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Piperidine renin inhibitors: from leads to drug candidates

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Abstract

Non-peptidomimetic renin inhibitors of the piperidine type represent a novel structural class of compounds potentially free of the drawbacks seen with peptidomimetic compounds so far. Synthetic optimization in two structural series focusing on improvement of potency, as well as on physicochemical properties and metabolic stability, has led to the identification of two candidate compounds **14** and **23**. Both display potent and long-lasting blood pressure lowering effects in conscious sodium-depleted marmoset monkeys and double transgenic rats harboring both the human angiotensinogen and the human renin genes. In addition, **14** normalizes albuminuria and kidney tissue damage in these rats when given over a period of 4 weeks. These data suggest that treatment of chronic renal failure patients with a renin inhibitor might result in a significant improvement of the disease status.

Keywords: Renin; Renin-inhibitor; Aspartic proteinase

1. Introduction

The renin–angiotensin system (RAS) is widely accepted as a key regulator of cardiovascular and renal function and plays a major role in water and salt homeostasis and blood pressure control [1,2]. Its implication in various pathological states has been demonstrated by the efficiency of blockers of this system in conditions such as hypertension [2], heart failure [3] and chronic renal failure [4]. The RAS consists of a two-step cascade: the aspartic proteinase renin cleaves the peptide bond between Leu_{10} and Val_{11} in angiotensinogen to form angiotensin (Ang) I. Then, the angiotensin-converting enzyme (ACE) generates the biologically active vasopressor octapeptide hormone angiotensin (Ang) II by removal of the two C-terminal amino acids. Renin inhibition results in a total blockage of the RAS, since the cleavage of angiotensinogen by renin represents its rate-limiting step and is highly specific. ACE, however, can be bypassed by the serine proteinase chymase [5] and degrades other pharmacologically active peptides such as bradykinin: In certain tissues, e.g. human heart, chymase has even been shown to be the

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major Ang II-forming enzyme [6]. Ang II is known to act on two receptor subtypes: AT_1 and AT_2. With the recently discovered novel systems Ang 1–7 [7] and Ang IV [8] and their specific receptors AT_3 and AT_4, the RAS becomes even more complex. Chymase is not inhibited by ACE inhibitors and the available AT receptor antagonists only block receptors of the subtype AT_1. Thus, renin inhibition provides the most specific and complete inhibition of the RAS and displays antihypertensive effects comparable to those seen with ACE inhibitors and Ang II receptor antagonists [9–11], but free of side effects due to insufficient specificity. Several lines of experimental evidence suggest an improved efficacy of renin inhibitors in the tissual systems of the heart [5,6] and kidney [4,12–14], indicating the potential for improved prevention and treatment of end organ damage [15]. A significant number of peptidomimetic inhibitors of human renin designed as stable transition state analogues of the scissile amide bond in human angiotensinogen have been developed up to clinical phase II [16–18]. Despite the established clinical efficacy for several of them, almost all development compounds were abandoned for reasons of limited oral bioavailability, rapid biliary elimination and/or too high cost of goods [19]. Non-peptidomimetic compounds of the piperidine type represent an entirely novel class of renin inhibitors [20,21] potentially free of the drawbacks seen with peptidomimetic compounds so far. The first nanomolar compounds obtained in this series, however, proved to be highly lipophilic [20]. Recent compounds with improved physicochemical properties [21] show potent and long-lasting blood pressure lowering effects in conscious sodium-depleted marmoset monkeys and thus serve as useful leads for the development of drug candidates.

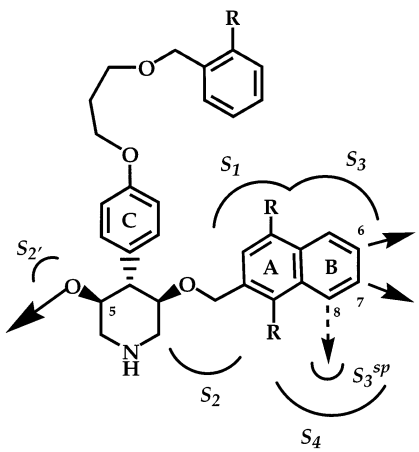


Fig. 1. Design of potential hydrophilic extensions to piperidine renin inhibitors (arrows); positions of binding pockets S as seen in X-ray structures with peptidomimetic inhibitors are indicated; S_3^{sp} refers to a non-substrate sub-pocket accessible from the S_3 pocket [22,23].

