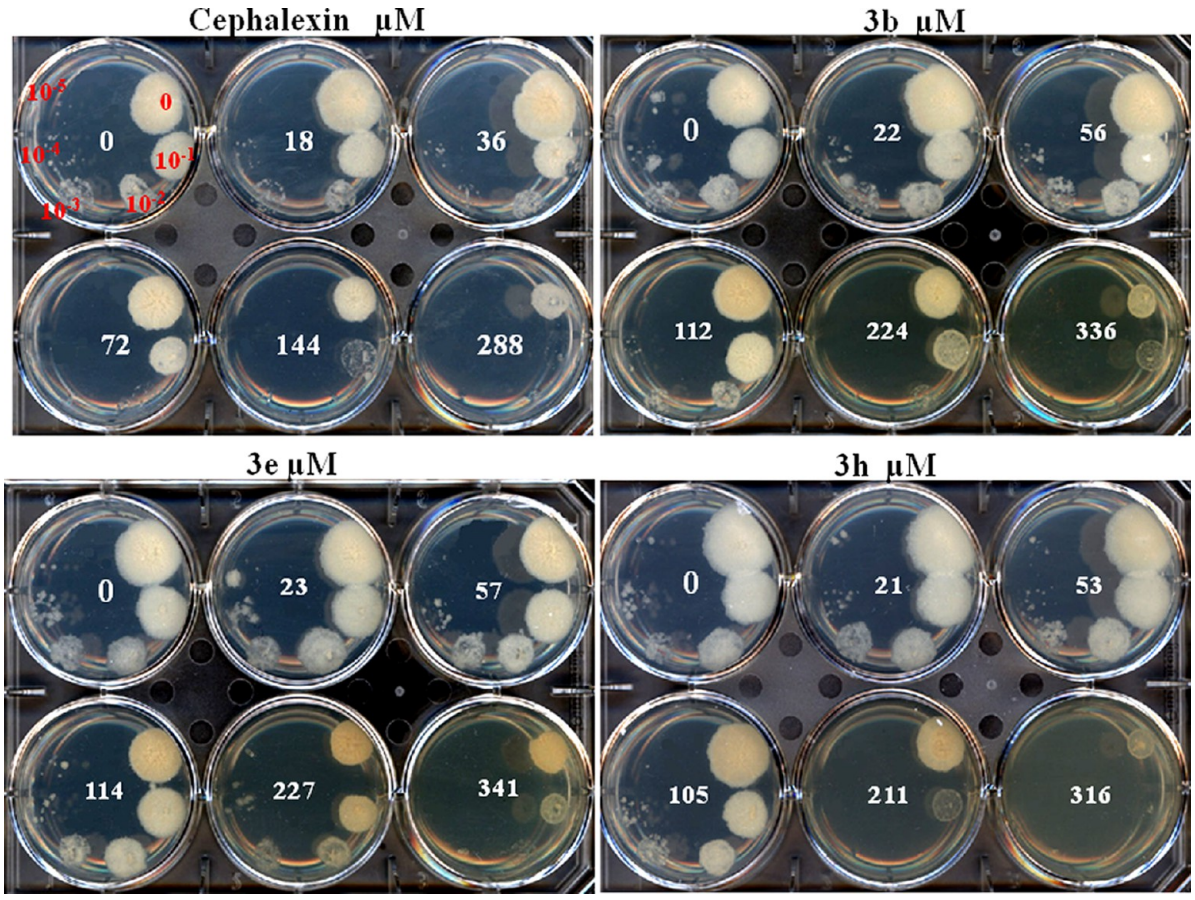

Figure 3. Cephalexin along with isatin–ferrocene hybrids (**3b**, **3f** and **3h**) inhibit the growth of *M. tuberculosis*. The susceptibility of *M. tuberculosis* was determined on Middlebrook 7H10 solid medium containing OADC enrichment, pantothenic acid with increasing inhibitor concentrations (indicated in white, μM). Serial 10-fold dilutions (indicated in red on the control plate) of actively growing culture were plated and incubated at 37 °C for 2–3 weeks prior to growth visualization. The synthesized hybrids were dissolved in DMSO for the assay.

with a longer chain length (n = 3) in case of isatin–ferrocene hybrids. The introduction of chalcone nucleus resulted in the improvement of antimycobacterial activity of the synthesized isatin–ferrocenylchalcone hybrids, independent of the presence of C-5 substituents as well as the alkyl chain length. Further work on improving the antitubercular profiles of isatin–ferrocene hybrids via the intoduction of longer alkyl chain lengths as well as halogen substituents on the isatin nucleus are underway and will soon be communicated.

