Bioorganic & Medicinal Chemistry Letters 19 (2009) 1305–1309

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of novel non-peptidic β-alanine piperazine amide derivatives and their optimization to achiral, easily accessible, potent and selective somatostatin sst_1 receptor antagonists

Thomas Troxler *, Konstanze Hurth, Henri Mattes, Mahavir Prashad, Philippe Schoeffter, Daniel Langenegger, Albert Enz, Daniel Hoyer

Novartis Institutes for BioMedical Research, Neuroscience Chemistry, WSJ-088.3.06, CH-4002 Basel, BS, Switzerland

ARTICLE INFO

Article history:
Received 15 December 2008
Revised 20 January 2009
Accepted 22 January 2009
Available online 27 January 2009

Keywords:
Somatostatin
GPCR
Somatostatin sst1 receptor
Selective sst1 receptor antagonists
Achiral, Non-peptidic somatostatin analogs

ABSTRACT

Structural simplification of the core moieties of obeline and ergoline somatostatin sst_1 receptor antagonists, followed by systematic optimization, led to the identification of novel, highly potent and selective sst_1 receptor antagonists. These achiral, non-peptidic compounds are easily prepared and show promising PK properties in rodents.

The somatostatin sst_1 receptor is one of five somatostatin receptor subtypes (sst_1 to sst_5) that have been cloned and characterized so far.[1–3] It belongs to the G-protein-coupled receptor superfamily and is present in human brain[4], human retina[5], neuroendocrine cells[6], endothelial cells[7] and various human tumors.[8–13] Sst_1 receptors are involved in the intra-hypothalamic regulation of growth hormone (GH) secretion[6,14–17] and modulate somatostatin release in basal ganglia.[18] There is increasing evidence that sst_1 receptors act as inhibitory auto-receptors located on somatostatin neurons in hypothalamus, basal ganglia, retina and possibly hippocampus.[19] Thus, compounds that selectively interact with sst_1 receptors may play a role in various diseases, such as retinal and endocrine dysfunctions, cancer and neuropsychiatric disorders.[5,18–20] For instance, sst_1-selective agonists have been shown to mimic the inhibitory effect of SRIF on GH secreting pituitary tumors,[21] whereas in medullary thyroid carcinoma, they inhibit calcitonin secretion and gene expression.[22,23] Furthermore, sst_1-selective agonists inhibit endothelial activities, suggesting their utility in angiogenesis.[7] Finally, we have reported that sst_1 antagonists promote social interactions, reduce aggressive behavior and stimulate learning in rodents.[24,25] In order to further evaluate the potential of somatostatin sst_1 receptor ligands for the treatment of various disorders, we are interested in developing non-peptidic, orally available, brain penetrating, potent and subtype-selective sst_1 receptor antagonists.

Recently, we have described antagonists of the sst_1 receptor subtype based on the octahydrobenzo[g]quinoline (obeline, e.g., **1**)[26,27] as well as the octahydro-indolo[4,3-fg]quinoline (ergoline, e.g., **2**)[28] scaffolds (Fig. 1).

Both chemical classes provide ligands with very high affinity and selectivity for the sst_1 receptor subtype, however, the chemical structure of both cores is relatively complex. Obelines as well as ergolines contain three chiral centers, which requires a long and low-yielding total synthesis including the resolution of a racemate in the case of the obelines,[29,30] or the use of expensive natural products as starting materials in the case of ergolines.[31] In addition to these accessibility issues, both structural classes show considerable affinity to some monoamine receptors. Obeline derivative **1** for instance binds to the dopamine D_4 receptor with a pK_D of 8.30, whereas the ergoline derivative **2** is a ligand of the dopamine

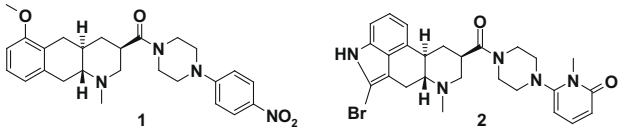


Figure 1. Typical representatives of obeline (**1**) and ergoline (**2**) sst_1 antagonists.

