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DESIGN AND SYNTHESIS OF NOVEL 2,7-DIALKYL SUBSTITUTED 5(*S*)-AMINO-4(*S*)-HYDROXY-8-PHENYL-OCTANECARBOXAMIDES AS *IN VITRO* POTENT PEPTIDOMIMETIC INHIBITORS OF HUMAN RENIN

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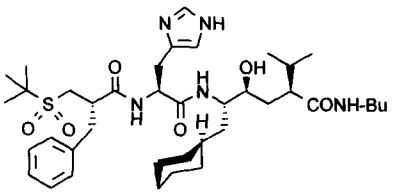
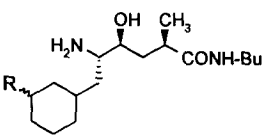
Abstract: Novel low-molecular weight transition-state peptidomimetic renin inhibitors characterized by an all-carbon 8-phenyl substituted octanecarboxamide skeleton have been discovered based on a topographical design approach. The *in vitro* most potent inhibitors **21**, **25** and **26** incorporating a strong H-bond acceptor group linked to the benzyl spacer of the (P_3-P_1)-unit had IC_{50}s in the low nanomolar range against human renin.

Renin inhibitors which specifically block the first, rate limiting step of the blood-pressure regulating renin-angiotensin system (RAS) are an attractive target in drug discovery as novel agents for the treatment of hypertension and other cardiovascular diseases.[1a,b] However, development of substrate-based transition-state renin inhibitors usually spanning the P_4-P_1' minimal sequence has been hampered in most cases by limited oral bioavailability, rapid metabolism or extensive first-pass biliary excretion.[2]

Problems associated with unfavourable pharmacokinetic properties could be potentially overcome by generating structurally distinct renin inhibitors. Recently, a novel approach based on the extension of the P_1 cyclohexyl group of peptide-based inhibitors directly towards P_3 and partial truncation of the N-terminal backbone has been reported[3,4] as a strategy in order to reduce molecular size. The crystal structure of a (P_4-P_1)-spanning inhibitor complexed to rh-renin confirmed that its (P_3-P_1)-modified side chain could indeed be accomodated by the S_3-S_1 site.[4] Furthermore, elimination of the P_4-P_3 portion led only to a small drop in binding affinity,[4] with IC_{50}s of these inhibitors in the micromolar range. On the other hand, the significance of the H-bond accepting and -donating P_4-P_3 amide group for strong binding interactions has been emphazised.[3b]



CGP 38560 (**1**)



2: R = H
(*rac-trans*)-**3**: R = ^{t}Bu-$(CH_2)_3$-

This has prompted us to disclose, in a preliminary communication,[5] part of our efforts towards a similar topographical[6] design concept based on the enzyme-bound conformation of the peptide-based renin inhibitor CGP 38560 (**1**),[7] as predicted by modeling[8] and confirmed by X-ray crystallography.[9] Initially, our strategy was guided by the paradigm that the key binding forces between the enzyme and a ligand result from interactions involving the amino acid side chains rather than the amide backbone of the peptide-like inhibitors.[10,11] Several approaches were extensively investigated to design various hydrophobic conformationally rigid (P_3-P_1)-moieties appending a transition state mimetic, that would optimally fill the large, contiguous S_3/S_1 binding

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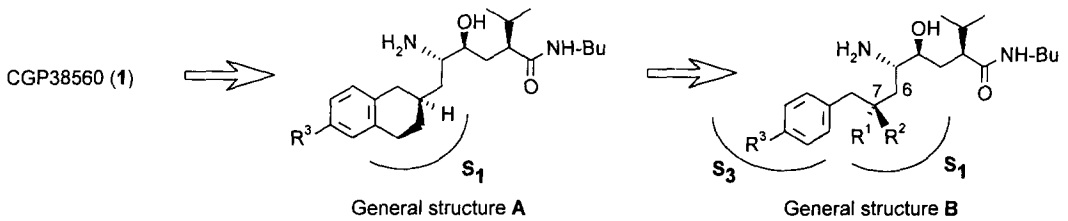
pocket of the enzyme, and which would allow to sacrifice the P_4-P_2 spanning backbone and side chains of a topological inhibitor such as **1**.[5] As a first result, the hydroxyethylene mimetic **3** bearing a free NH_2 group was found to inhibit human renin in the sub-micromolar range, thus being 100 times more potent than compound **2**.[12] We report herein the synthesis and *in vitro* potency of a novel class of peptidomimetics incorporating a benzyl spacer that directly links the P_3 residue to an alkyl P_1 group of the dipeptide isostere. Attachment of H-bond acceptor groups to the phenyl template led to inhibitors with low nanomolar binding affinities.

