

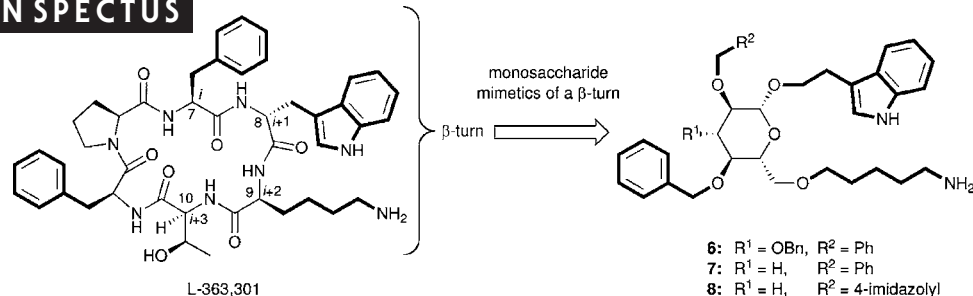
## The $\beta$ -D-Glucose Scaffold as a $\beta$ -Turn Mimetic

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### CON SPECTUS



**A**ctivity and selectivity are typically the first considerations when designing a drug. However, absorption, distribution, metabolism, excretion, and toxicity (ADMET) are equally important considerations. Peptides can provide a combination of potent binding and exquisite selectivity, as evidenced by their pervasive use as enzymes, hormones, and signaling agents within living systems. In particular, peptidic turn motifs are key elements of molecular recognition. They may be found at the exposed surfaces of globular proteins, where they are available for binding interactions with other peptides and small molecules.

However, despite these advantages, peptides often make poor drugs. The amide backbone is subject to rapid enzymatic proteolysis, resulting in short half-lives. Furthermore, the ability of the amide backbone to hydrogen bond with water restricts its ability to cross membranes and, consequentially, results in poor oral bioavailability. Accordingly, the development of nonpeptidic scaffolds that mimic peptidic turn motifs represents a promising means of converting peptidic agents into more drugable molecules. In this Account, we describe the design and synthesis of  $\beta$ -turn mimetics that use a  $\beta$ -D-glucose scaffold, the first use of a sugar scaffold for this purpose.

Somatostatin (SRIF) is a small protein (14 amino acid residues) human hormone; a shorter (6 amino acid residues) synthetic peptide, L-363,301, is a fully peptidic agonist. These two cyclic peptides share the  $\beta$ -turn motif comprising Phe<sup>7</sup>-Trp<sup>8</sup>-Lys<sup>9</sup>-Thr<sup>10</sup> (D-Trp<sup>8</sup> in the case of L-363,301), of which the tryptophan and lysine residues in the  $i + 1$  and  $i + 2$  positions, respectively, are critical for binding. In 1988, we initiated a program that tested and validated the then-novel proposition that the  $\beta$ -D-glucose scaffold can mimic the  $\beta$ -turn in L-363,301. The  $\beta$ -D-glucose scaffold proved to be an attractive mimic of a  $\beta$ -turn in part because it permits the convenient attachment of amino acid side chains via facile etherification reactions, rather than carbon–carbon bond formations; it is also an inexpensive starting material with well-defined stereochemistry. From the beginning, biological assays were used alongside physical measurements to assess the relevance of the design. Our first two synthetic targets, compounds **6** and **7**, bound the SRIF receptors on benchmark (AtT-20) cells, albeit weakly, consistent with the objective of the design. Subsequently, a better ligand (**8**) and two congeners were found to be agonists at the SRIF receptors, providing convincing evidence that the peptide backbone is not required for receptor binding or signal transduction.

The unexpectedly high level of receptor affinity of selected analogs, as well as the fortuitous discovery that our peptidomimetics were active against several chemically distinct receptors, led us to hypothesize that these monosaccharides could access multiple potential binding modes. Our later studies of this sugar scaffold confirmed this property, which we termed pseudosymmetry, whereby multiple similar but nonidentical motifs are displayed within a single analog. We propose the presence of pseudosymmetry to be an element of privilege and an advantage for lead discovery.

## Introduction

Peptides play a fundamental role in biology. However, their use as therapeutics has been limited by their poor pharmacokinetic properties.<sup>1</sup> Peptides are subject to proteolysis, which results in short biological half-lives even after parenteral administration. Furthermore, peptides have low bioavailability because of their poor cellular transport properties. Rapid proteolysis of peptides can be overcome in several ways, including the use of amide surrogates, retro-enantiomeric peptides,<sup>2</sup> or simplified cyclic peptides. Additionally, D-amino acids may be incorporated.<sup>3</sup> Stein noted that the cellular transport of organic compounds correlated inversely with their ability to hydrogen bond with water and concluded that solvation impedes transport because the desolvation process during the extraction of a molecule into a lipid bilayer from an aqueous phase requires energy.<sup>1c</sup> Similarly, Diamond and Wright found that 1,2-cyclohexanediol crosses cell membranes more readily than 1,3-diols, a result attributed to the fact that the former can form an intramolecular hydrogen bond, thus reducing solvation and, in turn, decreasing the energy required for desolvation.<sup>1d</sup> More recently, we reported that  $\beta$ -strands in which the peptide backbone is replaced by a pyrrolinone scaffold show enhanced transport kinetics, presumably because of the reduced energetic cost of desolvation.<sup>4,5</sup>

The poor metabolic stability and transport properties associated with the backbone of potential peptidic therapeutic agents led us to investigate the development of peptidomimetics.<sup>6</sup> The design of peptidomimetics was anticipated by Farmer, who proposed, but did not explore, the then-novel idea of replacing a peptide scaffold with a cyclohexane ring and attaching relevant amino acid side chains to this construct.<sup>7</sup> Subsequently, Bélanger and Dufresne implemented this proposal, describing nonpeptidic mimic **1** (Figure 1) of the enkephalins (see **4** and **5**, Figure 2), which incorporated the bicyclo[2.2.2]-octane scaffold.<sup>8</sup> Later, Olson and collaborators reported peptidomimetic **2** (Figure 1), which was designed to mimic the tripeptide thyroid releasing hormone (TRH).<sup>9</sup> Although **2** did not bind the endocrine receptor for which it was designed, it showed oral activity in animal models of cognitive dysfunction.