* Corresponding author. Tel.: +41 61 3246604; fax: +41 61 3246760.
E-mail address: thomas.troxler@novartis.com (T. Troxler).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.01.072

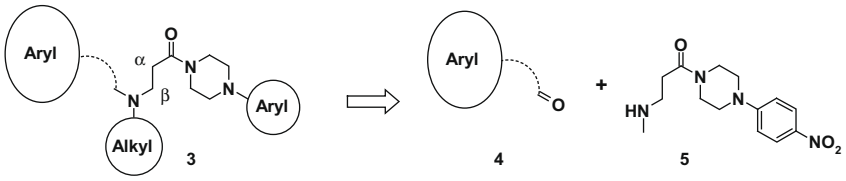


Figure 2. General pharmacophore **3** for sst_1 antagonists, and outline of synthetic strategy towards first derivatives.

D_2 and the $5HT_{1A}$ receptors (pK_Ds of 7.25 and 7.30, respectively). Due to these potential shortcomings, we set out to identify alternative sst_1 receptor ligands with retained sst_1 affinity and selectivity versus sst_2–sst_5, but a simpler chemical structure and reduced affinity to monoamine receptors.

Comparison of structures for sst_1 antagonists from the obeline and ergoline classes reveals that these non-peptidic ligands share a common pharmacophore, schematically represented by **3** (Fig. 2, left). In this model, a central tertiary amine is substituted by (i) a small alkyl group, (ii) an aryl piperazine amide moiety separated from the amine by a two carbon linker (β-substitution), and (iii) a functionalized aromatic moiety connected by an aliphatic spacer.

In order to assess the utility of this simple pharmacophore model for the identification of structurally less complex sst_1 ligands, we decided to retain the first two structural features (i) and (ii) in the simplest possible way, namely as the achiral *N*-methyl-β-alanine piperazine amide **5** (Fig. 2, right), and experimentally probe the less defined third amine substituent. To this end, a collection of aldehydes of the general structure **4** was assembled. These building blocks were selected based on approximate match with the requirements outlined in **3**, structural simplicity, attractiveness as potential drug substructures, and availability of the corresponding acid, ester or alcohol precursors. In total, 17 aldehydes of type **4** were prepared by oxidation of the corresponding primary alcohol precursors (data not shown), reacted with secondary amine **5** under reductive amination conditions, and the resulting tertiary amines tested for their affinity to rat sst_1 and sst_2 receptors.[32] Gratifyingly, this small collection of amines revealed as best example the achiral dibenzosuberane derivative **6** (prepared from aldehyde **4a**, Scheme 1), which retained surprisingly high sst_1 affinity (pK_D 7.74) and selectivity versus sst_2 (>100-fold) despite its apparently flexible structure. **6** was therefore chosen for further optimization.

In a first round of derivation, the tricyclic dibenzosuberane moiety was further probed. The central 7-membered ring of the dibenzosuberane system was replaced by an unsaturated 7-membered ring (**7**, Table 1), carbo- and hetero-cyclic 6-membered (**8**–**10**) as well as 5-membered rings (**11** and **12**), always by retaining the symmetry of the polycyclic system in order to avoid introduction of a chiral center. In addition, the number of annelated rings was reduced (**13**–**15**). Derivatives **7**–**15** were prepared in analogy to the synthesis of **6** (Scheme 1), and tested in the sst_1 and sst_2 receptor binding assays.

All these modifications were well tolerated by the sst_1 receptor, with the exception of carbazole derivative **12** and naphthalenes **13** and **14**. Introduction of xanthenyl and fluorenyl moieties (derivatives **10** and **11**, respectively) improved the sst_1 affinity by more than 20-fold to the subnanomolar range while at the same time further enhancing the selectivity over sst_2 to >1000-fold. For further optimization, the most potent and selective compound (fluorene derivative **11**) was chosen.

