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Design and synthesis of potent, orally-active DGAT-1 inhibitors containing a dioxino[2,3-*d*]pyrimidine core

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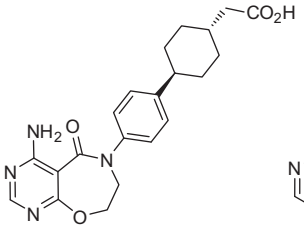
ABSTRACT

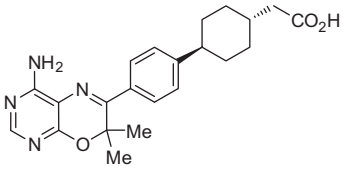
A novel series of potent DGAT-1 inhibitors was developed originating from the lactam-based clinical candidate PF-04620110. Incorporation of a dioxino[2,3-*d*]pyrimidine-based core afforded good alignment of pharmacophore features and resulted in improved passive permeability. Development of an efficient, homochiral synthesis of these targets facilitated confirmation of predictions regarding the stereochemical-dependence of DGAT-1 inhibition for this series. Compound **10** was shown to be a potent inhibitor of human DGAT-1 (10 nM) and to suppress triglyceride synthesis at oral doses of ≤3 mg/kg.

Increases in lipid stores in peripheral tissues, especially skeletal muscle, have been implicated in the development of insulin resistance[1] and the constellation of lipotoxic disorders associated with metabolic syndrome.[2] Lipid burden is largely controlled by triglyceride biosynthetic pathways. Acyl-CoA:diacylglycerol acyltransferases (DGAT) catalyze the terminal and rate-determining step in triglyceride biosynthesis.[3] DGAT-1 is expressed in key tissues involved in lipotoxicity, including skeletal muscle, heart, liver, as well as high expression in small intestine and adipose.[4] Inhibition of this key enzymatic step has thus garnered significant attention as a potential target for the treatment of disease states driven by excessive triglyceride burdens.[5]

Our team recently disclosed the discovery and pharmacology profile of the selective DGAT-1 inhibitor **1** (PF-04620110).[6] Compound **1** is currently in Phase I human clinical trials for the treatment of Type I diabetes. Design priorities leading to **1** centered on mimicking the key pharmacophore attributes present in **2**[7] and minimizing the potential for phototoxicity/photostability associated[6] with the pyrimido[4,5-*b*]oxazine core of **2**.[7] Following the discovery of **1**, our research efforts shifted to the identification of a follow-on candidate with an orthogonal risk profile. Given the excellent preclinical attributes of **1**, there were limited options for improvement/differentiation. While the fraction absorbed of **1** is moderate to high in preclinical species, it has poor passive membrane permeability (1×10^{-6} cm/s) which is driven by the high polarity ($\log D_{7.4} = -0.15$) of this compound.[8] Targeting reduced polarity became a goal for the design of second generation DGAT-1 inhibitors in our laboratory.



1
(PF-04620110)



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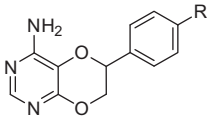

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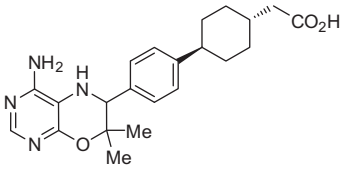

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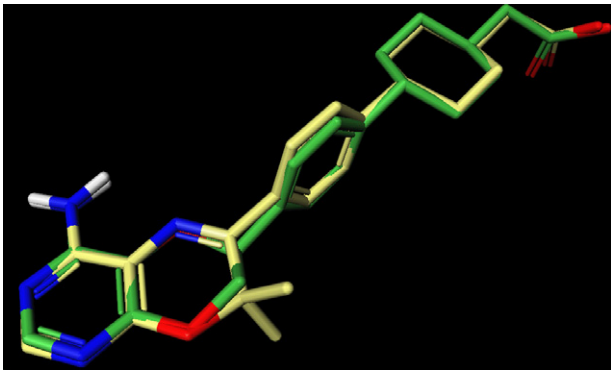


Figure 1. Overlay of minimized[10] conformations of **2** (yellow) and **10** (green).

