Somatostatin sst_4 Ligands: Chemistry and Pharmacology

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Abstract: Several classes of compounds (thioureas, ureas, β-glucosides, sulfonamides, and cyclic peptides) show enhanced binding affinity and selectivity at somatostatin subtype 4 receptors (sst_4). Pharmacophore models have recently been proposed to explain receptor subtype selectivity. The chemistry and therapeutic potential of sst_4 ligands will be the subject of this review.

INTRODUCTION

Brazeau *et al*. [1] first isolated somatostatin [somatotropin release-inhibiting factor, SRIF] from ovine hypothalamic extracts. SRIF occurs as a tetradecapeptide (SRIF-14, **1,** Fig. **1**) and a *N*-terminally extended form (SRIF-28). Both biologically active forms are derived from presomatostatin and contain a single internal disulfide bond which links cysteine residues at the 3 and 14 positions of the polypeptide chain. These two forms of SRIF exhibit similar biological activities with potency differences depending on the tissue [2]. SRIF exhibits its pharmacological effects by binding to a family of structurally-related receptors that belong to the G-protein-coupled receptor superfamily. Five receptor subtypes (ssts) have been cloned and characterized and these are designated sst_1-sst_5. The five subtypes have been grouped into two major families on the basis of structural and functional characteristics. The $SRIF_1$ family is comprised of the sst_2, sst_3, and sst_5 subtypes, whereas the sst_1 and sst_4 subtypes constitute the $SRIF_2$ family [3]. The physiological effects of SRIF are mainly inhibitory. SRIF is known to inhibit a variety of secretions including prolactin and growth hormone (GH) from the pituitary, thyroid stimulating hormone (TSH) from the thyroid gland, glucagon, insulin, and pancreatic polypeptide (PP) from the pancreas, and most of the hormones found in the gastrointestinal tract [4]. Additionally, SRIF exhibits antiproliferative effects and modulates cognitive and motor activity in the central nervous system (CNS) [5].

SRIF receptors are widely distributed including the CNS, periphery, and in various tumors; however, specific physiological functions have only been clearly identified with sst_2 and sst_5 [6]. Subtypes 2 and 5 have been linked to the release of growth hormone (GH) and prolactin [7], and insulin release from the pancreas has been associated with sst_5 [8]. Linking sst_4 to specific physiological conditions has been slow to develop. Nevertheless, several recent studies have suggested a role for sst_4 receptors in neurogenic pain, inflammation, and neuropsychiatric disorders [9,10].

Various SRIF-related peptides have also been found, which lend further understanding of SRIF structure-activity relationships (SAR) and potential development of novel pharmaceutical treatments. Cortistatin (CST-17, **2,** Fig. **1**) is one such peptide. CST is named due to its predominate cortical expression. CST has also been found in peripheral tissues including kidney, pancreas, stomach, and in the immune system [11,12]. This neuropeptide was first cloned from rat tissue and subsequently was cloned from mouse and human tissue [12]. CST is derived from a prohormone, preprocortistatin, which is structurally quite similar to preprosomatostatin, and shares relevant functional properties with SRIF. The human form of preprocortistatin has 114 amino acid residues and is processed to yield CST-17 and CST-29. The two forms of CST are analogous to the two biological forms of SRIF, SRIF-14 and SRIF-28. Although CST binds to all five ssts, many of its physiological effects are distinctly different from SRIF. These include induction of slow-wave sleep, activation of cation currents that are not affected by SRIF, and a reduction in locomotor activity. Unlike SRIF, CST is distributed in human immune cells leading to the speculation that it could be an endogenous regulatory factor in the human immune system [13]. Although specific receptors for CST have not been identified, CST binds to an orphan receptor, MrgX2. The MrgX2 receptor is a member of the Mrg (Mas-related genes) family that consists of more than 50 G-protein-coupled receptors and is recognized by ligands of diverse chemical structures [14]. This suggests the possibility that CST may bind to specific receptors that are presently undiscovered [15].