EXPERIMENTAL SECTION

General Information. Melting points were determined by open capillary using a Veego precision digital melting point apparatus (MP-D) and are uncorrected. ^{1}H NMR spectra were recorded in deuterochloroform and dimethylsulfoxide-d_6 with Jeol 300 (300 MHz) spectrometers using TMS as an internal standard. Chemical shift values are expressed as parts per million downfield from TMS, and J values are in hertz. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, double doublet; ddd, doublet of a doublet of a doublet; and br, broad peak. ^{13}C NMR spectra were recorded on Jeol 300 (75 MHz) spectrometers in deuterochloroform and dimethylsulfoxide-d_6 using TMS as internal standard. Elemental analyses were performed on Heraus CHN-O-Rapid Elemental Analyzer. Mass spectra were recorded on a BRUCKER high resolution mass spectrometer (microTOF-QII). Column chromatography was performed using silica gel (60–120 mesh).

Procedure for the Preparation of Isatin–Ferrocene Hybrids (3a–h). To a stirred solution of ethynyl-ferrocene **2** (1 mmol) and *N*-alkylated azido-isatins **1** (1 mmol) in an ethanol–water mixture was added copper sulfate (0.05 mmol) and sodium ascorbate (0.13 mmol). The reaction mixture was allowed to stir at room temperature for 7–10 h, and the progress was monitored using TLC. After the reaction was complete, water (20 mL) was added, and the reaction mixture was extracted twice with dichloromethane (2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a crude product, which was purified via column chromatography using 40:60 (EtOAc:hexane) mixture.

Procedure for the Preparation of Isatin–Ferrocenylchalcone Hybrids (8a–h). To a stirred solution of *O*-propargylated-ferrocenylchalcone **7** (1 mmol), prepared by the reported protocol involving an initial propargylation of 4-hydroxyacetophenone and subsequent aldol condensation with ferrocene carboxaldehyde,[31,32] and *N*-alkylated azido-isatins **1** (1 mmol) in an ethanol–water mixture was added copper sulfate (0.05 mmol) and sodium ascorbate (0.13 mmol). The reaction mixture was allowed to stir at room temperature for 10–11 h, and the progress was monitored using TLC. After the reaction was complete, water (20 mL) was added, and the reaction mixture was extracted twice with dichloromethane (2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a crude product, which was purified via column chromatography using 45:55 (EtOAc:hexane) mixture.

Characterization of Compounds. *1-[2-(4-Ferrocenyl-[1,2,3]-triazol-1-yl)-ethyl]-1H-indole-2,3-dione (**3a**).* Yield 84%. Brown solid: mp 222–223 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.96 (s, 5H, H^6), 4.28 (s, 4H, H^1+H^5), 4.64 (s, 2H, H^4), 4.68 (t, J = 6.6 Hz, 2H, H^2), 7.14–7.33 (m, 2H, –ArH), 7.45 (s, 1H, H^3), 7.65–7.69 (m,

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2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 38.3, 46.8, 66.2, 68.4, 69.6, 75.4, 110.1, 117.5, 121.2, 124.7, 132.7, 138.9, 146.4, 149.3, 158.2, 182.3; HRMS Calcd for $C_{22}H_{18}FeN_4O_2$ $[M]^+$ 426.0774, found 426.0770. Anal. Calcd (%) for: C, 61.97; H, 4.23; N, 13.15. Found: C, 61.88; H, 4.16; N, 13.19.