Increasing the size of the alkyl substituent of **11** from methyl to ethyl, isopropyl, allyl and cyclopropylmethyl (**16**–**19**, Table 2) successively decreased sst_1 affinity and sst_2 selectivity. Therefore, the methyl group was retained as the preferred substituent in this position.

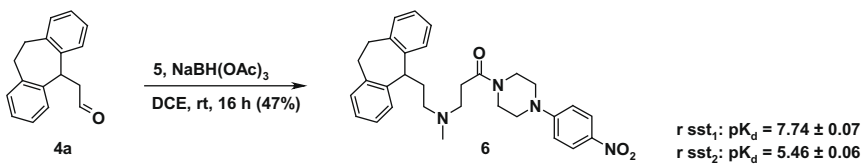
In order to optimize the aryl piperazine part of fluorene derivative **11**, a collection of 18 aryl- and heteroaryl piperazines[27] **21a–r** (Scheme 2 and Fig. 3) were coupled with acid chloride **20** applying a Schotten-Baumann-type reaction protocol in a multi-parallel fashion (Scheme 2).

Each aryl piperazine was shaken with a slight excess of **20** in a biphasic mixture of aq. $NaHCO_3$ and DCM for 5 h. After separation of the phases and drying of the organic phase, the crude mixtures were loaded on pre-packed SiO_2 cartridges and eluted with DCM/MeOH 9:1. Fractions collected based on tlc analysis were treated with HCl, evaporated and analyzed by HPLC. Purities of crude products **22a–r** ranged from 22% to 95% (Table 3) and were deemed good enough to provide a first assessment of binding affinities. Therefore, the crude hydrochlorides were directly submitted for rat sst_1 receptor binding studies. Based on these preliminary binding results (Table 3), the 3,4-difluorophenyl piperazine moiety of **22g**, the benzoxadiazole piperazine of **22p**, and to a lesser extent the imidazo[1,2-b]pyridazine piperazine of **22q**, offered themselves as interesting options to replace the nitrophenyl piperazine group of **11**.

Combination of the most promising structural moieties identified in the course of this optimization process led to the fluorenyl and xanthenyl derivatives **22g**, **22p**, **23** and **24** (Table 4). All four derivatives were prepared and characterized in binding studies with rat and human somatostatin receptor subtypes.

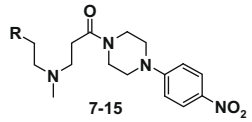
Compounds **22g**, **22p**, **23** and **24** bind to rat sst_1 receptors with subnanomolar affinities (pK_Ds 9.11–9.55) and show excellent selectivity versus rat sst_2 receptors ($\geqslant$10,000-fold). These attractive binding features were confirmed in cell lines expressing the five human receptor subtypes.[25] All four compounds exhibit single-digit nanomolar affinities to h sst_1 receptors, and bind to h sst_2–h sst_5 with affinities >1 μM (Table 4).

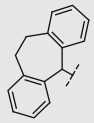
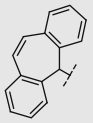
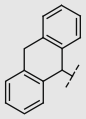
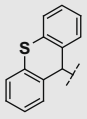
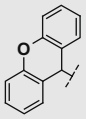
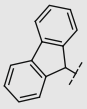
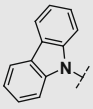
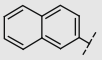
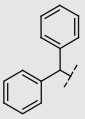
Since there were no major differences in the binding profile for these four derivatives, the two difluorophenyl piperazine derivatives **22g** and **23** were selected for further profiling, mainly based on the easier accessibility of the piperazine building block.



Scheme 1. Synthesis of tertiary amine **6**, and somatostatin receptor binding affinities.

