Recent Advances in the Development of Nonpeptide Somatostatin Receptor Ligands

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Abstract: Somatostatin (SRIF) is a cyclic peptide that occurs in two biologically active forms, SRIF-14 and SRIF-28. These peptides inhibit the secretion of many other peptides, including insulin and glucagon, function as neurotransmitters or neuromodulators, and exhibit potent antiproliferative activity. Recent research has led to the development of nonpeptide SRIF ligands with high affinity and selectivity at all SRIF receptor subtypes. Additionally, the newly discovered sst_2 and sst_3 antagonists will greatly facilitate our understanding of these receptors. These novel nonpeptide SRIF agonists and antagonists may have therapeutic potential in a variety of disease states.

INTRODUCTION

Somatostatin [somatotropin release-inhibiting factor, SRIF, **1**, Fig. (**1**)] is a cyclic peptide that was initially isolated and characterized by Brazeau *et al.*. [1]. Shortly therafter, Rivier [2] reported the solid-phase synthesis of this peptide. SRIF is widely distributed throughout the body with important regulatory effects on a variety of endocrine and exocrine functions. SRIF-14 and SRIF-28, a 28-amino acid form extended from the *N*-terminal end of SRIF-14, display similar biological activities with a different pattern of potency depending on the tissue [3]. SRIF potently inhibits the release of several hormones including growth hormone (GH) from the anterior pituitary [1], insulin and glucagon from the pancreas, and gastrin from the gastrointestinal tract [4]. Additionally, SRIF exhibits potent antiproliferative activity [5] and acts as a neurotransmitter or neuromodulator in the brain with effects on motor and cognitive functions [6].

SRIF and its analogues are utilized in the diagnosis and treatment of a variety of tumors [7], acromegaly, and gastrointestinal disorders [8]. Also, peptide agonists of SRIF have shown therapeutic potential in inhibiting angiogenesis in certain tumors and in diseases such as rheumatoid arthritis [9a-9c]. Recent studies suggest that derivatives of SRIF may be useful in the treatment of diabetic retinopathy [10,11] and cystoid macular edema [12,13].

SRIF has been linked to several central nervous system (CNS) disorders including Alzheimer's disease [14], Huntington's disease [15], Parkinson's disease [16], and epilepsy [17]. Although a number of SRIF agonist peptides have been reported, the development of SRIF antagonists has been slow. SRIF receptor subtype selective antagonists should be valuable pharmacological tools for studying receptor function. Additionally, selectively-acting SRIF antagonists may offer therapeutic utility in stimulating the release of a variety of hormones including insulin and GH [18].

Cortistatin-14 (CST-14), a novel neuropeptide that contains 11 of of the 14 amino acids that are found in SRIF-14, was recently discovered [19]. Unlike SRIF-14, the distribution of CST-14 is mainly localized in the cerebral cortex. *In vitro*, CST-14 binds with high affinity to all SRIF receptor subtypes. Although some of the pharmacological effects of CST-14 are similar to SRIF-14, distinct differences exist between these two peptides. The question remains unanswered as to whether CST-14 binds to CST-specific receptors in the CNS [20,21].

SRIF exerts its potent inhibitory effects by interaction with a family of G protein-coupled receptors. Five receptor subtypes (sst_1-sst_5) have been cloned and identified [22]. Two isoforms of the sst_2 receptor are found in mice and rats. These isoforms, termed sst_{2A} and sst_{2B}, differ only in their amino acid composition at their C-termini [23-25].

The binding of SRIF to one of its G protein-coupled receptors results in a variety of cellular responses that are mediated by numerous second messenger systems. These include adenylyl cyclase, K^+ and Ca^{++} channels, a Na^+/H^+ exchanger, guanylyl cyclase, phospholipase A_2 (PLA_2), phospholipase C (PLC), phosphotyrosine phosphatases (PTPs), and mitogen-activated protein kinases (MAPK) [26]. The five SRIF receptor subtypes are found in the CNS, the periphery, and in various tumors [27]. Specific physiological functions have only been attributed to the sst_2 and sst_5 receptors. An *in vitro* study using mouse pancreatic islets showed that insulin release was regulated by sst_5, while glucagon release was mediated by sst_2 receptors. The release of GH from primary cultures of rat anterior pituitary cells was shown to be regulated by both receptor subtypes [28]. Another recent study showed that in SRIF receptor 2