Design Concept

Intrigued by the close spatial proximity of both the P_1 cyclohexyl and P_3 phenyl sidechains of **1** in its predicted binding mode within the S_3/S_1 site,[5] we envisaged the possibility to extend P_1 by annulating a phenyl ring, for tethering P_3, to the C3'-C4' bond of the cyclohexyl, which was predicted to be distal to the surface of the S_1 site, as illustrated in Figure 1 (Structure **A**). Modeling of such a tetrahydronaphthalene substituted dipeptide isostere, as well as its 'ring-opened' congener (Figure 1, structure **B** with R^1=H, R^2=Et) suggested that in both cases the rigid phenyl spacer would direct a hydrophobic substituent R^3, such as aryl or bulky alkyl, towards the S_3 pocket, and that the P_1 alkyl group would be well accomodated by the S_1 site. Furthermore, these initial design considerations predicted the β-configuration at P_1 (**B**, R^1=H, R^2=alkyl) to be preferred over the α-configuration (**B**, R^1=alkyl, R^2=H) with respect to a better fit in the S_3/S_1 pocket.[13]

Figure 1. Design Approach towards Novel Peptidomimetic Hydroxyethylene Mimetics extended at P_1

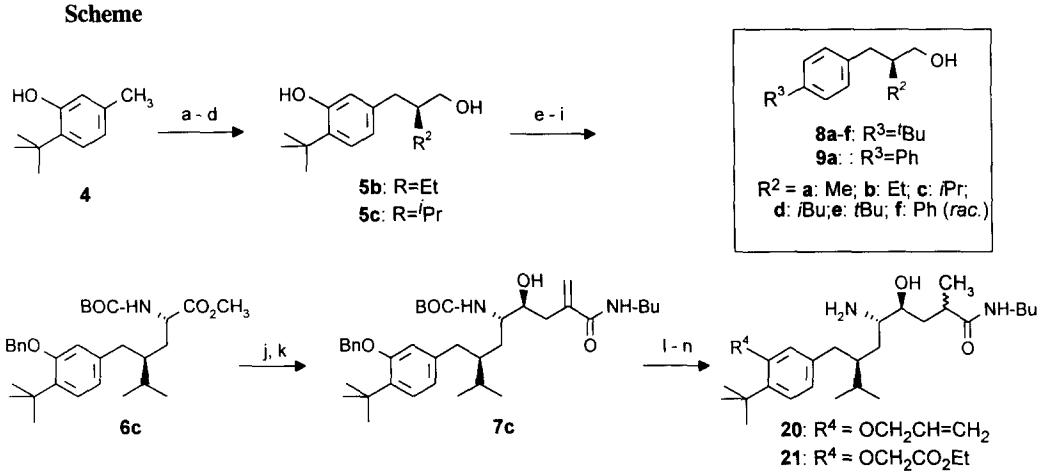


Synthesis

The novel (P_3-P_1)-extended transition-state mimetic renin inhibitors **10-26** with varying P_1 side chains and tethered P_3 residues (Table) were prepared by the linear route as exemplified for compounds **20** and **21** in the Scheme.[14,15] Commercially available **4** (Aldrich Ltd.) was protected as its acetate and subsequently treated with NBS to give the corresponding benzylbromide which was used for the diastereoselective alkylation (de ≥ 95%) of the N-acyl-oxazolidinone chiral auxiliaries (*R*)-**27b** and (*R*)-**27c** according to the method of Evans *et al.*[16] Reductive cleavage of the chiral auxiliary with $LiAlH_4$ afforded alcohol (*S*)-**5b** in good (70%), but (*R*)-**5c** in only poor (12%) yields, the major side products resulting from reductive endocyclic cleavage of the oxazolidinone. Similarly, the regioselectivity of the $LiAlH_4$ reduction dropped dramatically with increasing steric hindrance[16b] in the case of the *para* mono-substituted analogues **8a-d**[17] and **9a** (for example, 94% yield for **8a** *vs.* 43% for **8c** *vs.* 0% for **8e**; *cf.* Scheme). On the other hand, removal of the auxiliary through reaction with lithium benzyl mercaptide and $LiAlH_4$ reduction of the intermediate thioester in one pot by the method of Damon and Coppola[18] gave enantiomerically pure **5c** in excellent 86% yield and even moderate to good yields

for **8e** (37%). In the case of the phenyl-substituted alcohol **8f**, the presence of the nucleophilic and poorly basic benzyl mercaptide caused complete racemisation at the benzylic stereocenter.[19]

