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DESIGN AND SYNTHESIS OF A PROTOTYPE MODEL ANTAGONIST OF TACHYKININ NK-2 RECEPTOR

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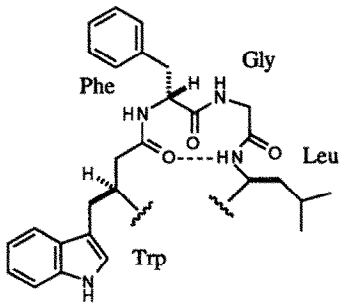
Abstract: A conformationally biased bicyclic lactam containing strategically placed hydrophobic groups was synthesized as a prototype model antagonist molecule of the NK-2 receptor.

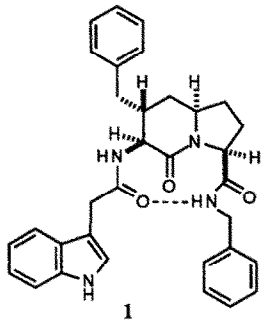
Tachykinins, including the undecapeptide substance P and related neurokinins, are generally associated with physiological events leading to pain and inflammation.[1,2] These mediators of neurotransmission or neuromodulation in the central and peripheral nervous systems have affinities for certain receptors designated as NK-1, 2 and 3.[3] Substance P and the decapeptides, neurokinin A and B have a common C-terminal sequence consisting of Phe-X-Gly-Leu-MetNH$_2$.[4] This minimal structural information, in conjunction with extensive studies on peptide and non-peptide analogs,[5] have led to the development of antagonists[6] to these tachykinins particularly those with high affinities to NK-1 and NK-3 receptors.[7] Although somewhat more elusive, selective antagonists to neurokinin A at the NK-2 receptor have also been reported.[8] A recent conformational study[9] in solution of a cyclic hexapeptide potent antagonist by NMR techniques has revealed information regarding the shape and relative disposition of the pendant groups as well as the existence of a β-turn subunit involving Trp-Phe-Gly-Leu residues (Figure 1).

Based on these observations, and data available from the literature on some of the more potent and selective antagonists of NK-2,[5-8] we have derived a prototype for an antagonist model which is shown in expression **1** (Figure 1). The intention was to deploy hydrophobic groups that could simulate the Trp-Phe portion, on a rigid

Figure 1



Partial structure of a cyclic hexapeptide (ref. 9)



