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Synthesis and antitubercular activity of ferrocenyl diaminoalcohols and diamines

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ABSTRACT

A total of 21 ferrocenyl and benzyl diaminoalcohols and diamines were synthesized and evaluated against *Mycobacterium tuberculosis* H37Rv. Interestingly, ferrocenyl diamines exhibit better activities than ferrocenyl diaminoalcohols.

1. Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, still remains the leading cause of worldwide death among infectious diseases.[1] Two billion people are infected with latent TB and are at risk for developing the active disease, and annually, approximately eight million of these infected people develop active TB more. TB kills nearly two million people over the world every year. Even though improved methods of prevention, detection, diagnosis and treatment have greatly reduced the number of people who contract the disease and unfortunately die from it, the emergence of multidrug-resistant (MDR) strains and the global human immunodeficiency virus (HIV) pandemic have amplified the incidence of TB. Currently, TB chemotherapy is composed by a cocktail of the first-line drugs, isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB), given for six months. The increasing problem of MDR-TB has focused attention on developing new drugs that are not only active against drug resistant TB, but also shorten the lengthy therapy. Consequently, there is urgent need and significant interest in developing new TB drugs.[2–4]

Despite its modest efficiency against *M. tuberculosis*, ethambutol (EMB) (Fig. 1) is still a first-line drug used against TB in part because its very low toxicity and its chemical simplicity.[5] Studies concerning the structural modification of EMB have focused on the diamine or diaminoalcohol analogues with enhanced efficiency compared to EMB.[6–11] Among diamines, compounds SQ 109, SQ 775 and SQ 786 (Fig. 1) exhibit enhanced activities in comparison to EMB.[7,8]

The use of metal complexes capable of enhancing the activity of biological compounds has become a relevant strategy of research in both communities of organometallic chemists and biologists.[12] Ferroquine (SSR97193), resulting from the incorporation of a metallocenic moiety into chloroquine, proved to be a new effective drug with a powerful antimalarial activity in vitro and in vivo.[13,14] In particular, the high lipophilicity and electrochemical behaviour (redox potential of the ferrocene/ferrocinium couple, $E_0 = +0.400$V vs saturated calomel electrode) of ferrocene render it very attractive for designing antimalarial drugs.[15] This strategy, which consists of incorporate a ferrocenyl moiety into a 'standard' drug offers new possibilities in therapeutic applications and reversal of drug resistances.[16–18]

In a preliminary communication, we reported the synthesis of ferrocenyl diamines and the evaluation of their antitubercular activity.[19] Herein we describe the full details of our investigations. A strategy based on the modification of ethambutol is presented here: insertion of ferrocene between the two amine functions, insertion of ferrocene between alcohol and amine, replacement of alcohol by ferrocene: synthesis of diamines (Fig. 2).

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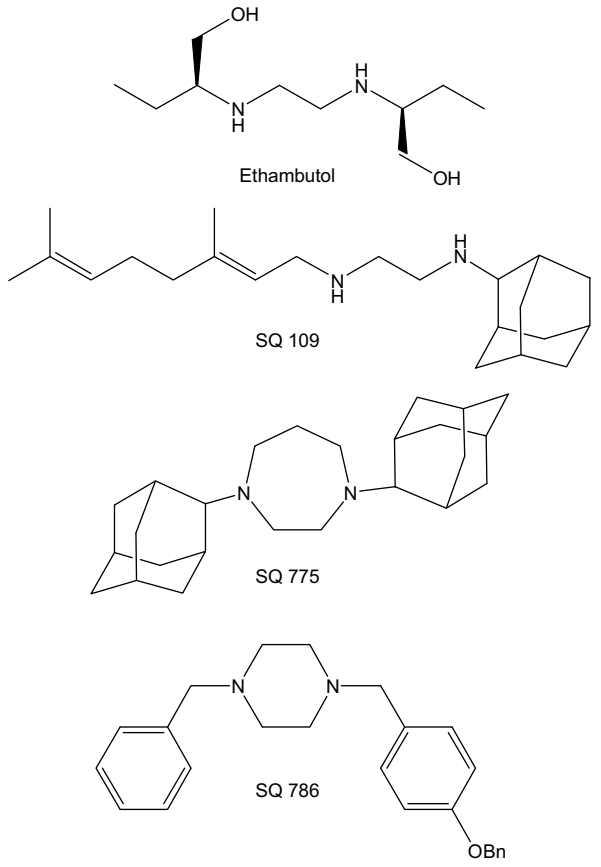


Figure 1. Structure of ethambutol (EMB) and three analogues.

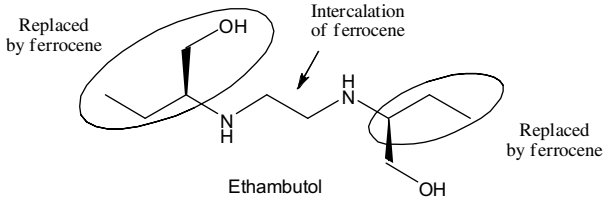


Figure 2. Chemical modifications of EMB.

2. Results and discussion

2.1. Synthesis of ferrocenyl amino alcohols

The racemic ferrocenyl diamino alcohols **4**–**6** were synthesized according to the reported procedure (Scheme 1). Racemic 2-*N*,*N*-dimethylaminomethylferrocenecarbox-aldehyde **1** was first reacted with acetic anhydride to give **2** in 89% yield. The saponification of ester **2** was carried out in the presence of sodium hydroxide in methanol providing **3** in 89% yield after work-up.[20]

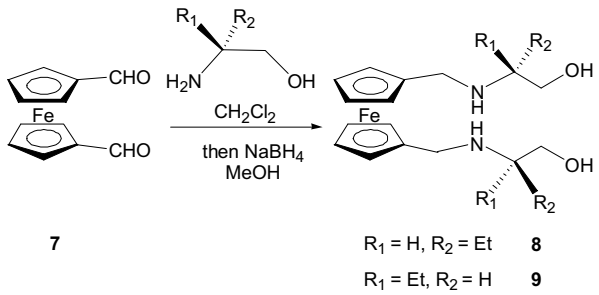
The ferrocenyl amino alcohols were then obtained in two steps. First, the hydroxy aldehyde **3** was reacted in CH_2Cl_2 with commercially available diamines giving the corresponding imines. Then, a reduction with sodium borohydride in methanol provided the amino alcohols **4**, **5** and **6** in 42%, 66% and 88% overall yields, respectively. Compounds **4**–**6** were obtained as mixtures of diastereomers. To simplify, only the meso form of **4**–**6** has been represented on Scheme 1.

