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Design and discovery of new (3*S*,5*R*)-5-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]piperidine-3-carboxamides as potent renin inhibitors

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ABSTRACT

Utilizing X-ray crystal structure analysis, (3*S*,5*R*)-5-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]piperidine-3-carboxamides were designed and identified as renin inhibitors. The most potent compound **15** demonstrated favorable pharmacokinetic and pharmacodynamic profiles in rat.

Hypertension is a major risk factor for cardiovascular disease, including chronic heart and kidney failures, myocardial infarction and stroke and is one of the leading causes of death in the developed world.[1] The renin–angiotensin–aldosterone system (RAAS) plays an important role in the regulation of blood pressure and fluid homeostasis.[2] The inhibition of either the formation or the action of angiotensin II (Ang II), the main product of the RAAS, represents a major therapeutic approach in the treatment of hypertension and the prevention of associated comorbidities. Presently, inhibitors of the angiotensin-converting enzyme (ACE) and antagonists of the Ang II type-1 receptor (AT1R) are known as major drugs which modulate the RAAS.[3] It has long been hypothesized that inhibitors of renin, which is the rate-limiting enzyme in the RAAS cascade, may represent the most attractive therapeutic strategy to block the RAAS.[4] Despite the fact that many pharmaceutical companies have researched and developed renin inhibitors suitable for clinical development during the past few decades, only Aliskiren (**1**) has reached the market for the treatment of essential hypertension (Fig. 1).[5,6]

Recently, we discovered a novel class of renin inhibitors which contain our original 2,2-dimethyl-4-phenylpiperazin-5-one part in the P_3–P_1 portion.[7] These inhibitors showed potent renin inhibitory activity and specificity against other aspartic proteases without using the S_3^{sp} interaction, which is suggested to play an important role in the potent renin inhibitory activity and the specificity of Aliskiren.[8] Further chemical modifications of this series successfully led to the identification of a clinical candidate, DS-8108b (**4**).[9] Encouraged by this success, we explored a structurally new type of renin inhibitor possessing 2,2-dimethyl-4-phenylpiperazin-5-one in the P_3–P_1 portion to improve efficacy and oral bioavailability. Herein, we report our efforts to design and characterize the novel (3*S*,5*R*)-5-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]piperidine-3-carboxamides that demonstrate both favorable pharmacokinetic and pharmacodynamic profiles as renin inhibitors.

When we started our design of structurally new types of renin inhibitors, we focused on Roche's piperidine-based renin inhibitor **2** (Fig. 1).[10] The scaffold of compound **2** has served as the inspiration for the design of piperidine-based renin inhibitors, represented by **3** (ACT-077825, MK-8141) which has entered human clinical trials (Fig. 1).[11] Based on the reported structural analysis of piperidine-based inhibitors complexed with human renin,[12] it appears that the naphthyl group in compound **2** is located in the S_3–S_1 region. The large phenyl substituent at the 4-position of the piperidine ring is assumed to occupy the flap region, which is formed by the break of the hydrogen bond between Tyr75 and Trp39. The remaining substituent at the 3-position potentially

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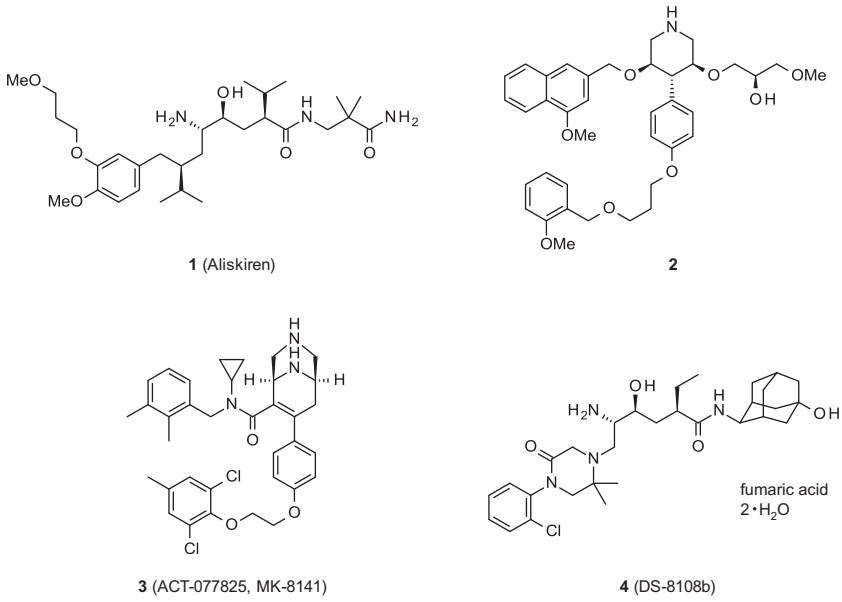