2. Design and synthesis

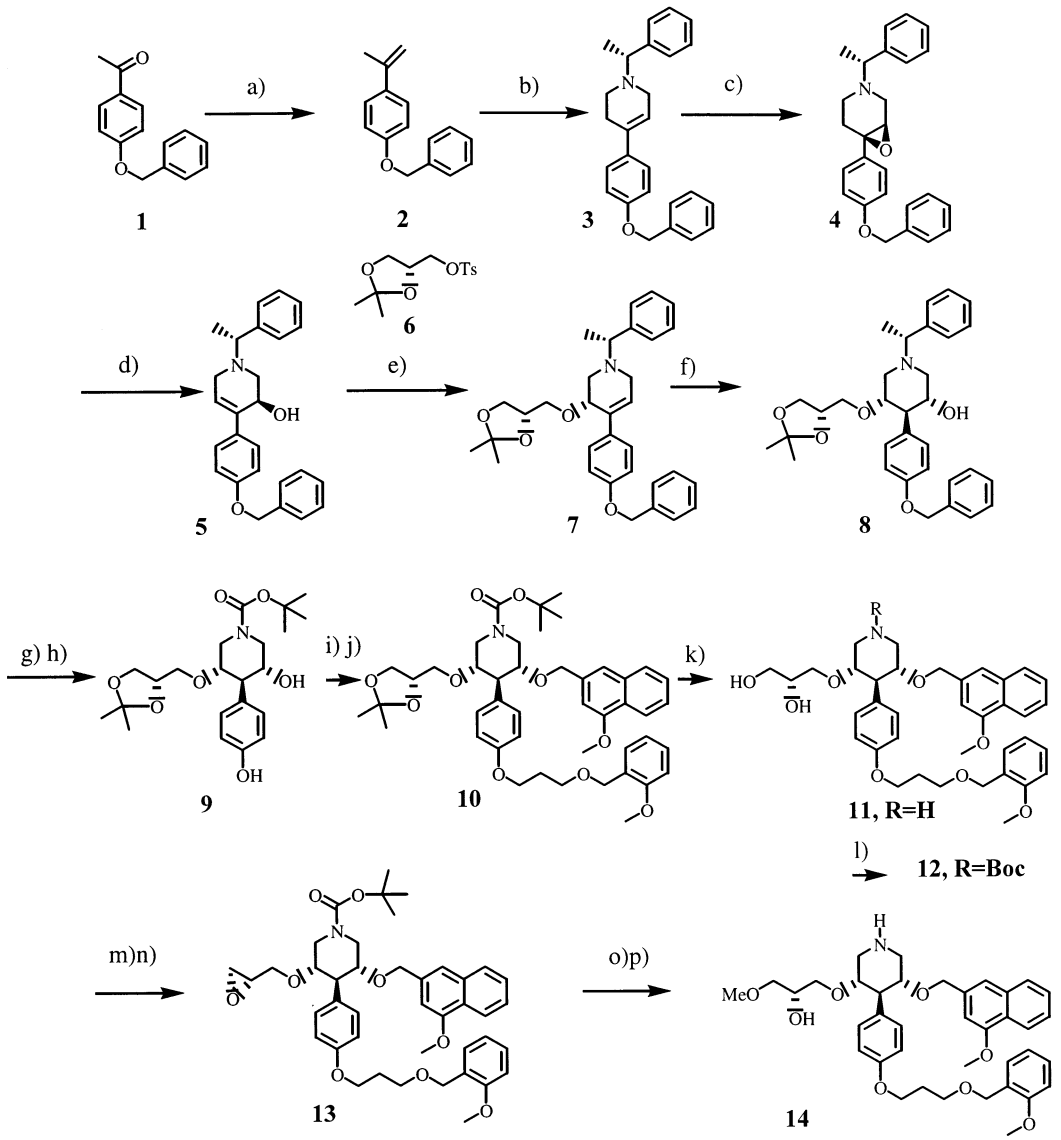
Fig. 1 shows a schematic representation of the binding mode of a sub-nanomolar piperidine human renin inhibitor in the active site of the enzyme [20]. Most more-hydrophilic structural modifications in the core of these inhibitors have dramatically reduced their inhibitory potency [21]. Thus, the attachment of suitable hydrophilic extensions pointing either towards bulk water (arrows in Fig. 1) or into a mixed polar hydrophobic and human renin specific non-substrate S_3 subpocket (S_3^{sp}; dashed arrow in Fig. 1) became the favored approach for the modulation of their physicochemical properties. X-ray data of renin inhibitors bearing substituents pointing into this sub-pocket have recently been described [22,23]. Scheme 1 shows the synthesis of compound **14** bearing an equatorial 3-methoxy-2-hydroxy-propoxy moiety attached to the position 5 of the piperidine ring together with optimized substituents in positions 3 and 4. The synthetic scheme is prototypic for piperidine renin inhibitors with analogous extensions; compare Refs. [20,21,24].