Scheme



Reagents: (a) Ac_2O (93%); (b) NBS, CCl_4 (95%); (c) 3-butyroyl-4(*R*)-benzyl-oxazolidin-2-one (**27b**) or 3-isovaleroyl-4(*R*)-benzyl-oxazolidin-2-one (**27c**), LiHMDS, THF, -78 °C to 0 °C (46-52%); (d) BnSH, *n*-BuLi, $LiAlH_4$, THF (**5c**:86%); (e) **5c**, BnBr, Cs_2CO_3, DMF (78%); (f) NBS, PPh_3, CH_2Cl_2 (98%); (g) (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, *n*-BuLi, THF, -75 to -20 °C (91%); (h) 1N HCl, MeCN (96%); (i) $(BOC)_2O$, $NEt(iPr)_2$, CH_2Cl_2 (96%); (j) DIBAH, toluene (quant.); (k) i. N-butylmethacryl-amide, *n*-BuLi, $TiCl(OiPr)_3$, THF, -78 °C; ii. RCHO, THF, -78 °C; iii. silica gel chromatography (19%); (l) H_2, Pd/C, MeOH (88%); (m) allylbromide, Cs_2CO_3, acetone (90%) or $BrCH_2CO_2Me$, Cs_2CO_3, acetone, NaI (80%); (n) 4N HCl-dioxane (**20**:32%; **21**:74%).

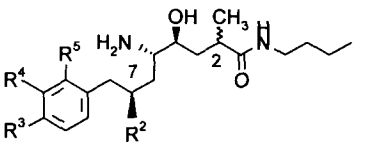
The N-*BOC*-protected α-amino ester 2(*S*),4(*S*)-**6c** was expediciously prepared from **5c** (after reprotection of the phenolic OH group) in 62% overall yield following the procedure of Schöllkopf *et al.*[20] Subsequent DIBAH reduction afforded the N-*BOC* amino aldehyde, which was reacted with the dianion generated from *n*-butyl acrylamide in the presence of $Ti(OiPr)_3Cl$ similar to the method by Kempf,[21,22] to give separable mixtures of both 4(*S*)/4(*R*)-configured diastereoisomers **7c** in good yields (ratio 4(*S*),5(*S*),7(*R*)-**7c**:4(*R*),5(*S*),7(*R*)-**7c** ca. 1:2).[23] Hydrogenation (10% Pd/C) of the alkene with concomitant removal of the benzyl protecting group yielded a pair of 2(*R*)/2(*S*)-diastereomers which were difficult to separate by silica gel chromatography and thus further transformed as epimeric mixtures.[24] O-Alkylation of the phenol intermediates with the corresponding alkylhalogenides (iodoacetamide for **25**) was followed by N-deprotection to afford inhibitors **20**, **21** and **25**,[25] whereas the carboxylic acid **24** (Table) was obtained by hydrogenolysis of the benzyl ester precursor. The methylsulfone **26** was prepared by oxidation (oxone, MeOH-H_2O, 16h, r.t, 54%) of the corresponding thioether obtained by alkylation of the phenol precursor with methylthiomethyl chloride (66%).

Results and Discussion

The hydroxyethylene mimetic **10** bearing a hydrophobic biphenyl residue at P_1 assumed to be directed towards the S_3 enzyme sub-pocket according to modeling showed weak binding affinity for purified human renin at the micromolar level (Table). Thus, **10** had a 10 fold increased activity in this assay (determined at pH=7.2)[7] as compared to the non-extended dipeptide isostere **2**.[12] Replacement of the terminal phenyl with the bulky *tert*-butyl group gave inhibitor **11** with similar *in vitro* potency. This is in agreement with previous results for **3** and some analogues, that an appended *tert*-butyl is equally well tolerated at P_3 as phenyl which is the commonly more preferred P_3 residue in peptide-based inhibitors.[12] Further optimisation of these initial

target inhibitors was performed within the P_3 *tert*-butyl substituted series, partially in view of more readily available precursors bearing additional substituents on the phenyl ring.

