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Diamine Derivatives as Novel Small-Molecule, Potent, and Subtype-Selective Somatostatin SST3 Receptor Agonists

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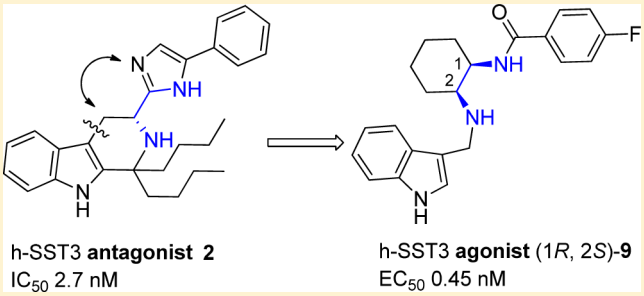
Supporting Information

ABSTRACT: A novel class of small-molecule, highly potent, and subtype-selective somatostatin SST3 agonists was discovered through modification of a SST3 antagonist. As an example, (1*R*,2*S*)-**9** demonstrated not only potent in vitro SST3 agonist activity but also in vivo SST3 agonist activity in a mouse oral glucose tolerance test (OGTT). These agonists may be useful reagents for studying the physiological roles of the SST3 receptor and may potentially be useful as therapeutic agents.



KEYWORDS: *Somatostatin, GPCR, somatostin receptor subtype 3 (SST3), small-molecule SST3 agonists*

Somatostatins (somatotropin-release inhibiting factors [SRIF]) are a family of cyclopeptides that are produced by normal endocrine, gastrointestinal, immune, and neuronal cells, as well as by certain tumors.[1,2] The actions of SRIF are mediated by five distinct somatostatin receptors (SST1−5) that belong to the seven-transmembrane, G-protein-coupled receptor (GPCR) family.[3,4] SRIF exhibits multiple biological functions such as inhibition of the release of growth hormone, insulin, glucagon,[5] and gastrin.[6] SRIF also acts as a neuromodulator in the central nervous system (CNS).[7,8] Various SRIF-related peptides, including SRIF-14 and SRIF-28, containing 14 and 28 amino acids, respectively, have been identified.[9] The pan-antisecretory profile of natural SRIF-14 has led to exploratory clinical trials for the treatment of a range of conditions, including diabetes (types I and II), hypersecretory tumors, such as growth hormone-secreting pituitary adenomas, gastrinomas, insulinomas, glucagonomas, and VIPomas, and gastrointestinal disorders.[9,10] These studies also showed that the full therapeutic potential of SRIF cannot be exploited owing to its short plasma half-life (<3 min).[11] Peptide analogues of SRIF with enhanced metabolic stability have been developed for clinical use. For example, cyclic peptide analogue SMS 201−995 (octreotide) was introduced into clinical practice as an injectable depot formulation for the treatment of acromegaly (growth hormone oversecretion), diarrhea associated with vasoactive intestinal peptide-secreting tumors (VIPomas), and carcinoid syndrome.[12] There is also strong interest in developing subtype selective, small molecule ligands to reduce the side effects that are associated with pan-somatostatin agonist activity.[13] The objective to identify orally bioavailable low molecular weight antagonists/agonists is also desirable. Herein, we report the discovery of potent SST3 small-molecule agonists.

Somatostatin receptor subtype 3 (SST3) has been shown to be present in brain, pituitary, stomach, pancreas, thymus, thyroid, prostate, and vascular endothelial cells. In addition to suppressing the secretion of several hormones, SST3 is implicated in apoptotic signaling and proliferation, and several studies have indicated that this signaling proceeds via modulation of phosphotyrosine phosphatase activity and localization. Preclinical studies assessing angiogenesis and tumorigenesis in both cultured endothelial cells and in vivo tumor xenograft models have suggested that SST3 agonists may be useful in cancer therapy.[14−16] To date only one small-molecule peptidyl partial SST3 agonist, L-796,778 (K_i = 24 nM, Figure 1), has been discovered about two decades ago.[13]