Figure 1. Chemical structures of **1** (Aliskiren), piperidine-based compounds **2** and **3** (ACT-077825, MK-8141), and our renin inhibitor **4** (DS-8108b).

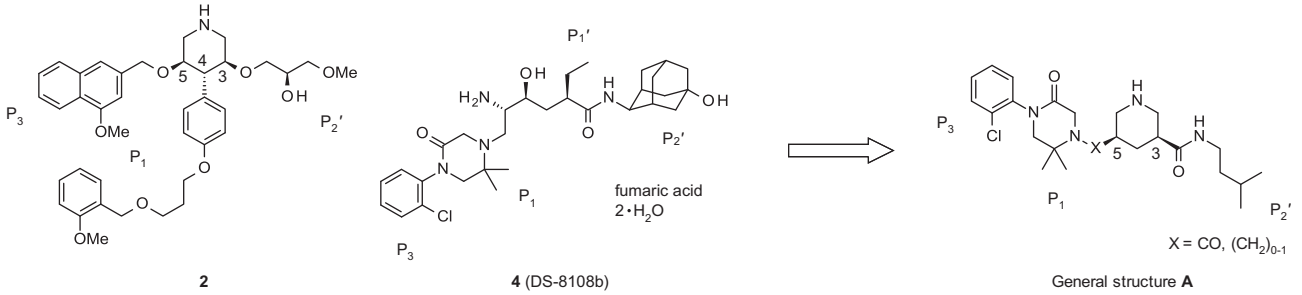


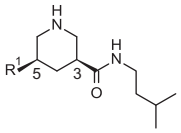
Figure 2. Design of a new series of 3,5-disubstituted piperidines having 2,2-dimethyl-4-phenylpiperazin-5-one.

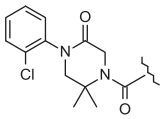
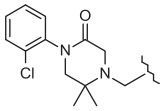
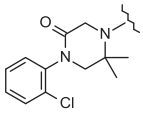
extends into the S_2' pocket. In the case of **1** or **4**, the flap region is closed and the *N*-terminal secondary amide part of the molecule is known to be docked in the S_2' pocket.[8b,9] Taking this into consideration, we initially designed a 3,5-disubstituted piperidine (General structure **A**) that possessed a tethered characteristic S_3–S_1 favored 2,2-dimethyl-4-phenylpiperazin-5-one substituent at the 5-position of the piperidine ring (Fig. 2). The large phenyl substituent at the 4-position was removed not only to reduce the molecular weight and lipophilicity, but to close the flap region similar to the case of **1** or **4**. Thus, the preference of the S_2' pocket for a secondary amide group, (3-methylbutylamino)carbonyl group, would be applicable to the substituent at the 3-position.

To evaluate the newly designed 3,5-disubstituted piperidine, the *in vitro* renin inhibitory activities of compounds **5** and **6** were initially measured (Table 1).[13] Compound **5**, which has a carbonyl group as a linker of ketopiperazine and piperidine, did not show any interesting renin inhibitory activity. However, the conformationally more flexible methylene-tethered compound **6** exhibited weak inhibitory activity for purified human renin, although the activity was insufficient. To identify the reason for the weak affinity, the X-ray crystal structure of **6** in complex with human renin was obtained. From the X-ray structure, it was found that the piperidine moiety of compound **6** interacted to the catalytic Asp residues as previously reported piperidine-based renin inhibitors.[11,12] However, the substituent on the 5-position of piperidine was revealed to adopt a presumed unstable pseudo-axial conformation relative to the ketopiperazine ring, and the piperidine ring was located spatially close to the ketopiperazine ring (Fig. 3). Based on this result, the direct connection between the piperidine ring and ketopiperazine part may be helpful at eliminating the presumed unstable conformation. Thus, we redesigned and synthesized compound **7** with an aim to find a more appropriate lead compound by locating the ketopiperazine part at a more suitable place in the binding pocket of human renin (Table 1). Piperidine analog **7**, which is directly substituted by ketopiperazine, had potent human renin inhibitory activity (IC_{50} = 7.7 nM in purified human renin). X-ray crystal structure analysis of **7** in complex with human renin indicated that the piperidine-5-yl group adopted a favorable pseudo-equatorial conformation against the ketopiperazine ring as expected (Fig. 4). This suggests that this favorable conformation contributed to the potent inhibitory activity of **7** against purified human renin.