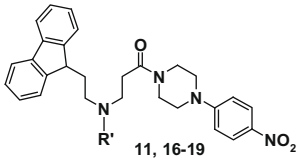
Table 1
Binding affinities of β-alanine piperazine amide derivatives to rat sst_1 and sst_2 receptors: modifications at the polycyclic moiety



R										
Compound	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
pK_d r sst_1[a]	7.74 ± 0.07	7.94 ± 0.02	7.53 ± 0.02	7.90 ± 0.01	9.05 ± 0.06	9.15 ± 0.10	6.48 ± 0.03	7.11 ± 0.03	6.56 ± 0.03	7.86 ± 0.04
pK_d r sst_2[a]	5.46 ± 0.06	5.29 ± 0.04	4.73 ± 0.07	5.22 ± 0.01	5.17 ± 0.03	5.16 ± 0.03	4.84 ± 0.05	5.06 ± 0.02	4.78 ± 0.04	5.08 ± 0.05

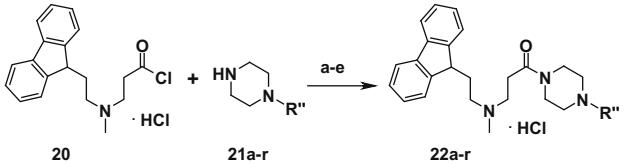
[a] Mean ± SEM. Number of experiments: $n = 3–6$.

Table 2
Binding affinities of fluorene derivatives to rat sst_1 and sst_2 receptors: modifications at the alkyl moiety



R′	Me	Et	iPr	Allyl	$-CH_2cPr$
Compound	**11**	**16**	**17**	**18**	**19**
pK_d r sst_1 [a]	9.15 ± 0.10	9.02 ± 0.02	8.33 ± 0.06	8.15 ± 0.04	7.34 ± 0.01
pK_d r sst_2 [a]	5.16 ± 0.03	5.74 ± 0.01	6.04 ± 0.02	5.39 ± 0.03	5.16 ± 0.22

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



Scheme 2. Parallel synthesis of fluorene derivatives with modified arylpiperazine moieties. Reaction conditions: (a) Arylpiperazine **21a–r** (0.1 mmol), acid chloride **20** (0.13 mmol), 1 M aq. $NaHCO_3$ (1 ml), DCM (2 ml), shake for 5 h. (b) Pipette off aqueous phase, add 100 mg Na_2SO_4, shake for 30 min. (c) Load on cartridge containing 500 mg SiO_2, wash with DCM (1 ml). (d) Elute with 3 × 1 ml DCM/MeOH 9/1 (tlc control). (e) Add 0.5 N HCl/EtOH (0.5 ml), evaporate, HPLC analysis.

In a cAMP-based functional assay, **23** and **22g** behaved as antagonists, devoid of agonist activity, with a pK_b of 7.93 and 8.55, respectively. Both **23** and **22g** act as antagonists at the human recombinant sst_1 receptor driven luciferase activity with pK_b-values of 8.13 and 8.46, respectively, and are devoid of intrinsic activity.[25]

Radioligand binding affinities of **23** and **22g** were tested for a panel of 40 monoamine or peptide receptors, ion channels and transporters.[25] Highest affinities were found for the α1 receptor (pK_Ds of 6.55 and 6.53), the D2 receptor (pK_Ds of 6.31 and 6.11) and the D4 receptor (pK_Ds of 6.31 and 6.90), indicating that these new β-alanine piperazine amide derivatives have an improved selectivity profile as compared to obelines and ergolines.

The pharmacokinetics and brain levels of **23** and **22g** were studied in mice after dosing of 10 μmol/kg i.v. and 30 μmol/kg p.o. Both compounds were well absorbed after oral administration, with an estimated bioavailability of 7% for **22g** and 19% for **23**. They penetrated readily and significantly into the brain with a brain/plasma ratio >1 after oral and i.v. dosing. Maximum concentrations of **23** and **22g** in plasma and brain were reached at about 1 h. Apparent terminal half-lives in plasma of 11 and 6 hours could be estimated for intravenously and orally administered **23** and **22g**, respectively.

