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Letter

Discovery of Paltusotine (CRN00808), a Potent, Selective, and Orally Bioavailable Non-peptide SST2 Agonist

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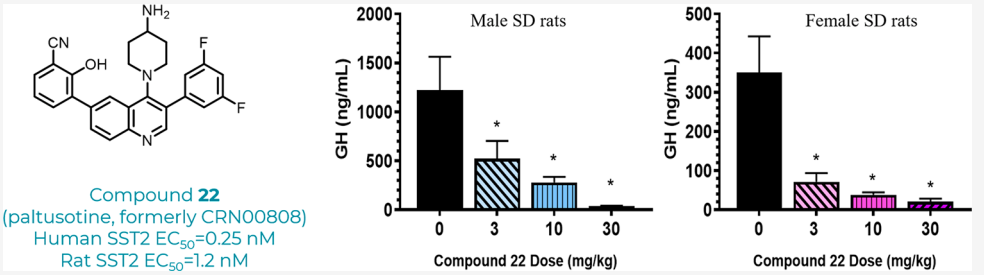

ABSTRACT: The discovery of a novel 4-(4-aminopiperidinyl)-3,6-diarylquinoline series of potent SST2 agonists is described. This class of molecules exhibit excellent selectivity over SST1, SST3, SST4, and SST5 receptors. The compound 3-[4-(4-aminopiperidin-1-yl)-3-(3,5-difluorophenyl)quinolin-6-yl]-2-hydroxybenzonitrile (**22**, paltusotine, formerly known as CRN00808) showed no direct inhibition of major cytochrome P450 enzymes or the hERG ion channel and had sufficient exposure in rats and excellent exposure in dogs upon oral dosing. In pharmacodynamic studies, compound **22** dose-dependently suppressed growth hormone (GH) secretion induced by an exogenous growth-hormone-releasing hormone (GHRH) challenge in both male and female rats following a single oral dose and suppressed IGF-1 levels with repeated oral administration in both rats and dogs. To the best of our knowledge, compound **22** is the first non-peptide SST2 agonist to advance to human clinical trials and is currently in Phase 3 trials in acromegaly patients and a Phase 2 trial in neuroendocrine tumor patients suffering from carcinoid syndrome.

KEYWORDS: *Somatostatin, paltusotine, SST2 agonist, acromegaly, neuroendocrine tumors*

Somatostatin (SS14) is a 14 amino acid peptide hormone that acts through endocrine, paracrine, and neural pathways to regulate multiple biological processes, typically by suppressing the secretion of other hormones via a family of five related somatostatin receptor subtypes: SST1, SST2, SST3, SST4, and SST5.[1] Somatostatin receptors are members of the class-A subgroup of the G-protein-coupled receptor (GPCR) superfamily and activate $G_{i/o}$ proteins resulting in inhibition of adenylate cyclase (AC) and a decrease in intracellular cAMP levels. This decrease in cAMP is the primary pathway responsible for SS14's antisecretory effects. In the pituitary gland, SS14 inhibits the secretion of growth hormone (GH) mainly via activation of SST2 and SST5, which subsequently decreases the production of growth-promoting insulin-like growth factor 1 (IGF-1) from the liver.[2]

Parentally administered synthetic analogues of SS14 have been effective treatment options for patients with acromegaly and SST2-receptor-expressing neuroendocrine tumors (NETs). Acromegaly is a slowly progressing disease caused by a pituitary adenoma that results in the oversecretion of GH and subsequently increased IGF-1 levels.[3,4] NETs are the second most common gastrointestinal cancers and represent a group of heterogeneous malignancies found in the intestine, lung, and pancreas and the parathyroid, adrenal, thyroid, and pituitary glands that often highly express somatostatin receptors, particularly SST2.[5,6] To date, three synthetic somatostatin receptor ligands (SRLs) have been developed as intramuscular or deep subcutaneous injection agents:[7,8] octreotide has been approved for treatment of acromegaly, carcinoid tumors, and vasoactive intestinal peptide tumors (VIPomas); lanreotide has been approved for treatment of acromegaly, carcinoid syndrome, and gastroenteropancreatic NETs;[9] and pasireotide has been approved for treatment of Cushing's disease and acromegaly.[10] However, office visits are often required for the administration of depot formulations of

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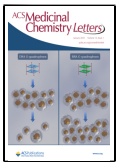

