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Derivatized Oxopiperazine Rings From Amino Acids

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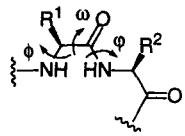
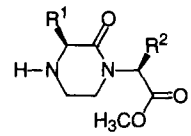
Abstract: *Two routes for the synthesis of derivatized oxopiperazines, which may act as constrained peptide mimics, are reported. The syntheses employ reductive amination and sulfonamide approaches for generating N-allylic amino acid ester derivatives and utilizing them for assembling the ring systems. An aspartame analog was prepared using this methodology.* © 1997 Elsevier Science Ltd.

The design of non-peptide ligands for membrane-bound peptide receptors is an active area of pharmaceutical research.[2] An attractive approach to the identification of lead compounds acting at peptide receptors is the transformation of peptides into conformationally restricted peptide analogs.[3] These aim to mimic the conformations and actions of the natural peptidic ligand. We looked at simple templates that could mimic dipeptides.[4] The oxopiperazine ring was chosen as a model template in which the two nitrogen atoms of the dipeptide are linked by an ethylene bridge thus restricting the ω, ϕ and φ torsional angles as shown in Figure 1.

Figure 1



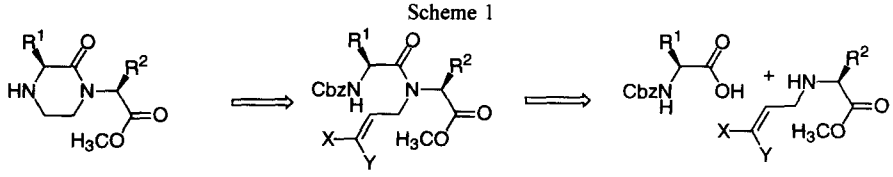
Dipeptide



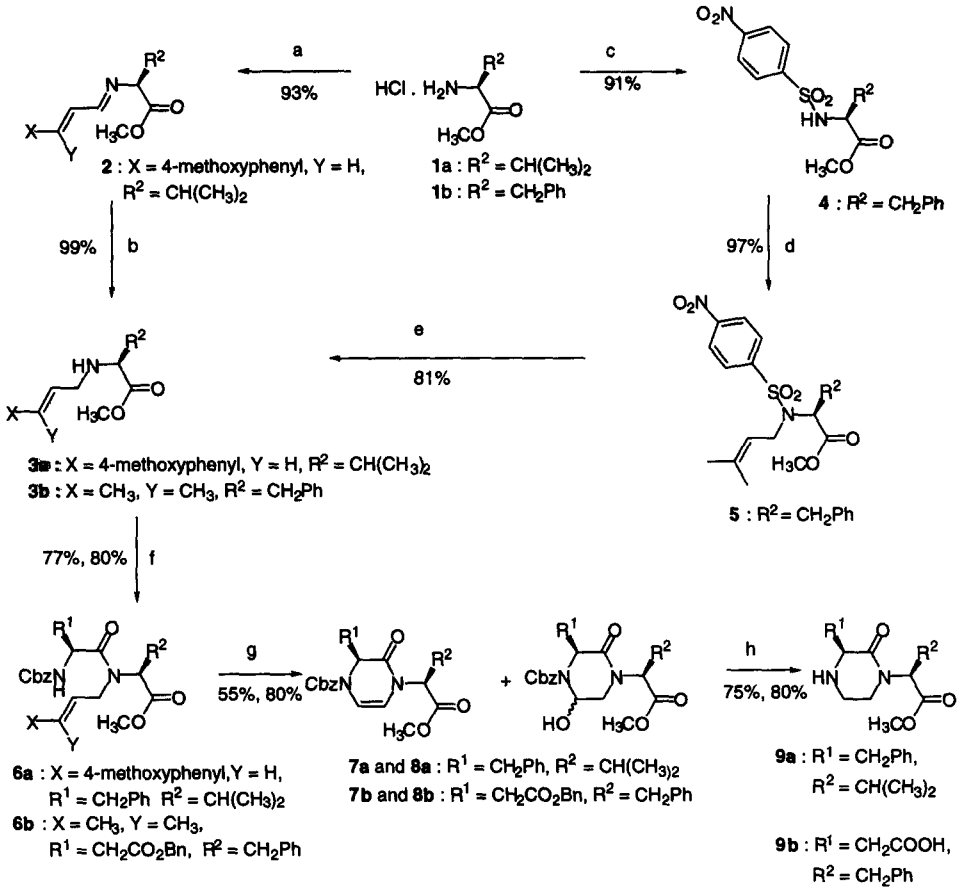
Oxopiperazine ring

Various attempts to synthesize these peptidomimetics by reacting dipeptides with 1,2-dibromoethane failed to give high yields of desired products. Our approach then focused on the generation of N-allylic secondary amino acid esters which could be coupled with other amino acids as depicted in Scheme 1.[5] The aldehyde required for the cyclization could then be generated by oxidation of the alkene functionality.

Scheme 1



Scheme 2



(a) NEt_3, 4-methoxycinnamaldehyde, $HC(OMe)_3$, RT, 8hrs ; (b) $NaBH_4$, MeOH, 0 °C,15mins;
(c) NEt_3, 4-nitrobenzenesulfonyl chloride, RT, 6hrs; (d) Dimethylallyl bromide, K_2CO_3, DMF, RT, 3hrs;
(e) PhSH, K_2CO_3, DMF, RT, 6hrs ; (f) CbzNH-CHR^1-COF, 4-ethyl morpholine, CH_2Cl_2, RT, 24hrs;
(g) O_3, -78 °C, MeOH then SMe_2, 12hrs; (h) H_2, Pd ($BaSO_4$), MeOH, 6hrs.