After identifying the appropriate position of the 2,2-dimethyl-4-phenylpiperazin-5-one part relative to the piperidine ring, we focused on modifying the amide part at the 3-position of the piperidine ring to obtain a more potent lead compound. We obtained the X-ray crystal structure (S_1' and S_2' regions) of compound **7** (Fig. 5. A). The S_2' pocket was occupied by the isobutyl group (R^2) as expected. In addition, the existence of the empty S_1' pocket located around the R^3 moiety encouraged us to evaluate compounds having alkyl groups at R^3 (**8** and **9**). Installation of ethyl (**8**) or the slightly larger isobutyl (**9**) group improved the renin inhibitory activity. To confirm the substitution effect at R^3, benzyl amide derivatives were also synthesized (**10**–**12**). Compounds having an

Table 1
In vitro renin inhibitory activities (IC_{50}) of initial compounds[a]



Compound	R^1	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
5		>1000	>1000
6		406	>1000
7		7.7	54

[a] Compounds were obtained as fumarate salts.

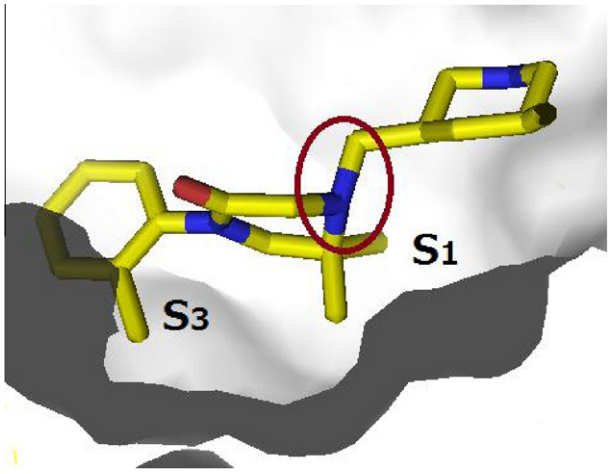


Figure 3. X-ray crystal structure of **6** in complex with human renin.[14] Pseudo-axial bond between the piperidine ring and ketopiperazine ring is indicated.

ethyl (**10**), propyl (**11**), or isobutyl (**12**) group showed about the same inhibitory activity as compounds **8** and **9** (Table 2). To verify the interaction of the alkyl substituent at R^3 with the S_1' pocket, the X-ray crystal structure of **9** bound to renin was obtained. The results indicated that, as expected, the isobutyl substituent at R^3 occupied the S_1' pocket (Fig. 5. B).

We then investigated the variation of the functionality at the P_2' portion (Table 3). While retaining the isobutyl group as a substituent of R^3, we evaluated the compounds having a hydroxyl (**13** and **14**), ether (**15**), dimethyl amide (**16**), phenyl (**12**), or 3-pyridyl (**17**) group at R^2. Although the dimethyl amide (**16**) decreased renin inhibitory activity, other compounds (**13**–**15**, **12**, and **17**) exhibited similar IC_{50} values against purified human renin as compound **9**. In particular, compound **15** containing an ether functionality showed potent inhibitory activity against monkey plasma renin (IC_{50} = 1.4 nM) as well as purified human renin (IC_{50} = 1.3 nM).

Since compound **15** appeared to possess potent inhibitory activity in both the purified human and monkey plasma renin assays, a pharmacokinetic study and a blood pressure lowering study were conducted to further characterize the compound. As listed in Table 4, good oral bioavailability was observed in SD rat (F = 45%). The antihypertensive efficacy of compound **15** was investigated in double transgenic rat (dTG rat) harboring both the human angiotensinogen and the human renin gene (Fig. 6).[15] Vehicle or 10 mg/kg of compound **15** was orally administered.[16] Compound **15** induced a significant reduction in mean arterial blood pressure (MAP) sustained over a period of 24 h. Based on these results, we concluded compound **15** was an attractive new lead compound for further exploration.

