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Catechol: A Minimal Scaffold for Non-Peptide Peptidomimetics of the *i* + 1 and *i* + 2 Positions of the β-Turn of Somatostatin

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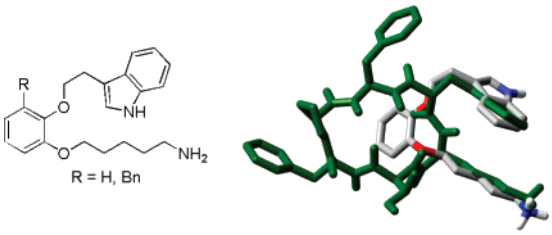
ABSTRACT



The design, synthesis, and evaluation of a series of catechol-based non-peptide peptidomimetics of the peptide hormone somatostatin have been achieved. These ligands comprise the simplest known non-peptide mimetics of the *i* + 1 and *i* + 2 positions of the somatostatin β-turn. Incorporation of an additional side chain to include the *i* position of the β-turn induces a selective 9-fold affinity enhancement at the sst_2 receptor.

Elucidation of the bioactive conformation of somatostatin-14 (**1**, SRIF-14, Figure 1) by Veber and his collaborators at Merck,[1] in conjunction with the earlier results of an alanine scan by Rivier and co-workers,[2] resulted in the design and synthesis by Veber of both the cyclic hexapeptide L-363,-301 (**2**) and the more potent super agonist MK-678 (**3**).[3] The earlier insightful observation by Walter that there was no definite evidence for the direct interaction of the amide backbone of peptide hormones and neurotransmitters with their receptors,[4] a proposition that was strongly supported by the report by Freidinger et al. of a potent retro-enantio congener of these peptides,[5] allowed Hirschmann, Nicolaou, Smith, and co-workers to exploit the β-D-glucoside scaffold[6] for the attachment of mimics of the three side chains of the β-turn of **1**[7] that are critical for both binding and receptor

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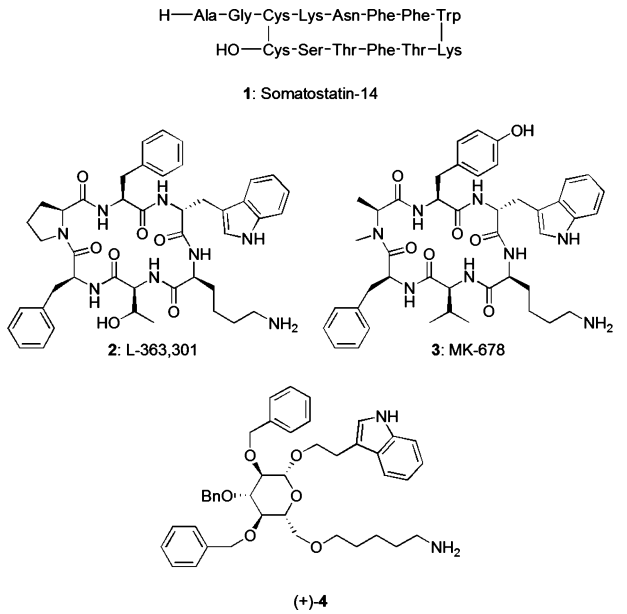

Figure 1. Structures of somatostatin (**1**), cyclic hexapeptide agonists **2** and **3**, and the β-D-glucoside peptidomimetic (+)-**4**.

activation, along with the incorporation of a mimic of the second Phe of **2**, which was known to enhance binding.

With these achievements in hand, we recently sought to identify the simplest scaffold that can replace the β-D-glucose ring, while maintaining the side chain topology of a β-turn. We reasoned that a benzene ring might serve this function. As with the β-D-glucose scaffold, we used ether linkages to attach the two most important side chains, an ethylindole to mimic Trp[8] and an aminopentyl moiety to simulate the Lys[9] side chain, to arrive at the catechol-derived ligand **5** (Figure 2). Herein, we report that **5** and the subsequently designed catechol-based SRIF ligands **6**−**8** bind to human somatostatin receptor subtypes 2 and 4 (sst_2 and sst_4). Pleasingly, **5** is among the simplest β-turn mimetics known, comparable in size to the 3-thio-1,2,4-triazole[8] and imidazopyrazine[9] derivatives reported recently by Contour-Galcéra et al. and smaller than the tetrahydro-β-carbolines of Poitout and co-workers,[10] Hiroshi's 4,1-benzoxazepin-2-ones,[11] and Ellman's 1,4,7-thiadiazonane-3,6-dione scaffolds.[12] This discovery is made