Ferrocene-1,1′-dicarboxaldehyde **7** was reacted in CH_2Cl_2 with commercially available (*R*)-(−) and (*S*)-(+) 2-amino-1-butanol in the presence of molecular sieves providing the corresponding imines. Then, a reduction of the crude reaction mixtures with sodium borohydride in methanol provided respectively the amino alcohols **8** and **9** in 76–85% overall yields after work-up (Scheme 2). Following the same procedure from ferrocene-1,2-dicarboxaldehyde **10**, the amino alcohols **11** and **12** were obtained in 70–88% overall yields (Scheme 3).

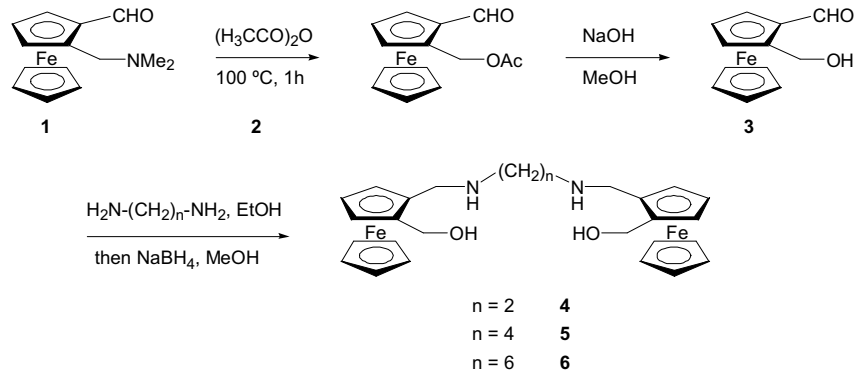
2.2. Synthesis of ferrocenyl and benzyl diamines

To increase the structural diversity of EMB analogues and to assess the influence of a modified linker on the activity of structurally diverse diamines against *M. tuberculosis*, we prepared derivatives incorporating a series of ferrocenyl and alkyl substituents in the spacer between the two amino alcohol residues.

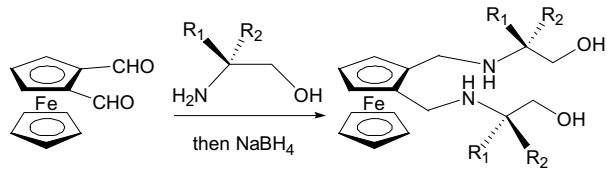
The condensation of diamines with ferrocene carboxaldehyde, ferrocene-1,1′-dicarboxaldehyde **7**, ferrocene-1,2-dicarboxaldehyde **10** or benzaldehyde in methanol followed by reduction with $NaBH_4$ led to the ferrocenyl diamines **13**–**23** or benzyl diamines **24**–**26** in 25–84% global yields (Table 1).[21–23]



Scheme 2. Synthesis of ferrocenyl-1,1'-diaminoalcohols.



Scheme 1. Synthesis of ferrocenyl diamino alcohols **4**–**6**.



10 $R_1 = H, R_2 = Et$ **11**

$R_1 = Et, R_2 = H$ **12**

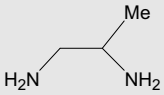
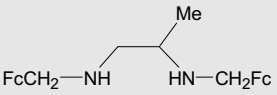
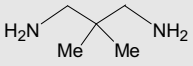
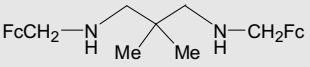
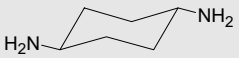
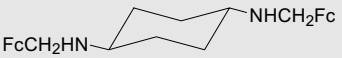
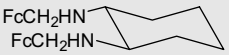
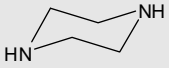
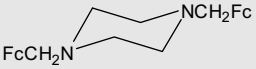
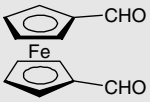
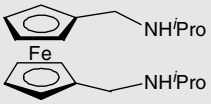
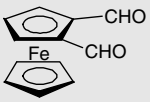
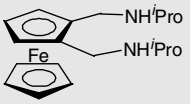
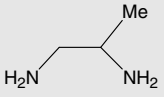
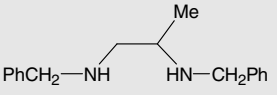
Scheme 3. Synthesis of ferrocenyl-1,2-diaminoalcohols.

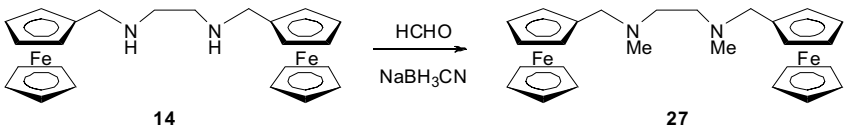
Tertiary diamine **27** was obtained by reductive *N*-methylation of **13** in the presence of formaldehyde and $NaBH_3CN$ (Scheme 4) in 16% yield after purification.

