Bioorganic & Medicinal Chemistry Letters 20 (2010) 1728–1734

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Decahydroisoquinoline derivatives as novel non-peptidic, potent and subtype-selective somatostatin sst_3 receptor antagonists

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ARTICLE INFO

Article history:
Received 30 November 2009
Revised 6 January 2010
Accepted 7 January 2010
Available online 21 January 2010

Keywords:
Somatostatin
GPCR
Somatostatin sst_3 receptor
Non-peptidic somatostatin receptor ligands
Subtype-selective sst_3 receptor antagonists

ABSTRACT

Starting from non-peptidic sst_1-selective somatostatin receptor antagonists, first compounds with mixed sst_1/sst_3 affinity were identified by directed structural modifications. Systematic optimization of these initial leads afforded novel, enantiomerically pure, highly potent and sst_3-subtype selective somatostatin antagonists based on a (4*S*,4a*S*,8a*R*)-decahydroisoquinoline-4-carboxylic acid core moiety. These compounds can efficiently be synthesized and show promising PK properties in rodents.

Somatostatin (somatotropin release-inhibiting factor, SRIF) is a cyclic peptide expressed throughout the CNS (central nervous system), in endocrine tissues and in the gastrointestinal tract (GIT). SRIF exerts a wide range of biological actions via five somatostatin receptor subtypes (sst_1 to sst_5),[1–3] including inhibition of secretion of growth hormone, insulin, glucagon and gastrin as well as other hormones secreted by the pituitary and the GIT.[4] SRIF also acts as a neuromodulator in the CNS and in addition has marked anti-proliferative effects on a wide range of cancer cells.[5] Clinically, SRIF receptor modulation is targeted primarily in the endocrine and gastro intestinal sphere, especially in a number of gastro-entero-pancreatic cancers, although preclinical evidence points at a number of other diseases,[4] such as inflammation, pain, migraine, epilepsy,[6] additional cancers,[7] and neuropsychiatric disorders such as depression and Alzheimer disease.[5,8–11] These effects seem to be mediated primarily through sst_2 and sst_5 receptors. The sst_1 receptor appears to play a role as autoreceptor in the brain and the eye,[12] and sst_4 may be involved in memory and epilepsy,[13,14] whereas the sst_3 receptor is the least studied of the family. It is present in the brain,[15] apparently limited to neuronal cilia, and in the periphery, primarily in tumors.[16,17,7] It has been proposed to play a role in epilepsy,[18,19] depression[20] and tumor growth.[21]

Up to now, only one class of non-peptidic sst_3 receptor antagonists has been described, namely D-Trp derived imidazolyl-β-carbolines.[22–25] In the course of our efforts towards non-peptidic, subtype-selective somatostatin receptor antagonists, we initiated a program aimed at the identification of novel, sst_3 receptor selective and brain penetrable compounds.

Recently, we have described non-peptidic somatostatin antagonists with exquisite selectivity for the sst_1 receptor subtype, based on octahydrobenzo[*g*]quinoline (obeline),[26,27] octahydro-indolo[4,3-*fg*]quinoline (ergoline)[28] and β-alanine[29] (e.g., **1**, Fig. 1) scaffolds. During optimization of the β-alanine series, we realized that increasing the size of the small alkyl substituent at the tertiary amine from methyl (**1**) to cyclopropylmethyl (**2**) reduced sst_1 affinity while increasing binding to the sst_3 receptor (Table 1). We decided to explore this trend further by increasing steric bulk even more, and restrict conformational flexibility by cyclizing the β-alanine amide core. Indeed, the resulting (racemic) nipecotic acid amide derivative **3** showed further improved sst_3 affinity and was the first compound that was equipotent on sst_1 and sst_3. Initial variation of the fluorenyl-ethyl moiety using parallel synthesis techniques[30] led to the identification of methylendioxyphenyl derivative **4** (Fig. 1). Although **4** is still a mixture of four stereoisomers, it showed promising sst_3 affinity and a first hint of selectivity over sst_1 (Table 1), therefore it was chosen as novel lead towards sst_3-selective somatostatin ligands.

First, we evaluated whether the stereogenic center introduced by the methyl group at the propyl linker of **4** could be avoided. However, both the corresponding des-methyl as well as the dimethyl derivative of **4** showed considerably reduced sst_3 affinity

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doi:10.1016/j.bmcl.2010.01.063

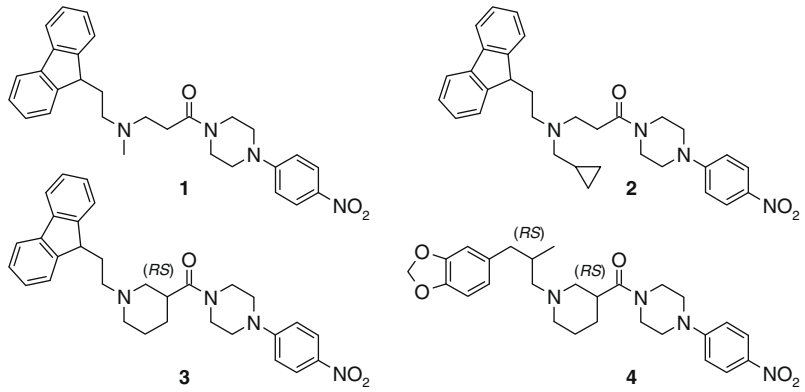


Figure 1. Evolution from sst_1 receptor antagonist **1** to mixed sst_3/sst_1 ligand **4**.