It has been found that the aromatic ring B (Fig. 1) is the only part in the core of the piperidine renin inhibitors that allows hydrophilic modifications [21]. Thus, 3,4-disubstituted piperidine compounds bearing a tetrahydroquinoline-methoxy substituent in position 3 have shown good inhibitory potency against human renin and a reduced lipophilicity [21].

Suitably designed tetrahydroquinoline N-substituents can fit into the non-substrate S_3 sub-pocket. Scheme 2 describes the synthesis of the 3,4-disubstituted piperidine compound **23** bearing an acetylaminoethyl substituent attached to the tetrahydroquinoline N-function prototypic for a series of analogous compounds; compare Refs. [20,21,26].

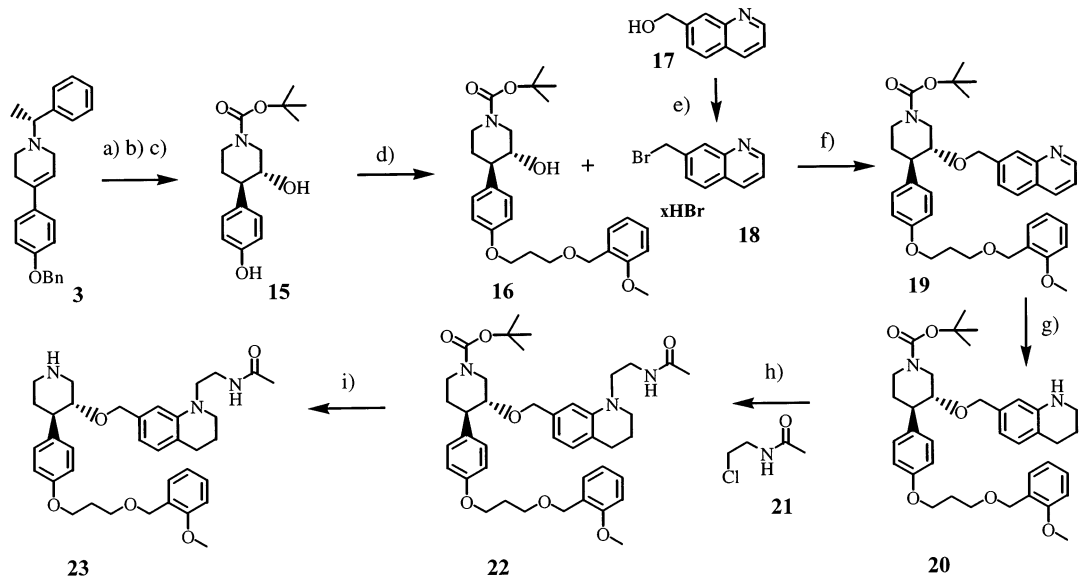
3. Biological results and discussion

There is a high degree of freedom for structural variations at the 5 position of the piperidine ring (equatorial substitution, see Table 1). No substantial differences can be seen for all compounds shown with respect to their inhibitory potency against purified recombinant human renin in buffer and an IC_{50} range between 2 and 20 nM with respect to their inhibitory potency against human renin in plasma. The series covers compounds bearing hydroxy- and alkoxy-substituted alkoxy- and alkoxy-methyl groups and a compound with an imidazolylmethyl function at position 5. These compounds represent a group of rather hydrophilic piperidine analogues suitable for a more profound characterization in pharmacokinetic and pharmacodynamic models. Compound **14** (with a 3-methoxy-2-hydroxy-propoxy moiety at position 5 of the piperidine ring and having the



Scheme 1. Synthesis of **14**, prototypic for piperidine renin inhibitors with hydrophilic extensions at position 5; compare Refs. [20,21,24]. *Reagents and conditions*: (a) $Ph_3P^+MeCl^-$, *tert*-BuOK, THF, room temperature (r.t.), 2 h, 90%. (b) i. *R*-(+)-1-Phenyl-ethylamine, H_2CO (aq.), HCl (aq.), dioxane, 40°C, 4 h; 74°C, 16 h; ii. H_2SO_4 (aq.)