2.3. Biological activity

The in vitro antimycobacterial activity of ferrocenyl diaminoalcohols and diamines 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 de-

Table 1
Structure and yields of ferrocenyl (Fc = ferrocene) and benzyldiamines

Compound	Aldehyde	Amine or diamine	Ferrocenyl or benzyl diamine	Yield (%)
13	FcCHO	$H_2N(CH_2)_2NH_2$	$FcCH_2NH(CH_2)_2NHCH_2Fc$	76
14	FcCHO	$H_2N(CH_2)_3NH_2$	$FcCH_2NH(CH_2)_3NHCH_2Fc$	54
15	FcCHO	$H_2N(CH_2)_4NH_2$	$FcCH_2NH(CH_2)_4NHCH_2Fc$	77
16	FcCHO	$H_2N(CH_2)_6NH_2$	$FcCH_2NH(CH_2)_6NHCH_2Fc$	46
17	FcCHO			25
18	FcCHO			77
19	FcCHO			41
20	FcCHO			48
21	FcCHO			62
22		H_2N^iPro		48
23		H_2N^iPro		72
24	PhCHO	$H_2N(CH_2)_2NH_2$	$PhCH_2NH(CH_2)_2NHCH_2Ph$	69
25	PhCHO	$H_2N(CH_2)_6NH_2$	$PhCH_2NH(CH_2)_6NHCH_2Ph$	84
26	PhCHO			67



14 27

Scheme 4. Synthesis of tertiary diamine.

tected by BACTEC 960. The MIC, defined at the lowest concentration of compound inhibiting 90% of the inoculum relative controls, is summarized in Table 2.

It appeared that compounds with ferrocenyl groups **13** and **14** having only two or three carbon atoms spacer between the two amino functions are more active than the analogue **24** with two phenyl groups. This proves the beneficial effect of the presence of ferrocenyl residue on EMB analogues. We observed also that the substitution of the spacer in **17** or the amine in **27** affects the activities of these analogues of compound **13**.

It would have been interesting to compare the activity of the ferrocenyl piperazine **21** with SQ786 (Fig. 1). Unfortunately, the low solubility of **21** did not allow the evaluation of the biological activity.

A weak activity was obtained in the presence of cyclohexyl as the spacer between the two amines in **19** and **20**.

No antimycobacterial activity was observed when the ferrocene was placed between the two amines (compounds **22** and **23**). Moreover, it appears that the presence of the hydroxymethyl group in ferrocenyl diaminoalcohols **6**, **8**–**9** and **11**–**12** inhibited the biological activity (MIC > 64).

3. Conclusion

In conclusion we have synthesized and evaluated a series of ferrocenyl diamines and diaminoalcohols as inhibitors of *M. tuberculosis* H37Rv. This study has revealed that the presence of a ferrocenyl moiety in the structure of diamines is essential for a good antimycobacterial activity. The best activity was obtained for ferrocenyl diamines having only a two or three carbon atoms spacer between the two amino functions. Other studies are currently underway in our laboratories to better understand the importance of the presence of a ferrocenyl unit on TB drugs.

Table 2
Antimycobacterial in vitro activity against *Mycobacterium tuberculosis* H37Rv

Compound	MIC H37Rv (μg/mL)
4	ND[a]
5	32
6	>64
8	>64
9	>64
11	>64
12	>64
13	8
14	8
15	32
16	32
17	16
18	64
19	64
20	32
21	ND
22	64
23	64
24	>64
25	>64
26	>64
27	64
EBM	2

[a] ND, not determinated. Compounds **4** and **21** were not completely dissolved in MeOH and DMSO.

4. Experimental

4.1. General methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer using tetramethylsilane (TMS) as the internal standard and $CDCl_3$, MeOH-d_4 or DMSO-d_6 as the solvents. MS-MALDI TOF spectra were obtained using a Vision 2000 time-of-flight instrument (Finnigan MAT, Bremen, Germany) equipped with a nitrogen laser operating at wavelength of 337 nm. The matrix used was trihydroxyacetophenone (thap). Thin layer chromatography (TLC) was carried out on aluminium-baked Macherey-Nagel silica gel 60. Column chromatography was performed on silica gel (35–70 mesh). Melting points were determined on a Kofler apparatus and are uncorrected.

4.2. 2-(Acetoxymethylferrocene)carboxaldehyde 2

A mixture of 2-(*N*,*N*-dimethylaminomethylferrocene) carboxaldehyde **1** (206 mg, 0.75 mmol) and acetic anhydride (2.5 mmol) was stirred at 100 °C for 10 h. The solution was allowed to room temperature. After addition of CH_2Cl_2 (10 mL), the organic layer was washed by aqueous solution of sodium hydroxide (0.5 N). The solvent was evaporated from the filtrate under reduced pressure. After purification by column chromatography (eluent: ethyl acetate), the ester **2** is obtained as a red oil (89%).[20] ^{1}H NMR ($CDCl_3$) δ 10.05 (s, 1H, CHO), 5.17 (m, 2H, CH_2O), 4.79 (m, 1H, Cp), 4.68 (m, 1H, Cp), 4.57 (m, 1H, Cp), 4.26 (s, 5H, Cp′), 2.04 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 193.3, 170.8, 83.4, 77.6, 75.4, 72.3, 71.6, 70.2, 60.6, 20.9. MS (*m/z*): 325 (M^++K), 309 (M^++Na), 286 (M^+).

4.3. 2-(Hydroxymethylferrocene)carboxaldehyde 3

A mixture of 2-(acetoxymethylferrocene)carboxaldehyde **2** (136 mg, 0.475 mmol) and sodium hydroxide 1 N (6 mL) in MeOH (14 mL) was stirred at room temperature. After 1 h, the solvent is evaporated under reduced pressure. Dichloromethane (20 mL) was added to the residue. The organic mixture was washed by water and the organic layer was dried over Na_2SO_4. After evaporation under reduced pressure, the oil was purified by column chromatography (eluent: CH_2Cl_2/MeOH: 15–1) to give **3** as red crystals (89%).[20] Mp 92 °C. ^{1}H NMR ($CDCl_3$) δ 9.92 (s, 1H, CHO), 4.70 (d, 1H, Cp, J = 2.7 Hz), 4.67 (m, 1H, Cp), 4.53 (m, 2H, CH_2O), 4.47 (m, 1H, Cp), 4.32 (s, 5H, Cp′). ^{13}C NMR ($CDCl_3$) δ 196.2, 90.5, 74.9, 73.3, 71.7, 70.3, 59.4. MS (*m/z*): 283 (M^++K), 267 (M^++Na), 244 (M^+).