Table 1
Binding affinities of somatostatin receptor ligands **1**–**4** to h rec. sst_3 and sst_1 receptors

Compound	1	2	3	4
pK_D h sst_3[a]	5.98 ± 0.02	6.52 ± 0.02	6.93 ± 0.02	7.07 ± 0.05
pK_D h sst_1[a]	8.12 ± 0.04	7.11 ± 0.03	6.92 ± 0.10	6.99 ± 0.04

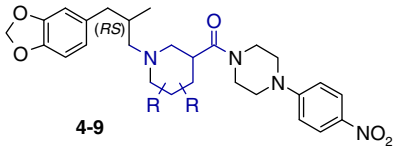
[a] Mean ± SEM. Number of experiments: $n = 3–6$.

(pK_Ds of 6.19 and 5.70 as compared to 7.07 for **4**). Therefore, the methyl group was retained at this position.

Next, we explored whether sst_3 potency and selectivity could be improved by further increasing steric bulk around the nipecotic acid piperidine ring. To this end, the nipecotic acid core of **4** was replaced with three different diastereoisomers of decahydroquinoline-3-carboxylic acid (**5**–**7**, Table 2) and two diastereoisomers of decahydroisoquinoline-4-carboxylic acid (**8** and **9**, Table 2). For synthetic simplicity, these bicyclic core building blocks were introduced as racemic mixtures; structures in Table 2 show relative configurations only. In combination with the racemic stereogenic center at the methyl propyl linker, this leads to mixtures of four stereoisomers (two racemic diastereoisomers) for **5**–**9**. Testing such mixtures carries some risk that initial SAR obtained in this way does not fully translate to enantiomerically pure compounds, however, this approach considerably simplified initial synthetic efforts and allowed for a fast first assessment of these new core moieties. Synthetically, the corresponding bicyclic β-amino acids were obtained by exhaustive hydrogenation of the ethyl esters of quinoline-3-carboxylic acid and isoquinoline-4-carboxylic acid, respectively, followed by separation of diastereoisomers by chromatography or crystallization. While all three decahydroquinoline derivatives (**5**–**7**) and one decahydroisoquinoline derivative (**9**) lost sst_3 affinity to some or to a considerable extent, the decahydroisoquinoline core of **8** (relative configuration determined by NMR NOE experiments) turned out to confer both increased affinity for sst_3 and improved selectivity over sst_1. Although still a mixture of four stereoisomers, **8** binds to sst_3 with an affinity of 10 nM and displays selectivity over sst_1 by a factor of nearly 100.

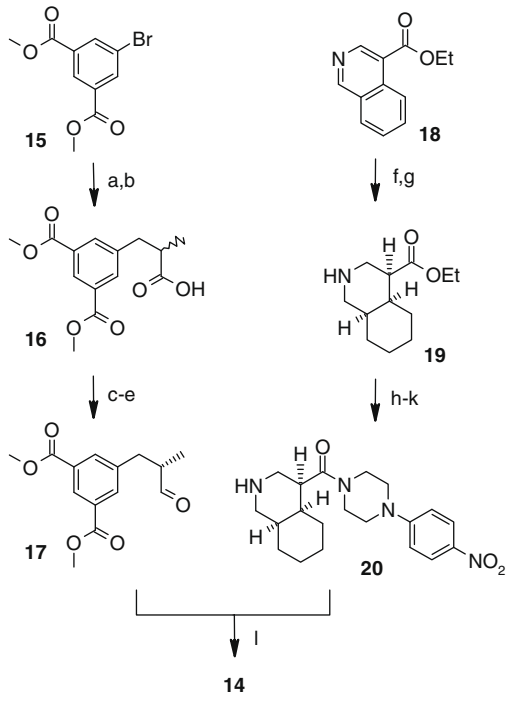
Having identified this promising new core moiety, we set out to determine the optimal absolute configurations at the linker stereogenic center and the bicyclic core (synthesis discussed below, see Scheme 1). For this assessment, the slightly more potent dimethyl isophthalate derivative **10** (Table 3) was chosen. First, two derivatives of **10** were prepared with enantiomerically pure core moieties (**11**: (4*R*,4a*R*,8a*S*) and **12**: (4*S*,4a*S*,8a*R*)) while the methyl stereogenic center was kept racemic (therefore, **11** and **12** are mixtures of two diastereoisomers). Binding studies revealed that nearly all sst_3 affinity resided in the core with (*SSR*) configuration (Table 3, compound **12**). Next, this more active enantiomerically pure core moiety was combined with both pure enantiomers at the methyl propyl linker moiety (**13**: (*R*) and **14**: (*S*)), which showed that at this position, the (*S*) configuration is preferred both with regard to sst_3 affinity as well as sst_1 selectivity. With the enantiomerically pure (*S*) (*SSR*) derivative **14**, a remarkably potent sst_3 ligand (K_D = 1.2 nM) with good sst_1 selectivity (760-fold) had been identified.[31]