/dioxane, 100°C, 7 h, 58%. (c) i. HBr (aq. 48%), Br_2, dioxane/water, 2.5 h, 3–5°C; ii. NaOH (aq.), 2.5 h, 3–5°C; iii. Cryst. from MeOH with Et_3N, 47%. (d) i. PhLi, *tert*-butyl-methyl ether, −15°C, 90 min; ii. Cryst. from MeOH, 91%. (e) i. NaH, DMF, r.t.; ii. (*R*)-(−)-2,2-Dimethyl-4-(hydroxymethly)-1,3-dioxolane *p*-toluenesulfonate, r.t., 2 h, 84%. (f) i. Borane–THF, DME, r.t., 5.5 h; ii. Sodium percarbonate (aq.), 50–55°C, 17 h; 74%. (g) H_2, Pd/C, MeOH, r.t., 23 h, quant. (h) Di-*tert*-butyldicarbonate, dioxane/water, sodium hydrogencarbonate, r.t., 1 h, 85%. (i) 1-(3-Chloro-propoxymethyl)-2-methoxy-benzene [20], potassium carbonate, DMF, 120°C, 21 h, quant. (j) 3-Chloromethyl-1-methoxy-naphthalene (prepared from (4-methoxy-naphthalen-2-yl)-methanol [25] and methanesulfonyl chloride, triethylamine at r.t.) NaH, DMF, r.t., 1.5 h, 95%. (k) HCl/MeOH (2 N), MeOH, r.t., 1 h, quant. (l) Di-*tert*-butyldicarbonate, dioxane/water, sodium hydrogencarbonate, r.t., 1 h, 87%. (m) Toluene-4-sulfochloride (5 equiv.), pyridine, r.t., 15 min, 72%. (n) NaOH (5 N, aq.), DMSO, r.t., 1 h, 98%. (o) NaOMe, MeOH, DMF, r.t., 9 h, 96%. (p) HCl/MeOH (2 N), MeOH, r.t., 5 h, 97%.

following physicochemical characteristics: $pK_a = 6.4$, $\log P = 5.7$, $\log D_{(pH\ 7.4)} = 5.6$, aqueous solubility as amorphous hydrochloride of $> 1\%$ and aqueous solubility at pH 6.6 of 3 μg/ml) clearly showed the most promising set of data within this compound series. This data set comprised pharmacodynamic blood pressure lowering effects in conscious sodium-depleted marmoset monkeys (Fig. 2) and in double transgenic rats harboring both the human angiotensinogen and the human renin gene [28,29] (Fig. 3), as well as pharmacokinetic properties (plasma concentrations after oral administration to normal rats). The data obtained in the marmoset monkey model compare well with those reported for other potent orally active renin inhibitors [17,18,22,30–32]. In addition, compound **14** was able to normalize blood pressure and coronary resistance and prevent cardiac hypertrophy and albuminuria in double transgenic rats harboring both the human angiotensino-



