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Communications to the Editor

Spiro[1*H*-indene-1,4′-piperidine] Derivatives As Potent and Selective Non-Peptide Human Somatostatin Receptor Subtype 2 (sst_2) Agonists

Lihu Yang,* Liangqin Guo, Alexander Pasternak, Ralph Mosley, Susan Rohrer,† Elizabeth Birzin,† Forrest Foor,† Kang Cheng,† James Schaeffer,† and Arthur A. Patchett

Departments of Medicinal Chemistry and Biochemistry & Physiology, Merck Research Laboratories, Rahway, New Jersey 07065

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Somatostatin (somatotropin release-inhibiting factor, SRIF) is a widely distributed peptide occurring in two biologically active forms, a tetradecapeptide $SRIF_{14}$ (**1**) and a 28-residue peptide $SRIF_{28}$.[1] SRIF has multiple functions which includes modulating the secretion of growth hormone (GH), insulin, glucagon, pancreatic enzymes, and gastric acid, in addition to having potent antiproliferative activity.[2] In the central nervous system, SRIF is a neurotransmitter, it increases cognitive function, and it modulates locomotor activity.[3] Because of these properties, SRIF agonists may be used for the treatment of acromegaly, diabetes, cancer, rheumatoid arthritis, and Alzheimer's disease among others. On the other hand, the broad biological activities of SRIF present the potential for side effects. Recently, five SRIF receptor subtypes (sst_{1-5}),[4] all belonging to the G-protein-linked receptor family, have been cloned and characterized.[5] Studies utilizing subtype selective SRIF analogues[6] in both in vivo and in vitro experiments suggest that sst_2 mediates the inhibition of growth hormone release from pituitary somatotrophes, glucagon release from the pancreas, and gastrin and acid secretion,[7] whereas sst_5 selective analogues are believed to inhibit insulin release.[8] These results have especially suggested the usefulness of sst_2 selective analogues in the treatment of acromegaly, retinopathy, and diabetes.[9]

† Department of Biochemistry & Physiology.

It has been recognized that the Trp^8-Lys^9 residue is essential for bioactivity (GH release inhibition) based on the studies of SRIF analogues.[10] Smaller and highly potent peptidyl SRIF analogues have been synthesized and studied, and proved to be efficacious in GH release inhibition in man. The best known of these is the cyclic peptide, octreotide (H-D-Phe-$^{<}$Cys-Phe-D-Trp-Lys-Thr-Cys$^{>}$Thr-ol, **1a**, SMS 201−955, Sandostatin),[11] which is clinically used for the treatment of certain endocrine tumors and acromegaly. A different class of cyclic peptide, seglitide (c(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe), **1b,** MK-678),[12] was also studied with insulin for the treatment of insulin-dependent diabetes but not developed. Both peptides have poor oral bioavailability and are administered by subcutaneous or intravenous injection. These agonists were discovered through the rat pituitary GH release inhibition assay, which is now known to be mediated through sst_2. To extend their usefulness, nonpeptide, orally active compounds that are sst_2 selective would be highly desirable. To date, only two types of nonpeptide SRIF agonists have been reported, one was based on carbohydrate cores as a peptidomimetic scaffold,[13] the other on a benzodiazepine core.[14,15] Both designs used templates to direct the Trp and Lys side chains in approximate β-turn conformations to mimic their orientations in the cyclic peptides. Although conceptually important, the agonists generated from these approaches were quite weak (IC_{50}s in the micromolar range in SRIF binding). In this paper we describe our studies resulting in the development of a class of small molecules (MW <550) that exhibited potent SRIF agonist activities. Among them, a bis-(aminomethyl)cyclohexane analogue, 2(*R*)-[(spiro[1*H*-indene-1,4′-piperidin]-1′-ylcarbonyl)amino]-N-[3(*S*)-aminomethyl-1(*R*)-cyclohexylmethyl]-3-(1*H*-indol-3-yl)propanamide (L-054,264, **2a**), exhibited low nanomolar binding to human sst_2, functional potency, and high selectivity (>1000-fold) toward the other receptor subtypes. To the best of our knowledge, this is the first potent and selective small molecule sst_2 agonist reported.

