Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 3637–3642

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

DESIGN AND SYNTHESIS OF NOVEL CONFORMATIONALLY RESTRICTED HIV PROTEASE INHIBITORS

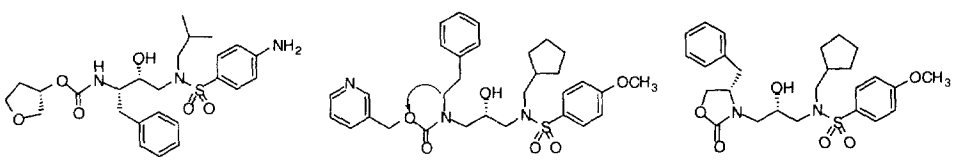
Francesco G. Salituro,* Christopher T. Baker, John J. Court, David D. Deininger, Eunice E. Kim, Biquin Li, Perry M. Novak, Bhisetti G. Rao, S. Pazhanisamy, Margaret D. Porter, Wayne C. Schairer, and Roger D. Tung

Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, MA 02139, U.S.A.

Received 21 August 1998; accepted 30 October 1998

Abstract: A set of HIV protease inhibitors represented by compound **2** has previously been described. Structural and conformational analysis of this compound suggested that conformational restriction of the P_1/P_2 portion of the molecule could lead to a novel set of potent protease inhibitors. Thus, probe compounds **3–7** were designed, synthesized, and found to be potent inhibitors of HIV protease.

In the preceding paper,[1] we introduced a series of compounds derived from amprenavir (**1**),[2] which incorporate a simplified sulfonamide backbone structure; these compounds display nanomolar potency against HIV protease. Structural information on one key compound (**2**) revealed that the bound molecule exists in a high energy conformation relative to the calculated energy minimum resulting in a significant loss of relative binding energy. Since several compounds in this series, co-complexed with HIV protease, all displayed essentially similar bound structural features, we concluded that the molecular backbone of this series imposed structural constraints that precluded the formation of essential interactions with the protease without concomminant intramolecular distortions.



1 **2** **3**

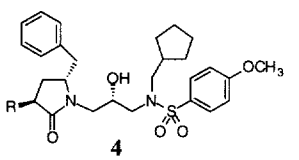
Figure 1. The crystal structure of compound **2**[1] suggests the cyclization of the P_1/P_2 moieties of the molecule could result in more potent inhibitors. Compound **3** was prepared as a probe compound to test the general hypothesis.

Further analysis of structure **2** suggested the possibility that connecting the P_1/P_2 portion of the molecule within a rigid framework could relieve the observed carbonyl bond and backbone distortions and still retain critical binding interactions to the enzyme, in particular with the S_2-S_2' binding pockets as well as the flap and catalytic waters.[3] We therefore postulated that the elimination of intramolecular conformational distortions in these compounds could result in a series of more potent inhibitors. This paper describes the design, synthesis, and enzyme analysis of several novel conformationally restricted molecules.

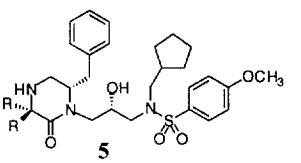
In order to test the scaffolding hypothesis, we first designed a simplified set of oxazolidinone based probe

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00670-2

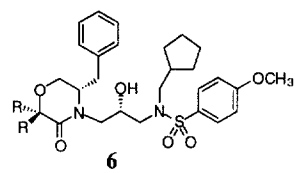
compounds (Figure 1, compound **3**). Upon synthesizing and testing all four possible diastereomers of compound **3**[4] and found that one of the compounds (*S,S* isomer, **3**) exhibited significant potency against the enzyme (Table 1), while the remaining isomers displayed no enzyme inhibition at 10 μM. Based on this result, implying significant specificity of binding, we focused our further efforts on the design of more refined scaffolds which would incorporate the critical P_2 moiety. Lead compounds **4**–**7** were proposed as structures that could provide a diversity of both bond vectors to access P_2 and of molecular physicochemical properties.



