

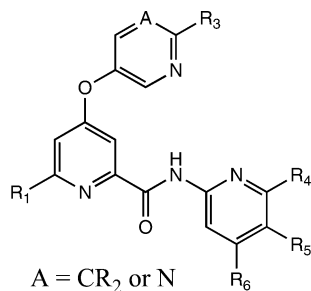
# Negative Allosteric Modulators of Metabotropic Glutamate Receptor Subtype

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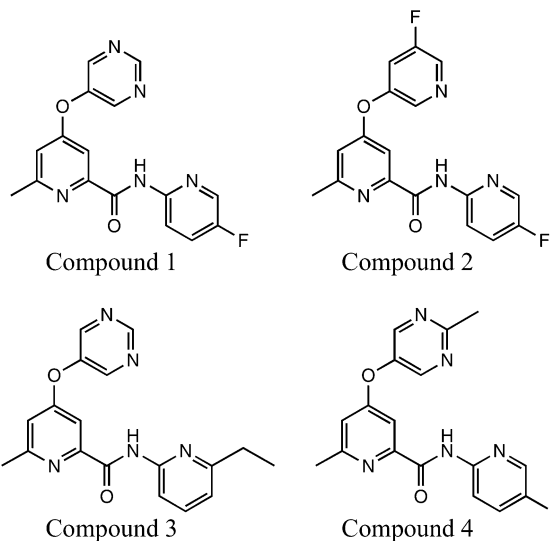
Structure Guided Chemistry, Dart Neuroscience LLC, 7473 Lusk Boulevard, San Diego, California 92121, United States, and Adjunct Associate Professor, Department of Pharmacology and Physiology, Drexel University, College of Medicine, New College Building, 245 North 15th Street, Philadelphia, Pennsylvania 19102, United States

**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:** Neurological 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:



**Received:** April 11, 2013

**Published:** April 19, 2013

## 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 <sub>50</sub> , 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.

## ■ AUTHOR INFORMATION

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## Notes

The authors declare no competing financial interest.