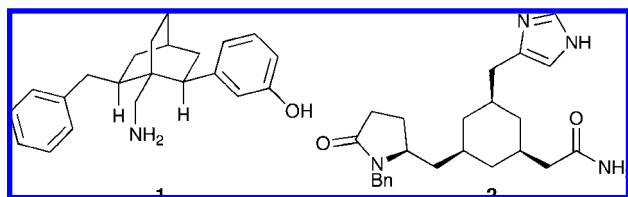


FIGURE 1. Early designed peptidomimetics.

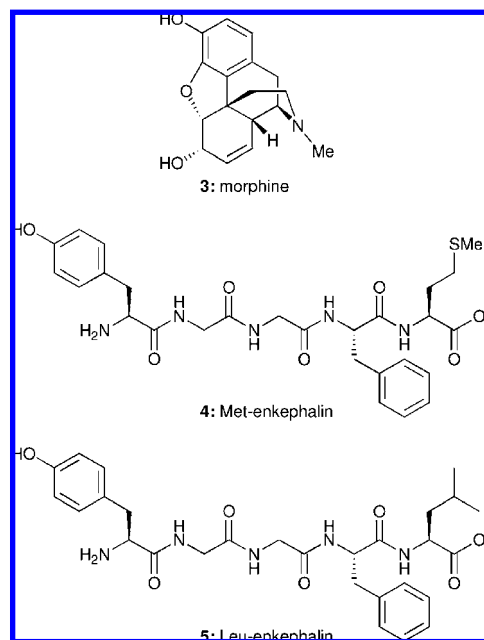
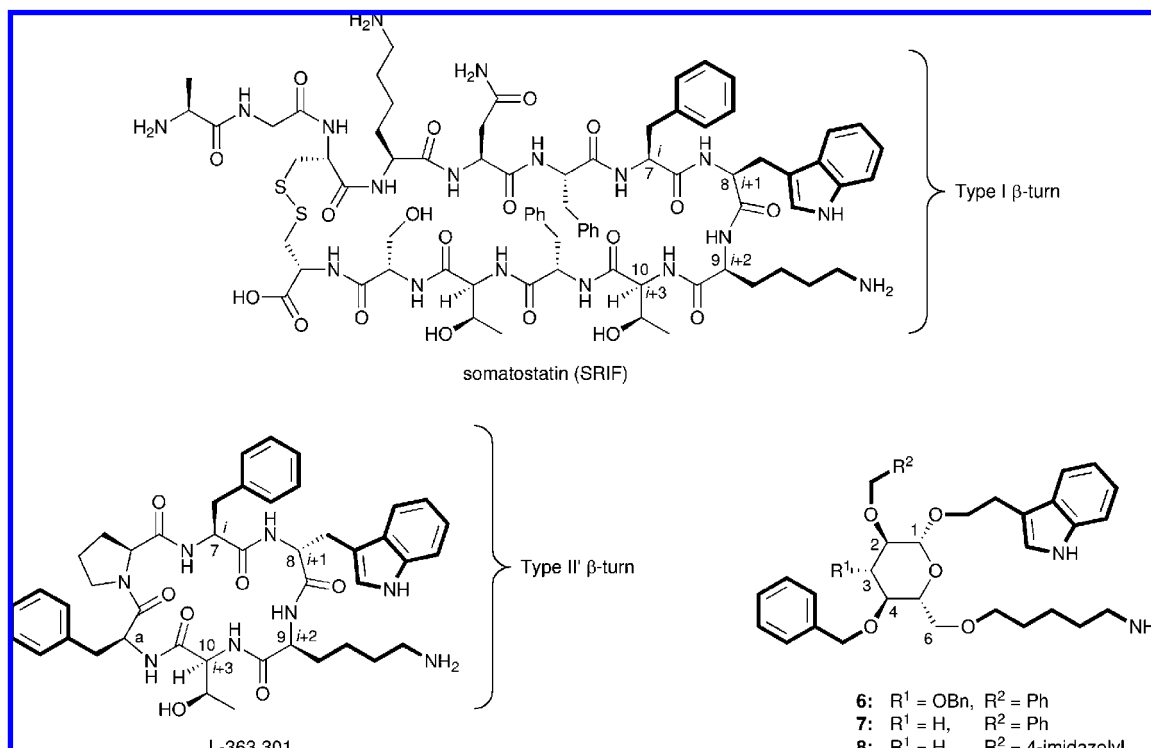


FIGURE 2. Morphine (**3**) and enkephalins (**4**, **5**).

Replacing the amide backbone with a nonpeptidic scaffold devoid of the capacity to hydrogen bond with the receptor can succeed only if the hydrogen bonds between the amide backbone of the peptide ligand and that of the receptor are not required for binding or signal transduction.<sup>10</sup> The enkephalins (**4** and **5**) are the endogenous peptide ligands for the morphine receptor.<sup>11</sup> The activity of the nonpeptidic natural product morphine (**3**, Figure 2) provides compelling evidence that an amide backbone is not always required for binding of peptidic receptor ligands or, indeed, for signal transduction by peptide hormones or neurotransmitters.<sup>7</sup>

In contrast, ligands and inhibitors of proteolytic enzymes often take advantage of critical backbone hydrogen bonds. The importance of these interactions has been well established by X-ray crystallography,<sup>12</sup> emphasizing the functional role of the amide backbone in enzymatic catalysis. For example, backbone hydrogen bonds contribute to the optimal strict alignment of proteolytic enzymes with their substrates and facilitate the efficient catalysis of the resulting reactions. This does not preclude a role for induced fit, and, indeed, Kern et al. demonstrated in NMR studies that rapid motion of one residue of cyclophilin A is required during catalysis.<sup>12</sup> In contrast with proteolytic enzymes, guanine nucleotide-binding protein-coupled receptors (GPCRs) interact with ligands through helical bundles in which hydrogen-bonding opportunities with ligands are largely unavailable.<sup>13</sup>

