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# Synthesis and in vitro antitubercular activity of a series of quinoline derivatives

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ABSTRACT

A series of 33 quinoline derivatives have been synthesized and evaluated for their in vitro antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the Alamar Blue susceptibility test and the activity expressed as the minimum inhibitory concentration (MIC) in μg/mL. Compounds **5e** and **5f** exhibited a significant activity at 6.25 and 3.12 μg/mL, respectively, when compared with first line drugs such as ethambutol and could be a good starting point to develop new lead compounds in the fight against multidrug resistant tuberculosis.



## 1. Introduction

The quinoline nucleus is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities, such as antiviral[1], anticancer[2], antibacterial[3], antifungal[4], antiobesity,[5] and anti-inflammatory[6], which can be well illustrated by the large number of drugs in the market containing this heterocyclic class. However, in spite of its wide range of pharmacological activities, few studies have been described against tuberculosis in comparison with others classes.

Nowadays, tuberculosis (TB), a contagious disease transmitted through the air, and caused by the bacterium *Mycobacterium tuberculosis*, is an important world-wide public health problem, which was declared a global health emergency in 1993 by the World Health Organization (WHO). According to statistics, one-third of the world's population is currently infected with the TB bacillus, each year, 8 million people world-wide develop active TB and about 1.7 million people die.[7] Currently, an important problem in TB treatment is the development of multi-drug resistant tuberculosis (MDR-TB), which can be defined as strains that are resistance to at least isoniazid and rifampicin, important first line drugs used in TB treatment. The spread of MDR-TB could cost between 100 and 1400 times the available treatment costs and further threatens to make TB incurable. Exact data are hard to estimate, but at least 4% of all world-wide TB patients are resistant to at least one of the current first line drugs. Another serious problem, in the context of MDR-TB, is the XDR-TB, abbreviation for extensively drug-resistant tuberculosis (TB), which are strains resistant to first and second line anti-TB drugs. XDR-TB is commonly defined as strains resistant to all the current first line drugs, as well as any fluoroquinolone and at least 1 of 3 injectable second line drugs (capreomycin, kanamycin, or amikacin).[8,9] A study made by CDC (US Centers for Disease Control and Prevention) and WHO (World Health Organization) in 17.690 isolates from 49 countries during 2000–2004 have demonstrated that 20% of the strains were MDR-TB and 2% XDR-TB.[10] Due to the high impact of MDR and recently XDR in TB treatment, we urgently need new drugs and strategies to treat this disease efficiently. In this context, the aim of this article is to describe the synthesis and biological activity of a series of quinoline derivatives.

The start point for the preparation of the quinoline derivatives to be evaluated against TB were malaria drugs, such as quinine, chloroquine, mefloquine, primaquine, and amodiaquine (Fig. 1), which possessed moderate biological activity against TB, also being evaluate by us using the Microplate Alamar Blue Assay (MABA).

Another reason for the searching of new leading compounds based on quinoline derivatives is the diarylquinoline TMC207 (ex R207910) (Fig. 2), which was developed at Johnson & Johnson Pharmaceutical Research & Development. This compound possesses a new mechanism of action based on the interaction with the enzyme adenosine triphosphate (ATP) synthase, which is the energy source for the bacterium. Currently this drug is in phase 2 clinical trials and is very promising against MDR-TB.[11]

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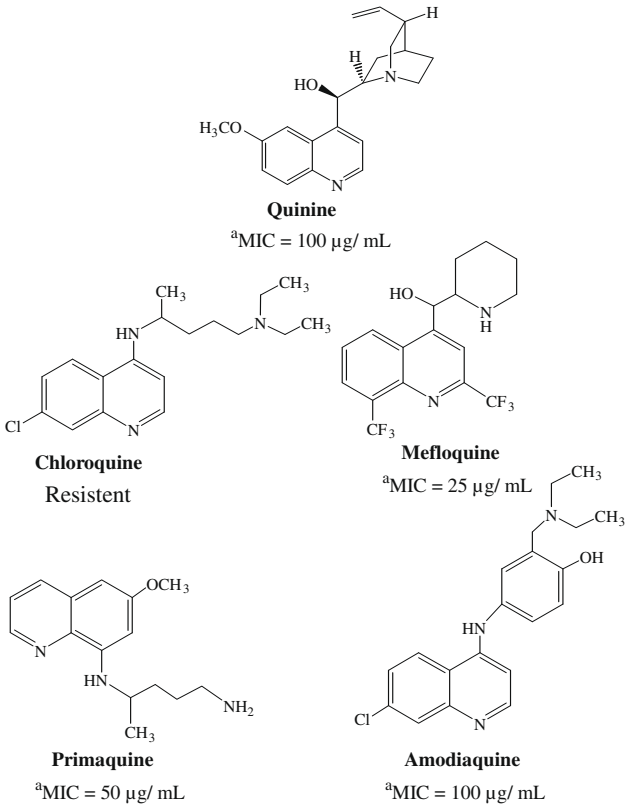



**Figure 1.** Malaria drugs. [a]MIC (minimal inhibition concentration) was defined as the lowest drug concentration, which prevented a color change from blue to pink.

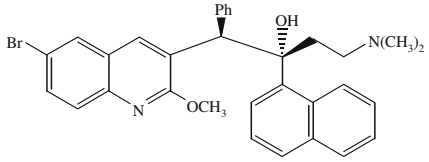


**Figure 2.** Diarylquinoline TMC207.

The design concept of quinoline derivatives attempts to introduce the ethambutol pharmacophore, a first line TB drug, into the core structure of the starting material 4,7-dichloroquinoline, in the expectation to improve its activity, possible by the incorporation of a different mode of action through a different target (Fig. 3).

Based on this design concept, we proposed the synthesis of 7-chloroquinoline C(4)-functionalized derivatives. Furthermore, in some derivatives the chorine atom was replaced by hydrogen atom at C(7) position, with the aim of establishing the importance of this substituent for the biological activity of this compounds (Fig. 4).

