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Syntheses and studies of hydantoin derivatives as potential anti-tuberculosis inhibitors

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Abstract

A short and efficient synthesis of (*Z*)-2-substituted-5-(4-((2-substitued-5-oxoimidazolidin-4-ylidene)methyl)benzamido)benzoic acid derivatives (**8a**–**g**) as potential type of FabH inhibitors is described. Their structures were confirmed by MS, NOE and ^{1}H NMR.

Keywords: Tuberculosis; *Mycobacterium tuberculosis* FabH; Enzyme inhibitor; Synthesis; NOE

According to the data of the World Health Organization, tuberculosis (TB) caused by *Mycobacterium tuberculosis*, is considered to be a major cause of death from a single infectious agent in the world especially in countries lacking the necessary health care organization to provide the long and costly treatment adapted to patients [1]. As resistant strains of *Mycobacterium tuberculosis* and increasing HIV-positive TB cases have emerged, treatment failure is too often a fact [2,3]. An urgent requirement exists for the development of new anti-mycobacterial agents with a unique mechanism of action.

Fatty acid synthase (FAS) is a single multifunctional polypeptide that catalyzes all the reactions in the elongation pathway [4,5]. Mycobacteria contain both type I (FAS I) and type II (FAS II) pathways. *M. tuberculosis* β-ketoacyl–acyl carrier protein synthase III (*mt*FabH) is a key condensing enzyme responsible for initiation of FAS II fatty acid biosynthetic pathway, and has emerged as an attractive new target for novel anti-mycobacterial agents in recent years. We studied all available information concerning *mt*FabH inhibitors [6,7], substrates, and the active site topology from available *mt*FabH crystal structures. According to the known anti-mycobacterial 5-arylidene derivatives of hydration [8], we designed a serials scaffold of hydantoin derivatives. We chose *mt*FabH (PDB ID: 1HZP) [9] as the docking target, and used an automated molecular docking and database screening program DOCK 4.0 (http://www.cmpharm.ucsf.edu/kuntz/, University of California at San Francisco) [10]. The top 500 hydantoin derivatives from computer screening were carefully investigated. After taking drug-like property and synthetic accessibility into account, a subset of 7 candidate compounds were firstly chosen to be synthesized. The synthesis of a serious of potential *mt*FabH inhibitors are reported in this paper.

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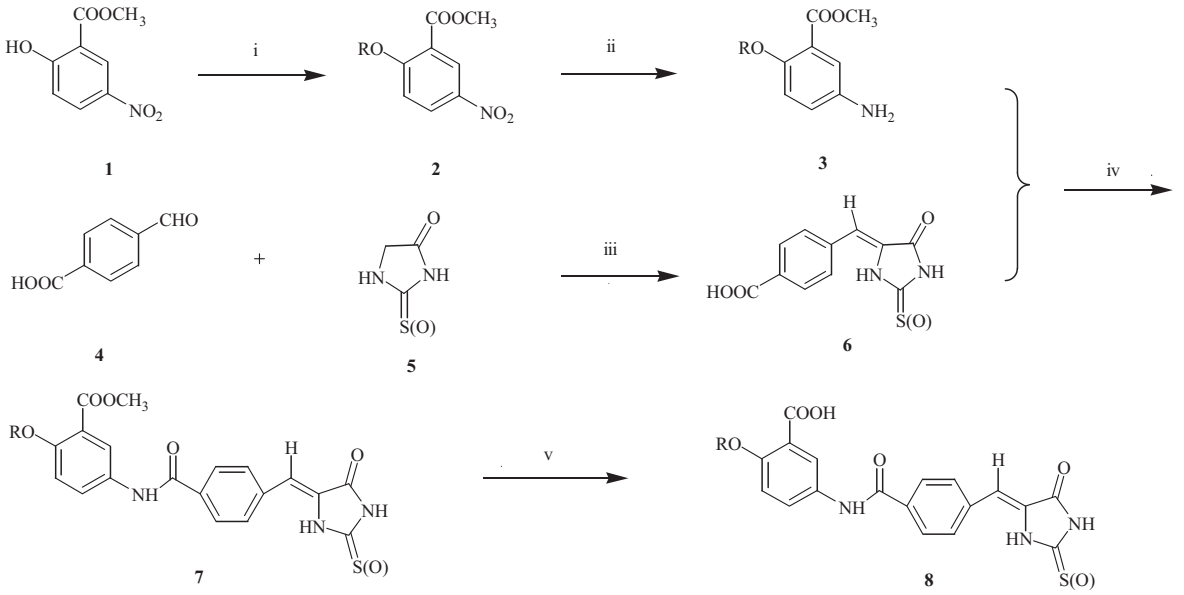

Scheme 1. Reagents and conditions: (i) RBr, K_2CO_3, DMF; (ii) $SnCl_2 \cdot H_2O$, C_2H_5OH; (iii) CH_3COOH, CH_3COONa; (iv) EDC HOBT, DIEA, DMF; (v) LiOH, CH_3OH, THF, H_2O.