Our peptidomimetic program, initiated in 1988, employed monosaccharide scaffolds for the attachment of amino acid-mimicking side chains via ether linkages.<sup>14</sup> Supported by



**FIGURE 3.** Somatostatin (SRIF), L-363,301 (a potent agonist), and first-generation monosaccharide peptidomimetics (**6–8**).

extensive biological studies, our research has provided strong support for Farmer's speculations.<sup>7</sup>

### Somatostatin (SRIF)

Somatostatin (somatotropin release inhibiting factor, SRIF, see Figure 3) is a peptide hormone that was isolated, characterized, and synthesized by Guillemin, Rivier, Vale, and co-workers at the Salk Institute.<sup>15</sup> SRIF is a cyclic tetradecapeptide that inhibits the release of several physiologically important substances, including growth hormone, glucagon, insulin, and gastric acid. SRIF is produced and released throughout the central nervous system and in major peripheral organs, such as the stomach and pancreas.<sup>16</sup> Within the nervous system, SRIF acts as a neuromodulator with physiological effects on neuroendocrine, motor, and cognitive functions. At the periphery, SRIF is a modulator of endocrine and exocrine functions and also regulates the differentiation and proliferation of normal and tumor cells.<sup>17</sup>

Somatostatin is present in two forms, SRIF-14 and SRIF-28, which contain 14 and 28 amino acids, respectively.<sup>18</sup> Both are formed by selective cleavage of prosomatostatin, a common precursor, and bind to SRIF receptors that are coupled to heterotrimeric guanine nucleotide-binding proteins. The SRIF receptors thus belong to the GPCR family.<sup>13</sup> Five human SRIF receptor subtypes (hSSTR1–5) have been cloned and expressed, and the localization of specific receptor subtypes

within the body has facilitated the elucidation of their individual functions.<sup>18,19</sup> It is worth noting that the lack of specificity of SRIF for the receptor subtypes does not result in undesirable physiological side effects since SRIF is released in close proximity to the intended receptors and rapidly metabolized.

Since peptides normally exist in solution as an equilibrium mixture of conformers, knowing the bioactive conformation is invaluable when seeking to simplify the hormone or design a peptidomimetic. Building on structure–activity relationships (SARs) established at the Salk Institute,<sup>20</sup> Merck scientists proposed a bioactive conformation of SRIF, which has served as the basis for subsequent research related to this hormone.<sup>21</sup> The fact that D-Trp<sup>8</sup>-SRIF is 10-fold more potent suggested that Trp<sup>8</sup> might occupy the  $i + 1$  position of a  $\beta$ -turn.<sup>20</sup> This hypothesis was based on theoretical calculations by Ramachandran establishing that a D-amino acid in the  $i + 1$  position of a  $\beta$ -turn stabilizes the motif<sup>22</sup> and subsequently validated by Veber and collaborators.<sup>21</sup> This information, together with extensive SARs elucidated at both the Salk Institute<sup>23</sup> and Merck,<sup>24</sup> revealed that the residues required for binding and signal transduction are contained in the tetrapeptide sequence Phe<sup>7</sup>-Trp<sup>8</sup>-Lys<sup>9</sup>-Thr<sup>10</sup> that defines the  $\beta$ -turn motif. Arison, Hirschmann, Veber, and their collaborators recognized that the bioactive conformation, especially in the D-Trp<sup>8</sup> series (possessing a type II'  $\beta$ -turn), places the indole

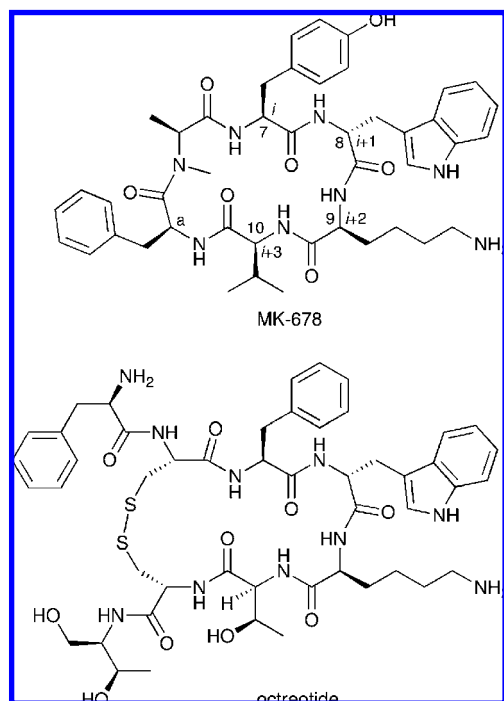


FIGURE 4. MK-678 and octreotide.

side chain of Trp<sup>8</sup> in close proximity to the side chain of Lys<sup>9</sup>.<sup>21,25</sup> Extensive NMR studies in combination with the SAR data led the Merck team to propose that the bioactive conformation of SRIF resembles more closely the solution conformation of the *D*-Trp diastereomer.<sup>25</sup>

### Constrained SRIF Analogs

The importance of SRIF in physiology has suggested a potential therapeutic role for a longer acting analog or peptidomimetic of this hormone.<sup>26</sup> Having established the bioactive conformation of SRIF, the Merck team set out to develop a lower molecular weight peptide in hopes of improving both stability toward proteases and oral bioavailability.<sup>1b</sup> Veber and associates designed and synthesized cyclic hexapeptides, known at the time to be metabolically stable, that incorporated the critical  $\beta$ -turn.<sup>21</sup> Due to limits in molecular modeling capabilities, the choice of the dipeptide Phe-Pro linkage in L-363,301 (Figure 3) was the result of a systematic variation of the dipeptide linker unit. Importantly, the side chains of the critical Phe<sup>7</sup>-*D*-Trp<sup>8</sup>-Lys<sup>9</sup>-Thr<sup>10</sup>  $\beta$ -turn of L-363,301 displayed the same orientation as in *D*-Trp<sup>8</sup>-SRIF. Later, the more potent cyclic hexapeptide MK-678 (Figure 4) was prepared.<sup>27</sup> The Phe<sup>9</sup> residue in both analogs was found to be important and thought to mimic the hydrophobic region defined by amino acids Asn<sup>5</sup> and Thr<sup>12</sup> of SRIF. Clinical evaluation of MK-678 confirmed the hoped-for longer duration of action (>4 h) when administered orally.<sup>1a</sup> However, the oral bioavailability of