The synthetic pathway leading to compounds **7**–**17** is outlined in Scheme 1. Chiral carboxylic acid **20** was successfully obtained by the enantioselective ring opening of the known carboxylic acid anhydride **18**[17] with methanol in the presence of the sulfonyl amide **19**[18] as an asymmetric catalyst. Conversion of the carboxylic acid **20** to the *N*-allyloxycarbonyl protected amine by the Curtius rearrangement, replacement of the *N*-(*tert*-butoxycarbonyl) (Boc) group with the *N*-(2-nitrobenzenesulfonyl) (Ns) group[19], and *N*-allyloxycarbonyl group deprotection led to the corresponding amine **21**. Condensation of isobutylaldehyde with the amine **21** and chlorination with *N*-chlorosuccinimide yielded α-chloro

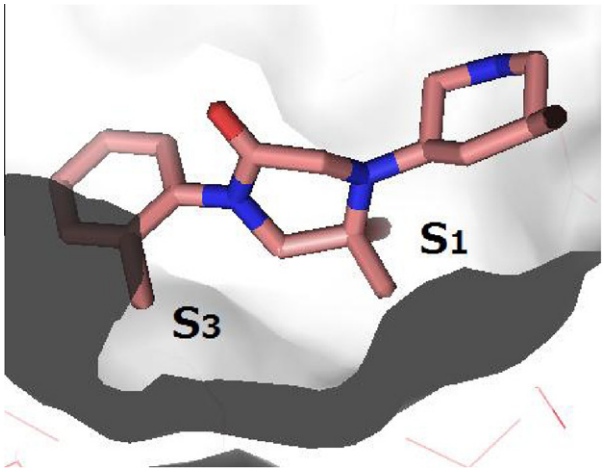


Figure 4. X-ray crystal structure of **7** in complex with human renin.[14]

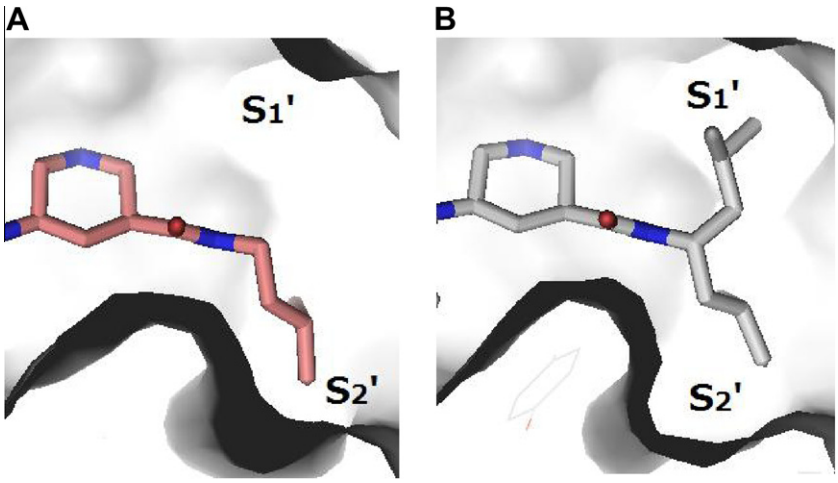
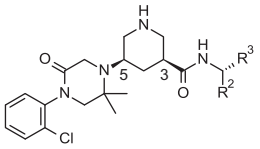


Figure 5. Crystal structures of human renin (S_1' and S_2' regions) in complex with **7** (A) or **9** (B).[14]

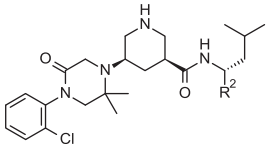
Table 2
In vitro renin inhibitory activities (IC_{50}) with modification of the amide part[a]



Compound	R^2	R^3	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
7	Isobutyl	H	7.7	54
8	Isobutyl	Ethyl	2.8	16
9	Isobutyl	Isobutyl	1.6	10
10	Ph	Ethyl	2.1	6.6
11	Ph	Propyl	2.5	18
12	Ph	Isobutyl	2.1	9.0

[a] Compounds were obtained as fumarate salts.