*1-[2-(4-Ferrocenyl-[1,2,3]triazol-1-yl)-ethyl]-5-fluoro-1H-indole-2,3-dione (**3b**).* Yield 81%. Brown solid: mp 219−220 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 5H, H^6), 4.24 (s, 4H, H^1+H^5), 4.63 (s, 2H, H^4), 4.67 (t, J = 5.4 Hz, 2H, H^2), 6.94−6.98 (m, 1H, −ArH), 7.27−7.36 (m, 2H, −ArH), 7.61 (s, 1H, H^3); ^{13}C NMR ($CDCl_3$, 75 MHz) 38.6, 48.7, 66.5, 68.7, 69.7, 75.7, 110.5, 117.7, 121.4, 124.9, 132.7, 138.6, 146.6, 149.5, 158.1, 182.4; HRMS Calcd for $C_{22}H_{17}FFeN_4O_2$ $[M]^+$ 444.0680, found 444.0673. Anal. Calcd (%) for: C, 59.46; H, 3.83; N, 12.61. Found: C, 59.54; H, 3.79; N, 12.56.

*1-[2-(4-Ferrocenyl-[1,2,3]triazol-1-yl)-ethyl]-5-methyl-1H-indole-2,3-dione (**3c**).* Yield 79%. Brown solid: mp 223−224 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H, $-CH_3$), 3.94 (s, 5H, H^6), 4.27 (s, 4H, H^1+H^5), 4.62 (s, 2H, H^4), 4.69 (t, J = 5.4 Hz, 2H, H^2), 6.58 (d, J = 8.1 Hz, 1H, −ArH), 7.28−7.35 (m, 2H, −ArH), 7.43 (s, 1H, H^3); ^{13}C NMR (DMSO-d_6, 75 MHz) 20.1, 38.4, 46.9, 66.3, 68.2, 69.3, 75.8, 110.3, 117.3, 121.3, 124.9, 132.8, 138.8, 146.5, 149.1, 158.4, 182.5; HRMS Calcd for $C_{23}H_{20}FeN_4O_2$ $[M]^+$ 440.0930, found 440.0926. Anal. Calcd (%) for: C, 62.73; H, 4.55; N, 12.73. Found: C, 62.78; H, 4.59; N, 12.69.

*5-Chloro-1-[2-(4-ferrocenyl-[1,2,3]triazol-1-yl)-ethyl]-1H-indole-2,3-dione (**3d**).* Yield 82%. Brown solid: mp 220−221 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 5H, H^6), 4.25 (s, 4H, H^1+H^5), 4.63 (s, 2H, H^4), 4.67 (t, J = 5.4 Hz, 2H, H^2), 6.92−6.98 (m, 1H, −ArH), 7.27−7.37 (m, 2H, −ArH), 7.60 (s, 1H, H^3); ^{13}C NMR ($CDCl_3$, 75 MHz) 38.2, 46.4, 66.6, 68.6, 69.5, 75.4, 110.6, 117.2, 121.5, 124.7, 132.6, 138.7, 146.6, 149.3, 158.7, 182.4; HRMS Calcd for $C_{22}H_{17}ClFeN_4O_2$ $[M]^+$ 460.0385, found 460.0381. Anal. Calcd (%) for: C, 57.39; H, 3.70; N, 12.17. Found: C, 57.35; H, 3.67; N, 12.22.

*1-[2-(4-Ferrocenyl-[1,2,3]triazol-1-yl)-propyl]-1H-indole-2,3-dione (**3e**).* Yield 80%. Brown solid: mp 215−216 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.42 (m, 2H, H^2), 3.80 (t, J = 6.6 Hz, 2H, H^1), 4.0 6 (s, 5H, H^7), 4.32 (s, 2H, H^6), 4.42 (t, J = 6.6 Hz, 2H, H^3), 4.71 (s, 2H, H^5), 7.12−7.35 (m, 2H, −ArH), 7.61 (s, 1H, H^4), 7.64−7.70 (m, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 27.3, 37.4, 47.3, 66.3, 68.7, 69.4, 71.6, 111.3, 112.7, 119.8, 124.6, 125.3, 128.5, 130.8, 146.1, 158.6, 182.3; HRMS Calcd for $C_{23}H_{20}FeN_4O_2$ $[M]^+$ 440.0930, found 440.0922. Anal. Calcd (%) for: C, 62.72; H, 4.55; N, 12.73. Found: C, 62.67; H, 4.57; N, 12.68.