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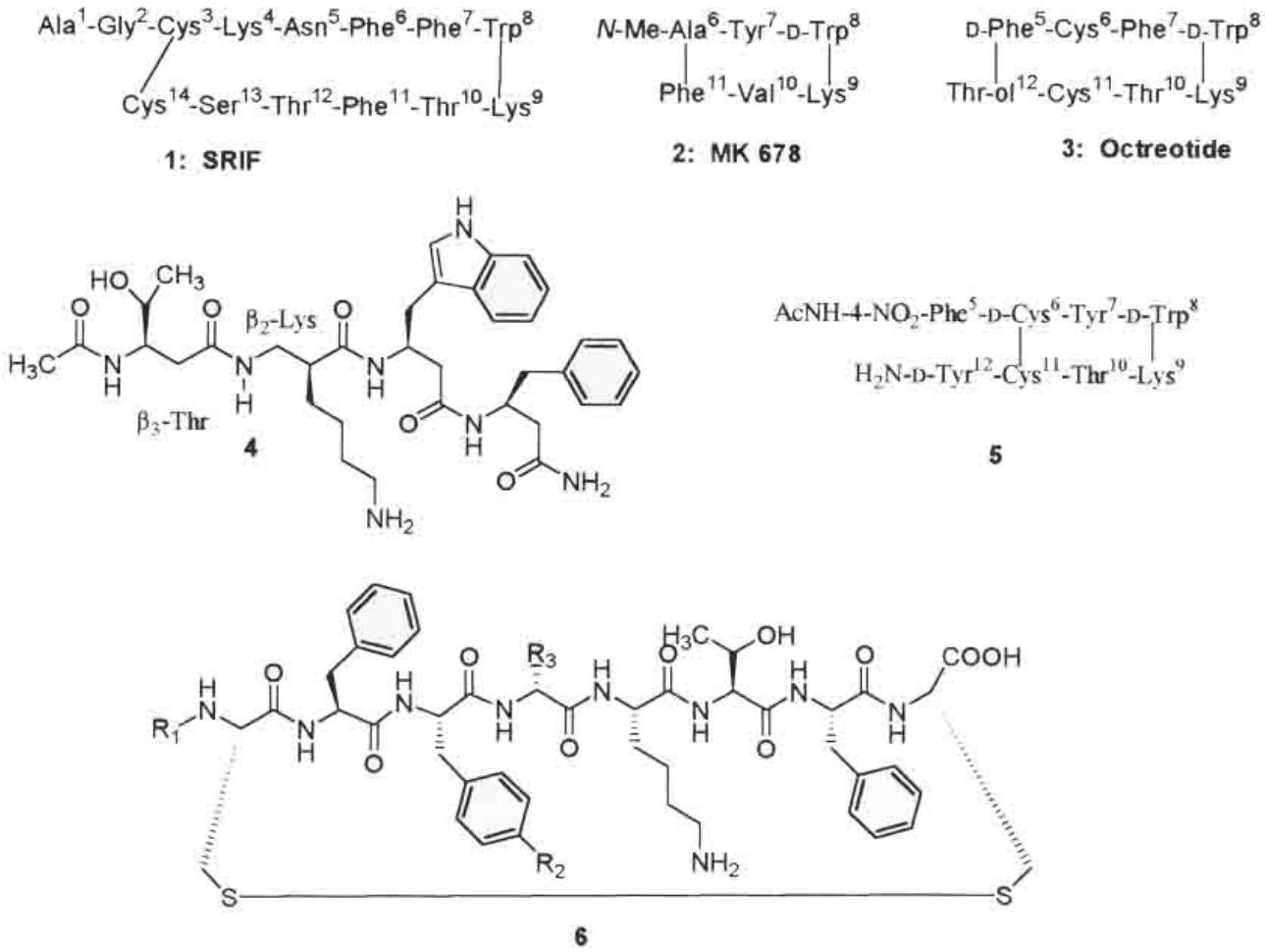

Fig (1). Structures of SRIF and Related Peptide Ligands (**1**-**6**).

knockout mice, glucagon release was linked to sst_2 receptors, whereas insulin release was modulated by sst_5 [29].

PEPTIDE AGONISTS AND ANTAGONISTS

The therapeutic effectiveness of SRIF is severely limited by poor bioavailability and rapid degradation by endogenous peptidases. Because of these limitations, orally effective and metabolically stable analogues, termed peptidomimetics [30], have been the focus of extensive research. Detailed structure-activity relationship (SAR) studies have revealed that the Trp^8 and Lys^9 residues are essential for biological activity. These residues are part of the tetrapeptide, Phe^7-Trp^8-Lys^9-Thr^{10}, that comprise the critical β-II-turn of SRIF. The tripeptide, Phe^7-Trp^8-Lys^9, and Phe^{11} are believed to constitute the pharmacophore of SRIF [31]. These studies led to the discovery of seglitide [MK 678, **2**, Fig (**1**)] [32] and the cyclic octapeptide [SMS 201-955, sandostatin®, **3**, Fig (**1**)] [33]. Long-acting preparations of octreotide are available for use in the treatment of gastrointestinal disorders, neuroendocrine tumors, and acromegaly; however, subcutaneous or intravenous administration is necessary [8, 34].

On the basis of these observations on MK 678 and octreotide, numerous peptide analogues of SRIF have been prepared and their solution conformations examined. Analogues of the cyclic hexapeptide *c*-[Phe^{11}-Pro^6-Phe^7-D-Trp^8-Lys^9-Thr^{10}] were prepared, and their solution conformations and biological activities were evaluated [35]. Substitution of *N*-alkylated glycine residues in place of Pro resulted in compounds with enhanced sst_2 selectivity. In the octreotide series, the effects of stereochemistry of the Thr residues at position 10 and 12 on binding affinity and conformation were studied. These studies demonstrated that octreotide analogues with (*S*)-configuration at the C^α of the Thr^{10} residue bind to ssts and adopt the β-II-turn around the D-Trp^8 and Lys^9 residues, whereas those analogues with opposite configuration at this position failed to adopt this conformation and were biologically inactive.

A series of undecapeptide SRIF analogues, devoid of amino acid residues 1, 2, and 5, and containing either a D-Trp of D-Nal^8 and a 4-(*N*-isopropyl)aminomethyl] phenylalanine ($Iamp^9$), were reported by Rivier *et al.* [36]. Several of these derivatives demonstrated high binding affinity and selectivity at sst_1. Two radiolabeled [^{125}I]Tyr derivatives were shown to be effective in the detection of sst_1 tumors using audioradiography.

In an effort to eliminate the intramolecular hydrogen bonding sites and increase the metabolic stability, the cyclic octapeptides, D-Phe^5-*c*[Cys^6-Phe^7-D-Trp^8-Lys^9-Thr^{10}-Cys^{11}]Thr^{12}-NH_2 and Tyr^5-*c*[Cys^6-Phe^7-D-Trp^8-Lys^9-Thr^{10}-Cys^{11}]-Thr^{12}-NH_2 NH_2, were *N*-methylated at every residue using a solid phase method [37]. The binding studies on these derivatives at sst_1-sst_5 in CHO cells showed that *N*-methylation of Phe^7, Thr^{10}, Cys^{11}, and Thr^{12} essentially eliminated activity, whereas *N*-methylation of Tyr^5 or Cys^6 resulted in analogues with potent sst_3 affinity. In the D-Phe^5 series, *N*-methylation on Trp^8 resulted in an analogue with excellent sst_5 binding affinity.