4.4. General procedure for the synthesis of ferrocenyl amino alcohols 4–6

A mixture of 2-(hydroxymethylferrocene)carboxaldehyde **3** (810 mg, 3.32 mmol) and the appropriate diamine (1.6 mmol) in anhydrous ethanol (50 mL) containing molecular sieves (4 A, 5 g) was stirred at room temperature. After 6 h, the mixture was filtered through Celite 545. The solvent was evaporated from the filtrate under reduced pressure. The residue was dissolved in MeOH (30 mL) and $NaBH_4$ (20 mg, 0.5 mmol) was added in small portions. The mixture was stirred at room temperature for 1 h, hydrolysed by addition of a saturated solution of NH_4Cl (50 mL) and extracted

with CH_2Cl_2 (3 × 30 mL). An aqueous solution of HCl (1 N, 40 mL) was added to the organic layer. The mixture was extracted by diethyl ether (3 × 100 mL). Sodium carbonate was then added to the aqueous layer until neutralisation. The product was then extracted by CH_2Cl_2 (3 × 100 mL). The organic layer was dried over sodium sulfate before removing the solvent under reduced pressure. The oil was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 88:2:10).

4.5. 1,2-Bis[2-(hydroxymethyl)ferrocenylmethylamino]ethane 4

Following the general procedure starting from 2-(hydroxymethylferrocene)carboxaldehyde **3** (810 mg, 3.32 mmol) and 1,2-ethylenediamine (99.5 mg, 1.66 mmol), 1,2-bis[2-(hydroxymethyl)ferrocenylmethylamino]ethane **4** was obtained as yellow crystals (360 mg, 42%). Mp 90 °C. ^{1}H NMR ($CDCl_3$) δ 4.62 (d, 2H, CH_2O, J = 12.2 Hz), 4.15 (m, 2H, Cp), 4.15 (d, 2H, CH_2O, J = 12.2 Hz), 4.07 (m, 2H, Cp), 4.04 (s, 10H, Cp′), 3.99 (m, 2H, Cp), 3.78 (d, 2H, $FcCH_2$, J = 12.5 Hz), 3.36 (d, 2H, $FcCH_2$, J = 12.5 Hz), 2.65 (s, 4H, CH_2N). ^{13}C NMR ($CDCl_3$) δ 87.1, 84.9, 70.3, 69.7, 68.8, 65.8, 59.6, 48.6, 47.7. MS (*m/z*): 555 $(M+K)^+$, 541, 539 $(M+Na)^+$, 527, 517 $(MH)^+$. Anal. Calcd for $C_{26}H_{32}Fe_2N_2O_2$: C, 60.49; H, 6.25; N, 5.43. Found: C, 60.82; H, 6.36; N, 5.62.

4.6. 1,2-Bis[2-(hydroxymethyl)ferrocenylmethylamino]butane 5

Following the general procedure starting from 2-(hydroxymethylferrocene)carboxaldehyde **3** (800 mg, 3.28 mmol) and 1,4-diaminobutane (131 mg, 1.49 mmol), 1,2-bis[2-(hydroxymethyl)ferrocenylmethylamino]butane **5** was obtained as yellow crystals (535 mg, 66%). Mp decomposition before fusion. ^{1}H NMR ($CDCl_3$) δ 4.68 (d, 2H, CH_2O, J = 12.4 Hz), 4.18 (d, 2H, CH_2O, J = 12.4 Hz), 4.17 (m, 2H, Cp), 4.10 (m, 2H, Cp), 4.07 (s, 10H, Cp′), 4.01 (m, 2H, Cp), 3.81 (d, 2H, CH_2N, J = 12.4 Hz), 3.79 (d, 2H, CH_2N, J = 12.4 Hz), 2.57 (t, 4H, CH_2N, J = 7.1 Hz), 1.45 (t, 4H, CH_2, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 87.4, 84.9, 70.2, 69.7, 68.8, 65.6, 59.7, 48.5, 47.8, 27.2. MS (*m/z*): 583 $(M^+$+K), 567 $(M^+$+Na), 545 (MH^+), 544 (M^+). Anal. Calcd for $C_{28}H_{36}Fe_2N_2O_2$: C, 61.79; H, 6.67; N, 5.15. Found: C, 61.43; H, 6.33; N, 5.03.

4.7. 1,2-Bis[2-(hydroxymethyl)ferrocenylmethylamino]hexane 6

Following the general procedure starting from 2-(hydroxymethylferrocene)carboxaldehyde **3** (864 mg, 3.54 mmol) and 1,6-diaminohexane (187 mg, 1.61 mmol), 1,2-bis[2-(hydroxymethyl)ferrocenylmethylamino]hexane **6** was obtained as yellow crystals (810 mg, 88%). Mp 106 °C. ^{1}H NMR ($CDCl_3$) δ 4.69 (d, 2H, CH_2O, J = 12.3 Hz), 4.15 (d, 2H, CH_2O, J = 12.3 Hz), 4.14 (m, 2H, Cp), 4.09 (m, 2H, Cp), 4.07 (s, 10H, Cp′), 3.99 (m, 2H, Cp), 3.78 (d, 2H, $FcCH_2$, J = 11.3 Hz), 3.44 (d, 2H, $FcCH_2$, J = 11.3 Hz), 2.58 (t, 4H, CH_2N, J = 7.1 Hz), 1.43–1.41 (m, 4H, CH_2), 1.28–1.27 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$) δ 87.6, 85.3, 70.2, 69.6, 68.6, 65.4, 59.8, 48.8, 47.9, 29.5, 26.9. MS (*m/z*): 611 $(M^+$+K), 595 $(M^+$+Na), 573 (MH^+), 572 (M^+). Anal. Calcd for $C_{30}H_{40}Fe_2N_2O_2$: C, 62.96; H, 7.04; N, 4.89. Found: C, 62.48; H, 6.85; N, 4.62.

4.8. General procedure for the synthesis of ferrocenyl amino alcohols 8–9 and 11–12

A mixture of ferrocene-1,1′-dicarboxaldehyde **7** or ferrocene-1,2-dicarboxaldehyde **10** (200 mg, 0.83 mmol) and the appropriate amino alcohol (2.5 mmol) in anhydrous CH_2Cl_2 (50 mL) containing molecular sieves (4 A, 5 g) was stirred under reflux for 10 h. The mixture was filtered through Celite 545. The solvent was evaporated from the filtrate under reduced pressure. The residue was dissolved in MeOH (30 mL) and $NaBH_4$ (0.15 g, 4.2 mmol) was added in small portions. The mixture was stirred at room temperature for 1 h, hydrolysed by addition of a saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The solvent was removed from the combined organic layers and the residue purified by column chromatography (petroleum ether/diethyl ether/triethyl-amine = 80:10:10).

