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Solid-Phase Synthesis of Potential Aspartic Acid Protease Inhibitors Containing a Hydroxyethylamine Isostere

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Abstract: A series of 1,3-diamino-2-propanol derivatives have been synthesized on solid phase as potential aspartic acid protease inhibitors. The developed methodology allows the incorporation of either an alkyl group or H at the R^2 site of hydroxyethylamine isostere.

Keywords: aspartic acid protease; inhibitors; hydroxyethylamine isostere; solid-phase synthesis.

Aspartic acid proteases, characterized by having two acid residues in the active sites, are important therapeutic targets for a variety of diseases.[1] Among this widely distributed family of enzymes, HIV-1 protease has proved to be an effective target for the treatment of AIDS,[2] while renin has been implicated in hypertension,[3] cathepsin D in breast tumor metastasis,[4] and plasmepsins I and II in malaria.[5] One powerful approach in the design of potent aspartyl protease inhibitors is the incorporation of an isostere that mimics the geometry of the tetrahedral intermediate generated from protease-catalyzed amide bond hydrolysis.[6] Many such mechanism-based inhibitors have been reported, among which most nonpeptide small molecule inhibitors are derived from statine, hydroxyethylene and hydroxyethylamine isosteres.[7] Small organic molecules as drugs are in general more therapeutically promising than peptides due to their higher bioavailability and greater resistance to proteolytic degradation. Our group has been exploring hydroxyethylamine isosteres as general small molecule aspartyl protease inhibitors. During the course of our systematic studies on all four diversity sites (R^1, R^2, R^3 and R^4) around the hydroxyethylamine isostere, we realized the lack of literature precedent where either R^1 or R^2 equals H rather than any other alkyl groups (e.g. **1a-c**). Although aspartic acid proteases are known to specifically cleave peptide bonds located between large hydrophobic residues, some peptidomimetic structures containing the (hydroxyethyl)amide isostere do inhibit HIV protease activity at low nanomolar concentrations.[8] Herein, we wish to report a solid-phase synthesis that allows the incorporation of either an alkyl group or H at either R^1 or R^2 position as demonstrated in the preparation of **1a-d**.

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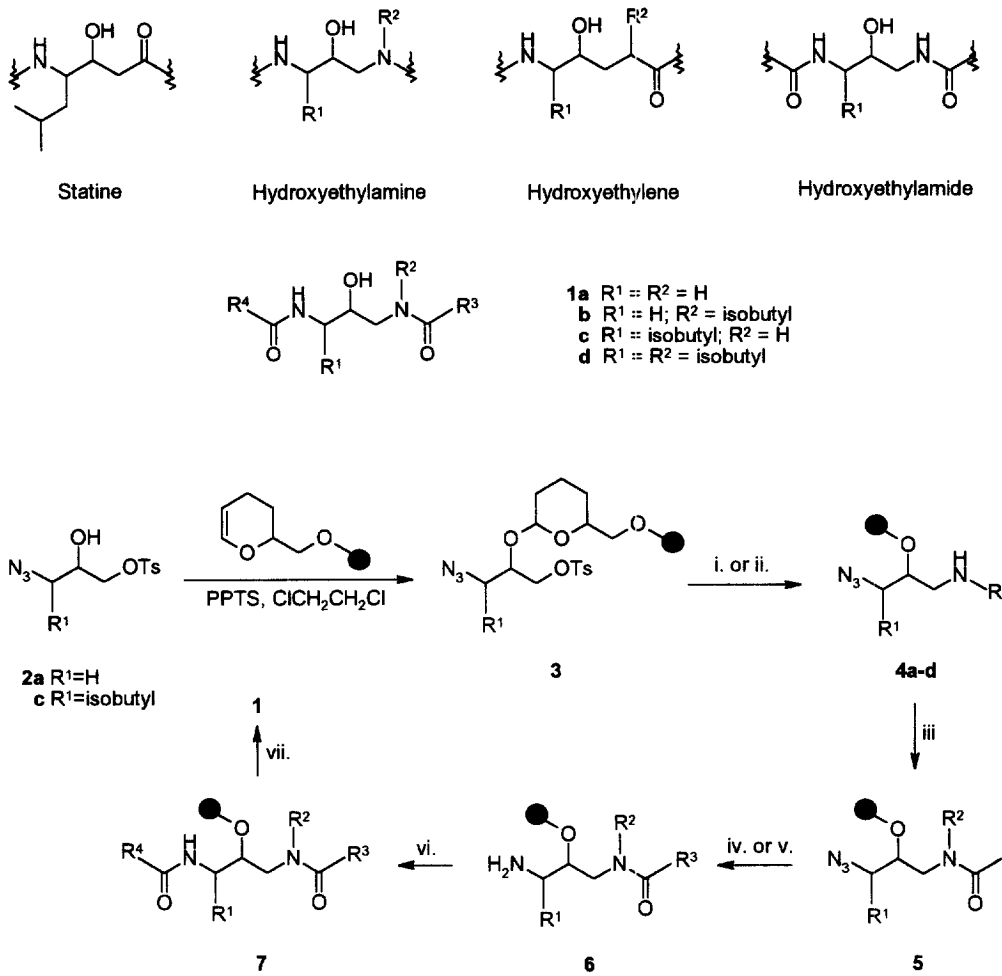

