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Design and optimization of novel (2*S*,4*S*,5*S*)-5-amino-6-(2,2-dimethyl-5-oxo-4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropylhexanamides as renin inhibitors

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ABSTRACT

Introduction of the 2,2-dimethyl-4-phenylpiperazin-5-one scaffold into the P_3–P_1 portion of the (2*S*,4*S*,5*S*)-5-amino-6-dialkylamino-4-hydroxy-2-isopropylhexanamide backbone dramatically increased the renin inhibitory activity without using the interaction to the S_3^{sp} pocket. Compound **31** exhibited >10,000-fold selectivity over other human proteases, and 18.5% oral bioavailability in monkey.

Hypertension is the most prevalent cause for cardiovascular diseases, such as heart failure, stroke and kidney failure.[1] It has been estimated that there are currently about 1 billion people who suffer from hypertension. Although lowering blood-pressure can considerably reduce the above risks, about 70% of patients with hypertension still do not reach their target blood pressure levels.[2] Thus, well-tolerated effective medicines for sufficient blood pressure control are desired.

The renin–angiotensin–aldosterone system (RAAS) controls blood pressure and body fluid electrolytes homeostasis.[3] In this system, renin is the first rate-limiting step which leads to generation of angiotensin I. Inhibition of this step would not only provide a better potential for the blood pressure lowering effect and end organ protection,[4] but also cause fewer mechanism-based adverse events than the current therapeutic medicines, angiotensin converting enzyme inhibitors and angiotensin receptor 1 blockers, that target downstream events of the RAAS pathway.[5]

Accordingly, several renin inhibitors based on diverse scaffolds such as peptidomimetic **1** (remikiren),[6] 8-phenyloctanamide **2** (aliskiren),[7] piperazine **3** (ACT-077825, MK-8141),[8] and alkyl amine **4** (VTP-27999)[9] with different renin active-site binding topologies have entered human clinical trials (Fig. 1). To date, aliskiren is the only compound which has been launched to the market.[2b]

Recently, we and Novartis group discovered novel renin inhibitors (2*S*,4*S*,5*S*)-5-amino-6-dialkylamino-4-hydroxy-2-isopropylhexanamides, replaced a chiral center at the 7-position of 8-phenyloctanamides with nitrogen, as exemplified by compound **5**, respectively (Fig. 2).[10,11] This replacement offers several advantages over 8-phenyloctanamides such as decrease in chemical complexity, ease of synthesis, and accessibility to the structure–activity relationship (SAR) studies. However, compound **5** was less active than aliskiren and the potential attractiveness of this series for more extensive investigations was limited.[11] Thus, we attempted to modify the P_3–P_3^{sp}–P_1 portion of compound **5** to find a new lead compound. In this letter, we report the design and initial optimization of novel (2*S*,4*S*,5*S*)-5-amino-6-(2,2-dimethyl-5-oxo-4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropyl-hexanamides.

By comparison of the P_3 and P_1 pharmacophores of peptidomimetic **1** and compound **5**, we initially designed the tethered compound (General structure **A**), bearing a phenyl group appended to a piperidine ring directly (Fig. 2).[12] This piperidine ring was intended

