Optimization of Preclinical Metabolism for Somatostatin Receptor Subtype 5-Selective Antagonists

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Supporting Information

ABSTRACT: A series of structurally diverse azaspirodecanone and spirooxazolidinone analogues were designed and synthesized as potent and selective somatostatin receptor subtype 5 (SSTR5) antagonists. Four optimized compounds each representing a subseries showed improvement in their metabolic stability and pharmacokinetic profiles compared to those of the original lead compound **1** while maintaining pharmacodynamic efficacy. The optimized cyclopropyl analogue **13** demonstrated efficacy in a mouse oral glucose tolerance test and an improved metabolic profile and pharmacokinetic properties in rhesus monkey studies. In this Communication, we discuss the relationship among structure, in vitro and in vivo activity, metabolic stability, and ultimately the potential of these compounds as therapeutic agents for the treatment of type 2 diabetes. Furthermore, we show how the use of focused libraries significantly expanded the structural class and provided new directions for structure–activity relationship optimization.

KEYWORDS: Somatostatin, SSTR5 antagonists, Type 2 diabetes mellitus (T2DM), Glucose-dependent insulin secretion (GDIS), Metabolic stability

Somatostatin (SST) is a peptide hormone that exists in two isoforms of 14 and 28 amino acids (SST-14 and SST-28), respectively,¹ and is widely distributed throughout the body.² The SST-mediated biological effects involve a broad range of functional regulation and hormonal secretion control and are effected through interaction with five distinct G-protein-coupled receptors (SSTR1–5). The target SSTR5 is prominently expressed in pancreatic islet β cells as well as in enteroendocrine cells of the gastrointestinal (GI) tract,³ inhibiting the secretion of both insulin and the insulinotropic glucagon-like peptide 1 (GLP-1).⁴ SSTR5 knockout (KO) mice displayed decreased susceptibility to high fat diet (HFD)-induced insulin resistance,⁵ and SSTR5 selective small molecular antagonists have been reported to lower glucose and insulin excursion during an oral glucose tolerance test (OGTT) in both mice and rats.^{6–8} On the basis of these cellular and preclinical pharmacology studies, SSTR5 is an attractive investigational target for treatment of type 2 diabetes mellitus (T2DM).

In the preceding manuscript in this issue, we reported the discovery of the azaspirodecanone analogue **1** as a novel and highly potent and selective SSTR5 antagonist.⁹ Compound **1** demonstrated a significant glucose lowering effect in a dose-dependent manner in rodent diabetic models and instigated increased pancreatic insulin secretion as well as total and active GLP-1 release. This SSTR5 antagonist also showed synergistic effects in combination with a dipeptidyl peptidase IV (DPP-4) inhibitor.

Unfortunately, advanced profiling of **1** revealed impediments to developing the compound as a clinical candidate. The metabolic turnover of **1** was low in liver microsomes from human, rat, and dog with >80% of the parent compound remaining intact following 30 min incubation in microsomes from each species. Therefore, dogs were investigated as a nonrodent species for safety assessment studies. However, we found persistent emesis in dogs in a 7 day tolerability study at 5–45 min post oral administration for doses of 20 mg/kg or greater.¹⁰ This persistent canine emesis would confound preclinical safety observations in this species and limit exposure of **1** in advanced profiling investigations.

Preclinical profiling in rhesus monkeys was pursued. We found significantly greater metabolic turnover of **1** in rhesus monkey microsomes as compared to that in other species with only 28% of the parent compound remaining following 30 min incubation. In rhesus oral dose tolerability studies, administration of **1** for 5 days (50 mg/kg QD) was well tolerated without emesis. Metabolite identification was performed using LC-MS-MS plasma analysis on day 5 (Figure 1), showing significant metabolism in vivo. Glucuronidation was observed on the carboxylic acid, resulting in metabolite M6 and a small amount of hydroxylation on the benzoic acid (M5). However, the majority of metabolites were from oxidation on the

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Figure 1. Representative HPLC chromatogram of plasma from a rhesus monkey treated with 50 mg/kg of compound **1** QD (day 5).

