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STRUCTURE BASED DESIGN: NOVEL SPIROCYCLIC ETHERS AS NONPEPTIDAL P_2-LIGANDS FOR HIV PROTEASE INHIBITORS

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Abstract: A series of novel spirocyclic ethers were designed to function as nonpeptidal P_2-ligands for HIV-1 protease inhibitors. Incorporation of designed ligands in the (*R*)-(hydroxyethylamino)sulfonamide isostere afforded potent HIV protease inhibitors.

Since the discovery that a virally encoded HIV protease is vital for propagation, inhibition of this enzyme has become an important target for AIDS chemotherapy.[1] Recently, three peptidomimetic protease inhibitors in combination with reverse transcriptase inhibitors have been approved by the FDA for treatment of AIDS. The early indications have heightened the hope for a cure for AIDS.[2] As part of our continuing effort on the structure-based design of nonpeptidal inhibitors, we reported that the urethanes of stereochemically defined cyclic ether and cyclic sulfone derivatives are novel ligands for the HIV protease substrate binding site.[3] One of the important features of our design strategy is that the ligand oxygens are appropriately positioned on a constrained framework to effectively hydrogen bond to residues corresponding to the quinaldic amide-asparagine amide fragment of the Ro 31-8959 based protease inhibitors.[2c] A number of protease inhibitors incorporating such designed ligands provided potent inhibitors with novel structural features, reduced molecular weight as well as excellent pharmacological profiles in laboratory animals.[4] In our ongoing efforts in designing structurally diverse protease inhibitors, we have now developed novel spirocyclic ethers to function as nonpeptidal ligands for the HIV protease substrate binding-site. These new ligands are incorporated in the (*R*)-(hydroxyethylamino)sulfonamide derived isostere as the N-terminus carboxamide derivatives. Herein, we report our preliminary results of these investigations.

Based upon the examination of the X-ray crystal structures of inhibitors Ro 31-8959[2c] and VX-478[4a] bound to HIV-1 protease, we have hypothesized that a spirocyclic ligand with an oxygen positioned properly could effectively hydrogen bond to the NH of the Asp 29 and 30 residues. It is evident that the asparagine amide fragment of the Ro 31-8959 inhibitor interact with these residues. Elaboration of such a spirocycle on a tetrahydropyran ring system was chosen with emphasis on ease of synthesis utilizing Danishefsky's hetero Diels-Alder chemistry. Conformationally constrained spirocyclic structures were designed to maximize the specificity of interaction with the active site. An energy-minimized active model of this designed inhibitor **14** is shown in Figure 1. The synthesis of

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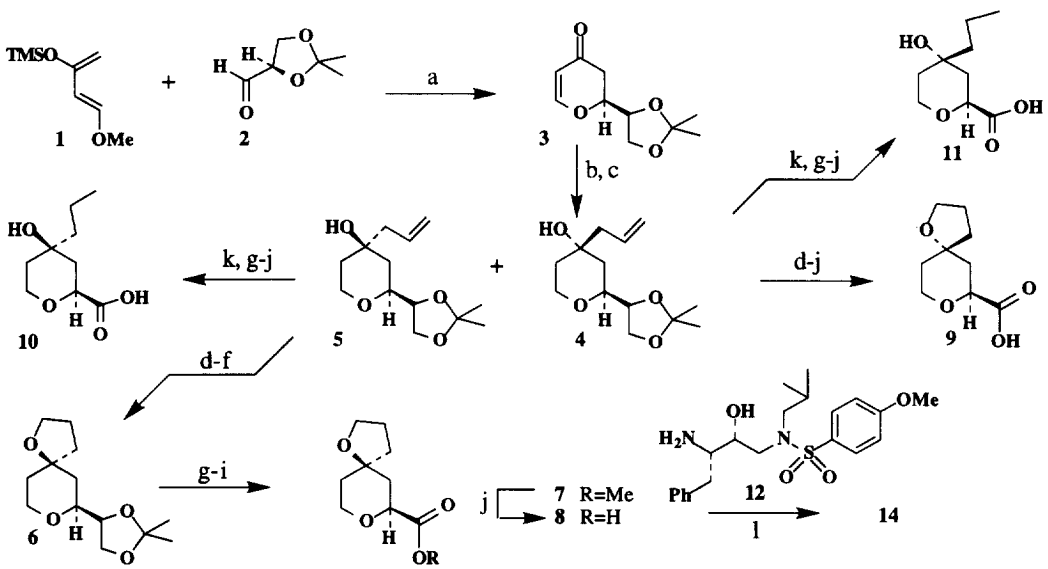
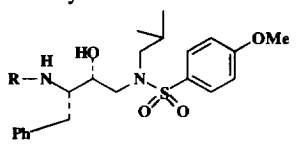
Figure 1. Stereoview of the optimized bound conformations of inhibitors **14** (green) and Ro 31-8959 (magenta) superimposed in the HIV-1 protease active site.[4]