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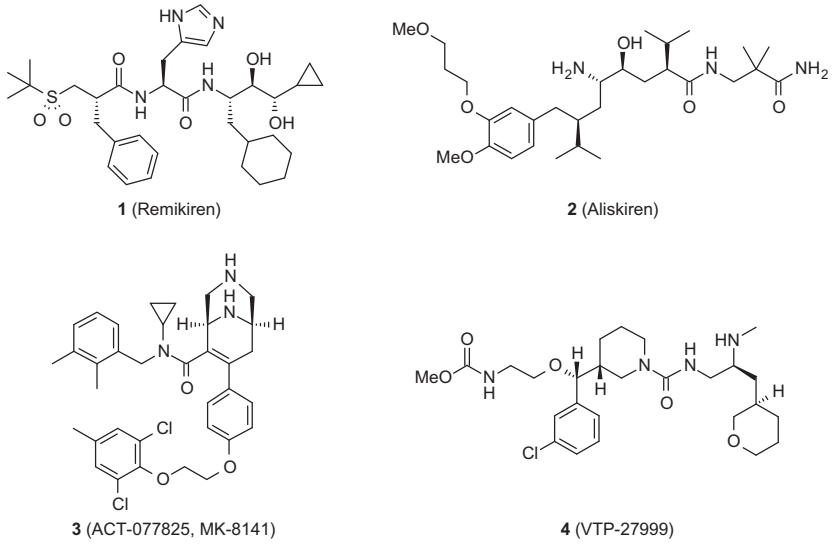


Figure 1. Structures of renin inhibitors.[6–9]

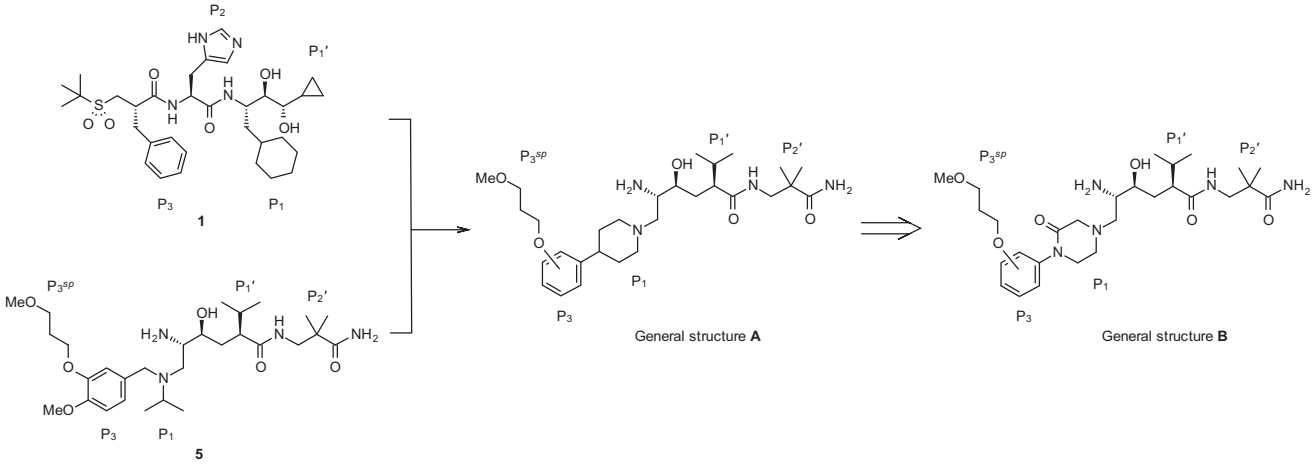


Figure 2. Design of a new series of (2*S*,4*S*,5*S*)-5-amino-6-(4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropylhexanamides.

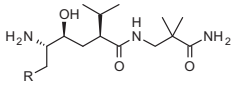
to avoid any chiral center at the P_1 position and utilize our synthetic procedure developed for the synthesis of compound **5**.[13] At the same time, a methoxypropoxy sidechain was installed to the *ortho* or *meta* position of the phenyl portion in the hope to further increase potency by interaction with the $S_3{}^{sp}$ pocket.[12c,14] As the next step, we considered the piperazine ring was proposed to have a similar conformation compared to the piperidine ring. To reduce the number of basic nitrogen and electron density on the tethered benzene ring, the ketopiperazine analogue (General structure **B**) was eventually designed as an alternative for the piperazine ring.