4.9. (*R*,*R*)-Bis [*N*-2-(1-hydroxy)butyl]-1,1′-ferrocenylmethyl diamine 8

Following the general procedure starting from ferrocene-1,1′-dicarboxaldehyde **7** (200 mg, 0.83 mmol) and (*R*)-(−)-2-amino-1-butanol (221 mg, 2.5 mmol), (*R*,*R*)-bis[*N*-2-(1-hydroxy)butyl]-1,1′-ferrocenylmethyldiamine **8** was obtained as yellow oil (273 mg, 85%). $[\alpha]_D^2$0 −6 (*c* 0.36, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.23 (m, 2H, Cp), 4.14 (m, 2H, Cp), 4.10 (m, 4H, Cp), 3.68 (d, 2H, CH_2N, J = 11.0 Hz), 3.51 (m, 2H, CH_2O), 3.36 (d, 2H, CH_2N, 11,0 Hz), 3.29 (m, 2H, CH_2O), 2.63 (m, 2H, CH), 1.52 (m, 2H, CH_2), 1.36 (m, 2H, CH_2), 0.91 (t, 6H, CH_3, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 87.9, 68.6, 68.2, 68.1, 67.9, 62.9, 60.7, 45.7, 24.0, 10.5. MS (*m/z*): 427 $(M^+$+K), 411 $(M^+$+Na), 389 (MH^+). Anal. Calcd for $C_{20}H_{32}FeN_2O_2$: C, 61.86; H, 8.31; N, 7.21. Found: C, 61.42; H, 8.03; N, 7.34.

4.10. (*S*,*S*)-Bis [*N*-2-(1-hydroxy)butyl]-1,1′-ferrocenylmethyl diamine 9

Following the general procedure starting from ferrocene-1,1′-dicarboxaldehyde **7** (150 mg, 0.62 mmol) and (*S*)-(+)-2-amino-1-butanol (154 mg, 1.7 mmol), (*S*,*S*)-bis[*N*-2-(1-hydroxy)butyl]-1,1′-ferrocenylmethyldiamine **9** was obtained as yellow oil (182 mg, 76%). $[\alpha]_D^2$0 6 (*c* 0.36, $CHCl_3$).

4.11. (*R*,*R*)-Bis [*N*-2-(1-hydroxy)butyl]-1,2-ferrocenylmethyl diamine 11

Following the general procedure starting from ferrocene-1,2-dicarboxaldehyde **10** (223 mg, 0.84 mmol) and (*R*)-(−)-2-amino-1-butanol (245 mg, 2.75 mmol), (*R*,*R*)-bis[*N*-2-(1-hydroxy)butyl]-1,2-ferrocenylmethyldiamine **11** was obtained as yellow oil (286 mg, 88%). $[\alpha]_D^2$0 −62 (*c* 0.81, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.16 (m, 1H, Cp), 4.14 (m, 1H, Cp), 4.05 (s, 5H, Cp′), 4.02 (m, 1H, Cp), 3.93 (d, 1H, CH_2N, J = 12.5 Hz), 3.67 (d, 1H, CH_2N, J = 12.9 Hz), 3.57 (d, 1H, CH_2N, J = 12.9 Hz), 3.45 (d, 1H, CH_2N, J = 12.5 Hz), 3.37 (m, 4H, CH_2O), 2.63 (m, 1H, CH), 2.47 (m, 1H, CH), 1.44–1.42 (m, 4H, CH_2), 0.91 (t, 6H, CH_3, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 85.1, 84.6, 70.5, 69.9, 69.0, 66.4, 63.2, 63.0, 61.0, 59.7, 44.9, 24.2, 23.5, 24.2, 23.5, 10.6, 10.5. MS (*m/z*): 427 $(M^+$+K), 411 $(M^+$+Na), 389 (MH^+). Anal. Calcd for $C_{20}H_{32}FeN_2O_2$: C, 61.86; H, 8.31; N, 7.21. Found: C, 62.21; H, 8.12; N, 7.48.

4.12. (*S*,*S*)- Bis [*N*-2-(1-hydroxy)butyl]-1,2-ferrocenylmethyl diamine 12

Following the general procedure starting from ferrocene-1,2-dicarboxaldehyde **10** (314 mg, 1.18 mmol) and (*S*)-(+)-2-amino-1-butanol (336 mg, 3.77 mmol), (*S*,*S*)-bis[*N*-2-(1-hydroxy)butyl]-1,2-ferrocenylmethyldiamine **12** was obtained as yellow oil (279 mg, 61%). $[\alpha]_D^2$0 65 (*c* 0.72, $CHCl_3$).

4.13. General procedure for the synthesis of ferrocenyl diamines

A mixture of ferrocenecarboxaldehyde (4.50 mmol) and the appropriate diamine (2.2 mmol) in anhydrous MeOH (50 mL) was stirred at room temperature. After 4 h, $NaBH_4$ (4.2 mmol) was

added in small portions. The mixture was stirred at room temperature for 1 h, hydrolysed by addition of a saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). An aqueous solution of HCl (1 N, 40 mL) was added to the organic layer. The mixture was extracted by diethyl ether (3 × 100 mL). Sodium carbonate was then added to the aqueous layer until neutralisation. The product was then extracted by CH_2Cl_2 (3 × 100 mL). The organic layer was dried over sodium sulfate before removing the solvent under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH/Et_3N = 19:1:1).

