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BIOACTIVE HYDROXYETHYLENE DIPEPTIDE ISOSTERES WITH HYDROPHOBIC (P_3-P_1)-MOIETIES. A NOVEL STRATEGY TOWARDS SMALL NON-PEPTIDE RENIN INHIBITORS

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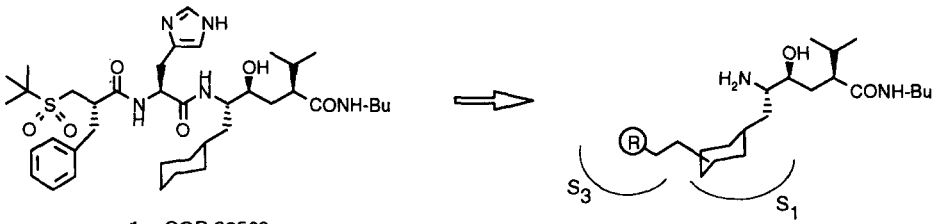
Abstract: The design and synthesis of new truncated δ-amino hydroxyethylene dipeptide isosteres lacking the P_4-P_2 peptide backbone is described. The most active compounds **15c** and **30c** inhibited human renin in the sub-micromolar range. This promising concept may offer the possibility to discover completely non-peptide, low-molecular weight renin inhibitors with improved pharmacokinetic properties. Copyright © 1996 Elsevier Science Ltd

The importance of the renin-angiotensin system (RAS) as a major regulatory system for blood pressure and fluid balance has been well documented.[1] Blockade of the formation of the strong vasopressor peptide angiotensin II by inhibition of the angiotensin-converting enzyme (ACE) has culminated in the development of effective anti-hypertensives.[1b] Recently, the discovery of potent non-peptide angiotensin II receptor antagonists has been described as a novel class of blood pressure lowering agents.[1c] Considerable effort has been focused on the design of orally active inhibitors of renin[2] which is the first, rate-limiting and highly substrate-specific enzyme of the RAS cascade. However, the limited oral bioavailability and rapid biliary elimination of many potent peptide-derived renin inhibitors mainly due to unfavourable lipophilicity and molecular size has been a major hurdle in the field, although several such inhibitors with improved pharmacokinetics were reported recently.[3]

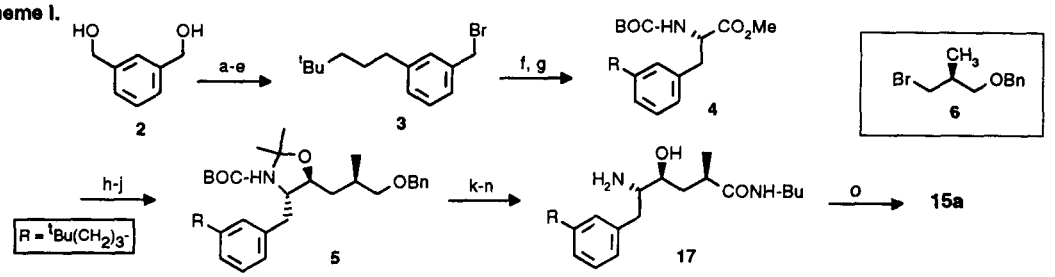


1 CGP 38560

Our previous modeling efforts towards the conformational analysis of the binding mode of CGP 38560 (**1**) to human renin[4,5] based on a model of the enzyme active site[6] indicated that the S_1 and S_3 pockets constitute a large contiguous, hydrophobic binding site accommodating the P_1 cyclohexyl side chain and the P_3 phenyl of the inhibitor in close proximity to each other. These results were recently confirmed by the elucidation of the X-ray crystal structure of the complex of human renin and inhibitor **1**.[7] Based on similar observations[8,9,10b], conformationally restricted macrocyclic peptide inhibitors with the P_3 and P_1 sites covalently linked have been designed for renin[10] and related aspartyl proteinases.[11] Truncated tetrapeptide amino alcohols lacking the P_4-P_2 sequence showed increased binding affinity to renin when P_1 was more lipophilic and extended towards P_3.[12] Recently, the design of linear peptidomimetic renin inhibitors spanning the S_4-S_1' enzyme pockets as well as of some truncated P_2-P_1' analogues was reported, in which the P_3 residue was directly connected to a cyclohexyl

or phenyl group at P_1 and in which the linkage of P_3 to the peptide backbone was eliminated.[13,14] Herein, we wish to report preliminary results[15] of our work towards novel dipeptide transition state mimics containing a spacer-linked P_3-P_1 motif and lacking completely the P_4-P_2 portion, as a novel concept for the design of small-molecule renin inhibitors.