The direct reductive amination of α,β unsaturated aldehydes with amino acid esters gave low yields of the desired secondary amine after tedious chromatography. We then concentrated on the initial preparation of the imine and its subsequent 1,2 reduction as outlined in Scheme 2. Reaction of valine methyl ester hydrochloride **1a** with 4-methoxy cinnamaldehyde in presence of triethylamine in trimethylorthoformate gave the imine **2** in 93% yield.[6] Attempts to reduce the α,β unsaturated imine with sodium cyanoborohydride in the presence of $CeCl_3.7H_2O$, or of anhydrous $CeCl_3$ yielded both 1,2 and 1,4 reduction products. Replacing $NaCNBH_3/CeCl_3$ with $NaBH_4$ yielded exclusively the 1,2 reduction product **3a** in 99% yield with no detectable 1,4 reduction product.[7]

The next step required the coupling of this relatively hindered secondary amine to the second amino acid. Traditional reagents for peptide coupling produced low yields (DCC : 5%, BOP < 1%, PyBroP 16%).

Our attention was then drawn to the use of acid fluorides which have shown promise in coupling hindered amines.[8] Activating the CbzPheOH as an acid fluoride[9] led to a dramatic increase in the yield of the desired derivatized dipeptide **6a**. We have now been able to get greater than 90% yield for similar couplings. The derivatized dipeptide was then subjected to ozonolysis followed by dimethyl sulfide reduction to yield a mixture of cyclized alcohol **7a** and alkene **8a**. This mixture proved difficult to separate and hence was hydrogenated directly in 75% yield to yield the 2-oxopiperazine ring **9a**.[10]

In a parallel approach, we used N-4-nitrosulfonamide as an activating group for achieving mono-N-alkylation, as recently described by Fukuyama and coworkers.[11] The reaction of 4-nitrobenzenesulfonyl chloride with phenylalanine methyl ester hydrochloride **1b** proceeded in excellent yield to give the crystalline sulfonamide **4,** m.p 147-150 °C. It was then prenylated with dimethylallyl bromide to give **5**. Subsequent reaction with PhSH gave the desired secondary amine **3b**. The coupling with the acid fluoride of CbzAsp(OBn)OH proceeded smoothly as before to yield **6b**. Ozonolysis of the derivatized dipeptide gave the cyclized products **7b** and **8b**. These were then subjected to hydrogenation to yield the aspartame analog **9b**.[12] Studies to evaluate the sweetness of this derivative are under investigation.

In conclusion we have described two simple syntheses of the oxopiperazine peptide mimic.[13] Further studies to eliminate chromatography and synthesize such compounds on solid support are in progress. Biological studies will be reported in due course.

