Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 823–828

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

THE SYNTHESIS AND EVALUATION OF CYCLIC UREAS AS HIV PROTEASE INHIBITORS: MODIFICATIONS OF THE P1/P1' RESIDUES

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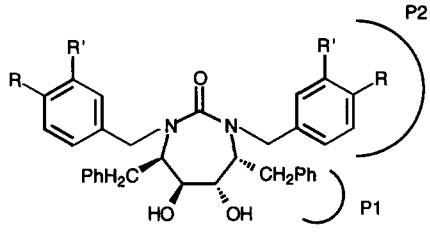
Received 9 December 1997; accepted 20 February 1998

Abstract. Two series of cyclic ureas modified at the P1/P1' residue were prepared and evaluated for HIV protease inhibition and whole cell antiviral activity. Compounds **8b**, **10** (3- and 4-pyridylmethyl analogs) and **6b** (4-methoxy analog) showed significant improvement in antiviral activity relative to lead compounds DMP323 and DMP 450.

Human immunodeficiency virus (HIV) has been identified as the causative agent for AIDS.[1] The HIV protease is required for the successful replication of the virus and therefore is a target for chemotherapeutic intervention in the progression of AIDS.[2] Several classes of HIV protease inhibitors are currently undergoing vigorous studies both at the discovery and clinical levels.[3] Our efforts have resulted in the design, synthesis, and evaluation of cyclic ureas (DMP 323 and DMP 450) as potent inhibitors of HIV protease.[4]



		Ki (nM)	IC_{90} (nM)
DMP 323	R = CH_2OH, R' = H	0.29	91
DMP 450	R = H, R' = NH_2	0.28	126

Predictions based on modeling studies of L-685,434 a potent HIV protease inhibitor, bound in the native enzyme active site, led Thompson and coworkers to consider attaching polar substituents via an appropriate tether on the P1/P1' phenyl rings. Structure-activity data based on the *para* hydroxylations of one or both phenyl rings reinforced the conclusions drawn from the modeling studies and led to the preparation of a series of potent HIV-1 protease inhibitors modified at the P1 phenyl ring.[5] Based on the positive results observed by Thompson and coworkers and in an effort to improve upon both the water solubility and the potency of the cyclic ureas under study, the preparation of tyrosine based cyclic urea was inititated. We decided to profile the modified P1/P1' analogs with two P2/P2' groups: a simple benzyl and benzyl-3(1*H*)-pyrazole.[6]

Chemistry

The synthesis of cyclic ureas starting with commercially available D-amino acids has been previously described.[7] The key step in the synthetic sequence is a vanadium trichloride mediated pinacol coupling reaction to provide the Cbz protected diol (eq 1).[8] This diol was subsequently converted to the cyclic urea.