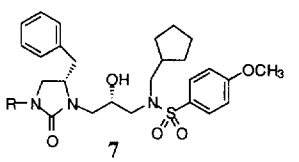
4



5



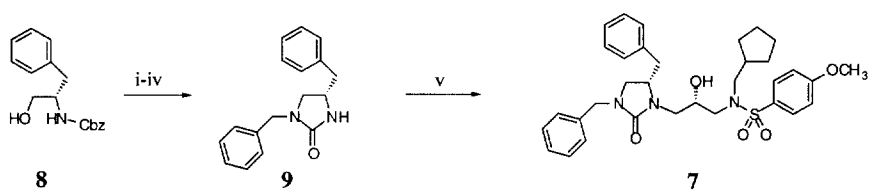
6



7

The general synthetic strategy (Schemes 1–4) involved the synthesis of the specific P_1/P_2 scaffold (compounds **9**, **11**, **13**, and **15**) followed by incorporation into the sulfonamide backbone utilizing an epoxide intermediate previously described (compound **5**, Scheme 1[1]). Schemes 1–4 detail the specific examples of a urea, piperidinone, lactam, and morpholinone scaffold, respectively. Each compound, in addition to establishing a unique entry into the P_2 pocket by virtue of the fixed vector angles associated with each specific scaffold, offers a variety of possibilities in terms of the origin of the P_2 group itself. For example, in the urea case, the P_2 moiety originates from the amine used to displace the activated hydroxyl of an alpha amino alcohol (Scheme 1, step ii). In piperidinone compounds, the P_2 function originates from the side chain of the α-amino acid utilized in the reductive amination (Scheme 2, step i). In the lactam example, the electrophile used to quench the anion α to the lactam carbonyl is the source of the P2 moiety (Scheme 3, step iv).

Scheme 1 Cyclic Urea Synthesis

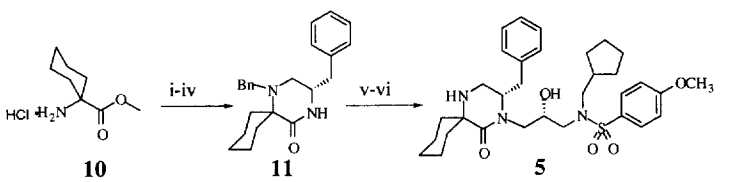


8 **9** **7**

(i) Mesyl chloride, triethylamine, methylene chloride. (ii) Benzylamine, sodium iodide, acetonitrile, reflux. (iii) HBr/HOAc, chromatography (90/10/1, methylene chloride/methanol/ammonium hydroxide). (iv) carbonyldiimidazole, methylene chloride. (v) Sodium hydride, epoxide **5**[1], DMF.

More specifically, the urea scaffold **9** was prepared starting with commercially available Cbz-L-phenylalinol. Activation with mesyl chloride, followed by displacement with benzyl amine in the presence of sodium iodide and deprotection of the Cbz group afforded a diamine which was chromatographed utilizing methylene chloride/ methanol/ammonium hydroxide (90/10/1) as eluent. The resulting free base was then treated with carbonyldiimidazole to yield the desired scaffold **9**. Compound **7** was then prepared by reaction of the sodium anion of the **9** with the sulfonamide epoxide intermediate (compound **5**[1]) in DMF.

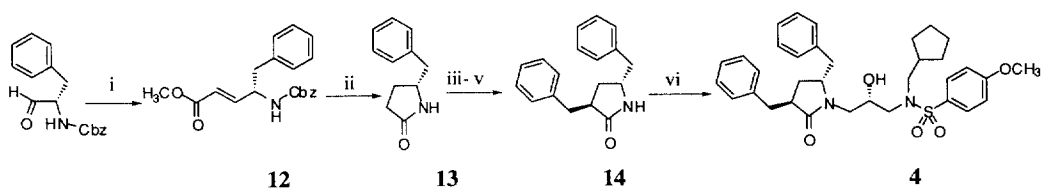
Scheme 2 Piperidinone Synthesis



(i) Cbz-L-Phenylalinal, sodiumcyanoborohydride, 1% HOAc/DMF. (ii) HBr/HOAc. (iii) Diisopropylamine, methanol. (iv) Sodium hydride, benzyl bromide, DMF. (v) Sodium hydride, epoxide **5**[1], DMF. (vi) $H_2/Pd(OH)_2$, methanol.

The piperidinone scaffold **11** was prepared through reductive amination of the spiro amino ester **10** and Cbz-L-phenylalinal. Deprotection of the Cbz group followed by free-basing, resulted in spontaneous ring closure to form the six membered lactam. Protection of the secondary amine with a benzyl moiety, reaction of the scaffold as described previously, and subsequent deprotection of the benzyl group afforded the desired final product **5**.