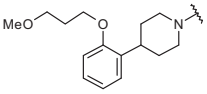
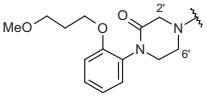
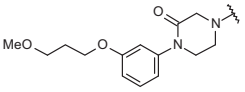
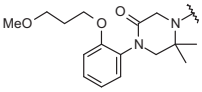
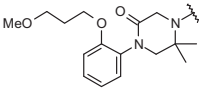
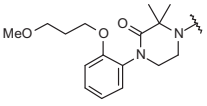
An early SAR study of the P_3–$P_3{}^{sp}$–P_1 portion found that the ketopiperazine ring was resulting in higher potencies as compared to the piperidine ring as a P_1 motif (Table 1, *rac*-**6** vs *rac*-**7**), and the *ortho* position was preferable for the $P_3{}^{sp}$ aryl sidechain than the *meta* position (*rac*-**7** vs *rac*-**8**).[15] These results were explained by the X-ray crystal structure of compound **7** in complex with human renin; a hydrogen bond interaction was observed between Thr77 and the carboxamide oxygen of the ketopiperazine with a distance of 2.7 Å, and the methoxypropoxy sidechain was well accommodated by the $S_3{}^{sp}$ (Fig. 3a).[16] Thus, compound **7**, which possessed modest potency, was selected as a reasonable starting point for further chemical modification. The superposition of the X-ray crystal structures of compound **7** and aliskiren (**2**) suggested that introduction of geminal dimethyl groups at the 6′ position of the ketopiperazine ring could enhance potency through additional hydrophobic interactions with the S_1 pocket (Fig. 3b). To test this hypothesis, we prepared compound **9**. As expected, *rac*-**9** exhibited dramatically improved potency in both the purified human and the cynomolgus monkey plasma renin assays. On the other hand, introduction of geminal dimethyl groups into the 2′ position, which might be tolerated through rotation around C6-N1′, showed no improvement (compound **10**). A further enhancement was observed when *rac*-**9** was converted to optically active (2*S*,4*S*,5*S*)-**9**.

As the next step, we modified the $P_3{}^{sp}$ aryl sidechain, which is essential for aliskiren to contribute to high potency (Table 2).[12c,14] To our surprise, compounds **11–13** with a shortened chain length exhibited strong inhibitory activities against human renin with only slight reductions in monkey plasma. In addition, compound **14** lacking the $P_3{}^{sp}$ aryl sidechain retained strong human renin inhibitory activity. These interesting results prompted further modifications of the P_3 portion with small substituents (Table 3).

Introduction of small substituents to the *ortho* position retained high human renin inhibitory activities (compounds **15–17**, and **23**). On the other hand, introduction to the *meta* position (compounds **18**, **19**, and **24**) resulted in decreased potencies except for compound **20**. However, incorporation of an additional substituent to

Table 1
In vitro activities of renin inhibitors with P_3–P_3^{sp}–P_1 modifications[a]



Compound	R	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
rac-**6**		370	12,500
rac-**7**		130	2800
rac-**8**		400	3000
rac-**9**		3.3	10
9		1.2	5.3
rac-**10**		170	875

[a] Compounds were obtained as fumarate salts.

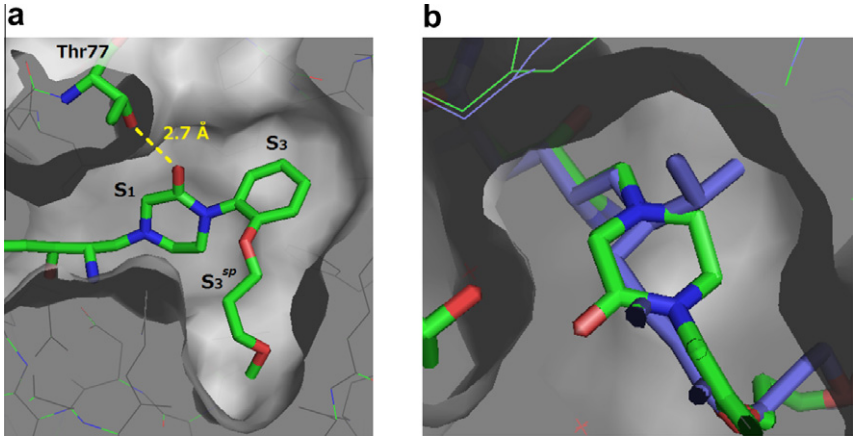
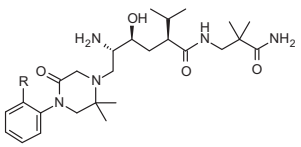