Scheme 2. Synthesis of **23**, prototypic for piperidine renin inhibitors with hydrophilic extensions pointing into the S_3^{sp} pocket; compare Refs. [20,21,26]. *Reagents and conditions*: (a) i. BH_3xTHF (1 M), THF, 1 h, r.t.; ii. NaOH (aq.), H_2O_2 (aq.), 45°C, 3 h, 50% as crystalline pure diastereomer. (b) H_2/Pd/C, MeOH, r.t., 15 h. (c) Di-*tert*-butyldicarbonate, Et_3N, MeOH, −10 to 0°C, 3 h, 96% (two steps), 98.8 to 100% e.e. (d) 1-(3-Chloro-propoxymethyl)-2-methoxy-benzene [20], potassium carbonate, DMF, 66 h, 120°C, 80%. (e) HBr, AcOH, 1 h, 75°C, 97%. (f) NaH, DMF, 24 h, r.t., 94%. (g) $NaBH_4$, $NiCl_2$, MeOH, 1 h, 0°C, 1 h, r.t., 91%. (h) Na_2CO_3, MeCN, KI, 16 h, reflux, 90%. (i) $ZnBr_2$, dichloroethane, 2 h, 50°C, 71%.

gen and the human renin gene when given at a dose of 30 mg/(kg day) over a period of 4 weeks [29]. In these rats, a triple therapy with hydralazine at a dose of 80 mg/l, reserpine at a dose of 5 mg/l, and hydrochlorothiazide at a dose of 25 mg/l in the drinking water was equally effective with respect to lowering of blood pressure, but displayed only marginal effects on albuminuria. In consecutive studies, it could be demonstrated that Ang II-mediated inflammatory responses via NFκB activation play a key role in this model [33]. Thus, renin inhibitors are able to prevent Ang II-induced end-organ damage, pro-inflammatory responses and cellular growth, effects that are largely independent of blood pressure.

Compounds with tetrahydroquinoline nitrogen substituents, of a length of four to five atoms bearing at least one non-basic H-bond acceptor function, show a substantially improved inhibitory potency against human renin in buffer in comparison with the non-substituted analogue **29** (Table 2). X-ray data obtained with compound **23** confirm that the acetylaminoethyl substituent binds into the S_3 sub-pocket (data not shown). The hydroxyethyl-substituted compound **30** cannot entirely fill the pocket and, therefore, does not show a potency improvement; an aminopropyl substituent (compound **35**) is not accepted in the pocket, probably due to its charged amino function, and the acetylaminopropyl-substituted compound **36** shows a dramatically reduced inhibitory potency, due to the too long acetylaminopropyl chain. Compound **23** with the acetylaminoethyl substituent is the only compound in the whole piperidine series with sub-nanomolar potency in the plasma assay (Table 2). This, together with its physicochemical characteristics ($pK_a = 8.4$ and < 2; $\log P = 4.0$, $\log D_{(pH\ 7.4)} = 3.0$, aqueous solubility in presence of two equivalents of hydrochloric acid of $> 1\%$ and aqueous solubility at pH 6.6 of 124 μg/ml), makes it the most promising compound out of this series. The pharmacodynamic blood pressure lowering effects in conscious sodium-depleted marmoset mon-

Table 1
IC_{50} values (against purified recombinant human renin[a] and human plasma renin[b]) of piperidine renin inhibitors with hydrophilic extensions at position 5

R	R'	No	IC_{50} (nM) (buffer)	IC_{50} (nM) (plasma)
H	OMe	24	0.086	14
	H	11	0.060	2.2
	H	14	0.067	8.9
	H	25	0.037	2.1
	H	26	0.065	20
 [rac]	H	27	0.035	18
 [rac]	H	28	0.13	12

[a] For assay conditions see Ref. [20]. The IC_{50} values depicted are mean values of two to five independent determinations.