CHEMISTRY

Peptide Ligands at sst_4

Poor oral bioavailability and rapid degradation by peptidases severely limit the therapeutic utility of SRIF. As a result, the development of stable peptidomimetics of SRIF has been the focus of considerable research [6]. SAR studies have shown that the core residues, Trp^8-Lys^9, of SRIF are essential for receptor activation and pharmacological activity [4]. Numerous truncated peptidomimetics of SRIF have been discovered with high binding affinity at sst_4 [5]. Rivier *et al*. [16] performed a N^{β}-methylated aminoglycine (Agl) scan of the octapeptide H-c[Cys^3-Phe^6-Phe^7-D-Trp^8-Lys^9-Thr^{10}-Phe^{11}-Cys^{14}]-OH (ODT-8, SRIF numbering). The ODT-8 analogue H-c[D-Cys-Phe-L-Agl (*N*-Me, benzoyl)-D-Trp-Lys-Thr-Phe-Cys]-OH exhibited an IC_{50} = 3.4 nM at sst_4 with >50-fold selectivity at other ssts. The analogue was shown to be an agonist when evaluated for inhibition of forskolin-

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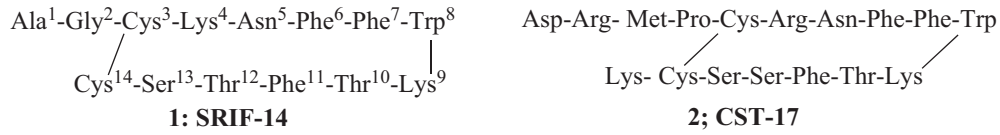


1: SRIF-14 **2; CST-17**

Fig. (1). Structures of SRIF-14 and CST-17.

induced cAMP in CCL 39 cells. Further SAR studies by this group [17] involved introduction of β-methyl-3-(2-naphthyl) alanine (β-Me2Nal) at the 8-position of H-c[Cys^3-Phe^6-Phe^7-D-Trp^8-Lys^9-Thr^{10}-Phe^{11}-Cys^{14}]-OH. Introduction of L-*threo*-β-Me2Nal at position 8 and substitution of Tyr^7 for Phe^7 resulted in an agonist with over 100-fold selectivity at sst$_4$ compared to other ssts. Additional modifications of these analogues in which a Tyr^2 in combination with L-Trp^8 led to H-Tyr-c[Cys^3-Phe^6-Ala^7-Trp^8-Lys^9-Thr^{10}-Phe^{11}-Cys^{14}]-OH, which exhibited an IC$_{50}$ = ~2 nM at sst$_4$ with over 250 selectivity versus other ssts [18]. Similar substitutions (Tyr^2 and Trp^8) with an L-*threo*-β-MeTrp at position 8 resulted in a loss of sst$_4$ selectivity. Interestingly, substitution of Ala^7 for Phe^7 resulted in analogues with high affinity for sst$_4$ indicating that Phe^7 does not play a major role in sst$_4$ binding. Grace *et al*. [19] determined the three-dimensional NMR conformations of a series of octapeptides having the general structure H-c[Cys^3-Phe^6-Xxx^7-Yyy^8-Lys^9-Thr^{10}-Zzz^{11}-Cys^{14}]-OH. The results of this study showed that these octapeptides do not have the typical β-turn that had been previously described for sst$_2$ analogues [20]. The proposed pharmacophore for sst$_2$/sst$_5$-selective analogues indicates that Phe^7, D-Trp^8, and Lys^9 are the key residues for receptor recognition. In this model, the D-Trp^8 and Lys^9 are only about 4 Å apart; however, the Phe^7 residue was a greater distance from D-Trp^8 (7-9 Å) and Lys^9 (9-11 Å). In contrast, the pharmacophore model developed by Grace *et al*. [19] for sst$_4$-selective analogues places Phe^6 or Phe^{11} much closer to Trp^8 (5.5-9.5 Å) and Lys^9 (4.5-6.5 Å). These results suggest that the backbone conformation is not important for receptor recognition, rather the backbone serves to position the side chains (aromatic ring at position 6, indole nucleus at position 8, and the aminoalkyl group at position 9) in the correct spatial arrangement. Hirshmann's group [21] prepared two derivatives of D-Trp-SRIF-14 in which Phe^6 and Phe^{11} were replaced by pyrazinylalanine. Their earlier work had demonstrated that Phe^6 and Phe^{11} interacted with each other to stabilize the bioactive conformation of SRIF [22]. NMR and binding studies showed that Phe^{11} stabilized the bioactive conformation of D-Trp-SRIF-14 by π-bonding and aromatic-aromatic interactions. Although their earlier study had shown that neither Phe^6 or Phe^{11} interacted with the ssts, this study demonstrated that Phe^6 was important for receptor binding. These conclusions were supported by an alanine scan study on SRIF-14 carried out by Lewis *et al*. [23]. These workers [23] again demonstrated that the Trp^8-Lys^9 core was essential for binding at ssts. Furthermore, their work showed that Phe^6, Phe^7, and Phe^{11} were important for high affinity binding at sst$_2$, sst$_3$, and sst$_5$; however, only Phe^6 was important for sst$_4$ receptor activation.