Scheme 1. *Reagents and Conditions*: i. **4a,c**, R^2 = H, a) potassium phthalimide, DMF, 100°C; b) NH_2NH_2, EtOH, reflux; ii. **4b,d**, R^2 = isobutyl, isobutylamine, NMP, 80°C; iii. R^3COOH, DIC, HOBT, DMF; iv. **5a,b**, R^1 = H, Ph_3P-H_2O, THF; v. **5c,d**, R^1 = isobutyl, $SnCl_2$/PhSH/Et_3N, THF; vi. R^4COOH, DIC, HOBT, DMF; vii. 95% TFA-H_2O.

The synthesis of **1** was accomplished by modifying a general method previously reported by Ellman.[7d] The scaffolds **2a** and **2c** were first coupled with dihydropyran (DHP) functionalized polystyrene resin in the presence of *p*-toluenesulfonate (PPTS) in 1,2-dichloroethane.[9] While the isobutyl group was easily introduced at the R^2 position via displacement of the primary tosylate **3** with isobutylamine as described in Ellman's approach, the incorporation of an amino group to provide **4a,c** required the reaction of the **3** with potassium phthalimide followed by the hydrolysis with hydrazine. The next coupling of primary or secondary amines **4** with acids was completed under the standard coupling conditions using HOBT/DIC. Treatment of azides **5c-d** with $SnCl_2$/PhSH/Et_3N provided exclusively the desired products **6c-d**. However, the reduction of primary

azides **5a-b** with tin chloride (II) in the presence of thiophenol and triethylamine was repeatedly accompanied by the nucleophilic displacement of the unhindered azides by thiophenol. The desired amines **6a-b** were exclusively obtained by using Ph_3P-H_2O in THF. Standard coupling conditions were employed in the last coupling of amines **6** with acids to give **7**, which was cleaved from the resin with 95% trifluoroacetic acid in H_2O.

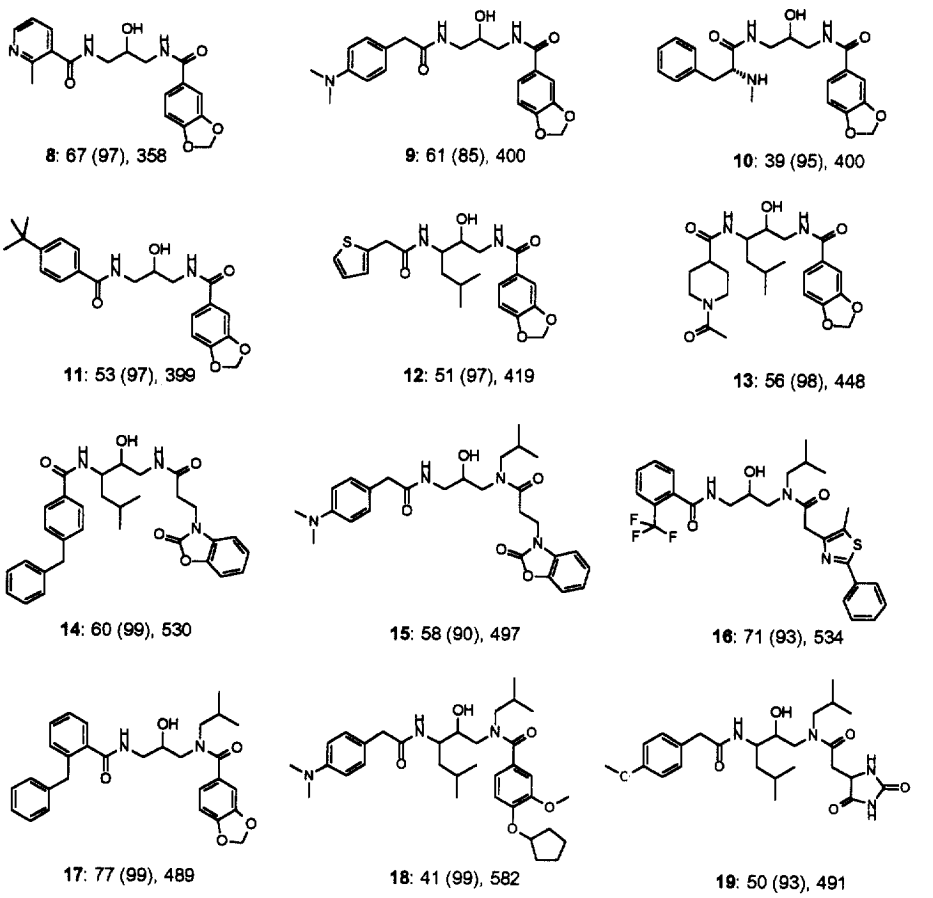

Table 1. Representative products and results from a validation library. The first number refers to the yield, the number in parentheses to purity, the third number to MS (ESI, *m/z*, MH^+).