Table 2
Evaluation of bicyclic core moieties: binding affinities to h rec. sst_3 and sst_1 receptors



Core moiety[a]						
Compound	4	5	6	7	8	9
pK_D h sst_3[b]	7.07 ± 0.05	6.79 ± 0.02	5.91 ± 0.03	6.81 ± 0.03	7.96 ± 0.03	5.95 ± 0.05
pK_D h sst_1[b]	6.99 ± 0.04	6.31 ± 0.08	5.61 ± 0.01	6.27 ± 0.03	6.04 ± 0.02	5.21 ± 0.10

[a] Drawings represent relative configurations only. Core moieties were 1:1 mixtures of the stereoisomer as drawn, and its enantiomer.
[b] Mean ± SEM. Number of experiments: $n = 3–6$.



Scheme 1. Synthesis of enantiomerically pure decahydroisoquinoline sst_3 antagonist **14**. Reagents and conditions: (a) 2-methylacrylic acid, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, Bu_3N, DMF, microwave, 10 min (64%, *cis* and *trans* isomers combined); (b) H_2, Pd/C, EtOH (98%); (c) crystallization from Et_2O as salt of (*S*)-(−)-phenethylamine, recrystallization from *i*-PrOH (53% relative to pure enantiomer); (d) ClCOOEt, Et_3N, THF, then $NaBH_4$, MeOH, −70 °C (45%, $[\alpha]_D^{20} = -12.3$ (EtOH, $c = 1$)); (e) Dess–Martin periodinane, DCM, 0 °C to rt, 1 h (70%); (f) H_2, 5% Rh/C, HOAc, 60 °C, 150 bar, 5 h (89% as mixture of diastereoisomers). Crystallization from EtOH/MTBE affords pure racemic (4*RS*, 4a*RS*, 8a*SR*) isomer (61%); (g) crystallization from EtOH as [L]-di-*p*-toluoyl tartrate (37% relative to pure enantiomer, $[\alpha]_D^{20} = -2.8$ (EtOH, $c = 1$)); (h) Boc_2O; (i) LiOH (88%); (j) hexachloroacetone, PPh_3, DCM, 0 °C, then 4-nitrophenyl piperazine, Et_3N (82%); (k) TFA, DCM (82%); (l) $NaBH(OAc)_3$, DCE, rt (90%).

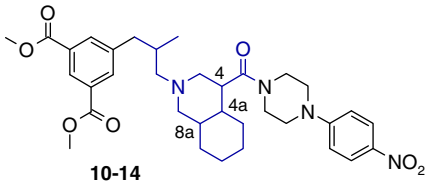
Preparation of enantiomerically pure building blocks was achieved as exemplified for derivative **14** (Scheme 1). Racemic 2-methyl-3-aryl propionic acid **16** (obtained by a Heck reaction, followed by hydrogenation of the resulting mixture of *cis* and *trans* acrylic acids) was resolved into the pure enantiomers by fractionated crystallization of diastereoisomeric (*S*)-(−)-phenethylamine salts.[32] The enantiomerically pure carboxylic acid was then converted to aldehyde **17** using mild conditions in order to prevent racemization. Enantiomerically pure decahydroisoquinoline-4-carboxylic acid ethyl ester **19** was obtained from the corresponding racemate by crystallization as [L]-di-*p*-toluoyl tartrate. The absolute configuration of **19** was determined both by NMR and X-ray crystallography after conversion to a Mosher's acid amide. Absolute configurations at all stereogenic centers were confirmed later with X-ray structures of more advanced final compounds (vide infra). Ester **19** was converted to piperazine amide **20** by Boc protection of the amine, ester hydrolysis, amide formation and amine deprotection. A reductive amination reaction of **17** with **20** afforded **14** which contained only <3% of any other diastereoisomer or enantiomer as determined by HPLC on chiral stationary phase.