[b] For assay conditions see Ref. [27]. The IC_{50} values depicted are mean values of two or three independent determinations.

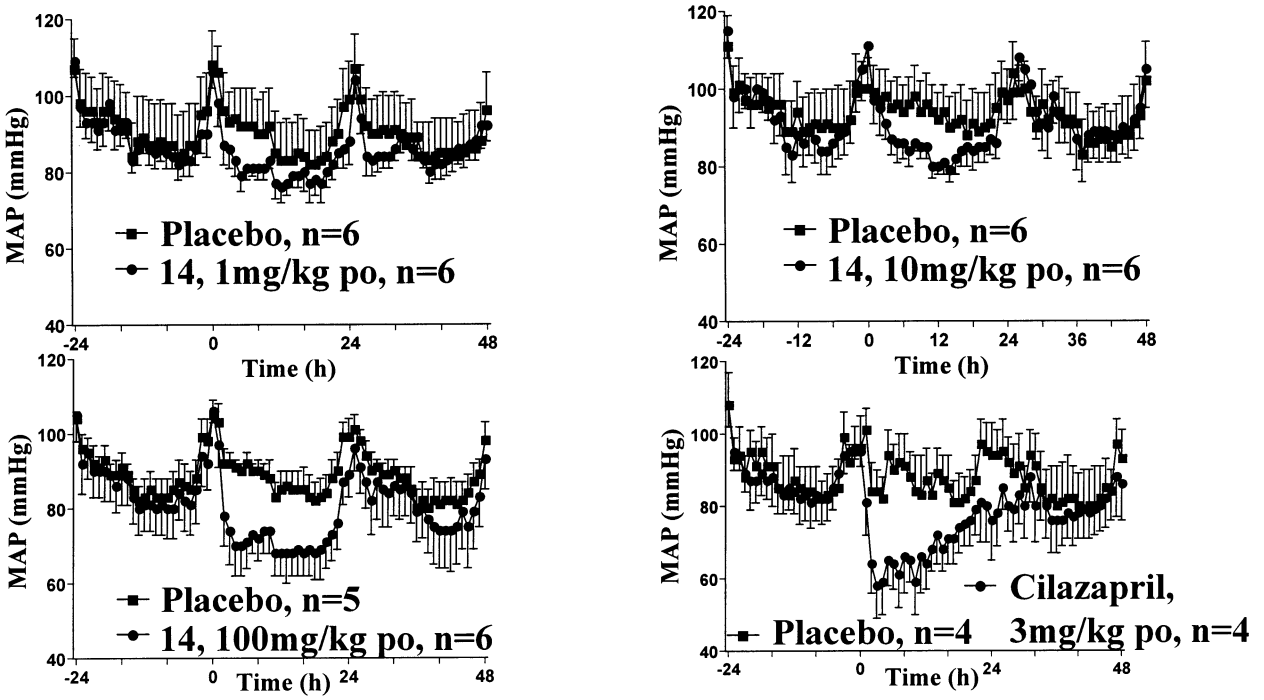


Fig. 2. Blood pressure lowering effects obtained with compound **14** in conscious sodium-depleted marmoset monkeys in comparison with the ACE inhibitor Cilazapril.