Employing the described reaction sequence, a validation library containing 92 compounds was synthesized. The structure, yield, purity and MS data obtained for a representative set of compounds (**8-19**) are summarized in Table **1**.[10] These library compounds are in the process of being assayed against a number of aspartic acid proteases.

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References and Notes

1. (a) Dunn, B. M. In *Structures and Function of the Aspartic Proteinases: Genetics, Structures, and Mechanisms*; Plenum Press: New York, **1991**; Vol. *306*, xviii, 585 pp. (b) Takahashi, K. In *Aspartic Proteinases: Structure, Function, Biology and Biomedical Implications*; Plenum Press: New York, **1995**.
2. Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305-2314.
3. Greenlee, W. J. *Med. Chem. Rev.* **1990**, *10*, 173-236.
4. Johnson, M. D.; Torri, J. A.; Lippman, M. E.; Dickson, R. B. *Cancer Res.* **1993**, *53*, 873-877.
5. Moon, R. P.; Bur, D.; Loetscher, H.; D'Arcy, A.; Tyas, L.; Oefner, C.; Grueninger-Leitch, F.; Mona, D.; Rupp, K.; Dorn, A.; Matile, H.; Certa, U.; Berry, C.; Kay, J.; Ridley, R. G. *Adv. Exp. Med. Biol.* **1998**, *436*, 397-406.
6. Whittaker, M. *Curr. Opin. Chem. Biol.* **1998**, *2*, 386-396.
7. (a) Thaisrivongs, S. *Annu. Rep. Med. Chem.* **1994**, *29*, 133. (b) Katz, R. A.; Skalka, A. M. *Annu. Rev. Biochem.* **1994**, *63*, 133. (c) Ghosh, A. K.; Fidanze, S. *J. Org. Chem.* **1998**, *63*, 6146-6152. (d) Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735-9747. (d) Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427-1430. (e) Dolle, R. E. *Mol. Diversity* **1997**, *2*, 223-236.
8. Beaulieu, P. L.; Wernic, D.; Abraham, A.; Anderson, P. C.; Bogri, T.; Bousquet, Y.; Croteau, G.; Guse, I.; Lamarre, D.; Liard, F.; Paris, W.; Thibeault, D.; Pav, S.; Tong, L. *J. Med. Chem.* **1997**, *40*, 2164-2176.
9. (a) Bennett, F.; Girijavallabhan, V. M.; Patel, N. *J. Chem. Soc., Chem. Commun.* **1993**, 737-738. (b) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185-5187.
10. (a) Analytical data for compound **15**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, *J*=6.5 Hz , 6H), 1.84 (m, 1H), 2.85 (m, 2H), 2.92 (m, 8H), 2.97 (m, 2H), 3.04 (m, 2H), 3.30 (m, 2H), 3.45 (m, 1H), 3.72 (s, 1H), 4.12 (m, 2H), 6.24 (s, 1H), 7.05-7.18 (m, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.0, 27.9, 31.2, 38.8, 40.8, 42.8, 43.7, 51.2, 56.9, 70.7, 109.2, 110.1, 113.2, 122.5, 124.0, 128.9, 130.2, 131.1, 142.8, 150.0, 154.7, 172.2, 173.6. (b) Analytical data for compound **17**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, *J*=4.5 Hz , 6H), 1.86 (m, 1H), 3.14 (m, 1H), 3.24 (dd, *J*=8.3, 13.8 Hz , 2H), 3.47 (d, *J*=17.4 Hz , 2H), 3.66 (m, 1H), 3.91 (m, 1H), 4.23 (s, 2H), 6.01 (s, 2H), 6.67 (s, 1H), 6.80-6.85 (m, 3H), 7.16 (m, 2H), 7.21 (t, *J*=6.7 Hz, 1H), 7.23-7.27 (m, 5H), 7.34 (t, J=7.3 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.1, 27.5, 29.9, 39.1, 43.8, 50.3, 59.0, 71.0, 101.7, 108.0, 108.5, 121.5, 126.2, 126.7, 127.4, 128.8, 129.3, 130.5, 131.3, 136.3, 139.3, 141.1, 148.0, 149.0, 171.6, 174.0.