*1-[2-(4-Ferrocenyl-[1,2,3]triazol-1-yl)-propyl]-5-fluoro-1H-indole-2,3-dione (**3f**).* Yield 84%. Brown solid: mp 213-214 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (m, 2H, H^2), 3.82 (t, J = 6.6 Hz, 2H, H^1), 4.08 (s, 5H, H^7), 4.31 (s, 2H, H^6), 4.43 (t, J = 6.6 Hz, 2H, H^3), 4.72 (s, 2H, H^5), 6.92−6.97 (m, 1H, −ArH), 7.29−7.35 (m, 2H, −ArH), 7.63 (s, 1H, H^4); ^{13}C NMR (DMSO-d_6, 75 MHz) 27.5, 37.5, 47.3, 66.6, 68.8, 69.5, 71.7, 111.5, 112.5, 119.9, 124.8, 125.1, 128.7, 130.9, 146.2, 158.4, 182.1; HRMS Calcd for $C_{23}H_{19}FFeN_4O_2$ $[M]^+$ 458.0836, found 458.0833. Anal. Calcd (%) for: C, 60.26; H, 4.15; N, 12.23. Found: C, 60.18; H, 4.19; N, 12.18.

*1-[2-(4-Ferrocenyl-[1,2,3]triazol-1-yl)-propyl]-5-methyl-1H-indole-2,3-dione (**3g**).* Yield 82%. Brown solid: mp 215−216 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.33 (s, 5H, $-CH_3$+H^2), 3.78 (dd, J = 1.5 Hz, 5.1 Hz, 2H, H^1), 4.04 (s, 5H, H^7), 4.27 (s, 2H, H^6), 4.47 (dd, J = 1.5 Hz, 5.1 Hz, 2H, H^3), 4.69 (s, 2H, H^5), 6.95 (d, J = 7.8 Hz, 1H, −ArH), 7.37−7.44 (m, 2H, −ArH), 7.92 (s, 1H, H^4); ^{13}C NMR (DMSO-d_6, 75 MHz) 20.5, 27.5, 36.9, 47.0, 66.3, 68.3, 69.3, 76.0, 110.0, 117.7, 120.7, 123.2, 124.5, 138.1, 145.2, 150.4, 158.4, 183.3; HRMS Calcd for $C_{24}H_{22}FeN_4O_2$ $[M]^+$ 454.1087, found 454.1084. Anal. Calcd (%) for: C, 63.44; H, 4.85; N, 12.33. Found: C, 63.37; H, 4.81; N, 12.28.

*5-Chloro-1-[2-(4-ferrocenyl-[1,2,3]triazol-1-yl)-propyl]-1H-indole-2,3-dione (**3h**).* Yield 81%. Brown solid: mp 212−213 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (m, 2H, H^2), 3.80 (t, J = 6.6 Hz, 2H, H^1), 4.05 (s, 5H, H^7), 4.14 (s, 2H, H^6), 4.45 (t, J = 6.6 Hz, 2H, H^3), 4.71 (s, 2H, H^5), 6.91−6.99 (m, 1H, −ArH), 7.28−7.36 (m, 2H, −ArH), 7.62 (s, 1H, H^4); ^{13}C NMR ($CDCl_3$, 75 MHz) 27.6, 37.4, 47.4, 66.5, 68.6, 69.3, 71.5, 111.4, 112.6, 119.8, 124.7, 125.0, 128.6, 130.7, 146.4, 158.5, 182.4; HRMS Calcd for $C_{23}H_{19}ClFeN_4O_2$ $[M]^+$ 474.0541, found 474.0535. Anal. Calcd (%) for: C, 58.23; H, 4.01; N, 11.81. Found: C, 58.15; H, 4.07; N, 11.89.

