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THE SYNTHESIS OF SYMMETRICAL AND UNSYMMETRICAL P1/P1' CYCLIC UREAS AS HIV PROTEASE INHIBITORS

Mona Patel,*[a] Robert F. Kaltenbach III,[a] David A. Nugiel,[a] Robert J. McHugh Jr.,[a] Prabhakar K. Jadhav,[a] Lee T. Bacheler,[b] Beverly C. Cordova,[b] Ronald M. Klabe,[b] Susan Erickson-Viitanen,[b] Sena Garber,[b] Carol Reid,[b] and Steven P. Seitz*[a]

Departments of [a]Chemical & Physical Sciences and [b]Virology, The DuPont Merck Pharmaceutical Company, Experimental Station, E500/4803, P. O. Box 80500, Wilmington, DE 19880-0500, U.S.A.

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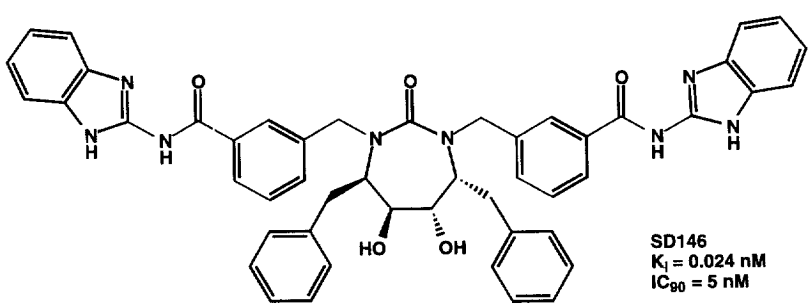
Abstract. Cyclic urea SD146, a potent HIV protease inhibitor bearing a flat resistance profile, possessed poor solubility and bioavailability, which precluded further development of the compound. In an effort to improve upon the pharmacokinetic profile of the compound, several analogs modified at the P1/P1' residues were prepared and evaluated. Several of those compounds displayed significant improvement of physical properties.

During the development of cyclic ureas as HIV protease inhibitors, Jadhav et al. identified SD146 as a potent HIV protease inhibitor bearing a flat resistance profile against most known mutations and clinical isolates.[1] However, the poor bioavailability of this compound as a result of negligible water and lipid solubility, precluded further development. The X-ray analysis of SD146 bound to the active site of HIV protease showed a high level of interaction between the compound and the enzyme, with eight hydrogen bonds being observed between the heteroatoms of the benzimidazole moiety and the backbone of the enzyme. The four hydrogen bonds with both the P2 and P2' residues of the molecule are as follows: (i) the NH functionality of the benzimidazole and the beta-carbonyl (CO) functionality of the Asp30/Asp30' residues, (ii) CONH of the amide bond with the amine (NH) functionality of the Asp30/Asp30' residues, (iii) -N=C-(NH)NH of the benzimidazole ring and the amine (NH) functionality of the Gly48/Gly48' residues, and (iv) CONH of the amide bond with the carbonyl (CO) moiety of the Gly48/Gly48' residues. This intricate hydrogen bonding network, among other factors, appear to contribute towards a flat resistance profile.[1] As a result, the benzimidazole portion of the compound was deemed indispensible for the retention of the remarkable resistance profile and has been included in the SAR described below. Therefore, modifications on the P1/P1' residues were carried out in an effort to improve upon the pharmacokinetic profile while retaining both the potency and the resistance profile.



