Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 4, pp. 539-542, 1994

0960-894X/94 $6.00+0.00

0960-894X(94)E0004-X

THE EFFECT OF HETEROATOM SUBSTITUTION ON A SERIES OF PHOSPHONATE INHIBITORS OF NEUTRAL ENDOPEPTIDASE 24.11

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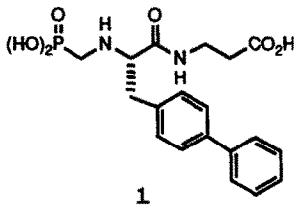
Abstract: A series of phosphonic acids, **7a-d**, with heteroatom and carbon variations in the template backbone were prepared and tested for inhibition of neutral endopeptidase 24.11. The structure-activity relationship of these derivatives is presented and discussed.

Atrial natriuretic peptide (ANP), a 28-amino acid hormone, shows potent natriuretic, diuretic and vasorelaxant properties *in vivo*.[1] The rapid clearance of ANP appears to be regulated by both clearance receptors[2] and enzymatic degradation by neutral endopeptidase 24.11 (EC 3.4.24.11).[3] Since neutral endopeptidase (NEP) inhibitors enhance the biological activity of ANP,[4] we initiated a program to identify novel NEP inhibitors as a potential treatment for hypertension and congestive heart failure.



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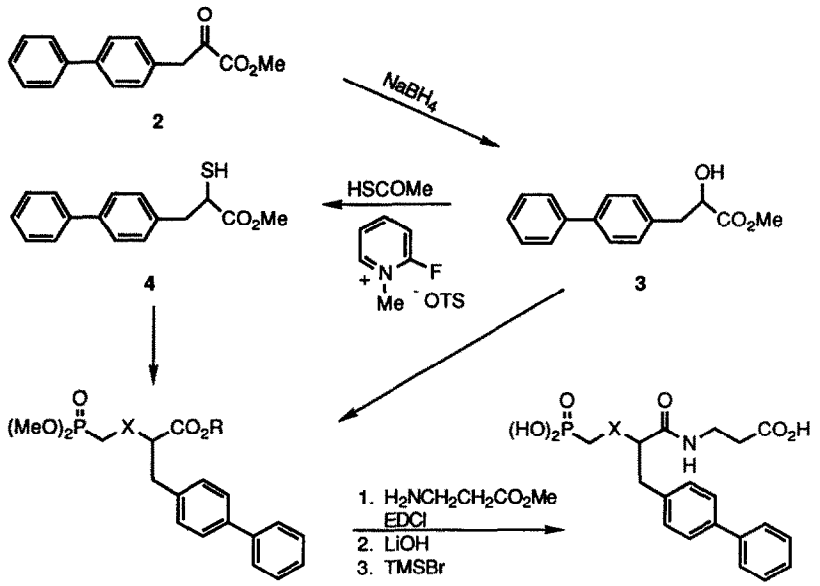
With the discovery of biphenyl-substituted amino phosphonate derivatives such as **1** as potent NEP inhibitors,[5] we set out to explore the effect of replacing the amino group with an ether, thioether, sulfone or methylene group. The heteroatom substituted target compounds **7a-c** were prepared as shown in Scheme I. Methyl 4-biphenylacetate was condensed with ethyl oxalate, hydrolyzed, decarboxylated and re-esterified to yield keto ester **2**.[6] Sodium borohydride reduction of **2** gave hydroxy ester **3**. The corresponding thiol **4** was prepared by treatment of **3** with 2-fluoro-1-methylpyridinium *p*-toluenesulfonate and thiolacetic acid[7] followed by hydrolysis of the intermediate thioacetate and re-esterification of the carboxylic acid group.

Conversion of **3** and **4** to **5a** and **5b** respectively was achieved in 37% and 66% respectively by alkylation with dimethyl phosphonomethyl triflate.[8] Alkaline hydrolysis of **5a** and **5b** generated carboxylic acids **6a** and **6b**. Thioether **6b** was converted to sulfone **6c** by oxidation with *m*-chloroperoxybenzoic acid. Amidation of **6a-c** with β-alanine methyl ester produced the intermediate triesters. Sequential deprotection of the carboxylate and phosphonate esters with lithium hydroxide and bromotrimethylsilane[9] generated the target compounds **7a-c**.[10]

The methylene analog **7d** was synthesized as outlined in Scheme 2. 3-(Biphenylmethyl)oxetane (**8**)[11] in the presence of boron trifluoride etherate underwent alkylation with the lithium salt of dimethyl methylphosphonate to give **9** in 21% yield. The reaction was not optimized.