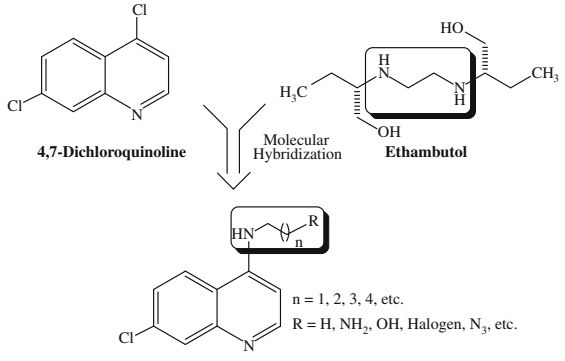



**Figure 3.** Design concept of quinoline derivatives.

## 2. Results and discussion

### 2.1. Chemistry

The synthetic routes for the preparation of 7-chloroquinoline C(4)-functionalized derivatives (**1** to **6a–j**) are summarized in Scheme 1. From 4,7-dichloroquinoline, the derivatives (**1**), (**5a–f**), and (**6a–j**) were obtained by chorine substitution at C(4) position for appropriate amines, diamines, or aminoalcohols in good yields (51–96%). Afterwards, the terminal hydroxyl of derivative (**1**) was replaced by a cyano or chorine substituent, leading to the compounds (**2**) and (**4**) in 94% and 35% (2 steps) yields, respectively. Besides that, the compounds (**3a–f**) were prepared from derivative (**2**) by chorine substitution in the aliphatic portion for an azide group or other amines or aminoalcohols in 46–95% yields.

All these compounds were identified by spectral data. In general, the $^{1}$H NMR spectrum showed the five quinoline protons at 8.20–6.44 ppm and the aliphatic protons at 3.90–1.02 ppm. The $^{13}$C NMR spectrum showed the nine quinoline carbons signals at the region of 153.3–90.5 ppm and the aliphatic carbons signals at 64.5–11.0 ppm.

Moreover, the derivatives (**7a–c**) were prepared from compounds (**1**), (**2**), (**6b**), and (**6f**) by catalytic hydrogenation that promotes the C–Cl bond cleavage leading to the desired substances (**7a–d**) in 81–98% yields (Scheme 2). These derivatives also were identified by spectral data. In general, when we compare the $^{1}$H NMR spectrums of derivatives (**7a–c**) with their corresponding precursors, there is a different proton signal at 7.93–7.98 ppm as a double doublet that confirms the chloro substitution for a hydrogen atom.

Furthermore, two chloro derivatives (**8a** and **8b**) were synthesized from the hydroxyl derivatives **6g** and **6j** (Scheme 3), with the aim of establishing the importance of these groups (OH and Cl) for the biological activity of quinoline derivatives. These derivatives also were identified by spectral data. In general, when we compare the $^{13}$C NMR spectrums of derivatives (**8a–b**) with their corresponding precursors, we observe that the HO-$CH_2$ signal moved from 60.9–64.3 to 43.4–47.0 ppm for the Cl-$CH_2$ signal that confirms this molecular modification.

### 2.2. Antimycobacterial activity

The antimycobacterial activities of all synthesized compounds were assessed against *M. tuberculosis* ATTC 27294 using the Microplate Alamar Blue Assay (MABA)[12,13] (Tables 1–4). This methodology is nontoxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric methods.[14,15]

Firstly, for the 7-chloro-4-amino-quinolines (**1–4**) series, we can observe that the most active derivative was (**2**) (MIC = 12.5 μg/mL), which has a chorine atom in a terminal position. The antimycobacterial activity decreases when this atom is replaced by other groups, such as azide ($N_3$) or other amines that indicates the relevance of chorine atom for the biological activity in this series of compounds (Table 1).

For the 7-chloro-4-diamino-quinolines derivatives (**5a–f**), the addition of carbon atoms in the alkyl chain leads to improved biological activity, which can be demonstrated by MIC variation that changes from 25 μg/mL (**5d**, $n = 6$) to 6.25 μg/mL (**5e**, $n = 8$) and to 3.12 μg/mL (**5f**, $n = 10$). Furthermore, it is important to remark that *c*log*P* values could be contributing to increase the antituber-

