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Novel benzoylpiperidine-based stearoyl-CoA desaturase-1 inhibitors: Identification of 6-[4-(2-methylbenzoyl)piperidin-1-yl]pyridazine-3-carboxylic acid (2-hydroxy-2-pyridin-3-ylethyl)amide and its plasma triglyceride-lowering effects in Zucker fatty rats

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ABSTRACT

Starting from a known piperazine-based SCD-1 inhibitor, we obtained more potent benzoylpiperidine analogs. Optimization of the structure of the benzoylpiperidine-based SCD-1 inhibitors resulted in the identification of 6-[4-(2-methylbenzoyl)piperidin-1-yl]pyridazine-3-carboxylic acid (2-hydroxy-2-pyridin-3-yl-ethyl)amide (**24**) which showed strong inhibitory activity against both human and murine SCD-1. In addition, this compound exhibited good oral bioavailability and demonstrated plasma triglyceride lowering effects in Zucker fatty rats in a dose-dependent manner after a 7-day oral administration (qd).

Stearoyl-CoA desaturase-1 (SCD-1) is a rate-limiting enzyme in the synthesis of monounsaturated fatty acids from their saturated fatty acid precursors.[1,2] SCD-1, complexed with NAD(P)H, cytochrome b5 reductase, and cytochrome b5 introduces a double bond at the Δ9 position of the stearoyl (C18:0) and palmitoyl-CoA (C16:0).[1,2] The products of SCD-1, oleic (C18:1 *n*-9) and palmitoleic acids (C16:1 *n*-7), are the most abundant fatty acids found in phospholipids, cholesterol esters, and triglycerides. There are four isoforms (SCD1-4) in the mouse genome and two in the human genome (1 and 5).[3] The human SCD-1 gene shows 85% homology to murine SCD-1.[4]

SCD-1 has recently been shown to be a crucial factor in lipid metabolism and body weight control.[1–5] In adult mice, SCD-1 isoform is expressed in lipogenic tissues including the liver and adipose tissue. Deficiency of SCD-1 has been shown to cause defective hepatic cholesterol ester and triglyceride synthesis[5], resistance against obesity[5], and reduced liver steatosis in rodents.[6] In humans, the higher desaturation index (the ratio of oleate to stearate or 18:1/18:0) is strongly correlated with higher plasma triglyceride levels.[7] Even though the detailed mechanism by which SCD-1 deficiency affects body weight and adiposity is not completely understood, inhibition of SCD-1 may represent a novel approach for the treatment of metabolic syndrome.

In 2005, Xenon Pharmaceuticals published the first example of small molecule SCD-1 inhibitors (**1**, Fig. 1).[8a] Subsequently, Merck Frosst[8b–e] and Abbott Laboratories[8f–h] reported a series of piperazine- or phenoxypiperidine-based SCD-1 inhibitors (**2** and **3**, Fig. 1). In regard to other structural motifs for SCD-1 inhibitors, a group from CV Therapeutics reported 2-oxo-2*H*-quinoxalin-based structures[8i] and subsequently disclosed the structures of CVT-11,563 (**4**)[8j] and CVT-12,012 (**5**).[8k] We also previously reported 3-(2-hydroxyethoxy)-*N*-(5-benzylthiazol-2-yl)benzamides (**6**) as potent SCD-1 inhibitors.[9]

In our continuing investigation of the novel SCD-1 inhibitors as new pharmacological agents for the treatment of metabolic disorders such as dyslipidemia, obesity and diabetes, we initiated SAR studies of the pyridazine carboxamide structures reported by Xenon, Merck Frosst and Abbott. In a preliminary analysis of the compounds listed in Xenon's patents, we explored the SAR of the core pyridazine by replacing it with other 6-membered aryls such as in **7**, **8** and **9**. As shown in Table 1,[10] the replacements resulted in