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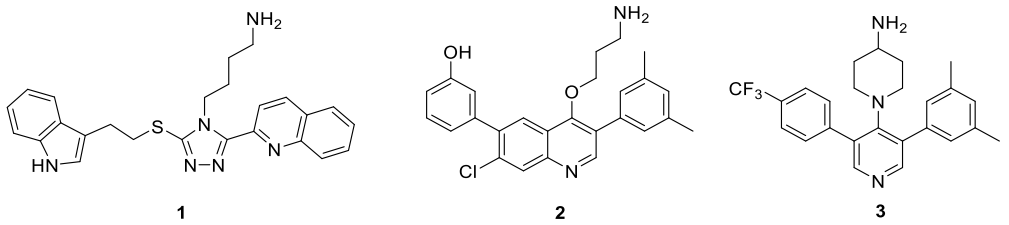
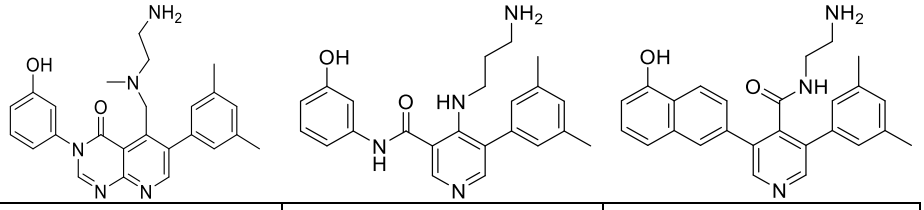


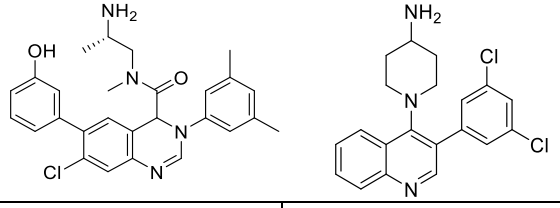
Figure 1. Representative reported non-peptide SST2 agonists.

a) dual SST2/4 agonist hits



Compd	4	5	6
hSST2 pEC_{50}±SEM (Avg EC_{50})	7.4±0.1 (36 nM)	6.1±0.1 (840 nM)	7.2±0.2 (63 nM)
hSST4 pEC_{50}±SEM (Avg EC_{50})	7.7±0.1 (20 nM)	6.5±0.1 (320 nM)	8.3±0.2 (5.5 nM)

b) selective SST2 agonist hits



Compd	7	8
hSST2 pEC_{50}±SEM (Avg EC_{50})	7.4±0.1 (38 nM)	6.9±0.1 (140 nM)
hSST4 pEC_{50}±SEM (Avg EC_{50})	6.0±0.3 (960 nM)	<5 (>10000 nM)

Figure 2. Representative non-peptide SST2 agonist hits identified in-house.

SRLs, and patients often experience discomfort or pain at the injection site.[11] In addition, patients commonly report reoccurrence of symptoms toward the end of the injection interval.[12] This return of symptoms could arise because of variable pharmacokinetics and metabolism within the patient population and also because of misadministration. A recent study found that only approximately half of intramuscular injections of octreotide depot were successfully delivered by trained staff and that after specific retraining the success rate improved to only 75%.[13] Many patients may welcome an alternative treatment that eliminates the requirement for travel, avoids painful injections, and maintains long-term efficacy.[14,15] To this end, an oral formulation of octreotide that uses a gut-permeabilizing technology to achieve low oral bioavailability has recently become available, though this compound requires twice per day dosing and a significant daily fasting regimen.[16] Therefore, a selective SST2 agonist that can be orally administered once per day at home with minimal side effects is highly desirable and could represent a significant advance for acromegaly and NET patients.

Some of the first non-peptides that targeted a peptide GPCR were a series of SST2 agonists discovered through molecular modeling and combinatorial chemistry that were published almost 25 years ago.[17] Later, two separate groups reported non-peptide SST2 agonists in 2005 and 2011.[18,19] Specifically, triazole analogues as exemplified by compound **1** were found to be potent dual agonists of SST2 and SST5, and 4-alkoxyquinolines such as compound **2** that derived from a gonadotropin-releasing hormone (GnRH) antagonist were identified as selective SST2 agonists (Figure 1). A more recent report described the identification of an initial hit compound with a quinoline core from a screen of potential SST2 agonists.[20] However, those authors stated that a three-dimensional pharmacophore model based on compounds **1** and **2** suggested that a more potent scaffold would be attainable using scaffold hopping, and subsequent medicinal chemistry efforts led to 3,4,5-trisubstituted pyridine derivatives (e.g., compound **3**) as SST2 agonists. We began our non-peptide SST2 agonist discovery campaign by designing and synthesizing a small, focused library featuring novel scaffolds. Such efforts led to the discovery of multiple series exhibiting

