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CYCLIC UREA HIV PROTEASE INHIBITORS CONTAINING ALKYNYL- AND ALKENYL-TETHERED HETEROCYCLES IN THE P2 REGION

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Abstract. A series of cyclic urea HIV protease inhibitors containing alkynyl- and alkenyl-tethered heterocycles in the P2 region were synthesized. The alkynyl compounds exhibited poor activity against the HIV protease enzyme. However, reduction of the triple bond afforded *trans*-alkenyl derivatives (**XU348** and **XU430**) which displayed superb potency (sub-nanomolar K_i).

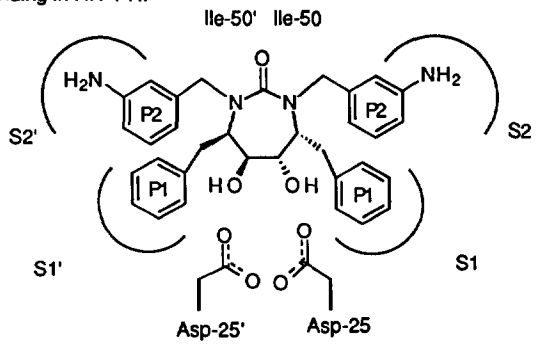
Background

The treatment of AIDS has entered a new era with the introduction of the first HIV (human immunodeficiency virus) protease inhibitor. Saquinavir (Roche's Invirase) has recently been approved by the US FDA[1] and indinavir (Merck) and ritonavir (Abbott) may be launched in 1996. In vivo, protease inhibitors have been shown to be effective in reducing viral load and/or improving CD4 lymphocyte count; many are being investigated as adjuncts in combination therapy due to the emergence of resistant viral epitodes. The inhibition of protease can complement and perhaps synergize other therapies such as the inhibition of HIV reverse transcriptase and thereby offer a promising strategy for combating resistance. For this reason, many companies are pursuing an array of structurally diverse HIV protease inhibitors.[2]

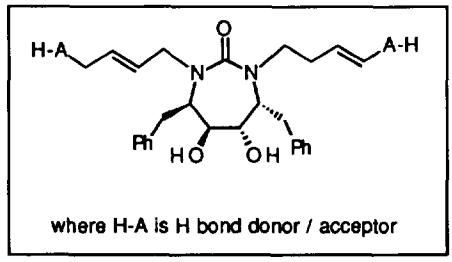
The Dupont Merck program[3] has been focused upon a cyclic urea scaffolding that places a diol moiety within hydrogen bond distance of the enzyme's aspartic acid dyad and projects benzylic-derived substituents into the S1/S1' and S2/S2' pockets. The most unique feature of this interaction is that the water molecule normally found in binding to native substrate as well as non-cyclic urea PR inhibitors, is displaced by the urea carbonyl oxygen atom. Although two clinical candidates have emerged from this program (DMP323 and DMP450 (Figure 1)), the search continues for superior compounds that combine potency with oral bioavailability and a favorable pharmacokinetic profile. With these issues in mind, we decided to construct congeners in which the P2-benzylic appendages were replaced with smaller alkenyl and alkynyl "arms" (Figure 1).

Figure 1

Representation of
DMP450 binding in HIV-PR:



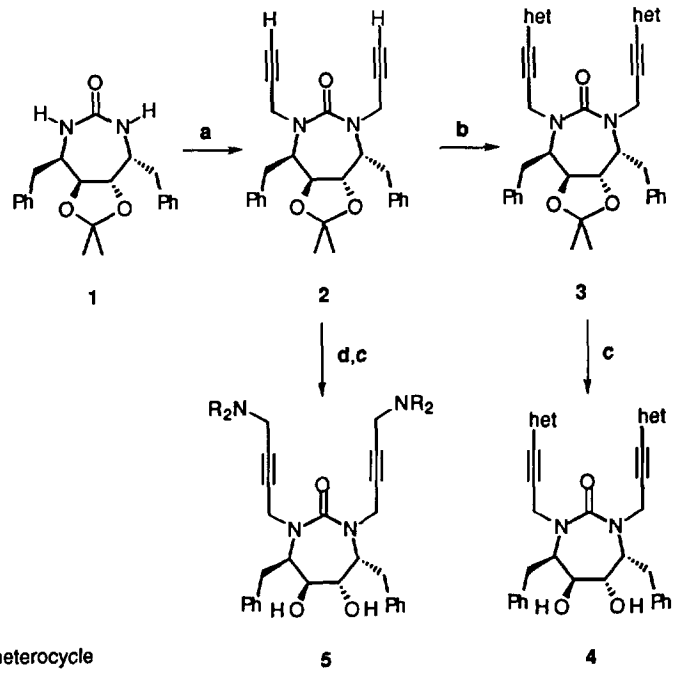
Proposed Alkenyl-tethered derivatives:



Chemistry and Results

A series of cyclic urea HIV protease inhibitors that contain alkynyl- and alkenyl-tethered heterocycles in the P2 region were synthesized: The cyclic urea acetonide **1** was reacted with base and then treated with propargyl bromide to afford the bis-alkyne **2**.[4] The key synthetic manipulation was the coupling of this cyclic urea intermediate to a series of halo-heterocycles / -carbocycles using Heck conditions (Pd(0), Cu(I)) to provide adducts **3** (Table 1).[5] In examples where a heterocycle was chosen that contained a free N-H linkage, protecting group manipulations (i.e., use of a MEM group[6]) were employed to improve isolated yields. Alternatively, reaction of the bis-alkyne **2** with (para)formaldehyde and a secondary amine, in the presence of copper (I), produced the corresponding Mannich product (Table 2).[7] Removal of the acetonide protecting group under standard conditions[8] yielded the diols **4-5**. Unfortunately, these alkynyl derivatives were only weakly active against HIV-PR[9] ($K_i \geq 1$ uM).

Scheme 1: Symmetrical cyclic ureas



1 2 3 5 4

het = heterocycle

a: (1) NaH/DMF; (2) propargyl bromide; 98%
b: (see Table 1): halo-heterocycle, $Pd(PPh_3)_4$, CuI, amine / THF
c: HCl/MeOH; 80 ->95%
d: (see Table 2): paraformaldehyde, H-NR_2, Cu(I)Br·$S(CH_3)_2$ / THF reflux

Table 1

heterocycle (het in Scheme 1)	yield of 3	carbocycle	yield of 3
3-pyridyl	65%	2-naphthyl	66%
5-pyrimidinyl	77%	3-phenyl	42%
4-pyrazolyl	—	3-anilino	26%
4-(1-t-Boc)-pyrazolyl	57%	3-nitrophenyl	60%
4-(1-MEM)-pyrazolyl	65%	3-cyanophenyl	98%
3-quinolyl	61%	3-chlorophenyl	59%
3-isoquinolyl	64%	3-methoxyphenyl	37%
2-thienyl	33%	3-(carboxamido)phenyl	40%
3-thienyl	16%		

Table 2

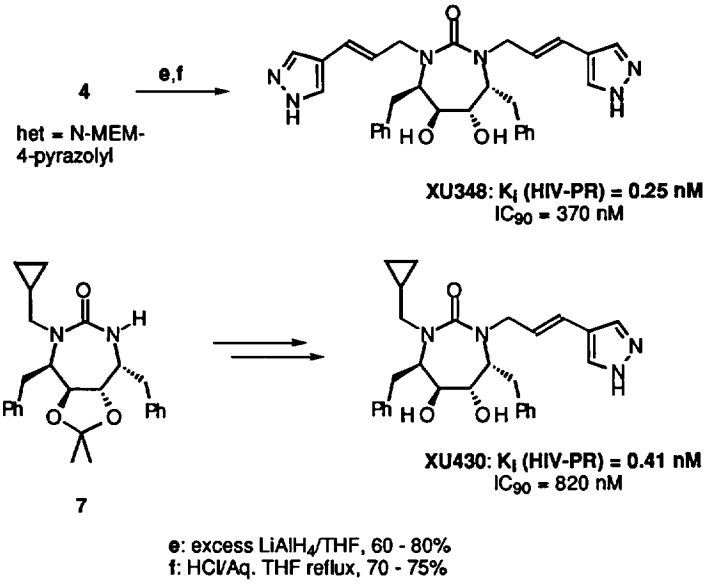
amine (NR_2 in Scheme 1)	yield
morpholine	55%
piperidine	63%
N,N-diethylamine	90%
t-butyl-L-proline-carboxylate	57%
N,N-diisopropylamine	53%

Evidently, the HIV-PR enzyme is unable to accommodate the heterocyclic alkyne array; the carbon-carbon triple bond, by nature being extended and inflexible, forces groups at its termini to protrude towards the wall of the S2/S2' pockets. While small groups such as hydrogen and methyl are tolerated somewhat (K_i = 22 nM for the un-substituted bis-alkyne), even simple heterocycles are apparently too large to fit within the enzyme pocket.