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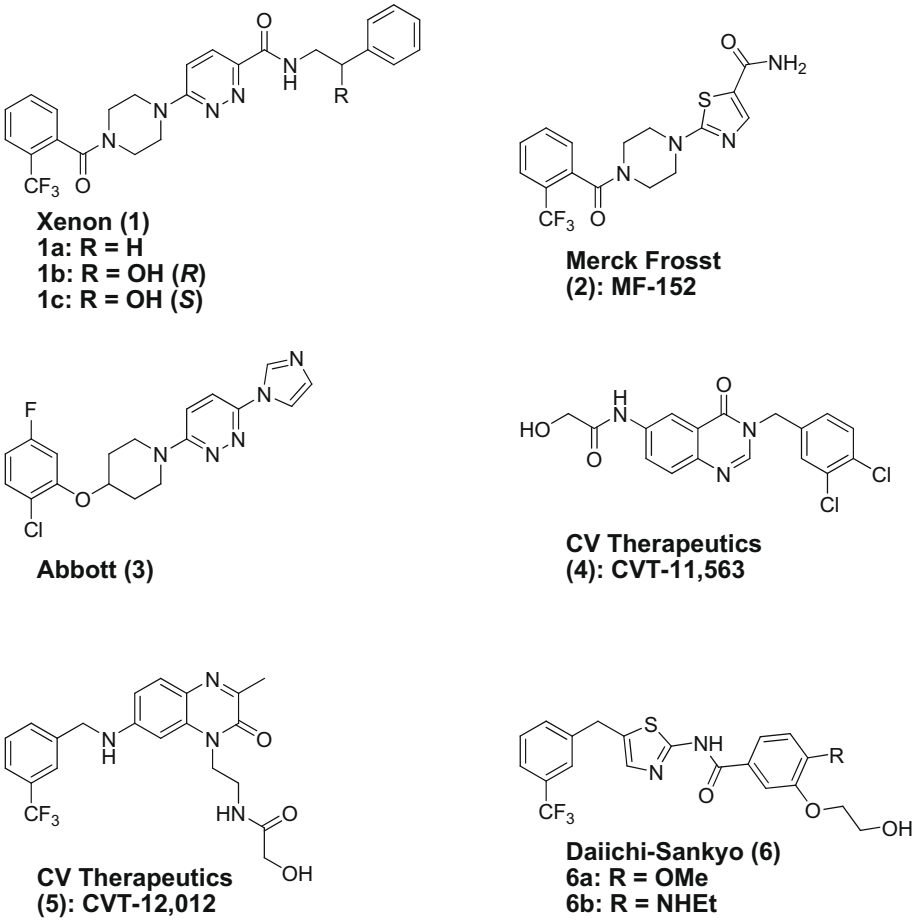
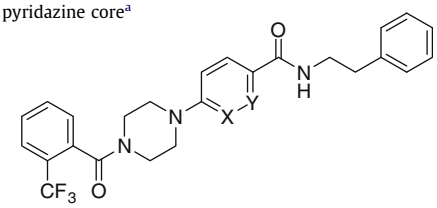


Figure 1. Structures of previously reported small molecule SCD-1inhibitors.

substantial loss of activity. These data convinced us that we should keep the pyridazine core for further structural modification. We then became interested in the modification of the piperazine fragment in **1**, particularly in the replacement of the benzoylpiperazine with benzoylpiperidine.[11a] Herein, we would like to disclose our efforts in SAR studies of benzoylpiperidine-based SCD-1 inhibitors and our evaluation of the plasma triglyceride (TG) lowering effects in Zucker fatty rats in response to the representative compound.

Table 1
Evaluation of pyridazine core[a]



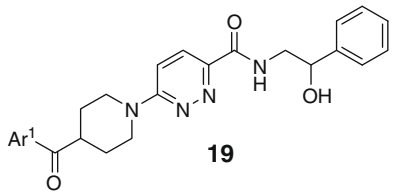
Compound	X	Y	Enzymatic assay[b]	
			IC_{50} (nM) Mouse microsomal Δ9	IC_{50} (nM) Human cell (293A) microsomal Δ9
1a	N	N	6	9
7	CH	N	370	250
8	N	CH	194	99
9	CH	CH	150	820

[a] Values are the arithmetic means of at least two experiments.
[b] See Supplementary data for the experimental procedures for the desaturase assay.