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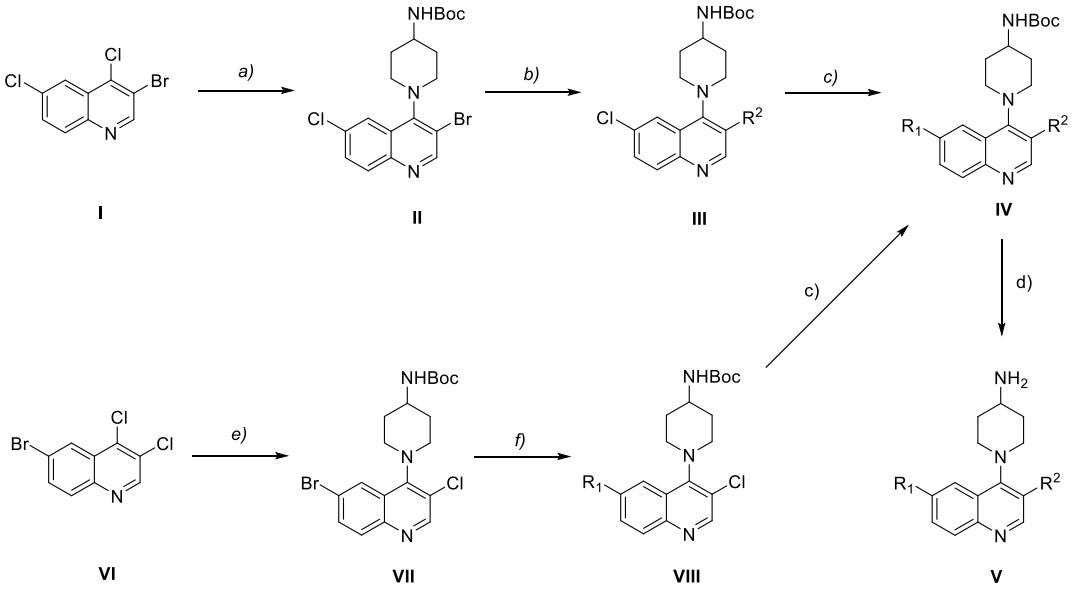
Scheme 1. Representative Synthesis of 4-(4-Aminopiperidinyl)-3,6-diarylquinolines



SST2 agonist activity in *in vitro* functional assays, as exemplified by compounds **4**–**8** in Figure 2. These provided starting points for lead optimization. Further characterization of these hits demonstrated that compounds **4**, **5**, and **6** are dual agonists that also carry SST4 agonist activity, and thus, our medicinal chemistry efforts were focused on both improving the SST2 potency and reducing the SST4 activity. Lead optimization work centered on pyrimidin-4(3*H*)-one **4** and led to the discovery of SST2 agonists with subnanomolar activity, with the leading compound showing excellent efficacy in suppressing GH secretion induced by a growth-hormone-releasing hormone (GHRH) challenge in rats. However, human SST4 agonist activity remained present in these compounds.[21] Compounds **7** and **8** were found to be more selective SST2 agonists, and a structure–activity relationship (SAR) study centered on compound **7** led to the discovery of several 3,4-dihydroquinazoline-4-carboxamides as potent and highly selective SST2 agonists.[22] However, this class of compounds suffered poor oral exposure. Further medicinal chemistry efforts focused on the lead optimization of compound **8** resulted in a series of drug-like 4-(4-aminopiperidinyl)-3,6-diarylquinolines as potent and selective SST2 agonists. Herein we describe our SAR study centered on that series and the discovery of clinical compound **22** (paltusotine, formerly known as CRN00808) as a potent, selective, and orally bioavailable non-peptide SST2 agonist for potential treatment of acromegaly and NETs. Paltusotine has completed a double-blind placebo-controlled Phase 1 trial in healthy volunteers that demonstrated good tolerability and dose-dependent reduction in acutely stimulated GH secretion and basal IGF-1 over the course of the study.[23] It is currently in Phase 3 trials in acromegaly patients and a Phase 2 trial in neuroendocrine tumor patients that suffer from carcinoid syndrome.

