Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 2371–2374
Bioorganic & Medicinal Chemistry Letters

Equipotent activity in both enantiomers of a series of ketopiperazine-based renin inhibitors

Noel A. Powell,* Emma H. Clay, Daniel D. Holsworth, John W. Bryant, Michael J. Ryan, Mehran Jalaie, Erli Zhang and Jeremy J. Edmunds

Pfizer Global Research and Development, Michigan Laboratories, Ann Arbor, MI 48105, USA

Received 18 November 2004; revised 25 February 2005; accepted 28 February 2005
Available online 30 March 2005

Abstract—We have found that both enantiomeric configurations of the 6-alkoxymethyl-1-aryl-2-piperazinone scaffold display equipotent renin inhibition activity and similar SAR patterns. This enantiomeric flexibility is in contrast to a previously reported 3-alkoxymethyl-4-arylpiperidine scaffold.

1. Introduction

Hypertension is a leading risk factor for cardiovascular disease, such as congestive heart failure, stroke, myocardial infarction, and is the leading cause of death in the Western world.[1] The renin angiotensin system (RAS) is well established as an endrocrine system involved in blood pressure regulation and fluid electrolyte balance (Fig. 1).[2] Activation of the RAS is stimulated by several signals, including a drop in blood pressure, a decrease in the circulating volume, or a reduction in plasma sodium concentration. These signals stimulate the release of renin, which cleaves angiotensinogen to angiotensin I (AngI). Angiotensin converting enzyme (ACE) then converts AngI into the vasopressor peptide angiotensin II (AngII). The binding of AngII to the AT_1 receptor initiates a number of physiological effects, such as sodium and water retention and vasoconstriction, leading to an increase in blood pressure. Since renin is the rate-limiting step in the RAS cascade, renin inhibition is considered to be an attractive antihypertensive strategy. Renin inhibitors have been predicted to be more efficacious with fewer side effects than ACE inhibitors and AT_1 receptor antagonists, which target downstream events.[3]

Several pharmaceutical companies have attempted to advance renin inhibitors to the clinic. Although potent in vitro renin inhibitory activity was obtained, most programs were based on peptidic or peptidomimetic scaffolds. Poor pharmacokinetic properties, including low oral bioavailability and high clearance, and a high cost of goods for large scale synthesis greatly diminished the clinical utility of these agents.[4]

In 1999, an initial series of non-peptidic renin inhibitors were disclosed. These inhibitors were based on a

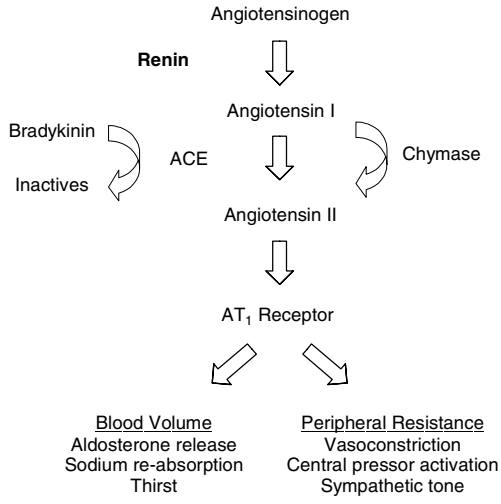


Figure 1. The renin angiotensin system (RAS).

Keywords: Renin inhibitor; Ketopiperazine.
* Corresponding author. Tel.: +1 734 622 2151; fax: +1 734 622 3909; e-mail: noel.powell@pfizer.com

