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Solid-Phase Synthesis of Aspartic Peptidase Inhibitors: 3-Alkoxy-4-Aryl Piperidines

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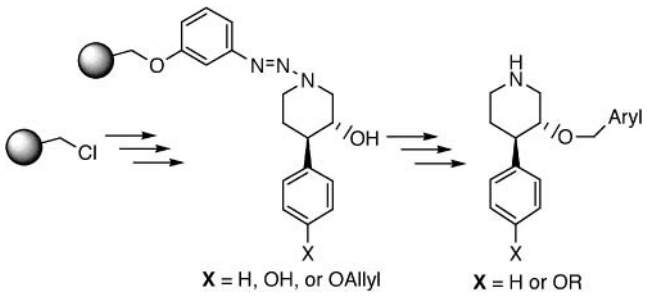
ABSTRACT



The 3-alkoxy-4-aryl piperidines are non-peptide peptidomimetic inhibitors of several aspartic peptidases. The solid-phase functionalization of 3,4-disubstituted piperidine scaffolds using a traceless linker strategy is described. Synthesis of diverse analogues based on this scaffold provides the potential to generate selective inhibitors of this important class of peptidase.

Roche scientists recently discovered via high throughput screening that the 3-alkoxy-4-aryl substituted piperidine **1** inhibited human renin.[1] By use of structure-based design they obtained orally bioavailable analogues, e.g., **2**, that lowered blood pressure in primates. In addition, analogues of **1** and **2** were found that inhibited plasmepsin, a potential target for treatment of malaria. These inhibitors constitute a major advance in methods for the inhibition of aspartic peptidases. The compounds are simple, are low molecular weight, and contain no amide bonds, and some show promising pharmacokinetic properties. Furthermore, these piperidines are structurally related to paroxetine,[2] a known CNS active drug; consequently this scaffold may become especially effective at inhibiting aspartic peptidases located in the CNS.

Following the Roche lead and using structure-based design, we developed inhibitors of porcine pepsin and *R. chenensis* pepsin, two aspartic peptidases not inhibited in the Roche reports.[3] Subtle modifications in the side chain functionality gave non-peptide peptidomimetic aspartic peptidase inhibitors with altered specificities, e.g., **3** and **4**. In view of the importance of aspartic peptidases as potential therapeutic targets (AIDS, Alzheimer's disease, hypertension, and malaria, with this list expected to grow as the human genome project continues) we have developed a solid-phase method for rapidly synthesizing libraries of piperidine analogues substituted at the 3- and 4′-positions. In designing a solid-phase functionalization method to prepare an array of 3,4-

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(1) (a) Oefner, C.; Binggeli, A.; Breu, V.; Bur, D.; Clozel, J.P.; D'arcy, A.; Dorn, A.; Fischli, W.; Gruninger, F.; Guller, R.; Hirth, G.; Marki, H.; Mathews, S.; Miller, M.; Ridley, R. G.; Stadler, H.; Viera, E.; Wilhelm, M.; Winkler, F.; Wostl, W. *Chem. Biol.* **1999**, *6*, 127. (b) Viera, E., Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Güller, R.; Hirth, G.; Märki, H. P.; Müller, M.; Oefner, C.; Scalone, M.; Stadler, H.; Wilhelm, M.; Wostl, W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1397. (c) Güller, R.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Hirth, G.; Jenny, C.; Kansy, M.; Montavon, F.; Müller, M.; Oefner, C.; Stadler, H.; Vieira, E.; Wilhelm, M.; Wostl, W.; Märki, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1403.

(2) For structural comparison, see Figure 2 in Supporting Information.
(3) Bursavich, M. G.; West, C. W.; Rich, D. H. *Org. Lett.* **2001**, *3*, 2317.

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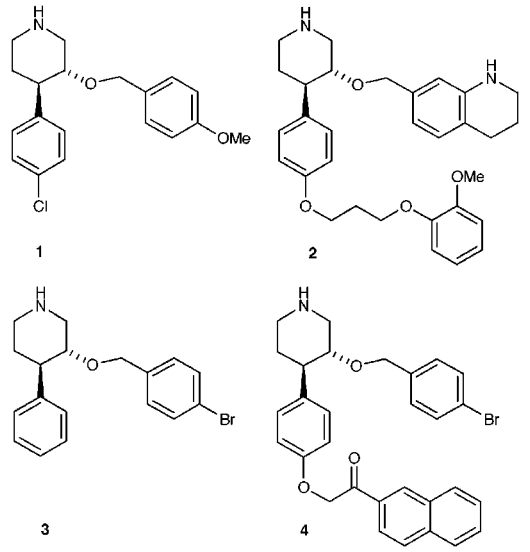
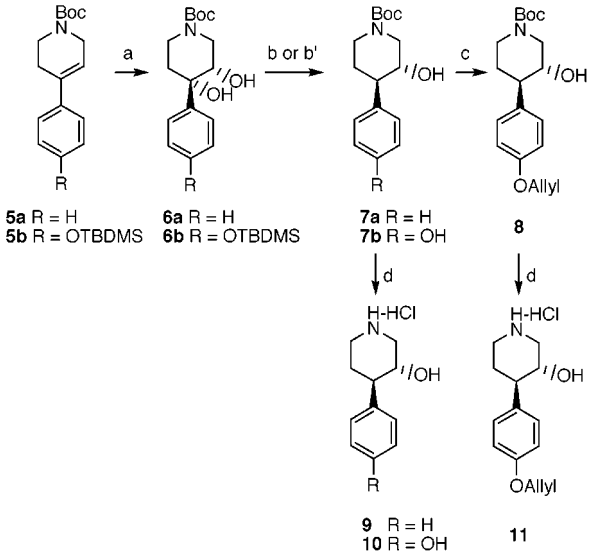


