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Synthesis and evaluation of carbamate prodrugs of SQ109 as antituberculosis agents

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ABSTRACT

The low bioavailability of **SQ109** in rats, resulting from first-pass effect in the liver, may be remedied by prodrug strategy. Based on esterase-sensitive carbamate prodrug strategy, a novel series of prodrugs of **SQ109** has been reported. Bioavailability of **SQ109** after administration of prodrug **7a** was 91.4% compared with 21.4% after oral administration of **SQ109**. After oral administration of compound **7a**, the parent drug **SQ109** exhibited preferential tissue distribution into lung and spleen, the target organs of tubercular infection and replication.

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Among infectious diseases, tuberculosis (TB) still remains the leading single-agent killer in the world, claiming over three million lives each year. The major challenges for tuberculosis control are the development of multidrug-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 an urgent need to develop new, potent, fast-acting antituberculosis drugs with low toxicity profiles that can be given in conjunction with other drugs used to treat HIV infection. Despite the increasing worldwide incidence of TB and its alarming threat toward the public health, no novel antituberculosis drugs have been introduced into clinical practice over the past four decades. Only within the last few years have several promising drug candidates emerged.[1,2]

N-Geranyl-*N*′-(2-adamantyl)ethane-1,2-diamine (**SQ109**, Fig. 1), a second-generation agent from the first-line drug ethambutol, entered clinical trail stage in 2005 and completed its phase Ia trial in 2007.[3–5] **SQ109** exhibited potent activity against *Mycobacterium tuberculosis* including multi-drug resistant mutants both in vitro and in vivo.[6] Unfortunately, **SQ109** showed poor oral bioavailability, only 12% in rats and 3.8–5% in dogs. The metabolism study of **SQ109** by Jia et al. in human liver microsomes suggested that the predominant metabolisms of **SQ109** were oxidation, epoxidation and N-dealkylation. It also indicated that the low bioavailability of **SQ109** might result from the effect of first-pass metabolism in the liver.[7]

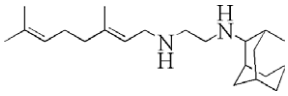

Figure 1. Structure of **SQ109**.

Prodrug strategy as a chemical/biochemical approach is often used to overcome various barriers which can hinder drug delivery, including minimization of the first-pass effect to improve oral bioavailability. Carbamate-based esterase-sensitive prodrug system has been used for prodrugs of amines and amidines.[8–12] The pioneering work in this area was done by Alexander and co-workers.[13,14] The results from these studies indicated that carbamate-based prodrugs had good chemical stability and were substrates of plasma esterases.

Herein, we report the synthesis and evaluation of compounds **7a–d,** carbamate prodrugs of **SQ109,** as antituberculosis agents. Synthesis of prodrugs **7a–d** is outlined in Scheme 1. The starting material geranylchloride **1** was converted to *N*-geranyl-2-aminoethanol **2** by treatment with 2-aminoethanol at ambient temperature, and then **2** was acylated to afford intermediates **4a–d** by treatment with corresponding chloroformates **3a–d** and triethylamine in THF at ambient temperature. Oxidation of **4a–d** by Swern oxidation procedure gave corresponding aldehydes **5a–d**. Reductive amination of these aldehydes with 2-admantylamine and $NaBH(OAc)_3$ yielded compounds **6a–d**. These intermediates were then

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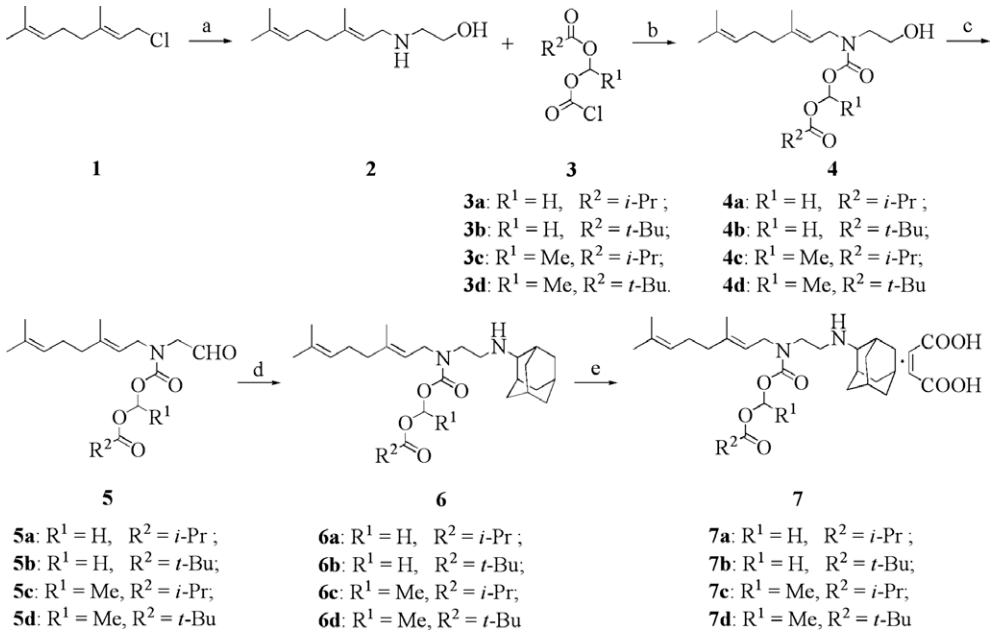