The synthetic routes for the compounds in Tables 2–4,[12] are outlined in Schemes 1–3. Starting from the commercially available 4-hydroxymethylpiperidine-1-carboxylic acid *tert*-butyl ester (**10**), the PCC oxidation, followed by addition of corresponding arylmagnesium bromide or aryllithium reagents, provided the secondary alcohol (**11**[13], Scheme 1). In the case of the CF_3-substituted analogs, special care must be taken because CF_3-substituted phenylmagnesium bromides have been reported to be explosive.[14] Specifically, residual magnesium dust resulting from the preparation of the Grignard reagents is presumed to be the cause of this explosiveness.[14] We recommend one of the following procedures for the preparation of CF_3-substituted derivatives; the use of aryllithium reagents prepared by lithium–halogen exchange protocols[13] or Knochel's procedure for low temperature magnesium–halogen exchange.[15] The secondary alcohol (**11**) was then subjected to Dess–Martin oxidation and deprotection to provide the benzoylpiperidines (**12**) for the subsequent coupling. The synthetic routes for the pyridazyl carboxamide intermediates are depicted in Scheme 2. The amino alcohols (**14**) or (**16**) were synthesized by sequential functional group manipulation, starting from the corresponding aldehyde (**13**) or ketone (**15**).

The commercially available 6-oxo-1,6-dihydropyridazine-3-carboxylic acid (**17**) was chlorinated and then condensed with the aminoalcohols (**14**) or (**16**) to provide the chloropyridazine (**18**). Both benzoylpiperidine (**12**) and chloropyridazine (**18**) in hand, the final coupling (Scheme 3) was carried out to provide the desired SCD-1 inhibitors for biological evaluation.

Table 2
Evaluation of benzoylpiperidines[a]



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Compound	Ar[1]	Enzymatic assay[b]		Cellular assay[b]	Enzymatic assay[b]
		IC_{50} (nM) Mouse liver microsomal Δ9	IC_{50} (nM) Human cell (293A) microsomal Δ9	IC_{50} (nM) Human cell (293A) Δ9	Inhibition% at 10 μM human Δ6
1b		25	25	71	NT[c]
1c		66	81	90	NT[c]
19a	2-CF_3-Ph	2	7	14	9
19b	2-Me-Ph	7	15	51	<5
19c	2-OMe-Ph	52	311	1048	<5
19d	2-OCF_3-Ph	5	10	103	<5
19e	Ph	153	292	108	<5
19f	4-F-Ph	74	118	80	12

[a] Values are the arithmetic means of at least two experiments.
[b] See Supplementary data for the experimental procedures for the desaturase assay and the cellular assay.
[c] NT = not tested.

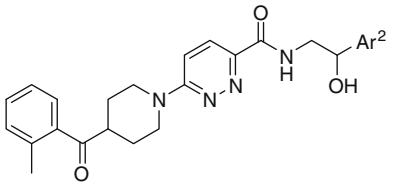
Table 3
ADME profiles[a] of representative benzoylpiperidine-based SCD-1 inhibitors

Compound	Solubility[b]		*c* Log *P*[c]	Murine liver S9
	JP-1 (μM) (pH 1.2)	JP-2 (μM) (pH 6.8)		Stability %[d] at 30 min
19a	84	<0.5	3.1	47
19b	88	3	2.6	58
19d	83	<0.5	3.4	22

[a] Values are the arithmetic means of at least two experiments.
[b] Aqueous acidic (JP-1) and neutral solution (JP-2) were purchased from Kanto Chemical Co., Inc. The sample solution was assayed using HPLC methodologies. 250 μM of the compound solution in aqueous CH_3CN solution (1:1 (v/v)) was prepared to make a calibration curve. The solubility was determined by comparing the UV peak area of the standard solution.
[c] The *c* Log *P* values were calculated by CLOGP software (Version 4.8.2, Daylight Chemical Information Systems, Inc.).
[d] Stability is described as% remaining after 30 min incubation with murine liver S9.