However, molecular modeling indicated that the trans-alkene arrangement would be favorable for intimate binding to the enzyme since the tether should be capable of adopting a configuration needed to accommodate terminal heterocycles. This hypothesis was tested as follows: Reduction of the triple bond of the MEM-protected 4-pyrazolyl alkyne was accomplished using excess lithium aluminum hydride in THF at reflux.[10] No *cis* product was detected, although if the reaction was quenched after only a short period at reflux (less than one hour) the corresponding alkyne-alkene hybrid was present. Cleavage of the acetonide and MEM groups afforded the bis-*trans*-alkene **XU348**. The same chemistry was applied to the unsymmetrical cyclopropylmethyl cyclic urea **7** to give **XU430**. Both alkenyl derivatives were extremely potent against the HIV-PR enzyme (K_i = 0.25 and 0.41 nM, respectively) and both exhibited good antiviral activity against HIV-PR in a cell-based assay[11] (IC_{90} = 370 and 820 nM, respectively).

The observed increase in potency is also attributed to the hydrogen bond donor/acceptor abilities of the pyrazole ring which likely establish favorable interactions within the S2/S2' pockets. Other variations on this general theme have been explored and will be reported at a later date.

Scheme 2



e: excess $LiAlH_4$/THF, 60 - 80%
f: HCl/Aq. THF reflux, 70 - 75%

Acknowledgments

We thank Sue Erickson-Viitanen, Ron Klabe, Jim Meek, Beverly Cordova, and Marlene Raynor for determining K_i and IC_{90} values.

References and Notes

1. SCRIP, December 27, 1995, pg. 21.

2. For an excellent review on anti-HIV chemotherapy, see: De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491.

3. Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Vittanen, S. *Science* **1994**, *263*, 380.

4. ^{1}HNMR (200 MHz, $CDCl_3$): δ 1.56 (s, 6H), 2.22 (t, 2H), 2.80 (d, 2H), 3.00 (m, 4H), 4.06 (br dd, 2H), 4.24 (app. s, 2H), 4.50 (d, 2H), 7.18 - 7.37 (m, 10H).

5. Representative reaction conditions: Bis-alkynyl cyclic urea **2** (4.0 g, 9.0 mmol, 1.0 equiv) is dissolved in oxygen-free tetrahydrofuran (50 mL) under nitrogen. Diethylamine (2.8 mL, 26.7 mmol, 1.5 equiv) is added followed by the halo-heterocycle (e.g., 4-iodo-(N-methoxyethoxmethyl)pyrazole) (7.52 g, 26.7 mmol, 1.5 equiv). Copper (I) iodide (0.36 g, 1.9 mmol, 0.2 equiv) and tetrakis(triphenylphosphine)palladium (0) (1.04 g, 0.9 mmol, 0.1 equiv) are added as solids. The mixture is heated at reflux overnight, cooled and product extracted into ethyl acetate and then purified via flash column chromatography.

6. Table 1, compound **3**; het = 4-(1-MEM)-pyrazolyl: ^{1}HNMR (200 MHz., $CDCl_3$): δ 1.52 (s, 6H), 3.00 - 3.10 (m, 6H), 3.38 (s, 6H), 3.49 (m, 4H), 3.60 (m, 4H), 4.06 (m, 2H), 4.30 (app. s, 2H), 4.64 (d, 2H), 5.41 (s, 4H), 7.20 - 7.35 (m, 10H).

7. Table 2; amine = piperidine (diol protected as acetonide): ^{1}HNMR (200 MHz, $CDCl_3$): δ 1.50 (s,6H), 1.30 - 1.60 (m, 12H), 2.40 - 2.51 (m, 8H), 2.83 (d, 2H), 2.96 - 3.04 (m, 4H), 3.25 (s, 4H), 4.06 (m, 2H), 4.22 (app. s, 2H), 4.53 (d, 2H), 7.17 - 7.37 (m, 10H).

8. Table 1, compound **4**; het = 4-pyrazolyl: ^{1}HNMR (200 MHz, $CDCl_3$ + trace DMSO-d_6): δ 2.83 (d, 2H), 2.90 - 3.11 (m, 4H), 3.73 (br d, 2H), 3.95 (app. s, 2H), 4.41 (br s, 2H), 4.50 (d, 2H), 7.10 - 7.20 (m, 10H), 7.43 (s, 4H), 12.25 (br s, 2H).

9. Erickson-Viitanen, S.; Manfredi, J.; Viitanen, P.; Tribe, D. E.; Tritch, R.; Hutchison (III) C. A.; Loeb, D. D.; Swanstrom, R. *AIDS Res. Hum. Retroviruses* **1989**, *5*, 577.

10. Scheme 1; compound **6**: ^{1}HNMR (200 MHz, CD_3OD): δ 2.81 - 3.11 (m, 4H), 3.01 (d, 2H), 3.50 - 3.70 (br s, 2H), 3.67 (br d, 2H), 3.92 (app. s, 2H), 4.17 (dd, 2H), 5.77 - 5.82 (m, 2H), 6.17 (d, 2H), 7.10 - 7.30 (m, 10H), 7.60 (br s, 4H).

11. RNA IC_{90} as described in ref 3.

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