Grace *et al*. [24] recently reported the 3D NMR structures of six octapeptide agonists analogues of SRIF. These derivatives had the general structure of H-D-Phe/Phe^2-c[Cys^3-Xxx^7-D-Trp^8-Lys^9-Thr^{10}-Cys^{14}]-Thr-NH$_2$ (Xxx = Ala or 4-NH$_2$Phe). The results of this study showed that these peptidomimetics have a similar type II β-turn that is found in sst$_2$/sst$_3$/sst$_5$ selective derivatives; however, the proposed pharmacophore developed in this investigation lacks the Phe^7 residue found in sst$_2$/sst$_3$/sst$_5$ ligands. This model suggests that the core residues Trp^8, Lys^9 and D-Phe^2 impart sst$_2$ selectivity. Interestingly, in this model the D-Phe^2 residue is outside the cyclic moiety. The main difference in the proposed sst$_2$ model and the previously reported sst$_4$ model [20] is that the Phe^6/Phe^{11} residue is closer to the Trp^8-Lys^9 fragment in the sst$_4$ model. Furthermore, this model [24] differs from the previously proposed model [20] for sst$_2$/sst$_3$/sst$_5$ analogues in that Phe^7 is not required for receptor activation. Nevertheless, it is important to point out that solution structures determined by NMR may not accurately depict the bioactive conformation of the peptides at ssts.

Gademann *et al*. [25] synthesized linear β-peptides that exhibited high affinity and selectivity for sst$_4$. The β-tetrapeptide (Ac-β^3-HThr-β^2-HLys-β^3-HTrp-β^3-HPhe-NH$_2$) exhibited a K$_D$ of 83 nM and at least 2-fold selectivity over other ssts. When the Lys residue was shifted by one carbon unit (β-position, Ac-β^3-HThr-β^3-HLys-β^3-HTrp-β^3-HPhe-NH$_2$), affinity at sst$_4$ was decreased by 1000-fold.

Nonpeptide Ligands at sst$_4$

Since the therapeutic effectiveness of SRIF is limited by poor oral bioavailability and rapid degradation by peptidases, the discovery of metabolically stable, orally effective nonpeptide SRIF analogues has been the focus of numerous research groups [5]. Ankersen *et al*. [26] were the first to report a nonpeptide having high affinity and selectivity at cloned human sst$_4$ receptors. The thiourea (**3,** NNC 26-9100, Fig. **2**) exhibited a K$_i$ value of 6 nM at sst$_4$ receptors with over 100-fold selectivity versus other ssts. Replacement of the thiourea group in compound **3** with an urea moiety (**4,** Fig. **2**) resulted in an analogue with essentially the same sst$_4$ binding affinity (14 nM), but with greater selectivity (300-fold). Compounds **3** and **4** were shown to be full agonists (EC$_{50}$ values of 26 nM and 24 nM, respectively) in an assay to measure inhibition of forskolin-induced cAMP accumulation [27]. Movement of the 3,4-dichlorobenzyl group to the *N*-1 position of the thiourea group (compound **5**, Fig. **2**) led to a dramatic decrease in sst$_4$ binding affinity and selectivity. Replacement of the 2-(aminoalkylamino)pyridine moiety in compound **5** with an 2-(1*H*-indol-3-yl)ethyl group resulted in an analogue (compound **6,** Fig. **2**) with high affinity for sst$_4$ and about 100-fold selectivity compared to sst$_2$ [28].

We originally postulated that in NNC 26-9100 the pyridine ring, the 3,4-dichlorobenzyl group, and the side chain imidazoyl moiety serve as side-chain surrogates for Trp^8, Phe^7, and Lys^9 in SRIF [26]. This hypothesis appears to be

