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Synthesis and in vitro antitubercular activity of ferrocene-based hydrazones

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ABSTRACT

We report here the synthesis and in vitro antitubercular activity of a new series of ferrocenyl derivatives. The quinoline-ferrocene hybrid **5** exhibited significant activity (MIC = 2.5–5 μg/ml) against *Mycobacterium tuberculosis*. Results indicate that such hybrid compounds provide an efficient approach for future pharmacological developments to fight against tuberculosis. Moreover, the antimalarial drug candidate ferroquine (FQ, SSR97193) was also evaluated mainly because of its structural similarity. FQ was found to display moderate inhibitory activity (MIC = 10–15 μg/ml) against *M. tuberculosis*. This new drug may offer an interesting alternative in endemic area where malaria and tuberculosis coexist.

Mycobacterium tuberculosis (*Mtb*), the causative agent of tuberculosis (TB), is responsible for the death of almost two million people each year.[1–3] The emergence of multidrug resistance (MDR) in *Mtb* has complicated and prolonged the treatment which makes the discovery of new molecular scaffolds a priority.[4] Indeed, no new drugs have been developed against mycobacteria since the 1960s and there is an urgent need to develop new anti-TB therapeutics.[5] In the last two decades, ferrocene has shown great promise in the area of medicinal organometallic chemistry.[6–11] Based on its unique properties such as stability, aromaticity, low toxicity and redox activity, the ferrocene core is an attractive pharmacophore for drug design.[12,13] Ferrocenyl compounds have shown potential as both antibacterial[14] and antifungal agents.[15] On the basis of these observations and as part of our program in the search for new antiparasitic and antibacterial bioorganometallics, we have designed and synthesized a new series of ferrocene derivatives. In these structures, the ferrocene core is connected to heterocyclic moieties via a hydrazone linker. Herein, we report the synthesis of ferrocene-based hydrazones and the evaluation of their in vitro antitubercular activity.

The general synthesis towards ferrocene-based hydrazones **5**–**10** derivatives started with the synthesis of required hydrazines (Fig. 1) using the reported methodologies.[16–18]

The 7-chloro-4-quinolylhydrazine **1**, 1-aryl-4-hydrazino pyrazolo[3,4-*d*]pyrimidine **2**, 3-aryl-6-hydrazino-[1,2,4]-triazolo[4,3-*b*]pyridazines **3** and **4** (Fig. 1) were obtained from their respective chloro derivatives using hydrazine hydrate (64%) in ethanol under reflux at 80 °C.[16–18] The progress of the reaction was monitored by TLC and on completion the ethanol was removed under reduced pressure. The 1-aryl-4-chloro-pyrazolo[3,4-*d*]pyrimidine, 3-*p*-tolyl-6-chloro-[1,2,4]-triazolo[4,3-*b*]pyridazine, 3-pyridine-6-chloro-[1,2,4]-triazolo[4,3-*b*]pyridazine were prepared using reported procedures.[18] The appropriate ferrocene containing aldehydes were purchased from Sigma–Aldrich (Fig 1). Finally, the hydrazones were obtained by reaction between above mentioned hydrazines **1**–**4** and commercially available ferrocene containing aldehydes in absolute ethanol for 2–24 h (Scheme 1) at room temperature or reflux. The progress of the reaction was monitored by TLC and on completion the resulting mixture was concentrated under reduced pressure. The crude mixture was purified by silica-gel column chromatography using ethylacetate/hexane (2:1) and methanol/dichloromethane (1:9) as solvent systems which lead to pure derivatives of the target hydrazones **5**–**10** as orange or red solids, unoptimized yields: 2–34% (see Supplementary data).

The newly synthesized compounds **5**–**10** were tested for their in vitro antitubercular activity against *M. tuberculosis* mc^{2}7000 (see Supplementary data). The observed MIC are summarized in Table 1.

The quinoline-ferrocene hybrid **5** showed potent activity, in a concentration range comparable to the one of EMB while all the

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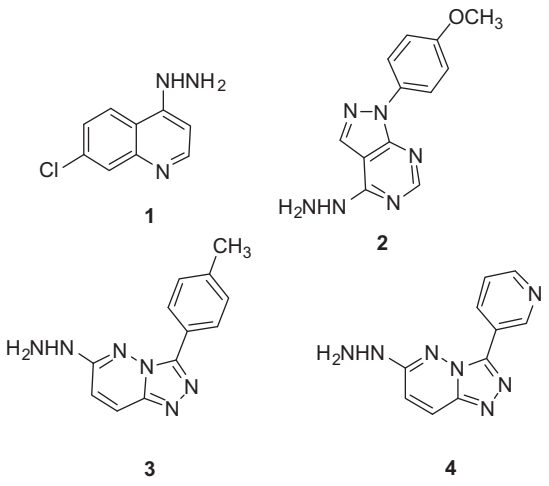


Figure 1. Starting hydrazines used in this study.

other compounds **6**–**10** failed to exhibit any activity to inhibit mycobacterial growth even at very high doses (Table 1). Introduction of a chloroethenyl substituent in the lateral side chain (**5** and **9**) severely compromised the activity of the molecules. The good anti-TB activity of **5** may be attributed to the presence of the quinoline ring. These results are consistent with a previous study where the quinoline ring was shown to confer anti-TB activity[16] and confirm that quinoline-based scaffolds are promising leads for new TB drug developments.