Figure 1. Piperidine-based aspartic peptidase inhibitors.

disubstituted piperidine derivatives, we decided to utilize a traceless triazine linker strategy for amines described by Brase et al.[4] This linker was chosen for our solid-phase functionalization because it provides (1) selective attachment of the piperidine secondary amine, (2) facile and orthogonal functionalization of the piperidine core, and (3) traceless cleavage of the resin-bound final products via mild conditions to afford products with high purity.

The piperidine cores for the solid-phase synthesis were constructed using our reported enantioselective syntheses (Scheme 1).[3] Key to the synthesis of these piperidines was

Scheme 1[a]

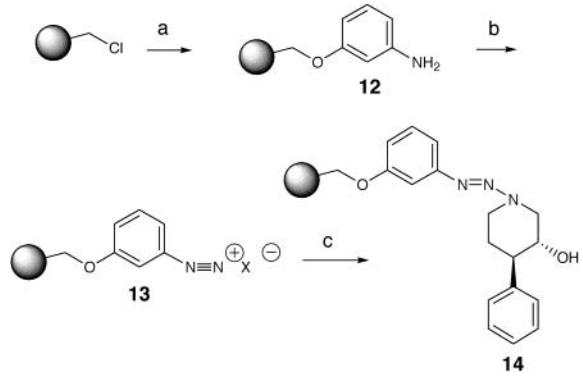


[a] Conditions: (a) AD-mix-α, $CH_3SO_2NH_2$; (b) Ra-Ni, refluxing EtOH; (b′) (1) TBAF, (2) Ra-Ni, refluxing EtOH; (c) Allyl-Br, Cs_2CO_3; (d) HCl/dioxane.

conversion of tetrahydropyridine **5** to the corresponding diol **6** using Sharpless asymmetric dihydroxylation (AD).[5] Subsequent stereoselective reduction of the resulting benzylic alcohol with Raney-nickel afforded **7** in both high yields and enantiomeric excesses.[6] Removal of the Boc protecting group or phenol protection followed by removal of the Boc protecting group provided the desired piperidines **9**−**11**.

Conditions for anchoring 3,4-disubstituted piperidines to the triazine-based solid support were determined using piperidine **9** as the model (Scheme 2). The aniline linker **12**

Scheme 2[a]



[a] Conditions: (a) *m*-hydroxy aniline, NaH, ^{n}Bu$_4$NI; (b) BF_3·OEt_2, ^{t}BuONO; (c) **9**, TEA, DCM/DMF; (d) 10% TFA/DCM.

was generated by alkylation of Merrifield resin with the phenolic anion of *m*-hydroxyaniline. The aniline nitrogen in **12** was converted to the diazonium resin **13** using a modified procedure described by Moore and co-workers.[7] The diazonium resin was quickly washed with cold DCM and DMF and treated with piperidine **9** in DCM (or DCM/DMF) to afford the resin-bound triazine **14** (1.44 mmol/g).

Conditions to functionalize the secondary alcohol of piperidine **14** were then developed. A variety of alkylation conditions were systematically investigated, including changing the solvent (DMF or THF), base (NaH or KO^{t}Bu), and additive (^{n}Bu$_4$NI and crown ethers). The optimal alkylation conditions were determined to be KO^{t}Bu in THF at approximately 50 °C with the addition of ^{n}Bu$_4$NI. The secondary alcohol of **14** was then alkylated with a variety of benzyl bromide derivatives using these conditions (Scheme 3) to afford **15**. The piperidines were cleaved from the resin by using mildly acidic conditions to provide the potential aspartic peptidase inhibitors **16a**−**e** (>98% crude purity).