*1-(2-{4-[4-(3-Ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-ethyl)-1H-indole-2,3-dione (**8a**).* Yield 87%. Dark red solid: mp 102−103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (s, 5H, H^9), 4.26 (t, J = 5.7 Hz, 2H, H^1), 4.48 (s, 2H, H^8), 4.60 (s, 2H, H^7); 4.73 (t, J = 5.7 Hz, 2H, H^2), 5.20 (s, 2H, H^4), 6.55 (d, J = 7.8 Hz, 1H, −ArH), 6.96 (d, J = 8.7 Hz, 2H, −ArH), 7.05 (t, J = 7.5 Hz, 1H, −ArH), 7.13 (d, J = 15.0 Hz, 1H, H^5), 7.40 (t, J = 7.8 Hz, 1H, −ArH), 7.56 (d, J = 7.5 Hz, 1H, −ArH), 7.64 (s, 1H, H^3), 7.77 (d, J = 15.0 Hz, 1H, H^6), 7.96 (d, J = 8.7 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 40.8, 47.8, 61.4, 68.9, 69.7, 71.2, 79.2, 110.7, 114.3, 118.1, 118.6, 124.2, 125.4, 130.5, 137.8, 137.9, 144.0, 146.0, 147.9, 161.2, 182.2, 187.9; HRMS Calcd for $C_{32}H_{26}FeN_4O_4$ $[M]^+$ 586.1298, found 586.1292. Anal. Calcd (%) for: C, 65.53; H, 4.44; N, 9.56. Found: C, 65.59; H, 4.41; N, 9.49.

*1-(2-{4-[4-(3-Ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-ethyl)-5-fluoro-1H-indole-2,3-dione (**8b**).* Yield 87%. Dark red solid: mp 101−102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (s, 5H, H^9), 4.24 (t, J = 5.7 Hz, 2H, H^1), 4.49 (s, 2H, H^8), 4.58 (s, 2H, H^7); 4.71 (t, J = 5.7 Hz, 2H, H^2), 5.23 (s, 2H, H^4), 6.44−6.60 (m, 1H, −ArH), 6.97 (d, J = 9.0 Hz, 2H, −ArH), 7.03−717 (m, 2H, 1ArH +H^5), 7.21−7.24 (m, 1H, −ArH), 7.72−7.74 (m, 2H, H^3+H^6), 7.98 (d, J = 8.7 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 40.3, 47.6, 61.4, 68.6, 69.6, 71.2, 79.0, 109.4, 114.2, 117.3, 118.8, 124.3, 124.4, 125.5, 130.4, 130.5, 131.9, 138.7, 143.6, 146.4, 149.7, 161.2, 182.5, 187.7; HRMS Calcd for $C_{32}H_{25}FFeN_4O_4$ $[M]^+$ 604.1204, found 604.1201. Anal. Calcd (%) for: C, 63.58; H, 4.14; N, 9.27. Found: C, 63.65; H, 4.08; N, 9.31.

*1-(2-{4-[4-(3-Ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-ethyl)-5-methyl-1H-indole-2,3-dione (**8c**).* Yield 84%. Dark red solid: mp 101−102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H, $-CH_3$), 4.18 (m, 7H, H^1+H^9), 4.48 (s, 2H, H^8), 4.60 (s, 2H, H^7), 4.70 (s, 2H, H^2), 5.20 (s, 2H, H^4), 6.42 (d, J = 8.7 Hz, 1H, −ArH), 6.98 (d, J = 8.4 Hz, 2H, −ArH), 7.09−7.20 (m, 2H, 1ArH+H^5), 7.35 (s, 1H, −ArH), 7.64 (s, 1H, H^3), 7.73 (d, J = 15.1 Hz, 1H, H^6), 7.96 (d, J = 8.1 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 20.2, 36.9, 47.3, 61.6, 68.5, 69.1, 70.5, 79.0, 109.6, 114.1, 117.0, 118.3, 123.7, 125.3, 130.2, 130.3, 131.4, 133.6, 138.6, 142.8, 145.5, 147.3, 161.3, 182.7, 187.8; HRMS Calcd for $C_{33}H_{28}FeN_4O_4$ $[M]^+$ 600.1455, found 600.1451. Anal. Calcd (%) for: C, 66.00; H, 4.67; N, 9.33. Found: C, 65.91; H, 4.61; N, 9.38.