biphenyl ring and de-ethylation of the ethoxyl group (M1–4). We suspected that the biphenyl ring was activated by the two electron donating ethoxyl groups and became susceptible to oxidation catalyzed by cytochrome P450 bioactivation. The multiple reactive phenols, biphenols, or triphenols generated from oxidation, hydroxylation, and de-ethylation of **1** posed a potential safety risk for the compound as a development candidate.¹¹

This biaryl tail piece in **1** was first reported by Mohr and co-workers as an optimal SSTR5 potency enhancing substituent,¹² and this moiety has been utilized in multiple subsequent studies.^{7,8,12} In light of the metabolic liabilities associated with this substituent in preclinical safety species, our focus turned to exploring the structure–activity relationship (SAR) of the tail piece of **1** with the objective of improving metabolic stability while maintaining SSTR5 antagonistic activity and other desired properties.

Small and focused libraries of analogues were designed with different replacements for the biaryl tail piece. Electron-withdrawing groups such as Cl, F, and CF₃ were introduced to limit oxidation on the aromatic ring. Positioning such as ortho, meta, and para was explored to optimize potency; cyclopropyl groups were introduced to replace aromatic rings to limit CYP-induced aromatic oxidation. The members of these libraries were synthesized and characterized as individual compounds, and libraries in this sense refer to collections of compounds prepared using solution-phase parallel synthetic techniques. The results from the synthesis and testing of these compounds are shown in [Tables 1](#) and [2](#). We monitored rhesus microsome stability to identify a suitable preclinical safety candidate with a development advantage over compound **1**.

The typical synthetic procedure is outlined in [Scheme 1](#) and involved reductive amination of the appropriate aryl aldehyde

Scheme 1. Synthetic Route of Spiropiperidine Analogues^a

^aReagents and conditions: (a) Na(OAc)₃BH, AcOH (method A) or MP-BH₃CN resin, AcOH (method B) as described in the [Supporting Information](#); yields range from 48 to 95%.

to the spiro-piperidine core piece. Details on the synthesis of the spiro-piperidine substituent and representative tail pieces are described in the preceding report⁹ and [Supporting Information](#). From over 200 prepared analogues, four structural classes of compounds emerged as lead series: the

biaryls, monoaryls, chromanes, and indoles. Each of these four classes was explored with traditional medicinal chemistry iteration.

[Table 1](#) lists representative examples from the biaryl and monoaryl subclasses of analogues. All compounds from these libraries were tested in SSTR5 ligand binding assay and cell-based cAMP functional assays to measure SSTR5 antagonism. Once the tractable SAR was established with a series, further analogues were prepared and evaluated for their metabolic stability in liver microsome incubation assays. Test compounds were incubated with microsomes from human, rat, dog, and/or rhesus monkey liver preparations. The results from human and rhesus monkey microsomes are presented in [Tables 1](#) and [2](#) as a comparator to the Phase I oxidative metabolism issues identified with **1**. However, these microsomal assays do not inform on the propensity for Phase 2 glucuronidation.

The biaryl series (**2**–**10**) was explored with halogens, trifluoromethyl, and alkyl groups replacing the diethoxy groups in **1** and at different positions to limit metabolism. The tolerated connection point of the biaryl was found to be either the para- (**2**–**5**) or ortho- (**6**–**10**) positions, and the second phenyl group can be substituted by pyridines (**6**) or other heterocycles such as a pyrazole (**10**). The ortho-connected biaryls are generally more potent than the para-connected biaryls, and larger alkyl substitutions in the meta position on the proximal aromatic ring (cyclopropyl or trifluoromethyl) are necessary for potency. These SAR iterations demonstrated that the metabolically labile diethoxyl groups of **1** can be eliminated or replaced. However, the resulting analogues (**3**, **5**, and **8**) were less potent in SSTR5 agonist functional (cAMP) activity. The loss of potency against the human receptor could be compensated for by modification of the spiro-piperidine core group by replacing the γ -lactam CH₂ substituent with oxygen. This permutation afforded compounds with similar SSTR5 potency (**1** vs **2**) or improved potency (**7** vs **8**) in SSTR5 functional activity. The potency gained by modification of the core group permitted the use of more diverse tail substituents that impart improved microsomal stability compared that of **1** and **2** and are devoid of the metabolically labile ethoxy substituents.¹³

