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# Synthesis of novel [1,2]-diamines with antituberculosis activity

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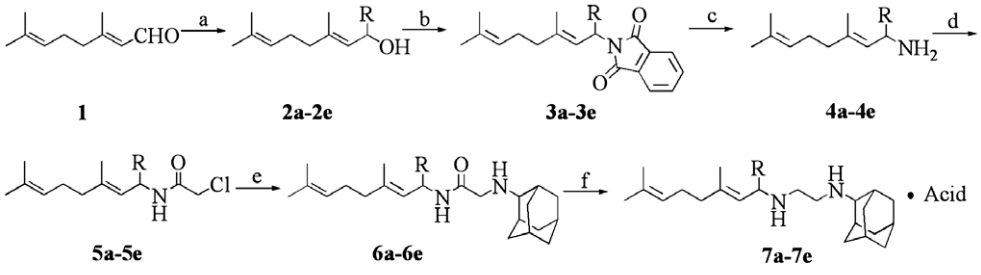
ABSTRACT

Guided by the metabolism information of **SQ109**, derivatives with substituted geranylamine moiety or substituted admantane ring of **SQ109** were synthesized and evaluated as antituberculosis agents. Among all tested compounds, compound **11c** showed the most potent antituberculosis activity with MIC value of 0.3 μM against *Mycobacterium tuberculosis* H37Rv.



Despite a 5000 year history, tuberculosis (TB) remains the leading single-agent infectious disease killer in the world. Almost a third of the world's population is infected with TB bacilli, and each year approximately 8 million people develop active TB and 2 million die as a result.[1] The major challenges for tuberculosis control are the development of mutidrug-resistant tuberculosis (MDR-TB) strains and the increasing numbers of immunocompromised individuals with HIV infectious who are highly susceptible to the disease. Consequently, there is a pressing need for new antitubercular agents acting with greater potency and efficacy than the current existing drugs. No novel antituberculosis drugs have been introduced into clinical practice over the past 4 decades. Only within the last few years have several promising drug candidates emerged.[2,3]

*N*-Geranyl-*N*′-(2-adamantyl)ethane-1,2-diamine (**SQ109**), a second-generation agent from the first-line drug ethambutol, entered clinical trail stage in 2005 and completed its phase Ia trial in 2007.[4–6] **SQ109** exhibited potent activity against *Mycobacterium*




**1-7a**: R = methyl; **1-7b**: R = Et; **1-7c**: R = benzyl;
**1-7d**: R = 4-fluoro-benzyl; **1-7e**: R = 4-trifluoromethyl-benzyl

**Scheme 1.** Reagents and conditions: (a) RMgBr, THF, rt, 1 h; (b) $Ph_3P$, DIAD, phthalimide, THF, 8 h; (c) $MeNH_2$, MeOH, reflux, 12 h; (d) chloroacetyl chloride, pyridine, THF, 0 °C, 0.5 h; (e) 2-admantylamine, $K_2CO_3$, THF, reflux, 12 h; (f) Red-Al, THF, reflux, 16 h, then HCl or maleic acid, MeOH.

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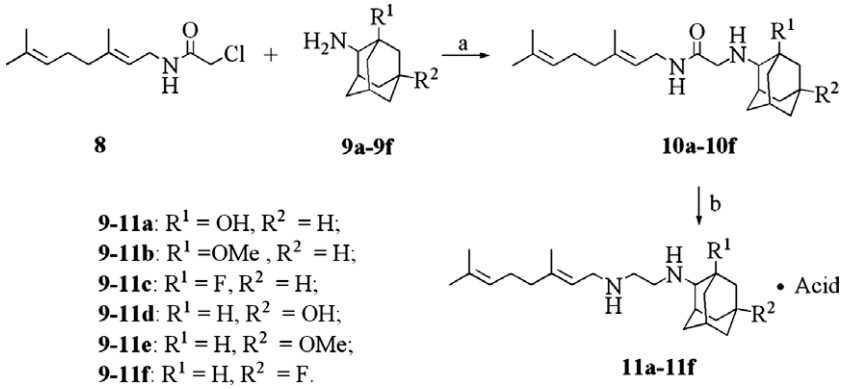
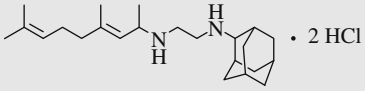
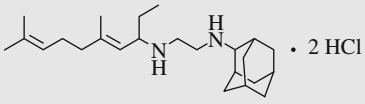
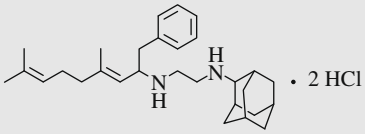
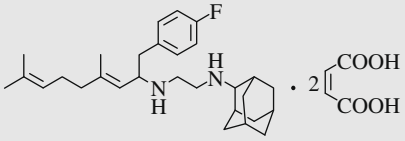
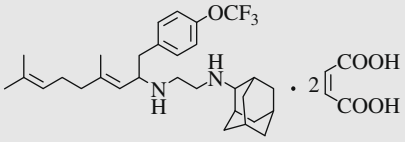
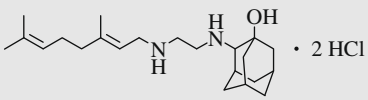
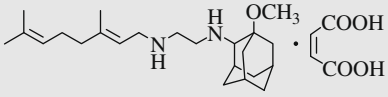



**Scheme 2.** Reagents and conditions: (a) $K_2CO_3$, THF, reflux, 12 h; (f) Red-Al, THF, reflux, 16 h, then HCl or maleic acid, MeOH.