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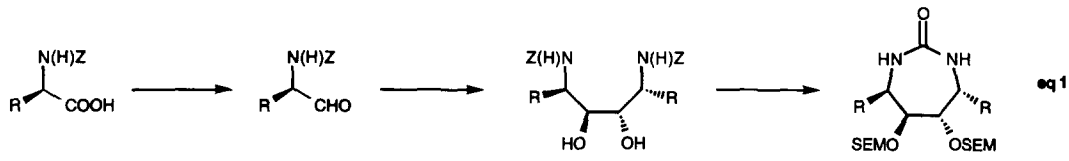
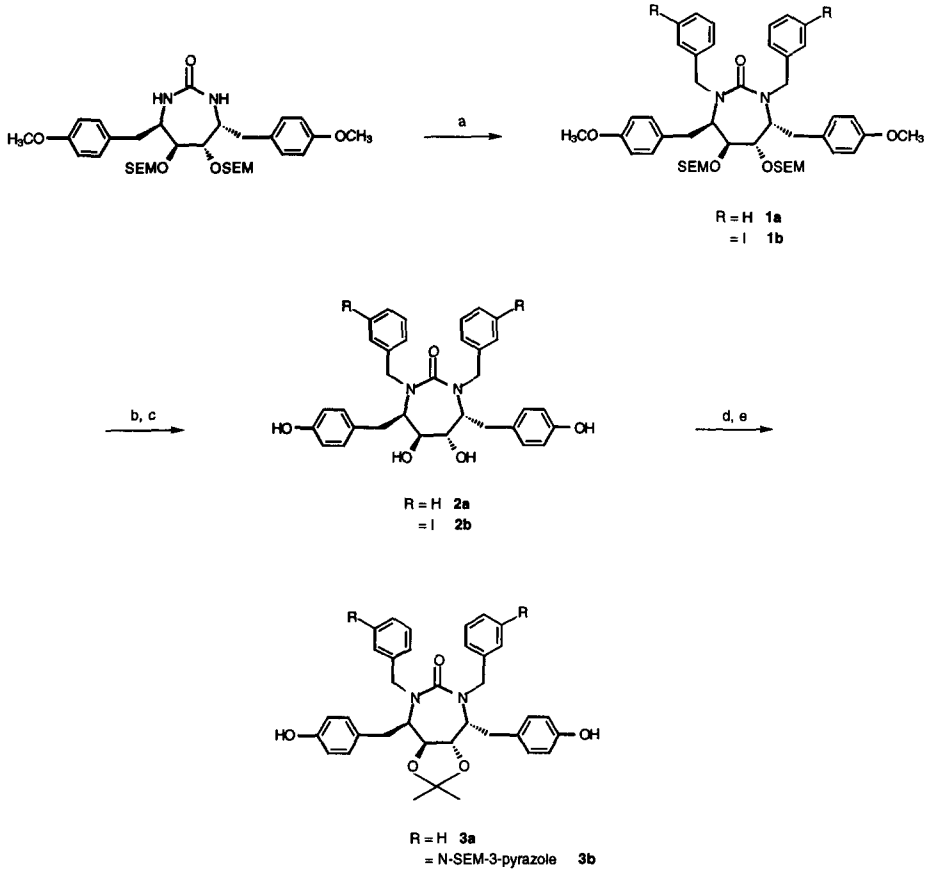


eq 1

In the case of cyclic ureas derived from D-phenylalanine, the introduction of the P2 groups was accomplished by treatment with base and an appropriate alkylating agent, followed by the final step of deprotection of the acetonide group to give DMP450 and its analogs.