The monoaryl series represented by **11**–**17** evolved from our SAR work on the biaryl series, where we noticed that replacement of the distal aryl by a cyclopropyl group retained most of the SSTR5 activity of the resulting compounds. Previous efforts removing or replacing the distal aryl with other groups such as simple alkyl, alkoxy, and halogen had all resulted in some loss of potency (**11**). Therefore, a focused library of these monoaryls with cyclopropyl substitutions was designed and synthesized in the form of individual analogues. Meta-cyclopropyl analogues (**12**) are slightly more potent than the ortho (**13**) or para (**14**) substituted analogues. Similar to the biphenyl series, compounds with spiro-oxazolidinone core group are more potent than their lactam counterparts (**15** vs **16**). Electron-withdrawing groups such as F, Cl, and CF₃ were introduced to minimize metabolism as well as increase potency. Replacement of the phenyl with pyridyl (**17**) was tolerated.

The chromane and indole series ([Table 2](#)) were first identified through synthesis and screening of libraries where a diverse set of aryl groups from commercial sources and our internal collections were attached to the spiro-piperidine core group. Potent compounds from this library were followed up with traditional medicinal chemistry, resulting in 30 chromane

Table 1. Representative Analogues from the Biaryl and Monoaryl Subclasses of Spiropiperidine SSTR5 Antagonists

Compound	Structure R =	X	hSSTR5 Binding ^a IC ₅₀ (nM) (% max) ^b	hSSTR5 cAMP ^c IC ₅₀ (nM) (% max) ^d	mSSTR5 cAMP IC ₅₀ (nM) (% max)	Microsomal stability ^e (H / Rh)	Ligand Efficiency (LE)
1		CH ₂	1.2 (99)	1.1 (78)	0.9 (80)	92 / 28	0.30
2		O	0.8 (100)	1.5 (66)	0.3 (75)	90 / N.D.	0.31
3		CH ₂	N.D.	78 (50)	994 (65)	N.D.	--
4		O	0.2 (100)	0.4 (90)	1.7 (97)	78 / 28	0.34
5		CH ₂	17 (102)	36 (54)	64 (61)	86 / 76	0.29
6		O	2.9 (97)	0.8 (71)	21 (88)	86 / 81	0.31
7		O	1.2 (98)	3.2 (112)	232 (104)	88 / 86	0.30
8		CH ₂	4.9 (94)	20 (43)	120 (63)	100 / 94	0.28
9		O	2.4 (95)	3.2 (64)	174 (81)	89 / 89	0.29
10		O	5.5 (93)	1.0 (95)	49 (84)	N.D.	0.30
11		O	95 (96)	66 (83)	>3000	N.D.	0.28
12		O	1.8 (98)	1.2 (67)	9.3 (90)	N.D. / 45	0.35
13		O	2.1 (100)	2.4 (111)	43 (78)	99 / 94	0.35
14		O	4.1 (99)	3.2 (36)	42 (51)	81 / 59	0.34
15		O	0.7 (98)	0.4 (87)	57 (86)	100 / 92	0.36
16		CH ₂	19 (93)	37 (62)	298 (72)	N.D. / 88	0.30
17		O	8.2 (108)	5.7 (105)	46 (90)	N.D. / 88	0.34

^aIC₅₀ values were calculated as the mean of minimally duplicate experiments with less than threefold variance for acceptance of results. ^bBinding inhibition at 10 μ M compound concentration. ^cInhibition of forskolin-induced cAMP in CHO cells expressing human (h) or mouse (m) SSTR5. ^dMaximal inhibition at 8.3 mM compound concentration. ^ePercent parent compound after incubation at 1 μ M for 30 min in 250 mg of protein/mL of microsomes from human (H) or rhesus monkey (Rh). N.D. = not determined.

analogues for SAR exploration. The most potent derivatives are the dihydrobenzopyrans with attachment positions at 6 (**18**) or

8 (**19**). Gem-dimethyl substitutions at α or γ dihydropyran and alkyl or chloro substitution on the phenyl ring next to pyran

Table 2. Representative Analogues from the Chromane and Indole Subclasses of Spiropiperidine SSTR5 Antagonists