Compounds **23** and **22g** were tested for inhibition of four human cytochrome P450 isoenzymes using a microplate-based, direct fluorometric assay. Estimated IC_{50}s for CYP450 1A2, 2C19 and 3A4 were in the μM range or higher than 10 μM for both compounds, and <1/1.3 μM for CYP 2D6, respectively, indicating a low to moderate potential for drug–drug interactions.

An initial genotoxicity assessments revealed that both **23** and **22g** were negative in the Ames test as well as the micronucleus test in V79 Chinese hamster cells.

Since good synthetic accessibility has been a main requirement for potential alternatives to obeline and ergoline sst_1 antagonists,

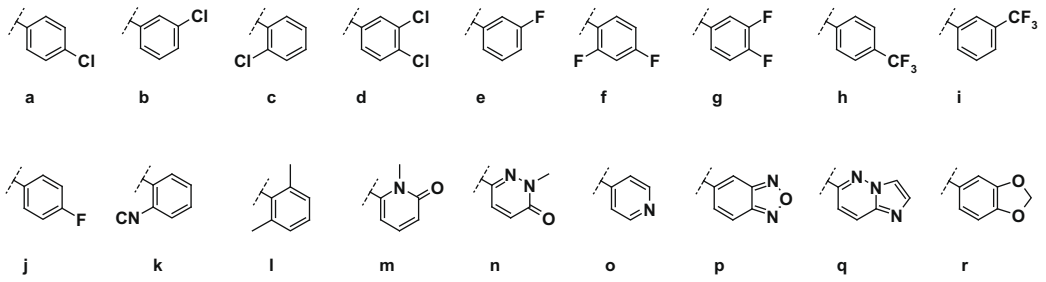


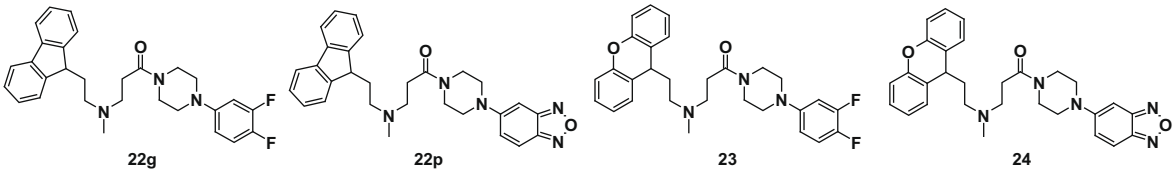
Figure 3. Structures of residues R″ for piperazines **21a–r** and products **22a–r**.

Table 3
HPLC purities and rat sst_1 binding affinities of crude parallel synthesis products **22a–r**

Compound	**22a**	**22b**	**22c**	**22d**	**22e**	**22f**	**22g**	**22h**	**22i**
HPLC purity [%]	77	74	84	55	79	78	81	90	89
pK_d r sst_1 [a]	8.77 ± 0.05	7.75 ± 0.11	7.62 ± 0.11	8.72 ± 0.08	8.44 ± 0.10	8.48 ± 0.07	9.24 ± 0.03	7.50 ± 0.06	7.21 ± 0.14
Compound	**22j**	**22k**	**22l**	**22m**	**22n**	**22o**	**22p**	**22q**	**22r**
HPLC purity [%]	81	95	91	52	68	23	33	22	58
pK_d r sst_1 [a]	8.71 ± 0.08	8.34 ± 0.06	< 6	8.67 ± 0.02	8.18 ± 0.10	7.67 ± 0.07	9.13 ± 0.02	8.96 ± 0.09	8.34 ± 0.05