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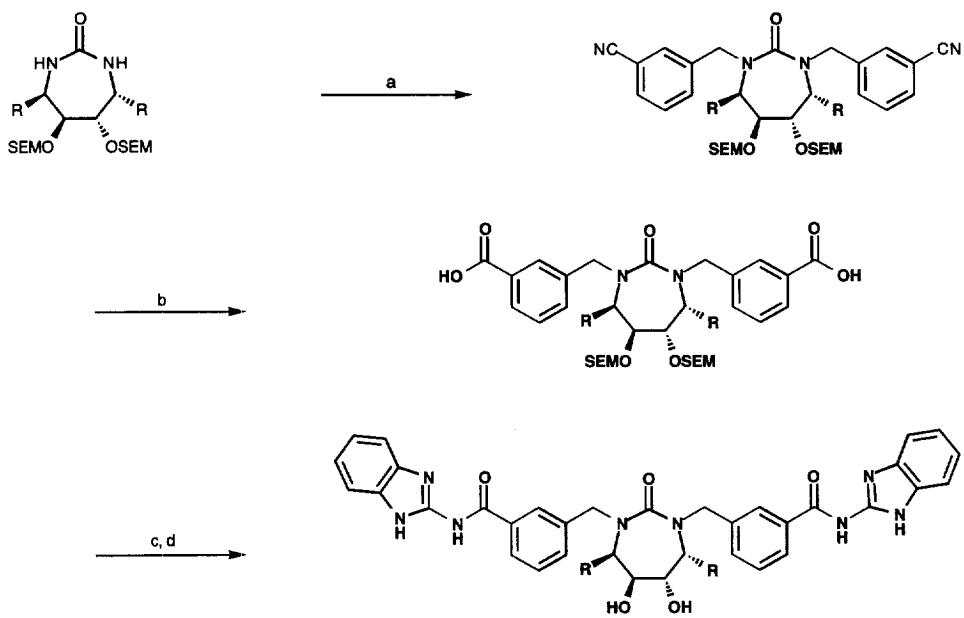
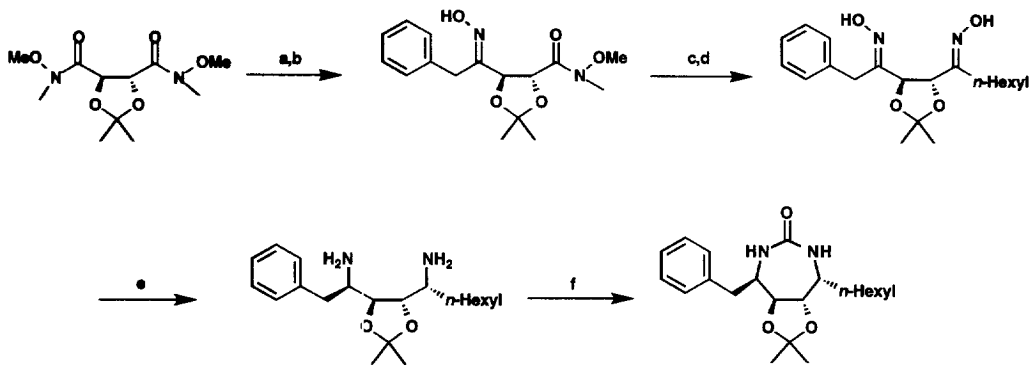
Three separate routes for the preparation of cyclic ureas bearing the required *R,S,S,R* configuration starting with commercially available reagents have been previously described.[2] Further conversion to the benzimidazole analogs listed in Table I is detailed in Scheme I.[3] Treatment of the unsubstituted cyclic urea with *m*-cyanobenzyl bromide and potassium *tert*-butoxide in DMF gave bis-alkylated material in good yield. Subsequent strong base hydrolysis with potassium hydroxide in ethylene glycol provided the bis-acid. Optimal conditions for the coupling of the bis-acid with 2-aminobenzimidazole required the use of BOP as the coupling agent and triethylamine in DMF. Acid hydrolysis of the SEM protecting groups resulted in the desired analogs.

Scheme I



Reagents and conditions: (a) 3-cyanobenzyl bromide, tBuOK, THF, 25 °C, 14 h, 86–98% ; (b) KOH, ethylene glycol, 140 °C, 14 h, 91–98%; (c) BOP, TEA, 2-aminobenzimidazole, DMF, 25 °C, 14 h, 57–88%; (d) HCl, MeOH, 25 °C, 14 h, 65–72%.