SCD-1 inhibition[13] by various 6-(4-benzoylpiperidin-1-yl)pyridazine-3-carboxylic acid (2-hydroxy-2-phenylethyl)amides (**19a–f**) are displayed in Table 2. In spite of a decrease in the inhibitory activity (5–10-fold) against both SCD-1s (murine and human) compared to the 2-phenylethylamide (**1a**), the (2-hydroxy-2-phenylethyl)amide (**1b** or **1c**) was chosen for the right-hand moiety because the hydroxyl group was expected to reduce lipophilicity. In regard to the stereochemistry of the hydroxyl group, the difference in potency was found to be insignificant (**1b** and **1c** in Table 2). The 2-CF_3-substituted benzoylpiperidine (**19a**) demonstrated stronger potency than the corresponding benzoylpiperazine analog (**1b** and **1c**), manifesting the favorable effect of the structural modification. The methyl (**19b**) and trifluoromethoxy (**19d**) presented comparably strong inhibitory activity against SCD-1s (both humans and mice) as the CF_3 (**19a**) while the methoxy (**19c**) and the non-substituted benzoyl (**19e**) showed weaker activity. The 4-F substitution (**19f**), employed in Xenon's SCD-1 inhibitor,[11] also resulted in weaker activity. As for heteroaryls other than phenyl, the pyridine analog (4-(3-methyl-pyridine-2-carbonyl)piperidine analog) showed more than 100-fold decrease in the human enzyme assay (IC_{50} = 2000 nM) compared to the corresponding phenyl analog (**19b**). In the context of selectivity towards other desaturase species, all of the compounds tested in this Letter exhibited very weak inhibitory activity, less than 50% inhibition at 10 μM, against Δ6 desaturase (Table 2). Among the potent substitutions (CF_3, OCF_3, and Me), the methyl substitution was chosen for further exploration of SAR since the lower lipophilicity provided by the Me substitution resulted in better solubility at neutral pH and more preferable metabolic stability in the presence of human liver microsome (Table 3).

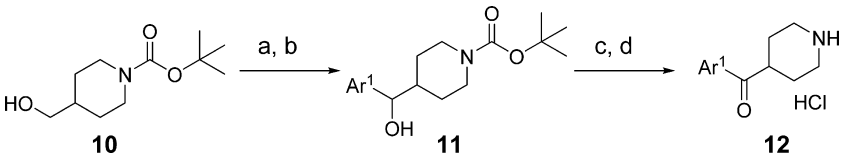
Table 4
Evaluation of the right-hand aryls[a]



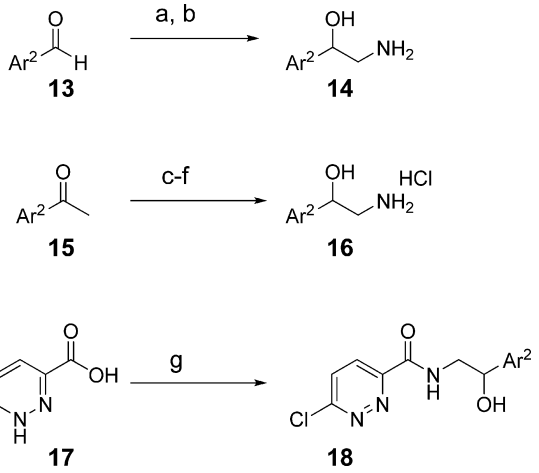
Compound	Ar[2]	Enzymatic assay[b]		Cellular assay[b]	db/db mice
		IC_{50} (nM) Mouse microsomal Δ9	IC_{50} (nM) Human cell (293A) microsomal Δ9	IC_{50} (nM) Human cell (293 A) Δ9	ID_{50}[b] (mg/kg)
19b	Ph	7	15	51	12
20	2-F-Ph	9	22	60	17
21	3-F-Ph	5	6	11	14
22	4-F-Ph	7	5	22	14
23	2-Py	95	180	390	NT[c]
24	3-Py	37	28	43	3
25	4-Py	34	187	144	NT[c]
26		3	7	21	16
27		7	44	25	14

[a] Values are the arithmetic means of at least two experiments.
[b] See Supplementary data for the experimental procedures for the desaturase assay, cellular assay, and the determination of ID_{50}.
[c] NT = not tested.

The SAR studies of the right-hand part of **19b** are displayed in Table 4. Substitution at the 2-position of the right-hand phenyl



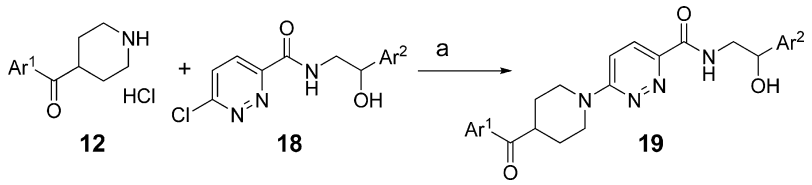
Scheme 1. Reagents: (a) PCC, CH_2Cl_2; (b) Ar^1MgBr or Ar^1Li, THF; (c) Dess–Martin periodinane; (d) 4 N HCl in 1,4-dioxane.