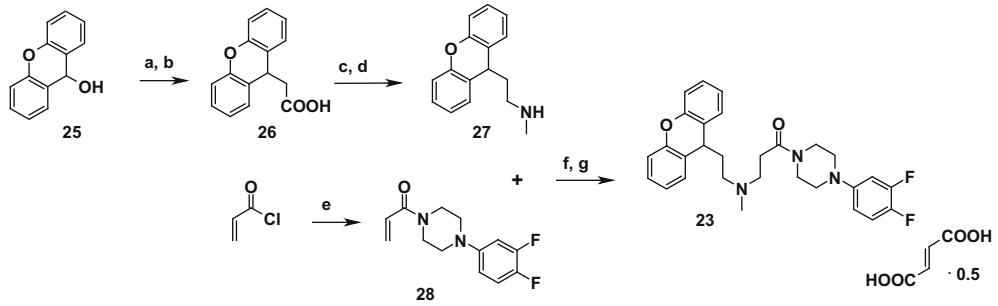
[a] Mean ± SEM. Number of experiments: $n = 3$.

Table 4
Compounds **22g**, **22p**, **23**, **24**: affinities for different somatostatin receptor subtypes

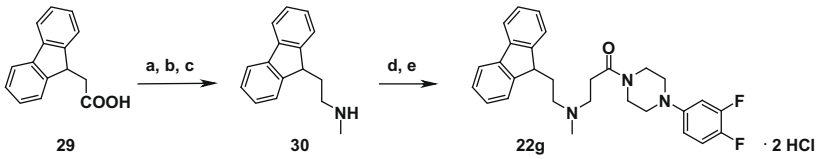


Compound	pK_d [a]						
	r sst_1	r sst_2	h sst_1	h sst_2	h sst_3	h sst_4	h sst_5
22g	9.29 ± 0.02	4.71 ± 0.10	8.27 ± 0.06	4.91 ± 0.07	5.57 ± 0.06	5.62 ± 0.01	n.d.
22p	9.55 ± 0.02	5.38 ± 0.05	8.58 ± 0.05	5.38 ± 0.07	5.92 ± 0.01	5.94 ± 0.02	n.d.
23	9.11 ± 0.11	5.19 ± 0.16	8.79 ± 0.06	5.16 ± 0.09	5.55 ± 0.04	5.47 ± 0.06	4.84 ± 0.10
24	9.49 ± 0.10	5.09 ± 0.05	8.67 ± 0.05	n.d.	5.79 ± 0.02	5.84 ± 0.02	n.d.

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



Scheme 3. Synthesis of achiral xanthenyl sst_1 antagonist **23**. Reaction conditions: (a) malonic acid (1.5 equiv), HOAc, rt, 1 h (quant). (b) NMP, 1 h, 100° (88%). (c) ClCOOiBu, Me_2NBn, EtOAc, −15°, then H_2NMe, rt, 1 h (91%). (d) Red-Al (3.5 equiv, 65% in toluene), toluene, −5° to rt, 3 h (86%). (e) **21g**, EtOAc, aq. $NaHCO_3$, 5° to rt, 1 h (88%). (f) EtOAc, 70°, 20 h (86%). (g) fumaric acid (0.5 equiv), ethanol/heptane, crystallization (85%).



Scheme 4. Synthesis of achiral fluorenyl sst_1 antagonist **22g**. Reaction conditions: (a) ClCOOiBu, Me_2NBn, EtOAc, −15°, then H_2NMe, rt, 1 h (80%). (b) $LiAlH_4/CHCl_3$, THF, 65°, 4 h. (c) H_2O, 4 N NaOH, then filter; HCl gas (50%). (d) NaOH; **28**, EtOAc, 65°, 20 h. (e). HCl, EtOAc/EtOH, crystallization (64%).

large scale syntheses have been worked out for both **22g** and **23**. Starting from commercial xanthene-9-ol **25**, 0.68 kg of **23** hemifumarate was prepared in a straightforward, chromatography-free, 7-step synthesis in an overall yield of 50% (Scheme 3). A similar chromatography-free 6-step process starting from commercially available fluoren-9-yl acetic acid **29** afforded 1 kg of **22g** di-hydrochloride salt in an overall yield of 26% (Scheme 4).