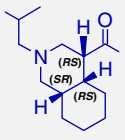
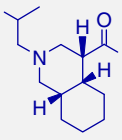
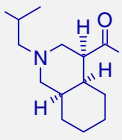
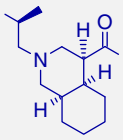
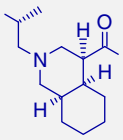
Although isophthalic acid dimethyl ester derivative **14** showed promising initial results in somatostatin receptor binding assays, we were concerned about (i) potential genotoxicity liabilities of the *p*-nitrophenyl piperazine moiety, and (ii) issues with chemical and metabolic stability of the methyl ester moieties. We therefore set out to individually optimize the aryl piperazine moiety as well as the aryl moiety at the propyl linker.

In order to quickly assess potential alternatives for the *p*-nitrophenyl piperazine moiety, we reacted carboxylic acid **21** (racemic mixtures of two diastereoisomers) with a set of 20 aryl piperazines[27] using parallel synthesis techniques (Scheme 2). Amide bond formation in DCE using polymer supported dicyclohexyl carbodiimide, followed by filtration and evaporation of the solvent afforded the desired piperazine amides in sufficient purity (>85%) for testing in the sst_3 binding assay. Affinity to the sst_1 receptor was not assessed at this point.

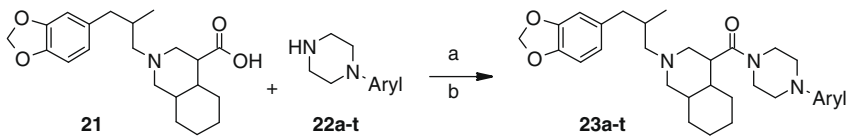
As apparent from Figure 2, variation at this position has a strong influence on sst_3 affinity, with pK_Ds ranging from <6 (e.g., **23i**, **23t**) to >7.5 (e.g., **23c**, **23m**, **23n**) (pK_Ds ± SEM for all 20 derivatives see[33]). The SAR is relatively steep; even small changes can have considerable effects on sst_3 affinity (e.g., **23p** vs **23q**). All aryl residues leading to good sst_3 affinity (e.g., **23c**, **23m**, **23n**) had also been found earlier to confer good sst_1 affinity in combination with the obeline, ergoline or β-alanine scaffolds.[26–29] On the other hand, some arly residues that were known to afford highly potent sst_1 li-

Table 3
Determination of preferred absolute configurations at methyl propyl linker and decahydroisoquinoline core: Binding affinities to h rec. sst_3 and sst_1 receptors



Core moiety					
Compound	**10**	**11**	**12**	**13**	**14**
Conf. at Me	(*RS*)	(*RS*)	(*RS*)	(*R*)	(*S*)
Conf. at core (4,4a,8a)	(*RS*,*RS*,*SR*)	(*R*,*R*,*S*)	(*S*,*S*,*R*)	(*S*,*S*,*R*)	(*S*,*S*,*R*)
$[\alpha]_D^{20}$ [a]	0	+24.6	−25.4	−1.0	−48.2
pK_D h sst_3 [b]	8.54 ± 0.08	6.97 ± 0.10	8.87 ± 0.03	8.65 ± 0.07	8.91 ± 0.05
pK_D h sst_1 [b]	6.00 ± 0.03	5.63 ± 0.03	6.40 ± 0.06	6.36 ± 0.05	6.03 ± 0.11

[a] EtOH, $c = 1$
[b] Mean ± SEM. Number of experiments: $n = 3$–6.



Scheme 2. Parallel synthesis of racemic decahydroisoquinoline sst_3 antagonists **23a–t**. Configurations for **21** and **23a–t**: (*RS*) at methyl group, (4*RS*,4a*RS*,8a*SR*) at decahydroisoquinoline core. Reagents and conditions: (a) **21** (1.5 equiv), **22** (1 equiv), polymer supported DCC (3 equiv), DCE, rt, 18 h; (b) filter, evaporate solvent (77–98% yield).