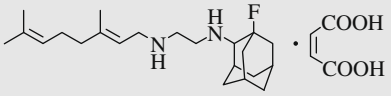
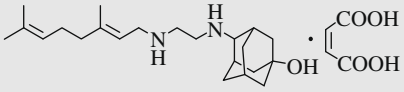
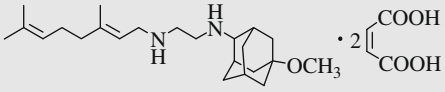
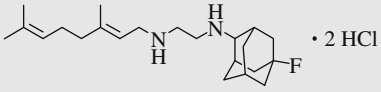
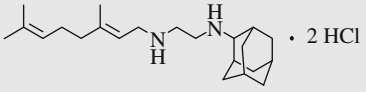
*tuberculosis* including muti-drug resistant strains both in vitro and in vivo.[7] Unfortunately, **SQ109** showed poor oral bioavailability, only 12% in rats and 3.8–5% in dogs, resulting from serious first-pass effect in liver. The metabolism study of **SQ109** by Jia et al. in human liver microsomes suggested that the predominant metabolisms of **SQ109** were oxidation and epoxidation of geranylamine moiety and admantane ring.[8] Guided by the metabolism information of **SQ109**, derivatives of **SQ109** with substituted geranylamine moiety and admantane ring were investigated to improve anti-tuberculosis activity and pharmacokinetic property. Herein, we described the synthesis and biological activity of these novel agents.

**Table 1**
The structures of synthesized compounds and their MICs against *M. tuberculosis* H37Rv

| Compound | Structure | MIC (μM) |
|---|---|---|
| **7a** |  | 1.2 |
| **7b** |  | 1.2 |
| **7c** |  | 1.0 |
| **7d** |  | 3.0 |
| **7e** |  | 5.2 |
| **11a** |  | 0.6 |
| **11b** |  | 0.5 |

(*continued on next page*)

**Table 1** (*continued*)

| Compound | Structure | MIC (μM) |
|---|---|---|
| **11c** |  | 0.3 |
| **11d** |  | 8.6 |
| **11e** |  | 1.7 |
| **11f** |  | 0.6 |
| **SQ109** |  | 0.6 |

The first objective of this investigation was to immediately synthesize a variety of derivatives with alkyl attached geranylamine moiety or substituted admantanamine moiety. Synthesis of compounds **7a**–**e** were outlined in Scheme 1. The starting material (*E*)-3,7-dimethylocta-2,6-dienal **1** was converted to **2a**–**e** by treatment with corresponding Grignard reagents in yields 93–97%. And these alcohols were treated with phthalimide in the presence of $Ph_3P$ and DIAD to give intermediates **3a**–**e**, which were converted to corresponding amines **4a**–**e** by treatment with methylamine. The yields of these two steps from **2a**–**e** to **4a**–**e** were 37–49%. Chloroacylation of **4a**–**e** using chloroacetyl chloride and pyridine in THF gave **5a**–**e** in 96–98% yield. Reaction of 2-admantylamines with **5a**–**e** afforded intermediates **6a**–**e** with yields of 64–73%. Finally, **6a**–**e** were treated with Red-Al in THF to provide the 1,2-diamines, and these diamines were treated with maleic acid or hydrochloride to afford target compounds **7a**–**e** in 52–63% yield. Derivatives with substituted admantane ring were synthesized as Scheme 2. The starting material **8** was synthesized according to the method described by Lee et al.[4] and it was converted to **10a**–**f** by treatment with corresponding substituted admantylamines **9a**–**f** and $K_2CO_3$ in THF at reflux temperature with yields of 67–75%. Then **10a**–**f** were treated with Red-Al in THF to provide the 1,2-diamines, and these diamines were treated with maleic acid or hydrochloride to give target compounds **11a**–**f** in 55–67% yield. The chemical structures of compounds **7a**–**e** and **11a**–**f** were determined by $^1$H NMR and HR-MS.[9]

All of the synthesized compounds **7a**–**e** and **11a**–**e** were evaluated for tuberculosis inhibition against *M. tuberculosis* H37Rv strain (ATCC 27294, susceptible both to rifampin and isoniazid) using microbroth dilution assay described by Lee et al.[4] and results are summarized in Table 1.