Chemistry. To enable facile modifications of both the R^1 and R^2 groups of the 4-(4-aminopiperidinyl)-3,6-diarylquinolines, we developed the two synthetic routes shown in Scheme 1. In the first sequence, nucleophilic replacement on 3-bromo-4,6-dichloroquinoline (**I**) generated *tert*-butyl (1-(3-bromo-6-chloroquinolin-4-yl)piperidin-4-yl)carbamate (**II**). This compound underwent selective coupling between a boronic acid/ester and the 3-bromo substituent to produce chloroquinoline intermediate **III**, which was subjected to another Suzuki coupling to generate 4-(4-aminopiperidinyl)-3,6-diarylquinoline **IV**. The second synthetic sequence started from 6-bromo-3,4-dichloroquinoline (**VI**), which was treated with protected 4-aminopiperidine to give intermediate **VII**. Subsequently, compound **VII** underwent consecutive Suzuki couplings to produce common intermediate **IV**. Removal of the protecting group under acidic conditions furnished the final compound **V**.

Primary Human SST2 cAMP Assay. All of the compounds were tested in cyclic adenosine monophosphate (cAMP) functional assays to measure SST2 receptor activation.[24] Human SST2 expressing Chinese Hamster Ovary (CHO-K1) cells were treated with NKH477, a soluble forskolin analogue, to induce the production of cAMP. Upon agonist activation, the level of intracellular cAMP decreases in a concentration-dependent manner, which allows calculation of the compound's potency (EC_{50}).

Optimization of the 6-Aryl Substituent R^1. Results from the SAR study on the 6-aryl substituent R^1 of the 4-aminopiperidinylquinoline pharmacophore are summarized in Table 1. The initial hit compound **8** (EC_{50} = 140 nM) bears a 3,5-dichlorophenyl group carrying high lipophilicity and molecular mass. The more drug-like 3,5-difluorophenyl-substituted compound **9** (EC_{50} = 1600 nM) was prepared, but it was 10-fold less potent than **8**. Adding a chloro group at the 6-position of the quinoline ring partially restored agonist activity (**10**, EC_{50} = 570 nM), and the more lipophilic compound **11** bearing a phenyl ring exhibited a 50-fold potency increase (EC_{50} = 9.2 nM). Compound **12**, with a 3-cyano substituent on the phenyl ring, was found to be more potent (EC_{50} = 1.4 nM), and relocating the CN group to other positions on the phenyl ring or replacing the 3-cyano group with a fluoro or methoxy group did not enhance the potency (**13**–**16**). Compounds bearing a proton donor such as an acid or amide group were also prepared (**17** and **18**). Although amide compound **18** turned out to be a very potent SST2 agonist (EC_{50} = 0.14 nM), the likelihood of acceptable oral exposure for a molecule containing four proton donors is

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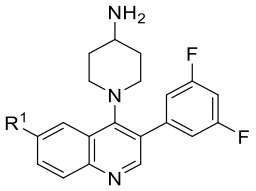
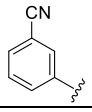
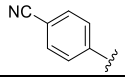
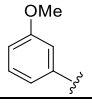
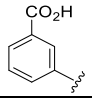
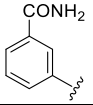
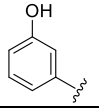
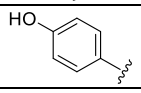
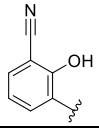
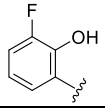
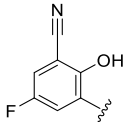
Table 1. SAR Study of the R^1 Substituent[a]



Compd	R^1	hSST2 pEC_{50}±SEM	hSST2 Avg EC_{50} (nM)
9	H	<6	1600
10	Cl	6.2±0.3	570
11		8.0±0.5	9.2
12		8.9±0.2	1.4
13		7.6±0.2	26
14		7.5±0.2	30
15		8.5±0.0	3.5
16		8.3±0.0	4.7
17		6.4±0.2	400
18		9.8±0.1	0.14
19		9.8±0.3	0.16
20		7.5±0.1	31
21		8.5±0.2	3.4
22		9.6±0.2	0.25
23		9.8±0.0	0.17
24		9.5±0.1	0.34

[a]The purities of the compounds were >95% as determined by LCMS or ^{1}H NMR analysis. pEC_{50} values are averages of two or more independent measurements. For EC_{50} values >1000 nM, the pEC_{50} is reported as <6.