Figure 3. (a) The X-ray structure of ketopiperazine analogue **7** in complex with human renin;[16] (b) Superposition of the crystal structures of aliskiren (**2**) (PDB 2V02;[7] violet) and **7** (green) in the S_1 pocket.

Table 2
In vitro activities of renin inhibitors with P_3^{sp} aryl sidechain modifications[a]

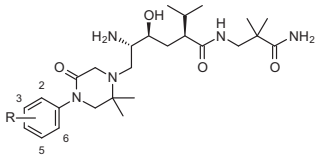


Compound	R	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
9	$O(CH_2)_3OMe$	1.2	5.3
11	$O(CH_2)_2OMe$	1.7	9.8
12	OCH_2OMe	1.4	6.4
13	OMe	1.9	19
14	H	3.1	49

[a] Compounds were obtained as fumarate salts.

the *ortho* position of *meta*-substituted analogues recovered high human renin inhibitory activities (compounds **21, 22** and **25**–**27**). The chloro group was suggested to be the most effective substituent of these for the *ortho* position, and the chloro analogues **17** and **25** exhibited excellent potencies in both purified human and monkey plasma renin assays. This SAR study suggested that the presence of a lipophilic substituent at the *ortho* position is important within the ketopiperazine series to obtain high potency without a P_3^{sp} sidechain. The crystal structure of compound **17** in complex with human renin evidenced that **17** did not indeed utilize the S_3^{sp}. Surprisingly, the chloro substituent was pointing into the opposite direction of the S_3^{sp}, which would provide additional potency through a halogen–π interaction with the Phe112 (Fig. 4). We assume that the structural feature of 4-phenylketopiperazine, which maintains orthogonality between benzene and ketopiperazine

Table 3
In vitro activities of renin inhibitors with modifications of P_3 phenyl portions[a]



Compound	R	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)
13	2-OMe	1.9	19
15	2-F	2.2	30
16	2-Me	1.7	24
17	2-Cl	1.4	7.0
18	3-OMe	4.2	58
19	3-F	3.0	23
20	3-Cl	2.1	25
21	2,3-F,F	2.0	11
22	2,5-F,F	2.0	30
23	2,6-F,F	2.4	12
24	3,5-F,F	5.5	90
25	2-Cl-5-F	2.1	7.0
26	2,5-Cl,Cl	2.1	28
27	2-Cl-5-OMe	2.4	33

[a] Compounds were obtained as fumarate salts.

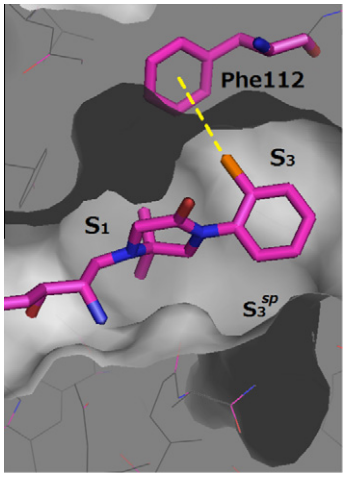
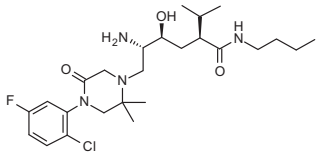


Figure 4. S_1–S_3 region of the crystal structure of compound **17** in complex with human renin.[16]

