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Letter

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Optimization of preclinical metabolism for somatostatin receptor subtype 5 (SSTR5) selective antagonists

Weiguo Liu*, Zahid Hussain, Yi Zang, Ramzi F. Sweis, F. Anthony Romero, Paul E. Finke, Remond Moningka, Jianming Bao, Michael A. Plotkin, Jin Shang, Karen H. Dingley, Gino Salituro, Beth Ann Murphy, Andrew D. Howard, Feroze Ujjainwalla, Harold B. Wood, Joseph L. Duffy

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ABSTRACT: A series of structurally diverse azaspirodecanone and spirooxazolidinone analogs 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 the original lead compound 1

while maintaining pharmacodynamic efficacy. The optimized cyclopropyl analog 13 demonstrated efficacy in mouse OGTT and an improved metabolic profile and pharmacokinetic properties in rhesus monkey studies. In this communication, we discuss the relationship between structure, in vitro and in vivo activity, metabolic stability, and ultimately the potential of these compounds as therapeutic agents for 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

36 Somatostatin (SST) is a peptide hormone that exists in two 37 isoforms of 14 and 28 amino acids (SST-14 and SST-28), 38 respectively,¹ and is widely distributed throughout the body.² 39 The SST-mediated biological effects involve a broad range of 40 functional regulation and hormonal secretion control, and are effected through interaction with five distinct G-protein-41 42 coupled receptors (SSTR1-5). The target SSTR5 is prominently 43 expressed in pancreatic islet β cells as well as in enteroendocrine cells of the gastrointestinal (GI) tract,3 44 inhibiting the secretion of both insulin and the insulinotropic 45 glucagon-like peptide 1 (GLP-1).4 SSTR5 knock-out (KO) mice 46 displayed decreased susceptibility to high-fat-diet (HFD)-47 induced insulin resistance⁵ and SSTR5 selective small 48 molecular antagonists have been reported to lower glucose 49 and insulin excursion during an oral glucose tolerance test 50 (OGTT) in both mice and rats.^{6,7,8} Based on these cellular and 51 preclinical pharmacology studies, SSTR5 is an attractive 52 investigational target for treatment of type 2 diabetes mellitus 53 (T2DM). 54

In the preceding manuscript in this issue, we reported the
discovery of the azaspirodecanone analog 1 as a novel, and
highly potent and selective SSTR5 antagonist.⁹ Compound 1

demonstrated a significant glucose lowering effect in a dosedependent 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 minute incubation in microsomes from each species. Therefore, dogs were investigated as a non-rodent species for safety assessment studies. However, we found persistent emesis in dogs in a 7 day tolerability study at 5 – 45 minutes 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 other species, with only 2 28% of the parent compound remaining following 30 minute incubation. In rhesus oral dose tolerability studies, administration of 1 for five days (50 mg/kg QD) was well tolerated without emesis. Metabolite identification was 6 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 8 9 M6 and a small amount of hydroxylation on the benzoic acid (M5). However, the majority of metabolites were from 10 oxidation on the biphenyl ring and de-ethylation of the 11 ethoxyl group (M1-4). We suspected that the biphenyl ring 12 was activated by the two electron donating ethoxyl groups and 13 became susceptible to oxidation catalyzed by cytochrome 14 P450 bioactivation. The multiple reactive phenols, biphenols, 15 or triphenols generated from oxidation, hydroxylation, and de-16 ethylation of 1 posed a potential safety risk for the compound 17 as a development candidate.¹¹ 18

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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).

This biaryl tail piece in 1 was first reported by Mohr and coworkers 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 analogs 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 aromatic ring. Positioning such as ortho, meta, and para were explored to optimize potency, cyclopropyl groups were introduced to replace aromatic rings in order to limit CYP induced aromatic oxidation. The members of these libraries were synthesized and characterized

as individual compounds, and libraries in this sense refers to collections of compounds prepared using solution-phase parallel synthetic techniques. The results from the synthesis and testing of these compounds are shown in Table 1. We monitored rhesus microsome stability to identify a suitable preclinical safety candidate with a development advantage over compound 1.