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.02.085

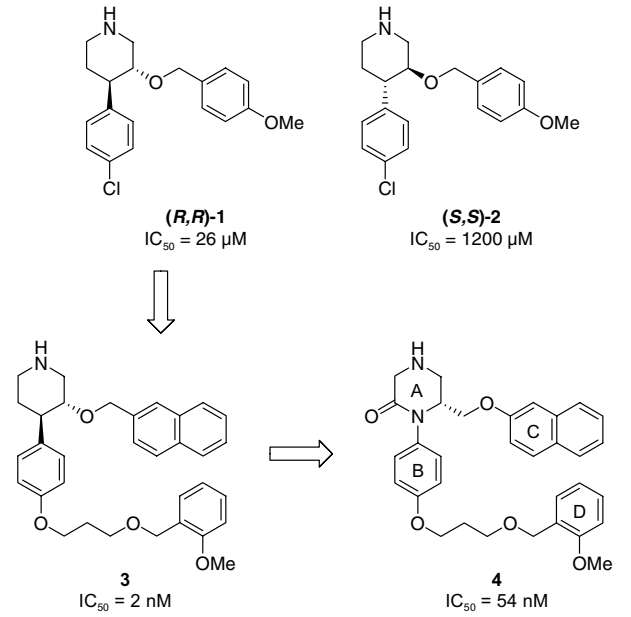
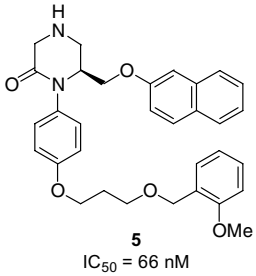


Figure 2. Stereochemical dependence of the *trans*-3-alkoxymethyl-4-arylpiperidine scaffold.

trans-3-alkoxymethyl-4-arylpiperidine scaffold **1** that was discovered by a high throughput screen (Fig. 2).[5] The absolute configuration of the piperidine ring was shown to be quite important for renin activity, as the (3*R*,4*R*)-enantiomer of **1** was >40× more potent than the (3*S*,4*S*)-enantiomer **2**.[5a] Further optimization of the *trans*-3-alkoxymethyl-4-arylpiperidine scaffold resulted in **3** (IC_{50} = 2 nM).

Our previous work had centered around the discovery of novel chemical matter related to the *trans*-3-alkoxymethyl-4-aryl piperidine scaffold by replacement of the 4-aryl piperidine chiral center in **3** with a nitrogen atom to reduce the synthetic complexity. These efforts resulted in the discovery of the 6-alkoxymethyl-1-aryl-2-ketopiperazine scaffold, exemplified by **4**, as novel lead chemical matter (Fig. 2).[6]

We focused our early SAR efforts on the *R*-enantiomer of **4**.[6] Since the aryl piperidine scaffold exhibited such a dramatic stereospecificity for renin potency, we were interested in determining if the 6-alkoxymethyl-1-aryl-2-ketopiperazine scaffold demonstrated a similar stereospecific renin inhibition pattern. Accordingly, we prepared the corresponding *S*-enantiomer **5**. Surprisingly, **5** exhibited almost identical renin inhibition activity (IC_{50} = 66 nM) as the *R*-enantiomer **4**. This result contrasted with the disparate inhibitory activities observed between the enantiomers of the *trans*-3-alkoxymethyl-4-aryl piperidine scaffold (i.e., **1** and **2**).[5a]

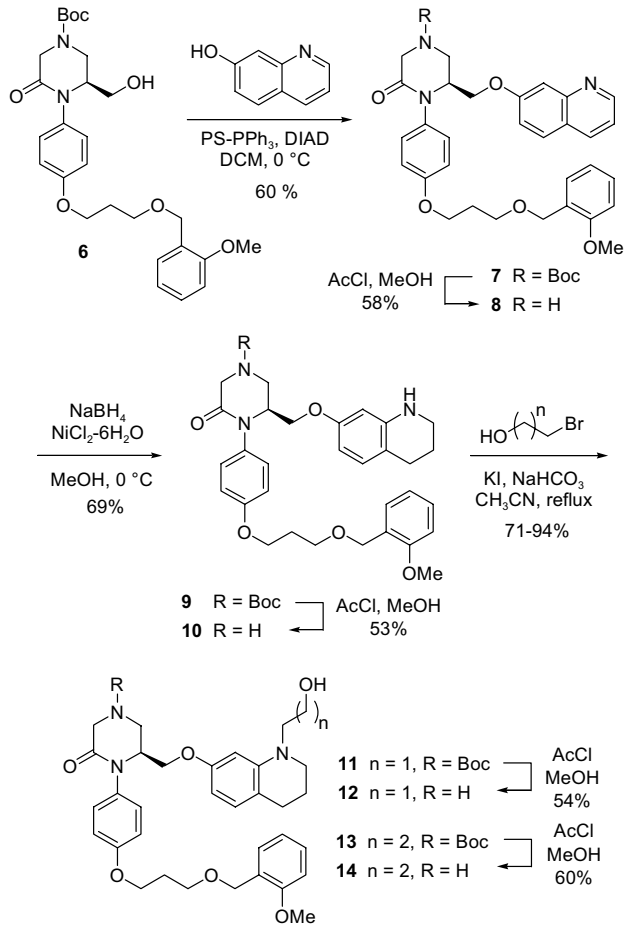


To further examine the SAR of the *S*-enantiomer series, several C ring analogs with the *S*-enantiomer configuration were prepared and compared with the corresponding analogs of *R*-enantiomer configuration.[7]