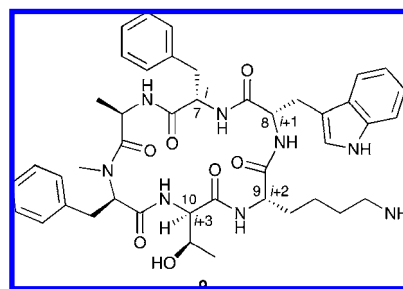


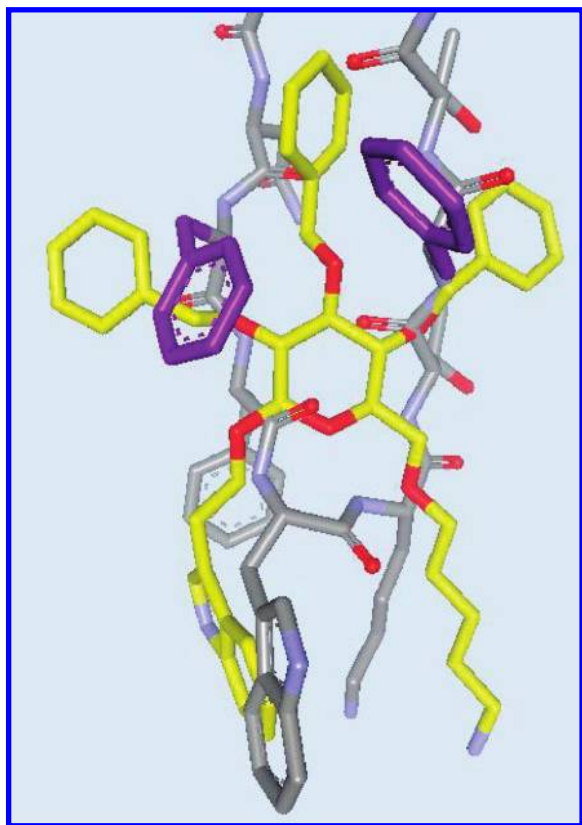
FIGURE 5. Retro-entio cyclic analog of MK-678 (**9**).

MK-678 is only 1–3%. In contrast, Sandoz discovered and successfully developed the SRIF octapeptide analog, octreotide (Figure 4), for cancer chemotherapy and the treatment of acromegaly.<sup>28</sup> Octreotide has to be administered parenterally but provides adequate plasma half-lives.

The observation that even small, metabolically stable peptides such as MK-678 lack adequate oral bioavailability suggested to Hirschmann in the 1980s that the amide backbone may be at least partially responsible for the poor transport properties. Therefore, the search for metabolically stable SRIF receptor ligands with good oral bioavailability continued. The discovery by Freidinger, Veber, and co-workers that a modified retro-entio cyclic analog of MK-678 (**9**, Figure 5) possessed biological activity<sup>29</sup> strengthened the proposition that the amide backbone of the cyclic hexapeptides and SRIF is not necessary for binding or signal transduction. Taken together, these facts suggested to us that the side chains of the  $\beta$ -turn of L-363,301, if attached to an appropriate nonpeptidic scaffold, might bind the SRIF receptors. This proposition resulted in the initiation of a research project for the development of peptidomimetics of SRIF at the University of Pennsylvania.

The main objective of the SRIF peptidomimetic program was the discovery of molecules with improved pharmacokinetic properties.<sup>14a</sup> Using the NMR-based solution conformation of cyclic hexapeptide L-363,301 as a guide, we eventually turned to the use of  $\beta$ -*D*-glucose as a scaffold. The resulting glucoside **6** (Figure 3) appeared to overlay well with L-363,301, with the side chains of **6** at C2, C1, and C6 mimicking the Phe<sup>7</sup>, *D*-Trp<sup>8</sup>, and Lys<sup>9</sup> residues of L-363,301 at the *i*, *i* + 1 and *i* + 2 positions of the  $\beta$ -turn, respectively. Thr<sup>10</sup>, the fourth amino acid of this  $\beta$ -turn, was not believed to be required for binding and, therefore, was not incorporated into the design of **6**. The choice of the sugar scaffold offered several advantages over hydrocarbon scaffolds as suggested by Farmer,<sup>7</sup> such as a well-defined conformation, stereochemical purity of diverse starting materials, and relatively well-precedented etherification reactions compared with carbon–carbon bond-forming reactions.





**FIGURE 6.** Comparison of SRIF-14 and glucoside **6** (yellow carbons). Note the overlap of the two essential side chains (Trp<sup>8</sup> and Lys<sup>9</sup> and their mimics in **6**). Phe<sup>6</sup> and Phe<sup>11</sup> of SRIF-14, which are thought to stabilize its bioactive conformation, are shown in purple.