Scheme 1. Reagents and conditions: (a) 2-aminoethanol, 25 °C, 24 h; (b) triethylamine, THF, 0 °C, 2 h; (c) oxalyl chloride, dimethylsulfide, CH_2Cl_2, −60 °C, 30 min; then triethylamine, 15 min; (d) 2-admantylamine, $NaBH(OAc)_3$, 1,2-dichloroethane, 25 °C, 0.5 h; (e) maleic acid, ethanol, 25 °C, 0.5 h.

treated with maleic acid to yield the target compounds **7a–d**. The chemical structures of compounds **7a–d** were determined by ^{1}H NMR, LR-MS, and elemental analysis.[15]

With compounds **7a–d** in hand, we first examined their pharmacokinetic profiles. Unfortunately, compounds **7c** and **7d** were hydrolyzed with pH 7.4 Sorensen's buffer at room temperature in the chemical stability experiment. Then **7a** and **7b** were selected for further pharmacokinetic studies in rats. The analytical method for determining **SQ109** in various biomatrices and the method for pharmacokinetic studies with **7a** and **7b** were similar to that described by Jia et al.[7] Plasma concentration–time profiles of **SQ109** after oral administration of compounds **7a**, **7b** and **SQ109** were shown in Figure 2. After oral administration of compounds **7a** and **7b,** the prodrug was rapidly metabolized so that **7a** and **7b** could not be detected in the plasma samples, and the plasma concentration of **SQ109** was higher than that after administration of **SQ109** in the same dosage. Some relevant pharmacokinetic parameters are listed in Table 1. Oral bioavailability of **SQ109** in rats was 21.9%, whereas bioavailability of **SQ109** was 91.4% and 72.6% after oral administration of compounds **7a** and **7b**, respectively. Based on the Student's *t*-test ($P < 0.01$), bioavailability of **SQ109** after administration of prodrugs **7a** and **7b** was significantly greater than that after oral administration of **SQ109**. Given compounds **7a** and **7b** being prodrugs of **SQ109**, the increased bioavailability might result from minimization of the first-pass effect in the liver.

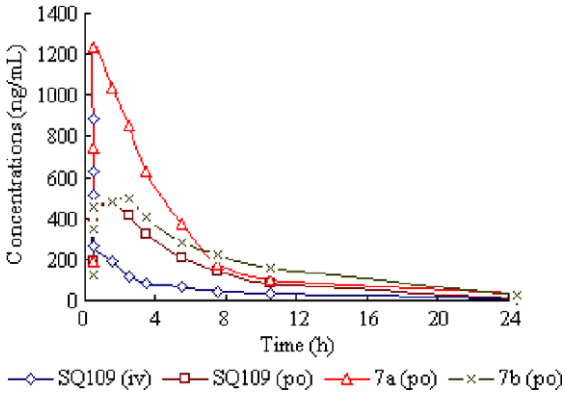

Figure 2. Mean plasma **SQ109** concentration–time curves after administration of **SQ109** (1.5 mg/kg iv and 13 mg/kg po) and administration of prodrugs (13 mg/kg po) in rats ($n = 4$).

After administration of compounds **7a** and **7b** (13 mg/kg, po) to rats, the concentration of **SQ109** in lung, liver, spleen and plasma were showed respectively in Figures 3 and 4. The concentration of **SQ109** in lung was higher than that in liver, spleen and plasma. Especially compound **7a**, at 4 h after po administration of 13 mg/kg dosage, the concentration of **SQ109** in lung was 35.08 μg/g, which was about 76-fold higher than the concentration in plasma; at

Table 1
Pharmacokinetic parameters of **SQ109** after administration of compounds **7a**, **7b** and **SQ109**.

($n = 4$)	**SQ109** (iv) 1.5 mg/kg	**SQ109** (po) 13 mg/kg	**7a** (po) 13 mg/kg	**7b** (po) 13 mg/kg
c_{max} (ng/mL)	888.76 ± 386.44	498.61 ± 125.31	1309.3 ± 797.5	585.6 ± 126.8
t_{max} (h)	na[a]	0.75 ± 0.29	1.0 ± 0.71	1.4 ± 0.8
$t_{1/2}$ (h)	5.06 ± 0.35	3.71 ± 0.47	4.58 ± 2.53	5.6 ± 0.8
Cl (L/kg/h)	1.05 ± 0.13	4.94 ± 0.77	2.49 ± 0.84	3.0 ± 0.8
$AUC_{0\to24}$ (ng h/mL)	1228.16 ± 314.14	2326.05 ± 1086.99	5441.2 ± 1773.5	4224.8 ± 1143.0
$F\%$[b]	na	21.9 ± 10.2	91.4 ± 29.8	72.6 ± 19.6

[a] Not available.
[b] $F\% = (AUC_{0\to24}\,(po) * M_{TD}/13\ mg/kg)/(AUC_{0\to24}\,(iv) * M_{SQ109}/1.5\ mg/kg)$. M_{TD} means the molecular weight of the tested drug, and M_{SQ109} means the molecular weight of **SQ109**. Values are expressed as mean ± S.D.