4.14. 1,2-Diamino-*N,N′*-di(ferrocenylmethyl)ethane 13

Following the general procedure starting from ferrocenecarboxaldehyde (1.268 g, 5.92 mmol) and 1,2-ethylenediamine (0.2 mL, 2.96 mmol), 1,2-diamino-*N,N′*-di(ferrocenylmethyl)ethane **13** was obtained as yellow oil (1.02 g, 76%).[21,22] ^{1}H NMR ($CDCl_3$) δ *4.19–4.17* (4H, m, Cp), 4.12 (10H, s, Cp′), 4.11–4.09 (4H, m, Cp), 3.49 (4H, s, Fc-CH_2-N), 2.74 (4H, s, CH_2–N). ^{13}C NMR ($CDCl_3$) δ 86.7, 68.7, 68.6, 48.7, 48.6. MS (*m*/*z*) 456 (M^+).

4.15. 1,3-Diamino-*N,N′*-di(ferrocenylmethyl)propane 14

Following the general procedure starting from ferrocenecarboxaldehyde (1.268 g, 5.92 mmol) and 1,3-propanediamine (0.25 mL, 2.96 mmol), 1,3-diamino-*N,N′*-di(ferrocenylmethyl)propane **14** was obtained as yellow oil (751 mg, 54%).[23] ^{1}H NMR ($CDCl_3$) δ *4.18–4.16* (4H, m, Cp), 4.11 (10H, s, Cp′), 4.10–4.08 (4H, m, Cp), 3.49 (4H, s, Fc-CH_2–N), 2.67 (4H, t, CH_2–N, *J* = 6.3 Hz), 1.67 (4H, q, CH_2, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$) δ 85.6, 68.7, 68.5, 48.6, 47.7, 39.2. Anal. Calcd for $C_{25}H_{30}Fe_2N_2$: C, 63.90; H, 6.40; N, 6.00. Found: C, 63.70; H, 6.20; N, 5.80.

4.16. 1,4-Diamino-*N,N′*-di(ferrocenylmethyl)butane 15

Following the general procedure starting from ferrocenecarboxaldehyde (1.40 g, 6.54 mmol) and 1,4-butanediamine (268 mg, 3.04 mmol), 1,4-diamino-*N,N′*-di(ferrocenylmethyl)butane **15** was obtained as yellow crystals (1.13 g, 77%). Mp 98 °C. ^{1}H NMR ($CDCl_3$) δ *4.15–4.14* (4H, m, Cp), 4.11 (10H, s, Cp′), 4.11–4.09 (4H, m, Cp), 3.56 (4H, s, Fc-CH_2–N), 2.63 (4H, t, CH_2–N, *J* = 6.1 Hz), 1.61–1.56 (4H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 86.1, 68.7, 68.5, 48.7, 48.2, 27.6. MS (*m*/*z*) 484 (M^+). Anal. Calcd for $C_{26}H_{32}Fe_2N_2$: C, 64.49; H, 6.66; N, 5.78. Found: C, 63.90; H, 6.87; N, 5.56.

4.17. 1,6-Diamino-*N,N′*-di(ferrocenylmethyl)hexane 16

Following the general procedure starting from ferrocenecarboxaldehyde (1.46 g, 6.82 mmol) and 1,6-hexanediamine (344 mg, 2.96 mmol), 1,6-diamino-*N,N′*-di(ferrocenylmethyl)hexane **16** was obtained as yellow crystals (697 mg, 46%). ^{1}H NMR ($CDCl_3$) δ *4.19–4.17* (4H, m, Cp), 4.11 (10H, s, Cp′), 4.11–4.09 (4H, m, Cp), 3.53 (4H, s, Fc-CH_2–N), 2.61 (4H, t, CH_2–N, *J* = 7.2 Hz), 1.53–1.49 (4H, m, –CH_2–), 1.35–1.30 (4H, m, –CH_2–). ^{13}C NMR ($CDCl_3$) δ 87.1, 68.5, 68.4, 49.7, 49.1, 30.1, 27.4. MS (*m*/*z*) 512 (M^+). Anal. Calcd for $C_{28}H_{36}Fe_2N_2$: C, 65.65; H, 7.08; N, 5.47. Found: C, 63.98; H, 7.22; N, 5.61.

4.18. 1,2-Diamino-*N,N′*-di(ferrocenylmethyl)propane 17

Following the general procedure starting from ferrocenecarboxaldehyde (1.479 g, 6.91 mmol) and 1,2-propanediamine (0.250 mL, 2.93 mmol), 1,2-diamino-*N,N′*-di(ferrocenylmethyl)propane **17** was obtained as yellow crystals (344 mg, 25%). Mp 188 °C. ^{1}H NMR ($CDCl_3$) δ 4.19 (2H, m, Cp), 4.14 (2H, m, Cp), 4.12 (5H, s, Cp′), 4.09 (5H, s, Cp′), 4.02 (4H, m, Cp), 3.60 (1H, d, Fc-CH_2–N–C*, *J* = 12.9 Hz), 3.40 (2H, s, Fc-CH_2–N), 3.34 (1H, d, Cp-CH_2–N–C*, *J* = 12.9 Hz), 2.76 (1H, m, CH–N), 2.64 (1H, dd, N–CH_2, *J* = 3.9 and 11.7 Hz,), 2.47 (1H, dd, N–CH_2, *J* = 8.8 and 11.7 Hz), 1.05 (3H, d, *J* = 6.4 Hz, –CH_3). ^{13}C NMR ($CDCl_3$) δ 87.2, 86.9, 68.4, 67.8, 67.7, 55.0, 52.1, 48.8, 46.27, 18.56. MS (*m*/*z*) 470 (M^+). Anal. Calcd for $C_{26}H_{32}Fe_2N_2$: C, 63.86; H, 6.43; N, 5.96. Found: C, 63.93; H, 6.77; N, 5.69.

4.19. 1,3-Diamino-*N,N′*-(diferrocenylmethyl)-2,2-dimethylpropane 18

Following the general procedure starting from ferrocenecarboxaldehyde (1.40 g, 6.54 mmol) and 1,3-diamino-2,2-dimethylpropane (0.337 mL, 2.8 mmol), 1,3-diamino-*N,N′*-di(ferrocenylmethyl)-2,2-dimethylpropane **18** was obtained as yellow oil (1.07 g, 77%). ^{1}H NMR ($CDCl_3$) δ *4.18–4.16* (4H, m, Cp), 4.13–4.10 (4H, m, Cp), 4.12 (10H, s, Cp′), 3.49 (4H, s, Cp-CH_2–N), 2.52 (4H, s, CH_2–N), 0.96 (6H, s, CH_3). ^{13}C NMR ($CDCl_3$) δ 85.1, 68.8, 68.6, 68.2, 59.2, 49.3, 34.0, 24.8. MS (*m*/*z*) 498 (M^+). Anal. Calcd for $C_{27}H_{34}Fe_2N_2$: C, 65.08; H, 6.88; N, 5.62. Found: C, 64.80; H, 6.75; N, 5.76.