Gratifyingly, biological evaluation of glucoside **6** against the SRIF receptors on membranes from both the cerebral cortex and the pituitary, as well as receptors on the surface of AtT-20 cells, demonstrated that **6** indeed binds the SRIF receptors. 3-Deoxy analog **7** (Figure 3) also possessed comparable affinity. Importantly, a functional assay performed at the Salk Institute revealed that **6** acted as an SRIF partial agonist.<sup>14b</sup> The success in the design of the peptidomimetic provided crucial experimental evidence that  $\beta$ -D-glucose does indeed represent a  $\beta$ -turn mimetic. The result confirmed our design premises, notably that only three of the four  $\beta$ -turn side chains of SRIF are necessary for binding and hydrogen bonding with the backbone of the receptor is not mandatory for activity. An overlay of glucoside **6** with SRIF-14 is shown in Figure 6.<sup>30</sup>

The expected  $\beta$ -turn mimicry of the design was validated by correlating the effects of side chain modifications on the potency of the glucoside **7** with the changes to binding affinities induced by the corresponding changes to L-363,301 (see Figure 7). As with the cyclic hexapeptides, the relative importance of the Lys<sup>9</sup> mimicking side chain for binding is readily

apparent. An additional pleasing result was the affinity enhancement induced both by the replacement of Phe<sup>7</sup> in L-363,301 with His<sup>7</sup> (i.e., **10**, Figure 8) and the analogous replacement of the C2 benzyl group of **7** by a methylimidazole side chain (i.e., **8**).<sup>14c</sup> Taken together, the SARs of the cyclic hexapeptide and the corresponding pyranoside comprise a proof of concept for a designed mimetic whereby the side chains of Phe<sup>7</sup>-D-Trp<sup>8</sup>-Lys<sup>9</sup> correspond to those attached to the sugar at C2, C1, and C6, respectively. Furthermore, there is substantial evidence suggesting that the benzyl group at C4 mimics Phe<sup>a</sup>.

### Pseudosymmetry: An Element of Privilege

Early on, we made two unexpected observations, which we now understand to have a common chemical origin. First, we discovered that **11** (Figure 9), which lacks a side chain mimicking Trp<sup>8</sup> of SRIF (a residue thought to be an absolute requirement for binding SRIF receptors), has higher affinity than **7** for SRIF receptors on AtT-20 cells.<sup>14b,31</sup> At the time, we explained this result by proposing an “alternative binding mode” involving a reorientation of **11** to give **11'**, which places the C4 benzyl group in a position so as to mimic the spatial relationship between the Trp<sup>8</sup> and Lys<sup>9</sup> side chains of SRIF and D-Trp<sup>8</sup>-SRIF.

More recently, we have recognized that this alternative binding mode of **11** (i.e., **11'**) places the C4-benzyl group into the tryptophan binding pocket (see Figure 9), a manifestation of what we have termed the *pseudosymmetry* of the glucose scaffold.<sup>32</sup> We were able to confirm this rationalization experimentally by preparing the C3-O-methylimidazole congener (structure not shown), which we were pleased to find possessed increased affinity for the SRIF receptor.<sup>31</sup> Failure of the 4-des-benzyl analog of **11** to bind the SRIF receptor is also consistent with the alternate binding mode hypothesis.<sup>14c,d</sup>

Equally unexpected was the discovery that **6** also binds the human neurokinin 1 (hNK1) receptor of substance P (SP) as an antagonist and with a higher affinity (IC<sub>50</sub> 150 nM) than for the SRIF receptors.<sup>14a</sup> This was surprising since the peptides SRIF and SP are chemically unrelated and do not bind each other's receptors. Although hNK1 and hSST1–5 are both GPCRs, they share little sequence homology in the ligand binding domain.<sup>33</sup> Nonetheless, there are likely to be similarities between GPCRs, as evidenced by the existence of “privileged” structures and the proposed common small molecule binding domain of GPCRs.<sup>34</sup> We have recently proposed that evolutionarily conserved ligand binding sites provide regions that accommodate the projections of side chains from the exposed surface of  $\beta$ - and  $\gamma$ -turns and their components or

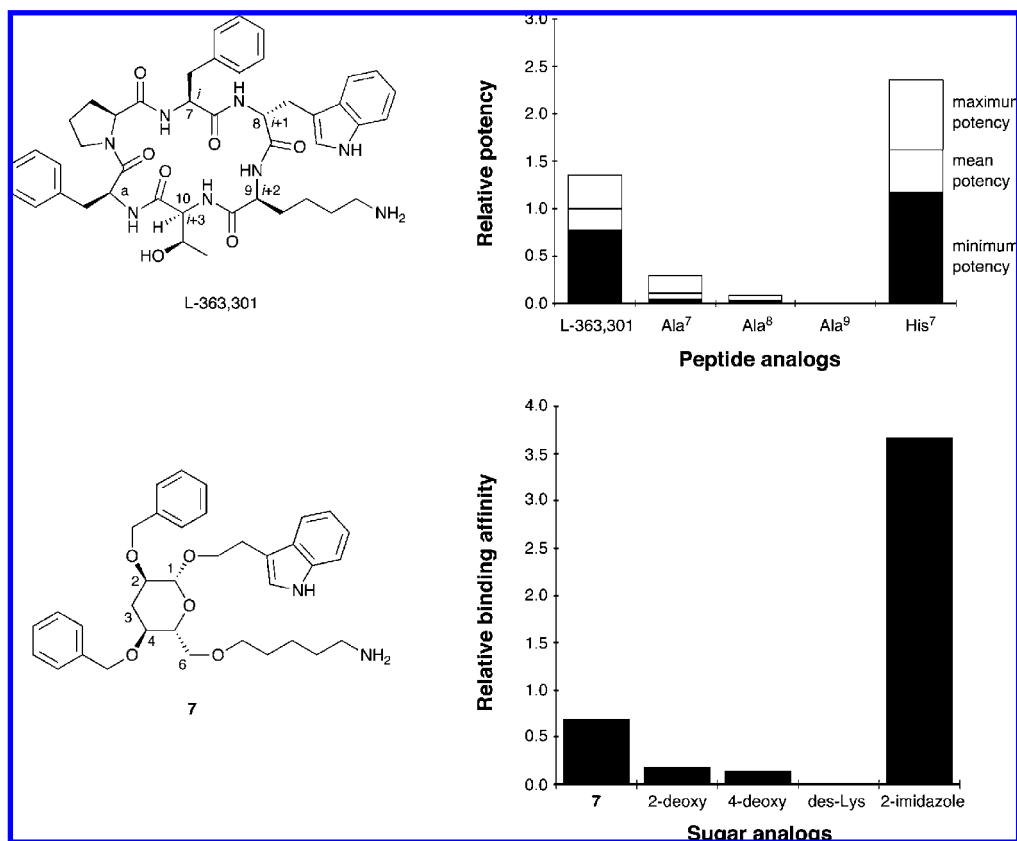


FIGURE 7. Comparison of the SAR profiles of peptide analogs and  $\beta$ -D-glucose-based peptidomimetics.