*5-Chloro-1-(2-{4-[4-(3-ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-ethyl)-1H-indole-2,3-dione (**8d**).* Yield 84%. Dark red solid: mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.17 (s, 5H, H^9), 4.25 (t, J = 5.7 Hz, 2H, H^1), 4.48 (s, 2H, H^8), 4.60 (s, 2H, H^7); 4.73 (t, J = 5.7 Hz, 2H, H^2), 5.20 (s, 2H, H^4), 6.84−6.89 (m, 1H, −ArH), 7.03−7.16 (m, 4H, 3ArH+H^5), 7.27−7.34 (m, 1H, −ArH), 7.72 (d, J = 15.3 Hz, 1H, H^6), 7.81 (s, 1H, H^3), 7.97 (d, J = 8.7 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 40.3, 47.4, 61.3, 68.6, 69.4, 70.9, 78.9, 108.8, 113.8, 116.6, 118.3, 123.5, 123.6, 125.4, 130.2, 130.3, 131.5, 138.4, 143.6, 145.5, 149.3, 161.7, 182.4, 187.5; HRMS Calcd for $C_{32}H_{25}ClFeN_4O_4$ $[M]^+$ 620.0909, found 620.0903. Anal. Calcd (%) for: C, 61.94; H, 4.03; N, 9.03. Found: C, 61.89; H, 4.08; N, 8.99.

*1-(2-{4-[4-(3-Ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-propyl)-1H-indole-2,3-dione (**8e**).* Yield 83%. Dark red solid: mp 82−83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (t, J = 6.3 Hz, 2H, H^2), 3.80 (t, J = 6.3 Hz, 2H, H^1), 4.17 (s, 5H, H^{10}), 4.45 (m, 4H, H^3+H^9), 4.58 (s, 2H, H^8), 5.28 (s, 2H, H^5), 6.53 (d, J = 7.8 Hz, 1H, −ArH), 6.97 (d, J = 8.7 Hz, 2H, −ArH), 7.04 (t, J = 7.5 Hz, 1H, −ArH), 7.11 (d, J = 15.0 Hz, 1H, H^6), 7.42 (t, J = 7.8 Hz, 1H, −ArH), 7.55 (d, J = 7.5 Hz, 1H, −ArH), 7.62 (s, 1H, H^4), 7.79 (d, J = 15.0 Hz, 1H, H^7), 7.97 (d, J = 8.7 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 27.4, 40.6, 47.7, 61.2, 68.8, 69.8, 71.0, 79.3, 110.5, 114.2, 118.0, 118.5, 124.0, 125.3, 130.4, 137.7, 137.9, 144.2, 146.1, 147.7, 161.1, 182.1, 187.6; HRMS Calcd for $C_{33}H_{28}FeN_4O_4$ $[M]^+$ 600.1455, found 600.1448. Anal. Calcd (%) for: C, 66.00; H, 4.67; N, 9.33. Found: C, 66.07; H, 4.63; N, 9.36.

*1-(2-{4-[4-(3-Ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-propyl)-5-fluoro-1H-indole-2,3-dione (**8f**).* Yield 88%. Dark red solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (m, 2H, H^2), 3.81 (t, J = 6.0 Hz, 2H, H^1), 4.17 (s, 5H, H^{10}), 4.45 (m, 4H, H^3+H^9), 4.59 (s, 2H, H^8), 5.29 (s, 2H, H^5), 6.87 (d, J = 8.1 Hz, 1H, −ArH), 7.06−7.15 (m, 3H, 2ArH+H^6), 7.53−7.56 (m, 2H, −ArH), 7.73 (d, J = 15.0 Hz, 1H, H^7), 7.81 (s, 1H, H^4), 8.00 (d, J = 7.8 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 27.8, 40.6, 47.8, 61.5, 68.8, 69.7, 71.2, 79.2, 109.3, 114.3, 117.2, 118.6, 124.1, 124.2, 125.5, 130.5, 130.6, 131.7, 138.6, 143.8, 146.0, 149.8, 161.3, 182.2, 187.9; HRMS Calcd for $C_{33}H_{27}FFeN_4O_4$ $[M]^+$ 618.1361, found 618.1356. Anal. Calcd (%) for: C, 64.08; H, 4.37; N, 9.06. Found: C, 63.99; H, 4.34; N, 8.98.