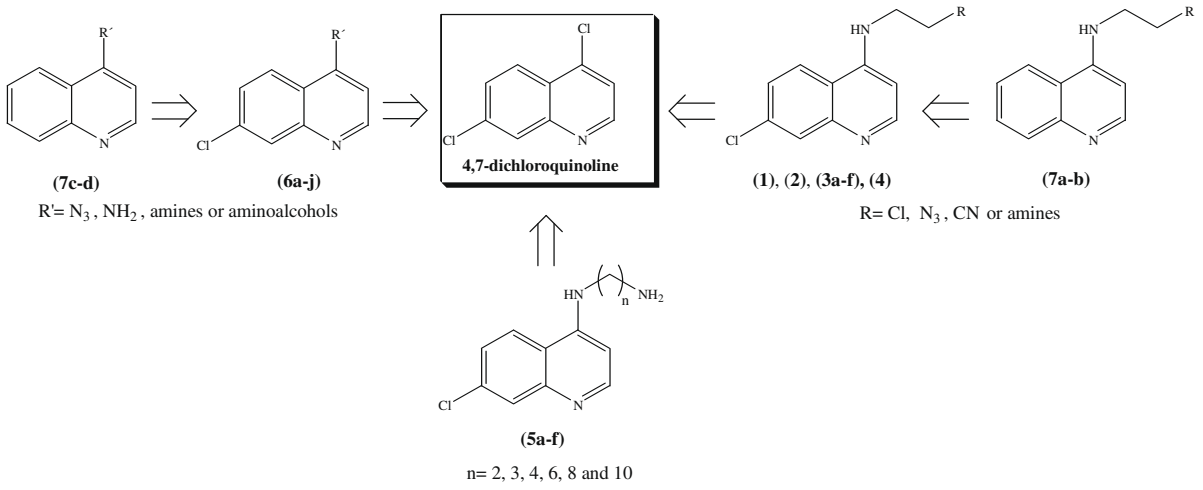
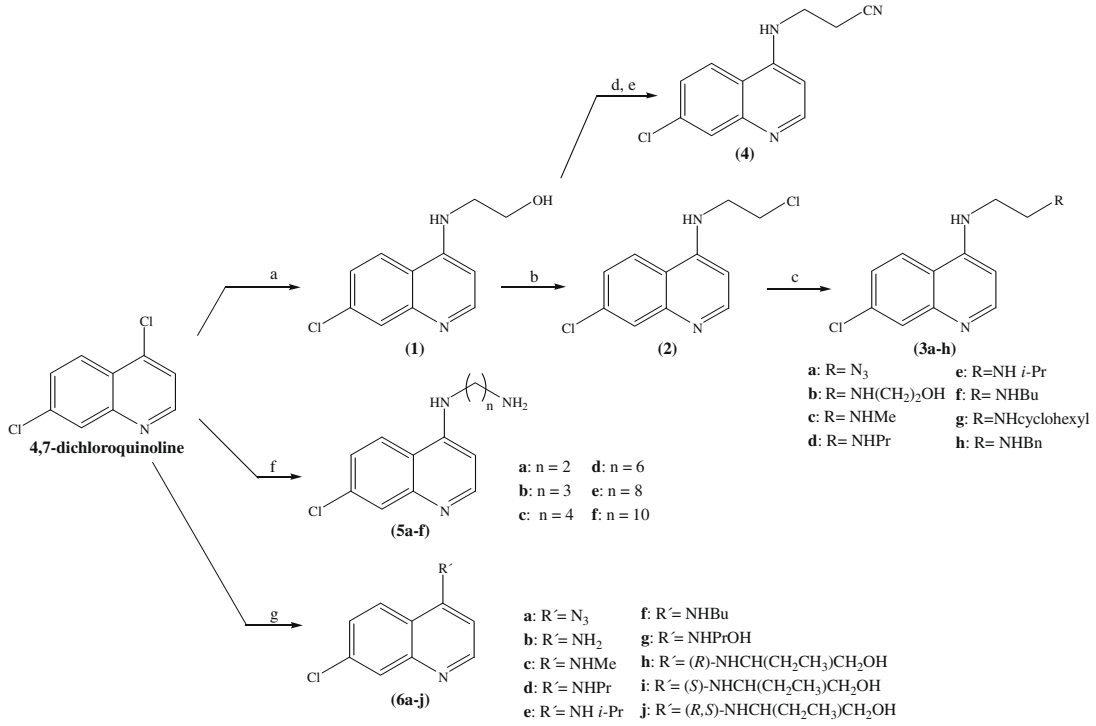
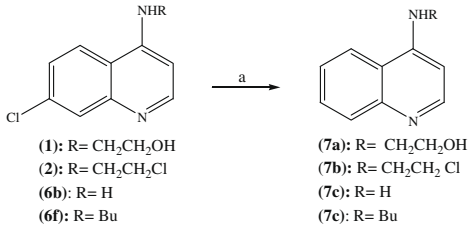


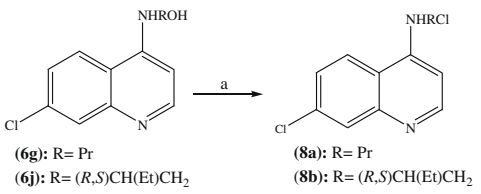

**Figure 4.** Retrosynthetic analysis of quinoline derivatives.




**Scheme 1.** Reagents and conditions: (a) 1-ethanolamine, $Et_3N$, 120 °C, 2 h, 94%; (b) $SOCl_2$, DMF, 24 h, 94%; (c) Compound **3a**: $NaN_3$; DMF; 4 h; 46%; Compounds **3b–f**: corresponding amine, $Et_3N$; 1–24 h, 80–120 °C, 72–95%; (d) TsCl, Py, 50 °C, 4 h; (e) KCN, DMF, 100 °C, 1 h, 35% in two steps; (f) corresponding diamine, 80–135 °C, 4 h, 51–94%; (g) Compound **6a**: $NaN_3$, DMF, 100 °C, 3 h, 70%; Compound **6b**: phenol, $NH_3$(g), 170 °C, 2 h, 82%; Compounds **6c–j**: corresponding amine or aminoalcohol, $Et_3N$, 60–120 °C, 2–24 h, 66–96%.



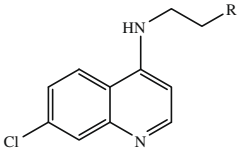

**Scheme 2.** Reagents and conditions: $H_2$ Pd–C, EtOH, rt, 1–3 h, 81–98%.




**Scheme 3.** Reagents and conditions: $SOCl_2$, DMF, rt, 2–24 h, 91–95%.

cular activity, because of that, the most active derivative (**5f**) shows the highest *c*log*P* value (5.55), indicating that lipophilicity is an important parameter to the biological activity in this series (Table 2).

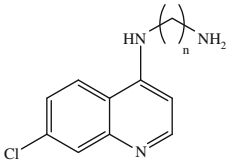
**Table 1**
The in vitro activity of compounds (**1**–**4**) against *M. tuberculosis* $H_{37}Rv$ strain (ATCC 27294, susceptible both to rifampin and isoniazid) and *c*log*P* measurements




| Compound | R | MIC (μg/mL) | *c*log*P*[a] |
|---|---|---|---|
| **1** | OH | >100.0[b] | 1.95 |
| **2** | Cl | 12.5 | 3.18 |
| **3a** | $N_3$ | 50.0 | 2.70 |
| **3b** | $NHCH_2CH_2OH$ | >100.0 | 1.54 |
| **3c** | NHMe | >100.0 | 2.07 |
| **3d** | NHPr | 100.0 | 3.14 |
| **3e** | NH*i*-Pr | >100.0 | 2.95 |
| **3f** | NHBu | >100.0 | 3.67 |
| **3g** | NHCyclohexyl | 100.0 | 4.13 |
| **3h** | NHBn | 50.0 | 4.08 |
| **4** | CN | >100.0 | 2.06 |

[a] Calculated on ACD/ChemSketch v.11.0 (Freeware).
[b] MIC > 100.0 μg/mL indicates that the strain is resistant to tested substance.