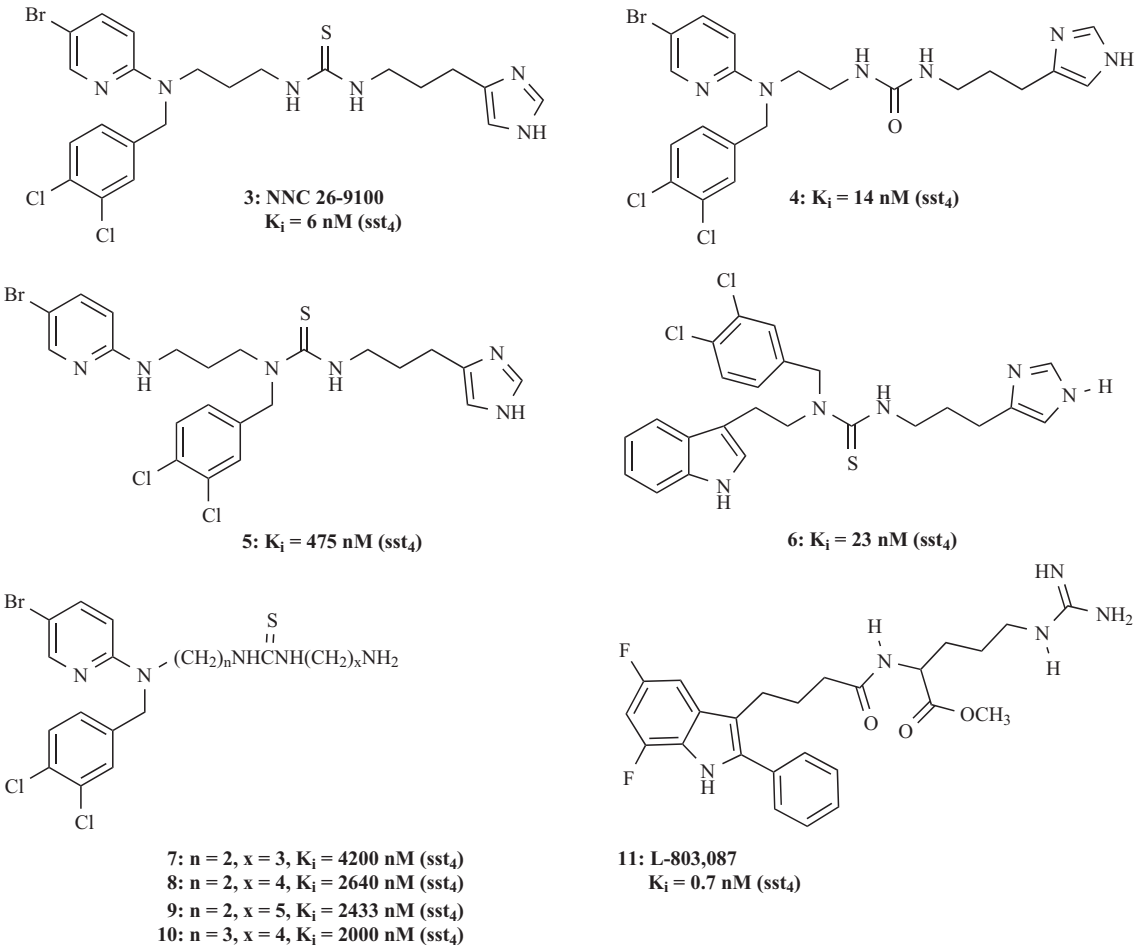


Fig. (2). Structures of Nonpeptides (**3-11**).

incorrect given the conformation studies of Hirschmann [21], Lewis *et al*. [23], and the recently proposed sst$_4$ pharmacophore model of Grace *et al*. [19]. Another perplexing issue is that thioureas containing an imidazoyl side chain (Lys^9-mimetic of SRIF) have a much greater affinity at sst$_4$ compared to aminoalkyl analogues (compounds **7-10**, Fig. **2**). The Lys^9 residue in SRIF is thought to electrostatically interact with a key Asp residue on transmembrane III in ssts [29]. Thioureas bearing an 3-(imidazol-4-yl)propyl group have dramatically reduced basicity in comparison with the ε-NH_2 group of Lys^9 of SRIF (pKa values of the side chain imidazole is about 7, whereas the ε-NH_2 group of Lys is about 10.5). Although much less basic than the aminoalkyl group, the planar imidazole ring may be able to fit more specifically in the sst$_4$ binding pocket in these thiourea derivatives compared with the aminoalkyl group in compounds **7-10**. A recent report by Isaacs *et al*. [30] on thrombin inhibitors showed that weakly basic imidazoles can function as surrogates for more basic alkylamines. In these derivatives, proper orientation of the imidazole ring in the thrombin receptor binding pocket more than offsets the weaker basicity of this nucleus compared to aminoalkyl derivatives. Previously, we speculated that the pyridine ring in compound **3** was acting as the Trp^8 mimic in SRIF [27]. Hirschmann [31,32] used electrostatic potential calculations to demonstrate that benzene, but not pyridine, could replace the indole ring in a series of glycoside-derived SRIF peptidomimetics. They concluded that Trp^8 of SRIF binds in an aromatic cavity at ssts, and this cavity requires a π-electron rich system. Electron-rich π-clouds are found in benzene and indole, but not in pyridine. The indole analogue (**11**, L-803,087, Fig. **2**), which was discovered by researchers at Merck, demonstrated high binding affinity and selectivity at sst$_4$. Modeling studies on compound **11** indicated that the 2-phenyl group and the 3-(4-butanoyl) side chain of the indole nucleus constituted the Trp^8 mimetic [33]. In compound **3**, it seems reasonable to speculate that the 3,4-dichlorobenzyl group may be mimicking the Phe^6 or Phe^{11} residues of SRIF. We are presently reevaluating our earlier hypothesis on which groups in **3** mimic the core Trp^8, Lys^9, and Phe$^{6/11}$ residues in SRIF.