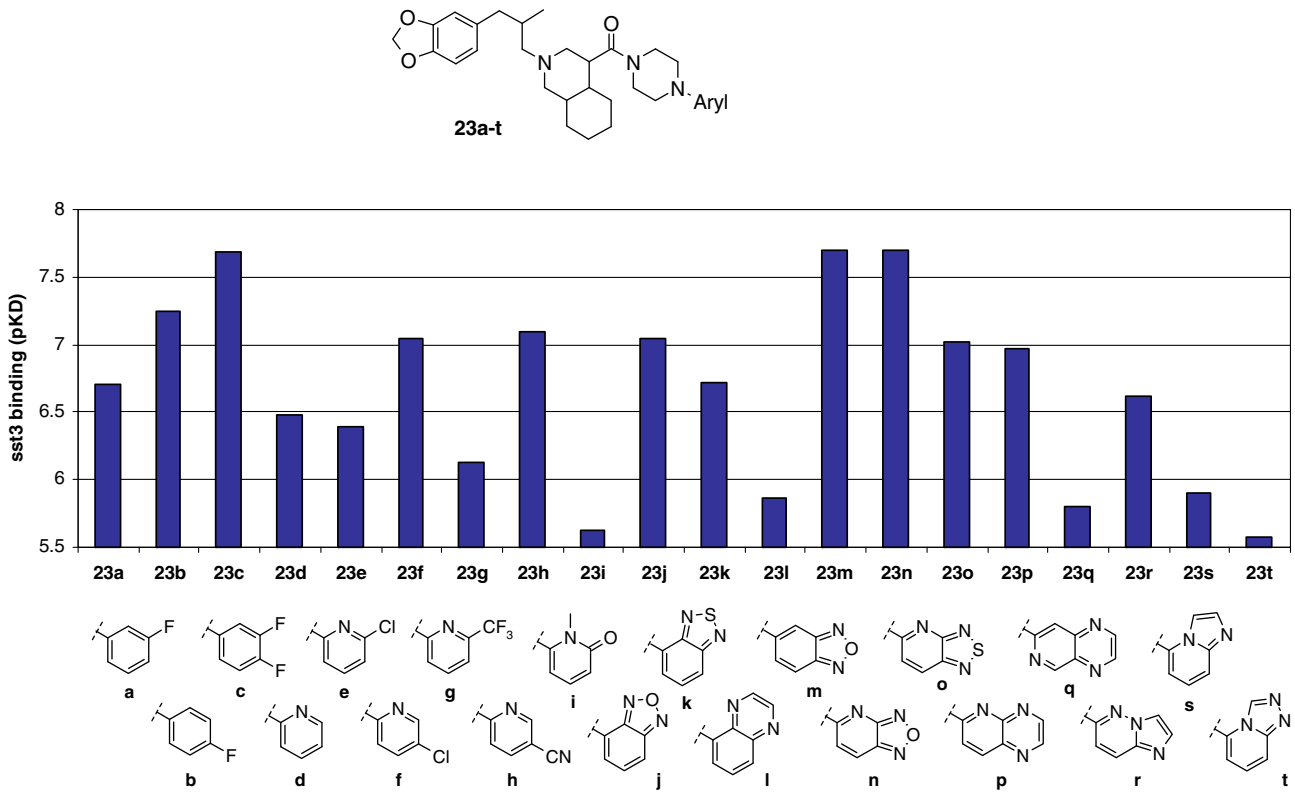
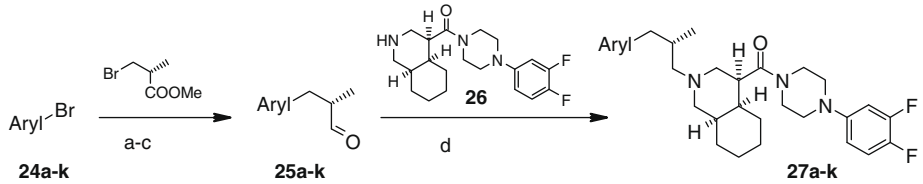


Figure 2. Structures of aryl residues for **22a–t** and **23a–t**. Binding affinities to h rec. sst_3 receptors for **23a–t**. Full numerical data given in Ref. 32.

gands[28] (e.g., 1-methyl-1*H*-pyridin-2-one of **23i**) were not tolerated by the sst_3 receptor (**23i**: $pK_D = 5.62$). Of the three aryl piperazine moieties resulting in sst_3 ligands with pK_Ds >7.5 (**23c**: $pK_D = 7.68$, **23m**: $pK_D = 7.70$ and **23n**: $pK_D = 7.71$), the 3,4-difluorophenyl piperazine moiety of **23c** was finally selected mainly due to its good synthetic accessibility.

For optimization of the aryl moiety at the methyl propyl linker, 11 aryl bromides **24** were converted to the corresponding enantiomerically pure 3,4-difluorophenyl piperazine derivatives **27** as outlined in Scheme 3. Reaction of commercial, enantiomerically pure (*R*)-3-bromo-2-methyl propionic acid methyl ester with Et_2Zn to an alkylzinc reagent (Mn/Cu catalyzed bromine-zinc exchange[34]), followed by Pd catalyzed coupling with aryl bromides **24**, afforded the corresponding enantiomerically pure 2-methyl-3-aryl propionic acid methyl esters in acceptable yields. Conversion of these esters to aldehydes **25**, followed by reductive amination with enantiomerically pure amine building block **26** afforded the desired derivatives **27**.

For derivatives **27a–k**, pK_D values for sst_3 and sst_1 are depicted in Figure 3 (full list of pK_Ds ± SEM see[35]). Most of the 11 derivatives retained good sst_3 affinity with pK_Ds >7. Considerable differences in sst_1 affinities were seen between closely related structures; especially noteworthy is the comparison between **27e** and **27g**, where the introduction of one additional nitrogen atom to the imi-



Scheme 3. Synthesis of enantiomerically pure decahydroisoquinoline sst_3 antagonists **27a–k**. Reagents and conditions: (a) (*R*)-3-bromo-2-methyl-propionic acid methyl ester, Et_2Zn, cat. $MnBr_2/CuCl$, DMPU, rt 4 h, then **24**, cat. $Cl_2Pd(dppf)$, microwave; (b) DIBAH, DCM, 0 °C, 1 h; (c) Dess–Martin periodane, DCM, rt, 2 h; (d) **26**, $NaBH(OAc)_3$, DCE, rt, 2 h.