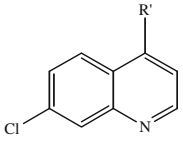
**Table 2**
The in vitro activity of compounds (**5a**–**f**) against *M. tuberculosis* $H_{37}Rv$ strain (ATCC 27294, susceptible both to rifampin and isoniazid) and *c*log*P* measurements




| Compound | *n* | MIC (μg/mL) | *c*log*P*[a] |
|---|---|---|---|
| **5a** | 2 | >100.0[b] | 1.84 |
| **5b** | 3 | >100.0 | 2.17 |
| **5c** | 4 | >100.0 | 2.56 |
| **5d** | 6 | 25.0 | 3.43 |
| **5e** | 8 | 6.25 | 4.49 |
| **5f** | 10 | 3.12 | 5.55 |

[a] Calculated on ACD/ChemSketch v.11.0 (Freeware).
[b] MIC > 100.0 μg/mL indicates that the strain is resistant to tested substance.

**Table 3**
The in vitro activity of compounds (**6a**–**j**) against *M. tuberculosis* $H_{37}Rv$ strain (ATCC 27294, susceptible both to rifampin and isoniazid) and *c*log*P* measurements



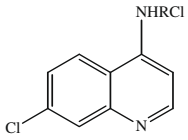

| Compound | R′ | MIC (μg/mL) | *c*log*P*[a] |
|---|---|---|---|
| **6a** | $N_3$ | >100.0[b] | 3.21 |
| **6b** | $NH_2$ | >100.0 | 2.38 |
| **6c** | NHMe | 100.0 | 2.72 |
| **6d** | NHPr | 50.0 | 3.78 |
| **6e** | NH*i*-Pr | 50.0 | 3.60 |
| **6f** | NHBu | 12.5 | 4.31 |
| **6g** | NHPrOH | >100.0 | 1.70 |
| **6h** | NH(*R*)CH(Et)$CH_2OH$ | >100.0 | 2.82 |
| **6i** | NH(*S*)CH(Et)$CH_2OH$ | >100.0 | 2.82 |
| **6j** | NH(*R,S*)CH(Et)$CH_2OH$ | >100.0 | 2.82 |

[a] Calculated on ACD/ChemSketch v.11.0 (Freeware).
[b] MIC > 100.0 μg/mL indicates that the strain is resistant to tested substance.

In the series of compounds (**6a**–**j**), the size of the alkyl chain is also a critical factor for increased anti-TB activity. For example, the biological activity of quinoline derivatives (**6c**–**f**) increases (>100 to 12.5 μg/mL) due to the enlargement of the alkyl chain. It is also important to be mentioned that the presence of a hydroxyl group in the structure of compounds (**6g–j**) could be responsible for the decrease of biological activity (Table 3). This hypothesis could be confirmed when the compounds (**6g**) and (**6j**) (100 μg/mL) were converted into their respective derivatives (**8a**) and (**8b**) (50 μg/mL) (Table 4).

Another important information about the structure–activity relationship of the 4-chloroquinoline derivatives is that the chorine atom at position C-7 in the quinoline nucleus is essential for the anti-TB activity. This fact can be demonstrated by the substitution of the chloro atom by hydrogen in the compounds (**1**) (MIC > 100.0 μg/mL), (**2**) (MIC > 100.0 μg/mL), (**6a**) (MIC > 100.0 μg/mL), and (**6f**) (MIC = 12.5 μg/mL), which was responsible for decrease of the antitubercular activity of compounds (**7d**) (MIC = 50.0 μg/mL) (Table 5).

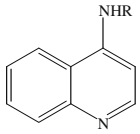
**Table 4**
The in vitro activity of compounds (**8a**–**b**) against *M. tuberculosis* $H_{37}Rv$ strain (ATCC 27294, susceptible both to rifampin and isoniazid) and *c*log*P* measurements




| Compound | R | MIC (μg/mL) | *c*log*P*[a] |
|---|---|---|---|
| **8a** | Pr | 50.0 | 3.62 |
| **8b** | (*R,S*)CH(Et)$CH_2$ | 50.0 | 4.06 |

[a] Calculated on ACD/ChemSketch v.11.0 (Freeware).

**Table 5**
The in vitro activity of compounds (**7a**–**c**) against *M. tuberculosis* $H_{37}Rv$ strain (ATCC 27294, susceptible both to rifampin and isoniazid) and *c*log*P* measurements



(7a-d)

| Compound | R | MIC (μg/mL) | *c*log*P*[a] |
|---|---|---|---|
| **7a** | $CH_2CH_2OH$ | >100.0[b] | 1.67 |
| **7b** | $CH_2CH_2Cl$ | >100.0 | 2.90 |
| **7c** | H | >100.0 | 2.08 |
| **7d** | Bu | 50.0 | 4.04 |

[a] Calculated on ACD/ChemSketch v.11.0 (Freeware).
[b] MIC > 100.0 μg/mL indicates that the strain is resistant to tested substance.

## 3. Experimental

### 3.1. General procedures

Melting points were determined on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer as potassium bromide pellets and frequencies are expressed in $cm^{-1}$. Mass spectra (CG/MS) were recorded on a Agilent Technologies 6890/5972A mass spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at 500 MHz ($^1H$) and 125 MHz ($^{13}C$) or 400 MHz ($^1H$) and 100 MHz ($^{13}C$), in deuterated methanol or dimethylsulfoxide. Chemical shifts are reported in ppm ($\delta$) relative to tetramethylsilane. Proton and carbon spectra were typically obtained at room

temperature. For TLC, plates coated with silica gel were run in ethyl acetate and spots were developed in Ultraviolet.

### 3.1.1. Synthesis of 2-[(7-chloroquinolin-4-yl)amino]ethanol (1)

A mixture of 4,7-dichloroquinoline (2.0 g, 10.1 mmol), ethanolamine (12.1 mL, 20.2 mmol), and $Et_3N$ (21.0 mL, 15 mmol) was stirred under nitrogen at 120 °C for 2 h. After cooling to room temperature, ice was added and the resulting mixture stored in the refrigerator for 1 h. The precipitate was filtered and the residue washed with cold water (2 × 5 mL) and then with cold ethyl ether (2 × 5 mL). Yield: 94%, mp: 220–222 °C (213–215 °C).[16]

### 3.1.2. Synthesis of 7-chloro-*N*-(2-chloroethyl)quinolin-4-amine (2)

A mixture of (**1**) (0.5 g, 2.2 mmol), thionyl chloride (33 mL, 45 mmol), and DMF (0.3 mL, 0.22 mmol) was stirred under nitrogen at room temperature for 24 h. After that, the resulting mixture was neutralized with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure to lead the compound (**2**) without further purification. Yield: 94%, mp: 153–154 °C (155 °C).[17]

### 3.1.3. General procedures for preparing 7-chloroquinolineamines derivatives (3a–h)

**3.1.3.1. *N*-(2-Azidoethyl)-7-chloroquinolin-4-amine (3a).** A mixture of (**2**) (0.5 g, 2.2 mmol), sodium azide (8.5 g, 13.2 mmol), and DMF (2 mL) was stirred under nitrogen at 100 °C for 4 h. After that, sodium azide was filtered and DMF was removed under reduced pressure. Then, the crude product was extracted with water (15 mL) and chloroform (3 × 20 mL) and the combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography column (hexane/ethyl acetate 7:3), to lead the desired product (**3a**). Yield: 70%, mp: 145–147 °C.