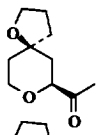
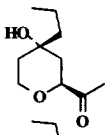
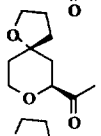
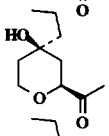
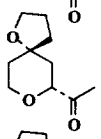
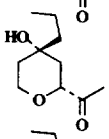
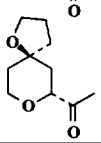
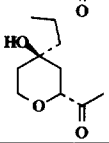
desired spirocyclic ligands is outlined in Scheme 1. The cycloadduct **3** was prepared as reported by Danishefsky *et al.*[5] Catalytic hydrogenation of **3** followed by addition of allylmagnesium bromide to the resulting ketone, afforded the mixture of alcohols **4** and **5** (ratio 3:2) in 65% yield. The alcohols were separated by chromatography (25% ethyl acetate in hexanes) and each was converted to the corresponding spirocyclic ether derivative as follows. Hydroboration of **5** with 9-BBN followed by treatment of the resulting diol with 1.1 equiv of mesyl chloride in pyridine provided the mono-mesylate, which was cyclized to spiroether **6** by reaction with NaH in THF (60% overall). Spiroether **6** was converted to ester **7** by the following three step sequence: (1) removal of the isopropylidene group with aqueous acetic acid (2) cleavage of the resulting diol with $NaIO_4$, and (3) oxidation



Scheme 1: (a) $ZnCl_2$, benzene, 23 °C, 17 h; (b) H_2, Lindlar catalyst, EtOAc; (c) CH_2=$CHCH_2MgBr$, THF, -40 °C, 4 h; (d) 9-BBN, THF, 23 °C, 14 h, aq H_2O_2-NaOH, 50 °C, 1 h; (e) MsCl, Py, 0 °C, 3 h; (f) NaH, THF, 23 °C, 15 h; (g) 40% aq AcOH, 100 °C, 4 h; (h) $NaIO_4$, CH_2Cl_2-H_2O, 3 h; (i) Br_2, aq MeOH, $NaHCO_3$, 4 h; (j) aq LiOH, THF, 4 h; (k) EtOAc, H_2, 10% Pd-C; (l) $Ph_2P(O)Cl$, Et_3N -10° to 23° C, 12 h.

Table 1. Structure and Inhibitory Potencies of Various Protease inhibitors[a]

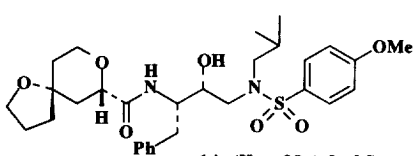


Comp.	R	K_i (nM)	ID_{50} (μM)	Comp.	R	K_i (nM)	ID_{50} (μM)
14.		20 ± 3 (n = 3)	2.4	**18.**		>1000	---
15.		150	4.5	**19.**		480	>10
16.		>2000	---	**20.**		150	3.4
17.		400	9.1	**21.**		>1000	---

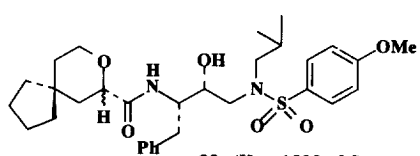
[a] Inhibitor **13** (Ro-31-8959)[2c] displayed, K_i = 1.4 ± 0.2 nM (n = 3) and ID_{50} = 18 nM (n = 2) in this assay.

of the resulting aldehyde with bromine to methyl ester (65% from **6**). Saponification of the methyl ester **7** provided the carboxylic acid **8**, which was coupled with isostere **12**[6] in the presence of diphenylphosphinic chloride and Et_3N in THF to provide the inhibitor **14** (76% yield). Alcohols **4** and **5** were also converted to ligand carboxylic acids **9-11** by similar synthetic steps.[7] Starting from (*S*)-isopropylidene glyceraldehyde,[8] the corresponding enantiomeric ligands were prepared by following the above synthetic scheme.