*1-(2-{4-[4-(3-Ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-propyl)-5-methyl-1H-indole-2,3-dione (**8g**).* Yield 88%. Dark red solid: mp 83−84 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H, $-CH_3$), 2.36 (m, 2H, H^2), 3.78 (t, J = 6.6 Hz, 2H, H^1), 4.17 (s, 5H, H^{10}), 4.45 (m, 4H, H^3+H^9), 4.59 (s, 2H, H^8), 5.29 (s, 2H, H^5), 6.76 (d, J = 8.1 Hz, 1H, −ArH), 7.06−7.15 (m, 3H, 2ArH+H^6), 7.36−7.41(m, 2H, −ArH), 7.73 (d, J = 15.0 Hz, 1H, H^7), 7.85 (s, 1H, H^4), 7.99 (d, J = 8.7 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 20.1, 27.2, 36.8, 47.2, 61.4, 68.4, 69.2, 70.7, 78.8, 109.4, 114.0, 117.1, 118.2, 123.5, 125.4, 130.0, 130.1, 131.3, 133.5, 138.4, 142.9, 145.4, 147.4, 161.1, 182.6, 187.5; HRMS Calcd for $C_{34}H_{30}FeN_4O_4$ $[M]^+$ 614.1611, found 614.1604. Anal. Calcd (%) for: C, 66.45; H, 4.89; N, 9.12. Found: C, 66.49; H, 4.94; N, 9.04.

*5-Chloro-1-(2-{4-[4-(3-ferrocenyl-acryloyl)-phenoxymethyl]-[1,2,3]triazol-1-yl}-propyl)-1H-indole-2,3-dione (**8h**).* Yield 88%. Dark red solid: mp 80−81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (m, 2H, H^2), 3.81 (t, J = 6.3 Hz, 2H, H^1), 4.17 (s, 5H, H^{10}), 4.47 (m, 4H, H^3+H^9), 4.59 (s, 2H, H^8), 5.28 (s, 2H, H^5), 6.87−6.91 (m, 1H, −ArH), 7.05−7.15 (m, 4H, 3ArH+H^6), 7.28−7.33 (m, 1H, −ArH), 7.73 (d, J = 15.3 Hz, 1H, H^7), 7.83 (s, 1H, H^4), 7.99 (d, J = 8.7 Hz, 2H, −ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) 27.6, 40.1, 47.3, 61.1, 68.4, 69.2, 70.8, 78.8, 108.9, 113.9, 116.8, 118.1, 123.7, 123.8, 125.1, 130.0, 130.1, 131.3, 138.2, 143.4, 145.6, 149.4, 160.9, 182.2, 187.4; HRMS; Calcd for $C_{33}H_{27}ClFeN_4O_4$ $[M]^+$ 634.1066, found 634.1063. Anal. Calcd (%) for: C, 62.46; H, 4.26; N, 8.83. Found: C, 62.38; H, 4.21; N, 8.87.

Bacterial Strains and Growth Conditions. *M. tuberculosis* $mc^2$7000, an unmarked version[33] of $mc^2$6030, was grown at 37 °C in Sauton's medium supplemented with 109 μM of pantothenic acid.

Drug Susceptibility Testing. The susceptibility of *M. tuberculosis* $mc^2$7000 to the various compounds was determined as reported previously.[34] In brief, Middlebrook 7H10 solid medium containing oleic-albumin-dextrose-catalase enrichment (OADC) and 109 μM of pantothenic acid was supplemented with increasing concentrations of the chemical analogues. Serial 10-fold dilutions of each actively growing culture were plated and incubated at 37 °C for 2−3 weeks. The MIC was defined as the minimum concentration required to inhibit 99% of the growth.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Structures and scanned (^{1}H, ^{13}C) NMR spectra for the compounds viz. **3c**, **3f**, **3g**, **8a**, **8f**, **8g**, **8h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

MIC, minimum inhibitory concentration; TB, tuberculosis; MDR, multidrug resistant; XDR, extensively drug resistant

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