In a recent report, Gademann *et al.*. [38] synthesized β-tetrapeptide derivatives as mimics of the β-turn of SRIF. The β-tetrapeptide **4** was synthesized utilizing solid-phase methods on Rink resins and was shown to bind with nanomolar affinity at sst_4 receptors. Movement of the side chain by one carbon in the β_2 Lys residue, resulting in a β_3 amino acid, decreased binding affinity at sst_4 by over 1000-fold.

Until recently, the development of peptidic antagonists of SRIF has been slow. In general, subtle modifications of peptide agonists have resulted in the discovery of SRIF antagonists. A highly potent sst_2 antagonist was described by Bas *et al.*. [39]. This cyclic octapeptide [**5**, Fig (**1**)] contains the core SRIF structure, with a D-Trp^8 residue to stabilize the β-turn and a D-Cys residue in the 6-position (SRIF numbering). Additional disulfide-cyclized octapeptide antagonists were synthesized by inverting the chirality of the disulfide-bridged octapeptide SRIF agonists at positions 5 and 6 (SRIF numbering; D^5, L^6 to L^5, D^6). One analogue derived from these studies DC 38-48, H-Nal-*c*[D-Cys-Pal-D-Trp-Lys-Val-Cys]-Nal-NH_2, is a selective sst_2 antagonist [40]. Further studies using the L^5, D^6 structural fragment demonstrated that the cyclic octapeptide H-Cpa-*c*[D-Cys^6-Tyr^7-D-Trp^8-Lys^9-Thr^{10}-Cys^{11}]-Nal^{12}-NH_2 exhibited high binding affinity at sst_2 receptors with a K_i = 26 nM. This analogue demonstrated potent antagonistic activity to SRIF in an *in vitro* rat pituitary assay [41]. Screening of a combinatorial library identified the hexapeptide Ac-D-His-D-Phe-D-Ile-D-Arg-D-Trp-D-Phe,which is comprised entirely

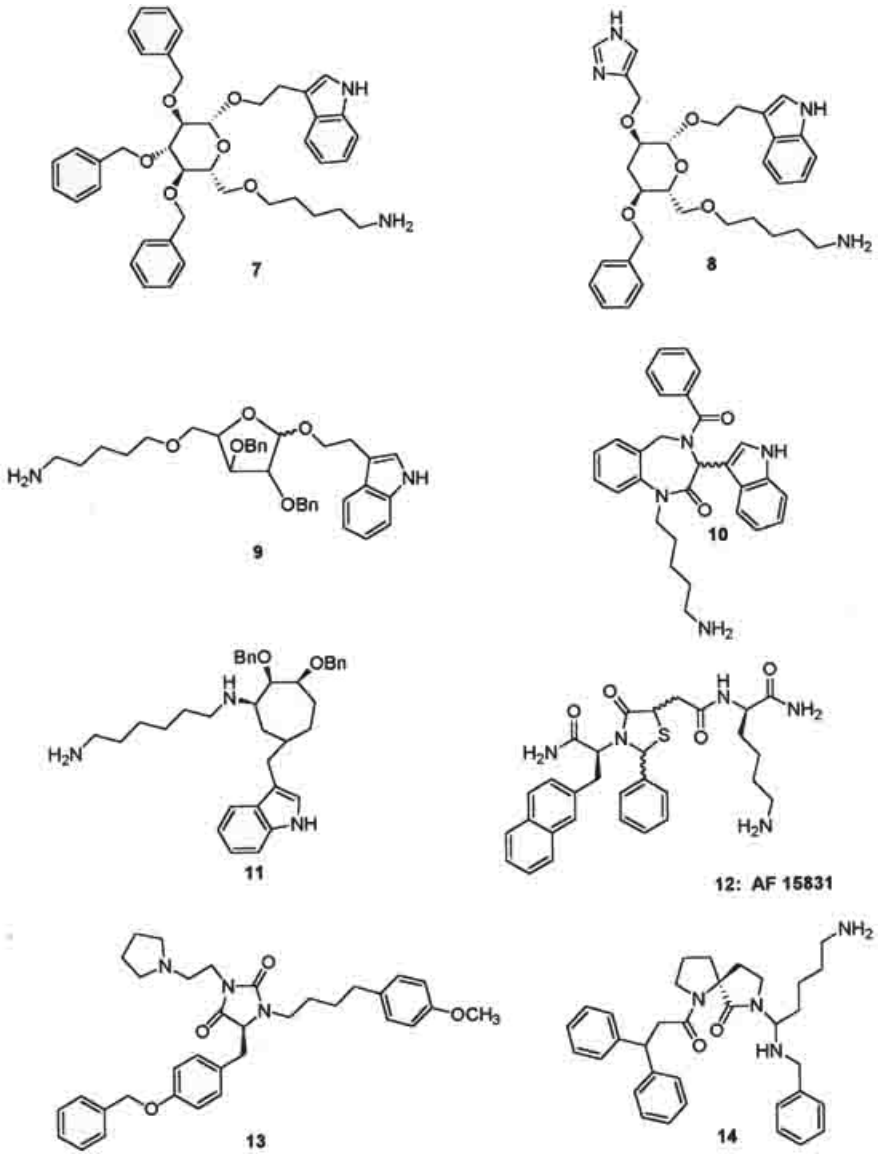

Fig (**2**)**.** Structures of SRIF Nonpeptide Ligands (**7**-**14**).

of D-amino acids, to be an antagonist at sst_2 receptors (K_i = 170 nM) [42]. Using a similar method that was employed for agonists, the *N*-methylation approach on the lead antagonist, Cpa-*c*[D-Cys-Pal-D-Trp-Lys-Thr-Cys]-Nal-NH_2, produced antagonists with high affinity at subtypes 2, 3, and 5 receptors. The derivative containing the *N*-Me-Lys^9 residue demonstrated slightly lower binding affinity at subtype 2 receptors; however, this analogue exhibited about four-fold greater potency in an *in vitro* GH assay. Additionally, this derivative showed high affinity for the subtype 5 receptor and inhibited calcium mobilization, which is mediated through this receptor in an *in vitro* assay in CHO-K1 cells. Replacement of the Lys^9 residue with a 2,4-diaminobutyric acid moiety (Dab) afforded an analogue with high selectivity at sst_3 [43].