Table 1
In vitro profiles of compounds **1**, **2**, **3**, **10–14** and **18**

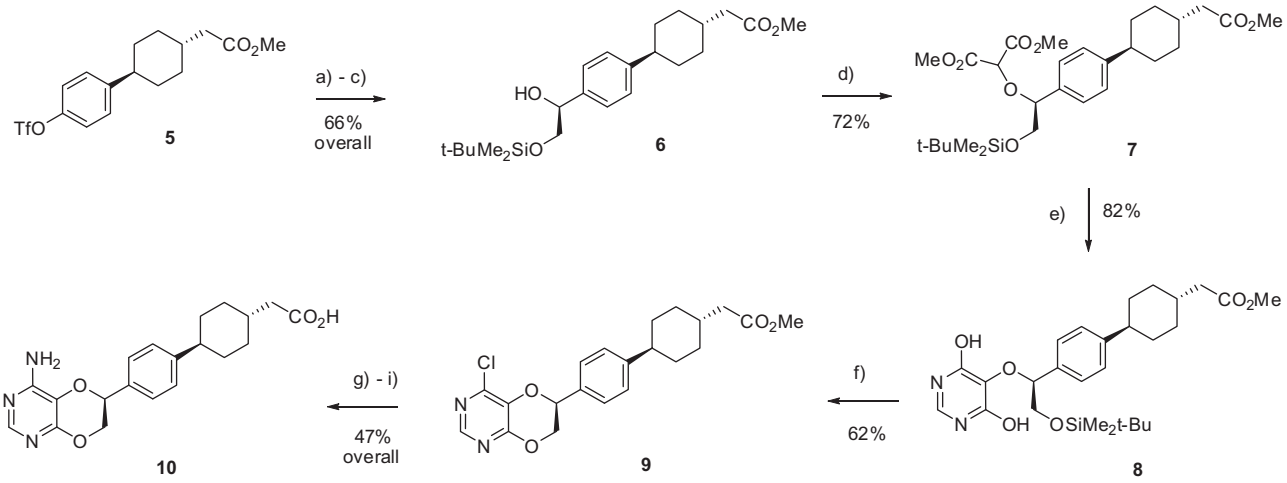
	DGAT-1 IC_{50}[a,b] (nM)	TG synthesis IC_{50}[b,c,d] (nM)	HLM Clapp[d] (mL/min/kg)
1	19	16	<8
2	72	8	<8
4	265	ND	<8
10	10	34	<8
11	18	77	<8
12	98	ND	<8
13	249	175	10
14	225	ND	ND
18	245	735	<8

[a] Average of ≥3 determinations, run in triplicate.
[b] Assay protocols can be found in Ref. 6.
[c] Inhibition of triglyceride synthesis determined in HT-29 cells. Average of ≥2 determinations run in triplicate.
[d] ND = value not determined.

Two key design elements drove the search for alternative chemotypes related to **1**: (1) retention of the key pharmacophore elements and (2) proper spatial relationship of these recognition elements as they are expressed in **1** and **2**. In evaluating a range of aminobicyclic cores, the dioxino[2,3-*d*]pyrimidine-based system (**3**) looked promising based on overlays of the minimized structure with either **1** or **2** (Fig. 1).[9] Structural constraints imposed on this 6,6-fused bicyclic suggested that both enantiomers of **3** would possess the desired near in-plane relationship between the core and the phenylcyclohexyl sidechain. We were encouraged by the finding that the dihydropyrimido[4,5-*b*]oxazine-based analog **4**[7] is within fourfold of **2** in potency (Table 1). In addition, substitution of this dioxinyl core for the lactam-based system of **1** was predicted to substantially increase lipophilicity (*c* Log *P* differential ~1.5 units) and thus favorably impact passive permeability.

The only reported synthesis of the aminobicyclic core of **3** is based on bis-alkylation of a 4-amino-5,6-dihydroxypyrmidine with dibromoethane.[11] The likelihood of poor regiocontrol/reactivity in utilizing such a transformation for the synthesis of compounds with a substituent on the dioxinyl ring led us to develop a stepwise approach to targets represented by **3** (Scheme 1). Two key hallmarks of the retro-synthetic strategy utilized in the development of an asymmetric synthetic route were: (1) construction of the pyrimidine ring from a functionalized sidechain precursor as a means of controlling regiochemistry and (2) application of Sharpless dihydroxylation[12] technology to generate homochiral products via a readily available vinyl sidechain intermediate.

Palladium catalyzed coupling of the previously reported triflate **5**[7] with potassium trifluoro(vinyl)borate provided the corresponding styrene intermediate.[13] Asymmetric dihydroxylation, followed by selective protection of the primary alcohol afforded **6** in 66% overall yield and >95% ee. Incorporation of a symmetrically-functionalized pyrimidine ring was accomplished via a two-step sequence. Insertion of the rhodium-carbene generated from dimethyl-diazomalonate gave ether **7** in 72% yield, along with 20% recovered **6**. Cyclization to this malonate with formamidine afforded dihydroxypyrimidine **8** in 82% yield. The initial approach developed to generate intermediate **9** involved a three-step sequence of silyl group deprotection, Mitsunobu cyclization and chlorination. However, it was subsequently found that heating **8** with phosphorus oxychloride in toluene directly afforded **9** in 62% yield. Displacement of the chloride with *p*-methoxybenzylamine, deprotection with trifluoro-acetic acid and ester hydrolysis provided *S*-isomer **10** in 47% overall yield from **9**. Compound **10** was confirmed to be of high stereochemical purity (>95% ee) by chiral HPLC.[14]



Scheme 1. Reagents and conditions: (a) potassium trifluoro(vinyl)borate, $PdCl_2(DPPF)_2$, TEA, *n*-propanol, reflux; (b) AD-mix-α, acetone, H_2O; (c) *t*-$BuMe_2SiCl$, imidazoles, DMF, −40 °C to 0 °C; (d) dimethyldiazo-malonate, $Rh_2(OAc)_4$, toluene, 100 °C; (e) formamidine acetate, NaOMe, MeOH; (f) $POCl_3$, toluene, reflux; (g) 4-methoxybenzylamine, *p*-dioxane, TEA, reflux; (h) TFA, 60 °C; (i) NaOH, *p*-dioxane, H_2O.