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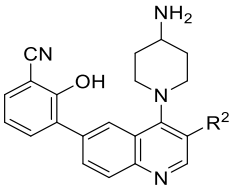
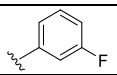
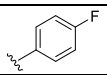
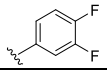
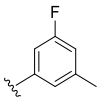
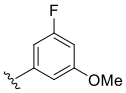
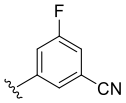
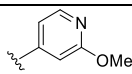
Table 2. SAR Study of the R^2 Substituent[a]



Compd	R^2	hSST2 pEC_{50}±SEM	hSST2 Avg EC_{50} (nM)
25		9.5±0.1	0.31
26		8.7±0.1	1.9
27		7.5±0.1	30
28		8.6±0.1	2.5
29		8.1±0.2	7.3
30		9.8±0.1	0.17
31		9.9±0.1	0.12
32		8.0±0.1	10
33		7.3±0.0	50

[a]The purities of the compounds were >95% as determined by LCMS or ^{1}H NMR analysis. pEC_{50} values are averages of two or more independent measurements.

low.[22] Phenol analogues **19**–**21** were prepared, and the 3-hydroxy compound **19** exhibited a remarkable human SST2 EC_{50} of 0.16 nM, showing that it is >100-fold more potent than the 4-hydroxy analogue **20** (EC_{50} = 31 nM). This trend is different from previous reports in the alkoxyquinoline series of compounds **2**, which demonstrated that a 4-hydroxy group was more potent than a 3-hydroxy group in a functional assay.[19] To reduce the electron density on the phenol ring, cyano and fluoro substituents were added at the 3-position to produce compounds **22** and **23**, respectively. Interestingly, these two compounds showed EC_{50} values of 0.25 and 0.17 nM, respectively, indicating that they are much more potent than the corresponding monosubstituted analogues (**12**, **15**, and **21**), which clearly suggested a synergistic effect between substituents at the 2- and 3-positions. Further addition of a fluoro group at the 5-position of the phenyl substituent of compound **22** to obtain compound **24** did not impact human SST2 functional activity but could further reduce the possibility of metabolic oxidation of the 2-phenol group.

Optimization of the 3-Aryl Substituent R^2. The impact of the 3-substituent R^2 on the human SST2 activity was evaluated by preserving the R^1 group as 3-cyano-2-hydroxyphenyl, and the corresponding functional activities are summarized in Table 2. Removing one fluoro group from the phenyl ring (**25**) had a marginal impact on the human SST2 activity (EC_{50} = 0.31 nM), whereas deleting both fluoro groups resulted in a 7-fold potency loss (**26**). Furthermore, the 4- and 2-fluoro-substituted analogues **27** and **28** turned out to be less potent than **25**. Compound **29** bearing a 3,4-difluorophenyl group was also less active than its 3,5-difluoro counterpart. These results clearly suggested that a 3,5-disubstitution pattern is preferred for SST2 receptor activity. Analogues bearing other functional groups on this phenyl ring were prepared, as exemplified by compounds **30**–**32**. It appears that the electron-donating methyl (**30**) and methoxy (**31**) groups were well-tolerated, exhibiting EC_{50} values of 0.17 and 0.12 nM, respectively, but the electron-withdrawing cyano group (**32**) was found to be detrimental (EC_{50} = 10 nM). Finally, replacing phenyl with its isostere pyridine to improve the physicochemical properties generated compound **33** with only moderate human SST2 activity (EC_{50} = 50 nM). These results indicated that a lipophilic R^2 can be beneficial to human SST2 agonist activity.

***In Vitro* Selectivity and ADME Profiles.** Potent SST2 analogues were tested for their ability to reduce cAMP in SST1-, SST3-, SST4-, and SST5-expressing cells as part of an assay cascade, and the results of representative examples are summarized in Table 3. Compounds in this series showed excellent selectivity versus two or more SST subtypes, typically >1000-fold. Selected compounds listed in Table 3 were

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Table 3. Human SST Subtype Selectivity of Selected 4-(4-Aminopiperidinyl)-3,6-diarylquinoline Analogues[a]

	pEC_{50}±SEM			
compd	SST1	SST3	SST4	SST5
19	<6	<6	7.8±0.1	<6
22	<6	<6	6.0±0.1	<6
23	<6	<6	7.6±0.0	<6
24	<6	6.4±0.1	<6	<6
25	<6	<6	6.0±0.2	<6
30	<6	<6	<6	<6
31	<6	<6	<6	<6