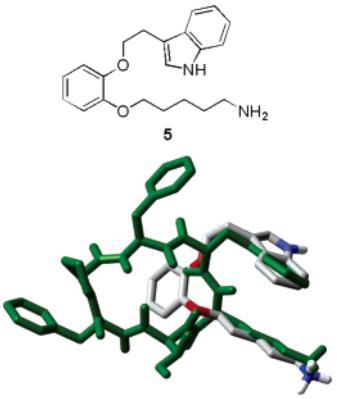

Figure 2. MacroModel overlay of **5** (gray) with the NMR solution structure of L-363,301 (green) in H_2O using the Merck Molecular Force Field 94.

even more impressive by the lack of stereogenic centers as in the previous examples.[8,9]

To assess the viability of the prospective scaffold as a mimetic of the peptide β-turn of SRIF, we initially performed molecular mechanics simulations employing the Merck Molecular Force Field (MMFF94) in aqueous solution and then compared the minimized structures of **5** to the NMR solution structure[13] of the cyclic hexapeptide L-363,301 (**2**). As illustrated in Figure 2, the tryptophan and lysine residues of **2** overlay well with the indol-3-ylethyl and 5-aminopentyl side chains, respectively, of **5**. A two-carbon linker was chosen to ensure chemical stability of the indole side chain (i.e., to prevent a gramine-type fragmentation).[14]

We therefore constructed **5** in four straightforward steps from catechol (see Supporting Information). Biological evaluation revealed that **5** binds the sst_4 receptor with an affinity (K_i) of 2.02 ± 0.38 μM, a value similar to that of our original β-D-glucose-based mimetic (+)-**4** (K_i = 1.65 ± 0.56 μM, sst_4).[15]

To improve the affinity further, three approaches were explored. First, on the basis of evidence that a fluorinated tryptophan surrogate enhances the affinity of SRIF tetradecapeptide analogues,[16] we proposed incorporation of a fluorine atom at the 5-position of the indole ring to furnish **6**. Second, the observation by Crider et al. of the increased hydrophobicity imparted by chloride substituents[17] suggested the design of the 4,5-dichlorocatechol congener **7**. Third, we

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expected that a C-linked benzyl group *ortho* to the Trp-mimicking side chain (**8**) would simulate the affinity-enhancing effect of the Phe[7] side chain of somatostatin (**1**). Indeed, overlaying the minimized structure of **8** with the NMR structure of L-363,301 reveals good congruency of the side chains (Figure 3). We thus surmised that the addition

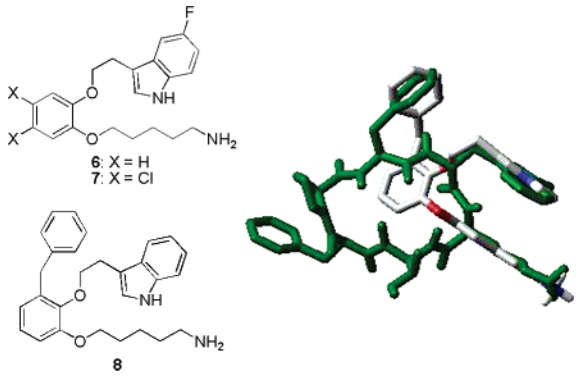
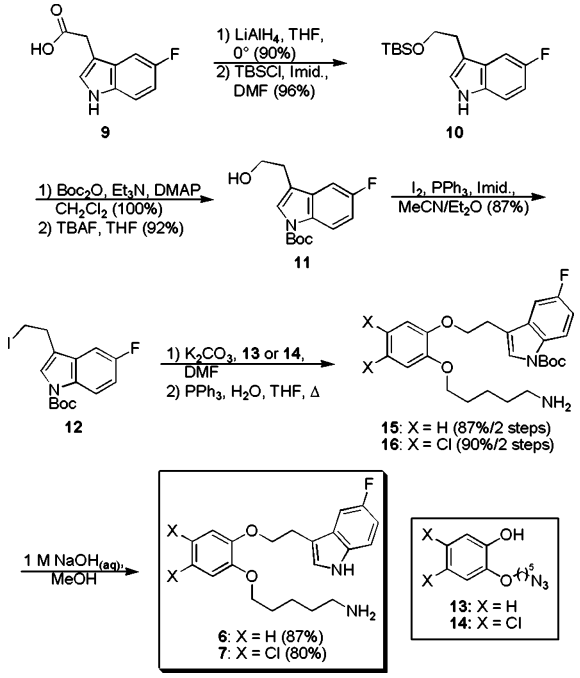


Figure 3. Proposed enhancements to the catechol scaffold. Benzylated catechol **8** (gray) was overlaid in MacroModel with L-363,301 (green) as before.

of a benzyl group to the prospective ligand would not interfere with binding.