Table 5
Monkey PK profile of compound **31**



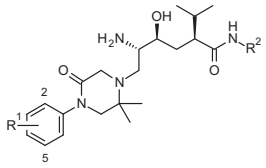
Cynomolgus monkey (10 mg/kg p.o.) (1 mg/kg i.v.)	*F* (%)	18.5
	C_{max} (ng/mL)	576
	AUC_{0-24} (ng h/mL)	2109
	CL (mL/min/kg)	14.7
	V_{ss} (L/kg)	16.3
	$T_{1/2}$ (h)	10.8

rings, might be one factor contributing to show high potency without using S_3^{sp} interaction, which is essential for aliskiren.[12c,14]

Having established optimal substitution patterns for the P_3 phenyl portion, we turned our attention to optimize the P_2' portion (Table 4). Within the 2-chlorophenyl series, increased human renin inhibitory activities were observed when alkyl groups were installed to the P_2' portion (compounds **28**–**30**). The 2-chloro-5-fluorophenyl series showed slightly reduced potencies compared to the corresponding 2-chlorophenyl series (compounds **31**–**33**). In each series, the corresponding (2*S*)-2-methylbutyl analogues (**29** and **32**) exhibited excellent potencies. However, these analogues were found to show poor metabolic stability in cynomolgus monkey liver microsomes (Table 4).[17] Based on these results, compound **31** was selected to evaluate the pharmacokinetics profile as the metabolically most stable representative of this series. The pharmacokinetics study (cynomolgus monkey, 10 mg/kg, p.o.) indicated that compound **31** had 18.5% bioavailability and 10.8 h half-life (Table 5). In addition, compound **31** showed >10,000-fold selectivity over other proteases such as BACE-1, chymotrypsin, cathepsin D, and trypsin. To the best of our knowledge, **31** is the first low nanomolar renin inhibitor, which showed great enzyme selectivity without using the interaction of S_3^{sp} in aliskiren related series.

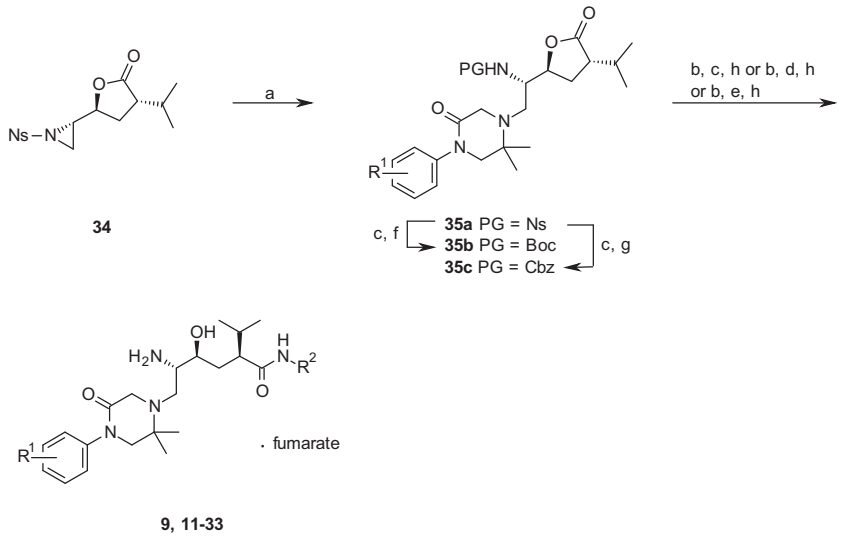
Our divergent synthetic route for the preparation of (2*S*,4*S*,5*S*)-5-amino-6-(2,2-dimethyl-5-oxo-4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropylhexanamides is depicted in Scheme 1. The key intermediate *N*-(2-nitrobenzenesulfonyl) (Ns)[18] protected aziridine **34** was prepared according to the procedure reported recently.[13] Ring opening of **34** with the corresponding ketopipera-

Table 4
In vitro activities and metabolic stabilities of renin inhibitors with modifications of P_3 and P_2' portions[a]