The synthesis of the target compounds is shown in Scheme 1. Methyl 2-hydroxy-5-nitrobenzoate **1** was alkylated by the halogenated aliphatic hydrocarbons with *n*-Bu_4NI and anhydrous K_2CO_3 to get compound **2** [11]. The reduction of nitro with stannous chloride in refluxing ethanol afforded compound **3** [12]. On the other hand, compounds **6** were prepared as a result of condensation of 2-thioxoimidazolidin-4-one or imidazolidine-2,4-dione with 4-formylbenzoic acid refluxed in acetic acid with anhydrous sodium acetate [13]. The compound **3** and compound **6** converted into amide which was catalyzed by EDC hydrochloride with DIEA and HOBT [14].

Table 1
Analytical data of the compound **8a-g**.

Compd.	R	S or O	FAB MS (*m/z*)	^{1}H NMR (400 MHz, DMSO-d_6)
8a	Hexyl	O	450.6	12.17 (s, 1H), 11.35 (s, 1H), 10.73 (s, 1H), 10.27 (d, 1H, *J* = 12 Hz), 8.07 (d, 1H, *J* = 2.8 Hz), 7.98 (d, 2H, *J* = 8.4 Hz), 7.89 (m, 1H), 7.75 (d, 2H, *J* = 8.4 Hz), 7.11 (m, 1H), 6.47 (s, 1H), 4.00 (m, 2H), 1.45 (m, 2H), 1.44 (m, 2H), 1.30 (m, 4H), 0.88 (t, 3H, *J* = 6.8 Hz).
8b	Pentyl	O	436.6	12.58 (s, 1H), 11.36 (s, 1H), 10.74 (s, 1H), 10.32 (m, 1H), 8.07 (d, 1H, *J* = 2.8 Hz), 8.01 (d, 2H, *J* = 8.4 Hz), 7.90 (m, 1H), 7.76 (d, 2H, *J* = 8.8 Hz), 7.11 (d, 1H, *J* = 9.2 Hz), 6.47 (s, 1H), 4.00 (m, 2H), 1.68 (m, 2H), 1.30 (m, 4H), 0.88 (t, 3H, *J* = 14.8 Hz).
8c	Propyl	O	408.6	12.59 (s, 1H), 11.34 (s, 1H), 10.73 (s, 1H), 10.27 (m, 1H), 8.07 (d, 1H, *J* = 2.8 Hz), 7.98 (d, 2H, *J* = 8.4 Hz), 7.90 (m, 1H), 7.76 (d, 2H, *J* = 8.4 Hz), 7.10 (d, 1H, *J* = 9.2 Hz), 6.47 (s, 1H), 3.97 (t, 2H, *J* = 12.4 Hz), 1.70 (q, 2H, *J* = 14 Hz), 0.98 (t, 3H, *J* = 17.2 Hz).
8d	Ethyl	S	410.5	12.67 (s, 1H), 12.53 (s, 1H), 12.34 (s, 1H), 10.51 (s, 1H), 8.12 (d, 1H, *J* = 2.4 Hz), 8.05 (d, 2H, *J* = 8.4 Hz), 7.94 (m, 1H), 7.88 (d, 2H, *J* = 8.4 Hz), 7.11 (d, 1H, *J* = 9.6 Hz), 6.54 (s, 1H), 4.06 (q, 2H, *J* = 21.2 Hz), 1.32 (t, 3H, *J* = 14 Hz).
8e	Propyl	S	424.4	12.70 (s, 1H), 12.52 (s, 1H), 12.33 (s, 1H), 10.47 (s, 1H), 8.11 (d, 1H, *J* = 2.4 Hz), 8.04 (d, 2H, *J* = 8.4 Hz), 7.93 (m, 1H), 7.89 (d, 2H, *J* = 8.8 Hz), 7.11 (d, 1H, *J* = 8.8 Hz), 6.54 (s, 1H), 3.97 (t, 2H, *J* = 12.8 Hz), 1.71 (m, 2H), 0.98 (t, 3H, *J* = 14.8 Hz).
8f	Hexyl	S	466.5	12.51 (s, 1H), 12.32 (s, 1H), 10.33 (s, 1H), 8.08 (d, 1H, *J* = 2.8 Hz),8.02 (d, 2H, *J* = 8.4 Hz), 7.89 (m, 3H), 7.11 (d, 1H, *J* = 9.2), 6.55 (s, 1H), 4.00 (t, 2H, *J* = 12.8 Hz), 1.69 (m, 2H), 1.29 (m, 6H), 0.86 (t, 3H, *J* = 14 Hz).
8g	Pentyl	S	452.6	12.65 (s, 1H), 12.52 (s, 1H), 12.33 (s, 1H), 10.46 (s, 1H), 8.11 (d, 1H, *J* = 2.8 Hz), 8.04 (d, 2H, *J* = 8.4 Hz) 7.89 (m, 3H), 7.11 (d, 1H, *J* = 8.8 Hz), 6.54 (s, 1H), 4.00 (t, 2H, *J* = 12.8 Hz), 1.70 (m, 2H), 1.33 (m, 4H), 0.88 (t, 3H, *J* = 14 Hz).