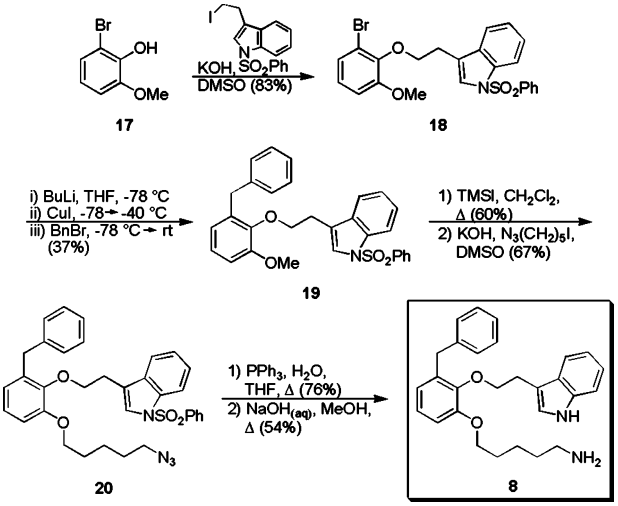
The syntheses of the prospective 5-fluoroindole ligands **6** and **7** and the benzyl congener **8** are outlined in Schemes 1

Scheme 1. Synthesis of **6** and **7**



and 2, respectively. For ligands **6** and **7**, commercially available (5-fluoroindol-3-yl)acetic acid (**9**) was converted

Scheme 2. Synthesis of **8**



to the requisite iodide **12** in 71% overall yield over five steps.[18] Alkylation of phenol **13** or the 4,5-dichloro counterpart **14** followed by Staudinger[19] reduction of the azide and alkaline hydrolytic removal of the *tert*-butyl carbamate furnished **6** and **7**.

To acquire prospective ligand **8**, known bromophenol **17**[20] was alkylated with 2-[1-*N*-(benzenesulfonyl)indol-3-yl]ethyl iodide to furnish **18** in 83% yield. Treatment of the aryl cuprate derived via lithium−halogen exchange and transmetalation of **18** with benzyl bromide led to **19**, albeit in modest yield.[21] Removal of the methyl group employing iodotrimethylsilane in dichloromethane at reflux, followed by alkylation of the phenol with 5-azidopentyl iodide, then furnished **20** in 40% yield for the two steps. Completion of the synthesis of **8** was achieved via Staudinger[19] reduction and alkaline hydrolysis.

Binding data for ligands **5**−**8** at the sst_2 and sst_4 receptors are provided in Table 1. The fluorinated congener **6** binds the sst_2 and sst_4 receptors with an affinity similar to that of the parent catechol ligand **5**. A noticeable affinity increase was observed for 4,5-dichlorocatechol **7** at both receptor subtypes due presumably to the increased hydrophobicity of the scaffold in the hydrophobic receptor environment. Of particular note, the benzylated catechol **8**, while showing no discernible improvement in activity at sst_4, displayed a 9-fold affinity enhancement selectively at the sst_2 receptor.

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Table 1. Biological Activities of the Catechol-Based Ligands Compared with Those of SRIF and β-D-Glucoside (+)-**4**

ligand	K_i, sst_2	K_i, sst_4
SRIF	6.83 ± 1.54 pM	0.462 ± 0.132 nM
(+)-**4**	4.52 μM[15]	1.65 ± 0.56 μM[15]
5	4.69 ± 0.37 μM	2.02 ± 0.38 μM
6	3.12 ± 0.33 μM	2.08 ± 0.28 μM
7	0.749 ± 0.065 μM	0.512 ± 0.120 μM
8	0.505 ± 0.031 μM	1.73 ± 0.11 μM

Thus, incorporation of a Phe[7]-mimicking moiety reinforces our contention that the minimal catechol scaffold can mimic a peptide β-turn. With a molecular weight of 338 for the parent ligand (**5**) and of 429 for **8**, these ligands fall well below the often proposed 500 Da upper limit for the optimal molecular weight for drug candidates,[22] in contrast to the glucoside ligands, which possess molecular weights of 600 Da or more.

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In summary, we have designed, constructed, and evaluated a series of catechol-based ligands, which comprise the simplest known non-peptide mimetics of the $i + 1$ and $i + 2$ positions of the somatostatin β-turn. That the catechol scaffold is sufficiently versatile to permit incorporation of an additional side chain to include the *i* position of the β-turn (**8**), a modification that induces a selective 9-fold affinity enhancement at the sst_2 receptor, is particularly significant. Efforts toward the synthesis of related congeners are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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