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Synthesis and antimycobacterial activity of ferrocenyl ethambutol analogues and ferrocenyl diamines

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Abstract—A new series of ferrocenyl diamino alcohols and diamines were synthesized and their inhibitory potencies were probed with *Mycobacterium tuberculosis*. Interestingly, ferrocenyl diamines **6a** and **b** display significant activities against *M. tuberculosis* H37Rv.

1. Introduction

Tuberculosis (TB) an infection of *Mycobacterium tuberculosis* is a contagious disease with high worldwide mortality.[1,2] Every year, millions of people die worldwide because of this epidemic disease and the problem is amplified by the apparent synergism with HIV.[3,4] First-line drugs, with superior efficacy and acceptable toxicity, used for treating infections caused by *M. tuberculosis* include isoniazid, rifampicin, ethambutol, streptomycin and pyrazinamide.

However, the increase of multidrug-resistant (MDR) strains of *M. tuberculosis*, indicates the need for new effective anti-tuberculosis drugs[5,6] and for alternative therapy regimens.[7,8]

Some years ago, a new strategy, based on incorporation of a ferrocenyl moiety in the side chain of chloroquine, was developed.[9] The presence of ferrocene remarkably enhanced the antimalarial activity of the synthetic compound.[10] Moreover, the stability and the lipophilic properties of the ferrocenyl moiety are of particular interest rendering such drugs compatible with almost any other. In continuation of our efforts to show the ability of ferrocene to enhance biological effect, we became interested in the synthesis of new antimycobacterial ferrocenyl ethambutol analogues. In this paper, we wish to report on the synthesis of a new series of ferrocenyl diamino alcohols and diamines and on the results of biologic activities against *M. tuberculosis* H37Rv.

2. Chemistry

The racemic ferrocenyl diamino alcohols **4a**–**c** were synthesized according to the reported procedure (Scheme 1). The dimethylamino group was first replaced by an acetoxy group by reaction of anhydride acetic on racemic 2-*N*-*N*-dimethylaminomethyl ferrocene carboxaldehyde **1**[11] in 89% yield. The resolution of planar chirality of compound **1** has not been realized. The saponification of the ester function of **2** was carried out in the presence of sodium hydroxide in methanol

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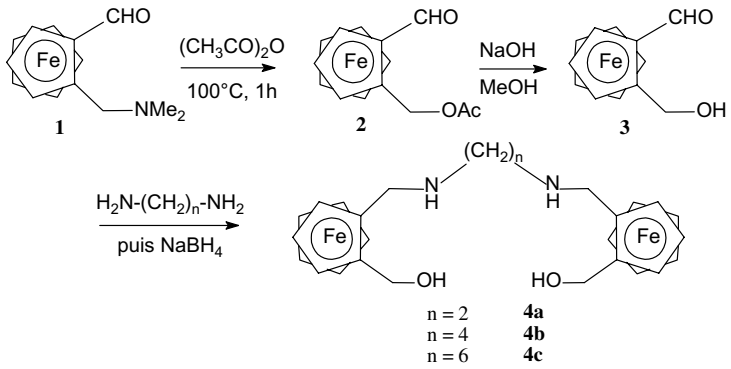
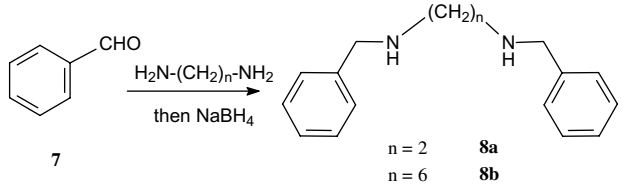


Scheme 1. Synthesis of ferrocenyl diamino alcohols **4a**–**c**.

to lead to **3** in 89% yield. The ferrocenyl amino alcohols were then obtained in two steps. First, hydroxy aldehyde **3** was reacted in CH_2Cl_2 with commercially available diamine giving the corresponding imines. Then, a reduction with sodium borohydride in methanol provided the amino alcohols **4a**,**b** and **c** in 42%, 66% and 88% overall yields, respectively. Only one of the enantiomer **4a**–**c** has been shown in Scheme 1.

The condensation of diamines with ferrocene carboxaldehyde **5** followed by reduction with $NaBH_4$ led to the ferrocenyl diamines **6a**,**b**,**c** and **d** in 76%, 54%, 77% and 46% global yields, respectively (Scheme 2).

Following the same procedure while starting from benzaldehyde **7**, the diamines **8a** and **b** were obtained in 69% and 84% yields, respectively (Scheme 3).



Scheme 3. Synthesis of diamines **8a** and **b**.

3. Antimycobacterial activity

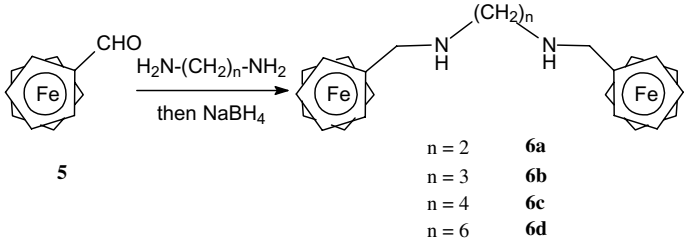
The antimycobacterial in vitro activity of ferrocenyl compounds **4a**–**c**, **6a**–**d** and **8a**–**b** for tuberculosis inhibition against *M. tuberculosis* H37Rv strain was carried out using the mycobacteria growth indicator tube system (MGIT) at a concentration of 2 μg/mL. The minimum inhibitory concentration (MIC, μg/mL) was detected by BACTEC 960. The MIC, defined at the lowest concentration of compound inhibiting 90% of the inoculum relative to controls, are summarized in Table 1.

Ferrocenyl diamino alcohols **4b** and **c** appeared to have low inhibitory antimycobacterial activity against drug-sensitive *M. tuberculosis* H37Rv strain.

Table 1. Antimycobacterial in vitro activity against *Mycobacterium tuberculosis* H37Rv

Compounds	MIC (μg/mL)
4a	ND
4b	>64
4c	>64
6a	8
6b	8
6c	32
6d	32
8a	>64
8b	>64
EBM	2

Surprisingly, the suppression of the hydroxy group in the diamines **6a**–**c** involves an increase of the antimycobacterial activity. Particularly, ferrocenyl diamines **6a** and **b** exhibited excellent inhibitory activity against *M. tuberculosis* H37Rv strain and produced MIC value of 8 μg/mL.[12] It is observed that increasing the carbon chain between both amino groups of the diamines induces a decrease of the antimycobacterial activity (compare **6a** and **d**). In recent studies, Barry III and Coll have



Scheme 2. Synthesis of ferrocenyl diamines **6a**–**d**.

also obtained equal or higher activities from [1,2]-diamines.[13]

We can then confirm the importance of the introduction of the ferrocene in the diamine structure regarding the in vitro antimycobacterial activity. Indeed, the replacement of the ferrocenyl group with the phenyl group results in complete loss of the anti-tuberculosis activity (compare **6a** with **8a** and **6d** with **8b**).

4. Conclusion

In the present study we have presented the simple and efficient synthesis of new ferrocenyl diamino alcohols and diamines and their promising anti-tuberculosis activity against *M. tuberculosis* H37Rv strain. Further studies to acquire more information about structure–activity are in progress in our laboratory.

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