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# Design, synthesis, and pharmacological evaluation of a novel series of hormone sensitive lipase inhibitor

Tomoko Ogiyama [a,*], Mitsuhiro Yamaguchi [b], Nobuya Kurikawa [c], Shoko Honzumi [d], Koji Terayama [e], Nobumi Nagaoka [a], Yuka Yamamoto [f], Takako Kimura [g], Daisuke Sugiyama [h], Shin-ichi Inoue [h]

[a] Modality Research Laboratories, Daiichi Sankyo Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[b] R&D Planning & Management Department, Daiichi Sankyo Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[c] Venture Science Laboratories, Daiichi Sankyo Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[d] Rare Disease & LCM Laboratories, Daiichi Sankyo Co., Ltd, 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[e] End-Organ Disease Laboratories, Daiichi Sankyo Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[f] Biological Research Department, Daiichi Sankyo RD Novare Co., Ltd., 1-16-13, Kita-Kasai, Edogawa-ku, Tokyo 134-8630, Japan
[g] Organic Synthesis Department, Daiichi Sankyo RD Novare Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[h] Drug Metabolism & Pharmacokinetics Research Laboratories, Daiichi Sankyo Co., Ltd., 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan

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ABSTRACT

HSL inhibition is a promising approach to the treatment of dyslipidemia. As a result of re-optimization of lead compound **2**, we identified novel compound **25a** exhibiting potent inhibitory activity against HSL enzyme and cell with high selectivity for cholinesterases (AChE and BuChE). Reflecting its potent in vitro activity, compound **25a** exhibited antilipolytic effect in rats at 1 mg/kg p.o., which indicated that this novel compound is the most potent orally active HSL inhibitor. Moreover, compound **25a** did not show bioactivation liability.



## 1. Introduction

Hormone sensitive lipase (HSL) is an intracellular neutral lipase that mediates the hydrolysis of broad substrates such as tri-, di-, and monoacylglycerol (TG, DG and MG), cholesterylester, retinyl ester and water soluble ester substrates.[1] HSL is highly expressed in adipose tissues (ATs) where it catalyzes lipolysis of triglyceride into glycerol and free fatty acid (FFA).[2] The activity of adipose HSL is controlled by several hormones depending on energy demand.[3] In the fasted state, HSL is stimulated by catecholamines, and FFA is released into circulation as an energy source for most tissues.[4]

Although FFA plays an important role in energy homeostasis, the rise in plasma FFA level is associated with obesity and insulin resistance. These conditions cause dysregulation of lipolysis as a result of enlarged AT mass and attenuated insulin-mediated AT lipolysis metabolism. In addition, the increased FFA flux to the liver contributes to increased secretion of very-low-density lipoprotein (VLDL), one of the hallmarks of dyslipidemia in the metabolic syndrome.[5] For this reason, HSL inhibitors could have significant beneficial effects on lipid profile and thereby may contribute to reducing the CVD risk, but to date only limited efforts have been made to identify HSL inhibitors.[6–15]

We previously reported that phenylboronic acid derivatives as potent and orally active HSL inhibitors (Fig. 1).[16,17] By exchanging a metabolic labile benzyl group in compound **1**, benzanilide **2** was discovered as a novel lead compound with decreased bioactivation liability. To enhance HSL inhibitory activity in enzyme assay, hydrophobic moieties such as a trifluoromethyl benzene ring and a chloro group were introduced into the left- and right-hand moieties, which led to the identification of a potent HSL inhibitor **3**. Although compound **3** showed potent in vitro enzymatic activity, these optimization resulted in an increase in the lipophilicity ($LogD_{7.4}$ = 4.3) that resulted in poor solubility (JP1 = 1.8 μg/mL, JP2 = 1.5 μg/mL, and FaSSIF = 12 μg/mL). Thus, it appeared that further improvement of HSL inhibitory activity starting from compound **3** was difficult and we reconsidered optimization from lead compound **2** to explore new scaffolds. In this paper, synthesized compounds were evaluated in relation to cellular inhibitory activity as well as enzymatic inhibitory activity, since the

* Corresponding author.
*E-mail address:* yamamoto.tomoko.me@daiichisankyo.co.jp (T. Ogiyama).