Scheme 2. Reagents and conditions: (a) TMSCN, Et_3N, CH_2Cl_2; (b) BH_3·THF; (c) NCS 4 N HCl, EtOAc; (d) $NaBH_4$, MeOH, H_2O; (e) NH_3 aq, MeOH; (f) concd HCl; (g) $SOCl_2$, DMF, $CHCl_3$, 50∼60 °C, then 14 or 16, Et_3N, CH_2Cl_2/DMF, 0 °C to rt.

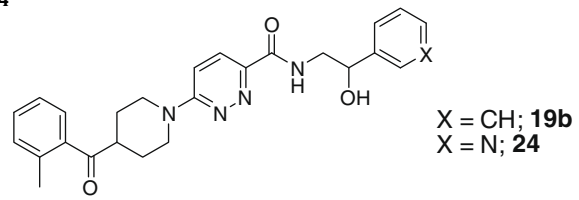
by the electron withdrawing fluorine (**20**) did not improve SCD-1 inhibition. However, substitution at the 3- or 4-position (**21** and **22**) resulted in about 3-fold improvement in the enzymatic and cellular SCD-1 inhibition. Replacement of the phenyl with pyridine resulted in weaker SCD-1 inhibition especially with 2- and 4-pyridine (**23** and **25**). The 3-pyridine (**24**) showed slightly weaker enzymatic activity compared to **19b** but maintained cellular inhibitory activity. The bioisosteric replacement of phenyl with thiophene (**26** and **27**) presented a twofold increase in the cellular inhibitory activity. The inhibitory activity of these compounds against SCD-1 in vivo was determined and compared by measuring the ratio of [^{14}C] stearate and [^{14}C] oleate in the liver of db/db mice.[13] The dose at which 50% of the conversion is inhibited is described as ID_{50}. The fluorine-substitution on the phenyl and the bioisosteric replacement of the phenyl with thiophene demonstrated in vivo potency comparable to **19b** with ID_{50} values of 12–17 mg/kg. The 2- and 4-pyridines (**23** and **25**) were not tested because of insufficient enzymatic and cellular inhibitory activity. The 3-pyridine (**24**), on the other hand, turned out to be the most potent compound in this series with an ID_{50} value of 3 mg/kg, indicating the importance of the position of the nitrogen atom in the right-hand pyridine.

The ADME and PK profiles of **19b** and **24** are shown in Table 5. For comparison, lead compound **1a** was not detected in the plasma of C57BL/6J mice at any time point (0–8 h) after oral administration (20 mg/kg). Compound **24** presented lower lipophilicity



Scheme 3. Reagents and conditions: (a) Et_3N, *n*-BuOH, 100 °C∼reflux.

Table 5
ADME and Pharmacokinetic profiles[a] of **19b** and **24**



No.	Solubility[b]		*c* Log *P*[c]	Murine liver S9 Stability %[d] at 30 min	PK[e] (iv, 5 mg/kg)			PK[e] (po, 20 mg/kg)			*F* (%)
	JP-1 (μM) (pH 1.2)	JP-2 (μM) (pH 6.8)			$t_{1/2}$ (h)	Cl (mL/min/kg)	V_d (L/kg)	C_{max} (μg/mL)	$t_{1/2}$ (h)	$AUC_{(0-8\ h)}$ (μg h/mL)	
19b	88	3	2.6	58	0.6	42	0.9	0.3	0.8	0.5	6
24	>100	29	1.1	78	1.3	29	2.4	6.3	0.9	7.8	68

[a] Values are the arithmetic means of at least two experiments.
[b] Aqueous acidic (JP-1) and neutral solution (JP-2) were purchased from Kanto Chemical Co., Inc. The sample solution was assayed using HPLC methodologies. 250 μM of the compound solution in aqueous CH_3CN solution (1:1 (v/v)) was prepared to make a calibration curve. The solubility was determined by comparing the UV peak area of the standard solution.
[c] The clog P values were calculated by CLOGP software (Version 4.8.2, Daylight Chemical Information Systems, Inc.).
[d] Stability is described as% remaining after 30 min incubation with murine liver S9.
[e] A dose of each compound was either intravenously (5 mg/kg, DMA/Tween80/saline = 10/10/80) injected into the tail vein of C57BL/6 J mice (n = 2) or orally (20 mg/kg, 0.5% MC, n = 3) administered using an intubation tube. Plasma samples (20 μL) were collected up to 8 h after intravenous or oral administration.