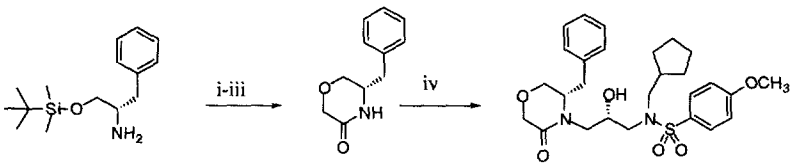
Scheme 3 Lactam Synthesis



(i) methyl (phosphorylidene) acetate, toluene. (ii) Magnesium in methanol. (iii) Di-*tert*-butyldicarbonate, DMAP, acetonitrile. (iv) LDA, benzyl bromide, THF. (v) TFA/methylene chloride. (vi) Sodium hydride, epoxide **5**[1], DMF.

The lactam scaffold **14** was prepared utilizing the method of Wei.[5] Thus, the Cbz protected α–β-unsaturated amino ester **12**, prepared from a wittig reaction of Cbz phenylalinal and methyl (triphenylphosphoranylidene) acetate, was treated with magnesium metal in methanol to afford the desired 2-pyrrolidinone **13**. Protection of the lactam with a boc group, followed by deprotonation and quenching with benzyl bromide afforded the desired 3*S*,5*S* isomer **14** in approximately a 4:1 ratio over the 3*R*,5*S* isomer. Deprotection and introduction of the scaffold in a manner parallel to the previous two examples afforded the desired compound **4**.

Scheme 4 Morpholinone Synthesis



15 **6**

(i) Bromoacetyl bromide, potassium carbonate, methylene chloride. (ii) Tetrabutylammonium fluoride, THF. (iii) Sodium Hydride, THF. (iv) Sodium hydride, epoxide **5**[1], DMF.

The morpholinone scaffold **15** was prepared by the method detailed in Scheme 4. *t*-Butyldimethylsilyl protected phenylalinol was treated with bromoacetyl bromide to form the amide, which was deprotected with TBAF to yield the free hydroxyl. Treatment with sodium hydride afforded ring closure to form scaffold **15,** which was used as previously described in Schemes 1–3 to prepare final product **6**.

Compounds **2–7** (Table 1) were assayed for inhibition against HIV protease. While P_2 unsubstituted compounds **3**, **5a**, and **6** were relatively weak inhibitiors, compounds bearing even simple P_2 moieties (compounds **7**, **5b**, and **4**) were found to display potent inhibitory activity. In particular, compound **4** is essentially equipotent with amprenavir (K_i = 0.6 nM) and represents a promising platform for designing further elaborations in the molecule to establish important contacts with enzyme S_2 pocket. In addition, it was determined that in each series only one hydroxyl isomer displayed potent inhibition against the enzyme distinguishing the scaffolded compounds from the linear counterparts which in some cases showed only three to fourfold selectivity.[6]

Table 1

Compound number	R	K_i (nM)
2	--	17
3	--	1500
4	Benzyl	0.5
5a	H,H	3000
5b	spirocyclohexyl	17
6	H,H	1000
7	Benzyl	15

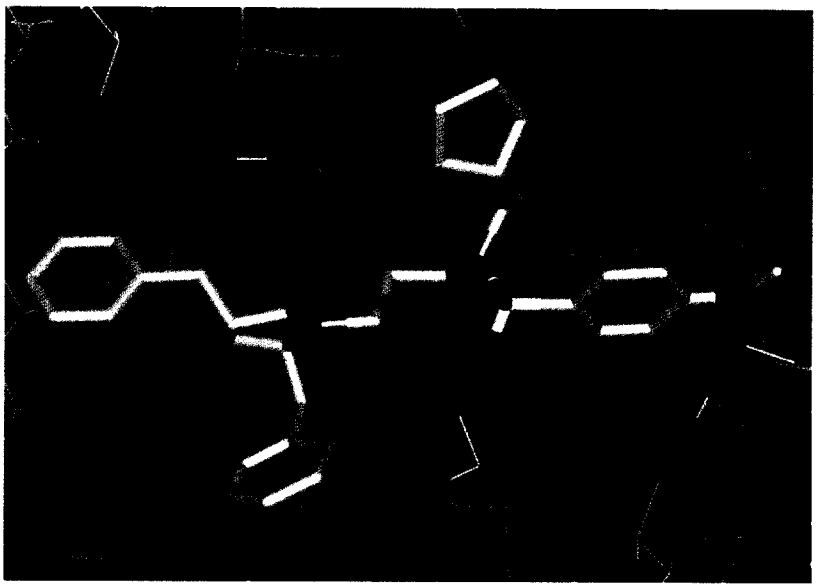


Figure 2. X-ray crystal structure of compound **4** bound to HIV protease.