[a]pEC_{50} values are averages of two or more independent measurements. For EC_{50} values >1000 nM, the pEC_{50} is reported as <6.

screened in a series of ADME assays to identify potential liabilities, and the results are presented in Table 4. Compounds **19**, **22**, **23**, **24**, and **25** were tested in an hERG inhibition binding assay to understand potential cardiovascular toxicity risks.[25] Compounds **19** and **23** are moderate hERG ion channel inhibitors ($pEC_{50} \geq 6$), while compounds **22**, **24**, and **25** are only weak inhibitors. These compounds were subjected to *in vitro* liver microsome stability assays to assess their metabolic stability in human and rats. Compound **25** exhibited high clearance in human liver microsomes ($T_{1/2}$ = 26 min) and is clearly not ideal for further development. Compounds **22** and **24** were more metabolically stable, and thus, they were tested for cytochrome P450 inhibition activity. As demonstrated in Table 4, both **22** and **24** showed slight or no direct inhibition of major cytochrome P450 enzymes even at the highest concentration tested (10 μM).[26]

***In Vivo* Pharmacokinetic Properties.** To understand the oral bioavailability of promising leads, a critical milestone for the development of non-peptide oral agents, compounds **22** and **24** were administered to male SD rats, and the pharmacokinetic profiles are listed in Table 5. Compounds **22** and **24** showed similar clearance *in vivo*, and although the overall oral bioavailability of both compounds in rat was low, compound **22** had higher oral bioavailability compared to **24**. Subsequently, the pharmacokinetic properties of compound **22** were further evaluated in male beagle dogs, and the results are summarized in Table 6. This study indicated that compound **22** not only possessed a reasonably long half-life of 7.5 h but also exhibited much-improved bioavailability (48%) in dog relative to rat (8.8%). In MDR1-MDCK cell monolayers, compound **22** was found to have a low apical to basolateral (A-to-B) apparent permeability coefficient (P_{app}) value of 0.62 × 10^{-6} cm/s and an efflux ratio (P_{app} B-to-A/P_{app} A-to-B) of 34, suggesting that **22** is a P-gp substrate, which may contribute to its low bioavailability in rats. It has been reported that animal bioavailability is generally qualitatively indicative but not necessarily quantitatively predictive,[27] given the biological differences across tested species. Therefore, the relatively low bioavailability of **22** in male SD rats did not prevent this compound from moving forward because the level of oral exposure in rat was determined to be suitable for efficacy and toxicity studies, particularly with the use of optimized vehicles. Indeed, compound **22** was found to have an oral bioavailability of ∼70% in healthy human volunteers in a Phase 1 study.[23]

***In Vivo* Efficacy of Compound 22.** The *in vivo* pharmacodynamic activity of this class of molecules was evaluated by examining suppression of GH stimulated by iv administration of GHRH in rats after a single oral administration and reduction of IGF-1 levels in rats and dogs after repeated daily oral dosing. GH and IGF-1 are relevant markers for predicted activity of somatostatin agonists and provide hallmark evidence of hormonal effects in rats that translate well to hormonal effects in healthy human volunteers and efficacy in acromegaly patients (reduction of GH and normalization of IGF-1). Because GH is secreted from the pituitary gland in a pulsatile manner,[28] we and others have used exogenous intravenous administration of rat GHRH to induce a surge in GH secretion that can then be suppressed by pharmacological treatments such as somatostatin agonists.[29] Intravenous administration of rat GHRH (3 μg/rat) induced a robust rise in plasma GH that was dose-dependently suppressed by a single oral administration (3, 10, or 30 mg/kg) of compound **22** (rat SST2 EC_{50} = 1.2 nM) in male and female SD rats measured either 3 or 1 h after administration of compound **22**, respectively (Figure 3). These results clearly demonstrated that an orally bioavailable non-peptide SST2 agonist can effectively suppress the secretion of GH *in vivo*.