1
Prototype model antagonist

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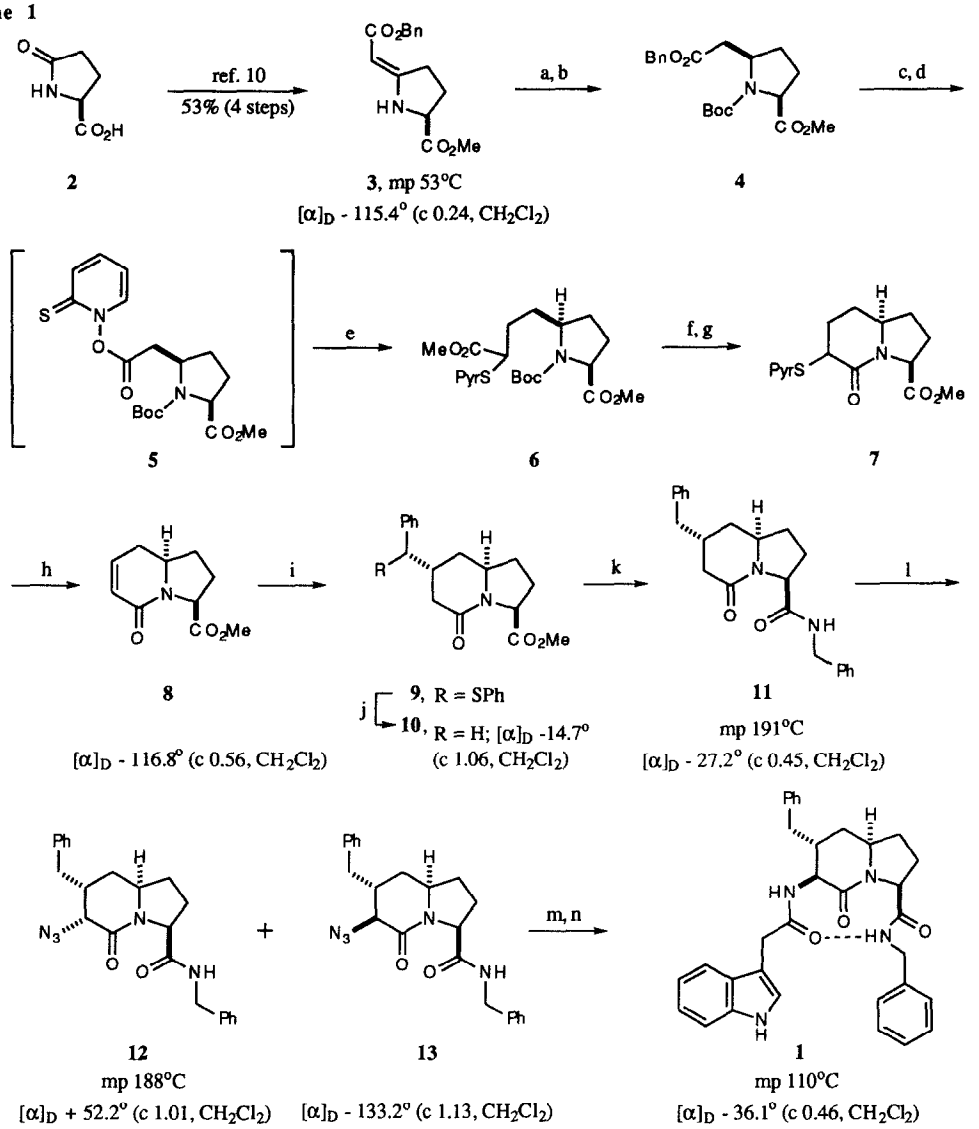
Scheme 1



a) H_2 - 4 Atm, Pt/C (5%), Toluene, rt, 110h; *cis:trans* = 9:1, separation by flash chromatography on silica gel (AcOEt/hexane 5/1). b) Boc_2O (1.1 eq), $(iPr_2)NEt$ (1.1 eq), CH_2Cl_2, rt, 18h, 50% (2 steps). c) H_2 - 1 Atm, Pd/C (10%), MeOH, rt, 1h. d) *N*-Methyl morpholine (1 eq), isobutyl chloroformate (1 eq), THF, -20°C, 20 min; 2-mercaptopyridine N-oxide, sodium salt hydrate (1.1 eq), -20°C in the dark 1h (quant.). e) Methyl acrylate (5 eq) hν 250 W, rt, 30 min, 80%. f) TFA (20 eq), CH_2Cl_2, rt, 16h; NH_4OH. g) Me_3Al (2 eq), CH_2Cl_2, rt, 1h, 50% (2 steps). h) mCPBA (1 eq), $CHCl_3$, 0°C, 1h; toluene, 110°C, 1h, 82%. i) benzyl phenyl sulfide (1.1 eq), HMPA (2.5 eq), nBuLi (1.1 eq), THF, -78°C, 1h, -78°C, 30 min; NH_4Cl, -78°C, 69%. j) W_2 Raney-Ni, EtOH, rt, 1h, 95%. k) $PhCH_2NHAlMe_2$ (3 eq), CH_2Cl_2, rt, 18h; aq. HCl, 50%. l) LDA (2 eq), THF, -10°C, 30 min; trisyl N_3 (2 eq), THF, -78°C, 5 min; AcOH (10 eq), -78°C; 30°C, 2h; separation by flash chromatography on silica gel (AcOEt/cyclohexane=1:1), 50%. m) H_2 - 4 Atm, Pd/C (10%), rt, 24h. n) indole -3-acetic acid (1.2 eq), EDCI (1.2 eq), DMF, rt, 16h, 36%.