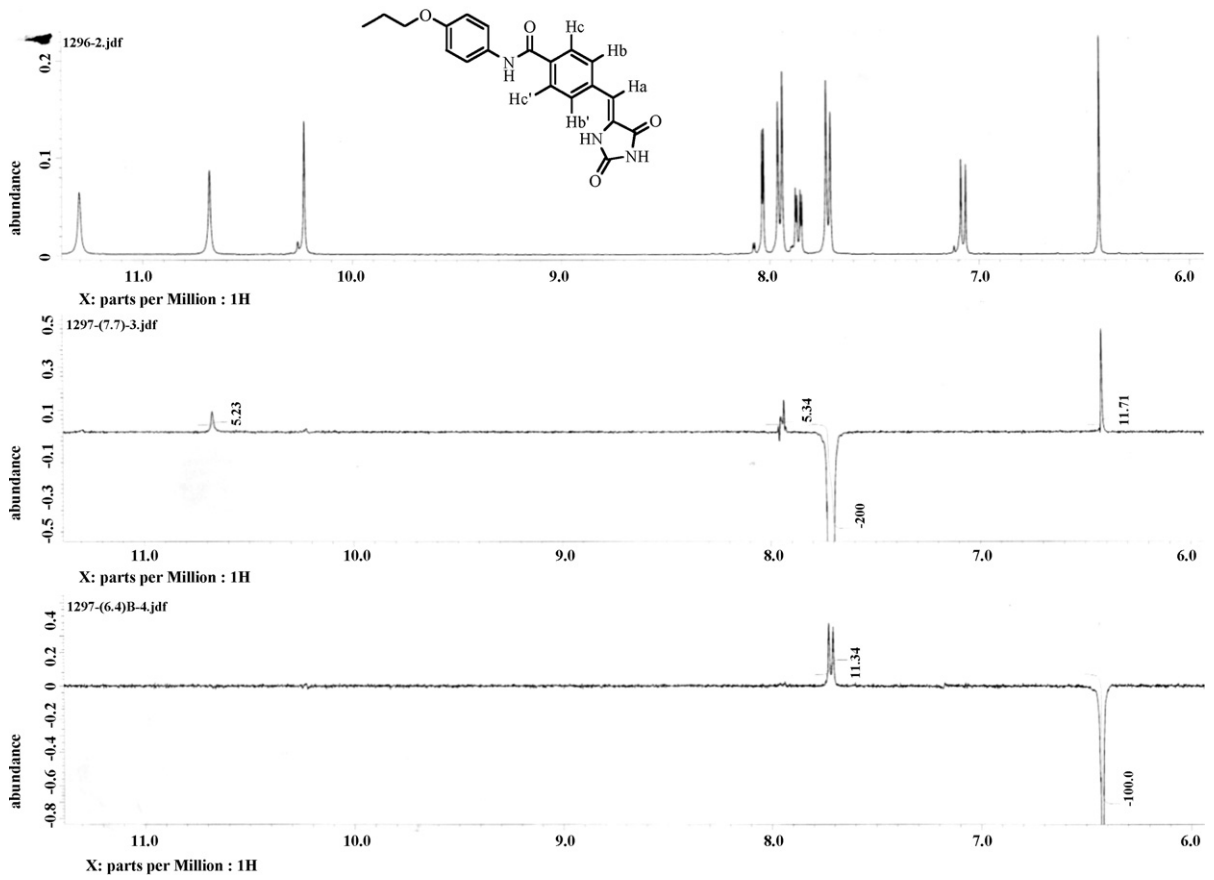

Fig. 1. The NOE analysis of compound **8c**.

The compound **7** underwent saponification by lithium hydroxide then were acidified by hydrochloride to yield the target compound **8** [15]. The target compounds were listed in Table 1.