4.20. *trans*-1,4-Diamino-*N,N′*-(diferrocenylmethyl)cyclohexane 19

Following the general procedure starting from ferrocenecarboxaldehyde (1.40 g, 6.54 mmol) and *trans -1,4-diaminocyclohexane* (354 mg, 3.11 mmol), 1,4-diamino-*N,N′*-(diferrocenylmethyl)cyclohexane **19** was obtained as yellow crystals (0.65 g, 41%). Mp 110 °C. ^{1}H NMR ($CDCl_3$) δ *4.18–4.16* (4H, m, Cp), 4.11–4.08 (4H, m, Cp), 4.09 (10H, s, Cp′), 3.52 (4H, s, CH_2–N), 2,45 (2H, m, CH), 1.92–1.88 (4H, m, CH_2), 1.29 (2H, m, CH_2), 1.18 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 87.3, 68.4, 68.3, 67.7, 56.0, 50.5, 46.4, 35.3, 32.1. MS (*m*/*z*) 510 (M^+). Anal. Calcd for $C_{28}H_{34}Fe_2N_2$: C, 65.91; H, 6.72; N, 5.49. Found: C, 65.81; H, 6.52; N, 5.54.

4.21. (1*R*,2*R*) 1,2-Diamino-*N,N′*-di(ferrocenylmethyl)cyclohexane 20

Following the general procedure starting from ferrocenecarboxaldehyde (1.40 g, 6.54 mmol) and (1*R*,2*R*) 1,2-diaminocyclohexane (354 mg, 3.11 mmol), (1*R*,2*R*) 1,2-diamino-*N,N′*-(diferrocenylmethyl)cyclohexane **20** was obtained as yellow crystals (0.76 g, 48%). Mp 188 °C. ^{1}H NMR ($CDCl_3$) δ *4.19–4.17* (4H, m, Cp), 4.11 (10H, s, Cp′), 4.08 (4H, s, Cp), 3.62 (2H, d, CH_2–N, *J* = 12.9 Hz), 3.35 (2H, d, CH_2–N, *J* = 12.9 Hz), 2.24 (1H, m, CH–N), 2.10 (1H, m, CH–N), 1.92 (2H, s, NH), 1.75–1.71 (4H, m, CH_2), 1.24 (2H, m, CH_2), 1.04 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ 88.0, 68.4, 68.1, 68.0, 67.5, 61.4, 46.1, 31.8, 25.1. MS (*m*/*z*) 510 (M^+). Anal. Calcd for $C_{28}H_{34}Fe_2N_2$: C, 65.91; H, 6.72; N, 5.49. Found: C, 66.30; H, 7.95; N, 5.63.

4.22. *N,N′*-Diferrocenylmethylpiperazine 21

Following the general procedure starting from ferrocenecarboxaldehyde (1.480 g, 6.91 mmol) and piperazine (354 mg, 3.23 mmol), *N,N′*-diferrocenylmethylpiperazine **21** was obtained as yellow crystals (0.965 g, 62%). Mp 106 °C. ^{1}H NMR ($CDCl_3$) δ *4.24–4.19* (4H, m, Cp), 4.18–4.14 (4H, m, Cp), 4.11 (10H, s, Cp′), 3.35 (4H, s, $FcCH_2N$), 2.61–2.35 (8H, m, CH_2). MS (*m*/*z*) 482 (M^+). Anal. Calcd for $C_{26}H_{30}Fe_2N_2$: C, 64.76; H, 6.27; N, 5.81. Found: C, 64.91; H, 6.32; N, 5.74.

4.23. *N,N′*-Diisopropyl-1,1′-ferrocenylmethyldiamine 22

Following the general procedure starting from ferrocene-1,1′-dicarboxaldehyde **7** (1.09 g, 4.5 mmol) and isopropylamine (0.77 mL, 9.0 mmol), *N,N′*-diisopropyl-1,1′-ferrocenylmethyldi-

amine **22** was obtained as yellow oil (709 mg, 48%). ^{1}H NMR ($CDCl_3$) δ *4.15–4.11* (4H, m, Cp), 4.08–4.05 (4H, m, Cp), 3.49 (4H, s, CH_2), 2.84 (2H, s, CH, J = 6.1 Hz), 1.07 (12H, d, CH_3, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ 87.3, 68.9, 68.4, 48.3, 46.5, 22.9. MS (*m*/*z*): 328 (M^+). Anal. Calcd for $C_{18}H_{28}FeN_2$: C, 65.86; H, 8.60; N, 8.53. Found: C, 65.97; H, 8.50; N, 8.40.

4.24. *N,N′*-Diisopropyl-1,2-ferrocenylmethyldiamine 23

Following the general procedure starting from ferrocene-1,2-dicarboxaldehyde **10** (371 mg, 1.53 mmol) and isopropylamine (0.326 mL, 3.8 mmol), *N,N′*-diisopropyl-1,2-ferrocenylmethyldiamine **23** was obtained as yellow oil (360 mg, 72%). ^{1}H NMR ($CDCl_3$) δ 4.12 (2H, m, Cp), 4.04 (5H, s, Cp′), 3.99 (1H, m, Cp), 3.66 (2H, d, CH_2N, J = 12.3 Hz), 3.40 (2H, d, CH_2N, J = 12.3 Hz), 2.78 (2H, m, CH), 1.05 (6H, d, CH_3, J = 6.3 Hz), 1.02 (6H, d, CH_3, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$) δ 86.0, 71.1, 71.0, 68.9, 65.6, 48.3, 45.6, 23.3, 22.5. MS (*m*/*z*) 328 (M^+). Anal. Calcd for $C_{18}H_{28}FeN_2$: C, 65.86; H, 8.60; N, 8.53. Found: C, 65.97; H, 8.78; N, 8.41.