Our initial work focused on exploring variants to the geranylamine moiety of **SQ109**. As shown in Table 1, by introducing an alkyl group, such as methyl, ethyl, to the geranylamine moiety of **SQ109**, compounds **7a** and **7b** displayed similar potency against *M. tuberculosis* H37Rv with the 1.2 μM compared with 0.6 μM of **SQ109**. However when substituted benzyl was attached, for example compound **7d** and **7e**, the antituberculosis potency reduced about 5–9 fold. It was interesting that removal of the substituted group of benzyl (**7c** vs **7e**) led to a fivefold increase in antituberculosis potency.

To further improve the antituberculosis potency, we also investigated the requirement for the 2-admantylamine moiety of **SQ109**. Guided by the metabolism information of **SQ109**, we attached the hydroxyl, halide, methoxyl group to the 1 and 5 position of the 2-admantylamine nucleus. As shown in Table 1, for the 5-substituted 2-admantylamine, 5-fluorine-2-admantylamine derivative **11f** showed MIC value of 0.6 μM, the same potency to the **SQ109**, whereas 14 fold increase in antituberculosis potency over 5-hydroxyl-2-admantylamine derivative **11d**. For the 1-substituted 2-admantylamine, as exemplified by compound **11c**, no significant change was observed compared to **SQ109**, MIC values of those compounds ranged from 0.3 to 0.6 μM. As far as the substitution of 2-admantylamine nucleus was concerned the fluorine appears to be the most favorable group. Among all tested compounds, compound **11c** showed the most potent antituberculosis activity with MIC value of 0.3 μM against *M. tuberculosis* H37Rv strain.

In summary, guided by the metabolism information of **SQ109**, derivatives of **SQ109** with substituted geranylamine moiety or substituted admantane ring were synthesized and evaluated as an anti-tuberculosis agent. Among all tested compounds, compound **11c** showed the most potent antituberculosis activity with MIC value of 0.3 μM against *M. tuberculosis* H37Rv.

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9. *Selected data*: *Compound* **7a**: mp 194–195 °C; HRESIMS 345.3264, $C_{23}H_{41}N_2$ ($[M+H]^+$ of free base) requires 345.3270; $^1$H NMR (DMSO-$d_6$ 400 MHz) $\delta$: 1.30 (d, $J$ = 6.5 Hz, 3 H), 1.51 (s, 1H), 1.55 (s, 5H), 1.63 (s, 4H), 1.67 (s, 6H), 1.73 (s, 2H), 1.78–1.88 (m, 5H), 1.96–2.08 (m, 4H), 2.17 (s, 4H), 2.21 (s, 1H), 3.96–4.04 (m, 1H), 5.02–5.08 (m, 1H), 5.16 (d, $J$ = 9.8 Hz, 1H), 9.38 (br s, 2H), 9.74 (br s, 2H). *Compound* **7c**: mp 62–64 °C; HRESIMS 421.3591, $C_{29}H_{45}N_2$ ($[M+H]^+$ of free base) requires 421.3583; $^1$H NMR (DMSO-$d_6$ 400 MHz) $\delta$: 1.03 (d, $J$ = 6.23 Hz, 1H), 1.22 (s, 2H), 1.53–1.62 (m, 7H), 1.68–1.78 (m, 4H), 1.82–1.97 (m, 8H), 2.11–2.20 (m, 4H), 2.76 (t, $J$ = 11.6 Hz, 1H), 3.30–3.42 (m, 6H), 4.18 (m, 1H), 4.95 (m, 1H), 5.12 (d, $J$ = 10.2 Hz, 1H), 7.20–7.30 (m, 5H), 9.30 (br s, 1H), 9.85 (br s, 1H). *Compound* **11b**: mp 109–111 °C; HRESIMS 361.3212, $C_{23}H_{41}N_2O$ ($[M+H]^+$ of free base) requires 361.3219; $^1$H NMR (DMSO-$d_6$ 400 MHz) $\delta$: 1.36–1.38 (m,1 H), 1.48–1.58 (m, 5H), 1.58–1.64 (m, 5H), 1.65–1.73 (m, 5H), 1.96–2.12 (m, 7H), 2.90 (br s, 3H), 3.05 (s, 2H), 3.10 (s, 3H), 3.59 (d, $J$ = 7.3 Hz, 2H), 5.04–5.07 (m, 1H), 5.17–5.22 (m, 1H), 6.02 (s, 2H). *Compound* **11c**: mp 109–110 °C; HRESIMS 349.3024, $C_{22}H_{38}N_2F$ ($[M+H]^+$ of free base) requires 349.3019; $^1$H NMR (DMSO-$d_6$ 400 MHz) $\delta$: 1.28 (d, $J$ = 10.6 Hz, 2H), 1.56–1.71 (m, 17H), 1.80–1.88 (m, 3H), 2.34 (s, 1H), 2.81–2.83 (m, 3H), 2.97 (t, $J$ = 6.7 Hz, 2H), 3.60 (d, $J$ = 7.3 Hz, 2H), 5.07–5.09 (m, 1H), 5.20–5.24 (m, 1H), 6.04 (s, 2H).