The use of a β-D-glucose scaffold to attach side chain mimetics contained in SRIF has been the focus of extensive research [34]. Side chain groups located at positions 1 and 6 of the β-D-glucose nucleus of SRIF were shown to provide good overlap with the Trp^8 and Lys^9 residues of SRIF [31,32]. Compound **12** (Fig. **3**) contained the Phe, Trp, and Lys-mimetic groups in a similar spatial arrangement as found in the peptidomimetic octreotide. This compound, however, showed only weak binding affinity in AtT-20 cells [35]. Re-

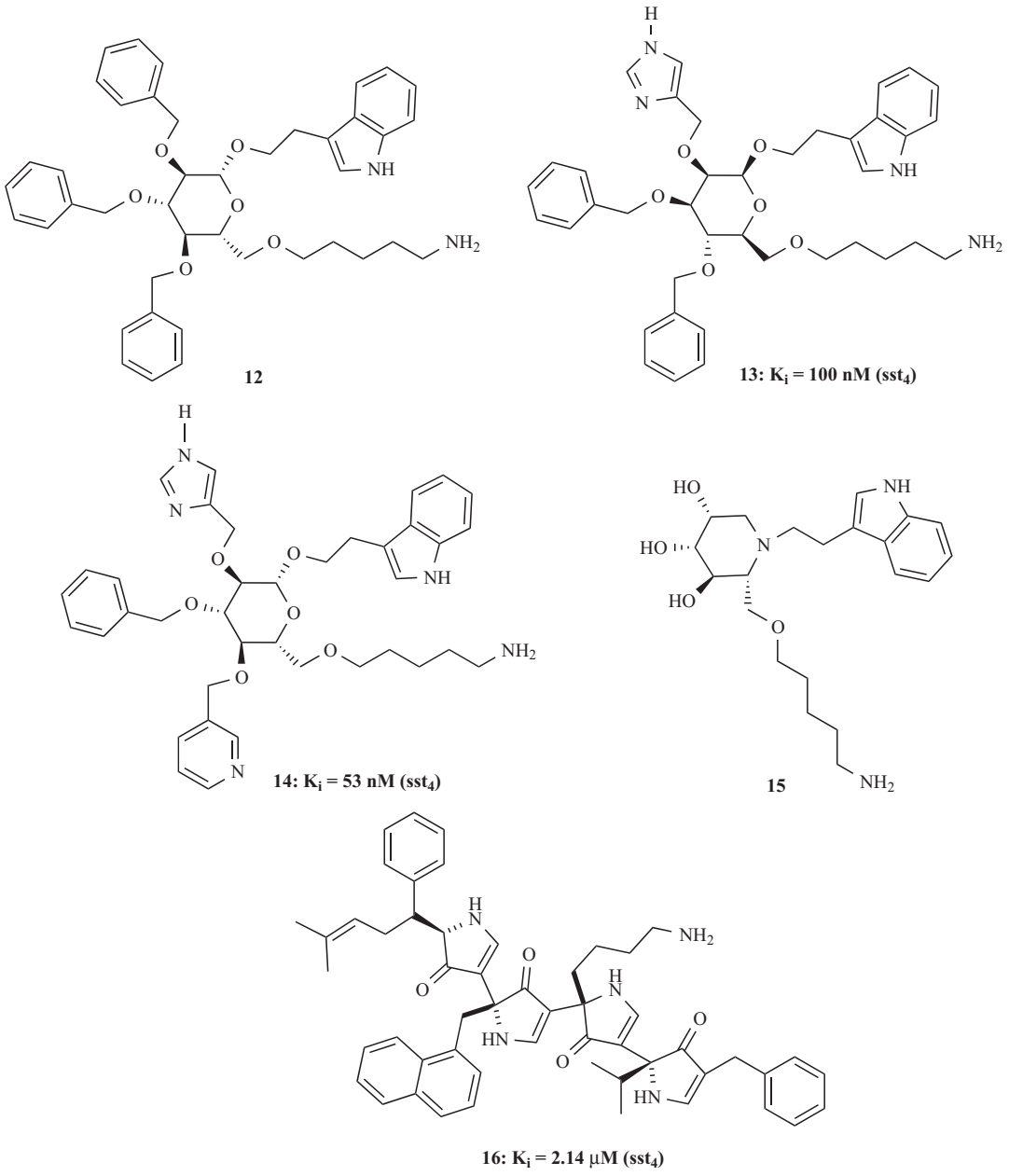


Fig. (3). Structures of Nonpeptides **12-16**.

placement of the 2-benzyl side chain by an imidazol-4-ylmethyl group in compound **12** increased receptor binding affinity. Further modifications led to the L-mannose derivative **13** (Fig. **3**), a compound with a K_i = 100 nM at sst_4 [36]. Introduction of an imidazol-4-ylmethyl at C2 and a pyridine-3-ylmethyl group at C4 of the β-D-glucose nucleus gave an analogue (**14,** Fig. **3**) with enhanced water solubility and sst_4 binding affinity [31].

