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A Simple and Efficient Synthesis of a Derivatized Pseudotripeptide Containing a Methylene Thioether Isostere and its Use for the Design of Bifunctional Rhenium and Technetium Chelating Agents

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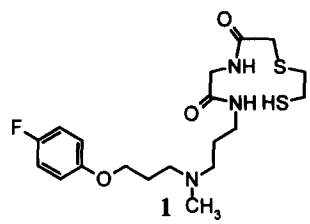
Abstract: A new approach to a pseudotripeptide based tetradentate chelating unit functionalizable with various bioactive groups has been developed. Using a one-pot reaction, a given ω-aminoalkyl compound has been converted to a methylene thioether peptide isostere by two consecutive ring opening reactions.

An increasing range of bifunctional chelating agents (BFCA) to form stable Re(V) or Tc(V) complexes for the development of new radiopharmaceuticals has been introduced during the last ten years[1]. These efforts are mainly inspired by a continuous need for new chelators to label monoclonal antibodies[2] or small bioactive molecules such as antagonists of biogenic amines[3], peptides[4] or other compounds of interest with ^{99m}Tc or ^{186}Re.

Amongst the different types of ligand frameworks that have been developed for this purpose, the most commonly used belong to the N_2S_2 class. This type of tetradentate ligands containing two thiol groups and two N-donor atoms in form of amino or amido groups and provides for attaching a spacer either at the ligand backbone or at one of the donor atoms for conjugation of an appropriate bioactive molecule.

The application of small peptide isosteres as new chelating agents to form neutral complexes with Re(V) and Tc(V) attracted our attention in connection with our ongoing work on potential serotonin receptor binding Tc- and Re-complexes[5].



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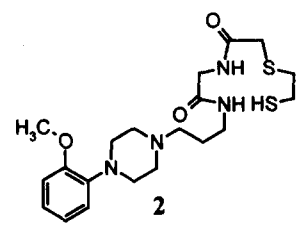

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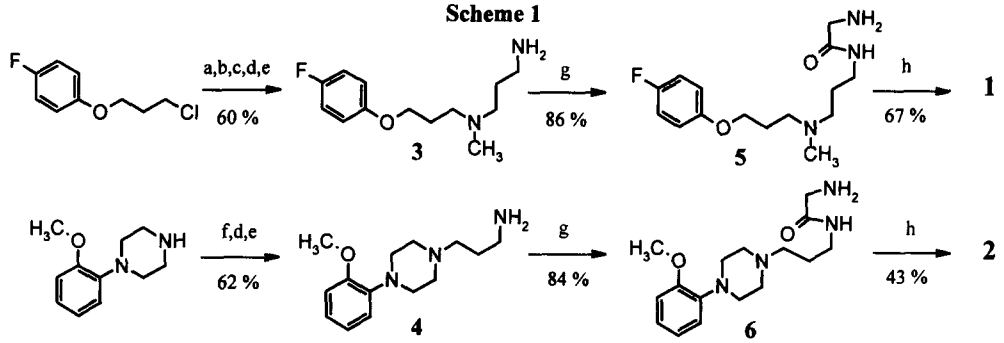
We herein report a simple and efficient synthesis of the Thac-ψ[CH_2S]-Gly-Gly-NH_2 sequence[6] (Thac: mercaptoacetic acid) and its first conjugation to structural units with known serotonin receptor binding properties (compounds **1** and **2**). For our investigations we have selected the *o*-methoxyphenylpiperazine moiety, the main pharmacophore of several 5-HT_{1A} receptor antagonists[7a] and the *p*-fluorophenoxypropylamino functionality which represents an important fragment of few compounds, displaying strong affinity to the 5-HT_{2A} receptor[7b].

The basic strategy developed involves the incorporation of an alkylene spacer attached to the terminal amino group of the parent structure leading to the 3-aminopropyl intermediates **3** and **4**. Thus, starting from

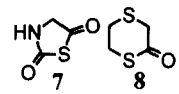
either *p*-fluorophenoxypropyl chloride[8] or commercially available *o*-methoxyphenylpiperazine both primary amines were obtained in several steps according to standard procedures (**Scheme 1**).

Preliminary attempts to prepare **5** and **6** by using *N*-protected glycine proved difficult owing to the water solubility of **5** and **6**, leading to substantial losses during the workup procedure of the deprotection step. However, it was found that thiazolidine-2,5-dione (**7**)[9] reacts smoothly with both **3** and **4** at 0°C to furnish the corresponding glycyl derivatives **5** and **6** in excellent yields. To directly access the pseudotripeptides **1** and **2** by means of [1,4]dithian-2-one (**8**)[10] it was more convenient not to isolate the intermediates **5** and **6** but to carry out both steps as a one-pot procedure. Both final products were purified by crystallization of their corresponding oxalate salts[11].

Scheme 1



Reagents and Conditions (yields are not optimized): a) 3-amino-1-propanol, K_2CO_3, butanol, reflux; b) HCOOH, 30% HCHO, 100°C; c) $SOCl_2$, distillation of the free base; d) $NaN(CHO)_2$, DMF, 110°C; e) 4N HCl, 100°C; f) 1-bromo-3-chloropropane, TEA, toluene, 80°C; g) **7**, $CHCl_3$, 0°C, 1h; h) **8**, $CHCl_3$, 22°C, 8h.



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6 Concurrent with our efforts *Archer et al.* already reported on a different approach, to obtain the same chelating sequence attached to an ethyl group: [1,4]Dithian-2-one(**8**) (1. Gly-OEt 2. $EtNH_2$) → Thac-ψ[CH_2S]-Gly-Gly-NHEt: Archer, C. M.; Canning, L. R.; Duncanson, P.; Gill, H. K.; Griffiths, D. V.; Hughes, J. M.; Kelly, J. D.; Pitman, M. A.; Storey, A. E.; Tran, A. M. *Technetium and Rhenium in Chemistry and Nuclear Medicine* Nicolini, M.; Bandoli, G.; Mazzi, U. Eds. Vol. 4, S. G. Editoriali, Padova, Italy, 1995; pp. 177 - 179.

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11 Selected spectral and analytical data for **1** and **2** follow: **1** (free base): ^{13}C–NMR ($CDCl_3$, 125.77 MHz) δ 24.2, 25.7, 27.1, 35.6, 36.8, 39.4, 41.9 (NCH_3), 43.1, 54.5, 56.6, 66.6, 115.4 (d, J = 8.3 Hz), 115.8 (d, J = 23 Hz), 155.0, 157.2 (d, J = 238.3 Hz), 167.9 (C=O), 169.2 (C=O); **1** (oxalate salt): Calcd. for $C_{19}H_{30}FN_3O_3S_2 \cdot C_2H_2O_4$: C, 48.36; H, 6.18; N, 8.06; S, 12.29. Found: C, 48.10; H, 5.94; N, 8.00; S, 12.13. **2** (oxalate salt): ^{13}C–NMR (CD_3OD, 125.77 MHz) δ 24.9, 25.3, 35.9, 37.0, 37.7, 44.0, 48.7, 53.5, 55.4, 56.1 (OCH_3), 113.1, 120.0, 122.2, 125.5, 140.7, 154.0, 166.7 (C=O, acid), 172.4 (C=O, amide), 173.2 (C=O, amide). Calcd. for $C_{20}H_{32}N_4O_3S_2 \cdot C_2H_2O_4$: C, 49.80; H, 6.46; N, 10.56; S, 12.08. Found: C, 49.58; H, 6.17; N, 10.39; S, 11.80.

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