Table 3
In vitro renin inhibitory activities (IC_{50}) with modification of the P_2' portion[a]



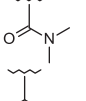
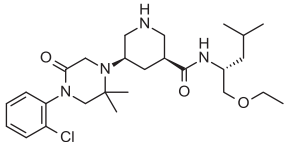
Compound	R^2		Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
9			1.6	10
13[b]		more polar	2.3	4.8
14[b,c]		less polar	2.5	7.5
15			1.3	1.4
16			8.4	23
12			2.1	9.0

Table 3 (*continued*)

Compound	R^2	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
17		2.1	4.2

[a] Compounds were obtained as fumarate salts.
[b] Stereochemistry is not determined.
[c] Compound **14** is the diastereomer of compound **13**.

Table 4
PK profile of compound **15** in SD rat



SD rat, male (10 mg/kg p.o., 0.5% MC)(1 mg/kg i.v., saline)	*F* (%)	45
	C_{max} (ng/mL)	540
	$AUC_{po,0-24}$ (ng∗h/mL)	1940
	CL (mL/min/kg)	31
	V_{ss} (L/kg)	5.8
	$t_{1/2}$ (h)	3.2

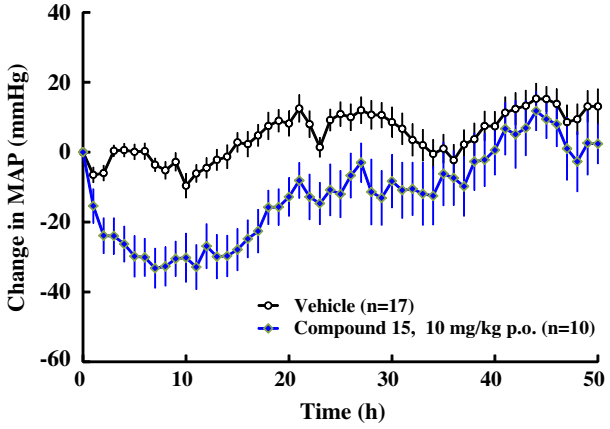
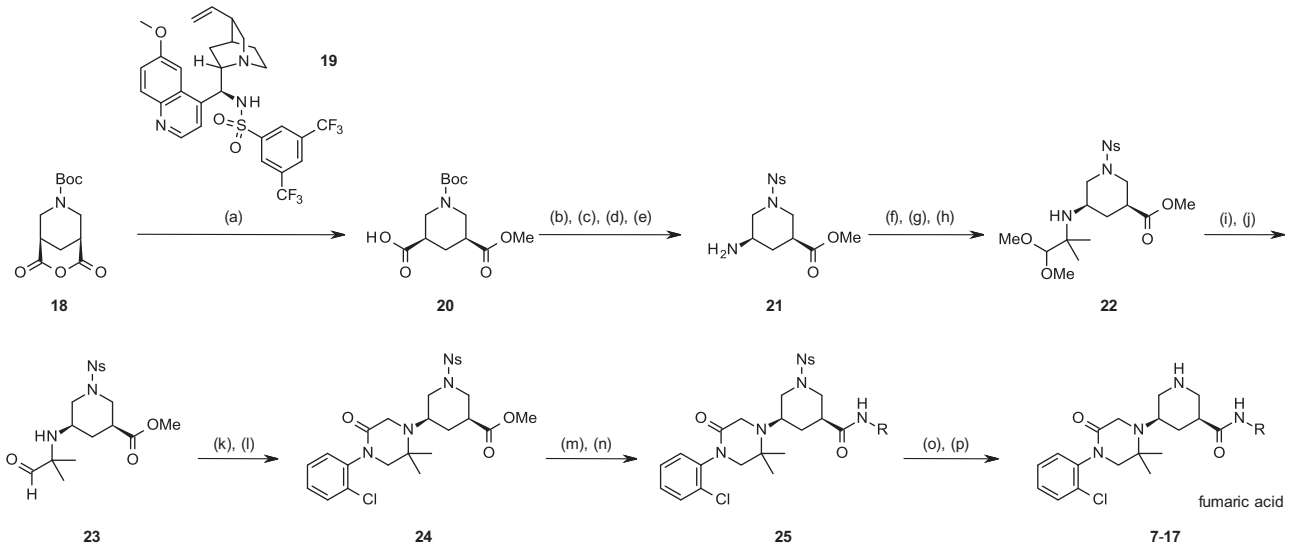


Figure 6. Effect of compound **15** on mean arterial pressure (MAP) in dTG rat.