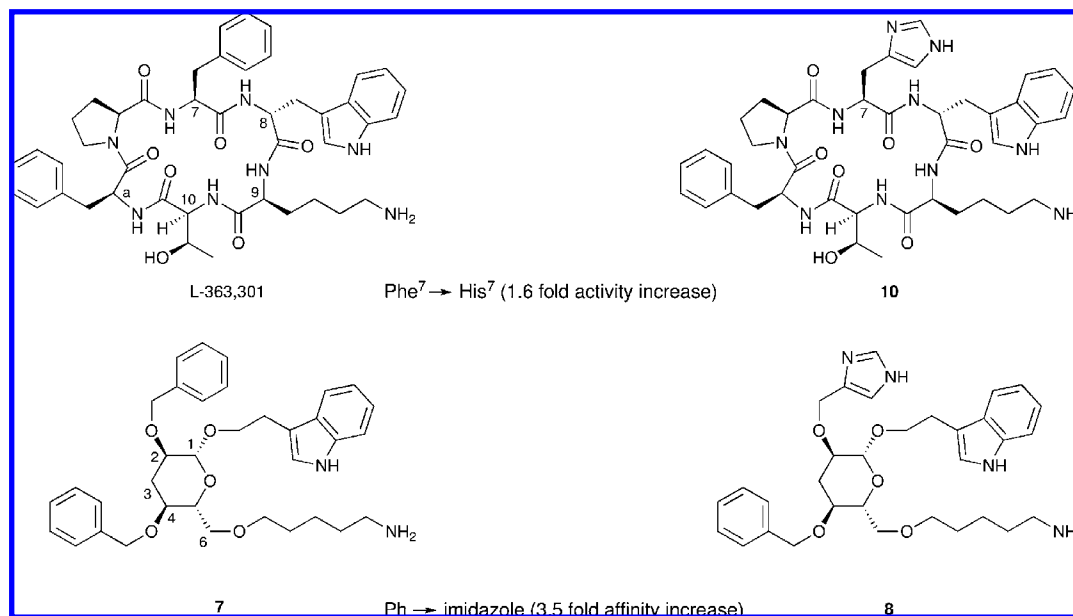
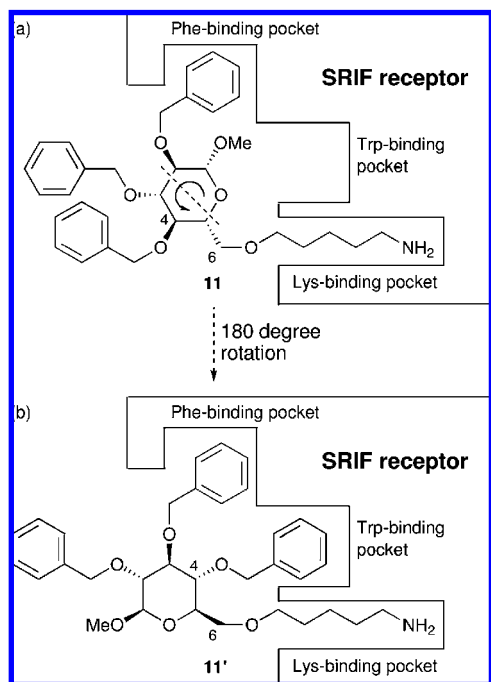


FIGURE 8. Incorporation of a methylimidazole group and the resulting enhancement in activity and affinity.

mimics, and helices may be similarly available for binding interactions.<sup>32</sup> We further suggested that the ability of GPCRs to recognize privileged ligand scaffolds makes them complementary to privileged platforms. We initially interpreted the ability of **6** to bind the hNK1 receptor to reflect only such similarities between the SRIF and hNK1 receptors. Additionally, we

now propose that the ability of **6** to bind the SRIF, SP, and  $\beta_2$ -adrenergic receptors<sup>14c</sup> reflects not only a similarity among the three corresponding GPCRs, but also the high degree of pseudosymmetry in the sugar scaffold.

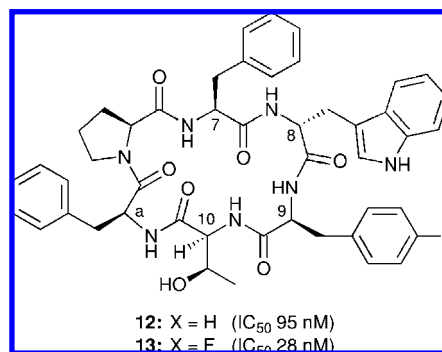
The term “privileged structure” was introduced by Evans et al. to describe the fact that the benzodiazepine scaffold can be



**FIGURE 9.** Desindole compound **11** shown (a) in a binding mode that is unable to present an aromatic, tryptophan-mimicking side chain to the receptor and (b) in an alternative binding mode (**11'**).

made to bind diverse receptors, especially (but by no means exclusively) GPCRs, by modulating the precise structure of the scaffold and substituents.<sup>35</sup> We use the word “polyvalent” (an extension of bivalent/divalent)<sup>36</sup> to describe compounds that bind more than one receptor or enzyme. Other structures such as the steroid scaffold, cyclic hexapeptides, and diketopiperazines<sup>37</sup> have long been recognized as being privileged; other structures have recently been added to the list.<sup>38</sup> The benzopyran core was identified by Murcko, who used shape description methods to identify molecular frameworks that are common among commercially available drugs,<sup>39</sup> and Nicolaou and collaborators later described natural product-like combinatorial libraries incorporating benzopyrans.<sup>40</sup> To our knowledge, there has been no report of a unifying chemical basis common to all of these scaffolds. We believe, however, that it may be possible to identify structural elements that confer polyvalency if one or more are present in a scaffold.