Based on these findings, we next evaluated the antimycobacterial activity of ferroquine (FQ, SSR97193, Fig. 2),[19] an antimalarial drug candidate because of its structural similarity to hybrid compound **5**. FQ is about to complete phase II clinical trials as a treatment for uncomplicated malaria. Unexpectedly, FQ also exhibited potent activity against *M. tuberculosis*, albeit its effect was more

Table 1
In vitro antimycobacterial activity of compounds **5**–**10** and FQ against *M. tuberculosis* mc^{2}7000

Compound	MIC[a] (μg/ml)
5	2.5–5
6	>100
7	>100
8	>100
9	>100
10	>100
FQ (SSR97193)	10–15
INH	0.1
EMB	1–2.5

[a] MIC_{99} was determined by dilution on solid agar medium 7H10 supplemented with OADC and pantothenic acid. INH, isoniazid; EMB, ethambutol.

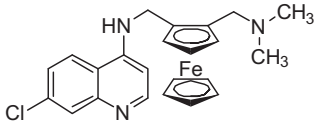
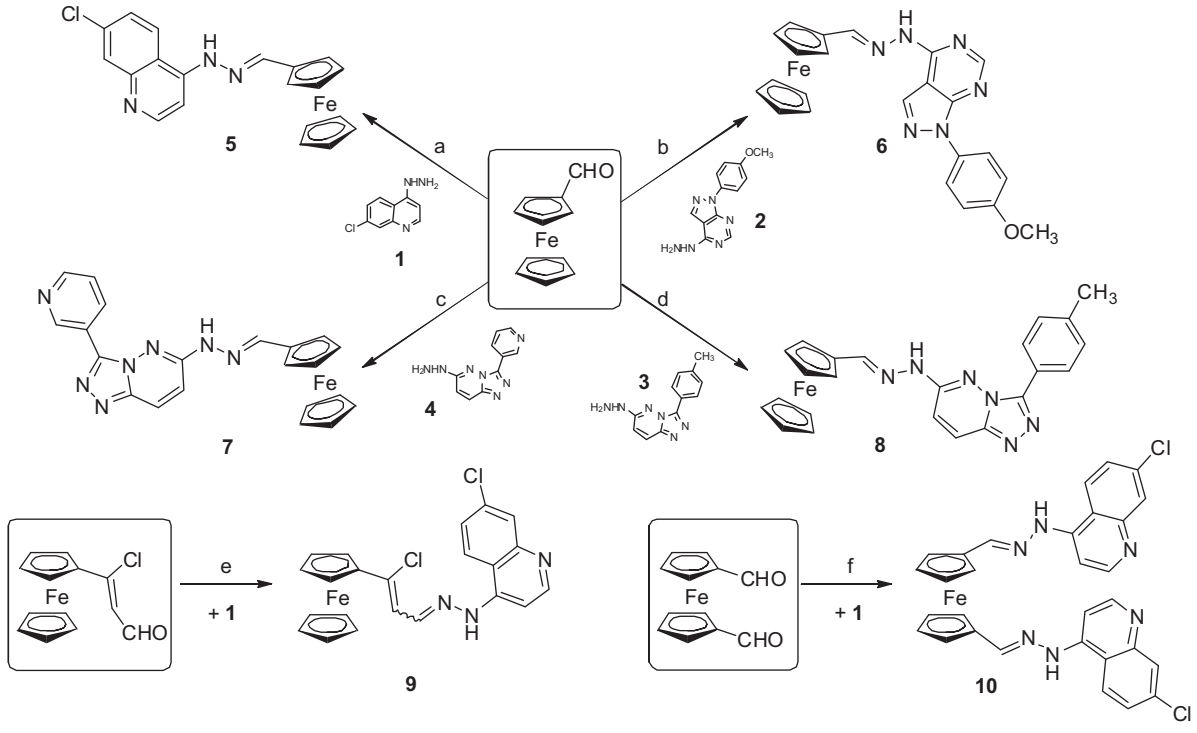


Figure 2. Chemical structure of FQ, SSR97193.

modest than that of compound **5** (Table 1). As malaria and TB are endemic in many areas of the world, this new drug may offer an interesting alternative for the simultaneous treatment of both *Plasmodium* and *Mycobacterium* in co-infected patients.

In conclusion, the present research study reports the successful synthesis and anti-TB activity of a new series of ferrocene-based hydrazones. In agreement with previous reports, the importance of the quinoline moiety in the antimycobacterial activity is also demonstrated in this study, with the ferrocenic-based chloroquinoline hydrazone **5** being the most active compound. Therefore, the



Scheme 1. Reagents and conditions: (a) ethanol, rt, 8 h; (b) ethanol, rt, 3 h; (c) ethanol, rt, 2 h; (d) ethanol, rt, 24 h; (e) ethanol, reflux, 2 h; (f) ethanol, rt, 24 h.

use of quinolines in combination with the ferrocenic moiety could provide a new basis for the design and synthesis of more efficient antitubercular agents. The activity exhibited by the antimalarial drug ferroquine (FQ, SSR97193)[19] also encourages further pharmacological evaluation of this drug in areas where both malaria and tuberculosis are endemic.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.03.082.

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