Recently, Moinet et al. reported the discovery of imidazolyl derivatives that bind selectively to SST3 with moderate affinity (Figure 2).[17] To introduce conformational rigidity, **1** was submitted to Pictet−Spengler cyclization to afford the corresponding tetrahydro-beta-carbolines, represented by **2**.[18] Biological studies showed that **2** exhibited high affinity to human SST3 (h-SST3, K_i = 0.64 nM) and acted as a potent SST3 antagonist by inhibiting SRIF-14 (1 nM) induced

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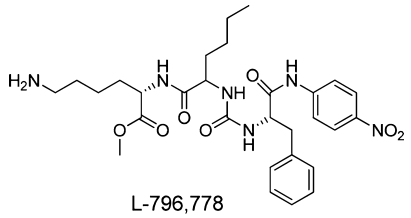


Figure 1. Structure of L-796,778 and its inhibition constant (K_i) on somatostatin subtype receptor-3 (SST3).

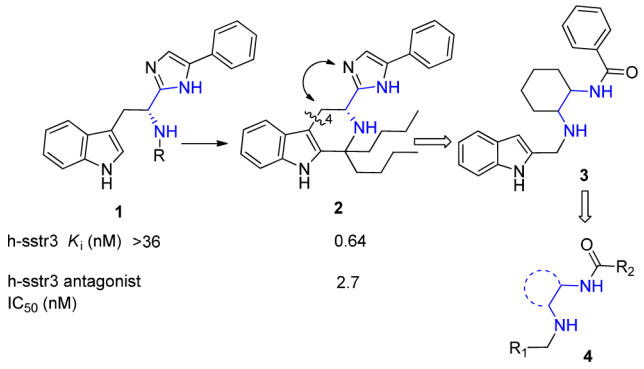


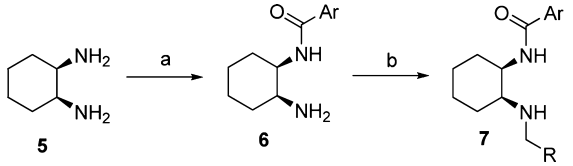
Figure 2. Analysis of tetrahydro-beta-carboline **2** lead to diamine analogues.

reduction of cAMP accumulation induced by forskolin (1 μM) in CHO-K1 cells expressing human SST3. The molecular constraint introduced into **1** to afford **2** suggests the spatial orientation of the two N-Hs created by this rigidity might be a key interaction for high affinity.

We were interested in simplifying this class of compounds to identify novel small molecule SST3 ligands. Incising C4 of **2** and introducing additional ring constraints would give a diamine, such as **3** (Figure 2), with a rigid orientation of the two N−Hs. Another advantage of this system is the diamines would expedite rapid analogue synthesis for biological evaluation (e.g., **4**).

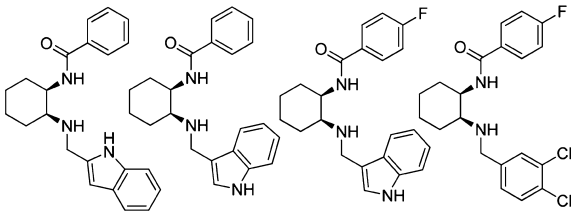
The initial synthesis of analogues began with monoacylation of *cis*-1,2-diaminocyclohexane **5**.[19] Reductive amination of aminoamide **6** afforded the desired racemic diamine analogues (Scheme 1).[20]

Scheme 1. Synthesis of Diamine Analogues[a]



[a]Reagents and conditions: (a) 9-BBN, THF, rt, 1 h, then ArCOCl, rt, 2 h; (b) RCHO, $NaBH(OAc)_3$, DCE, rt, overnight; or RCHO, 4 Å MS, MeOH, overnight, then $NaBH_4$.