Scheme I

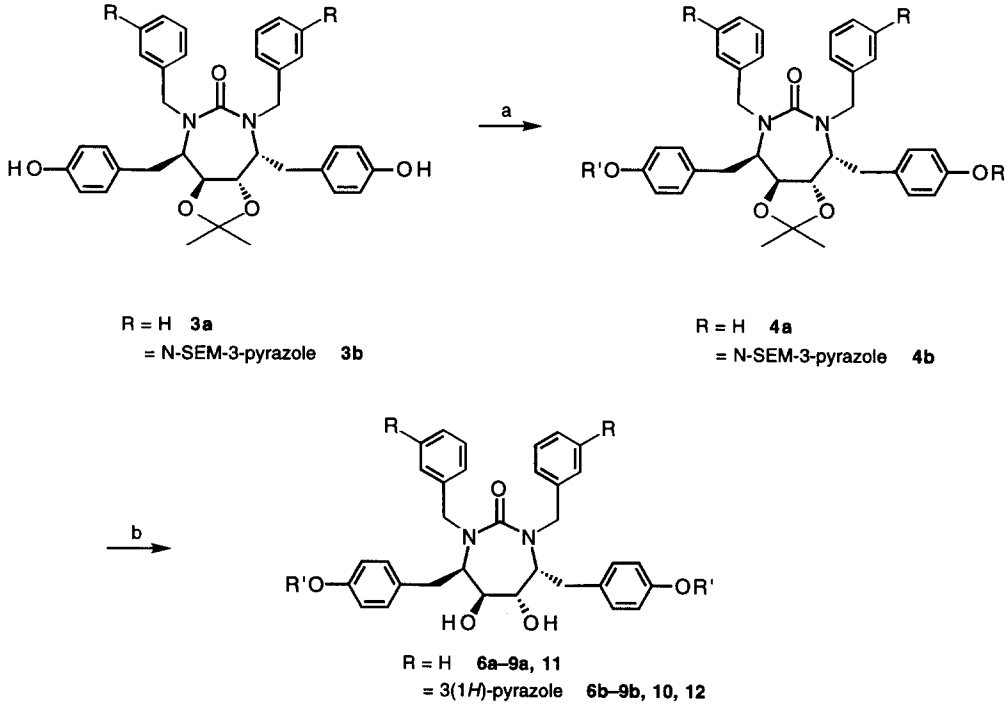


Reagents and conditions: (a) $ArCH_2Br$, cat. $(nBu)_4NI$, NaH, DMF, 25 °C, 18 h, 85–90%; (b) HCl in ether, MeOH, 25 °C, 15 min; (c) BBr_3 in CH_2Cl_2, 0–25 °C, 1 h, 80–85% over 2 steps; (d) 1,1-dimethoxypropane, cat. *p*-TsOH, CH_2Cl_2, 25 °C, 1 h 80–85%; for the conversion of **2b** to **3b**: (e) Na_2CO_3, N-SEM-pyrazole-3-boronic acid, $Pd(PPh_3)_4$, THF:H_2O, reflux, 18 h, 90–95%.

Modifications of this general scheme to accomodate the additional heteroatom of the *para* hydroxy functionality of D-tyrosine provided the cyclic urea shown in Scheme I. In the simple P2/P2' = Bn series, treatment with NaH and benzyl bromide provided compound **1a** in good yield. The SEM protecting group was removed by treatment with

HCl in methanol followed by demethylation of the aryl ether with BBr_3 in methylene chloride to give compound **2a** in 80% yield over two steps. This two-step deprotection protocol provides cleaner and higher yielding results as compared to one pot conversions. The diol was reprotected as the acetonide using 1,1-dimethoxypropane and catalytic CSA in methylene chloride. The use of alternate protecting groups such as benzyl and silyl groups was explored without success.[9] In the benzyl-3(1*H*)-pyrazole series, the cyclic urea was alkylated with NaH and *m*-iodobenzyl bromide to give **1b**. The *m*-iodo functionality was utilized to introduce a pyrazole ring using Suzuki methodology.[10] Treatment of the iodo compound with N-SEM pyrazole-3-boronic acid[11] and catalytic Pd(0) provided **4b** in quantitative yield.

Scheme II



R = H **3a**
= N-SEM-3-pyrazole **3b**

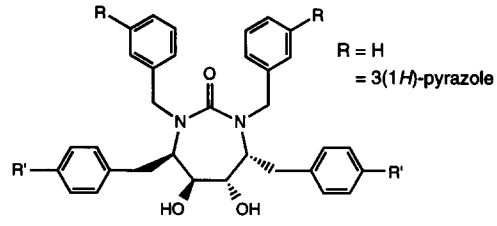
R = H **4a**
= N-SEM-3-pyrazole **4b**

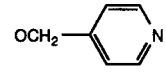
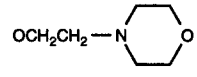
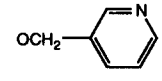
R = H **6a–9a, 11**
= 3(1*H*)-pyrazole **6b–9b, 10, 12**

Reagents and conditions:(a) Cs_2CO_3, R'Br, acetone, reflux, 1.5–3 h, 40–90%; (b) HCl in ether, MeOH, 25 °C, 15 min, 75–87%.

The introduction of hydrophilic nitrogen functionality (pyridyl rings, morpholinoethyl, *N*, *N*-dimethyl alkyl side chains) was accomplished by treatment with aryl or alkyl halides and Cs_2CO_3 in acetone in high yields.[5] In the case of compounds **7a** and **7b,** alkylation with ethyl bromoacetate was followed by LAH reduction to give the hydroxyethylene compounds. Removal of the SEM and acetonide protecting groups provided the target compounds shown in Scheme II.[12]