Scheme I.

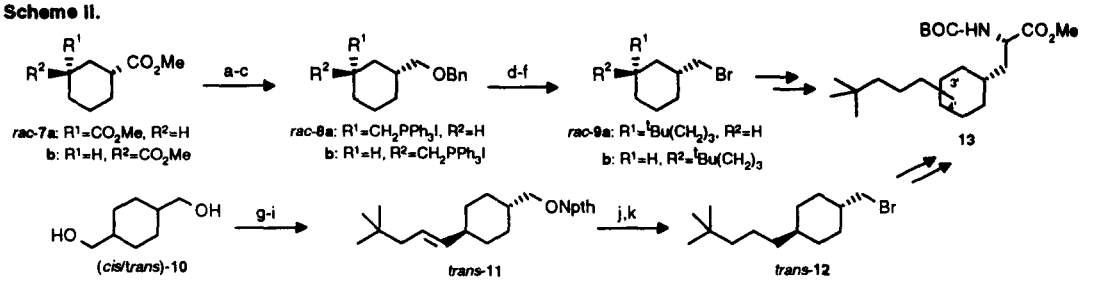


Reagents: (a) TBDMSiCl, imidazole, CH_2Cl_2 (50%); (b) MnO_2, $CHCl_3$, reflux (90%); (c) $^tBuCH_2CH_2PPh_3Br$, n-BuLi, THF, 0 °C to r.t. (81%); (d) i. TBAF, THF; ii. H_2, Pd/C (80%); (e) NBS, PPh_3, CH_2Cl_2, r.t. (88%); (f) 2(R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, n-BuLi, THF; (g) 1N HCl, MeCN; then BOC_2O, 1N NaOH, H_2O-dioxane 1:1 (42%, 3 steps); (h) i. NaOH; ii. $^iBuCO_2Cl$, HNMeOMe, NMM; iii. $LiAlH_4$, Et_2O (65%); (i) **6**, Mg, Et_2O, 0 °C (total 61%), then silica gel chromatography; (j) DMP, r.t. (73%); (k) H_2, Pd/C (81%); (l) PDC, DMF, 12h, r.t. (82%); (m) $^iBuO_2CCl$, NMM, THF, -20 °C; then n-$BuNH_2$, r.t. (68%); (n) TFA-H_2O (95:5), 1h, r.t. (70%); (o) H_2, PtO_2-Rh_2O_3, MeOH.

The initial approach evolved from the general consideration, that the huge hydrophobic surface of the S_3/S_1 'superpocket' of human renin should allow a further increase of the relative binding contributions of a bulky lipophilic (P_3-P_1)-moiety by optimization of its van der Waals contacts to the complementary pocket. Furthermore, it was hypothesized that such increased hydrophobic interactions as the major driving force for binding[16] could eventually compensate for the loss of binding free energy that would result from the envisaged truncation of the N-terminal P_4/P_2 backbone and appended side chains. At the outset, the cyclohexylmethyl group was selected as the P_1 template because of the known[17] preference of renin for larger hydrophobic residues at S_1, leading to increased inhibition and enzyme selectivity. Modeling studies suggested that either the 3-phenylpropyl or the more space filling 3-(*tert*-butyl)propyl appendage - preferentially at the 3-*trans* position of the P_1 cyclohexyl ring - would fit appropriately into the S_3 pocket.

Synthesis of the transition state analogues **14-18** proceeded via preparation of the 2(S)-configured amino acid derivatives **4** and **13**, followed by elaboration of the hydroxyethylene dipeptide mimic employing the known Grignard route[18] (Scheme I, II). Thus, the initial target compound **15a** (Table I) was prepared by conversion of diol **2** into benzyl bromide **3**. Stereoselective alkylation of the chiral Schöllkopf reagent[19] with **3**, acidic hydrolysis and N-BOC protection afforded intermediate **4** in good overall yield.[20] Reaction of the aldehyde derived from **4** with the Grignard reagent generated from optically pure bromide **6**[18] afforded a ca. 3:1 mixture of separable diastereomers. The desired major isomer[21] was N,O-protected to give **5**, which was carried forward to **17** in 4 steps (32% overall). Hydrogenation of the phenyl group afforded **15a** as a mixture of isomers. The marked *in vitro* activity of **15a** prompted us to prepare in a similar manner the 1,3-*cis* and 1,3-*trans* disubstituted cyclohexyl analogues **15b**, **15c**, starting from pure *cis*-**9a** and *trans*-**9b**, respectively. The latter were obtained via phosphonium iodides **8a,b** (from **7a,b**[22a]) by hydrogenation of the Wittig products and subsequent NBS bromination. For preparation of the 1,4-*trans* analogue, monoprotected diol **10** was oxidized to the *cis/trans* aldehyde which epimerized under the Wittig conditions to give predominantly *trans*-**11**. Inhibitors **16**, **18** were obtained from the corresponding α-amino ester **13** (Scheme II) and N-BOC-O-Benzyl-tyrosine, respectively.