bicyclic template that would act as a surrogate for a β-turn[10] much same as in the cyclic hexapeptide.[9] The C-terminal benzylamide group can also be found in a number of NK-1 and NK-2 selective peptidic antagonists.[7,8]

In order to secure a high level of internal asymmetric induction by a resident group, we chose L-pyroglutamic acid **2** as a logical starting material (Scheme 1). A sequence of known reactions[11] led to the diester **3** in good overall yield. Catalytic hydrogenation gave a 9:1 *cis/trans* mixture of the expected pyrrolidine derivatives which were separated by chromatography.[12] Protection of the amine as the Boc derivative, and catalytic debenzylation of the benzyl ester gave a monoester which was transformed into the corresponding thiopyridinyl hydroxamate ester **5**. Application of the Barton procedure[13] using methyl acrylate as a radical acceptor led to **6** in excellent overall yield. Unfortunately, the reaction failed when crotonate or 3-benzyl acrylate esters were utilized as radical Michael acceptors, in accord with previous observations.[14,15] The Barton reaction allowed the introduction of the required three-carbon acid branch with a functionally useful pyridylthio group for subsequent manipulation. Thus, removal of the N-Boc group and cyclization afforded the bicyclic lactam **7** as a mixture of two diastereomers. Oxidative elimination[15,16] led to the unsaturated lactam **8**. In view of the reluctance of cuprate-type reagents to cleanly add to the α,β-unsaturated lactam **8**, we resorted to a two-step, albeit, efficient protocol for the introduction of the C-benzyl group. Thus, treatment of **8** with benzylphenylsulfide anion in THF-HMPA[17] led to **9** as a mixture of diastereomers in good yield and excellent selectivity based on the NMR analysis of subsequent intermediates. In the absence of HMPA, a significant quantity of addition to the ester function occurred also. Removal of the phenylthio group by desulfurization gave **10** as an oil. There now remained to introduce the amino group in the lactam subunit and to complete the synthesis of our intended target molecule. As an obvious choice, we turned to the electrophilic transfer of azide from an arylsulfonyl azide[18-20] to the enolate generated from **10**. The latter proved somewhat sluggish to form under a variety of conditions. In fact treatment of **10** with LiHMDS in THF with trisyl or tosyl azide at -78°C, led to the introduction of an azide group adjacent to the ester function rather than at the desired site in 42% yield. Introduction of the benzylamide group using the Weinreb protocol[21] gave **11**, as a crystalline solid. Electrophilic addition of azide ion to the dianion generated from **11** at the desired site was now possible, resulting in a 1:1 mixture of **12** and **13**. Various attempts to change this ratio were not successful (solvent, temperature, azide source). The moderate yields in such reactions with dianions have been previously reported.[22,23] Although the two isomers were separable by chromatography, it was not possible to efficiently epimerize the undesired isomer **12** into **13**. Catalytic reduction of the *trans* isomer **13**, followed by acylation gave the intended target molecule **1** as a crystalline solid.[24] Although the dimensions of the crystals were not suitable for single crystal X-ray analysis, the structure of **1** was unambiguously assigned from detailed NMR analysis.[24] Furthermore, the presence of intramolecular H-bonding was strongly suggested from the FT-IR spectrum of **1** (3309 cm^{-1}, 3400 cm^{-1}).[25]

The prototype model antagonist **1** had no affinity for NK-1 receptor, and showed a low affinity for human recombinant NK-2 receptor with an affinity binding of 3μM,[26] which is a promising beginning for a new "designed" structure. We believe that further fine-tuning of the proposed basic template structure **1** may be possible, by attachment of other pendant groups on rings A and B, coupled with new information from the structures of emerging antagonists. Hopefully this will eventually lead to a new generation of "small", potent, and selective antagonists of these fascinating receptors.[27]

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27. All new compounds were adequately characterized by spectroscopic and microanalytical methods. Optical rotations were recorded at 25°C.

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