Table 1. Representative analog	s from four subclasses of spiropiperio	dine type of SSTR5 antagonists
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36 Table 1. Representative analogs from four subclasses of spiropiperidine type of SSTR5 antagonists								
37 38 30	Compound	Structure R =	Х	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)
40 41	1 2	OEt CEt	CH₂ O	1.2 (99) 0.8 (100)	1.1 (78) 1.5 (66)	0.9 (80) 0.3 (75)	92 / 28 90 / N.D.	0.30 0.31
42 43 44	3		CH2	N.D.	78 (50)	994 (65)	N.D.	
45 46	4	Cl F F	0	0.2 (100)	0.4 (90)	1.7 (97)	78 / 28	0.34
47 48 49	5	Me F	CH₂	17 (102)	36 (54)	64 (61)	86 / 76	0.29
50 51 52	6		0	2.9 (97)	0.8 (71)	21 (88)	86 / 81	0.31

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^a IC₅₀ values were calculated as the mean of minimally duplicate experiments with less than threefold variance for acceptance of results.

^b Binding inhibition at 10 µM compound concentration.

^c Inhibition of forskolin-induced cAMP in CHO cells expressing human (h) or mouse (m) SSTR5.

^d Maximal inhibition at 8.3 mM compound concentration.

^e Percent parent compound after incubation at 1 μM for 30 minutes in 250 mg protein / mL microsomes from human (H) or rhesus

monkey (Rh). N.D. = not determined

Scheme 1. Synthetic route of spiropiperidine analogs^a



^a Reagents and conditions: (a) Na(OAc)₃BH, AcOH, (Method A) or MP-BH₂CN resin, AcOH (Method B) as described in SI, yields ranging from 48-95%

36 The typical synthetic procedure is outlined in Scheme 1, and 37 involved reductive amination of the appropriate aryl aldehyde 38 to the spiropiperidine core piece. Details on the synthesis of 39 the spiropiperidine substituent and representative tail pieces 40 are described in the preceding report9 and supporting 41 information. From over 200 analogs prepared, four structural 42 classes of compounds emerged as lead series: the biaryls, 43 monoaryls, chromanes, and indoles. Each of these four classes 44 was explored with traditional medicinal chemistry iteration. 45

46 Table 1 lists representative examples from each of the 4 sub-47 classes of analogs. All compounds from these libraries were tested in SSTR5 ligand binding assay and cell-based cAMP 48 functional assays to measure SSTR5 antagonism. Once the 49 tractable SAR was established with a series, further analogs 50 were prepared and evaluated for their metabolic stability in 51 liver microsome incubation assays. Test compounds were 52 incubated with microsomes from human, rat, dog, and / or 53 rhesus monkey liver preparations. The results from human and 54 rhesus monkey microsomes are presented in Table 1 as a 55 comparator to the Phase I oxidative metabolism issues 56

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 trifluromethyl) are necessary for potency. These SAR iterations demonstrated that the metabolically labile diethoxyl groups of 1 can be eliminated or replaced. However, the resulting analogs (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 spiropiperidine 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 to 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

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potency. Replacement of the phenyl with pyridyl (17) was tolerated. 14 15 The chromane and indole series were first identified through 16 synthesis and screening of libraries where a diverse set of aryl 17 groups from commercial sources and our internal collections 18 were attached to the spiro-piperidine core group. Potent 19 compounds from this library were followed up with traditional 20 medicinal chemistry, resulting in 30 chromane analogs for 21 SAR exploration. The most potent derivatives are the 22 dihydrobenzopyrans with attachment positions at 6-(18) or 8-

most of the SSTR5 activity of the resulting compounds.

Previous efforts removing or replacing the distal aryl with

other groups such as simple alkyl, alkoxyl, 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 analogs.

Meta-cyclopropyl analogs (12) are slightly more potent than the ortho-(13) or para-(14) substituted analogs. 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 groups

were introduced to minimize metabolism as well as increase

23 (19). Gem-dimethyl substitutions at α or γ dihydropyran and 24 alkyl or chloro-substitution on phenyl ring next to pyran oxygen were introduced to block potential metabolic soft 25 spots. The oxygen of dihydrobenzopyran can be substituted 26 by sulphur (22), and sulphone (23). Again, the spiro-27 oxazolidinone analog was more potent than the corresponding 28 lactam (20 vs 21). 29

30 The indole series represented by 24-29 includes some of the 31 most potent SSTR5 antagonists in this work. The original lead 32 was a simple 1-isopropyl indole with attachment point at the 33 3-position (24). SAR optimization quickly led to 1-alkyl-4-34 arylindole analogs (25) with sub-nanomolar IC₅₀ in SSTR5 35 binding but poor microsomal stability. Replacing the 4-aryl 36 with cyclopropyl (26) yielded equally potent antagonists. Once 37 again, the spiro-oxazolidinone analog (26) was more potent 38 than the corresponding lactam (27), with the later displaying a 39 better microsomal metabolic profile. Focused sub-libraries with different 1-alkyl or 4 or 5-aryl groups were synthesized to 40 optimize potency and metabolic stability. Isosteres of indole 41 such as azaindole (28) are well tolerated while the analogous 42 43 indazole (29) lost potency.