Compounds **4**, **5**, and **7** were co-crystallized with HIV protease and the X-ray crystal structure of each complex was solved; Figure 2 illustrates one example structure with compound **4**. Analysis of this co-complex revealed that, as hoped, the amide bond and backbone distortions observed with the linear compounds are relieved by utilizing this scaffold. The lactam bond by virtue of the rigid five membered ring is inherently planar (177°), but more importantly, the interactions which stem from the scaffold (flap water and S_1/S_2 binding pockets) are maintained with the enzyme. The carbonyl of the lactam establishes a strong contact with the enzyme flap water (2.26 Å), while the phenyl rings of the 5-benzyl and the 2-benzyl moieties occupy the S_1 and S_2 pockets of the enzyme, respectively, in much the same manner as other potent inhibitors. In addition, the backbone distortions are essentially relieved in this compound with an N-C-C-OH torsion of -54_0. Moreover the central hydroxyl group now occupies an optimal position in the plane of the catalytic aspartate residues. In contrast, the hydroxyl group of **2**, by virtue of the backbone distortion, occupies a suboptimal nonplanar orientation with the catalytic aspartates.

Conclusions: Structural information on previously described compounds such as compound **2** suggested the possibility that scaffolding the $P_1$and P_2 moieties of these inhibitors could address intramolecular structural deformations inherent in binding of this linear series and thus lead to more potent inhibitors. Several prototype compounds were synthesized and co-crystallized with HIV protease to test the hypothesis. In general, we have

observed that the rigid compounds adopt the predicted conformations, overcoming the intramolecular distortions associated with the previously described linear compound class. In addition, we had postulated that the relatively poor selectivity between the *R* and *S* hydroxyl isomers in linear compounds directly stemmed from the significant backbone distortion observed. We therefore concluded that the increased selectivity of *S* over *R* hydroxy compounds observed in the rigid scaffolds6 is directly associated to the more favorable backbone torsion angles. Based on our modeling studies and the results observed with compounds **4–7**, we have directed our subsequent studies towards developing more highly optimized P2 moieties to more fully optimize interactions with the critical S_2 enzyme binding pocket. These studies will be reported in due course.

References and Notes

1. Baker, C. T.; Salituro, F. G.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Schairer, W. C.; Tung, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, preceeding paper.
2. (a) Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117* 1181. (b) Navia, M. A.; Sato, V. L.; Tung, R. D. *International Antiviral News* **1995**, *3*, 143. (c) Partaledis, J. A.; Yamaguchi, K.; Tisdale, M.; Blair, E. E.; Falcione, C.; Maschera, B.; Myers, R. E.; Pazhanisamy, S.; Futer, O.; Cullinan, A. B.; Stuver, C. M.; Byrn, R. A.; Livingston, D. J. *J. Virol.* **1995**, *69*, 5228. (d) Rao, B. G.; Dwyer, M. D.; Thomson, J. A.; Baker, C. T.; Deininger, D. D.; Murcko, M. A.; Tung, R. D.; Navia, M. A.; Kim, E. E. *Antiviral Ther.* **1996**, *1*, 13. (e) Painter, G. R.; Ching, S.; Reynolds, D.; St. Clair, M.; Sadler, B. M.; Elkins, M.; Blum, R.; Dornsife, R.; Livingston, D. J.; Partaledis, J. A.; Pazhanisamy, S.; Tung, R. D.; Tisdale, M. *Drugs Fut.* **1996**, *21*, 347.
3. (a) March, D. R.; Fairlie, D. P. In *Designing New Antiviral Drugs for AIDS: HIV-1 Protease and Its Inhibitors*; R. G. Landes Company: Austin, 1996. (b) Chrusciel, R. A.; Romines, K. R.; *Exp. Opin. Ther. Pat.* **1997**, *7*, 111. (c) Vacca, J.P.; Condra, J.H. *Drug Disc Today* **1997**, *2*, 261. (d) Flexner, C. *N. Engl. J. Med.* **1998**, *338*, 1281.
4. The synthesis of compound **3** and its diasteriomers followed the general procedures outlined in Schemes 1–4 utilizing the commercially available enantiomers of 5-benzyl-oxazolidinone.
5. Wei, Z. Y.; Knaus, E. E. *Tetrahedron Lett.* **1993**, *34*, 4439.
6. The *S* and *R* hydroxy isomers were prepared, separated and compared for several compounds. Selectivity for the *S* diastereomer over the *R* was observed in every case to be in excess of tenfold. The exact differences could not be determined due to the limits of solubility of the *R* isomers. Examples of K_i *S* isomer/K_i *R* isomer selectivity include: Compound **3** (*S*/*R* > 10), compound **6** (*S*/*R* > 20), compound **5b** (*S*/*R* > 30).