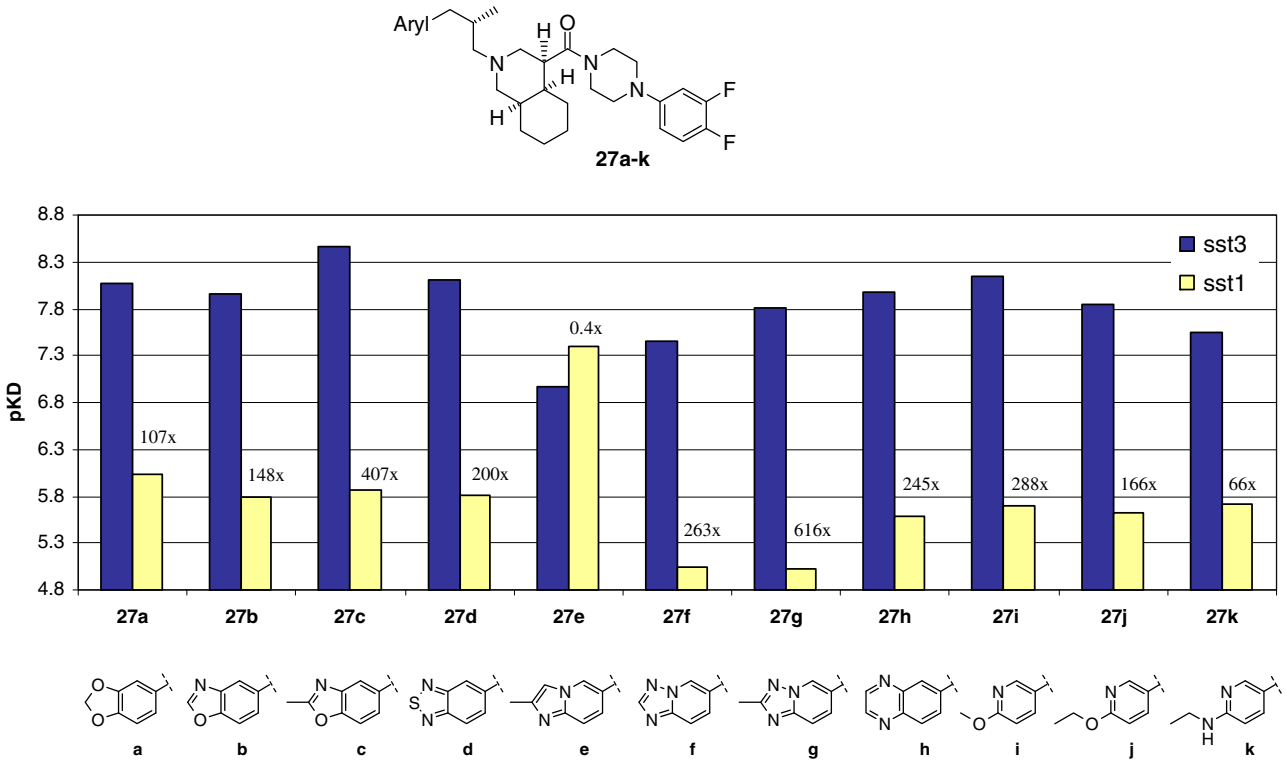


Figure 3. Structures of aryl residues for **24a–k**, **25a–k** and **27a–k**. Binding affinities to h rec. sst_1 and sst_3 receptors for **27a–k**. Full numerical data given in Ref. 34. Numbers on columns indicate selectivity for sst_3 over sst_1.

dazo[1,2-*a*]pyridine system of **27e** boosts selectivity for sst_3 over sst_1 from 0.4-fold to 620-fold. Of these 11 derivatives, **27c**, **27d** and **27i** were chosen for further assessment based on their good sst_3 potency (pK_D >8) and selectivity over sst_1 (>100-fold).

Compounds **27c**, **27d** and **27i** as well as the enantiomer of **27i** (**ent-27i**) were profiled in a panel of somatostatin radioligand binding assays performed either in rat cortex membranes (r sst_1 and r sst_2)[36] or cell lines expressing the five human receptor subtypes (h sst_1–h sst_5)[37] (Table 4).