44 Although the primary goal of this lead optimization was to 45 improve the metabolic stability of 1, particularly the rhesus 46 microsomal stability, improvements were also achieved in 47 ligand efficiency (Table 1). Several members of the monoaryl 48 series (12-17) chromane series (18-20, 22), and indole series 49 (24-28) afforded similar or better binding potency to 1 with 50 similar or reduced molecular weight. No clear correlation was 51 discerned between ligand efficiency and microsomal stability.

52 Table 2. Activity, metabolism, PK and efficacy of optimized lead 53 compounds from each subseries 54

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	15.2	4.6	3.4	19.6	14.4
(mL/min/kg)	1.67	6.6	8.5	1.94	0.66
AUC (µM•hr)	41	21	85	100	28
F (%)	1.9	1.9	1.6	2.8	0.84
$t_{1/2}$ (hr)					
OCTTC					
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% (mg/kg)	-94 (3)	-101 (10)	-65 (10)	-73 (10)	-69 (10)
mPPB: Fu (%)	4.6	6.2	2.3	56	31
$[3 hr]_{u}$ (µM)	0.016	0.057	0.018	0.228	0.356

^a Lipophilic ligand efficiency was calculated using the hSSTR5 biding potency and LogP determined by HPLC.

^b Rat Sprague; 2 mg/kg PO, 1 mg/kg IV; n = 2;

^c% 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 minutes prior to glucose, n=3. mPPB = mouse plasma free fraction. $[3 hr]_{u}$ = Free drug 3 hr post dose.

A representative compound from each of the four sub-classes was chosen for more advanced PK and efficacy profiling. Table 2 lists the relative potency, pharmacokinetic, and efficacy data of these compounds (4, 13, 18, and 27) and compares them to the reference compound 1.14 Each of the four chosen compounds preserves the head group 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, Cav1.2, and Na_v1.5 IC₅₀ > 10 μ M) 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 1 (Table 1). 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 2. Compound 13, 18 and 27 were less efficacious than 1 in this assay,9 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 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 μ M with 31.2 μ M·hr total AUC and a residual (24 h) plasma concentration of 0.47 µM. Analysis of pooled plasma samples from 0.5-24h in this experiment revealed that only the parent molecule (81%) and glucuronidated 13 (19%) were present. No oxidized metabolites were detected.

1 In conclusion, we have developed novel series of highly 2 selective and potent SSTR5 antagonists with diverse structural 3 features. Building on the chemotype of lead compound 1, 4 identified in the preceding report, we significantly expanded 5 the SAR of the tail group and identified four sub-series of 6 analogs with minimal off-target activity profiles. Metabolic 7 stability of these SSTR5 antagonists was optimized to achieve 8 minimal oxidative metabolism through multi-species liver 9 microsome incubation screens, which ultimately resulted in good oral bioavailability, exposure, and clearance in rat 10 pharmacokinetic studies. We also demonstrated that these 11 antagonists can significantly lower glucose excursions in a 12 mouse diabetic model. The improved metabolic profile of one 13 antagonist is confirmed in rhesus monkey pharmacokinetic 14 studies with 13. These results provide a strong foundation for 15 further investigation and development of selective SSTR5 16 antagonists as potential therapeutics for treatment of type 2 17 diabetes and other metabolic disorders. 18

19 ASSOCIATED CONTENT 20

Supporting Information 21

22 Supporting information is available free of charge on the ACS Publications website at http://pubs.acs.org. 23

Experimental procedures for the preparation of all compounds and full 24 characterization of compounds 4, 13, 18 and 27; in vitro and in vivo assay 25 protocols (PDF). 26

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Author Contributions

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ABBREVIATIONS

42 SSTR5, somatostatin receptor subtype 5; OGTT, oral glucose tolerance 43 test; GLP-1, glucagon-like peptide 1; SST, somatostatin; GI, 44 gastrointestinal; KO, genetic knockout; GDIS, glucose-dependent insulin 45 secretion; WT, genetic wild type; HFD, high fat diet; T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase-IV; QD, dosed once daily; 46 AUC, area under the curve; SAR, structure activity relationship; CYP, 47 cytochrome P450; CHO, Chinese hamster ovary; LE, ligand efficiency; 48 LLE, lipophilic ligand efficiency. 49

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