Analogue **3** afforded modest binding affinity to human SST3 (h-SST3) (Figure 3).[21] Interestingly, when **3** was evaluated for functional activity, it showed no antagonist activity and was unable to block the inhibitory effect of SRIF-14. However, **3** alone showed weak agonist activity by reducing the cAMP production elicited by forskolin. Its close analogue **8** showed a



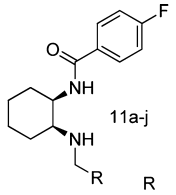
	3	**8**	**9**	**10**
h-SST3 K_i, nM	17	32	3.78	6.84
h-SST3 antagonist (% inhibition of SRIF-14 activation@2 uM)	(-27%)	(-21%)	(-14%)	(-10%)
h-SST3 agonist EC_{50}, nM (%activation@2 uM)	(43%)	(36%)	2.88 (97%)	6.1 (91%)

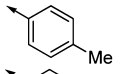
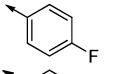
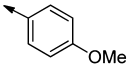
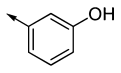
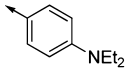
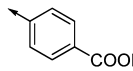
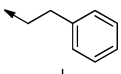
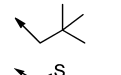
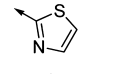
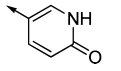
Figure 3. Racemic diamine analogues, and h-SST3 binding affinity and agonist/antagonist activity.

similar binding and agonist activity profile. Rapid structure−activity relationship (SAR) development revealed that 4-fluorophenyl analogue **9** showed single digit nanomolar h-SST3 affinity. More interestingly, it is a potent SST3 agonist with EC_{50} = 2.9 nM (97% activation at 2 μM). Replacement of the indole with a dichlorophenyl moiety gave **10**, which is also a potent SST3 agonist.

Improvements in h-SST3 binding affinity and/or agonist/antagonist activities were modulated by changing the substitution on the benzylamine. The compounds and SST3 results are listed in Table 1. It is clear that variation at this position has a strong influence on SST3 affinity. The simple

Table 1. Human SST3 Binding Affinity and Agonist Activity of Racemic Aminoamides 11a−j



	R	h-SST3 K_i, nM	Human agonist EC_{50} (nM) (%activation@2 uM)
a		65	122 (97%)
b		37	21 (98%)
c		21	13 (100%)
d		90	36 (93%)
e		101	26 (96%)
f		>12000	15200 (62%)
g		65	59 (100%)
h		76	11 (98%)
i		>12000	(11%)
j		>12000	(30%)

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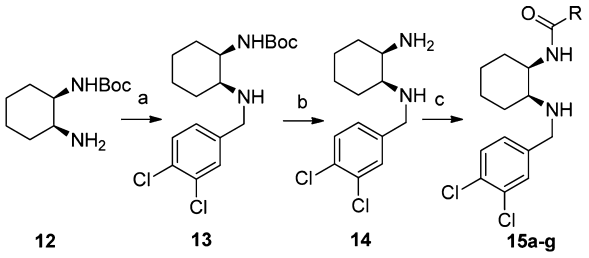
methylphenyl analogue (**11a**) shows modest SST3 affinity and agonist activity. Different substituted phenyl analogues with different electron properties (**11b–e**) had modest SST3 affinity but maintained agonist activity. However, benzoic acid analogue (**11f**) was not tolerated. Extension of the linkage to a two-carbon linkage (**11g**) had a small effect on affinity. The sterically bulky *tert*-butyl analogue (**11h**) showed modest affinity. Both the affinity and agonist activity were lost when heterocyles like thiazole (**11i**) and pyridone (**11j**) were incorporated.

Having identified the indole (**9**) and 3,4-dichlorophenyl (**10**) moieties as optimal substitution on the amine, efforts to study the SAR of the amide moiety were initiated. 3,4-Dichlorobenzyl was held constant on the amine end because of its chemical stability. The synthesis began from Boc-protected racemic *cis*-1,2-diaminocyclohexane. Reductive amination of racemic **12** gave **13**. Removal of the Boc protecting group of **13**, followed by monoacylation afforded the desired analogues **15a–g** (Scheme 2).