Scheme 1. Synthetic pathway leading to (3*S*,5*R*)-5-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]piperidine-3-carboxamides **7**–**17**. Reagents and conditions: (a) **19**, CH_3OH, THF, −20 °C, 1 d, 69%, 94% ee; (b) diphenylphosphoryl azide, Et_3N, toluene, allyl alcohol, 90 °C, 15 h, 90%; (c) TFA, CH_2Cl_2, r.t., 1 h; (d) NsCl, Et_3N, CH_2Cl_2, r.t., 1 h, 75% (2 steps); (e) $(PPh_3)_4Pd$, morpholine, THF, r.t., 1 h, 81%; (f) isobutylaldehyde, CH_2Cl_2, r.t., 2 h; (g) *N*-chlorosuccinimide, CH_2Cl_2, r.t., 2 h; (h) CH_3OH, 60 °C, 18 h, 49% (3 steps); (i) conc. HCl aq., CH_2Cl_2, 40 °C, 4 h; (j) $SOCl_2$, CH_3OH, r.t., 1 h, 68% (2 steps); (k) 2-chloroaniline, AcOH, toluene, 110 °C, 2 h, then $NaBH(OAc)_3$, r.t., 6 h, 76%; (l) bromoacetyl bromide, Et_3N, CH_2Cl_2, 0 °C, then 40 °C, 5 h, 66%; (m) 1*N* NaOH aq., CH_3OH, 50 °C, 0.5 h, quant.; (n) amine (R-NH_2), HBTU, diisopropylethylamine, DMF, r.t., 5 h; (o) PhSH, Cs_2CO_3, CH_3CN, r.t., 1.5 h; (p) fumaric acid, CH_3OH, r.t., 1 min.

aldimine. Treatment of the α-chloro aldimine with methanol gave the rearranged product **22** via the ring opening of the corresponding aziridine intermediate.[20] The dimethyl acetal and methyl ester in **22** were hydrolyzed with concentrated hydrochloric acid, then esterification of the carboxylic acid with thionyl chloride and methanol provided aldehyde **23**. The aldehyde **23** was converted into ketopiperazine **24** by reductive amination with 2-chloroaniline and subsequent ring formation with bromoacetyl bromide. The condensation of various amines[21] and carboxylic acid resulting from the hydrolysis of compound **24** afforded the amides **25**. Finally, removal of the *N*-Ns groups, then addition of fumaric acid gave compounds **7**–**17** as fumarate salts.

In summary, we have described the design and discovery of (3*S*,5*R*)-5-[4-(2-chlorophenyl)-2,2-dimethyl-5-oxopiperazin-1-yl]piperidine-3-carboxamides as new types of renin inhibitors by using X-ray crystal structure analysis. The application of the concept of using interactions with both S_1' and S_2' pockets resulted in an improvement of the renin inhibitory activities. The most potent compound **15** demonstrated 45% oral bioavailability in SD rat and was orally efficacious in a dTG rat model of hypertension. From these encouraging results, we selected compound **15** as a new lead compound. Further optimization to acquire a more promising compound is under investigation. These results will be reported in due course.

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13. Assays were performed with the same procedure described by in Ref. 9. Assay results are the average of at least two replicates.

14. The X-ray crystallographic studies were accomplished according to the procedure described in Ref. 9. Coordinates and statistics are available from the PDB using accession code 3VYD (complex with **6**), 3VYE (**7**), and 3VYF (**9**).
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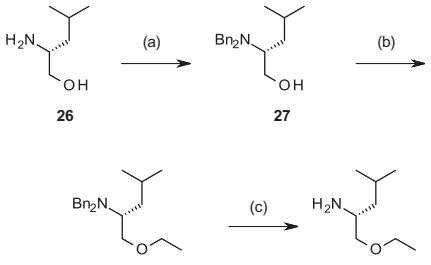
21. Chiral amine **29** used for the synthesis of compound **15** was prepared as follows.[a]



26 **27** **28** **29**

[a]Reagents and conditions: (a) BnBr, K_2CO_3, ethanol, r.t., 4 d, 85%; (b) ethyl iodide, NaH, THF, r.t., 1 d, 81%; (c) H_2, 20% $Pd(OH)_2$ on carbon, CH_3OH, r.t., 1 d, 98%.