These methods were applied to generate two other small libraries of potential aspartic peptidase inhibitors based on

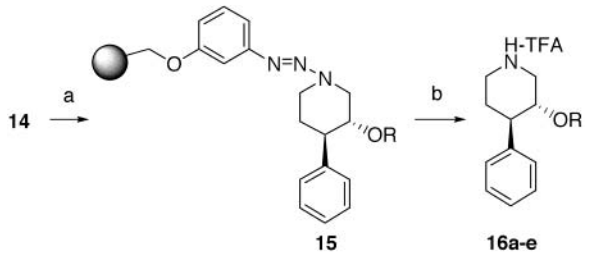
(4) (a) Brase, S.; Enders, D.; Kobberling, J.; Avemaria; F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3413. (b) Brase, S.; Kobberling, J.; Enders, D.; Lazny, R.; Wang, S.; Brandtner, S. *Tetrahedron Lett.* **1999**, *40*, 2105.

(5) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

(6) The silyl-ether must first be removed, as the protected analogue did not react presumably for steric reasons.

(7) Nelson, J. C.; Young, J. K.; Moore, J. S. *J. Org. Chem.* **1996**, *61*, 8160.

Scheme 3[a]

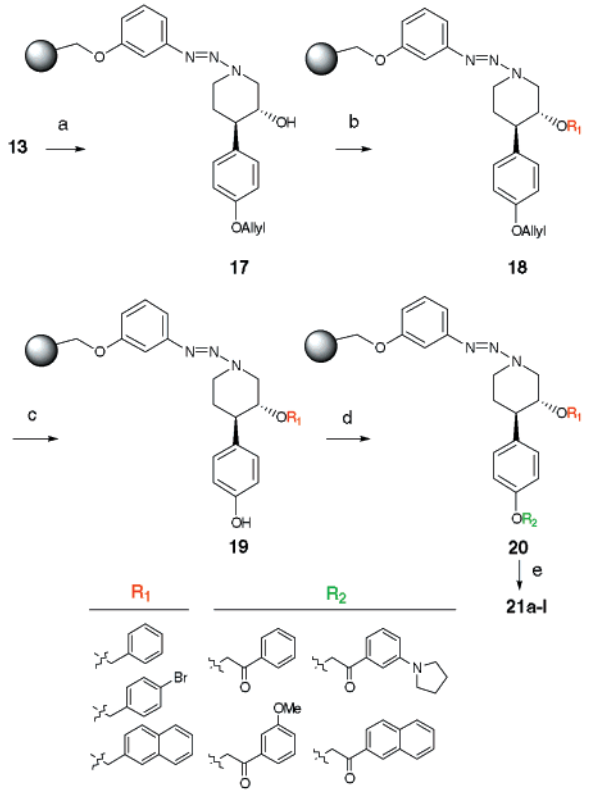


16a, R = benzyl (95%); **16b**, R = *p*-bromo benzyl (81%);
16c, R = *p*-iodo benzyl (77%); **16d**, R = *p*-phenyl benzyl (98%)
16e, R = 2-methyl naphthyl (88%)

[a] Conditions: (a) KO^{t}Bu, R-X, ^{n}Bu$_4$NI, 50 °C; (b) 10% TFA/DCM.

functionalizing both the 3- and 4′-positions of the 3,4-disubstituted piperidine scaffold. The synthesis of the first library (Scheme 4) began with the attachment of piperidine

Scheme 4[a]



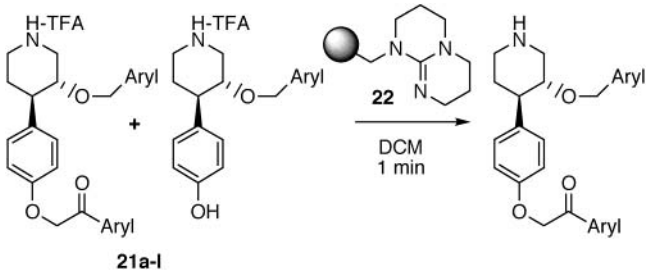
[a] Conditions: (a) **11**, TEA, DCM/DMF; (b) KO^{t}Bu, R_1-Br, ^{n}Bu$_4$NI, 50 °C; (c) Pd(PPh$_3$)$_4$, morpholine; (d) Cs_2CO_3, R_2-Br; (e) 10% TFA/DCM.

11 to the solid-phase diazonium resin **13** to give **17** (1.18 mmol/g). The secondary alcohol was then functionalized via our optimized alkyation conditions using a variety of benzyl bromide derivatives to generate **18**. Following some experimentation the allyl-protecting group was mildly and cleanly removed by using Pd(PPh$_3$)$_4$ and morpholine in DCM to provide phenol **19**.