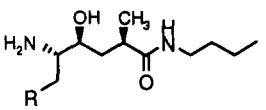
Scheme II.

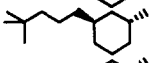
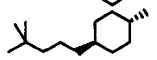
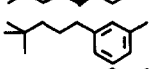
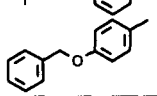


Reagents: (a) $LiAlH_4$, THF (95%); (b) BnBr, Ag_2O, $CHCl_3$ (71%); (c) NIS, PPh_3, CH_2Cl_2; then PPh_3, toluene, reflux (62%); (d) $^tBuCH_2CHO$, NaHMDS, THF, 0 °C (81%); (e) H_2, Pd/C (77%); (f) NBS, PPh_3 (95%); (g) 1-naphthylmethylchloride, NaH, DMF (61%); (h) Py·SO_3, DMSO (86%); (i) $^tBuCH_2CH_2PPhBr$, n-BuLi, THF, r.t. (95%); (j) H_2, Pd/C (75%); (k) NBS, CH_2Cl_2 (93%).

The *in vitro* potencies of compounds **15-18** against purified human renin (pH 7.2)[4] are shown in Table I. The sub-micromolar activity of the 1,3-disubstituted cyclohexyl derivative **15a** appeared to be 40-fold higher as compared to the parent, weakly active **14**. In agreement with modeling studies, the 1,3-*trans* configured **15c** as the most potent inhibitor prepared in this series (IC_{50}= 300 nM; mixture of two diastereomers) showed stronger binding by a factor of ≥10 relative to the *cis*-isomer **15b** and the (1,4-*trans*)-**16**. The good *in vitro* activity of **15c** is remarkable in so far as the replacement of a commonly preferred aromatic P_3 moiety by an appended *tert*-butyl group was well tolerated.[13b,23] The P_1 phenyl analogues **17** and **18** were much weaker inhibitors being almost equipotent to **14**. These preliminary results indicated that an appropriate lipophilic group linked to the cyclohexyl P_1 moiety may be directed towards the S_3 subsite when bound to the enzyme, thereby increasing binding affinity.

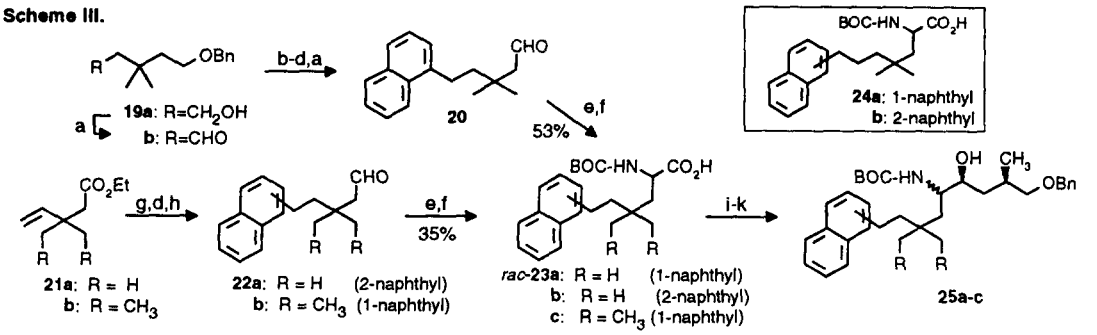
Table I.