Table. IC_{50}s of 5(*S*)-Amino-4(*S*)-hydroxy-8-phenyl-octanecarboxamides **10-26** against Purified Human Renin



No.[a]	R^2	R^3	R^4	R^5	Binding Affinity IC_{50}, μM (pH 7.2)
3					30
10	CH_3	phenyl	H	H	3
11	CH_3	*tert*-butyl	H	H	2
12	C_2H_5	*tert*-butyl	H	H	0.8
13	C_2H_5[b]	*tert*-butyl	H	H	3
14	$CH(CH_3)_2$	*tert*-butyl	H	H	0.1
15	$CH_2CH(CH_3)_2$	*tert*-butyl	H	H	4
16	$C(CH_3)_3$	*tert*-butyl	H	H	1.5
17	phenyl[d]	*tert*-butyl	H	H	39
18[c]	$CH(CH_3)_2$	*tert*-butyl	OH	H	0.13
19	C_2H_5	*tert*-butyl	OC_4H_9	H	0.24
20[c]	$CH(CH_3)_2$	*tert*-butyl	$OCH_2CH{=}CH_2$	H	0.11
21	$CH(CH_3)_2$	*tert*-butyl	$OCH_2CO_2CH_3$	H	0.006
22	$CH(CH_3)_2$	*tert*-butyl	H	$OCH_2CO_2C_2H_5$	0.29
23[c]	$CH(CH_3)_2$	H	$OCH_2CO_2CH_3$	H	0.037
24	$CH(CH_3)_2$	*tert*-butyl	OCH_2COOH	H	0.120
25	$CH(CH_3)_2$	*tert*-butyl	OCH_2CONH_2	H	0.020
26	$CH(CH_3)_2$	*tert*-butyl	$OCH_2SO_2CH_3$	H	0.013

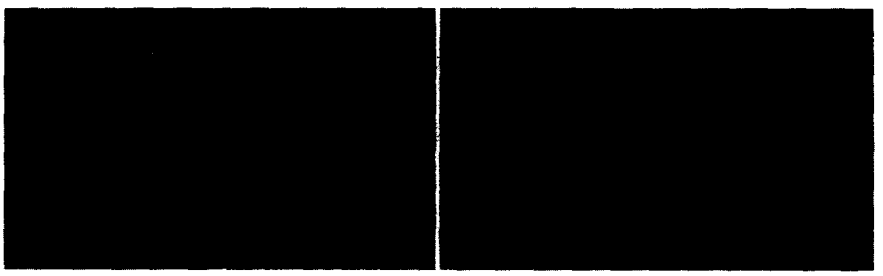
[a] Tested (single determination) as ca. 1:1-mixtures of C2(*R*,*S*)-diastereomers; [b] (*R*)-configured at C7; [c] Pure diastereomer of 2(*R*),4(*S*),5(*S*),7(*S*) absolute configuration; [d] (*R*,*S*)-configured at C7.

In the next step, the structure-activity relationship (SAR) of the putative P_1 residue as well as the required stereochemistry at this position was investigated. Increasing the steric bulkiness by replacing Me with Et and *i*Pr improved binding affinity 20 fold (**11** *vs.* **12** *vs.* **14**), which was attributed to an increase in the van der Waals contacts to the hydrophobic S_1 subsite. In order to prove that the C7(*S*) absolute stereochemistry at P_1 is required for strong binding of **12**, the corresponding (7*R*)-epimer **13** was prepared by the same route shown in the Scheme. Inhibitor **13** was found to be 3-4 times less active than **12**, as was also suggested by comparative docking analyses for both epimers.[13] Extension of the P_1 side chain by incorporation of isobutyl (compound **15**) led to a 15 fold drop of the IC_{50} value compared to **14**. Also, the additional CH_3 of the *tert*-butyl group in **16** appeared to interfere unfavourably with the S_1 binding site. A phenyl group at P_1 was not well tolerated as demonstrated by the markedly decreased IC_{50} value for **17**.

To improve the moderate binding affinity of **14**, we envisaged[3] introducing appropriate substituents having the potential of forming additional hydrogen bonds to the enzyme cleft at different positions of the benzyl spacer. In the case of peptide-like enzyme inhibitors, the contribution of H-bonding interactions of the backbone amide groups to the overall binding energy may be outweighed by unfavourable desolvation enthalpies,[26] however such interactions may play an important role in providing a proper inhibitor alignment within the enzyme active site.[11,3b] Previous reports on the SAR of peptide-based inhibitors of renin[2] and crystal structures of enzyme-inhibitor complexes,[27,28] indicated the importance of the conserved hydrogen bonding between a P_2/P_3 carbonyl group of various inhibitors to the backbone amide NH of the amino acid