The synthesis of unsymmetrical cyclic ureas is exemplified in Scheme II.[3] Preparation of the bis-Weinreb amide from commercially available (-)-dimethyl 2,3-*O*-isopropylidene-L-tartrate has been described earlier.[2] The addition of one equivalent of Grignard reagent is followed by treatment with hydroxylamine hydrochloride to provide the oxime. This sequence was repeated to introduce the P1' group. Stereoselective reduction of the bis-oxime with excess DIBAL provided the diamine bearing the required *R,S,S,R* configuration. Treatment of diamines with 1,1'-carbonyldiimidazole in refluxing tetrachloroethane provided the unsymmetrical cyclic ureas, which were converted to the benzimidazole analogs described in Table II.[2]



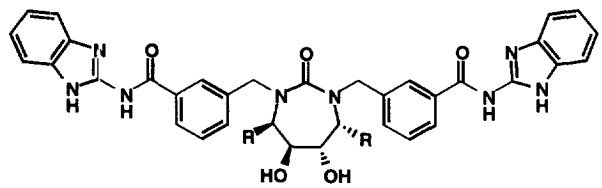
Reagents and conditions: (a) BnMgCl, THF,–78° to 0 °C, 3 h, 56%; (b) H_2NOH•HCl, EtOH, H_2O, 18 h, 95%; (c) *n*-HexylMgBr, THF, 0 °C, 3 h, 96%; (d) H_2NOH•HCl, EtOH, H_2O, 18 h, 85%; (e) DIBAl, toluene, 0° to 25 °C, 18 h, 50%; (f) 1,1'-CDI, tetrachloroethane, reflux, 1 h, 26%.

Results and Discussion

Aliphatic and substituted benzyl groups at P1/P1' were introduced in an effort to increase solubility by one of several methods: (a) decrease molecular weight (SD146 = 824), (b) decrease symmetry of the molecule and thereby reduce the crystallinity of the compound (c) introduce basic functional groups in order to make salts. To that end, compounds **1** and **2** containing aliphatic substituents were prepared in an effort to reduce the molecular weight and reduce the crystallinity. Initial studies had indicated that the isobutyl group was the optimal one among the aliphatic substitutions attempted.[2] However, the solubility of compound **2** was as poor as SD146 (SD146 = 0.05 μg/mL in 0.1N HCl). Compounds **3** and **4**[4] were prepared in an effort to reduce the level of crystallinity of the compounds thereby increasing the solubility. However, these compounds were relatively poor inhibitors of the enzyme, with compound **3** losing an order of magnitude of activity in the whole cell assay as well.

Compounds **5** through **9** contain substituted benzyl P1/P1' groups. The *p*-hydroxy and *p*-methoxy substituted benzyl P1/P1' groups (**7** and **9**) show activity comparable to SD146 against the protease enzyme but lose several fold (3 to 7x) in the whole cell assay. Compounds **5** and **6** represent the cyclic ureas bearing a basic nitrogen on the benzyl P1/P1' groups capable of forming salts.[2] As a result, significant improvement in the solubility profile of these compounds was observed with compound **5** having a solubility of 8.3 mg/mL in 0.1 N HCl and that of compound **6** being 13.2 mg/mL in the same solvent. Both compounds showed good activity against the enzyme as well as in the whole cell assay and therefore underwent further evaluation in the resistance assays.

Table I: Symmetrical Cyclic Ureas

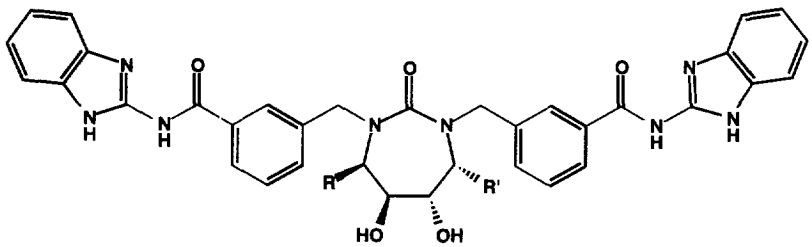


Compound	R	K_i (nM)[5a]	IC_{90} (nM)[5b]
SD146	benzyl	0.024	5
1	ethyl	4.5	570
2	isobutyl	0.3	59
3	hexyl	0.35	86
4	cyclohexyl	0.29	14
5	*p*-H_2N-benzyl	0.016	10
6	*p*-Me_2N-benzyl	0.038	8
7	*p*-OH-benzyl	0.035	35
8	*p*-OCH_2Ph-benzyl	3.7	125
9	*p*-OCH_3-benzyl	0.026	19