Gouin *et al*. [37] synthesized a structural analogue (**15**, Fig. **3**), based on Hirschmann's pyranose analogues that was derived 1-dexoymannojirimycin. In this compound, the Trp-mimetic is attached to the ring nitrogen and the Lys-mimetic is attached to the primary alcohol. Compound **15** showed only weak binding affinity at sst_4. The absence of a Phe-mimetic on the scaffold may explain the low binding affinity of **15**.

A 3,5-linked pyrrolindone scaffold was used by Smith *et al*. [38] as a β-turn peptidomimetic. These derivatives, as typified by the tetrapyrrolinone **16** (Fig. **3**), incorporate the core Phe^7-Trp^8-Lys^9-Thr^{10} mimetic groups of the β-turn of SRIF. Although compound **16** showed only weak binding at sst_4, these investigators speculated that the 3,5-linked pyrrolinone scaffold could be a future source of potent SRIF peptidomimetics.

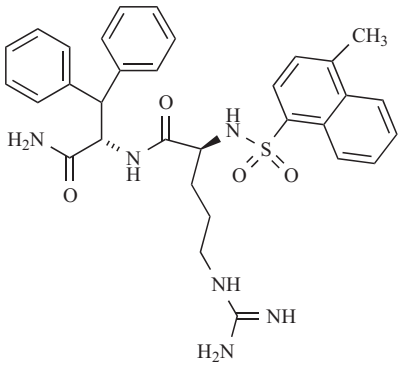
The solid phase synthesis of a series of 1-naphthalenesulfonylamino-peptidomimetics was reported in a WO

patent in 2005 [39]. Several of these compounds (**17-22,** Fig. **4**) exhibited high binding affinity and selectivity at sst$_4$.

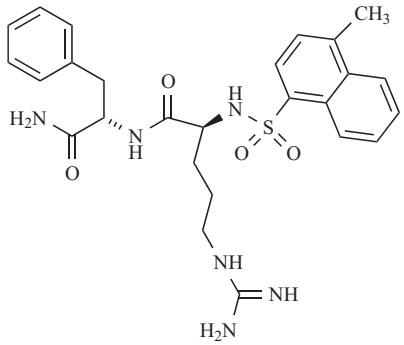
PHARMACOTHERAPEUTIC APPLICATIONS

Despite the diverse biological effects of SRIF, the therapeutic application of native SRIF therapy is limited due to its rapid degradation (<3 min half-life in the circulation [40]). SRIF is widely distributed in the body, both in neural and non-neural tissues, acting upon distinct SRIF receptor subtypes. The overlapping expression of SRIF receptor subtypes within tissues/cells likely reflects a differential regulation of biological and cellular function, which requires selective agonists for accurate assessment. Within the past decade, investigators have synthesized various high affinity sst$_4$ receptor binding peptides and non-peptide mimetics, shown to produce potent pharmacological activity [26-27,33,41-42]. Recently, specific pharmacotherapeutic actions have been attributed to sst$_4$ activity. High affinity sst$_4$ agonists have been shown to induce peripheral anti-nociceptive and anti-inflammatory effects [43]. In the central nervous system (CNS), SRIF acts as neurotransmitter and neuromodulator to regulate neuronal firing in a predominantly inhibitory manner, through actions on potassium and calcium channels. In this manner, SRIF can modulate complex behaviors, such as motor activity and cognition [4]. Due to the heightened expression of sst$_4$ in mammalian cerebral cortex, striatum, amygdala, hypothalamus, and hippocampus, sst$_4$-selective agonists have significant potential for use in the assessment and treatment of CNS disorders [44-46]. Moreover, the lack of sst$_4$ mRNA in normal human adult pituitary [47] provides an additional advantage for sst$_4$ selective agonists; as such selective sst$_4$ agonists would not exert classical SRIF effects within the pituitary, thus reducing the CNS/endocrine side-effect profile.