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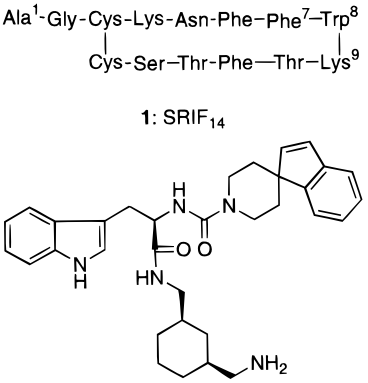


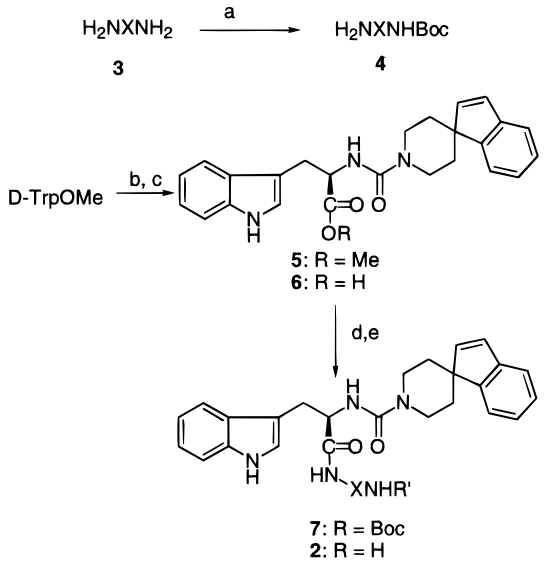
2a: L-054,264

Directed screening was used to discover the original lead from which the compounds of this report were developed. Extensive studies with the cyclic peptides have established that the key pharmacophoric elements of SRIF include Phe[7]-Trp[8]-Lys[9] and Phe[11].[16] The atomic coordinates of the side chain orientations in L-363,377 (c(Pro-Tyr-D-Trp-Lys-Thr-Phe), **1c**), which is a cyclic peptide related to **1b**, provided the initial probe for similarity searches. The peptide backbone of cyclic SRIF analogues serves as a scaffold for the side chains and is not itself important for activity.[17] Three-dimensional similarity searches[18] of the Merck flexibase[19] afforded **2b**, which was found to be a modest inhibitor of SRIF binding to murine sst_2 (K_i = 200 nM) and human sst_2 (K_i = 615 nM). Details of the searching strategy will be reported elsewhere.

Chemistry. The synthetic methods used in the preparation of these SRIF agonists are shown in Scheme 1. The mono-Boc-protected diamine **4** can be readily prepared by reacting di-*tert*-butyl dicarbonate (Boc_2O) and the diamine **3** in methanol. Treatment of D-tryptophan methyl ester with 1 equiv of *N*,*N*′-disuccinimidyl carbonate (DSC) and diisopropylethylamine (DIEA) in THF and dichloromethane (DCM) followed by addition of spiro(indene-1,4′-piperidine)[20] and DIEA gave the desired urea **5**. Saponification of the ester afforded the carboxylic acid **6**. Coupling of the acid **6** with mono-Boc-protected diamines **4** using 1-hydroxybenzotriazole (HOBT) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) in DCM yielded the Boc-protected precursor **7**, which, upon acidic deprotection, afforded compound **2**. Careful separation of the reaction intermediate **7**, where the diamine is 1,3-bis(aminomethyl)cyclohexane, by collecting the fast-moving fractions gave a single compound **2a** after Boc deprotection.

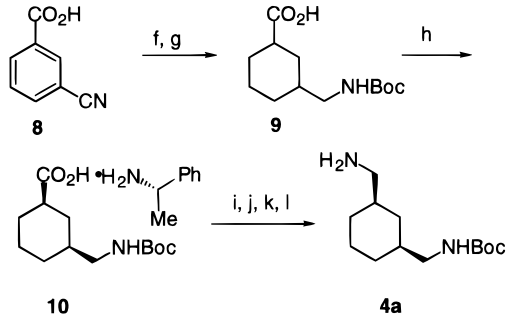
[3(*R*)-Aminomethyl-1(*S*)-cyclohexylmethyl]carbamic acid *tert*-butyl ester (**4a**) was prepared according to Scheme 2. 3-Cyanobenzoic acid (**8**) was reduced to 3-(aminomethyl)benzoic acid followed by Boc protection and hydrogenation of the benzene ring to give the predominantly (>10:1) *cis*-*N*-Boc-3-(aminomethyl)cyclohexanecarboxylic acid **9**. Chiral resolution with (*S*)-α-methylbenzylamine in ethyl acetate gave the optically pure 1*R*,3*S* compound **10**. Its stereochemistry was established through an X-ray crystal structure of the chiral salt **10**.[21] The carboxylic acid was converted to amine **4a** through a four-step procedure involving borane reduction, mesylation, azide displacement, and

Scheme 1. General Synthesis of SRIF Agonist 2



[a] Reagents: (a) Boc_2O/DCM/MeOH; (b) DSC/DCM−THF, DIEA, and then spiro(1*H*-indene-1,4′-piperidine) and DIEA; (c) LiOH/THF/MeOH/H_2O; (d) EDC−HOBT/DCM; (e) HCl/EtOAc.