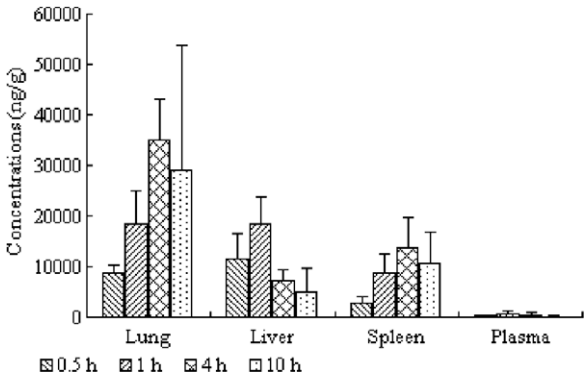

Figure 3. Mean administration of **SQ109** in tissues after administration of **7a** (13 mg/kg, po) in rats, S.D. for $n = 4$.

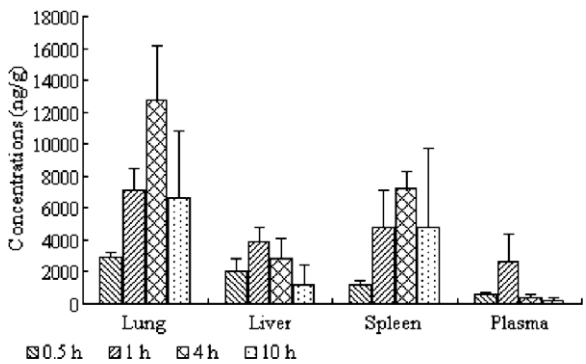

Figure 4. Mean administration of **SQ109** in tissues after administration of **7b** (13 mg/kg, po) in rats, S.D. for $n = 4$.

10 h, the concentration of **SQ109** in lung was still 29.03 μg/g, which was about 60-fold higher than the minimum inhibitory concentration (MIC) of **SQ109**. This tissue distribution experiment suggested that after oral administration of compounds **7a** and **7b,** the parent drug **SQ109** preferentially distributed into lung and spleen, the target organs of tubercular infection and replication. It is also in accordance with the result of tissue distribution experiment of **SQ109** by Jia et al.[6]

In summary, based on esterase-sensitive carbamate prodrug strategy, a novel series of prodrugs of **SQ109** has been reported. Bioavailability of **SQ109** after administration of prodrug **7a** was 91.4% compared with 21.4% after oral administration of **SQ109**. After oral administration of compound **7a**, the parent drug **SQ109** exhibited preferential tissue distribution into lung and spleen, the target organs of tubercular infection and replication. Further in vivo efficacy evaluation of compound **7a** is ongoing in our laboratories.

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15. *Compound* **7a**: white powder, mp: 151–153 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (d, $J = 7.0$ Hz, 6H), 1.56–1.60 (m, 5H), 1.64–1.74 (m, 10H), 1.85 (s, 4H), 1.90–2.12 (m, 8H), 2.55–2.61 (m, 1H), 3.05–3.10 (m, 3H), 3.43–3.53 (m, 2H), 3.84 (d, $J = 6.0$ Hz, 1H), 3.89 (d, $J = 5.6$ Hz, 1H), 5.06–5.11 (m, 2H), 5.71 (s, 2H), 6.01 (s, 2H), 8.20–8.40 (br s, 2H); ESI-MS (m/e): 475 $(M+H)^+$; Anal. Calcd for $C_{32}H_{50}N_2O_8$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.93; H, 8.46; N, 4.63. *Compound* **7b**: white powder, mp: 164–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.44 (s, 9H), 1.56–1.74 (m, 15H), 1.84–2.09 (m, 12H), 3.01–3.09 (m, 2H), 3.45–3.51 (m, 3H), 3.83 (d, $J = 6.4$ Hz, 1H), 3.90 (d, $J = 6.6$ Hz, 1H), 5.06–5.11 (m, 2H), 5.71 (s, 2H), 6.03 (s, 2H), 8.31 (br s, 2H); ESI-MS (m/e): 489 $(M+H)^+$; Anal. Calcd for $C_{33}H_{52}N_2O_8$: C, 65.54; H, 8.67; N, 4.63. Found: C, 65.53; H, 8.71; N, 4.47.