ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Treating Pain with Somatostatin Receptor Subtype 4 Agonists

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Title:	New Somatostatin Receptor Subtype 4 (SSTR4) Agonists		
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Priority Application:	EP 13168224.7	**Priority date:**	17 May 2013
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Disease Area:	Pain and inflammation	**Biological Target:**	Somatostatin receptor subtype 4 (SSTR4)

Summary:

The invention in this patent application relates to 3-aza-bicyclo[3.1.0]hexane-6-carboxamide derivatives represented generally by formula (I), which are agonists of somatostatin receptor subtype 4. These compounds may be useful for preventing or treating different forms of acute pain, neuropathic peripheral pain, chronic pain, or osteoarthritis.

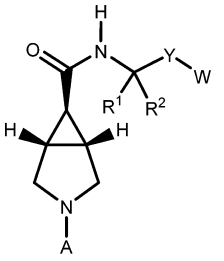
Somatostatin, or somatotropin-release inhibitory factor (SRIF), is a cyclic polypeptide produced by many human organs and tissues and acts both systemically and locally to inhibit the secretion of various hormones, growth factors, and neurotransmitters. The activities of somatostatin are mediated by a family of five G protein-coupled receptors named somatostatin receptors (SSTRs or SSTs). They are divided into two subfamilies; the first includes SSTR2, SSTR3, and SSTR5 and the second includes SSTR1 and SSTR4.

Somatostatin plays a critical role in the regulation of processes such as cellular proliferation, glucose homeostasis, inflammation, and pain. It is believed to inhibit nociceptive and inflammatory processes via the SSTR4 pathway. According to recent studies, somatostatin alleviates pain even in cases when opioids fail and has an important role in neuromodulations such as pain control, presumably via SSTR4 mediation. Additional studies showed that mice has become prone to sustained pain and devoid of analgesic effect in the absence of SSTR4. Therefore, selective SSTR4 agonists may potentially provide a useful treatment for pain and/or inflammation.

While selective SSTR4 agonists have been previously disclosed, there is a need for additional selective SSTR4 agonists, especially nonpeptidic agonists, which may possess better oral efficacy and metabolic stability.

The compounds described in this patent application are effective agonists of SSTR4 receptors. They display high selectivity for the SSTR4 receptor compared to the other member of the same subfamily, the SSTR1 receptor; a property that may lead to reduced side effects.

Important Compound Classes:



Formula (I)

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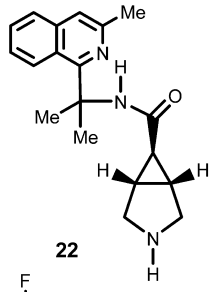
Key Structures: The inventors reported the structures of 184 examples representing formula (I) including the following four compounds:



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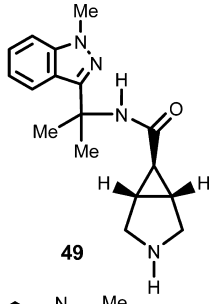

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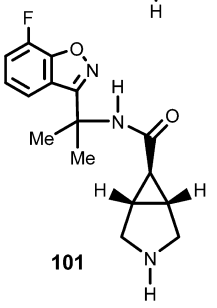

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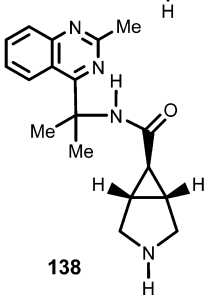

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Biological Assay:

- cAMP Assay
- Radioligand Binding Assays
- Metabolic Stability

Biological Data: The agonistic activity data for the representative examples obtained from the above assays are compiled in the following table:

Compound	SSTR4 agonism EC_{50} (nM)	Selectivity for SSTR4 over other SSTRs					Stability in human liver microsomes
		SSTR4 Binding K_i (nM)	SSTR1 Binding K_i (nM)	SSTR2 Binding K_i (nM)	SSTR3 Binding K_i (nM)	SSTR5 Binding K_i (nM)	Half-life $t_{1/2}$ [min]
22	0.4	3.7	848	>9590	>8580	>9850	>130
49	0.4	4.5	4535	>9600	>8615	>9855	>130
101	1.2	46.2	>9090	>9600	>8597	>9853	>130
138	4.3	70.3	7360	>9630	>8710	>9860	>130

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Somvanshi, R. K.; Kumar, U. *PLoS One* **2014**, *9* (1), e85193/1−e85193/14.
Liu, Z.; Crider, A. M.; Ansbro, D.; Hayes, C.; Kontoyianni, M. *J. Chem. Inf. Model.* **2012**, *52* (1), 171−186.
Chrubasik, J.; Chrubasik S.; Martin E. *Acta Neurobiol Exp.)* **1993** *53* (1), 289−296.

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Notes

The authors declare no competing financial interest.