4.25. *N,N′*-Dibenzyl-1,2-diaminoethane 24

Following the general procedure starting from benzaldehyde (1.22 mL, 11.8 mmol) and 1,2-ethylenediamine (0.332 mL, 4.9 mmol), *N,N′*-dibenzyl-1,2-diaminoethane **24** was obtained as yellow oil (811 mg, 69%). ^{1}H NMR ($CDCl_3$) δ *7.39–7.25* (6H, m, Ph), 7.24–7.22 (4H, m, Ph), 3.76 (4H, s, Ph–CH_2–N), 2.74 (4H, s, CH_2–N), 2.01 (2H, s, NH). ^{13}C NMR ($CDCl_3$) δ 140.3, 128.4, 128.0, 126.9, 54.0, 51.9. MS (*m*/*z*): 240 (M^+).

4.26. *N,N′*-Dibenzyl-1,6-diaminohexane 25

Following the general procedure starting from benzaldehyde (1.22 mL, 11.8 mmol) and 1,6-hexanediamine (572 mg, 4.9 mmol), **N,N′**-dibenzyl-1,6-diaminohexane **25** was obtained as yellow oil (1.22 g, 84%). ^{1}H NMR ($CDCl_3$) δ *7.31–7.28* (4H, m, Ph), 7.24–7.22 (4H, m, Ph), 7.21 (2H, m, Ph), 3.75 (4H, s, Ph–CH_2–N), 2.59 (4H, t, J = 7.1 Hz, CH_2–N), 1.52–1.47 (4H, m, –CH_2–), 1.35–1.29 (4H, m, –CH_2–). ^{13}C NMR ($CDCl_3$) δ 140.6, 128.4, 128.1, 126.9, 54.1, 49.5, 30.1, 27.3. MS (*m*/*z*): 296 (M^+).

4.27. *N,N′*-Dibenzyl-1,2-diaminopropane 26

Following the general procedure starting from benzaldehyde (1.22 mL, 11.8 mmol) and 1,2-propanediamine (0.43 mL, 4.9 mmol), *N,N′*-dibenzyl-1,2-diaminopropane **26** was obtained as yellow oil (833 mg, 67%). Yellow oil. Yield 67%. ^{1}H NMR ($CDCl_3$) δ *7.27–7.20* (10H, m, Ph), 3.83 (1H, d, Ph–CH_2–N–C^*, J = 15 Hz,), 3.70 (2H, s, Ph–CH_2–N) 3.65 (1H, d, Ph–CH_2–N–C^*, J = 15 Hz), 2.73 (1H, m, CH–N), 2.61 (1H, dd, N–CH_2–C^*, J = 3.9 and 11.9 Hz), 2.47 (1H, dd, N–CH_2–C^*, J = 8.6 and 11.9 Hz), 1.05 (3H, d, J = 6.1 Hz, –CH_3). ^{13}C NMR ($CDCl_3$) δ 140.8, 140.6, 128.3, 128.1, 128.0, 126.9, 126.8, 55.1, 53.9, 51.8, 51.3, 18.5. MS (*m*/*z*): 254 (M^+).

4.28. *N,N′*-Diferrocenylmethyl-N,N′-dimethyl-1,2-diaminoethane 27

A solution of ferrocenyl diamine **13** (0.894 g, 1.96 mmol), methanal (0.2 mL, 37% in water, 7.26 mmol) and sodium cyanoborohydride (0.377 g, 6 mmol) were added to anhydrous methanol (30 mL) in a round bottom flask. The mixture was allowed to stir at ambient temperature for 3 h. The solvent was then removed under reduced pressure. The residue was dissolved in dichloromethane and the solution filtered through Celite. The filtrate was concentrated by removing the dichloromethane under reduced pressure. The product was then purified using silica gel chromatography, eluting with diethyl ether: petroleum ether: triethylamine (80:10:10). Compound **27** was obtained as yellow crystals (16%). Mp 130 °C. ^{1}H NMR ($CDCl_3$) δ *4.13–4.12* (4H, m, Cp), 4.10–4.09 (4H, m, Cp), 4.09 (10H, s, Cp′), 3.36 (2H, s, Fc-CH_2–N), 3.35 (2H, s, Fc-CH_2–N), 2.38 (2H, s, CH_2–N), 2.36 (2H, s, CH_2–N), 2.14 (3H, s, –CH_3), 2.12 (3H, s, –CH_3). ^{13}C NMR ($CDCl_3$) δ 82.6, 70.3, 68.4, 67.9, 57.3, 53.7, 42.1. MS (*m*/*z*): 484 (M^+). Anal. Calcd for $C_{26}H_{32}Fe_2N_2$: C, 64.49; H, 6.66; N, 5.78. Found: C, 64.21; H, 6.57; N, 5.69.

4.29. Activity against *M. tuberculosis* H_{37}Rv strain

Susceptibility testing with the BACTEC MGIT 960 system (Becton Dickinson) was performed according to the manufacturer's recommendations. Test compounds were dissolved in dimethyl sulfoxide or in methanol. 390 µl of diluted test compounds was added to MGIT 7 ml tubes supplemented with 0.8 ml of the provided enrichment solution. Susceptibility testing was performed by minimal inhibitory concentration (MIC) determination. Serial twofold dilution of a 1280 mg/l solution of each drugs were added to MGIT tubes to achieve final concentration ranging from 64 to 0.25 mg/l. All the drug-containing tubes were inoculated with 0.5 ml of the positive broth culture. Mycobacterial suspensions were used undiluted from 2 days following the detection of growth, while the suspensions were diluted 1:5 with sterile saline from days 3 to 5. A SIRE drug-free control was inoculated with 0.5 ml of a 10^{-2} dilution of the positive culture broth in sterile saline. The tubes were then placed in an BACTEC 960 set carrier and incubated in the instrument. The tubes were continuously monitored until the results indicating susceptibility or resistance were automatically interpreted and reported using predefined algorithms that compared growth in the drug-containing tube to that in the control tube.

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