Selective 5-HT Receptor Modulators May Deliver Focused Targeting with Fewer Adverse Effects

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Title:	Serotonin Receptor Modulator
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Priority Application:	US 61/109,903
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Assignee Company:	Janssen Pharmaceutica NV, New Brunswick, CA (US)
Disease Area:	Diseases mediated by serotonin receptor activity

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Priority date:	30 October, 2008
Biological Target:	5HT-modulating activity, in particular 5HT7 and/or serotonin transporter modulating activity

Summary: The invention in this patent application relates to compounds represented generally by formula (I) that possess serotonin receptor modulator activity, particularly 5-HT7 and/or serotonin transporter modulating activity. These compounds may potentially be useful for the treatment of many disorders mediated by serotonin receptor activities.

The neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) functions via at least 15 different known receptors (5-HT receptors), with 14 of them expressed in the brain. These receptors are grouped in seven families (5-HT1 through 5-HT7). 5-HT has been implicated in the pathogenesis of many diseases, including central nervous system disorders such as depression, anxiety, schizophrenia, eating disorders, obsessive compulsive disorder, learning and memory dysfunction, migraine, chronic pain, sensory perception, motor activity, temperature regulation, nociception, sexual behavior, hormone secretion, and cognition. Therefore, modulation of 5-HT receptor activities is an attractive therapeutic target for the treatment of these disorders.

Many of the known antipsychotic, antidepressants and antimigraine drugs have nonselective affinities for multiple serotonin receptors in addition to other receptors. While the lack of selectivity may contribute to favorable therapeutic outcomes, it can also cause undesirable and dose-limiting adverse effects. For example, the tricyclic antidepressants display favorable therapeutic effects because of their inhibition of serotonin, norepinephrine and 5-HT2 receptor. However, their blockade of histamine H1, muscarinic and alpha-adrenergic receptors may cause unfavorable side effects such as sedation, blurred vision and orthostatic hypertension. Thus, there remains a need for the discovery of new potent serotonin receptor modulators with selective 5-HT receptor affinities to target distinctive therapeutic mechanisms, improve clinical responses and decrease undesirable side effects.
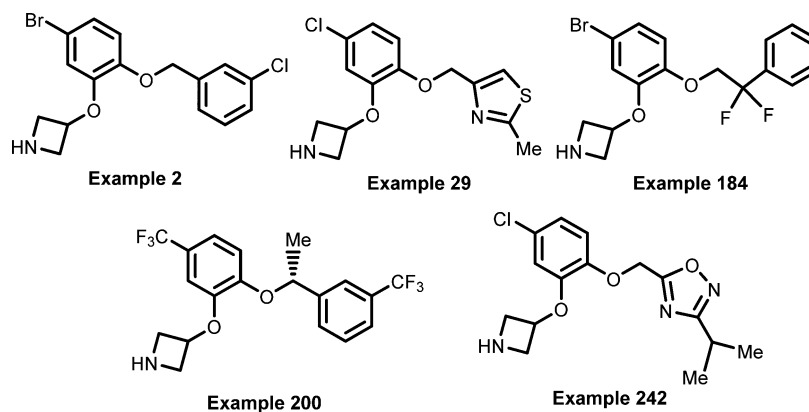
Important Compound Classes:
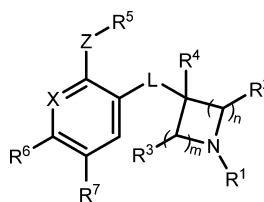
Formula (I)

Key Structures: The inventors reported the structures of 298 specific examples of formula (I) including the following five representative compounds:

Example 2

Example 29

Example 184

Example 200

Example 242

Biological Assay:
- Rat 5-HT7 binding assay
- Other binding assays (see table below)

Biological Data: Assay results were determined for the compounds of the invention. The rat 5-HT7 binding assay results were reported as K_i (in μM) for all examples, but only partial results were reported for the other assays. The data for the representative examples **2**, **29**, **184**, **200**, and **242** (structures above) are listed in the following table:

Compound	5-HT7-RAT Ki (μM)	hSERT binding Ki (μM)	h5-HT6 binding Ki (μM)	h5-HT2$_A$ binding Ki (μM)	h5-HT2$_B$ binding Ki (μM)	h5-HT2$_C$ binding Ki (μM)	R5-HT7 cAMP pK$_b$
Example 2	0.012	0.001	0.047	0.042	0.074	0.76	7.5
Example 29	0.083	0.027	ND	0.225	0.529	1.109	6.9
Example 184	0.023	0.124	ND	0.005	0.012	0.038	7.3
Example 200	0.031	0.224	ND	0.605	7.568	5.00	6.8
Example 242	0.273	ND	ND	ND	ND	ND	ND

ND = not determined

Claims: Claims 1−23: composition of matter; variations of formula (I)

Claim 24: composition of matter; 47 specific examples of formula (I)

Claims 25−27: pharmaceutical composition using compounds of formula (I)

Claims 28−31: Methods of treatments of listed variable diseases and disorders

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(1.) Bardin, L. *Behav. Pharmacol.* **2011**, *22* (5 & 6), 390−404.

(2.) Leopoldo, M.; Lacivita, E.; Berardi, F.; Perrone, R. *Expert Opin. Ther. Pat.* **2010**, *20* (6), 739−754.

(3.) Cifariello, A.; Pompili, A.; Gasbarri, A. *Behav. Brain Res.* **2008**, *195* (1), 171−179.

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Notes
The authors declare no competing financial interest.