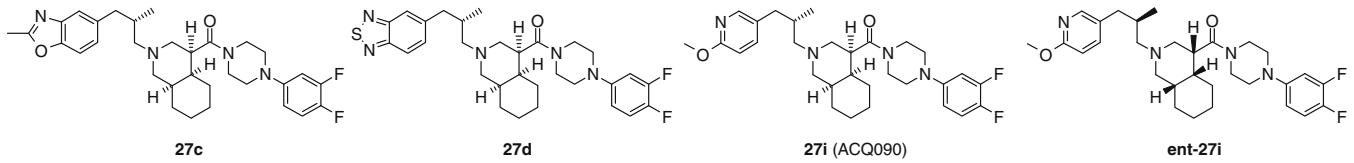
As indicated already in Scheme 3, **27c**, 27d and **27i** bind to the h sst_3 receptor with affinities below 10 nM. Selectivities over h sst_1, h sst_2 and h sst_5 are excellent (>150-fold), whereas some modest affinity to h sst_4 is retained (selectivity factors 120, 130 and 21, respectively). Affinities for the rat sst_1 and sst_2 receptors are somewhat higher than for the corresponding human receptors for all three compounds, but K_D values remain above 100 nM. As expected, the enantiomer of **27i** displays no appreciable affinity to any of the measured somatostatin receptors.

Since there were no major differences in the binding profile for **27c**, **27d** and **27i**, the methoxypyridine derivative **27i** (ACQ090) was selected for further profiling, mainly due to superior physicochemical properties and promising initial PK data in rodents.

The high affinity of ACQ090 for somatostatin sst_3 receptors was confirmed in a radioligand binding assay with recombinant mouse sst_3 receptors, using ^{125}I-SRIF28 as radioligand, with a pK_D of 8.31 ± 0.03 (n = 3).

Radioligand binding affinities of ACQ090 were tested for a panel of 70 monoamine or peptide receptors, ion channels and transport-

Table 4
Compounds **27c**, **27d**, **27i** (ACQ090) and **ent-27i**: comparison of physicochemical parameters and affinities for somatostatin receptor subtypes



Compound	$[\alpha]_D^{20}$ [b]	Mp (°C)	pK_D [a]						
			r sst_1	r sst_2	h sst_1	h sst_2	h sst_3	h sst_4	h sst_5
27c[c]	n.d.	58–62	6.34 ± 0.07	6.64 ± 0.02	5.86 ± 0.03	5.26 ± 0.04	8.47 ± 0.02	6.38 ± 0.01	5.96 ± 0.02
27d[d]	−3.4	152–155	5.93 ± 0.08	6.82 ± 0.07	5.81 ± 0.05	5.45 ± 0.08	8.11 ± 0.03	5.99 ± 0.04	5.78 ± 0.06
27i[d]	−0.2	119–121	6.23 ± 0.05	6.94 ± 0.02	5.69 ± 0.01	5.34 ± 0.03	8.15 ± 0.02	6.83 ± 0.02	5.95 ± 0.02
ent-27i[d]	+0.2	116–120	6.09 ± 0.01	4.68 ± 0.04	6.14 ± 0.02	4.42 ± 0.09	5.44 ± 0.01	5.21 ± 0.02	4.04 ± 0.10

[a] Mean ± SEM. Number of experiments: n = 3–6.
[b] EtOH, c = 0.5.
[c] Free base.
[d] Fumarate.

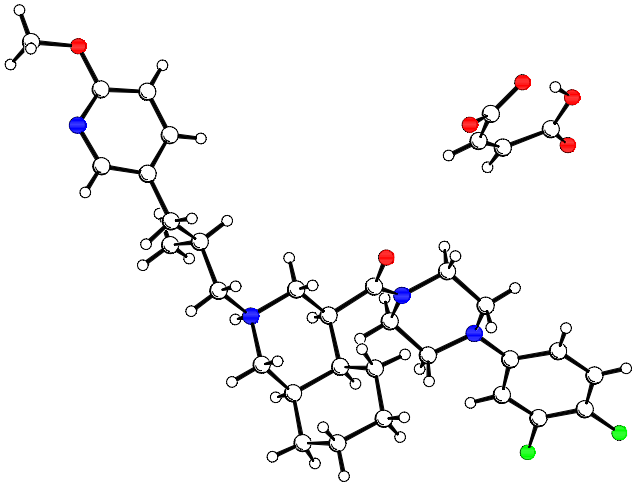


Figure 4. X-ray crystal structure of ACQ090 fumarate.

ers.[37] Only very modest affinities were found for few of these receptors (5-HT_{2C}: $pK_D = 6.37 \pm 0.17$, α1: $pK_D = 6.16 \pm 0.03$, Dopamine D_2: $pK_D = 6.13 \pm 0.12$), suggesting that ACQ090 is indeed very selective for sst_3 somatostatin receptors.

In a cAMP-based functional assay using human recombinant sst_3 receptors expressed in CHO cells, ACQ090 behaves as a silent and competitive antagonist of SRIF-14 ($pK_B = 7.88 \pm 0.18$, $n = 6$). As expected, its enantiomer shows only very weak antagonistic potency with a pK_B of 5.10.