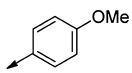
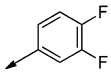
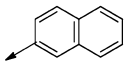
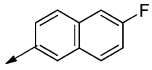
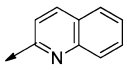
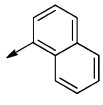
Scheme 2. Synthesis of 15[a]



[a]Reagents and conditions: (a) 3,4-dichlorobenzaldehyde, $NaBH(OAc)_3$, DCE, rt, overnight; (b) 4 N HCl in dioxane, MeOH, rt, overnight; (c) RCOCl, CH_2Cl_2, rt, 2 h.

Phenyl amide (**15a**), methoxyphenyl analogue (**15b**) showed modest h-SST3 affinities and very little agonist activity (Table 2). 3,4-Difluorophenyl (**15c**) was comparable to 4-fluorophenyl

Table 2. Binding Affinity and Agonist Activity on h-SST3 of Racemic 15a–g

	R	h-SST3 K_i, nM	Human agonist EC_{50} (nM) (%activation@2 uM)
a		97	(31%)
b		48	(47%)
c		4.48	4.53 (100%)
d		0.815	0.516 (97%)
e		3	1.6 (93%)
f		151	26 (63%@300nM)
g		42	22 (67%@300nM)

analogue (**10**) in terms of affinity and agonist activity. 2-Naphthyl analogue (**15d**) further boosted both SST3 affinity and potency as an agonist. Putting an additional fluorine atom on the 6 position (**15e**) did not enhance binding/agonism. 2-Quinoline analogue (**15f**) was much less potent compared with 2-naphthyl analogue (**15d**). 1-Naphthyl analogue (**15g**) was also less active.

The SAR of the diamine backbone was then explored (Figure 4). Interestingly, the racemic *trans*-cyclohexane diamine analogue (**16**) was equal potent as the cis-analogue (**9**), despite the very different orientation of the N–Hs in these two compounds. All four enantiomeric isomers of cyclopentane diamine analogues (**17–20**) were prepared starting from commercially available starting materials. In general, the amides with the absolute *R* configuration are more potent than those with the *S* configuration (**17** vs **18** and **19** vs **20**). This suggests that the more potent isomer of analogue **9** has the *R* configuration at the amide. Unlike six- and five-membered analogues, both of the racemic *cis*- and *trans*-cyclopropane diamine analogues (**21** and **22**) lost SST3 affinity and only showed weak agonist activity. Acyclic diamine analogue **23** also lost SST3 affinity.

This study suggested that the cyclohexane backbone is the optimal structural motif for SST3 affinity. We also studied the orientations of two N–Hs by changing 1,2 diamines to 1,3 and 1,4 diamines. The cis- and trans-isomers of **24** and **25** lost SST3 affinity and only showed weak agonist activity. Rigid phenyl diamine analogue **26** lost SST3 binding affinity.

Variations of the linkage on the cyclohexane ring were investigated next to better understand the role of the two N–Hs (Figure 5). The analogues were prepared as racemic isomers for synthetic expedience. Reductive amination of **9** with formaldehyde gave amine **27**, which showed modest SST3 binding affinity and agonist activity.

Diamide **28** greatly lost SST3 binding affinity. Replacement of the N–H with oxygen gave **29**, which also lost binding affinity and most agonist activity. These all suggested that basic N–H may play an important role in the binding and functional activities of these aminoamides, presumably through hydrogen bonding. Replacement of amide with ester (**30**) greatly lost SST3 binding affinity and all functional activity. While urea **31** maintained binding affinity and modest agonist activity, carbamate analogue **32** only showed weak agonist activity. The reverse amide, *cis*- and *trans*-*β*-amino acid analogues **33** and **34** were also synthesized. Interestingly, **33** showed modest SST3 binding and agonist activity. Unlike the diamine analogues, where cis- and trans-analogues (**9** and **16**) showed similar activity, the trans-analogue **34** was much less potent.