Believing that the ability of glucosides **6** and **7** to bind both the SRIF and hNK1 receptors reflects a hitherto unrecognized similarity between these receptors, we sought to convert the cyclic hexapeptide L-363,301, which binds only SRIF receptors, into a selective ligand for the hNK1 receptor. This was readily accomplished by replacing Lys<sup>9</sup> with Phe<sup>9</sup> (**12**, Figure 10) or *p*-F-Phe<sup>9</sup> (**13**).<sup>14d</sup> These results, though pleasing, raised new questions. Why does glucoside **6** bind both receptors, whereas an amino acid substitution is required in the  $i + 2$



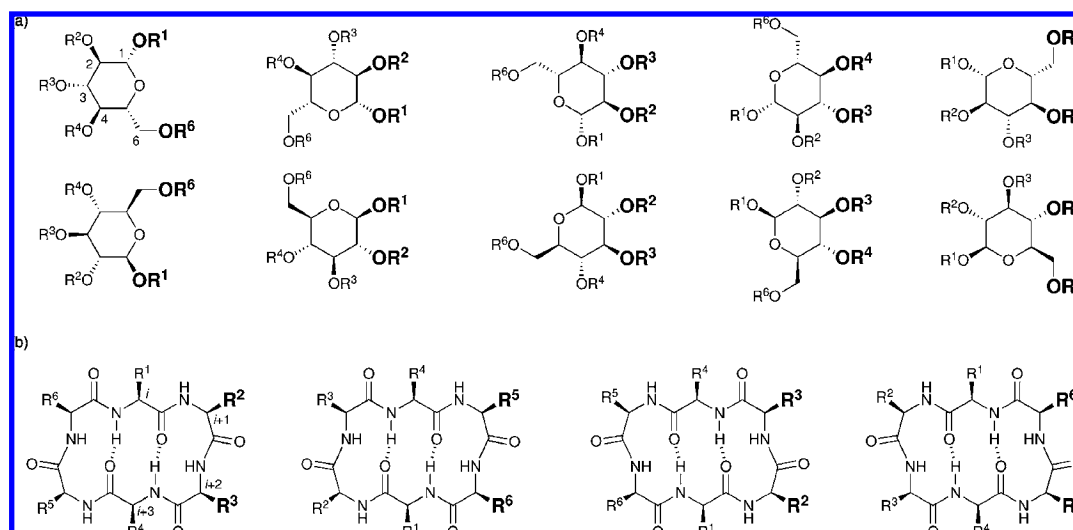
**FIGURE 10.** L-363,301-based hNK1 receptor ligands that do not bind to SRIF receptors.

position of L-363,301 (Lys<sup>9</sup> → Phe<sup>9</sup>) to generate a ligand for the hNK1 receptor? Moreover, why were we unable to use the discovery that **13** is a more potent peptidal hNK1 receptor antagonist than **12** to design a superior glucoside?

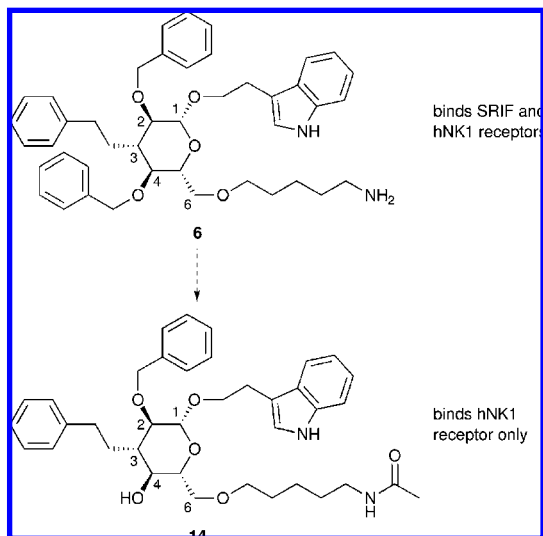
We attribute this difference between the peptides and the glucosides to the fact that the sugar scaffold, but not constrained cyclic hexapeptides such as L-363,301, presents a multitude of binding modes (i.e., high *pseudosymmetry*), as shown in Figure 11.<sup>32</sup> It is important to note that the cyclic hexapeptides L-363,301, **12**, and **13** all bind their respective receptors through the same key interactions, namely those of the  $i + 1$  and  $i + 2$  residues of their  $\beta$ -turns. In contrast, glucoside **6** binds the SRIF receptors via the C1 and C6 side chains but binds the hNK1 receptor via the C2 and C1 side chains.

The existence of multiple binding modes (i.e., *pseudosymmetry*) within the glucoside scaffold arises from the presence of nearest neighbor diols, which present appended functionality in a  $\beta$ -turn-like orientation in a similar, but nonidentical, manner. This property of glucoside **6** explains its ability to bind the SRIF and NK1 receptors via different side chains. Thus, the *pseudosymmetry* of a monosaccharide scaffold allows a single functionalized sugar to present a multitude of  $\beta$ -turn mimicking side chains to a receptor, enhancing the probability of finding a favorable interaction. *Therefore, for a compound library generated for lead discovery in diverse screens, incorporation of highly pseudosymmetric scaffolds that display several functionalities in a  $\beta$ -turn-like manner should increase the likelihood of obtaining one or more leads.*

Combinatorial chemistry/parallel synthesis, high-throughput screening, and database mining<sup>41</sup> have emerged as the principal underpinnings for the discovery of new leads.<sup>38</sup> A scaffold exhibiting multiple potential binding motifs should confer an enhanced opportunity to bind one or more receptors. We see such polyvalency as an advantage, not a liability, because we have demonstrated the ability to subsequently



**FIGURE 11.** The advantage of pseudosymmetry in lead discovery. Shown are (a) the ten possible ways one pyranoside can present  $i + 1$  and  $i + 2$  mimicking motifs (marked in bold) to a GPCR and (b) the four possible ways one cyclic hexapeptide can display the  $i + 1$  and  $i + 2$  residues of a  $\beta$ -turn.