Sustained suppression of GH release from the pituitary results in lowering of plasma IGF-1 levels. IGF-1 is both the registrational end point used to demonstrate clinical efficacy of therapeutics in acromegaly patients and a critical biomarker in clinical treatment. In contrast to rapid effects on GH response, IGF-1 levels drop more slowly and require chronic suppression of the GH axis to see meaningful changes. Therefore, we also measured IGF-1 levels after repeated daily oral administration of compound **22** in rats and dogs. Compound **22** (10 and 30 mg kg^{-1} day^{-1}) was administered once daily by oral gavage for 14 days to male SD rats (Figure 4). At 10 mg kg^{-1} day^{-1}, it significantly suppressed plasma IGF-1 levels relative to vehicle on days 2, 10, and 14 ($p < 0.05$). Compound **22** at 30 mg kg^{-1} day^{-1} significantly suppressed IGF-1 levels on all days measured ($p < 0.05$) with a greater degree of suppression than the 10 mg kg^{-1} day^{-1} dose. Both doses maintained a constant reduction in IGF-1 over the course of the 14 day experiment.

Table 4. ADME Profiles of Selected 4-(4-Aminopiperidinyl)-3,6-diarylquinoline Analogues[a]

			pIC_{50}±SEM			
compd	hERG pIC_{50}±SEM[b]	LM stability $T_{1/2}$ (min)	CYP2C9	CYP2C19	CYP2D6	CYP3A4
19	>6	46 (human), 70 (rat)	–	–	–	–
22	<5[c]	66 (human), 231 (rat)	5.1±0.0	5.3±0.1	<5	<5
23	6.0±0.2	231 (human), 173 (rat)	–	–	–	–
24	5.0±0.0	87 (human), 116 (rat)	5.2±0.1	5.4±0.0	<5	5.0±0.0
25	<5	26 (human), 70 (rat)	–	–	–	–

[a]For IC_{50} values <1.0 μM, the pIC_{50} is reported as >6; for IC_{50} values >10 μM, the pIC_{50} is reported as <5. [b]hERG binding assay. [c]Patch-clamp hERG assay IC_{50} = 9.9 μM.

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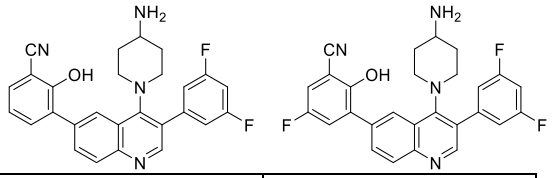
Table 5. Pharmacokinetic Properties of 22 and 24 in Male SD Rats[a]



Compound	**22**	**24**
iv $T_{1/2}$ (h)	2.8	2.7
iv CL (mL/min/kg)	9.1	8.5
iv V_{ss} (L/kg)	1.5	1.4
po $AUC_{(0\text{-inf})}$ (ng*hr/mL)	1610	632
po C_{max} (ng/mL)	129	109
Bioavailability F	8.8%	3.0%

[a]iv: 2.5 mg/kg, 10% v/v ethanol in sterile water; po: 10 mg/kg, 50% Kolliphor EL, 25% ethanol, 25% propylene glycol.

Table 6. Pharmacokinetic Properties of 22 in Male Beagle Dogs[a]

iv $T_{1/2}$ (h)	iv CL (mL/min/kg)	iv V_{ss} (L/kg)	po C_{max} (ng/mL)	po $AUC_{(0-\infty)}$ (ng h/mL)	bioavailability *F* (%)
7.5	9.4	3.5	1367	10430	48

[a]iv: 2.5 mg/kg, 10% v/v ethanol in water (solution); po: 10 mg/kg, PEG400:ethanol:water (40:10:50)

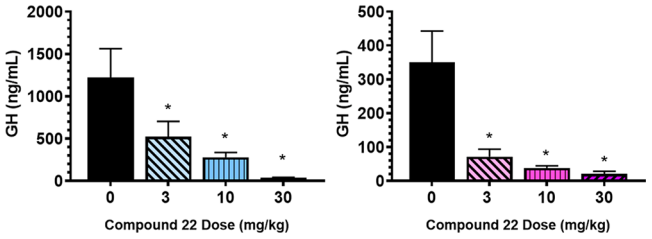


Figure 3. Suppression of GHRH-induced GH secretion by oral administration of compound **22** in (left) male and (right) female Sprague-Dawley rats. Compound **22** was formulated in 20% hydroxypropyl-*β*-cyclodextrin (HP*β*CD) in sterile water (v/v) for the male rat study and 50% propylene glycol, 10% vitamin E TPGS, 40% 0.1 N HCl (v/v/v) for the female rat study. Data are presented as mean±SEM of 6−8 rats per group. GH = growth hormone. *, $p < 0.05$.