Compound	Structure R =	X	hSSTR5 Binding ^a IC ₅₀ (nM) (% max) ^b	hSSTR5 cAMP ^c IC ₅₀ (nM) (% max) ^d	mSSTR5 cAMP IC ₅₀ (nM) (% max)	Microsomal stability ^e (H / Rh)	Ligand Efficiency (LE)
18		CH ₂	24 (94)	30 (68)	112 (37)	90 / 77	0.31
19		O	7.9 (98)	8.4 (114)	399 (85)	N.D. / 78	0.33
20		O	1.5 (94)	1.1 (83)	21 (89)	90 / 83	0.36
21		CH ₂	161 (64)	109 (80)	335 (77)	N.D.	0.28
22		O	0.6 (81)	1.5 (76)	39 (107)	81 / 13	0.38
23		O	31 (62)	30 (115)	283 (113)	94 / 79	--
24		CH ₂	33 (93)	28 (113)	18 (78)	100 / 95	0.30
25		O	0.2 (87)	0.5 (85)	1.0 (83)	53 / 17	0.31
26		O	0.3 (93)	0.1 (76)	6.0 (81)	78 / 61	0.36
27		CH ₂	0.8 (114)	0.7 (59)	25 (82)	92 / 83	0.34
28		O	0.4 (92)	0.4 (81)	17 (94)	N/D. / 76	0.32
29		O	222 (80)	276 (69)	15670 (9.8)	N.D.	0.23

^aIC₅₀ values were calculated as the mean of minimally duplicate experiments with less than threefold variance for acceptance of results. ^bBinding inhibition at 10 μM compound concentration. ^cInhibition of forskolin-induced cAMP in CHO cells expressing human (h) or mouse (m) SSTR5. ^dMaximal inhibition at 8.3 mM compound concentration. ^ePercent parent compound after incubation at 1 μM for 30 min in 250 mg of protein/mL of microsomes from human (H) or rhesus monkey (Rh). N.D. = not determined.

oxygen were introduced to block potential metabolic soft spots. The oxygen of dihydrobenzopyran can be substituted by sulfur (**22**) and sulphone (**23**). The spiro-oxazolidinone analogue was again more potent than the corresponding lactam (**20** vs **21**).

The indole series represented by **24**–**29** includes some of the most potent SSTR5 antagonists in this work. The original lead was a simple 1-isopropyl indole with attachment point at the 3-position (**24**). SAR optimization quickly led to 1-alkyl-4-arylindole analogues (**25**) with subnanomolar IC₅₀ in SSTR5 binding but poor microsomal stability. Replacing the 4-aryl

with cyclopropyl (**26**) yielded equally potent antagonists. Once again, the spiro-oxazolidinone analogue (**26**) was more potent than the corresponding lactam (**27**) with the later displaying a better microsomal metabolic profile. Focused sublibraries with different 1-alkyl or 4- or 5-aryl groups were synthesized to optimize potency and metabolic stability. Isosteres of indole such as azaindole (**28**) are well tolerated, whereas the analogous indazole (**29**) lost potency.

Although the primary goal of this lead optimization was to improve the metabolic stability of **1**, particularly the rhesus microsomal stability, improvements were also achieved in

Table 3. Activity, Metabolism, PK, and Efficacy of Optimized Lead Compounds from Each Subseries

compound	1	4	13	18	27
		Potency ^a			
LE/LLE	0.3/6.3	0.34/4.9	0.35/6.0	0.31/5.9	0.34/7.1
		Rat PK ^b			
Cl (mL min ⁻¹ kg ⁻¹)	15.2	4.6	3.4	19.6	14.4
AUC (μM hr)	1.67	6.6	8.5	1.94	0.66
F (%)	41	21	85	100	28
t _{1/2} (hr)	1.9	1.9	1.6	2.8	0.84
		OGTT ^c			
% (mg/kg)	−94 (3)	−101 (10)	−65 (10)	−73 (10)	−69 (10)
mPPB: Fu (%)	4.6	6.2	2.3	56	31
[3 h] _u (μM)	0.016	0.057	0.018	0.228	0.356

^aLipophilic ligand efficiency was calculated using the hSSTR5 binding potency, and logP was determined by HPLC. ^bRat Sprague; 2 mg/kg PO, 1 mg/kg IV; *n* = 2. ^cPercent decreased glucose AUC *t* = 0–120 min compared to vehicle in male C57BL/6 mice fed with high-fat-diet (D12492) for 21 days; compound (mg/kg) dosed 60 min prior to glucose, *n* = 3. mPPB = mouse plasma free fraction. [3 h]_u = free drug 3 h post dose.

ligand efficiency (Tables 1 and 2). Several members of the monoaryl series (12–17), chromane series (18–20, 22), and indole series (24–28) afforded similar or better binding potency to 1 with similar or reduced molecular weight. No clear correlation was discerned between ligand efficiency and microsomal stability.