Scheme 2. Synthesis of 4a[a]

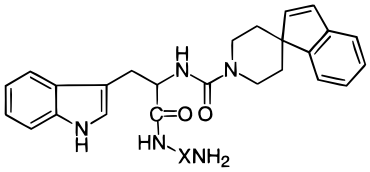


[a] Reagents: (f) Raney Ni/NH_3−EtOH, 1000 psi; Boc_2O, NaOH/H_2O−dioxane; (g) 50 psi, H_2, PtO_2, AcOH; (h) (*S*)-α-methylbenzylamine, EtOAc, 60−25 °C; (i) BH_3/THF; (j) MsCl, DMAP, DIEA, DCM; (k) NaN_3, DMF−H_2O, 60 °C; (l) H_2, 10% Pd/C, EtOH.

palladium-catalyzed hydrogenation. Incorporation of amine **4a** resulted in **2a** establishing its absolute stereochemistry.

Results and Discussion. The compounds reported here were first tested for their specific binding to the five cloned human somatostatin receptors (sst_{1-5}), expressed in CHO-K1 cell lines. Binding affinities for sst_{1-4} were determined by the displacement of [^{125}I]-Tyr[11]-$SRIF_{14}$ from the corresponding receptors. Similarly, radiolabeled $SRIF_{28}$ was used for sst_5 assay since it has a significantly greater affinity at this receptor subtype (8-fold).[5e] The functional activity was then investigated, first by the inhibition of forskolin-stimulated cAMP accumulation in stably transfected mouse L20ZH cells[22] and then by measuring the compound's ability to inhibit the release of growth hormone in vitro (rat pituitary cell assay). The latter assay is especially relevant to the sst_2 receptor, and it had been used for the earlier SRIF analogue work before the receptors were cloned.[12] Without exception, all of the compounds studied in this paper were full agonists (Table 1).There is a marked preference for the D stereochemistry in the current compounds since the D-Trp analogue (**2c**) is almost 30-fold more potent than the L isomer **2d**; such a difference was not observed with cyclic peptide SRIF

Table 1. sst_2 Receptor Binding Affinities of 2

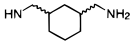
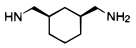
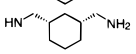


entry	Trp	-NHXNH$_2$	sst_2 K_i (nM)[a]
1c			0.5
2b	D/L	-NH(CH$_2$)$_4$NH$_2$	615
2c	D	-NH(CH$_2$)$_4$NH$_2$	300
2d	L	-NH(CH$_2$)$_4$NH$_2$	10000
2e	D	-NH(CH$_2$)$_3$NH$_2$	815
2f	D	-NH(CH$_2$)$_5$NH$_2$	46
2g	D	-NH(CH$_2$)$_6$NH$_2$	225
2h	D	-Lys-NH$_2$	53
2i	D	-Lys-OH	1108

[a] All compounds were examined over a range of concentrations from 0.01 nM to 10000 nM using full log dilutions and seven-point titrations to determine IC50 values. All experiments were performed in triplicate with replicate values varying less than 10%. Compounds were tested in at least two completely separate experiments. Reported values represent averages from pooled experiments.

and its agonists. In fact, (D-Trp^8)-SRIF$_{14}$ has the same potency as its native form, and the peptidyl SRIF analogues were mostly indiscriminate toward the stereochemistry of Trp^8.[23] Shortening the amino side chain of **2c** caused a 2−3-fold drop in affinity (**2e**), while extending it by one carbon resulted in more than 6-fold increase in binding (**2f**). Further lengthening the chain caused a drop in affinity (**2g**). The optimal linear amine is 1,5-diaminopentane with five carbons separating the amino groups, as is the case for lysine, suggesting correspondence at the D-Trp^8 and Lys^9 residues of the cyclic SRIF agonists. It is worth noting that the incorporation of a lysine amide (**2h**) did not further improve potency and incorporation of a lysine free acid (**2i**) renders the compound quite inactive. Possibly intramolecular hydrogen bonding causes the lysine amide to have a slightly different conformation than the Trp^8-Lys^9 amide has when presented in a cyclic peptide.

Table 2. Binding Affinities (K_i, nM) of SRIF Agonists at sst_{1-5} Receptors

entry	-NHXNH$_2$	sst_1	sst_2	sst_3	sst_4	sst_5
2b	-NH(CH$_2$)$_4$NH$_2$	4264	615	5686	>10000	>10000
2f	-NH(CH$_2$)$_5$NH$_2$	5382	46	2574	6840	>10000
2j		537	4	3614	2480	5017
2a		1740	1.6	2950	2000	4470
2k		2430	20	3688	2176	3316
1	SRIF$_{14}$	0.38	0.04	0.66	1.76	2.32