NMR-$^1$H (500 MHz, Acetone) $\delta$: 8.49 (1H; d; $J$ = 5.0 Hz; $H_2$); 8.17 (1H; d; $J$ = 9.0 Hz; $H_5$); 7.85 (1H; d; $J$ = 2.0 Hz; $H_8$); 7.40 (1H; dd; $J$ = 2.5 and 9.0 Hz; $H_6$); 6.89 (1H; s; NH); 6.64 (1H; d; $J$ = 5.5 Hz; $H_3$); 3.71 (2H; t; $J$ = 5.5 Hz; $H_1$ or $H_2$); 3.67 (2H; t; $J$ = 5.5 Hz; $H_1$ or $H_2$) ppm; NMR-$^{13}$C (125 MHz, Acetone) $\delta$: 153.0; 150.4; 150.6; 134.9; 129.2; 125.4; 123.9; 118.6; 99.9; 50.2; 43.1 ppm.

IR $\nu_{max}$ ($cm^{-1}$; KBr pellets): 3225 (N–H); 2131 ($N_3$); 1578 (C=C).

MS/ESI: $m/z$ $[M-H]^+$: 246.1.

**3.1.3.2. Compounds (3b–h).** The conditions employed for the preparation these compounds were those described above in the procedure of Section 3.1.1. However, 44.0 mmol of appropriated amine and 2.2 mmol (0.5 g) of (**2**) were used as starting materials.

*3.1.3.2.1. 2-({2-[(7-Chloroquinolin-4-yl)amino]ethyl}amino)ethanol (**3b**).* Yield: 80%, mp: 235–236 °C (239–241 °C).[18]

*3.1.3.2.2. N-(7-Chloroquinolin-4-yl)-N′-methylethane-1.2-diamine (**3c**).* Yield: 95%, mp: 110–111 °C (110–111.5 °C).[19]

*3.1.3.2.3. N-(7-Chloroquinolin-4-yl)-N′-propylethane-1.2-diamine (**3d**).* Yield: 91%, mp: 91–93 °C.

NMR-$^1$H (400 MHz, MeOD) $\delta$: 8.40 (1H; d; $J$ = 5.5 Hz; $H_2$); 8.17 (1H; d; $J$ = 9.0 Hz; $H_5$); 7.79 (1H; d; $J$ = 5.5 Hz; $H_8$); 7.44 (1H; dd; $J$ = 5.5 and 9.0 Hz; $H_6$); 6.64 (1H; d; $J$ = 5.5 Hz; $H_3$); 3.68 (2H; t; $J$ = 6.5 Hz; $H_{1'}$ or $H_{2'}$); 3.20 (2H; t; $J$ = 6.5 Hz; $H_{1'}$ or $H_{2'}$); 2.90–2.86 (2H; m; $H_{1''}$); 1.73–1.64 (2H; m; $H_{2''}$); 1.00 (3H; t; $J$ = 8.0 Hz; $H_{3''}$) ppm; NMR-$^{13}$C (100 MHz, MeOD) $\delta$: 152.8; 152.3; 149.3; 136.9; 127.5 126.6; 124.8; 119.0; 100.1; 51.7; 47.8; 41.7; 22.2; 11.7 ppm.

IR $\nu_{max}$ ($cm^{-1}$; KBr pellets): 3293 (N–H); 1582 (C=C).

MS/ESI: $m/z$ $[M-H]^+$: 262.4.

*3.1.3.2.4. N-(7-Chloroquinolin-4-yl)-N′-isopropylethane-1,2-diamine (**3e**).* Yield: 90%, mp: 129–130 °C (129–130 °C).[20]

*3.1.3.2.5. N-Butyl-N′-(7-chloroquinolin-4-yl)ethane-1,2-diamine (**3f**).* Yield: 93%, mp: 187–190 °C.

NMR-$^1$H (500 MHz, MeOD) $\delta$: 8.41 (1H; d; $J$ = 5.5 Hz; $H_2$); 8.18 (1H; d; $J$ = 9.0 Hz; $H_5$); 7.78 (1H; d; $J$ = 1.5 Hz; $H_8$); 7.44 (1H; dd; $J$ = 9.0 and 1.5 Hz; $H_6$); 6.64 (1H; d; $J$ = 5.5 Hz; $H_3$); 3.69 (2H; t; $J$ = 6.5 Hz; $H_{1'}$ or $H_{2'}$); 3.23 (2H; t; $J$ = 6.5 Hz; $H_{1'}$ or $H_{2'}$); 2.95–2.90 (2H; m; $H_{1''}$); 1.68–1.62 (2H; m; $H_{2''}$); 1.45–1.39 (2H; m; $H_{3''}$); 0.97 (3H; q; $J$ = 7.5 Hz; $H_{4'}$) ppm; NMR-$^{13}$C (125 MHz, MeOD) $\delta$: 152.7; 152.3; 149.3; 136.8; 127.4; 126.5; 124.8; 118.9; 100.0; 47.6; 41.5; 40.6; 30.6; 21.2; 14.20 ppm.

IR $\nu_{max}$ ($cm^{-1}$; KBr pellets): 3257 (N–H); 1579 (C=C).

MS/ESI: $m/z$ $[M-H]^+$: 278.2.