In summary, we have identified a novel class of achiral, highly potent and selective somatostatin sst_1 receptor antagonists that show promising PK properties in mice, are not genotoxic in vitro, and are easily prepared on large scale. Further details and results of in-vivo studies with these compounds will be published elsewhere in due course.

Acknowledgments

We thank Dr. Bin Hu and Mr. Yansong Lu for developing large scale syntheses of **22g** and **23**.

References and notes

1. Patel, Y. C. *Front. Neuroendocrinol.* **1999**, *20*, 157.
2. Hoyer, D.; Bell, G. I.; Berelowitz, M.; Epelbaum, J.; Feniuk, W.; Humphrey, P. P. A.; O'Carroll, A.-M.; Patel, Y. C.; Schonbrunn, A. *Trends Pharmacol. Sci.* **1995**, *16*, 86.
3. Bell, G. I.; Reisine, T. *Trends Neurosci.* **1993**, *16*, 34.
4. Piwko, C.; Thoss, V. S.; Schupbach, E.; Kummer, J.; Langenegger, D.; Probst, A.; Hoyer, D. *Naunyn Schmiedebergs Arch. Pharmacol.* **1997**, *355*, 161.
5. Thermos, K. *Vision Res.* **2003**, *43*, 1805.
6. Olias, G.; Viollet, C.; Kusserow, H.; Epelbaum, J.; Meyerhof, W. J. *Neurochemistry* **2004**, *89*, 1057.
7. Bocci, G.; Culler, M. D.; Fioravanti, A.; Orlandi, P.; Fasciani, A.; Colucci, R.; Taylor, J. E.; Sadat, D.; Danesi, R.; Del Tacca, M. *Eur. J. Clin. Invest.* **2007**, *37*, 700.
8. Reubi, J. C.; Schaer, J. C.; Waser, B.; Hoeger, C.; Rivier, J. *Eur. J. Pharmacol.* **1998**, *345*, 103.
9. Reubi, J. C.; Waser, B.; Laissue, J. A.; Gebbers, J. O. *Cancer Res.* **1996**, *56*, 1922.
10. Reubi, J. C.; Waser, B.; Schaer, J.-C.; Laissue, J. A. *Eur. J. Nucl. Med.* **2001**, *28*, 836.
11. Reubi, J. C.; Schaer, J. C.; Waser, B.; Mengod, G. *Cancer Res.* **1994**, *54*, 3455.
12. Reubi, J. C.; Waser, B.; Schaer, J. C.; Markwalder, R. J. *Clin. Endocrinol. Metab.* **1995**, *80*, 2806.
13. Miller, G. M.; Alexander, J. M.; Bikkal, H. A.; Katznelson, L.; Zervas, N. T.; Klibanski, A. J. *Clin. Endocrinol. Metab.* **1995**, *80*, 1386.
14. Weckbecker, G.; Lewis, I.; Albert, R.; Schmid, H. A.; Hoyer, D.; Bruns, C. *Nat. Rev. Drug Discov.* **2003**, *2*, 999.
15. Lanneau, C.; Bluet-Pajot, M. T.; Zizzari, P.; Csaba, Z.; Dournaud, P.; Helboe, L.; Hoyer, D.; Pellegrini, E.; Tannenbaum, G. S.; Epelbaum, J.; Gardette, R. *Endocrinology* **2000**, *141*, 967.
16. Kreienkamp, H.-J.; Akgün, E.; Baumeister, H.; Meyerhof, W.; Richter, D. *FEBS Lett.* **1999**, *462*, 464.
17. Zatelli, M. C.; Piccin, D.; Tagliati, F.; Ambrosio, M. R.; Margutti, A.; Padovani, R.; Scanarini, M.; Culler, M. D.; degli Uberti, E. C. J. *Clin. Endocrinol. Metab.* **2003**, *88*, 2797.