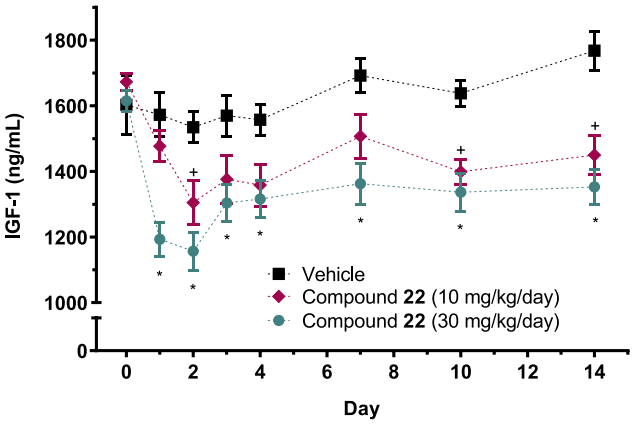


Figure 4. Suppression of plasma IGF-1 by daily oral administration of compound **22** formulated in propylene glycol over 14 days in male Sprague-Dawley rats. Data are presented as mean±SEM of 7−8 rats per group. IGF-1= Insulin-like growth factor 1. Compound **22** at 10 mg/kg vs vehicle: +, $p < 0.05$. Compound **22** at 30 mg/kg vs vehicle: *, $p < 0.05$.

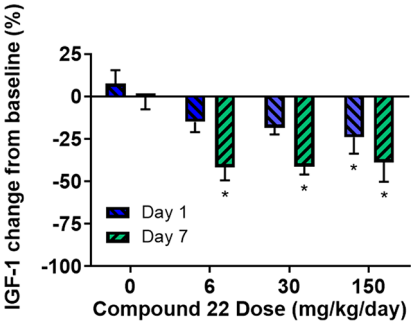


Figure 5. Reduction of plasma IGF-1 levels by compound **22** formulated in propylene glycol over 7 days of oral administration in male and female beagle dogs. Data are presented as mean±SEM of 4 dogs per group. IGF-1=insulin like growth factor 1. *, $p < 0.05$.

Compound **22** (6, 30, and 150 mg kg^{-1} day^{-1}) was also administered once daily by oral gavage for 7 days to male and female beagle dogs (Figure 5) (dog SST2 EC_{50} = 6.6 nM). Plasma IGF-1 was measured at baseline (before compound administration) and on days 1 and 7 of dosing. Due to the small number of animals in this study and biological variability among animals, IGF-1 levels were normalized by each dogs' individual baseline values on day 1 and day 7. Compound **22** at 6, 30, and 150 mg kg^{-1} day^{-1} significantly suppressed IGF-1 on day 7 compared to vehicle ($p < 0.05$). On day 1, the high-dose-treated group (150 mg kg^{-1} day^{-1}) was also significantly suppressed relative to the vehicle-treated group ($p < 0.05$).

Summary. We developed a focused compound library to identify novel non-peptide SST2 agonist hits, and subsequent SAR studies led to the discovery of the 4-(4-aminopiperidinyl)-3,6-diarylquinoline series as potent SST2 agonists. In particular, the clinical compound 3-[4-(4-aminopiperidin-1-yl)-3-(3,5-difluorophenyl)quinolin-6-yl]-2-hydroxybenzonitrile (**22**, paltusotine, formerly CRN00808) was identified as potent (human SST2 EC_{50} = 0.25 nM) and selective (>1000-fold over other SST receptor subtypes). This molecule showed limited off-target activity and acceptable oral exposure in SD male rats and beagle dogs. A single oral administration of compound **22** suppressed GHRH-stimulated GH secretion in both male and female rats. Repeated daily oral administration over 14 days in male rats and 7 days in male and female beagle dogs resulted in suppression of plasma IGF-1 levels. These examples of

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pharmacodynamic efficacy were mirrored in a Phase 1 clinical study in healthy volunteers, in which paltusotine acutely suppressed GHRH-stimulated GH secretion and lowered IGF-1 levels over the course of several days.[23] In a Phase 2 study, paltusotine was shown to maintain IGF-1 levels in acromegaly patients that switched from their parentally administered depots to oral paltusotine.[30] Currently, paltusotine is being evaluated in Phase 3 trials in acromegaly patients and a Phase 2 study in NETs patients with carcinoid syndrome.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.2c00431.

Representative synthetic procedures and characterization data and details of the somatostatin functional assays and ADME assays (PDF)

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Notes

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