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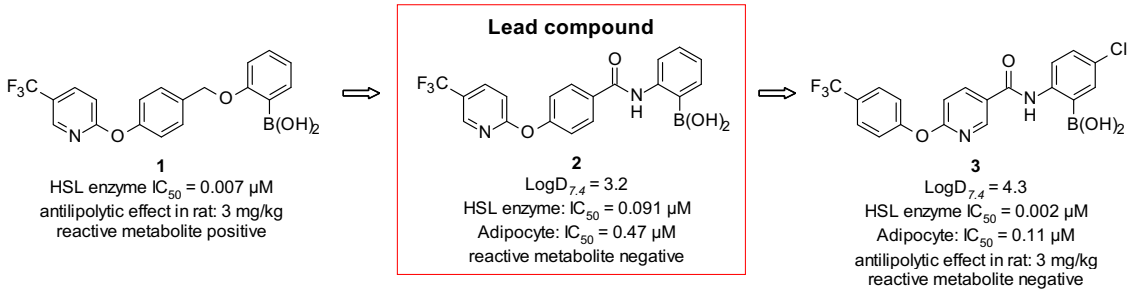
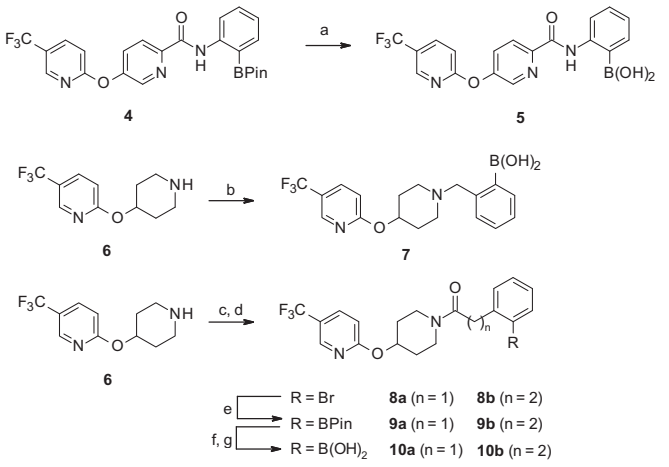



**Fig. 1.** HSL inhibitors.




**Scheme 1.** Reagents and conditions: (a) $NaIO_4$, THF, $H_2O$, then 1 M HCl; (b) 2-formylphenylboronic acid, $NaBH_4$, MeOH; (c) carboxylic acids, oxalyl chloride, DMF (cat.), $CH_2Cl_2$; (d) DIPEA, $CH_2Cl_2$; (e) Pd(dppf)$Cl_2$·$CH_2Cl_2$, bis(pinacolato)diboron, potassium acetate, 1,4-dioxane; (f) $KHF_2$, MeOH, $H_2O$; (g) TMSCl, $CH_3CN$, $H_2O$.

significant difference between cellular and enzymatic inhibitory activity was observed in the case of compound **2** and **3** (5.2 and 55-fold decrease, respectively).

## 2. Chemistry

Scheme 1 describes the synthesis of derivatives **5**, **7**, and **10a**-**10b**. Oxidative deprotection of pinacol (Pin) group in compound **4**[17] using sodium periodate led to **5**. Reaction of 2-formylphenylboronic acid under reductive amination conditions with amine **6** gave **7**. Intermediates **8a** and **8b** were synthesized by acylation of **6** with corresponding acids. Compound **10a** was obtained by Miyaura-Ishiyama borylation[18] of **8a** and following two-step deprotection of the pinacol group via fluorinated intermediates.[19] Compound **10b** was synthesized in a manner similar to that for compound **10a**.