The pharmacokinetics and brain penetration of ACQ090 were studied in mice and rats after oral (3 mg/kg) and intravenous (1 mg/kg) doses of unlabelled ACQ090. Plasma and brain samples were analyzed with an LC–MS-based method (LOQ 0.4 ng/ml for plasma and 2 ng/g for brain). ACQ090 was reasonably well absorbed after oral administration in both species, with an absolute bioavailability estimated as 15% and 21% for mice and rats, respectively. Apparent terminal half-lives in plasma after intravenous administration were determined as 1.5 h for mice and 5.6 h for rats. ACQ090 penetrates readily and significantly into the brain, leading to brain/plasma ratios of 2.4 and 0.4 for mice and rats, respectively, 1 h after oral administration.

ACQ090 was screened for inhibition of the five principal human cytochrome P450 isoenzymes using a microplate-based, direct fluorometric assay. IC_{50}s for CYP450 inhibition were >10 μM for all isoforms with the exception of CYP2D6 ($IC_{50} = 6.5$ μM). Therefore, ACQ090 is considered to be uncritical with regard to potential drug–drug interaction. In an initial genotoxicity assessment, ACQ090 was found to be negative in the Ames test as well as the micronucleus test in V79 Chinese hamster cells.

A highly efficient and convergent synthesis of enantiomerically pure ACQ090 has been published elsewhere.[38] Using this route, ACQ090 was prepared in 12 chemical steps starting from isoquinoline-4-carboxylic acid ethyl ester in an overall yield of 8.5%. The structure of ACQ090 was unambiguously confirmed by X-ray analysis of fumarate salt crystals (Fig. 4).

In summary, we have developed a novel class of non-peptidic, enantiomerically pure, highly potent and selective somatostatin sst_3 receptor antagonists that show promising PK properties in rodents, are not genotoxic in vitro, and can effectively be synthesized. Further details and results of in vivo studies with these compounds will be published elsewhere in due course.

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30. The 4-nitrophenyl piperazine amide of racemic nipecotic acid was reacted under reductive amination conditions as described before[29] with a number of commercial or custom-made aldehydes, among the former being 3-benzo[1,3]dioxol-5-yl-2-methyl-propionaldehyde (Helional).
31. Subsequently it was shown for several compounds in addition to **10** that this SAR trend applies in general to this series. In all cases, the (*S*) (*SSR*) isomers displayed best sst_3 affinity and selectivity over sst_1.
32. The absolute configuration of the pure enantiomer of **16** was determined by comparison of the optical rotation with a sample of the same compound prepared by a different route, starting from a commercial building block with known absolute configuration. Commercial, enantiomerically pure (*R*)-3-bromo-2-methyl propionic acid methyl ester was converted to an alkylzinc reagent (Mn/Cu catalyzed bromine–zinc exchange[33]), followed by Pd catalyzed coupling with 5-bromo-isophthalic acid dimethyl ester as outlined in Scheme 3. Hydrolysis of the resulting methyl ester afforded an enantiomerically pure sample of **16** with known absolute configuration.
33. Compound: pK_D h $sst_3 \pm$ SEM; **23a**: 6.70 ± 0.05; **23b**: 7.24 ± 0.03; **23c**: 7.68 ± 0.04; **23d**: 6.48 ± 0.13; **23e**: 6.39 ± 0.04; **23f**: 7.04 ± 0.15; **23g**: 6.13 ± 0.03; **23h**: 7.1 ± 0.17; **23i**: 5.62 ± 0.06; **23j**: 7.04 ± 0.04; **23k**: 6.72 ± 0.04; **23l**: 5.87 ± 0.06; **23m**: 7.7 ± 0.1; **23n**: 7.71 ± 0.06; **23o**: 7.02 ± 0.05; **23p**: 6.97 ± 0.07; **23q**: 5.8 ± 0.13; **23r**: 6.62 ± 0.16; **23s**: 5.9 ± 0.08; **23t**: 5.57 ± 0.1.
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35. Compound: pK_D h $sst_1 \pm$ SEM, pK_D h $sst_3 \pm$ SEM; **27a**: 6.04 ± 0.07, 8.07 ± 0.12; **27b**: 5.79 ± 0.02, 7.96 ± 0.04; **27c**: 5.86 ± 0.03, 8.47 ± 0.02; **27d**: 5.81 ± 0.05, 8.11 ± 0.03; **27e**: 7.4 ± 0.02, 6.97 ± 0.02; **27f**: 5.04 ± 0.01, 7.46 ± 0.01; **27g**: 5.02 ± 0.06, 7.81 ± 0.07; **27h**: 5.58 ± 0.05, 7.97 ± 0.06; **27i**: 5.69 ± 0.01, 8.15 ± 0.02; **27j**: 5.63 ± 0.04, 7.85 ± 0.06; **27k**: 5.72 ± 0.04, 7.54 ± 0.04.
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