Compound	R		Binding Affinity IC_{50}, μM (pH 7.2)
14	cyclohexyl		30
15a		*cis/trans* (*rac*)	0.8
b		*cis* (*rac*)	2.9
c		*trans* (*rac*)	0.3
16		*trans*	4.3
17			13
18			32

Next, our focus was directed towards the structural symmetrisation of the P_1 portion in order to avoid the stereochemical complexity encountered in the synthesis of the P_1 cyclohexyl derivatives. Inhibitors **30a-h** (Table II) were synthesized in which an aromatic P_3 residue is linked via a spacer group to the methine carbon of the *sec*-butyl side chain of the parent compound **33**[18b], hence without generating an additional stereocenter. Furthermore, the alkyl spacer was thought to participate in van der Waals contacts to the 'superpocket' and thus to compensate for the lower bulkiness of the *gem*-dimethyl group of the P_1 side chain in **33**.

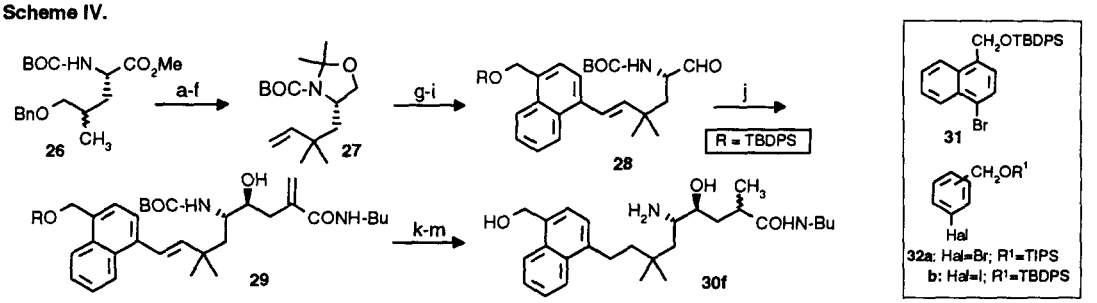
Scheme III.



Reagents: (a) $Py{\cdot}SO_3$, DMSO (82%); (b) 1-iodonaphthalene, Mg, THF (80%); (c) 1N HCl-MeCN (1:10), 1h reflux (70%); (d) H_2, Pd/C (76-91%); (e) i. NaCN, NH_4Cl, NH_4OH, r.t., 20-48h; ii. 6N HCl, 6h reflux; (f) BOC_2O, 1N NaOH, H_2O-dioxane 1:1; (g) 1- or 2-bromonaphthalene, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, Et_3N, 110 °C, 65h (38-75%); (h) DIBAH, -78 °C (60-85%); (i) $^iBuCO_2Cl$, HNMeOMe, NMM, THF (70-85%); (j) $LiAlH_4$ (95%); (k) i. **6**, Mg, THF, 50 °C, then aldehyde, r.t., 2h; ii. silica gel chromatography (80%).

The N-BOC protected α-amino acids **23a-c** and their three carbon spacer analogues **24a,b** were prepared as racemates by the classical Strecker reaction (Scheme III). The precursor aldehydes **20** and **22a,b** were obtained either from **19**[22b] via a Grignard-dehydration sequence or from olefins **21a,b**[22c,d] by Pd-catalyzed Heck arylation[24] followed by hydrogenation and $Py{\cdot}SO_3$ oxidation or DIBAH ester reduction, respectively. Similarly to **23a**, intermediates **24a,b** were obtained from **19b** and α- or β-naphthalenemethylbromide. Grignard reaction between the N-protected amino aldehydes prepared from **23a-c**, **24a,b** as described above and **6** afforded in each case, after separation on silica gel, the intermediate **25** as a mixture of 4(S),5(S)/4(R),5(R)-stereoisomers (ratio 4(S),5(S)/4(R),5(S) approx. 5:1)[21] which was further elaborated according to the sequence shown in Scheme I.

Scheme IV.

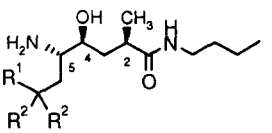


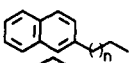
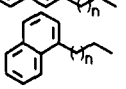
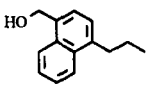
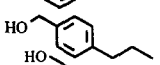
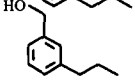
Reagents: (a) $Ca(BH_4)_2$, EtOH (98%); (b) DMP, p-TsOH (cat), CH_2Cl_2 (92%); (c) H_2, Pd/C (quant.); (d) Swern (89%); (e) KH, MeI, CH_2Cl_2 (64%); (f) Ph_3PCH_3Br, KHMDS, THF, -78 °C (77%); (g) MeOH, p-TsOH (95%); (h) **31**, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, Et_3N, 120 °C (61%); (i) Swern (90%); (j) N-butylmethacrylamide, n-BuLi, $Ti(^iPrO)_3Cl$, THF, -78 °C, then **28**, -78 °C (61%); silica gel chromatography; (k) H_2, Pd/C (95%); (l) TBAF, THF (90%); (m) 4N HCl, dioxane, 0 °C (80%).