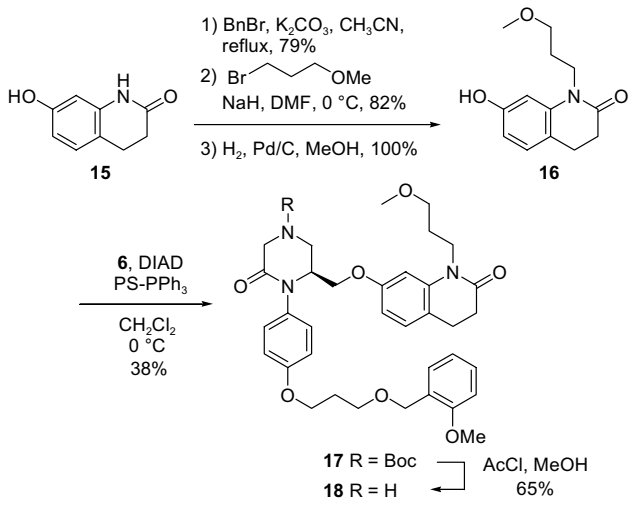
2. Chemical synthesis

The *S*-enantiomer **5** was synthesized as previously described.[6] Quinoline and tetrahydroquinoline analogs **8**, **10**, **12**, and **14** were prepared by the route shown in Scheme 1. Mitsunobu coupling of alcohol **6** and 7-hydroxyquinoline, followed by deprotection of the *tert*-Boc carbamate yielded analog **8**. Reduction of the quinoline ring and *tert*-Boc deprotection provided analog **10**. Alkylation of tetrahydroquinoline **9** with 2-bromoethanol and 3-bromo-1-propanol and *tert*-Boc deprotection gave analogs **12** and **14**, respectively.

Analog **18**, containing an optimized C ring,[7,8] was prepared via a similar Mitsunobu coupling of alcohol **6** and phenol **16** (Scheme 2). Phenol **16** was prepared from



Scheme 1.



Scheme 2.

7-hydroxy-3,4-dihydro-1*H*-quinolin-2-one **15** in a three-step sequence. Protection of the phenol as a benzyl ether, alkylation of the amide with 3-bromo-1-methoxypropane, and hydrogenolysis of the benzyl ether all proceeded in good yield.

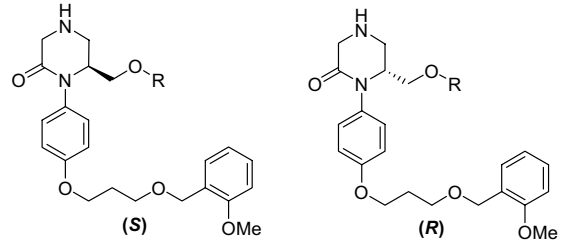
3. Results and discussion

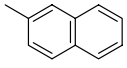
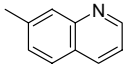
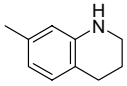
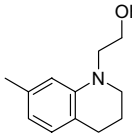
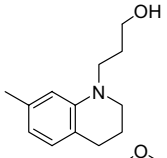
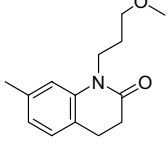
The SAR trends observed with bicyclic C rings in the *R*-configuration series were generally paralleled by the *S*-configuration series. (Table 1). Replacement of the 2-naphthalene with 7-quinoline resulted in a >10-fold loss of activity in both enantiomers (**8**, IC_{50} = 860 nM and **22**, IC_{50} = 820 nM). Interestingly, reduction of the quino- line ring to the tetrahydroquinoline provided a 3-fold increase in activity of the *S*-enantiomer **10** (IC_{50} = 23 nM), while the *R*-enantiomer **23** showed a >2-fold decrease in activity (IC_{50} = 120 nM). In the *S*-enantiomeric configuration series, introduction of a hydrogen bond donating hydroxyl group linked by a 2- or 3-carbon chain to the tetrahydroquinoline nitrogen atom led to analogs **12** (IC_{50} = 33 nM) and **14** (IC_{50} = 35 nM) with activity comparable to the unsubstituted tetrahydroquinoline **10** (IC_{50} = 23 nM), and approximately 2-fold more potent than the corresponding naphthalene analog **5** (IC_{50} = 66 nM). This pattern roughly paralleled the activity trend observed for the *R*-configuration series (analogs **24** and **25**). Introduction of a hydrogen bond accepting 3-methoxypropyl chain led to an increase in renin potency (**18**, IC_{50} = 17 nM).[8] This result mirrored the SAR of *R*-configuration analogs with hydrogen bond acceptors in the S3 subpocket side chain (**26**, IC_{50} = 7.0 nM). It is noteworthy that the alkylated tetrahydroquinoline analogs **10**, **12**, **14**, and **18** retained renin inhibition activity while decreasing clogP relative to the naphthalene analog **5**.