TABLE I



Compound	R	R'	K_i (nM)[13a]	IC_{90} (nM)[13b]
XL075	H	H	3.4	790
XN975	3(1*H*)-pyrazole	H	0.027	56
5a	H	OH	1.1	184
5b	3(1*H*)-pyrazole	OH	0.016	1345
6a	H	OCH_3	8.6	600
6b	3(1*H*)-pyrazole	OCH_3	0.078	10
7a	H	OCH_2CH_2OH	0.76	78
7b	3(1*H*)-pyrazole	OCH_2CH_2OH	0.059	462
8a	H		0.84	100
8b	3(1*H*)-pyrazole		0.071	18
9a	H		5.9	230
9b	3(1*H*)-pyrazole		0.13	1033
10	3(1*H*)-pyrazole		0.059	32
11	H	$OCH_2CH_2N(H)Me$	1.6	800
12	3(1*H*)-pyrazole	$OCH_2CH_2N(Me)_2$	0.061	5400

Results and Discussion

The results of enzyme inhibition and antiinfectivity assays have been summarized in Table I. In the benchmark P2/P2' = Bn series, compounds **5a**, **7a** and **8a** appear to have significantly improved upon the parent compound (**XL075**, K_i = 3.4 nM; IC_{90} = 790 nM), in both the enzyme as well as cell based assays. Although there is a modest improvement in the K_i values, there is a concurrent significant improvement in the cell based assay, with the values being up to an order of magnitude better as illustrated by **7a**. This may be due to the

moderation of the lipophilic nature of the parent compound with the introduction of polar substituents. Compound **9a** shows no significant improvement in inhibitory activity, but does appear to translate better than the parent with a threefold improvement in the IC_{90} value. Compounds **6a** and **11** show no enhancement in antiviral activity. The substituents that improve upon the antiviral activity were introduced in the next series of cyclic ureas bearing the more potent P2/P2' group in benzyl-3(1*H*)-pyrazole. The parent compound in this series [**XN975**, P2/P2' = benzyl-3(1*H*)-pyrazole] has a K_i = 0.027nM and IC_{90} = 56 nM. Analogs containing the relatively polar benzyl-3(1*H*)-pyrazole substituent were less tolerant of P1/P1' modification. In general, introduction of polar groups as in **7b** and **12** results in compounds with good enzyme activity but inferior cellular antiviral activity. The decrease in antiviral activity appears to arise from poor cell penetration, possibly a result of the increased polarity of the molecules. Compounds **6b**, **8b**, and **10** have shown activity comparable to that of the parent compound and a significant improvement relative to DMP323 and DMP450.

Conclusions

In the P2/P2' = benzyl series we were able to significantly improve upon the K_i and IC_{90} values with entries **5a**, **7a**, and **8a**. Significant effects were also observed with the introduction of the benzyl-3(1*H*)-pyrazole moiety while retaining the P1/P1' substituents. Improvements in antiviral activity observed in **6b** and **8b** has allowed us to develop a series that is comparable in potency to the best clinical candidates. Substituents with increased potency and water solubility using this approach (**8b** and **10**) are currently being incorporated in cyclic ureas bearing advanced P2/P2' groups and will be reported in due course.

Acknowledgments

We would like to thank the Mass Spectrometry Lab (Carl Schwarz, Robert Carney and Michael Haas) for ms data.

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11. N-SEM-pyrazole was converted to the boronic acid by treatment with nBuLi (1.2 equiv) at 0 °C followed by triisopropylborate (5 equiv). See: Wong, M. S.; Nicoud, J-F. *Tetrahedron Lett.* **1993**, *34*, 8237.

12. All compounds provided satisfactory spectral data (^{1}H NMR, CIMS/ESIMS and HRMS/peak match) and were homogenous by TLC.

13. (a) All compounds were assayed for enzyme inhibitory activity (K_i) according to the protocol described in: Erickson-Viitanen, S.; Klabe, R. M.; Cawood, P. G.; O'Neal, P. L.; Meek, J. L. *Antimicrob. Agents Chemother.* **1994**, *38*, 1628. (b) All compounds were assayed for whole cell based antiviral activity (IC_{90}) according to the protocol described in: Bacheler, L. T.; Paul, M.; Jadhav, P. K.; Otto, M.; Stone, B.; Miller, J. *Antiviral Chem. Chemo.* **1994**, *5*, 111.