We envisioned that alkylation of phenol **19** with Cs_2CO_3 and the appropriate alkyl bromides would generate the desired array of potential inhibitors. Initial alkylation attempts in DMF at 40 °C afforded only minimal conversion to the desired product; a slight increase was obtained when ^{n}Bu$_4$NI was added to the reaction. The reported success of a solid-phase K_2CO_3-mediated alkylation in a 2:1 mixture of $CHCl_3$/MeOH[8] prompted us to test this solvent system. We were able to significantly increase our conversion (~90% in our model study) by using Cs_2CO_3 in $CHCl_3$/MeOH. Alkylation of phenol **19** under these conditions with a variety of alkyl bromides afforded **20**. The difunctionalized piperidines were cleaved from the resin by using mildly acidic conditions to provide the array of potential aspartic peptidase inhibitors **21a**−**l** (70−95% crude purity).

The reduced purity of this library resulted from incomplete alkylation of phenol **19** in the penultimate step. After multiple unsuccessful attempts to circumvent this problem, we developed an expedient method to purify the desired final product by removing unreacted starting material with a scavanger resin.[9,10] The unreacted phenol was removed from the crude product mixture by reaction with a basic resin. Incubation with the P-TBD[11,12] scavenging resin **22** in DCM for 1 min and subsequent filtration afforded (Scheme 5) the potential aspartic peptidase inhibitors **21a**−**l** in ≥90% purity.

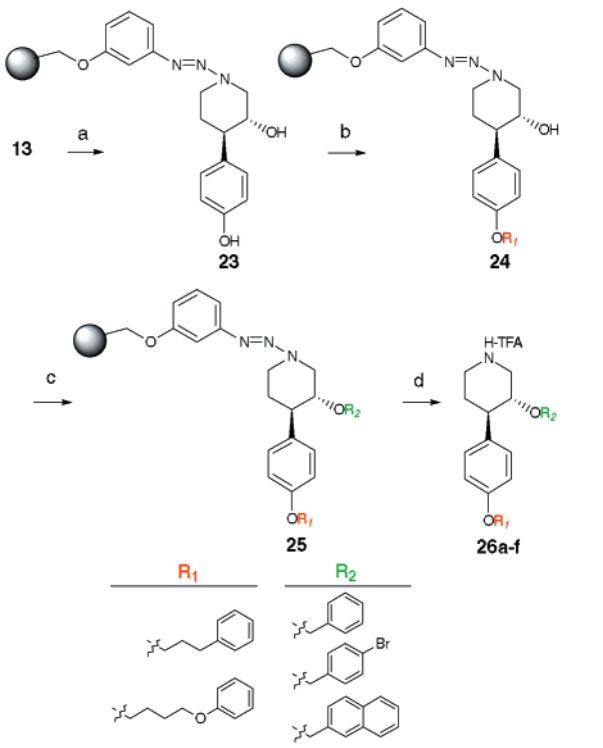
Scheme 5



The final library of potential aspartic peptidase inhibitors (Scheme 6) was synthesized via selective functionalizations without necessitating phenol protection and subsequent protecting group manipulations. Attachment of piperidine **10** to the solid-phase diazonium resin **13** generated **23** (1.25 mmol/g). Selective alkylation of phenol **23** using our optimized phenol alkylation conditions with two different alkyl bromides afforded piperidine **24**. The remaining secondary hydroxyl of **24** was then alkylated with a variety

(8) Pavia, M. R.; Whitesides G. M.; Hangauer, D. G.; Hediger, M. E. Patent Application WO9504277, 1995.
(9) Flynn, D. L. *Med. Chem. Res.* **1999**, *19*, 408.
(10) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320.
(11) Weidner, J. J.; Parlow, J. J.; Flynn, D. L. *Tetrahedron Lett.* **1999**, *40*, 239.
(12) Polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene

Scheme 6[a]



[a] Conditions: (a) **10**, TEA, DCM/DMF; (b) Cs_2CO_3, R_2-Br; (c) KO^{t}Bu, R_1-Br, ^{n}Bu$_4$NI, 50 °C; (d) 10% TFA/DCM.

of benzyl bromide derivatives to afford piperidine **25**. The piperidines were cleaved from the resin by using mild acidic conditions to provide the potential aspartic peptidase inhibitors **26a**−**e** (≥90% crude purity).

In summary, we have developed a solid-phase functionalization method to generate arrays of 3,4-disubstituted piperidines via three routes. Already this scaffold has proven useful in developing novel inhibitors for four different aspartic peptidases. The methods described in this Letter should enable preparation of more extensive libraries to generate the structure−activity relationships that will facilitate the design of more active and selective inhibitors. Further diversification of these libraries via palladium-mediated chemistries is under investigation. The new derivatives reported in this Letter are currently being evaluated as potential inhibitors of a variety of therapeutically interesting aspartic peptidase targets.

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Supporting Information Available: Detailed experimental procedures for the generation of all resins, product cleavage from resin, purification protocol via solid-phase extraction including a representative example, and a listing with crude purities of all final compounds (Tables 1−3) generated using these methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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