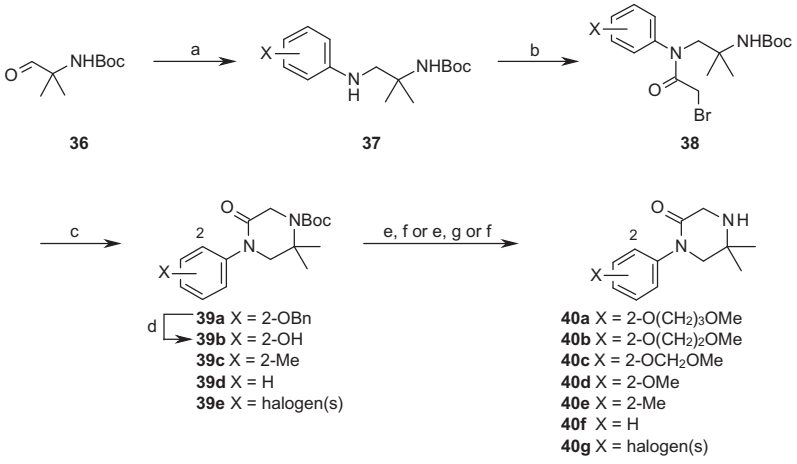


Compound	R^1	R^2	Purified human renin IC_{50} (nM)	Monkey plasma renin IC_{50} (nM)	Metabolic stability[b,c] (MLM, % remaining)
28	2-Cl	*n*-butyl	1.0	9.0	39.2
29	2-Cl	(2*S*)-2-methylbutyl	1.0	2.0	8.4
30	2-Cl	cyclohexyl	1.0	11	17.5
31	2-Cl-5-F	*n*-butyl	2.0	25	52.2
32	2-Cl-5-F	(2*S*)-2-methylbutyl	1.4	8.0	1.9
33	2-Cl-5-F	cyclohexyl	1.9	5.0	38.0

[a] Compounds were obtained as fumarate salts.
[b] MLM = monkey liver microsomes.
[c] Percent remaining after 30 min.



Scheme 1. Synthesis of (2*S*,4*S*,5*S*)-5-amino-6-(2,2-dimethyl-5-oxo-4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropylhexanamides. Reagents and conditions: (a) ketopiperazines, toluene, 110 °C; (b) P2′ amines[14c], cat. 2-hydroxypyridine, 80 °C; (c) PhSH, Cs_2CO_3, DMF, rt; (d) TFA, CH_2Cl_2, rt; (e) H_2, cat. Pd-C, EtOH, rt; (f) Boc_2O, Et_3N, CH_2Cl_2, rt; (g) CbzCl, Et_3N, CH_2Cl_2, rt; (h) fumaric acid, MeOH, rt.



Scheme 2. Synthesis of ketopiperazines. Reagents and conditions: (a) anilines[21], AcOH, $NaBH(OAc)_3$, CH_2Cl_2, rt; (b) bromoacetyl bromide, DMA, 0 °C; (c) *t*-BuOK, THF, 0 °C; (d) H_2, cat. Pd-C, EtOAc, rt; (e) alkyl halides, Cs_2CO_3, DMF, rt−100 °C; (f) TFA, CH_2Cl_2, rt; (g) TMSI, Et_3N, CH_2Cl_2, 0 °C.