Since racemic **9** proved to be the optimal SST3 agonist, it was separated into two enantiomers, by using SFC-HPLC with a Chiralpak AS.[22] One enantiomer was much more potent than the other and since only limited material was separated, the less potent enantiomer was subjected to recrystallization for single-crystal X-ray analysis. The structure determination proved the absolute configuration of the less potent enantiomer to be (1*S*,2*R*) (Figure 6) thereby determining the configuration of the potent enantiomer to be (1*R*,2*S*).[22] The more potent (1*R*,2*S*)-**9** was then tested against human, rhesus monkey, and dog SST3 in a binding assay and showed potent binding affinity with K_i = 0.89, 1.8, and 0.74 nM, respectively. Compound (1*R*,2*S*)-**9** also exhibited potent agonist activities in human, dog, and mouse SST3 agonist functional assays. Compound (1*R*,2*S*)-**9** was further profiled in a panel of cell lines expressing

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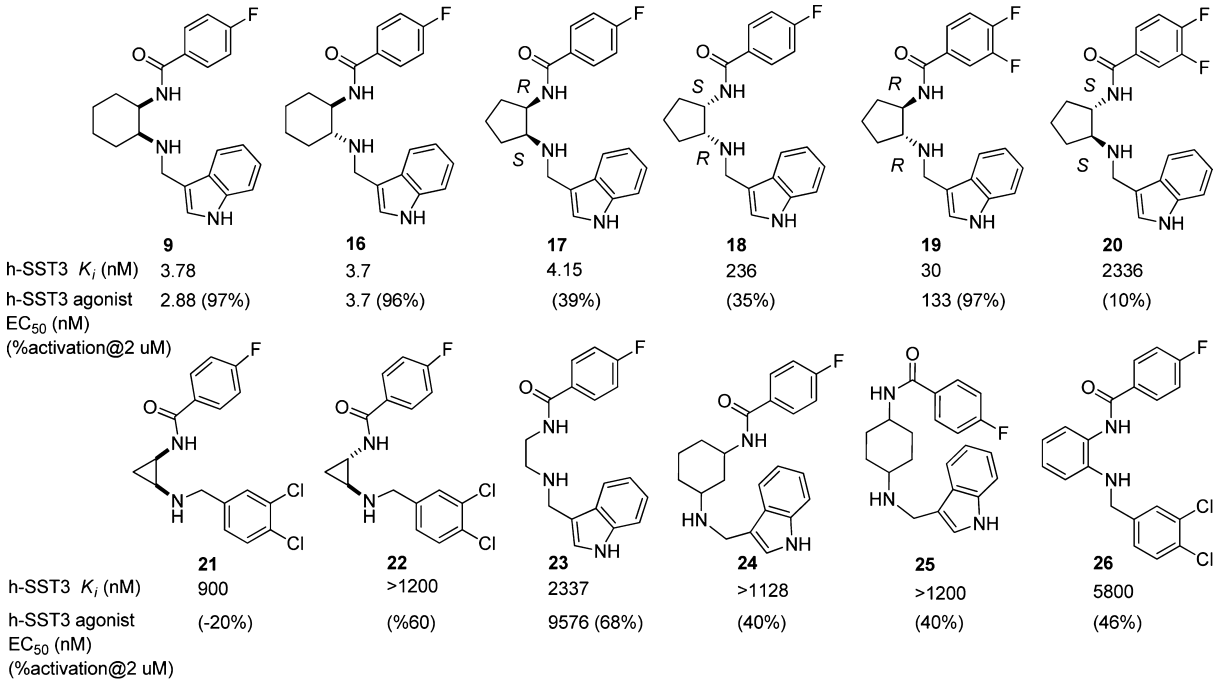

Figure 4. Structures, binding affinity, and agonist activity of diamine backbone analogues.