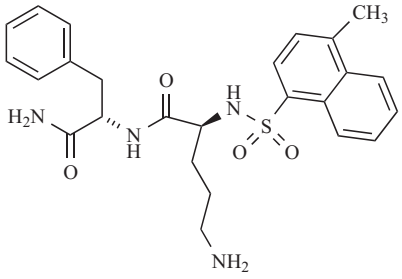
Recent examinations using high affinity sst$_4$ agonists TT-232 and J-2156 (compound **20**, Fig. **4**) have demonstrated significant anti-nociceptive and anti-inflammatory actions. TT-232, a peripherally acting cyclic heptapeptide (D-Phe-c[Cys-Tyr-D-Trp-Lys-Cys]-Thr-NH_2), exhibited anti-noci-



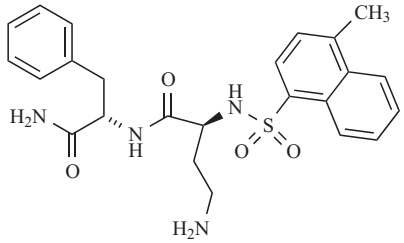
17: K_i = 3.6 nM (sst$_4$)



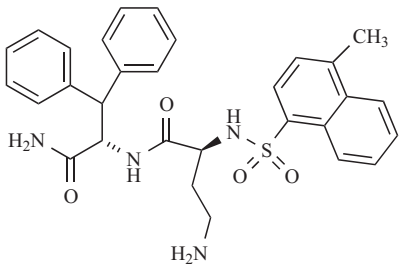
18: K_i = 1.5 nM (sst$_4$)



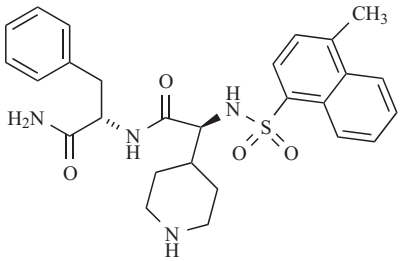
19: K_i = 6.5 nM (sst$_4$)



20: J-2156
K_i = 1.2 nM (sst$_4$)



21: K_i = 5.3 nM (sst$_4$)



22: K_i = 3.2 nM

Fig. (4). Structures of Nonpeptides **17-22**.

ceptive behavior in formalin induced pain, noxious heat, adjuvant-induced inflammatory allodynia and streptozotocin-induced diabetic neuropathic mechanical allodynia [41,48-49]. Additionally, TT-232 has shown a μg/kg dose range in regards to its anti-inflammatory effects both *in vivo* and *in vitro* [48,50]. Nevertheless, TT-232 also expresses affinity for the sst_1 receptor, believed to be responsible for its anti-tumor activity [51], which could be expected due to a 71% sequence homology between sst_1 and sst_4 [4,52]. J-2156, classified as a sulfonamide-peptidomimetic, is a more recently developed compound, which has shown to be over 400-fold more selective for the sst_4 receptor than for any other SRIF receptor subtype [42]. Not only has J-2156 demonstrated a greater affinity for sst_4 than native SRIF, but it has shown a lower propensity to cause receptor desensitization [42,53]. These combined attributes, make J-2156 a potentially potent therapeutic agent. Nevertheless, although characterized as a non-peptide agonist J-2156 does possess an amide bond, which could make it susceptible to peptidase degradation. Recent examinations have demonstrated that J-2156 possesses significant anti-nociceptive activity in acute and chronic models of pain, and is hypothesized to act with a similar mechanism of peripheral action as TT-232 [10]. Although the precise molecular mechanisms of the anti-nociceptive and anti-inflammatory activities of these compounds have not been fully elucidated, recent research has implicated an inhibition of the capsaicin "transient receptor potential vanilloid 1 (TRPV1) receptor" [43,49,54-55]. TT-232 has been shown to reduce neurogenic inflammation *via* capsaicin-sensitive sensory nerve endings, which expresses the TRPV1 receptor [48-49,56-57]. TT-232 has also shown to inhibit allodynia, induced by the potent TRPV1 agonist resiniferatoxin [41]. SRIF receptor- mediated tyrosine kinase inhibition or dephosphorylation of the TRPV1 receptor has been suggested for the anti-nociceptive action of TT-232 [41]. Interestingly, TRPV1 does not appear to be under tonic opioid receptor control, as the opioid antagonist naloxone does not change capsacin-induced excitation [54]. From a clinical perspective, a non-opioid based anti-nociceptive compound would be highly beneficial, especially in regards to neuropathic pain alleviation and elimination of opioid-based side-effects. Additionally, TT-232, and potentially J-2156, has been identified as being devoid of endocrine activity [58-59]. This not only eliminates highly problematic side-effects in the therapeutic arena, but also helps further delineate the biological function of the sst_4 receptor.