As the steric position of benzylidene substituent was restricted by C/C bond, the target compounds could occur in either *E*-or *Z*-configuration. The steric position of the (*Z*)-5-(4-((2,5-dioxoimidazolidin-4-ylidene)methyl)benzamido)-2-propoxybenzoic acid **8c** was established by the H-a ^{1}H NMR(400 MHz, DMSO-d_6): δ 6.47 (s, 1H), coupled H-bb′ ^{1}H NMR(400 MHz, DMSO-d_6): δ 7.75 − 7.77 (d, 2 H, J = 8 Hz), coupled H-cc′ ^{1}H NMR(400 MHz, DMSO-d_6): δ 7.98 − 8.00 (d, 2H, J = 8 Hz) and 1-NH ^{1}H NMR(400 MHz, DMSO-d_6): δ 10.724 (brs, 1H), as shown in Fig. 1. In the NOE difference experiment for compound **8c** in DMSO-d_6 (Fig. 1), the 2nd part shows enhancement of the H-a, H-cc′ and 1-NH on irradiation of the H-bb′, and the 3th part shows enhancement of the H-bb′ on irradiation of the H-a. The result indicated that the formation of compound **8c** is *Z*-configuration. Spectrum associated with the NOE difference experiment can be found in the supporting information.

The antimycobacterial activities in vitro of the target compounds were studied. At a concentration of 12.5 μg/mL, all compounds exhibited inhibition on the growth of *M. tuberculosis* strain H_{37}Rv at 2 weeks, the resistant strains of Mycobacterium tuberculosis activity evaluation is still in progress.

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[11] Methyl 2-substituted-5-nitrobenzoate **2**. General procedure: To a solution of ethyl 2-hydroxy-5-nitrobenzoate 1 (2.0 g, 10 mmol) and *n*-Bu_4NBr (6.4 g, 20 mmol) in DMF (20 mL) were added anhydrous K_2CO_3 (2.8 g, 20 mmol) and halogenated aliphatic hydrocarbons (15 mmol). After stirring for 4 h at room temperature, to the reaction mixture 1 mol/L HCl (30 mL) was added. The organic portion was extracted with EtOAc (3 mL × 40 mL). The combined organic phase was dried for a while and then Na_2SO_4 was filtered out, the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, gradient elution with hexane: EtOAc (v/v) = 1:10–1:5) to give the corresponding product.
[12] Methyl 5-amino-2-substituted benzoate **3**. General procedure: To a solution of compound 2 (8 mmol) in ethanol (60 mL) was added stannous chloride dehydrate (0.99 g, 48 mmol). The mixture was stirred at 70 °C for 7 h, and half of the solvent was removed in vacuo. The residue was added ethyl acetate (3 mL × 40 mL). The organic layer was washed with aqueous solution of sodium hydroxide, dried with anhydrous sodium sulfate, and evaporated in vacuo. Chromatography the residue on silica gel gave the title compounds.
[13] (*Z*)-4-((5-substitued-2-thioxoimidazolidin-4-ylidene)methyl)benzoic acid **6**. General procedure: 4-Formylbenzoic acid **4** (10.0 g, 67 mmol) with anhydrous sodium acetate (22.0 g, 268 mmol) were successively added to a stirred solution of 2-substitued-imidazolidin-4-one **5** (70 mmol) in acetic acid (300 mL). The mixture was stirred at 120 °C for 0.5 h and then poured into water. The resulting mixture was stood overnight to form the precipitation. The crude solid was collected through filtration and air dried. The crude solid was crystallized twice with EtOAc to give pure compound.
[14] (*Z*)-Methyl-2-substituted-5-(4-((2-substitued-5-oxoimidazolidin-4-ylidene)methyl)benzamido)benzoate **7**. General procedure: To a stirred solution of compoud **6** (4 mmol) and compound **3** (4 mmol) in anhydrous DMF (50 mL), were successively added EDC hydrochloride with DIEA and HOBT. The mixture was stirred at 40 °C for 24−48 h and then poured into water. The resulting mixture was stood overnight to form the precipitation. The solid was collected through filtration and air crystallized twice with MeOH to give the title compound.
[15] (*Z*)-2-Substituted-5-(4-((2-substitued-5-oxoimidazolidin-4-ylidene)methyl)benzamido)benzoic acid **8**. General procedure: To a stirred solution of compound **7** in MeOH (50 mL) was added 1 mol/L LiOH (10 mL) at 25 °C. The mixture was stirred at the same temperature for 30 min. The aqueous layer was separated and was acidified with 1 mol/L HCl to pH-4. The aqueous layer was extracted with EtOAc (3 mL × 50 mL). The combined organic layer was dried (Na_2SO_4), filtered, and crystallized twice with EtOAc to give pure **8a–g**.