A representative compound from each of the four subclasses was chosen for more advanced PK and efficacy profiling. Table 3 lists the relative potency, pharmacokinetic, and efficacy data of these compounds (4, 13, 18, and 27) and compares them to reference compound 1.¹⁴ Each of the four chosen compounds preserves the headgroup and core group in 1 that was optimized previously to reduce ancillary pharmacology.⁹ As a result, each of the compounds is devoid of significant potency against cardiovascular ion channels (hERG, Ca_v1.2, and Na_v1.5 IC₅₀ > 10 μM) or metabolic targets (CYP3A4, 2C9, 2D6, or activation of PXR). Each compound represents a different structural subclass of biaryls (4), monoaryls (13), chromanes (18), and indoles (27). All four compounds demonstrated good hSSTR5 antagonist activity as evaluated by LE/LLE but exhibited significantly diminished mSSTR5 potency as compared to that of 1 (Tables 1 and 2). The compounds exhibited moderate to good oral bioavailability and a wide range of unbound fraction (Fu) in mouse plasma.

Mouse oral glucose tolerance test (OGTT) experiments were carried out with these compounds, and the results from the 10 mg/kg dose (formulated in 0.5% methylcellulose suspension) are shown in Table 3. Compounds 13, 18, and 27 were less efficacious than 1 in this assay⁹ due to significantly diminished functional potency against the mouse SSTR5 receptor. However, compound 4, which is potent in the mSSTR5 cAMP assay (Table 1), showed similar efficacy to that of 1. Notably, all four of these compounds maintain comparable potency to 1 against the hSSTR5 receptor, and as such could be anticipated to have comparable intrinsic clinical efficacy.

From these optimized compounds, 13 exhibited the greatest metabolic stability in rhesus liver microsomes (Table 1), and the compound was further evaluated in vivo in rhesus monkeys for metabolic stability and pharmacokinetic properties. Dosed orally at 5 mg/kg, 13 reached a C_{max} of 2.99 μM with 31.2 μM hr total AUC and a residual (24 h) plasma concentration of 0.47 μM. Analysis of pooled plasma samples from 0.5 to 24 h in this experiment revealed that only the parent molecule

(81%) and glucuronidated 13 (19%) were present. No oxidized metabolites were detected.

In conclusion, we have developed novel series of highly selective and potent SSTR5 antagonists with diverse structural features. Building on the chemotype of lead compound 1, identified in the preceding report, we significantly expanded the SAR of the tail group and identified four subseries of analogues with minimal off-target activity profiles. Metabolic stability of these SSTR5 antagonists was optimized to achieve minimal oxidative metabolism through multispecies liver microsome incubation screens, which ultimately resulted in good oral bioavailability, exposure, and clearance in rat pharmacokinetic studies. We also demonstrated that these antagonists can significantly lower glucose excursions in a mouse diabetic model. The improved metabolic profile of one antagonist is confirmed in rhesus monkey pharmacokinetic studies with 13. These results provide a strong foundation for further investigation and development of selective SSTR5 antagonists as potential therapeutics for the treatment of type 2 diabetes and other metabolic disorders.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.8b00306.

Experimental procedures for the preparation of all compounds and full characterization of compounds 4, 13, 18, and 27 and in vitro and in vivo assay protocols (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

SSTR5, somatostatin receptor subtype 5; OGTT, oral glucose tolerance test; GLP-1, glucagon-like peptide 1; SST, somatostatin; GI, gastrointestinal; KO, genetic knockout; GDIS, glucose-dependent insulin secretion; WT, genetic wild type; HFD, high fat diet; T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase-IV; QD, dosed once daily; AUC, area under the curve; SAR, structure–activity relationship; CYP, cytochrome P450; CHO, Chinese hamster ovary; LE, ligand efficiency; LLE, lipophilic ligand efficiency.

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