Centrally acting sst_4 agonists would also be of great potential value, as the sst_4 receptor has a significant distribution within the brain. Levels of SRIF are altered in several human CNS pathologies, such as Alzheimer's disease (AD) [60-61]), temporal lobe epilepsy [62-63], Parkinson's disease [64-65], and cortical injury [66]. In fact, after cortical and hippocampal trauma, sst_4 expression has shown to be increased in both neuronal and non-neuronal cells [66]. A significant decrease in sst_4 receptor expression in AD cortical tissue has been found, with the reduced sst_4 receptor immunoreactive neurons thought to reflect neuronal loss in the AD brain [61]. Until recently, a major focus of AD research has been identifying and disrupting the mechanisms that lead to its formation. However, a new treatment strategy has emerged: increasing amyloid-beta (Aβ) degradation and clearance mechanisms. In order to overcome AD, it is necessary to lower the Aβ levels in the brain. Many studies have identified neprilysin (EC 3.4.24.11) as a physiological Aβ-degrading peptidase, showing that NEP regulates the steady-state levels of both $A\beta_{1-40}$ and $A\beta_{1-42}$ *in vivo* [67-68]. A recent investigation showed that only SRIF significantly elevated neuronal NEP activity, by increasing its expression and synaptic localization [69]. Interestingly, SRIF treatment resulted in a selective and significant reduction of $A\beta_{1-42}$, but not $A\beta_{1-40}$, in the culture medium of primary neurons [69]. It has been hypothesized that the aging-dependent reduction of SRIF causes a decrease in NEP activity, which then causes the steady-state Aβ levels in brain to increase [70]. Furthermore, chronic elevation of Aβ levels may result in further down-regulation of SRIF levels [71], oxidative inactivation of NEP [72], and increased expression of amyloid precursor protein and β-secretase (mediators of AD development) [73-74]. With this understanding, a blood–brain barrier-permeable stable sst_4 receptor agonist has the potential to act selectively in AD associated brain regions (i.e. frontal cortex, hippocampus), while limiting systemic side-effects. Crider and colleagues have designed a series of stable sst_4 non-peptide agonists, with a novel thiourea scaffold, which fills the appropriate parameters for CNS permeability [26-28]. Another potential CNS acting compound was developed *via* combinatorial chemistry by Merck, L-803,087 (compound **11**, Fig. **2**) [33]. L-803,087 is a non-peptide agonist with a 285-fold selectivity for the sst_4 receptor, which was shown not to inhibit secretion of growth hormone, insulin, or glucagon [33]. L-803,087 has been used to evaluate sst_4 receptor contribution to seizure susceptibility in mice [63]. L-803,087 pretreatment (5 nmol; intrahippocampal injection) doubled the kainite-induced seizure activity in wild-type (C57BL6) mice [63]. L-803,087 has also been used in *ex vivo* competition studies identifying sst_4 binding sites in mouse olfactory bulb and CA1 region of the hippocampus [75], as well as in *in vitro* examinations assessing potassium currents in rat neurons [76]. Additionally, Masmoudi *et al*. [10] evaluated the effect of L-803,087 on diazepam-binding inhibitor (DBI) mRNA level and endozepine release in cultured rat astrocytes. L-803,087 was evaluated in comparison with SRIF and selective sst_1, sst_2, and sst_3 agonists. The results of this study indicated that L-803,087 reduced DBI mRNA in cultured rat astrocytes mainly through binding at sst_4 receptors. The effect of endozepine release appears to be mediated by sst_1, sst_2, and sst_4 receptors coupled to adenylyl cyclase/ protein kinase A (PKA) pathways. This research suggests that selectively acting sst_4 agonists could potentially be beneficial in the treatment of certain neuropsychiatric disorders. However, to date no *in vivo* CNS activity has been evaluated from peripherally administered L-803,087.

Several high affinity sst_4 receptor agonists (NNC 26-9100, J-2156, and L-803,087) have been developed in recent years, providing the necessary research tools for the delineation of SRIF receptor subtype action and potentially as efficacious therapeutics. The ability of these compounds to treat peripheral and CNS disorders will depend on a combination of pharmacokinetic/pharmacodynamic properties, including stability, receptor selectivity, oral bioavailablity, blood-brain barrier permeability, plasma protein-binding, duration at the site of action, and side-effects. It is difficult to predict which

properties will be most relevant for the therapeutic potential of SRIF analogues. Thus, continued discovery and evaluation of SRIF receptor subtype selective compounds remains a formidable task, but not one without the significant potential for reward.

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Received: 03 August, 2006 Revised: 08 September, 2006 Accepted: 09 September, 2006

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