Acknowledgments

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References and Notes

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7. ^{1}H , ^{13}C NMR and MS (EI) showed complete absence of 1,4 reduction product even when 2 equivalents of hydride ion was added.
8. (a) For a recent review see Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M., *Acc. Chem. Res.* **1996**, *29*, 268-274.
   (b) Carpino, L.A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D.; *J. Org. Chem.* **1991**, *56*, 2611-2614.

9. A solution of N-protected amino acid (1 eq.) in dichloromethane was treated with pyridine (1.2 eq.) and cyanuric fluoride (3 eq.) at -20 °C to give the corresponding N-protected amino acid fluoride.[8b] Both acid fluorides were isolated and characterized (^{1}H and ^{13}C NMR) prior to the coupling step.

10. **9a**: ^{1}H NMR (500MHz, $CDCl_3$) δ 0.83 (d, J = 6.7 Hz, 3 H, $CH(CH_3)_2$) 0.96 (d, J = 6.4 Hz, 3 H, $CH(CH_3)_2$), 1.93 (br, 1 H, NH), 2.11-2.21 (m, 1 H, $CH(CH_3)_2$), 2.85-2.91 (m, 1 H, CH_2Ph), 2.90-3.01 (m, 1 H, $NHCH_2CH_2N$), 3.04-3.10 (m, 1 H, $NHCH_2CH_2N$), 3.20-3.30 (m, 1 H, $NHCH_2CH_2N$), 3.35 (dd, 1 H, J = 3.5 Hz and J = 13.5 Hz, CH_2Ph), 3.40-3.46 (m, 1 H, $NHCH_2CH_2N$), 3.69 (s, 3 H, OCH_3), 3.70-3.72 (m, 1 H, $CHCH_2Ph$), 4.92 (d, J = 10.8 Hz, 1 H, $CHCH(CH_3)_2$), 7.21-7.40 (m, 5 H, Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 19.14, 19.73 ($CH(CH_3)_2$), 26.90 ($CH(CH_3)_2$), 38.59 (CH_2Ph), 42.21 ($NHCH_2CH_2N$), 44.50 ($NHCH_2CH_2N$), 51.89 (OCH_3), 61.02 ($CHCH(CH_3)_2$), 61.11 ($CHCH_2Ph$), 126.75, 128.68, 129.57 (Aromatics), 138.19 Quaternary Aromatic), 169.91 (NC(O)), 171.62 ($C(O)OCH_3$); MS (FAB, NBA) m/e (%) 305 (100) $[MH]^+$, 277 (69.8), 217 (51.8), 213 (89.1).

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12. **9b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (A of ABX system, 1 H, J = 8.0 Hz and 16.0 Hz, $CHCH_2C(O)$), 2.48-2.52 (m, 1 H, $CHCH_2C(O)$), 2.52-2.58 (m, 1 H, $NHCH_2CH_2N$), 2.72-2.84 (m, 2 H, $NHCH_2CH_2N$), 3.06 (A of ABX system, 1 H, J = 11.0 Hz and J = 14.0 Hz, $CHCH_2Ph$), 3.18 (B of ABX system, 1 H, J = 5.5 Hz and J = 14.0 Hz, $CHCH_2Ph$), 3.24-3.30 (m, 1 H, $NHCH_2CH_2N$), 3.54 (X of ABX system, 1 H, J = 3.5 Hz and J = 8.0 Hz, $CHCH_2C(O)$), 3.63 (s, 3 H, OCH_3), 4.84 (X of ABX system, 1 H, J = 5.5 Hz and J = 11.0 Hz, $CHCH_2Ph$), 7.17-7.30 (m, 5 H, Ph); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 33.37 (CH_2COOH), 36.98 (CH_2Ph), 40.90 ($NHCH_2CH_2N$), 46.92 ($NHCH_2CH_2N$), 51.95 (OCH_3), 55.64 (NHCH), 58.73 (NCH), 126.43, 128.20, 128.95 (Aromatics), 137.41 (Quaternary Aromatic), 168.86 (NC(O)), 170.50 (COOH), 172.61 ($C(O)OCH_3$); MS (CI, NH_3) m/e (%) 321 (100) $[MH]^+$, 275 (13.3), 229 (51.0), 157 (35.8).

13. During the completion of this manuscript, we came across the following publication where similar compounds were prepared by a different route. Pohlmann, A.; Schanen, V.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P., *J. Org. Chem.* **1997**, *62*, 1016-1022.

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