Octapeptide analogues of SRIF of the general structure **6** [Fig (**1**)] were shown to bind with high affinity and selectivity at subtype 3 receptors. One analogue (**6**, R_1 = H_2NCO, R_2 = OH, R_3 = $N(CH_3)CO$-2-naphthyl) potently reversed the effects of SRIF-28-induced inhibition of forskolin-induced cAMP formation in transfected CCL 39 cells. Additionally, this peptide inhibited SRIF-28-induced stimulation of PLC in transfected sst_3 CCL 39 cells. Radioligands of several [^{125}I-Tyr^7] analogues demonstrated high binding affinity and selectivity at sst_3. The radioiodinated analogue [^{125}ITyr^7]**6** (R_1 = H_2NCO, R_2 = OH, R_3 = $N(CH_3)CO$-2-naphthyl) labeled several inactive pituitary adenomas that express subtype 3 receptors [44].

SRIF NONPEPTIDE AGONISTS AND ANTAGONISTS

Orally active, nonpeptide SRIF analogues with high selectivity at ssts may be useful therapeutic agents in a variety of disorders. The first nonpeptide SRIF analogue was reported by Hirschmann *et al.*. [45], in which a D-glucose scaffold was used to mimic the β-turn of SRIF. The pharmacophoric groups (benzyl, indolyl, and the Lys^9-surrogate) in **7** [Fig (**2**)] have a similar spatial arrangement as found in octreotide; however, this glycoside demonstrated

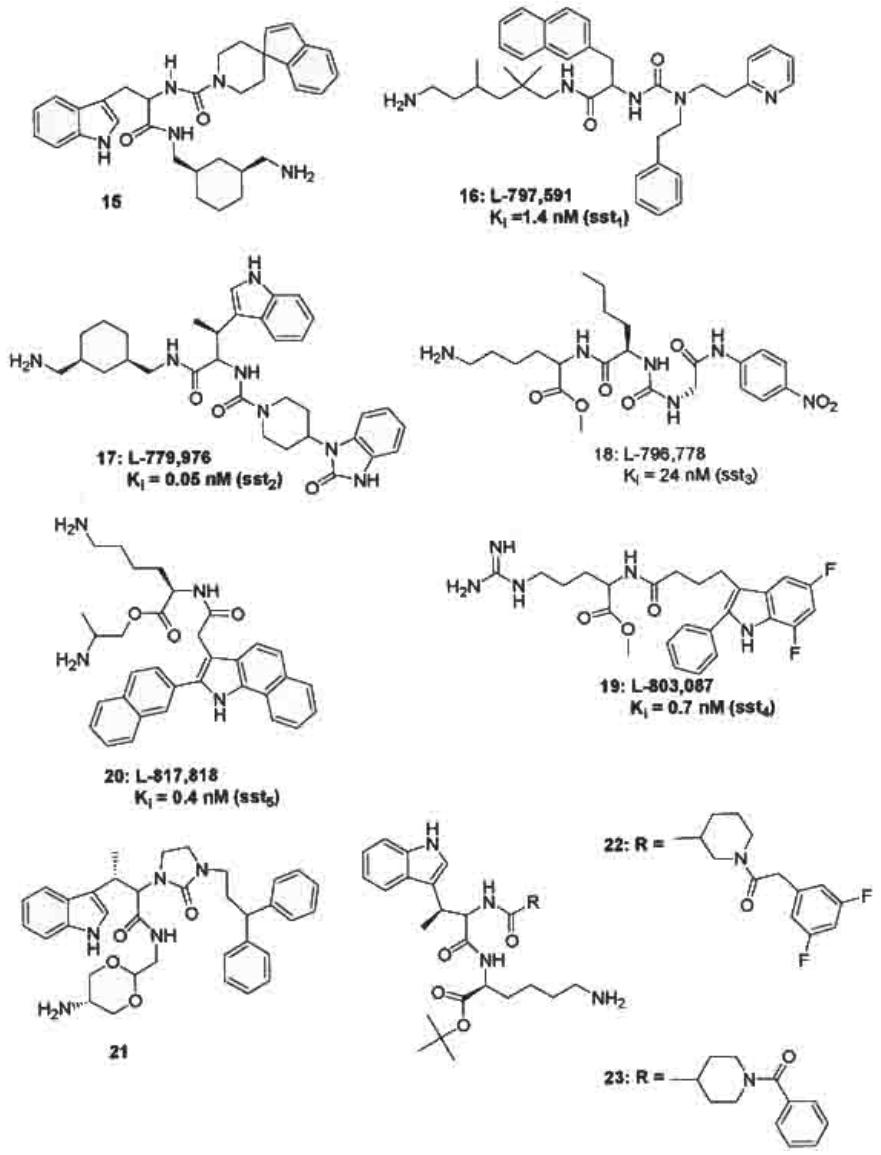

Fig (**3**)**.** Structures of SRIF Nonpeptide Ligands (**15-23**).

only weak agonist affinity in AtT-20 cells. Additional studies produced compound **8** [Fig (**2**)] , which exhibited a K_i of 100 nM at sst_4 [46].

The peptidomimetic **7** binds at several G protein-coupled receptors. This behavior has been attributed to pseudosymmetry of the D-glucose moiety. Pseudosymmetry allows the sugar freedom to assume a number of different binding modes, thereby imparting affinity for several different receptors. Although an agonist at ssts, the glycoside **7** demonstrates antagonist action at the human neurokinin 1 (hNK1) receptor. The peptidomimetic **7** and related analogues are proposed to interact with the precoupled form (precoupled ssts to their G proteins) of ssts. This activated state of the receptor is believed to impart agonism in most ligand binding at ssts. Support for this hypothesis is found in the scarcity of known SRIF antagonists [47].