X-ray crystal structures of analogs **10** (*S*-configuration) and **25** (*R*-configuration) complexed with renin were obtained (Fig. 3) to help explain how both of the enantiomers of the ketopiperazine scaffold exhibited similar renin inhibition activity, unlike the previously reported *trans*-3-alkoxymethyl-4-aryl piperidine scaffold.[10] When complexed with inhibitors of the ketopiperazine scaffold, the renin enzyme exists in the flap open conformation. The ketopiperazine NH of **10** and **25** formed a salt bridge between the Asp32 and Asp215 residues, while the 3-(2-methoxybenzyloxy)-propyl group occupied the large hydrophobic pocket formed by a conformation change of the flap region of the protein. The bicyclic portion of both analogs binds in the large S1/S3 pocket. The 3-hydroxypropyl chain of **25** extends into the S3 subpocket. Although the inversion of the chiral center results in a different vector orientation for the C6 hydroxymethyl linker in analog **10**, this linker was able to position the tetrahydroquinoline ring in the S1/S3 pocket, closely overlapping the corresponding ring in analog **25**. The S1/S3 pocket is sufficiently large enough to allow the change in ligand conformation without a high penalty in binding energy.

In summary, we have demonstrated that both enantiomeric configurations of the chiral 1-aryl-6-(hydroxymethyl)-2-ketopiperazine scaffold with bicyclic C rings

Table 1. SAR comparison of analogs with (*S*)- and (*R*)-configurations



R	(*S*)-analogs	IC_{50} (nM)[a]	(*R*)-analogs	IC_{50} (nM)[a]
	**5**	66	**4**	54
	**8**	860	**22**	820
	**10**	23	**23**	120
	**12**	33	**24**	64
	**14**	35	**25**	37
	**18**	17	**26**	7

[a] IC_{50} values obtained in duplicate using a fluorescent tGFP assay.[9]

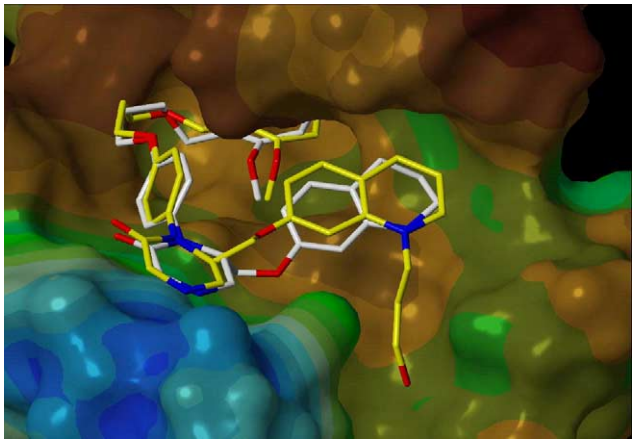


Figure 3. Overlap of the X-ray co-crystallization structures of analogs **10** (white atom coloring) and **25** (yellow atom coloring) complexed with renin.[10] Residues in the flap region have been removed for clarity. The blue regions of the Connelly protein surface represent hydrophilic regions and the brown regions represent hydrophobic regions.

display equipotent renin inhibition activity. This is in contrast to the enantiomeric specificity exhibited by a previously reported *trans*-3-alkoxymethyl-4-aryl piperidine scaffold, and is presumably due to the conformational flexibility of the C6 hydroxymethyl linker between the ketopiperazine and the C ring. The discovery that both enantiomers of the 1-aryl-6-(hydroxymethyl)-2-ketopiperazine scaffold possess equipotent renin inhibition activity is also significant because of the possibility that the separate enantiomers may display disparate pharmacokinetic, pharmacodynamic, or toxicology properties.