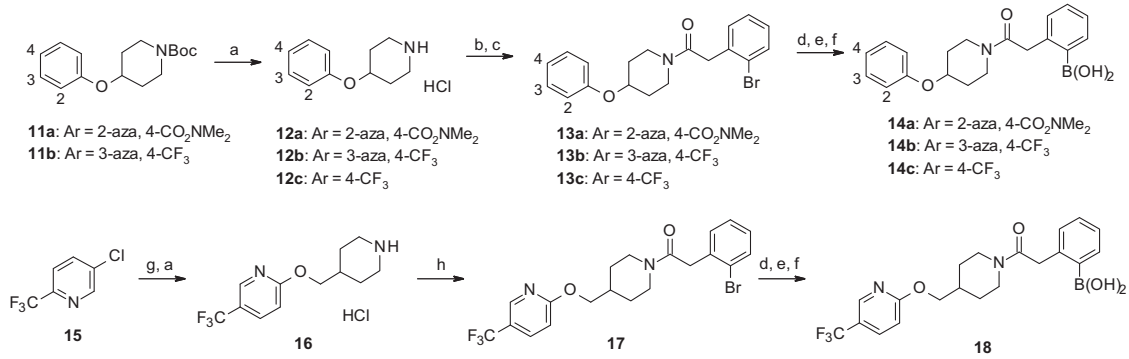
Scheme 2 illustrates the synthesis of compounds **14a**-**14c** and **18**. Deprotection of the Boc group in **11a**[20] and **11b**[21] yielded **12a** and **12b**, respectively. Amines (**12a**, **12b** and **12c**[22]) were condensed with 2-bromophenylacetic acid to give amides (**13a**-**13c**) which led to compounds **14a**-**14c** in a manner similar to that for compound **10a**. Condensation of **15** with 1-(*tert*-butoxycarbonyl)-4-piperidinemethanol furnished intermediate **16**, which was converted to compound **18** in a manner similar to that of compounds **14a**-**14c**.

Scheme 3 depicts the synthesis of derivatives **19**, **22** and **25a**-**25c**. Compound **9a** was converted to compound **19** using sodium periodate. Condensation of **20** with **6** afforded compound **21**, which was converted to compound **22** in a manner similar to that for compound **10a**. Compounds **25a**-**25c** were generated in a manner similar to that used for the synthesis of compound **22**.

## 3. Results and discussion

The inhibitory activity against HSL enzyme was measured by colorimetric assay using human HSL fractions and *p*-nitrophenyl butyrate (PNPB) as a substrate.[6] The cellular inhibitory activity was measured by glycerol concentration in rat subcutaneous fat tissue cells.

As mentioned above, the left- and right-hand moiety was thought to play a crucial role in enzyme activity; we first explored a central moiety (Table 1). Exchanging the benzene ring with pyridine ring resulted in a 10-fold decrease in inhibitory activity against HSL enzyme (**5**). Incorporation of methylpiperidine moiety led to a 6-fold decrease in HSL inhibitory activity (**7**). Introduction




**Scheme 2.** Reagents and conditions: (a) 4 M HCl/1,4-dioxane, 1,4-dioxane; (b) 2-bromophenylacetic acid, oxalyl chloride, DMF (cat.), $CH_2Cl_2$; (c) amines, DIPEA, $CH_2Cl_2$; (d) Pd(dppf)$Cl_2$·$CH_2Cl_2$, bis(pinacolato)diboron, potassium acetate, 1,4-dioxane; (e) $KHF_2$, MeOH, $H_2O$; (f) TMSCl, $CH_3CN$, $H_2O$; (g) 1-(*tert*-butoxycarbonyl)-4-piperidinemethanol, NaH, DMSO; (h) 2-bromophenylacetic acid, HBTU, DIPEA, DMF.