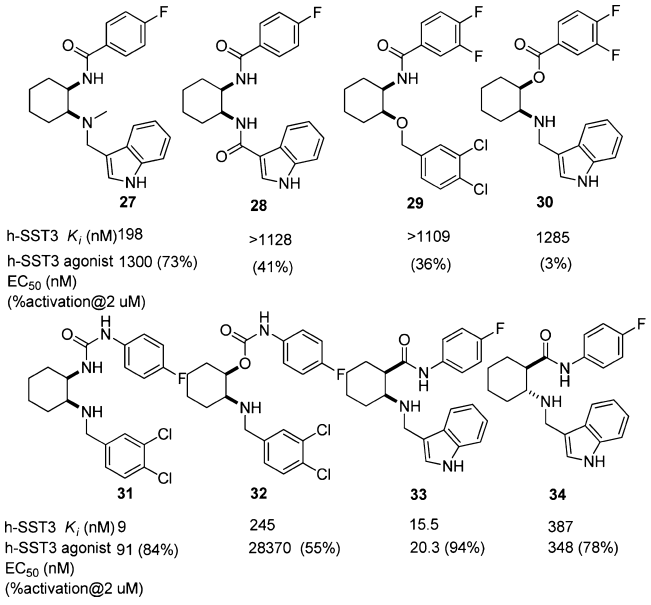

Figure 5. SAR of the linkages of diamine analogues.

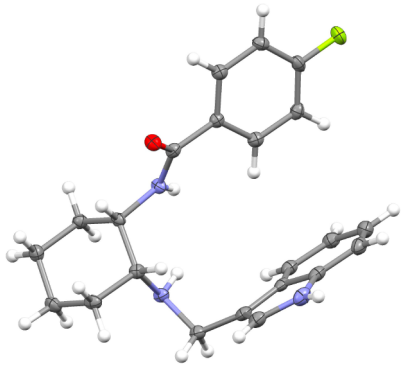

Figure 6. X-ray crystal structure of (1*S*,2*R*)-**9**.

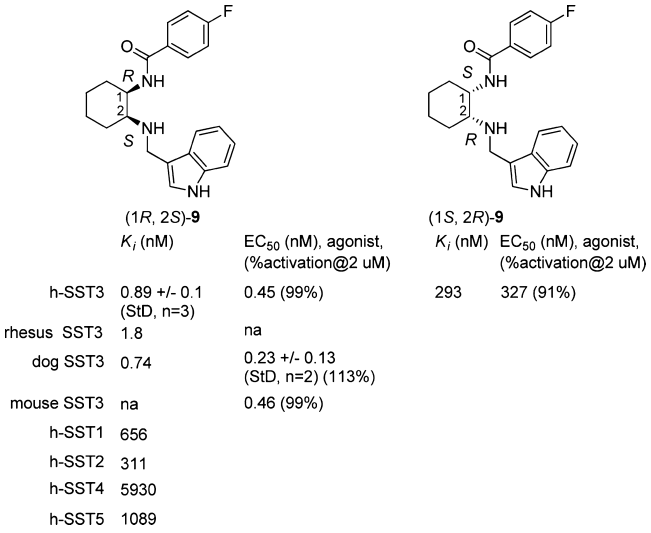

Figure 7. Binding affinity and agonist activity for human, rhesus monkey, dog, and mouse SST3 and other human somatostatin subtype receptors. StD is standard deviation.

the other four human receptor subtypes (h-SST1, 2, 4, 5). As indicated in Figure 7, the selectivity of (1*R*,2*S*)-**9** over h-SST1, 2, 4, 5 is excellent (>300-fold).