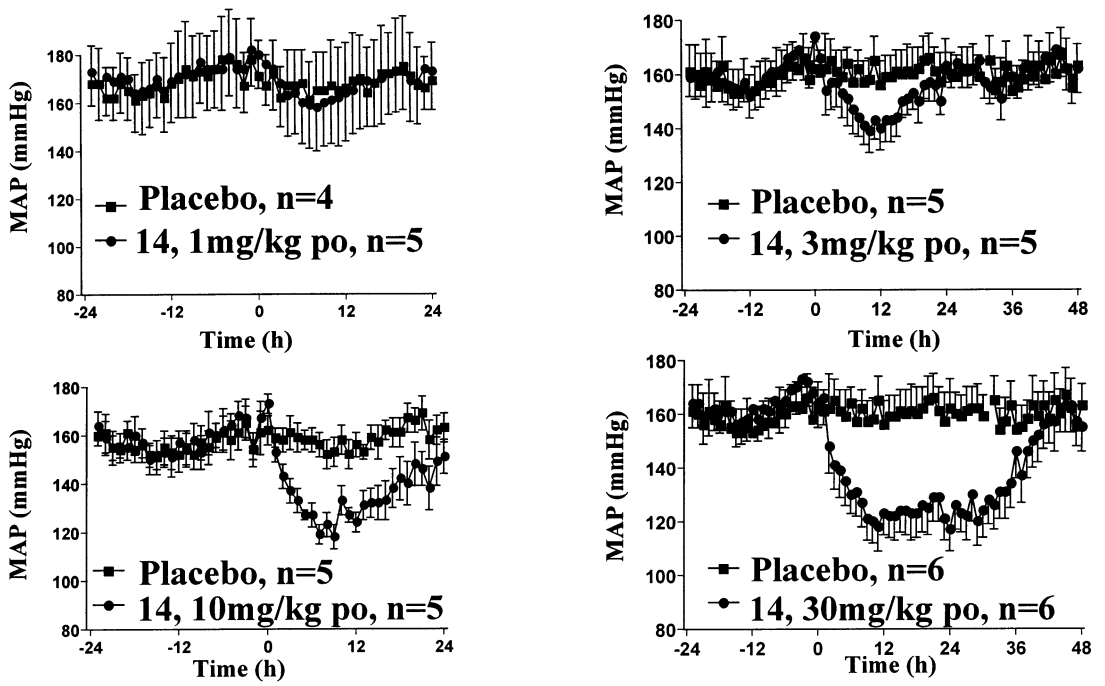
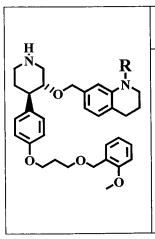


Fig. 3. Blood pressure lowering effects obtained with compound **14** in double transgenic rats harboring both the human angiotensinogen and the human renin gene.

Table 2
IC_{50} values (against purified recombinant human renin[a] and human plasma renin[b]) of piperidine renin inhibitors with hydrophilic extensions pointing into the S_3 sub-pocket



R	No	IC_{50} (nM) (buffer)	IC_{50} (nM) (plasma)
H	29	0.21	31
CH_2-CH_2-OH	30	0.30	18
CH_2-CH_2-CH_2-OH	31	0.079	19
CH_2-CH_2-NH-CO-NH_2	32	0.088	12
CH_2-CH_2-NH-SO_2-NH_2	33	0.064	5.3
CH_2-CH_2-NH-SO_2-CH_3	34	0.072	15
CH_2-CH_2-NH-CO-CH_3	23	0.039	0.60
CH_2-CH_2-CH_2-NH_2	35	8.0	n.d.
CH_2-$(CH_2)_2$-NH-CO-CH_3	36	2.5	n.d.

[a] For assay conditions see Ref. [20]. The IC_{50} values depicted are mean values of two to five independent determinations.
[b] For assay conditions see Ref. [27]. The IC_{50} values depicted are mean values of two or three independent determinations.

keys and in double transgenic rats confirm the potential of this compound (data not shown); but, unfortunately, it shows pharmacokinetic properties clearly inferior to those of compound **14**.

4. Conclusions

The optimization of the piperidine renin inhibitor series with respect to in vitro and in vivo potency, as well as physicochemical and pharmacokinetic properties, has led to the identification of the candidate compound **14**. It has been profiled in pharmacodynamic models of blood pressure reduction and in chronic experiments in double transgenic rats harboring both the human angiotensinogen and the human renin gene. The data obtained clearly demonstrate its potential not only as an antihypertensive drug, but also as a drug for prevention and treatment of end organ damage in the tissual systems of the kidney and the heart.

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