A number of nonpeptide SRIF agonists that are based on other scaffolds were subsequently prepared [**9-14**, Fig (**2**)]. A tetrasubstituted xylofuranose derivative **9** displaced [^{125}I]Tyr^{11}SRIF, with an IC_{50} of 23 μM in rat brain homogenates [48]. The benzodiazepine **10** exhibited about three-fold greater binding affinity than **9** [49], and the tetrasubstituted azepine **11** exhibited weak binding affinity (IC_{50} = 10 μM) in rat whole brain homogenates [50].

Screening of generic libraries by researchers at Affymax resulted in the identification of the thiazolidinedione (**12**, AF 15831) as a potent and selective sst_5 agonist [51]. Using compound **12** as a structural lead, a series of trisubstituted hydantoins were prepared by solid phase synthesis. The hydantoin **13** exhibited an IC_{50} of 300 μM in displacement of [^{125}I]Tyr^{11}-SRIF from sst_5 receptors expressed in CHO-K1 cells [52].

Damour *et al.*. [53] used a spirolactam scaffold as a novel β-turn mimetic. The spirolactam **14** showed only weak binding affinity (IC_{50} = 11 μM) in displacement studies in rat cerebral cortex membranes.

Yang *et al.*. [54] reported the first potent and selective nonpeptide sst_2 agonist in 1998. The indole **15** [Fig (**3**)] demonstrated low nanomolar binding affinity at sst_2 and high selectivity (> 1000-fold) over other SRIF receptor subtypes. Compound **15** showed full agonism in the inhibition of forskolin-induced cAMP accumulation, with an IC_{50} = 2 nM. Replacement of the D-Trp moiety with the corresponding L-isomer resulted in decreased receptor binding affinity. These workers speculated that the potency of these analogues arises from the key Trp^8-Lys^9 mimetic and the lipophilic spiroindene. The later group is thought to mimic either the Phe^6 or Phe^{11} residues of SRIF. Additional work from the Merck group led to a series of analogues related to compound **15** with high affinity and selectivity for sst_2 [55]. Using combinatorial chemistry methods, the Merck group generated a very large library of compounds which were evaluated by high throughput screening [56]. Compounds were identified with high affinity and selectivity for all SRIF receptor subtypes. The receptor subtype selective compounds **16-20** are shown in Fig (**3**). The sst_2 selective β-MeTrp derivative **17** potently inhibited forskolin-induced cAMP acculumation (IC_{50} = 0. 05 μM) in CHO-K1 cells, and the compound showed comparable potency to SRIF-14 in inhibiting GH release from rat pituitary cells. Additionally, compound **17** blocked arginine-induced glucagon release from mouse pancreatic cells, whereas blockade of insulin release required about a 1000-fold higher concentration. On the other hand, the sst_5 selective indole derivative **20** potently inhibited insulin release in mouse pancreatic islets, but failed to block glucagon secretion.

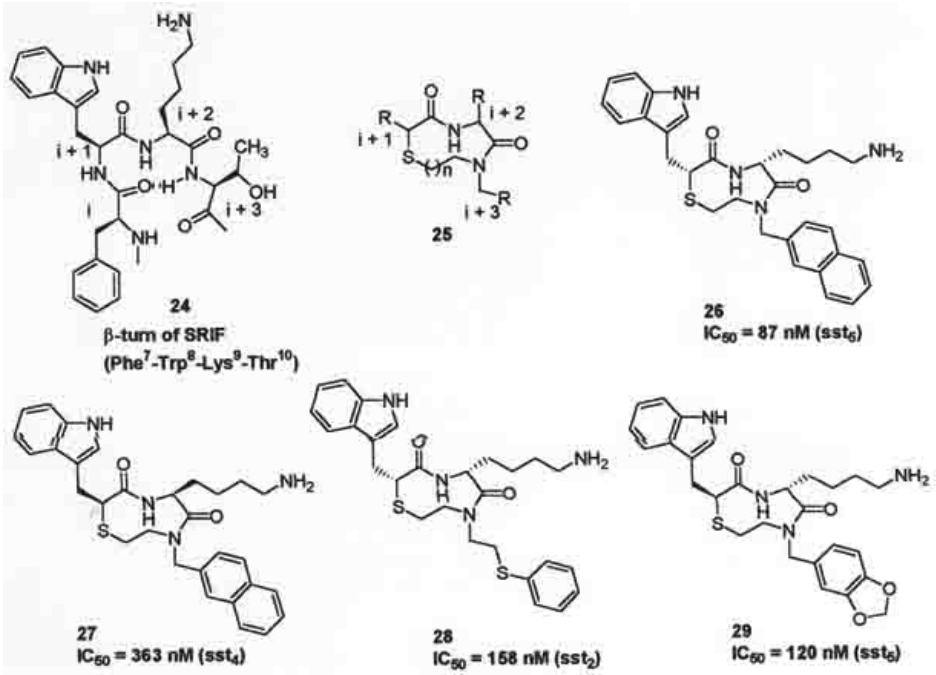

Fig (4). Structures of the β-Turn (**24**) and SRIF Ligands (**25**-**29**).

Pasternak *et al.*. [57] speculated that the low bioavailability of **17** and its analogues was attributable to the urea moiety. Elimination of hydrogen bonding accepting or donating ability of this group was suggested to enhance oral bioavailability. This hypothesis led to the development of the imidazolidinone **21** [Fig (**3**)], which showed high selectivity for sst_2 and an oral bioavailability of 64 %. These workers concluded that the urea *N*-H was not essential for receptor binding and that good bioavailability can be achieved by linking the urea nitrogens by a 2-carbon bridge. Along the same line, replacement of the urea moiety by either isonipecotamide or nipecotamide moieties was expected to enhance bioavailability of sst_2 selective analogues. A number of derivatives in the nipecotamide series demonstrated high affinity at sst_2. Substitution of arylmethyl or arylacetyl groups on the piperidine ring nitrogen led to potent compounds at sst_2. Introduction of fluoro-substituents [compound **22**, Fig (**3**)] on the aromatic ring tended to enhance binding affinity at sst_2. In the isonipecotamide series, compound **23** [Fig (**3**)] bound with high affinity (K_i = 0. 5 nM) at sst_2, and this derivative showed sst_5/sst_2 selectivity of over 800-fold. However, this derivative showed poor bioavailability [58].