*3.1.3.2.6. N-(7-Chloroquinolin-4-yl)-N′-cyclohexylethane-1.2-diamine (**3g**).* Yield: 82%, mp: 151–152 °C (151 °C).[20]

*3.1.3.2.7. N-Benzyl-N′-(7-chloroquinolin-4-yl)ethane-1.2-diamine (**3h**).* Yield: 75%, mp: 141–143 °C.

NMR-$^1$H (500 MHz, MeOD) $\delta$: 8.32 (1H; d; $J$ = 6.0 Hz; $H_2$); 8.06 (1H; d; $J$ = 9.0 Hz; $H_5$); 7.76 (1H; d; $J$ = 2.0 Hz; $H_8$); 7.38 (1H; dd; $J$ = 9.0 and 2.0 Hz; $H_6$); 7.32–7.35 (5H; m; $H_{1''}$–$H_{5''}$); 6.50 (1H; d; $J$ = 6.0Hz; $H_3$); 3.81 (2H; s; $H_{3'}$); 3.49 (2H; t; $J$ = 7.5Hz; $H_{1'}$ or $H_{2'}$); 2.93 (2H; t; $J$ = 7.5 Hz; $H_{1'}$ or $H_{2'}$) ppm; NMR-$^{13}$C (125 MHz, MeOD) $\delta$: 152.8; 152.5; 149.7; 140.6; 136.5; 129.7; 128.4; 127.7; 126.2; 124.4; 118.9; 99.9; 54.4; 47.8; 43.4 ppm.

IR $\nu_{max}$ ($cm^{-1}$; KBr pellets): 3217 (N–H); 1579 (C=C).

MS/ESI: $m/z$ $[M-H]^+$: 312.3.

### 3.1.4. Synthesis of 3-[(7-chloroquinolin-4-yl)amino] propanenitrile (4)

A mixture of (**1**) (0.5 g, 2.2 mmol), 4-toluenesulfonyl chloride (6.3 g, 3.3 mmol), and pyridine 10 mL was stirred under nitrogen at 50 °C for 4 h to obtain 2-[(7-chloroquinolin-4-yl)amino]ethyl-4-methylbenzenesulfonate. The resulting mixture was extracted with chloroform and the combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. Then, a mixture of the compound prepared previously (4.0 g, 1.0 mmol) and potassium cyanide (4.3 g, 6 mmol) in 4 mL *N,N*-dimethylformamide, was stirred under nitrogen at 100 °C for 1 h. The resulting mixture was extracted with chloroform (2 × 50 mL) and the combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography column (chloroform), to lead to the desired product (**4**). Yield: 35% (two steps), mp: 178–180 °C (174–175 °C).[21]

### 3.1.5. General procedures for the synthesis of 7-chloroquinoline diamines derivatives (5a–f)

A mixture of 4,7-dichloroquinoline (2.0 g, 10.1 mmol) and the appropriate diaminoalkane (20.2 mmol) was slowly heated to 80 °C and maintained at that temperature for 1 h without stirring and subsequently at 135 °C for 3 h with stirring to drive the reaction to completion. Ice was added to the reaction mixture and it was stored in the refrigerator for 1 h. The precipitate was filtered, washed with cold water (10 mL) and ethyl ether (2 × 10 mL), obtaining the pure derivatives (**5a**–**c**). The compounds (**5d**–**f**) were purified by chromatography column (chloroform/methanol 10% with 1% $Et_3N$).

**3.1.5.1. *N*-(7-Chloroquinolin-4-yl)ethane-1,2-diamine (5a).** Yield: 94%, mp: 137–139 °C (145–147 °C).[22]

**3.1.5.2. *N*-(7-Chloroquinolin-4-yl)propane-1,3-diamine (5b).** Yield: 90%, mp: 96–98 °C (96–98 °C).[23]

**3.1.5.3. *N*-(7-Chloroquinolin-4-yl)butane-1,4-diamine (5c).** Yield: 75%, mp: 122–124 °C (122–124 °C).[23]

**3.1.5.4. *N*-(7-Chloroquinolin-4-yl)hexane-1,6-diamine (5d).** Yield: 55%, mp: 133–134 °C (133–134 °C).[24]

**3.1.5.5. *N*-(7-Chloroquinolin-4-yl)octane-1,8-diamine (5e).** Yield: 51%, mp: 131–133 °C.

NMR-$^1$H (500 MHz, MeOD) $\delta$: 8.33 (1H; d; $J$ = 5.5 Hz; $H_2$); 8.09 (1H; d; $J$ = 9.0 Hz; $H_8$); 7.76 (1H; d; $J$ = 2.0 Hz; $H_5$); 7.37 (1H; dd; $J$ = 2.0 and 9.0 Hz; $H_6$); 6.48 (1H; d; $J$ = 6.0 Hz; $H_3$); 3.31 (2H; t; $H_{1'}$ or $H_{8'}$); 2.65 (2H; t; $J$ = 7.0 Hz; $H_{1'}$ or $H_{8'}$); 1.73 (2H; m; $J$ = 7.0 Hz; $H_{2'}$); 1.46 (10H; m; $J$ = 7.0 Hz; $H_{3'}$; $H_{4'}$; $H_{5'}$; $H_{6'}$; and $H_{7'}$); NMR-$^{13}$C (125 MHz, MeOD) $\delta$: 152.9; 152.5; 149.8; 136.4; 127.7; 126.0; 124.4; 118.9; 99.7; 44.1; 42.3; 33.0; 30.6; 30.6; 29.5; 28.3; 28.0 ppm.

IR $\nu_{max}$ (cm$^{-1}$; KBr pellets): 3323 (N–H); 1581 (C=C).

MS/ESI: $m/z$ [M−H]$^+$: 306.4.

