ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Negative Allosteric Modulators of Metabotropic Glutamate Receptor Subtype

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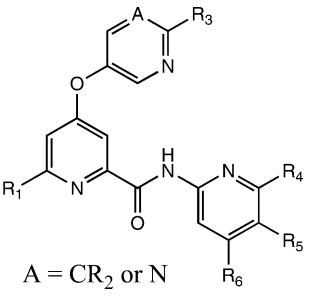
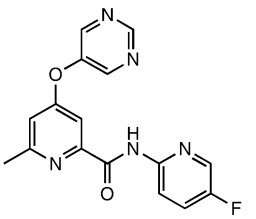
Title:	Negative Allosteric Modulators of Metabotropic Glutamate Receptor Subtype		
Patent/Patent Application Number:	WO 2012/118563 A2	**Publication date:**	September 12, 2012
Priority Application:	US 2011−449017P	**Priority date:**	March 3, 2011
Inventors:	Conn, P. J.; Lindsley, C. W.; Emmitte, K. A.; Rodriguez, A. I.; Felts, A. S.; Jones, C. K.; Bates, B. S.; Chauder, B. A.		
Assignee Company:	Vanderbilt University		
Disease Area:	Neuroogical and/or psychiatric disorder	**Biological Target:**	Metabotropic Glutamate Receptor Subtype 5 (mGluR5)

Summary: This application claims a series of 6-alkyl-*N*-(pyridyl-2-yl)-4-aryloxypicolinamide analogues may provide a treatment for a wide variety of disorders associated with glutamate dysfunction such as Alzheimer's disease, Parkinson's disease, fragile X syndrome, and autism.

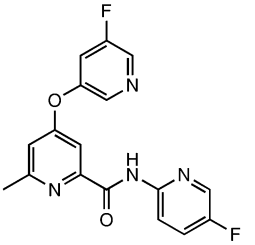
Important Compound Classes:



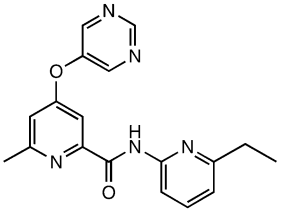
Key Structures:



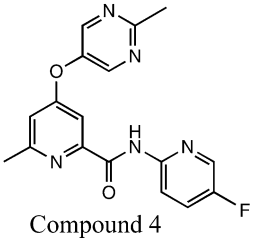
Compound 1



Compound 2



Compound 3



Compound 4

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Recent Review Articles:

Lindsley, C. W.; Stauffer, S. R. Metabotropic glutamate receptor 5-positive allosteric modulators for the treatment of schizophrenia (2004−2012). *Pharm. Pat. Anal.* **2013**, *2* (1), 93−108.

Emmitte, K. A. Recent advances in the design and development of novel negative allosteric modulators of mGlu5. *ACS Chem. Neurosci.* **2011**, *2* (8), 411−432.

Rocher, J.-P.; Bonnet, B.; Bolea, C.; Lutjens, R.; Le Poul, E.; Poli, S.; Epping-Jordan, M.; Bessis, A.-S.; Ludwig, B.; Mutel, V. mGluR5 negative allosteric modulators overview: a medicinal chemistry approach toward a series of novel therapeutic agents. *Curr. Top. Med. Chem.* **2011**, *11* (6), 680−695.

Biological Assay:

Calcium mobilization assay using HEK 293A cells expressing rat mGluR5

Prophetic assays

Mouse model of anxiolytic behavior: Inhibition of marble burying activity in mice

Pharmacological Data:

	Compound 1	Compound 2	Compound 3	Compound 4
mGluR5 (IC_{50}, nM)	7.8 +/- 1.4	3.4 +/- 0.4	11	36
hPPB (%)	91.4	98.5	96.6	-
Mouse BHB (%)	92.2	98.5	-	-
B/P (Mouse, P.O. @ 10 mg/kg)	5.9	4.7	-	-
%F (rat PK)	30-76	67-75	39	-
%F (Cynomolgus monkey)	42-45	25-45	-	-
Marble buried studies (effective dose after P.O. dosing)	10 mg/kg	30 mg/kg	10 mg/kg	10 mg/kg

Synthesis:

Preparation of 2 compounds

Claims:

Claims 142−176: Synthetic methods

Claims 200−208: Use of compounds for the treatment of a variety of diseases including Alzheimer's disease.

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Notes

The authors declare no competing financial interest.