The design and synthesis of peptidomimetics of SRIF utilizing a β-turn structure [**24**, Fig (**4**)] have been extensively investigated. Depending on the turn structure, three amino acid side chains can be displayed on a medium-ring heterocyclic scaffold [**25**, Fig (**4**)] employing a variety of synthetic methods. A focused library was designed using information which indicated that several alternative displays of Trp and Lys side chains could potentially provide active analogues [59]. All possible combinations of Trp and Lys side chains, with both D and L stereochemistry, were attached at the i + 1 and i + 2 positions of the β-turn, and twenty-two different amines were introduced at the i + 3

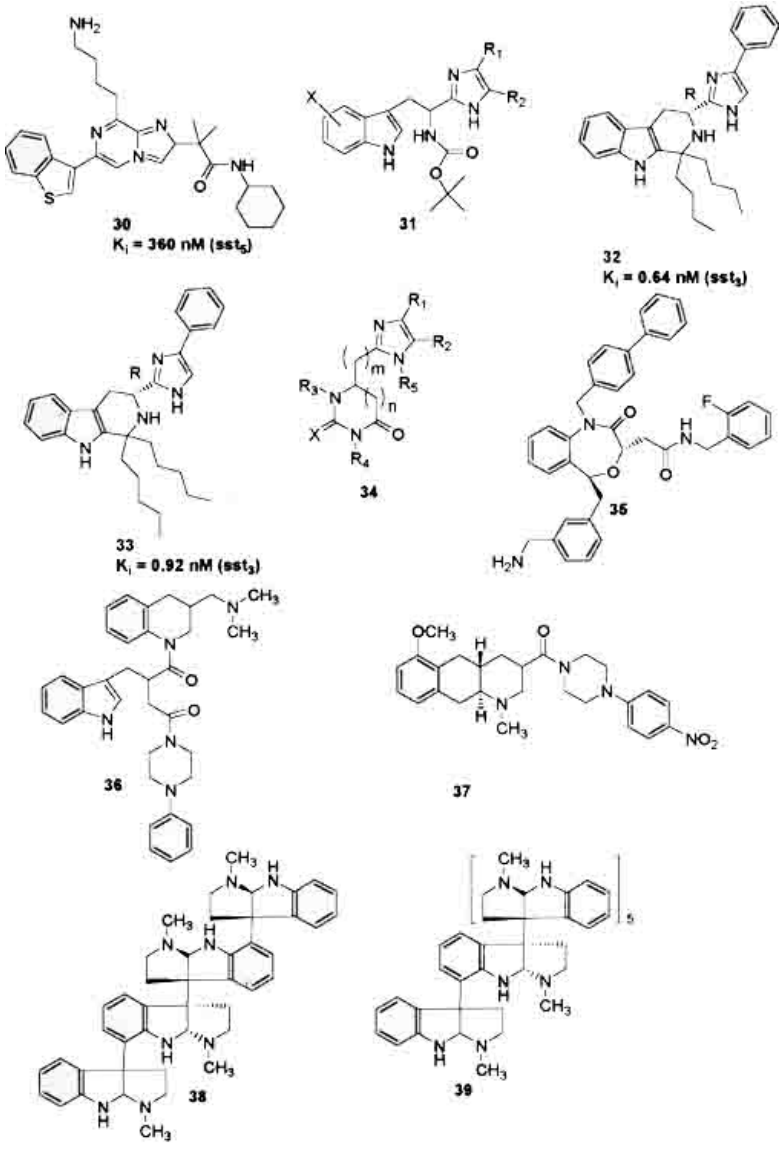

Fig (5). Structures of SRIF Nonpeptide Ligands (**30-39**).

position. A library of 172 compounds was generated and screened at sst_1-sst_5. A number of compounds showed potent binding affinities at ssts [compounds **26-29**, Fig (**4**)].

A series of imidazopyrazines and dihydroimidazopyrazines were prepared by parallel synthesis, and the compounds were evaluated for binding affinity at sst_1-sst_5 [60]. The most potent analogue arising from these studies was the imidazopyrazine **30** [Fig (**5**)]. This analogue bound with moderate affinity (K_i = 360 nM) at sst_5 and showed some selectivity versus the other SRIF receptor subtypes. In a functional assay in CHO-K1 cells, compound **30** exhibited an EC_{50} of 1600 nM ± 610 nM (n = 3) in reversal of forskolin-induced cAMP accumulation. Additional studies by this group led to analogues with the general structure **31** [Fig (**5**)]. Several of these imidazoyl derivatives were shown to bind with moderate affinity at sst_3 receptors [61]. In an effort to increase potency, analogues of **31** were modified to give the tetrahydro-β-carbolines **32-33** [Fig (**5**)]. These derivatives exhibited high affinity and selectivity (>1000-fold) at subtype 3 receptors. The tetrahydro-β-carbolines were assessed for functional activity by determining the effect on forskolin-induced cAMP acculumation in CHO-K1 cells which express sst_3. These compounds failed to inhibit forskolin-induced cAMP accumulation, a typical agonist response. However, these analogues blocked the inhibitory action of SRIF in this assay. Additional experiments showed that increasing concentrations of **32** elevated the EC_{50} value of SRIF in a dose-dependent manner in the cAMP assay. The results suggest that compound **32** acts as a competitive sst_3 antagonist. This work is particularly significant in that this is first report of a nonpeptide sst_3 antagonist.