**FIGURE 12.** Development of a receptor-specific peptidomimetic (**14**).

incorporate specificities into **6**. For example, **14** (Figure 12), lacking a C4-benzyl substituent, binds the hNK1 receptor ( $IC_{50}$  22 nM) but *does not bind* the SRIF receptors.<sup>14d</sup> Conversely, the C3 benzyl substituent is important for hNK1 receptor binding but not SRIF receptor binding, and incorporation of a methyl imidazole at C2 enhances SRIF affinity while eliminating hNK1 receptor binding.

## Summary and Prospects

In 1990, we reported the design and synthesis of glucose derivative **6**, a ligand that binds SRIF receptors, albeit weakly. It represented the first use of a sugar scaffold to mimic a  $\beta$ -turn. We found glucosides, like cyclic hexapeptides, to be a privileged class. Furthermore, we demonstrate herein that two

surprising biological results, namely, the unexpected finding that a glucoside lacking a tryptophan-mimicking side chain (**11**) is a better ligand than **6** for hSSTR4 and the serendipitous discovery that **6** also binds the hNK1 receptor, have a common chemical basis. These results are explained by pseudosymmetry, which is present to a larger extent in suitably substituted glucosides than in cyclic hexapeptides. This element of privilege allows a single functionalized sugar to offer many different combinations of  $\beta$ -turn mimicking side chains to a given receptor and appears to be a significant advantage for lead discovery.

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## BIOGRAPHICAL INFORMATION

**Ralph F. Hirschmann** was born in Bavaria, Germany, and came to the U.S. in his teens. He graduated from Oberlin College and then served in the U.S. Army in the Pacific Theater during World War II. He resumed his education at the University of Wisconsin, Madison, where he was the Sterling Winthrop Fellow. He completed his Ph.D. studies in 1950 under the guidance of W. S. Johnson and joined Merck & Co., Inc. In 1987, at age 65, he retired from Merck, where he was Senior Vice President for Basic Research, and joined the faculty at the University of Pennsylvania as the Makineni Professor. At Merck, his team discovered



Mevacor, Vasotec, Prinivil, Primaxin, Proscar, and Ivermectin. In 1969, Robert G. Denkewalter, Hirschmann, and their collaborators reported the first total synthesis of an enzyme in solution.

**K. C. Nicolaou** was born in Cyprus in 1946. He studied chemistry at the University of London (B.Sc., 1969, Bedford College; Ph.D., 1972, University College, Professors F. Sondheimer and P. J. Garratt). After postdoctoral appointments at Columbia University (1972–1973, Professor T. J. Katz) and Harvard University (1973–1976, Professor E. J. Corey), he joined the faculty at the University of Pennsylvania, where he became the Rhodes-Thompson Professor of Chemistry. In 1989, he accepted joint appointments at the University of California, San Diego, where he is Distinguished Professor of Chemistry, and The Scripps Research Institute, where he is Chairman of the Department of Chemistry and holds the Skaggs Professorship of Chemical Biology and the Darlene Shiley Chair in Chemistry. His dedication to chemical education is reflected in his training of hundreds of graduate students and postdoctoral fellows.

**Angie R. Angeles** was born in the Philippines in 1975. She received her B.S. degree (with distinction) in biochemistry/chemistry from the University of California, San Diego in 1999, where she conducted research as a Howard Hughes fellow under the direction of Professor Charles L. Perrin. After stints at Memorial Sloan-Kettering Cancer Center (Avon Foundation fellow, Professor Jon Thorson) and The Scripps Research Institute (Professor Jeffrey W. Kelly), she pursued graduate studies at the University of Pennsylvania, where she obtained her Ph.D. degree in organic chemistry in 2005 under the mentorship of Professors Ralph F. Hirschmann and Amos B. Smith, III. After a NIH postdoctoral fellowship with Professor Samuel J. Danishefsky at Memorial Sloan-Kettering Cancer Center, she joined Schering-Plough in Cambridge, MA, where she is a Senior Scientist.

**Jason S. Chen** was born in Taipei, Taiwan, in 1979. He received his A.B. and A.M. degrees in 2001 from Harvard University, where he performed research under the supervision of Professor Matthew D. Shair. He then joined Enanta Pharmaceuticals (Watertown, MA) as a medicinal chemist studying novel cyclosporine A analogs. He joined Professor K. C. Nicolaou's group at The Scripps Research Institute in 2003, where he was a National Defense Science and Engineering Graduate (NDSEG) Fellow. In 2008, he completed his Ph.D. studies on the total synthesis and biological evaluation of unciamycin. He is currently a research associate in Professor Nicolaou's laboratory.

**Amos B. Smith, III** was born in Lewisburg, PA, in 1944 and completed Bucknell University's inaugural B.S.–M.S. degree in chemistry in 1966 with Professor H. W. Heine. After a year of medical school at the University of Pennsylvania, he entered The Rockefeller University, completing his Ph.D. degree in 1972 and spending a year as a Research Associate, both with Professor W. C. Agosta. He then joined the University of Pennsylvania, where he is currently the Rhodes-Thompson Professor of Chemistry and a Full Member of the Monell Chemical Senses Center. From 1988 to 1996, he served as Chair of the Department of Chemistry. In addition, he holds Honorary Memberships in the

Kitasato Institute and the Pharmaceutical Society of Japan, and serves as the inaugural Editor-in-Chief of Organic Letters. In 2009, he was awarded a D.Sc. (*honoris causa*) from Queens University Belfast (Northern Ireland) for his contributions to Organic Chemistry.

#### FOOTNOTES

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