**3.1.5.6. *N*-(7-Chloroquinolin-4-yl)decane-1,10-diamine (5f).** Yield: 60%, mp: 90–92 °C.

NMR-$^1$H (500 MHz, MeOD) $\delta$: 8.32 (1H; d; $J$ = 5.7 Hz; $H_2$); 8.12 (1H; d; $J$ = 9.0 Hz; $H_8$); 7.76 (1H; d; $J$ = 2.1 Hz; $H_5$); 7.39 (1H; dd; $J$ = 2.1 and 9.0 Hz; $H_6$); 6.49 (1H; d; $J$ = 5.7 Hz; $H_3$); 3.35 (2H; t; $J$ = 7.3 Hz; $H_{1'}$ or $H_{10'}$); 2.87 (2H; t; $J$ = 7.6 Hz; $H_{1'}$ or $H_{10'}$); 1.73 (2H; m; $J$ = 7.2 Hz; $H_{2'}$); 1.61 (2H; m; $J$ = 7.0 Hz; $H_{9'}$); 1.43 (2H; m; $H_{3'}$); 1.33 (10H; m; $H_{4'}$; $H_{5'}$; $H_{6'}$; $H_{7'}$; and $H_{8'}$); NMR-$^{13}$C (125 MHz, MeOD) $\delta$: 153.1; 152.1; 149.4; 136.5; 127.4; 126.1; 124.5; 118.8; 99.7; 44.1; 41.0; 30.7; 30.5; 30.5; 30.3; 29.4; 29.0; 28.3; 27.6 ppm.

IR $\nu_{max}$ (cm$^{-1}$; KBr pellets): 3363 (N–H); 1581 (C=C).

MS/ESI: $m/z$ [M−H]$^+$: 334.6.

### 3.1.6. General procedures for preparing 7-chloroquinolineamines derivatives (6a–j)

**3.1.6.1. 4-Azido-7-chloroquinoline (6a).** The conditions employed for the preparation of this compound were those described above in general procedure of Section 3.1.3.1. Yield: 82%, mp: 110–112 °C (118 °C).[25]

**3.1.6.2. 7-Chloro-4-aminoquinoline (6b)[17].** Yield: 92%, mp: 147–148 °C (147–148 °C).

**3.1.6.3. Compounds (6c–i).** The conditions employed for the preparation of these compounds were those described above in the procedure of Section 3.1.1. However, the reaction time was modified to 4 h (derivatives **6c** and **6e**), 6 h (derivatives **6d** and **6f**), or 24 h (derivatives **6g–h**). In the case of derivatives (**6c–f**), the bath temperature also was modified to 80 °C.

*3.1.6.3.1. 7-Chloro-N-methylquinolin-4-amine (**6c**).* Yield: 90%, mp: 166 °C (247–248 °C).[26]

*3.1.6.3.2. 7-chloro-N-propylquinolin-4-amine (**6d**).* Yield: 73%, mp: 123–125 °C.[26]

*3.1.6.3.3. 7-Chloro-N-isopropylquinolin-4-amine (**6e**).* Yield: 66%, mp: 158–159 °C.

*3.1.6.3.4. 7-Chloro-N-butyl-quinolin-4-amine (**6f**).* Yield: 83%, mp: 128–130 °C (130–132 °C).[26]

*3.1.6.3.5. 3-[(7-Chloroquinolin-4-yl)amino]propan-1-ol (**6g**).* Yield: 96%, mp: 130–133 °C.[27]

*3.1.6.3.6. (2R)-2-[(7-Chloroquinolin-4-yl)amino]butan-1-ol (**6h**).* Yield: 82%, mp: 196–198 °C.

NMR-$^1$H (500 MHz, MeOD) $\delta$: 8.33 (1H; d; $J$ = 5.5 Hz; $H_2$); 8.20 (1H; d; $J$ = 9.2 Hz; $H_5$); 7.77 (1H; d; $J$ = 2.4 Hz; $H_8$); 7.40 (1H; dd; $J$ = 9.2 and 2.4 Hz; $H_6$); 6.60 (1H; d; $J$ = 5.5 Hz; $H_3$); 3.68–3.72 (3H; m; $H_{1'}$ and $H_{2'}$); 1.80–1.87 (1H; m; $H_{3'}$); 1.66–1.72 (1H; m; $H_{3'}$); 1.02 (3H; t; $J$ = 7.2 Hz; $H_{4'}$) ppm; NMR-$^{13}$C (100 MHz, MeOD) $\delta$: 152.2; 152.2; 149.7; 136.7; 127.5; 126.1; 124.6; 118.9; 100.2; 64.4; 57.7; 25.2; 11.1 ppm.

IR $\nu_{max}$ (cm$^{-1}$; KBr pellets): 3280 (N–H); 1582 (C=C); 1070 (C–O).

MS/ESI: $m/z$ [M−H]$^+$: 249.3.

*3.1.6.3.7. (2S)-2-[(7-Chloroquinolin-4-yl)amino]butan-1-ol (**6i**).* Yield: 80%, mp: 196–198 °C.

NMR-$^1$H (400 MHz, MeOD) $\delta$: 8.33 (1H; d; $J$ = 5.5 Hz; $H_2$); 8.17 (1H; d; $J$ = 9.2 Hz; $H_5$); 7.77 (1H; d; $J$ = 2.0 Hz; $H_8$); 7.38 (1H; dd; $J$ = 2.0 and 9.0 Hz; $H_6$); 6.59 (1H; d; $J$ = 5.5 Hz; $H_3$); 3.71 (3H; m; $H_{1'}$ and $H_{2'}$); 1.81–1.88 (1H; m; $H_{3'}$); 1.66–1.73 (1H; m; $H_{3'}$); 1.02 (3H; t; $J$ = 7.5 Hz; $H_{4'}$) ppm; NMR-$^{13}$C (100 MHz, MeOD) $\delta$: 153.9; 152.4; 149.9; 136.4; 127.6; 126.0; 124.4; 118.9; 100.1; 64.3; 57.5; 25.2; 11.0 ppm.

IR$\nu_{max}$ (cm$^{-1}$; KBr pellets): 3260 (N–H); 1579 (C=C); 1066 (C–O).

MS/ESI: $m/z$ [M−H]$^+$: 249.3

*3.1.6.3.8. 2-[(7-Chloroquinolin-4-yl)amino]butan-1-ol (**6j**).* Yield: 84%, mp: 196–198 °C.