18. Vasilaki, A.; Papasava, D.; Hoyer, D.; Thermos, K. *Neuropharmacology* **2004**, *47*, 612.
19. Thermos, K.; Bagnoli, P.; Epelbaum, J.; Hoyer, D. *Pharmacol. Ther.* **2006**, *110*, 455.
20. Dal Monte, M. D.; Petrucci, C.; Vasilaki, A.; Cervia, D.; Grouselle, D.; Epelbaum, J.; Kreienkamp, H. J.; Richter, D.; Hoyer, D.; Bagnoli, P. *Neuropharmacology* **2003**, *45*, 1080.
21. Matrone, C.; Pivonello, R.; Colao, A.; Cappabianca, P.; Cavallo, L. M.; Del Basso De Caro, M. L.; Taylor, J. E.; Culler, M. D.; Lombardi, G.; Di Renzo, G. F.; Annunziato, L. *Neuroendocrinology* **2004**, *79*, 142.
22. Zatelli, M. C.; Tagliati, F.; Piccin, D.; Taylor, J. E.; Culler, M. D.; Bondanelli, M.; degli Uberti, E. C. *Biochem. Biophys. Res. Commun.* **2002**, *297*, 828.
23. Zatelli, M. C.; Piccin, D.; Tagliati, F.; Bottoni, A.; Luchin, A.; Vignali, C.; Margutti, A.; Bondanelli, M.; Pansini, G. C.; Rosa Pelizzo, M.; Culler, M. D.; Degli Uberti, E. C. J. *Clin. Endocrinol. Metab.* **2006**, *91*, 2218.
24. Hoyer, D.; Dixon, K.; Gentsch, C.; Vassout, A.; Enz, A.; Jaton, A.; Nunn, C.; Schoeffter, P.; Neumann, P.; Troxler, T.; Pfaeffli, P. *The Pharmacologist* **2002**, *44*, A254.
25. Hoyer, D.; Nunn, C.; Hannon, J.; Schoeffter, P.; Feuerbach, D.; Schuepbach, E.; Langenegger, D.; Bouhelal, R.; Hurth, K.; Neumann, P.; Troxler, T.; Pfaeffli, P. *Neurosci. Lett.* **2004**, *361*, 132.
26. Troxler, T.; Hoyer, D.; Langenegger, D.; Neumann, P.; Pfäffli, P.; Schoeffter, P.; Sorg, D.; Swoboda, R.; Hurth, K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3983.
27. Hurth, K.; Enz, A.; Floersheim, P.; Gentsch, C.; Hoyer, D.; Langenegger, D.; Neumann, P.; Pfäffli, P.; Sorg, D.; Swoboda, R.; Vassout, A.; Troxler, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3988.
28. Troxler, T.; Enz, A.; Hoyer, D.; Langenegger, D.; Neumann, P.; Pfäffli, P.; Schoeffter, P.; Hurth, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 979.
29. Lueoend, R. M.; Baenziger, M.; Frey, P.; PCT Int. Appl. WO9703054, *Chem. Abstr.* **2000**, 133, 177338.
30. Neumann, P.; Pfaeffli, P.; Seiler, M. P.; Swoboda, R. PCT Int. Appl. WO9703054, 1997, *Chem. Abstr.* **1997**, 126, 171493.
31. Pfaeffli, P.; Neumann, P.; Swoboda, R.; Stütz, P. PCT Int. Appl. WO 9854183 1998; *Chem. Abstr.* **1998**, 130, 25220.
32. Hoyer, D.; Perez, J.; Schoeffter, P.; Langenegger, D.; Schüpbach, E.; Kaupmann, K.; Lübbert, H.; Bruns, C.; Reubi, J. C. *Eur. J. Pharmacol.* **1995**, *289*, 151.