As summarized in Table 1, inhibitor **14** with spirocyclic ligand **8** has shown enzyme inhibition constant (K_i) of 20 ± 3 nM in assay developed by Toth and Marshall.[9] The change in spirocyclic ether oxygen stereochemistry resulted in inhibitor **15** with nearly eightfold loss of potency. The change in the carboxamide bearing stereo center also exhibited nearly 20-fold loss of potency (inhibitor **17**). The corresponding mono-cyclic derivatives (inhibitor **18** and **19**) are substantially less potent than the spirocyclic inhibitors **14** and **15**. The removal of the spirocyclic ether oxygen resulted in inhibitor (compound **22**, 1:1 mixture) with substantial loss of potency, indicating specific binding interaction of the spiroether oxygen with the residues in the enzyme active site. Inhibitor **14** prevented the spread of HIV-1 in MT_4 human T-lymphoid cells infected with IIIB isolate at a concentration of 2.4 μM (ID_{50}).[10]



14 (K_i = 20 ± 3 nM)



22 (K_i = 1500 nM)

In conclusion, the structure-based designed spirocyclic ligands have shown promising preliminary results. Incorporation of these ligands afforded structurally diverse inhibitors. The stereochemistry and importance of the spiro tetrahydrofuranyl oxygen in inhibitor **14** (K_i = 20 nM) are evident in the inhibitory potencies of the inhibitors **15** and **22**. Further optimization of these novel ligands is the subject of our ongoing investigation.

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References and Notes:

1. (a) Katz, R. A.; Skalka, A. M. *Ann. Rev. Biochem.* **1994**, *63*, 133; (b) Debouck, C. *AIDS Res. Human Retroviruses* **1992**, *8*, 153 and references cited therein.
2. (a) Kempf, D. J; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavononda, S.; Flentge, C. A.; Green, B. G.; Fino, L.; Park, C. H.; Kong, X.-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H. L.; Robins, T.; Stewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J.; Norbeck, D. *Proc. Natl. Acad. Sci. U. S. A.* **1995**, *92*, 2484; (b) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci., U.S.A.* **1994**, *91*, 4096; (c) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358 and references cited therein.
3. (a) Ghosh, A. K.; Kincaid, J. F.; Walters, D. E.; Chen, Y.; Chaudhuri, N. C.; Thompson, W. J.; Culberson, C.; Fitzgerald, P. M.D.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Axel, M. G.; Lin, J.; Huff, J. R. *J. Med. Chem.*, **1996**, *39*, 3278; (b) Ghosh, A. K.; Thompson, W. J.; Munson, P. M.; Liu, W.; Huff, J. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 83; (c) Ghosh, A. K.; Thompson, W. J.; Fitzgerald, P. M.D.; Culberson, C. J.; Axel, M. G.; McKee, S. P.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2506; (d) Ghosh, A. K.; Lee, H. Y.; Thompson, W. J.; Culberson, C; Holloway, M. K.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Smith, A. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 1177; (e) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; Mckee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300 ; (f) Ghosh, A. K.; Thompson, W. J.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 924; (g) Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Chen, J. C.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292.
4. (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) Chen, X.; Li, L.; Kemp, D. J.; Sham, H.; Wideburg, N. E.; Saldivar, A.; Vasavanonda, S.; Marsh, K. C.; McDonald, E.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2847.
5. Danishefsky, S.; Kobayashi, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 1981.
6. Amine **12** was prepared from the known[3] azidoepoxide by reaction with isobutylamine followed by reaction of the resulting amine with *p*-methoxybenzenesulfonyl chloride and aq. $NaHCO_3$ to provide the corresponding azide. Catalytic hydrogenation of the azide over 10% Pd-C in EtOAc afforded the amine **12**. For the development of (*R*)-(hydroxyethylamino)sulfonamide isostere based protease inhibitors, see, Vazquez, M. L.; Bryant, M. L.; Clare, M.; DeCrescenzo, G. A.; Doherty, E. M.; Freskos, J. N.; Getman, D. P.; Houseman, K. A.; Julien, J. A.; Kocan, G. P.; Mueller, R. A.; Shieh, Huey-Sheng.; Stallings, W. C.; Stegeman, R. A.; Talley, J. J. *J. Med. Chem.* **1995**, *38*, 581.
7. All new compounds gave satisfactory spectroscopic and analytical results.
8. MaloneyHuss, K. E. *Syn. Comm.* **1985**, *15*, 273.
9. Toth, M. V.; Marshall, G. R. *Int. J. Pep. Prot. Res.* **1990**, *36*, 544.
10. In-house prepared **13** (Ro 31-8959) exhibited ID_{50} value (antiviral activity) of 18 nM. For Ro 31-8959, Craig and co-workers have reported IC_{90} values of 6-30 nM in cell culture assay.[11] However, the assay protocol differs widely in that syneytia formation rather than P_{24} production was monitored as endpoint, and cell types other than MT_4 were employed.
11. Craig, J. C.; Duncan, I. B.; Hockley, D.; Grief, C.; Roberts, N. A.; Mills, J. S. *Antiviral Res.* **1991**, *16*, 295, and references cited therein.