In a recent patent application, a number of hydantoin, thiohydantoin, pyrimidinedione, and thioxopyrimidinone derivatives [**34**, Fig(**5**)] were prepared for SRIF receptor binding affinity [62]. These derivatives contain the same imidazole nucleus as found in compound **31**.

A series of 4,1-benzoxazepines were designed as SRIF agonists and reported in a recent patent application [63]. The *trans*-4,1-benzoxazepine **35** [Fig (**5**)], at a dose of 3 mg/kg (ip), significantly reduced GH release in rats. In another patent application [64] by researchers at Takeda Chemical Industries, the synthesis of a variety of heterocyclic amines were described as SRIF agonists and antagonists. The tetrahydroquinoline **36** [Fig(**5**)] showed IC_{50} values of 9 nM and 0.8 nM at SRIF receptor subtypes 2 and 3, respectively.

A series of benzo[*g*]quinoline derivatives were described in an United States Patent as sst_1 antagonists [65]. The octahydrobenzo[*g*]quinoline **37** [Fig (**5**)] demonstrated high binding affinity for sst_1 receptors (pIC_{50} = 7.7), with little affinity for other receptors. Pharmacological evaluation of **37** [Fig (**5**)] indicated possible therapeutic utility in the treatment of depression, anxiety, and bipolar disorders such as mania.

A pyrrolidinoindoline alkaloid **38** [Fig (**5**)], isolated from *Psychotria oleoides*, was shown to exhibit antagonistic activity in a pituitary cell assay [66]. Additional studies [67] led to the isolation of additional alkaloids such as **39** [Fig (**5**)]. These compounds all showed SFIF antagonist activity.

In an effort to develop nonpeptide SRIF derivatives with high affinity and selectivity for ssts, a collaborative project

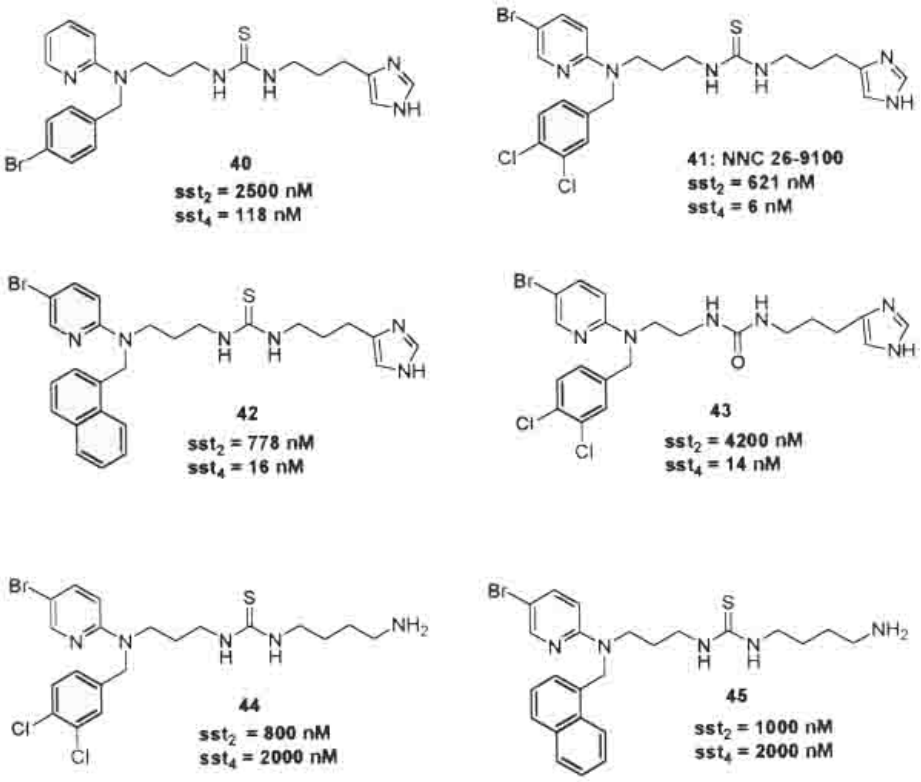

Fig (6). Structures of SRIF Nonpeptide Ligands (**40-45**).