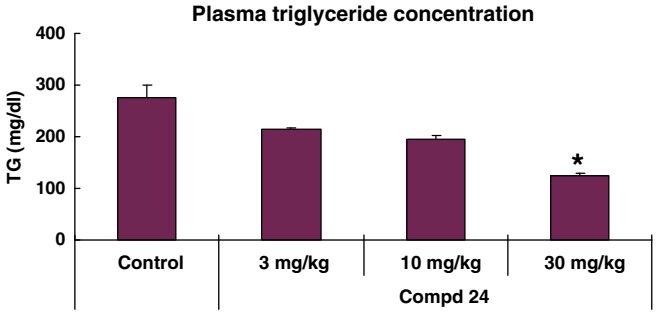


Figure 2. Plasma triglyceride reduction in Zucker fatty rats ($n = 4$, tested for significance in paired t-test,) after administration of **24** for 7 days (qd). $^{*}P = 0.012$ versus control.

(c Log $P = 1.1$) that resulted in better solubility at neutral pH and metabolic stability. With significant improvement in ADME profiles, **24** demonstrated a higher plasma concentration (C_{max} and AUC) and better bioavailability than those of **19b** in C57BL/6J mice after oral administration. It is fairly assumed that the favorable PK profiles of **24** led to a very strong inhibitory activity against liver SCD-1 in db/db mice.

For multiple dosing studies of SCD-1 inhibitors, **24** was tested in a 7-day efficacy study using Zucker fatty rats.[13] It is known that Zucker fatty rats incorporate a mutation in the leptin receptor that results in a 10-fold reduction in the binding affinity for leptin and significantly attenuated leptin signal.[16] The phenotype of the Zucker fatty rats includes components of Metabolic Syndrome such as obesity, insulin resistance and a dyslipidemia (e.g., hypertriglyceridemia and hypercholesterolemia).[17] After once-daily administration for 7 days, **24** dose-dependently reduced the plasma triglyceride levels (Fig. 2), with a 56% reduction at 30 mg/kg ($^{*}P = 0.012$ vs control). In addition, a 15% reduction (no statistical significance) in body weight gained was observed at 30 mg/kg, while there were only marginal changes in the plasma glucose and insulin levels. In the preliminary analysis, we did not observe severe abnormalities in the skin or eyes of the Zucker fatty rats at 30 mg/kg (cutaneous abnormalities and narrow eye fissure have been reported in studies on SCD-1 deficient mice[18]). We assume that the balanced combination of the strong potency and short plasma half life of **24** resulted in pharmacological efficacy in vivo and may be beneficial in preventing adverse events. Currently, we do not know the long term effect of **24** on Zucker fatty rats. However, some abnormalities[18] may be observable with an extended administration period. More detailed pharmacological studies of the 6-(4-benzoylpiperidin-1-yl)pyridazine-3-carboxamide-based SCD-1 inhibitors will be reported elsewhere.

In summary, we discovered a very potent and orally bioavailable SCD-1 inhibitor, 6-[4-(2-methylbenzoyl)piperidin-1-yl]pyridazine-3-carboxylic acid (2-hydroxy-2-pyridin-3-ylethyl)amide (**24**), by optimizing the structure of the piperazine-based SCD-1 inhibitor (**1**) that was reported in Xenon's patent. Structurally, the 2-Me substituted benzoylpiperidine on the left and 3-pyridyl on the right were the key elements to generate favorable PK profiles and in vivo potency. Further optimization of **24** and related compounds, especially structural modification of the 2-alkyl substituted benzoylpiperidine to develop novel ring structures, is currently in progress. Part of this effort will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.10.101.

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