A more convergent route was employed for the preparation of inhibitors **30f-h** bearing functional residues on the P_3 aromatic moiety (Scheme IV). The optically pure, N,O-protected olefinic amino alcohol **27** was prepared as a versatile key intermediate in 6 steps from 2(S),4(R,S)-configured amino ester **26**[25] in 38% overall yield. Heck olefination[24] between **27** after N,O-deprotection and **31** proceeded in good yield, followed by Swern oxidation of the coupling product to give aldehyde **28**. The hydroxyethylene mimic was elaborated in analogy to the method described by Kempf[26a] giving a 1:1 mixture of the separable 4(S)/4(R)-stereoisomers **29**. The desired less polar 4(S)-**29**[26b] was then hydrogenated in a non-stereoselective manner over Pd/C and deprotected to **30f**. Following this sequence, inhibitor **30g** was obtained from halide **32a**, and **30h** from **32b**.

A marked increase in binding affinity to human renin was observed for **30a-d** as compared to the dipeptide isostere **33** which was inactive in this assay (Table II). The two carbon spacer appendage from the naphthyl α-position appeared to be optimal with **30c** (IC_{50}=700 nM) being >100 times more potent than **33**. Increasing the steric bulk at P_1 by replacing dimethyl with diethyl (compound **30e**) did not further enhance the binding affinity. N-Acylation of inhibitors **30** gave inactive compounds (not shown). Modeling based on the energy minimized conformation of **30c** indicated the 'upper' portion of the naphthyl ring to be in close proximity to the P_3/P_2 carbonyl of inhibitor **1** which, in its predicted conformation, is positioned in hydrogen bonding distance to the backbone amide of Ser219 of the enzyme binding cleft. We reasoned that an appropriate hydrogen bond acceptor/donor group at C-3 or C-4 of the naphthyl ring might lead to tighter binding by interacting with Ser219.[27] The 4-$HOCH_2$-substituted naphthyl derivative **30f**, as well as its 3- and 4-substituted phenyl analogues **30g,h**, were synthesized to explore whether this approach would be feasible in this series, but were found to be less potent by a factor of >10 as compared to **30c**.[28]

Table II.



Compound[a]	R^1		R^2	Binding Affinity IC_{50}, μM (pH 7.2)
33[b]	H		CH_3	>100
30a		n = 1	CH_3	3
b		n = 2	CH_3	3.7
c		n = 1	CH_3	0.7
d		n = 2	CH_3	2.1
30e	c)		CH_2CH_3	2.7
30f[d]			CH_3	10
30g[d]			CH_3	79
30h[d]			CH_3	58

[a] mixture of 2(*R*),4(*S*),5(*S*)-/2(R),4(R),5(R)-diastereomers, if not indicated otherwise; [b] 2(R),4(S),5(S)-configured; [c] see above for **30c**; [d] mixture of 2(*R,S*),4(*S*),5(*S*)-isomers.

In conclusion, the synthesis of new truncated δ-amino-hydroxyethylene dipeptide isosteres lacking the P_4-P_2 peptide backbone is described, in which a hydrophobic P_3 moiety is covalently linked via an alkyl spacer to either the P_1 cyclohexylmethyl or the P_1 *sec*-butyl side chain of a transition state mimic. The most potent compounds **15c** and **30c** inhibited purified human renin at the sub-micromolar level, revealing a pronounced increase in binding affinity to the enzyme as compared to the non-tethered isosteres **14** and **33**. To our knowledge, **15c** and **30c** are the most potent renin inhibitors of such low molecular weight (MW <500) as yet described. This promising concept towards the design of completely non-peptide small molecule inhibitors offers potential for improving the overall physico-chemical and pharmacokinetic properties of this novel generation of renin inhibitors. We will report on further progress from our efforts towards this direction in due course.

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27. Hydrogen bonds between the P_3 amide bond of peptide inhibitors and residue 219 (threonine or serine; numbering refers to renin) of renin and other aspartyl proteases are commonly observed in enzyme inhibitor complexes: see for example Ref. [8].
28. In the course of our work, incorporation of hydrogen bond donor/acceptor substituents into the P_3 moiety has led to a pronounced enhancement of binding affinity in other series of small molecule renin inhibitors. These results will be reported elsewhere.

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