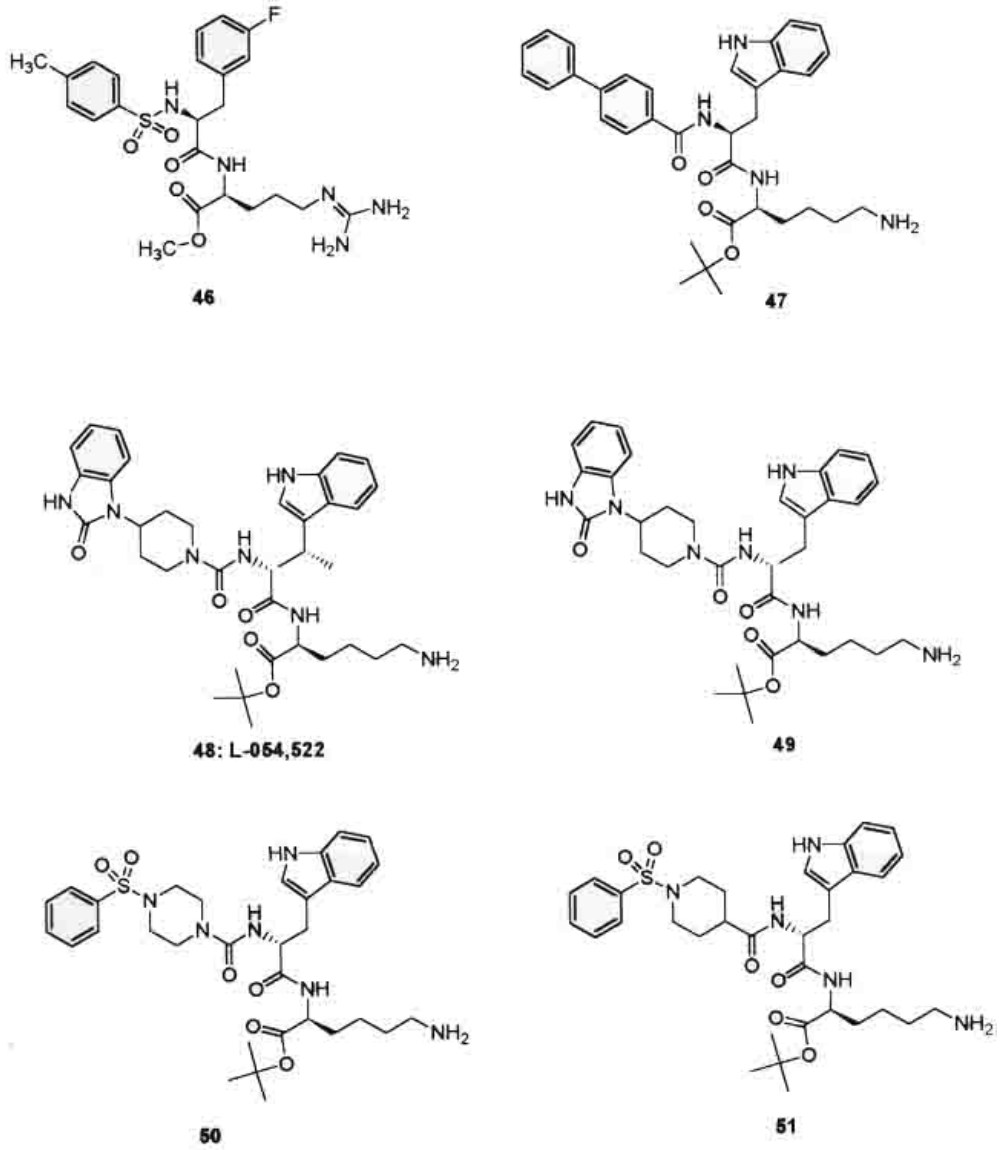

Fig (7). Structures of SRIF Nonpeptide Ligands (**46**-**51**).

was undertaken in our laboratory with scientists at Novo Nordisk A/S. Our strategy focused on a scaffold with Phe^7, Trp^8, and Lys^9-mimetics, three of the residues found in the β-turn of SRIF, attached. A limited screening identified the thiourea **40** [Fig (**6**)] as a structural lead, with K_i values at sst_2 and sst_4 of 2500 nM and 118 nM, respectively [68]. Modification of the lead **40** gave potent sst_4 agonists **41**-**43** [Fig (**6**)]. The thiourea **41** (NNC 26-9100) and the urea **43** potently inhibited cAMP accumulation with EC_{50} values of 26 nM and 24 nM, respectively [69]. These data demonstrate that the compounds act as full agonists at sst_4 receptors.

On the basis of our results, several conclusions can be made. The pyridine ring may mimic the Trp^8 of SRIF, and the nonheteroaromatic benzyl or α-naphthyl group may mimic Phe^7. Although less basic than the ε-NH_2 group of Lys^9, the imidazolyl moiety apparently mimics Lys^9 in SRIF and interacts with a key Asp residue on transmembrane III of ssts. Alternatively, this functionality may be involved in π-π interactions with aromatic groups on the receptor. Support for this suggestion stems from the fact that the aminobutyl derivatives **44** and **45** demonstrate greatly reduced binding affinity at sst_4. The role of the urea or thiourea groups may be that of a scaffold to properly orient the heteroaromatic, nonheteroaromatic, and basic groups on sst_4. Hydrogen bonding differences may partially explain the enhanced binding affinity of thioureas compared to ureas at sst_2. Another possibility is that the lipophilic sulfur atom of the thioureas interacts with a lipophilic pocket on the subtype 2 receptor, thereby enhancing the receptor binding of these derivatives [70].

Using in situ hybridization techniques, Mori *et al.*. [71] showed that in the eye, sst_4 is predominately expressed in the posterior iris and ciliary body. Previously, SRIF was shown to inhibit cAMP production in the ciliary processes [72]. The exact mechanism by which α_2-adrenergic agonists decrease formation or increase outflow of aqueous humor is not completely understood. However, Bausher and Horio [73] provided evidence for a direct correlation between cAMP levels in human ciliary tissue and the formation of aqueous humor. Furthermore, a study of signaling

characteristics between α_2 receptors and ssts indicates that similarities exist between these receptors [74-75]. These studies suggest that sst_4 agonists could reduce intraocular pressure and have therapeutic potential in the treatment of glaucoma.

Scientists at Pfizer have recently reported the first small molecule sst_2 antagonists [76]. Using the initial screening lead **46** [Fig (**7**)], a D-Trp-derived antagonist **47** [Fig (**7**)] was found to bind at subtype 2 receptors (IC_{50} = 85 nM). These workers combined the structural features of the Merck sst_2 agonist **48** [L-054,552, Fig (**7**)] with those of the antagonist **47** to afford the des-methyl analogue of **48** [compound **49**, Fig (**7**)]. Replacement of the 4-(benzimidazolone)-piperidinyl moiety by either a *N*-substituted piperazinyl (**50**) or a *N*-isonipecotate (**51**) resulted in full sst_2 antagonists [Fig (**7**)]. These researchers speculated that the sp^2 nitrogen of the sulfonamide group in **50** and **51** plays an important role in orienting the terminal phenyl group to access a hydrophobic pocket on the sst_2 receptor.

SUMMARY

Since the first nonpeptide agonists were reported in 1998, with high affinity and selectivity for human SRIF receptor subtypes 2 and 4, novel ligands have been discovered for all ssts. The recent reports of small molecule antagonists at sst_2 and sst_3 will greatly facilitate research on the functional role of these receptors. Additionally, many of these analogues have possible clinical application in numerous diseases including the treatment of various tumors, CNS diseases, glaucoma, and endocrine disorders. Since several research groups are actively engaged in new compound discovery, novel agonists and antagonists with high affinity and selectivity at all ssts should be expected in the future.

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