NMR-$^1$H (400 MHz, MeOD) $\delta$: 8.33 (1H; d; $J$ = 5.6 Hz; $H_2$); 8.18 (1H; d; $J$ = 8.8 Hz; $H_5$); 7.77 (1H; d; $J$ = 2.0 Hz; $H_8$); 7.38 (1H; dd; $J$ = 2.0 and 8.8 Hz; $H_6$); 6.59 (1H; d; $J$ = 5.6 Hz; $H_3$); 3.71 (3H; m; $H_{1'}$ and $H_{2'}$); 1.82–1.88 (1H; m; $H_{3'}$); 1.66–1.73 (1H; m; $H_{3'}$); 1.02 (3H; t; $J$ = 7.2 Hz; $H_{4'}$) ppm; NMR-$^{13}$C (100 MHz, MeOD) $\delta$: 153.0; 152.4; 149.9; 136.5; 127.6; 126.1; 124.5; 118.9; 100.1; 64.3; 57.6; 25.2; 11.1 ppm.

IR $\nu_{max}$ (cm$^{-1}$; KBr pellets): 3280 (N–H); 1582 (C=C); 1070 (C–O).

MS/ESI: $m/z$ [M−H]$^+$: 249.3.

### 3.1.7. General procedures for the synthesis of quinolineamines derivatives (7a–d)

To a solution of (**1**), (**2**), (**6b**), and (**6f**) (1.5 mmol) in EtOH (10 mL) catalytic amounts of 10% Pd–C (10 wt% of the substrate, 0.02 mmol) were added, and the mixture was treated with $H_2$ for 3 h. The catalyst was filtered off and washed with EtOH (2 × 20 mL), and the filtrate was concentrated to lead the pure products (**7a–d**).

**3.1.7.1. 2-(Quinolin-4-ylamino)ethanol (7a).** Yield: 98%, mp: 158–160 °C (153–154 °C).[28]

**3.1.7.2. *N*-(2-Chloroethyl)quinolin-4-amine (7b).** Yield: 88%, mp: 85–87 °C.

NMR-$^1$H (500 MHz, MeOD) $\delta$: 8.44 (2H; d; $J$ = 7.5; $H_2$ and $H_8$); 7.98 (1H; ddd; $J$ = 8.5, 7.5, and 1.0 Hz; $H_7$); 7.94 (1H; d; $J$ = 8.5; 1.0 Hz; $H_5$); 7.74 (1H; ddd; $J$ = 8.5, 7.5, and 1.0 Hz; $H_6$); 6.99 (1H; d; $J$ = 7.0 Hz; $H_3$); 4.01 (2H; t; $J$ = 6.0 Hz; $H_{1'}$ or $H_{2'}$); 3.94 (2H; t; $J$ = 6.0 Hz; $H_{1'}$ or $H_{2'}$) ppm; NMR-$^{13}$C (125 MHz, MeOD) $\delta$: 158.1; 143.4; 139.4; 135.1; 128.4; 123.9; 121.2; 118.4; 99.5; 46.2; 42.7 ppm.

IR $\nu_{max}$ (cm$^{-1}$; KBr pellets): 3272 (N–H); 1572 (C=C);

MS/ESI: $m/z$ [M−H]$^+$: 269.2.

**3.1.7.3. Quinolin-4-amine (7c).** Yield: 93%, mp: 153–154 °C.[29]

**3.1.7.4. *N*-Butylquinolin-4-amine (7d).** Yield: 92%, mp: 123–125 °C (130–132 °C).[30]

### 3.1.8. General procedures for the synthesis of derivatives (8a–b)

The conditions employed for the preparation of these compounds were those described above in the procedure of Section 3.1.2.

**3.1.8.1. 7-Chloro-*N*-(3-chloropropyl)quinolin-4-amine (8a).** Yield: 96%, mp: 130–133 °C.[31]

**3.1.8.2. 7-Chloro-*N*-[1-(chloromethyl)propyl]quinolin-4-amine (8b).** Yield: 95%, mp: 120–121 °C.

NMR-$^1$H (400 MHz, MeOD) $\delta$: 8.37 (1H; d; $J$ = 5.6 Hz; $H_2$); 8.21 (1H; d; $J$ = 8.8 Hz; $H_8$); 7.80 (1H; d; $J$ = 2.5 Hz; $H_5$); 7.42 (1H; dd; $J$ = 8.8 and 2.5 Hz; $H_6$); 6.60 (1H; d; $J$ = 5.6 Hz; $H_3$); 3.97–3.90 (1H; m; $H_{2'}$); 3.79–3.72 (2H; m; $H_{1'}$); 1.98–1.73 (2H; m; $H_{3'}$); 1.77 (1H; m; $H_{3'}$); 1.03 (3H; t; $J$ = 7.2 Hz; $H_{4'}$) ppm; NMR-$^{13}$C (100 MHz, MeOD) $\delta$: 152.5; 151.4; 149.9; 136.5; 127.8; 126.2; 124.4; 118.8; 100.2; 56.8; 47.0; 26.2; 10.9 ppm.

IR $\nu_{max}$ ($cm^{-1}$; KBr pellets): 3324 (N–H); 1601 (C=C); MS/ESI: $m/z$ $[M-H]^+$: 207.2.

### 3.1.9. General procedures for biological tests

Briefly, 200 μL of sterile deionized water was added to all outer-perimeter wells of sterile 96 well plates (falcon, 3072: Becton Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The 96 plates received 100 μL of the Middlebrook 7H9 broth (Difco Laboratories, Detroit, MI, USA) and a serial dilution of the compounds **1–8b** was made directly on the plate. The final drug concentrations tested were 0.01–10.0 μL/mL. Plates were covered, sealed with parafilm and incubated at 37 °C for 5 days. After this time, 25 μL of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, Westlake, Ohio) reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC (minimal inhibition concentration) was defined as the lowest drug concentration, which prevented a color change from blue to pink.

## 4. Conclusions

Amongst the 33 synthesized compounds, the derivatives **2**, **3a**, **3d**, **3g**, **3h**, **5d–f**, **6c–f**, **7b**, **8a**, and **8b** exhibited activity between 3.12 and 100.0 μg/mL. The antimycobacterial activities of the quinoline derivatives described here suggest that they may be selectively targeted to *M. tuberculosis* growth. These compounds are not cytotoxic to host cells at the concentrations effective in inhibiting *M. tuberculosis* infection. Compounds **5e** and **5f** exhibited a significant activity at 6.25 and 3.12 μg/mL, respectively, when compared with first line drugs such ethambutol and could be considered a good starting point to develop new lead compounds in the fight against multi-drug resistant tuberculosis.

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