It has been previously shown that breaking the C2 symmetry of cyclic ureas with different substitutions on the urea nitrogens gives compounds with decreased crystallinity.[6] Application of this concept to the P1/P1' substituents is shown in Table II. The ethyl substituted compound **10**, showed a loss of activity against both the isolated enzyme as well as whole cell assay. However, the isobutyl and hexyl substituted compounds **11** and **12** were of greater interest as these unsymmetrical compounds not only exhibited activity comparable to SD146, but showed an improvement in their aqueous solubilty. Compounds **11** and **12** have a solubilities of 0.16 mg/mL and 0.118 mg/mL in 0.1 N HCl.

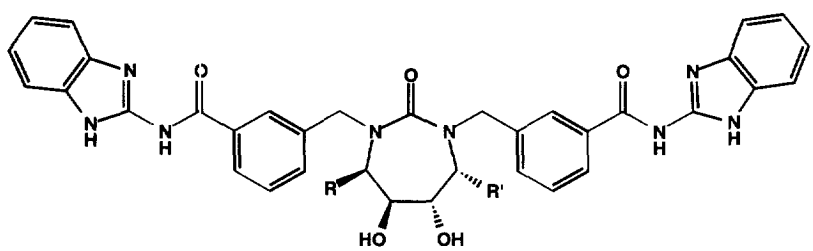
Table III describes the resistance data generated for SD146 as well as the best P1/P1' modified analogs. The single mutant I84V and the double mutant I84V/V82F have been included in the resistance profile as strains bearing these single and double amino acid changes were isolated upon passage of HIV-1 in the presence of DMP323, an earlier clinical candidate.[7]

Table II: Unsymmetrical Cyclic Ureas



Compound	R	R'	K_i (nM)	IC_{90} (nM)
SD146	benzyl	benzyl	0.024	5
10	ethyl	benzyl	0.069	26
11	isobutyl	benzyl	0.038	10
12	hexyl	benzyl	0.046	9

Table III: Resistance Profile



Compound	R	R'	WT IC_{90} (nM)	I84V IC_{90} (nM)	I84V/V82F IC_{90} (nM)
SD146	benzyl	benzyl	5	5	21
2	isobutyl	isobutyl	26	20	12
5	*p*-H_2N-benzyl	*p*-H_2N-benzyl	10	23	76
6	*p*-Me_2N-benzyl	*p*-Me_2N-benzyl	8	8	22
11	isobutyl	benzyl	10	9	82
12	hexyl	benzyl	9	24	24

Compound **2** bearing isobutyl substitutions at P1/P1' was less potent than SD146 against wild type but was more potent than SD146 against the double mutant strain and therefore remained a compound of interest. Compound **6** appeared to be the best analog overall whereas compound **5** showed a 4- to 5-fold loss against the single mutant strain and a similar loss against the double mutant. Cyclic urea **6** bearing two basic nitrogens in the P1/P1' residues had comparable potency, resistance profile and a vastly improved aqueous solubility when compared to SD146. Of the two unsymmetrical alkyl substituted cyclic ureas **11** and **12**, the isobutyl compound **11** was the preferred compound for further pharmacokinetic studies.

The analysis of the resistance data led us to conclude that compounds **2**, **6**, and **11** would be ideal candidates for IV studies in both dog and rat models to determine pharmacokinetic parameters. However, rapid clearance of compounds **2**, **6**, and **11** was observed, resulting in negligible blood levels for all time points during IV pharmacokinetic studies in both rat and dog models.

In summary, we have prepared P1/P1' analogs with comparable activity and vastly improved solubility over SD146 in an attempt to improve bioavailablity. Although the compounds are much more soluble, the high clearance rate (>5L/h/kg) observed during IV pharmacokinetic studies in dogs effectively precluded further development.

Acknowledgments

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References and Notes

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

4. For the preparation of compound **4** the following reduction reaction was carried out on SEM protected unsubstituted cyclic urea bearing benzyl groups at P1/P1': Rhodium on Alumina, ethanol:acetic acid:water (6:6:1), 200 psi H_2, 72 h, 96%.

5. (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.

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