Since (1*R*,2*S*)-**9** demonstrated highly potent in vitro SST3 agonist activity, its in vivo agonist activity was investigated. Recently, antagonism of SST3 was reported to have the potential to be a novel glucose-dependent insulin secretion (GDIS) mechanism for the treatment of type 2 diabetes mellitus (T2DM).[23,24] SST3 is highly expressed in β-cells of human and rodent islets. Silencing the expression of SST3 with siRNA significantly enhanced GDIS in a rat insulinoma cell line, INS-1 cells. The importance of SST3 in regulating GDIS and glucose homeostasis was further supported by the reports that a selective SST3 antagonist MK-4256[25] (Figure 8, human

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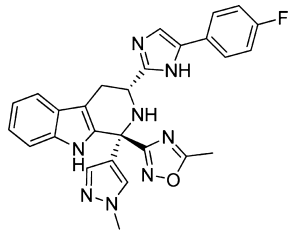

MK-4256

h-SST3 antagonism IC50, nM (% inh.)	0.95 +/- 1.72 (StD, n=26) (83%)
mouse SST3 antagonism IC50, nM (% inh.)	0.46 +/- 0.75 (StD, n=30) (87%)

Figure 8. Structure of MK-4256 and its human and mouse SST3 antagonism activity. StD is standard deviation.

antagonism IC_{50}, 0.95 nM (83% inhibition @ 2 μM), mouse antagonism IC_{50}, 0.46 nM (87% inhibition @ 2 μM), and human agonism (6% activation @ 20 μM)) reduced blood glucose levels (97% reduction of glucose excursion at 1 mg/kg) during a mouse oral glucose tolerance test (OGTT) (Figure 9,

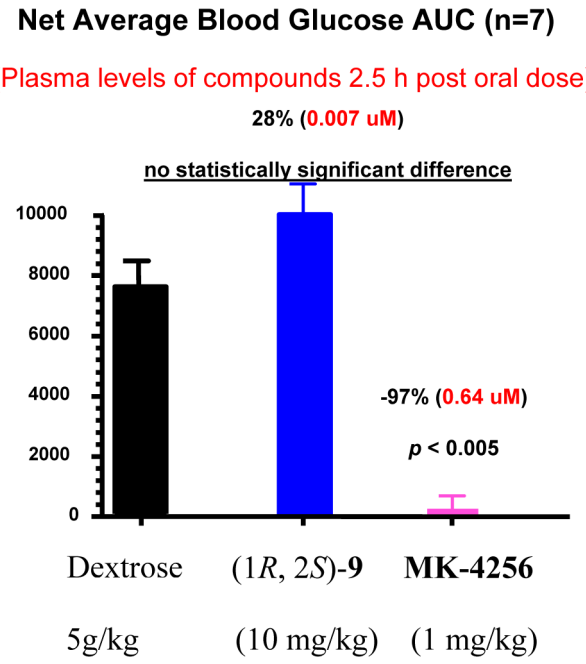

Figure 9. Compound (1*R*,2*S*)-**9** increased glucose excursion in mouse oGTT model. For MK-4256, $P < 0.005$ via ANOVA and Dunnett's test.

the black bar represents the glucose excursion when the mice were challenged orally with dextrose only (5 g/kg)).[26] Therefore, SST3 agonists would, in theory, increase blood glucose levels during OGTT. Indeed, when (1*R*,2*S*)-**9** (10 mg/kg) was subjected to mouse OGTT (by oral gavage, 30 min prior to glucose loading), it increased blood glucose level by 28% (Figure 9) relative to dextrose alone. The plasma concentrations of (1*R*,2*S*)-**9** were determined at the completion of the OGTT study (2.5 h postadministration) and found to be low (0.007 μM).

In summary, a novel class of small-molecule, highly potent, and subtype-selective somatostatin SST3 agonists has been described. Compound (1*R*,2*S*)-**9** also demonstrated in vivo SST3 agonist activity in a mouse OGTT model. These agonists are useful tools for studying the physiological roles of the SST3 receptor and have the potential to be potent leads for developing effective therapeutic agents including cancer therapy.

■ ASSOCIATED CONTENT

Supporting Information

Syntheses and characterization data for compound **9**; X-ray and assay protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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