corresponding to Ser219 of human renin for strong inhibitor binding. The overlap of the enzyme-docked inhibitors **14** and CGP38560 (**1**) within the human renin model revealed the phenyl of **14** to be in a remote position several bond lengths distant from the Ser219 main-chain amide bond of the enzyme. Accordingly, and due to its large distance to other H-bonding groups of the enzyme, the additional phenolic OH of inhibitor **18** does not lead to an increase in binding affinity as compared to **14**. However, we realized that attaching an ester group via a two-atom spacer preferentially *ortho* to the P_3 residue would position the ester carbonyl in reasonable hydrogen bonding geometry to the NH of Ser219, similar to the P_3 carbonyl of **1** (Figure 2).[29] Inhibitor **21** with a low nanomolar IC_{50} value revealed a 15 fold enhancement in binding affinity over **14** (Table), which would be in agreement with the formation of an additional hydrogen bonding interaction. On the other hand, the *meta* substituted regioisomer **22** was much weaker in binding, indicating the requirement of the proper spatial orientation of the ester group. The markedly reduced affinities of the alkoxy derivatives **19** and **20**, being only equipotent to their unsubstituted congeners **12** and **14**, appeared to further support the validity of our design model. The importance of the van der Waals forces of the P_3 *tert*-butyl group within the hydrophobic S_3 subsite for strong binding is demonstrated by the 6 fold drop of the IC_{50} of **23** (Table).

Figure 2. Stereoview of the overlay of the energy-minimized Monte Carlo conformations of CGP38560 (**1**) and inhibitor **21** within the human renin active site model.[8,11] Both centers of the enzyme S_3 and S_1 contiguous binding pockets are indicated by red colored spots. The close distances of the P_2/P_3 carbonyl of **1**, as well as of the ester carbonyl of **21**, to the Ser219 (orange colored) amide NH suggested in both cases a strong H-bond.



Replacement of the terminal carboxylic ester with a carboxamide or methylsulfonyl residue as strong H-bonding acceptors led to inhibitors **25** and **26** with comparable *in vitro* potencies, whereas the carboxylic acid **24** was only a weak inhibitor of purified human renin. Finally, N-acetylation of the amino group of several inhibitors in the Table resulted in a loss in binding affinity by 2 to 3 orders of magnitude (data not shown).

In summary, a novel class of small-sized, *in vitro* highly potent peptidomimetic transition-state renin inhibitors which incorporate a constrained benzyl-spacer-linked (P_3-P_1)-moiety has been designed using a topographical approach. Introduction of additional hydrogen bond acceptor/donor residues at the position *ortho* to the P_3 substituent and in appropriate distance to the phenyl template, as suggested by previous SAR data of peptide-based inhibitors and computational modeling, resulted in a remarkable enhancement in binding affinities as compared to the parent inhibitor **14**. The most potent compounds within this series, the carboxylic ester **21**, the carboxamide **25** and the methylsulfonyl derivative **26**, showed IC_{50} values at the low nanomolar level towards purified human renin. Further optimization of the *in vitro* potency of this compound class and evaluation of the oral activities on blood pressure in Na^+-depleted marmosets will be reported in due course.

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References and Notes

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23. Stereochemical assignments within this series were tentatively based on the relative *in vitro* binding affinities of 2(R,S),4(*S*)-configured **22** (Table) and its 2(R,S),4(*R*)-epimer obtained after silica gel flash chromatography separation of the C2 methylene intermediate, with **22** being 10 fold more active towards human renin than the 4(*R*)-isomers. For **7c** and analogues, assignment was based on the generally observed relative ^{1}H-NMR up-field shifts of the *BOC*-NH signals (ca. 0.2 ppm, DMSO-d_6) for the 4(*S*)- *vs.* 4(*R*)-isomers. In all cases, the 4(*R*)-diastereomers corresponding to **7c** appeared to be more polar by t.l.c..
24. In the course of this work, it was discovered for related N-*BOC* protected hydroxyethylene dipeptide isosteres substituted with different (P_3-P_1)-moieties [Ref. 5] that catalytical hydrogenation of the methylene group at the C-2 position occurred highly diastereoselectively in the presence of optically active $[Ru_2Cl_4((S)\text{-BINAP})_2]\cdot NEt_3$ [see: Takaya, H.; Noyori, R. *et al.*, *J. Am. Chem. Soc.* **1987**, 109, 1596] to give the desired 2(*R*)-methyl isomers (H. Rüeger, personal communication).
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29. In a parallel effort within different series of peptidomimetic renin inhibitors, a similar strategy was applied successfully to design *in vitro* highly potent P_3 extended dipeptide isosteres in our laboratories [Ref. 5].

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