References and notes

1. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*.
2. MacGregor, G. A.; Markandu, N. D.; Roulston, J. E.; Jones, J. E.; Morton, J. J. *Nature* **1981**, *291*, 329.
3. Stanton, A. *Am. J. Cardiovasc. Drugs* **2003**, *3*, 389–394.
4. Fisher, N. D. L.; Hollenberg, N. K. *Expert Opin. Invest. Drugs* **2001**, *10*, 417–426.
5. (a) Vieira, E.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Güller, R.; Hirth, G.; Märki, H. P.; Müller, M.; Oefner, C.; Scalone, M.; Stadler, H.; Wilhelm, M.; Wostl, W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1397; (b) Güller, R.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Hirth, G.; Jenny, C.; Kansy, M.; Montavon, F.; Müller, M.; Oefner, C.; Stadler, H.; Vieira, E.; Wilhelm, M.; Wostl, W.; Märki, H. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1403; (c) Oefner, C.; Binggeli, A.; Breu, V.; Bur, D.; Clozel, J.-P.; D'Arcy, A.; Dorn, A.; Fischli, W.; Grüninger, F.; Güller, R.; Hirth, G.; Märki, H. P.; Mathews, S.; Müller, M.; Ridley, R. G.; Stadler, H.; Vieira, E.; Wilhelm, M.; Winkler, F. K.; Wastl, W. *Chem. Biol.* **1999**, *6*, 127; (d) Marki, H. P.; Binggeli, A.; Bittner, B.; Bohner-Lang, V.; Breu, V.; Bur, D.; Coassolo, Ph.; Clozel, J. P.; D'Arcy, A.; Doebeli, H.; Fischli, W.; Funk, Ch.; Foricher, J.; Giller, T.; Gruninger, F.; Guenzi, A.; Guller, R.; Hartung, T.; Hirth, G.; Jenny, Ch.; Kansy, M.; Klinkhammer, U.; Lave, T.; Lohri, B.; Luft, F. C.; Mervaala, E. M.; Muller, D. N.; Muller, M.; Montavon, F.; Oefner, Ch.; Qiu, C.; Reichel, A.; Sanwald-Ducray, P.; Scalone, M.; Schleimer, M.; Schmid, R.; Stadler, H.; Treiber, A.; Valdenaire, O.; Vieira, E.; Waldmeier, P.; Wiegand-Chou, R.; Wilhelm, M.; Wostl, W.; Zell, M.; Zell, R. *Farmaco* **2001**, *56*, 21.
6. Holsworth, D. D.; Powell, N. A.; Downing, D. M.; Cai, C.; Cody, W. L.; Ryan, M.; Ostroski, R.; Jalaie, M.; Bryant, J. W.; Edmunds, J. *J. Bioorg. Med. Chem.* **2005**, *13*, 2657.
7. Powell, N. A.; Holsworth, D. D.; Cody, W. L.; Cheng, X.-M.; Lee, C.; Erasga, N.; Downing, D. M.; Cai, C.; Clay, E. H.; Jalaie, M.; Bryant, J. W.; Ryan, M.; Edmunds, J. J.; Li, T.; Kasani, A.; Hall, E.; Subedi, R.; Rahim, M.; Maiti, S. *228th National ACS Meeting*, Philadelphia, PA, MEDI271.
8. The C ring carbonyl in analogs **18** and **26** was introduced to reduce the electron density of the tetrahydroquinoline ring. See Ref. 7.
9. Cody, W. L.; Holsworth, D. D.; Powell, N. A.; Jalaie, M.; Zhang, E.; Wang, W.; Samas, B.; Bryant, J.; Ostroski, R.; Ryan, M. J.; Edmunds, J. *J. Bioorg. Med. Chem.* **2005**, *13*, 59.
10. Coordinates for the renin/**10** (2bkt) and renin/**25** (2bks) complexes have been deposited at www.rcsb.org.