The unconstrained amino side chain of these compounds is an obvious site for improvement,[24] and fortunately, such studies proved to be very fruitful. We sought to decrease flexibility by introducing ring restrictions and thereby identify an optimal binding conformation. Extensive studies with different cyclohexane and piperidine-based diamines confirmed that a five-carbon spacer between the two nitrogens is essential for high potency.[25] Also important was the observation that the side chain preferred a fully extended form. Among them, commercially available 1,3-bis(aminomethyl)-cyclohexane showed the best potency enhancement. The diamine is a mixture of cis and trans isomers with cis being predominant. As can be seen from Table 2, the isomeric mixture **2j** is 10-fold more potent than the linear compound **2f**. More importantly, compound **2j** exhibited higher receptor selectivity toward sst_2 than **2f**. The single isomer **2a** showed marked improvement in sst_2 affinity (K_i = 1.6 nM) and selectivity (>1000-fold) in the receptor binding assay over the other four receptors. Compound **2a** showed full agonism on sst_2 in the inhibition of forskolin-stimulated accumulation of cAMP with an IC_{50} of 2 nM, and it also inhibited the release of growth hormone in the rat pituitary assay with IC_{50} of 6 nM. The other isomer **2k** was less active than **2a**. A comparison of our small molecule SRIF agonists with SRIF$_{14}$ is shown in Table 2.

The excellent potency and selectivity for sst_2 which was achieved with **2a** may be due to a combination of

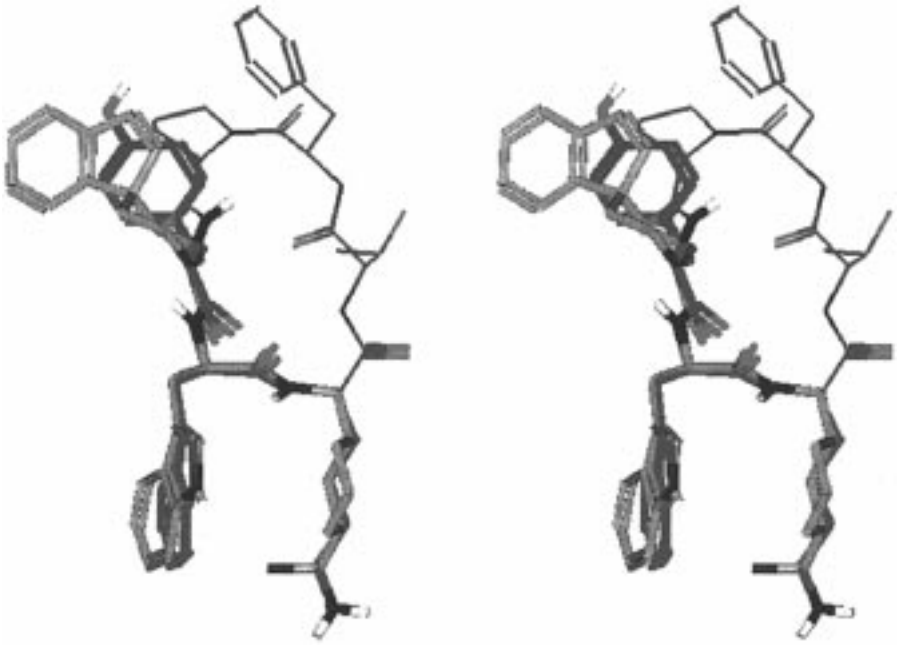


Figure 1. Stereoview of the superposition of **2a** and the cyclic peptide **1c**.

factors. Potency presumably derives from three critical binding elements of SRIF, the Trp^8-Lys^9 mimetic and a lipophilic spiroindene moiety capable of binding in the receptor pockets occupied by Phe^6 and/or Phe^{11} of the native ligand. Improved selectivity as well as potency arises from the use of a ring to enforce conformational rigidity onto the amino side chain to reduce the flexibility of the lysine surrogate, making it fit particularly well to sst_2. Our work demonstrates that one can approach the agonist potency of the large peptide SRIF with a small molecule like **2a**, and improved selectivity is an added bonus. Figure 1 depicts the superposition of **2a** onto the peptide probe originally used to identify the lead compound. The conformation of **2a** was derived by energy minimization using MMFF94(s).[26] As shown in the figure, the D-Trp bis(aminomethyl)cyclohexane amide portion of the **2a** maps to the Trp^8-Lys^9 of **1c**. The spiroindene reaches the space occupied by either the Tyr^7 or the Pro. These modeling studies provided us a convenient way to visualize and compare our small molecule ligands with the cyclic peptides in three dimensions and generated stimulating ideas in the design of even more potent and selective compounds.

In summary, **2a** is a structurally novel, potent and selective sst_2 receptor agonist. The further exploitation of the SAR and optimization of this class of SRIF agonists will be reported subsequently.

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Supporting Information Available: Details of experimental and spectral data for compounds **2a** and **2k** (7 pages). Ordering information is given on any current masthead page.

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