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Novel Benzoisoxazole as Partial Agonist of the 5-HT4 Receptor

Patent Highlight

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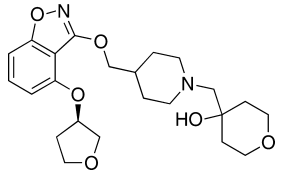
Title:	Novel Benzoisoxazole as Partial Agonist of the 5-HT$_4$ Receptor		
Patent/Patent Application Number:	WO 2011/101774 A1	**Publication date:**	August 25, 2011
Priority Application:	US 2010-304921P	**Priority date:**	February 26, 2010
Inventors:	Noguchi, H.; Waizumi, N.		
Assignee Company:	Pfizer Inc., USA		
Disease Area:	Neurodegenerative disease or disorder	**Biological Target:**	5-HT$_4$ receptor

Summary: This application claims a single compound, the serotonin 5-HT$_4$ receptor partial agonist (*R*)-4-((4-((4-(tetrahydrofuran-3-yloxy)benzo[*d*]isoxazol-3- yloxy)methyl)piperidin-1-yl)methyl)tetrahydro-2*H*-pyran-4-ol, as potential treatment for neurodegenerative diseases and disorders such as Alzheimer's disease, dementia, depression, schizophrenia, anxiety, mood disorders, and attention deficit/hyperactivity disorder.

Key Structures:



Recent Review Articles:

1. Ahmad, I.; Nirogi, R. 5-HT$_4$ receptor agonists for the treatment of Alzheimer's disease. *Neurosci. Med.* 2011, *2* (2), 87−92.

2. Modica, M. N.; Pittala, V.; Romeo, G.; Salerno, L.; Siracusa, M. A. Serotonin 5-HT$_3$ and 5-HT$_4$ ligands: an update of medicinal chemistry research in the past few years. *Curr. Med. Chem.* 2010, *17* (4), 334−362.

Biological Assay: Agonist-induced cAMP elevation in human 5-HT$_{4d}$ transfected HEK293. Intrinsic activity (IA) is reported as percent agonist effect. THLE assay to predict cell health and measure cell depletion. Human liver microsome (HLM) stability assay. Clearance is expressed as an extraction ratio (Er), which is calculated as hepatic clearance/hepatic blood flow.

Biological Data:

Profile	Compound 1
cAMP (%IA, 37°C)	41
HLM (Er)	0.62
THLE (μM)	300
Rat PK (subcutaneous, 5 mg/kg):	
Brain AUC (ng*h/g)	1790
Plasma AUC (ng*h/g)	1760
B/P	1.02

Synthesis: Two different synthetic routes are described. Route 1 is for kiloscale synthesis.

Claims: Claims 4−7: Use of compounds for the treatment of neurodegenerative diseases and disorders.

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Notes

The authors declare no competing financial interest.

Special Issue: Alzheimer's Disease

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