zines afforded lactones **35a** in excellent yields. Subsequent *N*-terminal amide bond formations with P2′ amines[14c] under neat conditions in the presence of 2-hydroxypyridine as catalyst,[19] deprotection of the Ns group with PhSH and Cs_2CO_3,[18] followed by treatment with fumaric acid afforded the desired compounds **9** and **12** as fumarate salts. Compounds **11** and **13**–**33** were prepared by a similar procedure after the *N*-Ns group of **35a** have been replaced with either the *N*-Cbz or the *N*-Boc protecting group. The preparation of ketopiperazines are shown in Scheme 2. Reductive amination of aldehyde **36**[20] with anilines,[21] followed by acylation with bromoacetyl bromide in DMA gave **38**. Cyclisation reaction by treatment of **38** with *t*-BuOK in THF afforded *N*-Boc-2,2-dimethylketopiperazines **39a** and **39c–e**. The P_3^{sp} aryl sidechains were introduced by deprotonation of phenol **39b** with Cs_2CO_3, followed by addition of the corresponding alkyl halides. Finally, removal of the *N*-Boc protecting group with TFA, or the combination of TMSI and Et_3N, delivered ketopiperazines **40**. In addition, other compounds listed in Table 1 were prepared following the same synthetic route depicted in Scheme 1. Racemic form of aziridine **34** (*rac*-**34**) was used for the syntheses of *rac*-**6**–**10**. The syntheses of the corresponding amine intermediates (piperidine **42**, ketopiperazines **46a**, **46b** and **48**) used for the ring opening reaction with aziridine **34** are outlined in the references.[22,23]

In conclusion, we have described the discovery and the SAR of novel (2*S*,4*S*,5*S*)-5-amino-6-(4-phenylpiperazin-1-yl)-4-hydroxy-2-isopropylhexanamides. Introduction of the 2,2-dimethyl-4-phenylpiperazin-5-one P_3–P_1 scaffold resulted in a significant improvement of in vitro potency without binding interactions to the S_3^{sp} pocket. Compound **31** showed specificity over other aspartyl proteases, and 18.5% oral bioavailability in cynomolgus monkey. From these encouraging results, we selected compound **31** as a new lead compound and have started further modifications to acquire more promising compounds, which show excellent in vivo efficacy in animal models. Further details of these efforts will be reported in due time.

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15. Assays were performed with the same procedure described in Ref. 10.
16. The X-ray crystallographic studies were accomplished according to the procedure described in Ref. 7. Coordinates and statistics are available from the PDB using accession code 3VSW (complex with compound **7**) and 3VSX (**17**).
17. The stability in monkey liver microsomes was determined by a high throughput in-house assay, in which 1 μM of compound was incubated with a NADPH generating system and 0.5 mg/mL of microsomal protein at 37 °C.
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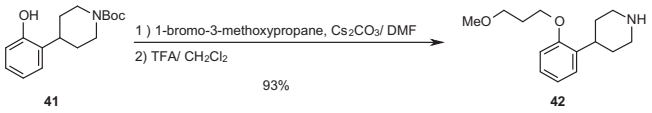
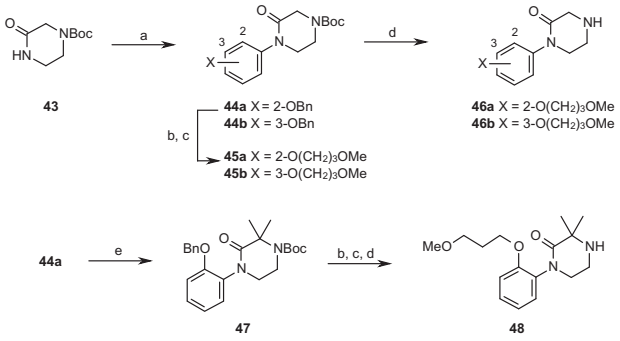
22. Piperidine **42** was prepared from **41**.[24]



23. Ketopipiperazines **46a**, **46b** and **48** were prepared as followed.[a]



[a]Reagents and conditions: (a) CuI, 2- or 3-benzyloxyiodo-benzene[25], K_3PO_4, *N,N'*-dimethylethylenediamine, DMF, 100 °C; (b) H_2, cat Pd-C, EtOAc, rt; (c) 1-bromo-3-methoxypropane, Cs_2CO_3, DMF, 100 °C; (d) TFA, CH_2Cl_2, rt; (e) LDA, MeI, THF, rt.

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