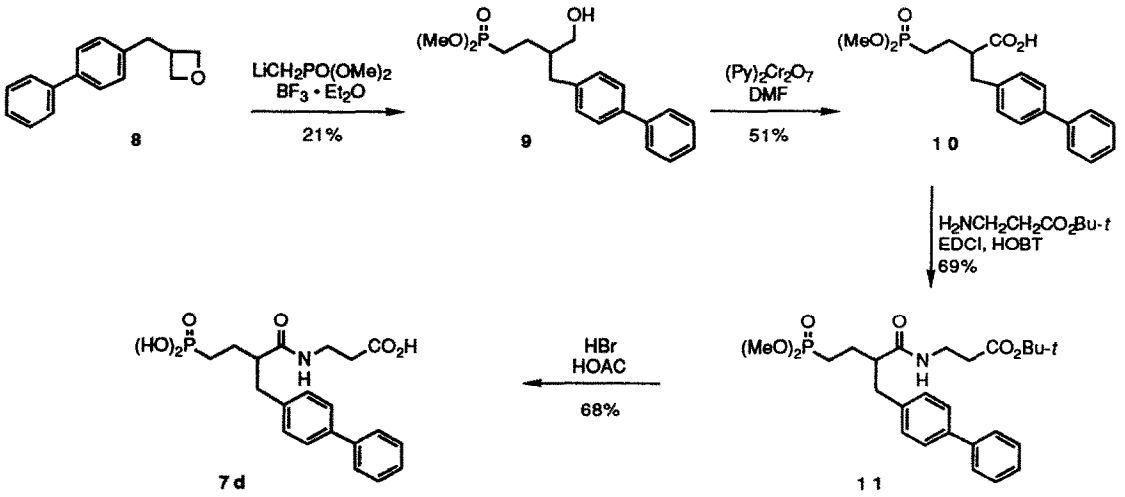
Scheme 1



5a; X = O, R = Me
5b; X = S, R = Me
6a; X = O, R = H
6b; X = S, R = H
6c; X = SO_2, R = H

7a; X = O (racemate)
7b; X = S (racemate)
7c; X = SO_2(racemate)

Scheme 2



Oxidation of alcohol **9** with pyridium dichromate[12] in DMF produced the carboxylic acid **10** in 51% yield. Amide formation with **10** and β-alanine *t*-butyl ester in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) and 1-hydroxybenzotriazole (HOBT) led to **11** in 69%. Deprotection of **11** with HBr in acetic acid generated the target phosphonic acid **7d**.[10]

Table 1.
***In vitro* NEP 24.11 Inhibition of 7a-d**

No.	IC_{50}(nM)[a]
7a	9.5
7b	797
7c	>10,000
7d	1000
1	1.6
thiorphan[b]	5.0

[a] NEP 24.11 was obtained from rat kidney cortex membranes. Assays were carried out as described in ref. 13.
[b] Lit.[14] IC_{50} = 3.5 nM.

Compounds **7a-d** were tested for *in vitro* inhibition of NEP 24.11[13] and the results are summarized in Table 1. Considering that **1** is a single enantiomer and that **7a-d** are racemates with activity probably in only one of the enantiomers, oxygen analog **7a** showed inhibitory potency comparable to amino phosphonate **1**, differing only by approximately a factor of three in activity. On the other hand thioether **7b** and methylene analog **7d** were found to be approximately one hundred-fold less active and sulfone **7c** was essentially inactive. The results indicate that a hydrogen bond donating group (NH) is not required for high activity but that a small "hard" electronegative group is apparently needed. Assuming identical binding modes, a variety of factors could contribute to the observed data, including differences in direct binding of the heteroatom to the zinc cation in the active site, differences in energies of zinc coordination, differences in acidity of the phosphonic acid groups, differences in chain length from the phosphonic acid to the P_1'-P_2' amide, and differences in inhibitor solvation. The observed results may be a combination of these differences in active site and solvent interactions.

The effects of heteroatom substitution on binding to NEP 24.11 differ from those seen for thermolysin[15] and angiotensin converting enzyme.[16] The results contribute to our understanding of the overall requirements for effective inhibitory binding with NEP 24.11.

Acknowledgements: *The authors express their thanks to Dr. S. De Lombaert for useful discussions, Dr. R. Ghai for performing the enzyme inhibition tests, and Ms. A. Navarrete for preparing the manuscript.*

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10. (a) Compound **7a**: ^{1}H NMR (DMSO-d_6) 2.32 (t, 2 H, J = 4 Hz), 2.98 (m, 2 H), 3.26 (m, 2 H), 3.55 (d, 2 H, J = 10 Hz), 4.11 (t, 1 H, J = 3 Hz), 7.27-7.65 (m, 9 H), 7.87 (t, 1 H, J = 3 Hz). (b) Compound **7b**: mp 108-110 °C; ^{1}H NMR (DMSO-d_6) 2.31 (t, 2 H, J = 4 Hz), 2.74 (m, 2 H), 2.9 (m, 1 H), 3.18 (m, 3 H), 2.67 (m, 1 H), 7.27-7.67 (m, 9 H), 8.10 (t, 1 H, J = 3 Hz). (c) Compound **7c**: mp > 270 °C; ^{1}H NMR (DMSO-d_6) 2.29 (t, 2 H, J = 4 Hz), 3.20 (m, 4 H), 3.35 (m, 2 H), 4.77 (m, 1 H), 7.25-7.63 (m, 9 H). (d) Compound **7d**: mp 75-80 °C; ^{1}H NMR (DMSO-d_6) 1.5 (m, 3 H), 2.4 (m, 4 H), 2.6 (m, 1 H), 2.8 (m, 1 H), 3.2 (m, 2 H), 3.5 (d, 1 H, J = 12 Hz), 7.2 (d, 2 H, J = 6 Hz), 7.3 (d, 1 H, J = 6 Hz), 7.42 (t, 2 H, J = 6 Hz), 7.5 (d, 2 H, J = 6 Hz), 7.6 (d, 2 H, J = 6 Hz), 7.9 (m, 1 H).
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(*Received in USA* 12 *October* 1993; *accepted* 14 *December* 1993)