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PATENT HIGHLIGHT

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Allosteric Modulators: An Emerging Concept in Drug Discovery

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

Most current drugs are designed to bind directly to the primary active sites (also known as orthosteric sites) of their biological targets. A drug binds to the active site of a biomolecule such as an enzyme or a receptor causing the inhibition or modification of the function of the biomolecule. Binding of a drug to the active site of an enzyme prevents substrates from binding to this site and thus inhibits the function of this enzyme. Similarly, binding an agonist or antagonist to the orthosteric site of receptors may cause activation or deactivation of receptors' functions. Thus, most drugs are designed to fit into the primary active sites of the biological targets to induce a therapeutic effect. This classical drug design approach is well studied and its effectiveness has been proven judging by the large number of successful drugs on the market. Many drugs possess high affinity and high specificity for the osteosteric binding sites to target a specific disease or disorder with high degrees of specificity. However, adverse side effects may still occur because many enzymes or receptors with related functions may have very similar active sites. Another disadvantage of these drugs may result from being complete inhibitors or activators rather than modulating the functions of the biomolecule.

A new emerging approach to drug design is based on secondary binding site effects. In this approach, small molecule drugs are designed to bind into secondary binding sites on the targeted biomolecules rather than the main orthosteric sites. These secondary sites are named allosteric sites, and the approach is termed allosterism. A successful potential drug (referred to as an allosteric modulator) will be capable of binding to an allosteric site and remotely altering (or modifying) the conformation of the primary orthosteric binding site of the biological target. This conformational modification may affect the binding of the natural ligands to the orthosteric site of the enzyme or receptor protein in one of two ways:

1. The allosteric modification may result in enhancement in the binding affinity of the ligand with the orthosteric site causing boosting of a signal or increased activity. The compounds that show such effects are referred to as positive allosteric modulators (PAMs).
2. The allosteric modulation may result in slowing or inhibition of binding of ligands to the orthosteric binding site causing weakening of a signal or decreased activity. The compounds that cause such an effect are called negative allosteric modulators (NAMs).

It is important to note that many compounds may bind to allosteric sites without affecting the binding properties of the orthosteric sites. Thus, not all allosteric binding sites are suitable targets to cause favorable conformational changes. The design of effective allosteric modulators depends on identifying the allosteric sites and then designing the molecules that can bind to these sites and cause the desired conformational changes in the biomolecule of interest.

While this drug discovery approach is much newer and still emerging, there are already approved allosteric modulator drugs such as Cinacalcet (Amgen) for the treatment of hyperpara thyroidism and Maraviroc (Pfizer) for the treatment of AIDS, and there are many candidates at different stages of development. Proponents of this approach point to many possible potentials and advantages that can be realized by adopting the allosteric modulation to drug design. Some of the potential advantages are as follows:

- Unique allosteric sites can be identified to target disorders narrowly and more specifically by new drugs potentially producing drugs with fewer side effects.
- There are currently many diseases that lack drug therapy because of the difficulty in designing drugs to interact with the orthosteric sites or the lack of specificity; the use of allosteric modulators may provide better alternatives to the discovery of new drugs to treat these disorders.
- Allosteric modulators can provide the option of regulating the drug effects so that it may behave like a dimmer switch rather than acting as an on/off switch by being a complete inhibitor or activator.

The following two patent highlights represent some recent examples of new inventions in the emerging field of allosteric modulation.

General References:

1. Grover, A. K. *Med. Prin. Pract.* **2013**, *22* (5), 418−426.
2. Wenner, M. *Sci. Am.* **2009**, *301* (2), 70−76.
3. *Chem. Eng. News* **2009**, *87* (47), 12−15.

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1. POSITIVE ALLOSTERIC MODULATORS FOR THE TREATMENT OF PARKINSON'S DISEASE AND SCHIZOPHRENIA

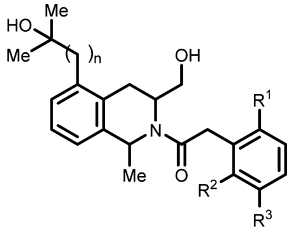
Title:	3,4-Dihydroisoquinolin-2(1*H*)-yl Compounds		
Patent Application Number:	WO 2014/193781 A1	**Publication date:**	4 December 2014
Priority Application:	US 61/828,740	**Priority date:**	30 May 2013
	US 61/905,329		18 November 2013
Inventors:	Beadle, C. D.; Coates, D. A.; Hao, J.; Krushinski, J. H., Jr.; Reinhard, M. R.; Schaus, J. M.; Wolfangel, C. D.		
Assignee Company:	Eli Lilly and Company; Lilly Corporate Center, Indianapolis, Indiana 46285, USA		
Disease Area:	Parkinson's disease and schizophrenia	**Biological Target:**	Dopamine 1 receptor (D1)

Summary: The invention in this patent application relates to 3,4-dihydroisoquinolin-2(1*H*)-yl derivatives represented generally by formula (I), which are positive allosteric modulators (PAMs) of the dopamine 1 receptor (D1) and may be useful for the treatment of Parkinson's disease and schizophrenia.

The current treatment of Parkinson's disease includes direct acting dopamine therapies such as the dopamine precursor levodopa and dopamine agonist pramipexole. These treatments suffer from low safety and limited effectiveness due to high dose associated cognition impairment and seizure risk.

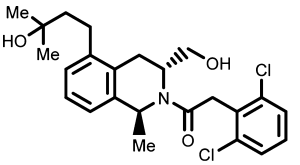
Positive allosteric modulators of the dopamine 1 receptor (D1) such as the compounds described by the inventors may be useful for providing an alternative treatment of conditions in which D1 plays a role such as Parkinson's disease and schizophrenia. These compounds may also relieve the associated symptoms such as mild cognitive impairment and and negative symptoms in schizophrenia. Other potential uses of these compounds may include treating symptoms of Alzheimer's disease such as cognitive impairment and improving motor symptoms in Parkinson's disease as a monotherapy. Additionally, they may also be beneficial in treating depression and attention deficit-hyperactivity disorder (ADHD).

Important Compound Classes:

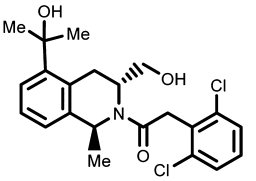


Formula (I)

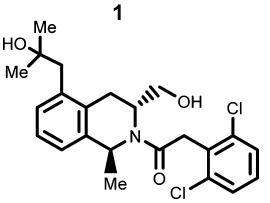
Key Structures: The inventors described the structures and synthesis of 32 compounds as examples of formula (I) including the four examples listed below:



1



3



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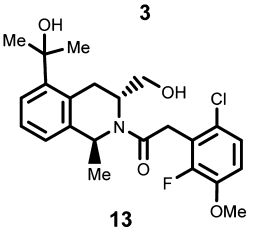

13

Biological Assay:

- Human Dl Receptor Positive Allosteric Modulation Assay
- Generation of Human D1 Receptor Knock-in Mouse
- Basal (Habituated) Locomotor Activity
- Reversal of Resemine-Induced Akinesia

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Biological Data: The results of basal locomotor activity assay were reported for 5 examples at different dosages ranging from 1 mg/kg to 30 mg/kg. Some elected results for examples **1**, **3**, **4**, and **13** (structures above) are listed in the following table:

Basal Locomotor Activity (Total Ambulations for 60 min) (Means, SEM, %SE)				
	Example 1	Example 3	Example 4	Example 13
Vehicle, n = 8 (20% hydroxypropyl betacyclodextrine	Means 542 SEM 111 %SE 30	Means 347 SEM 88 %SE 25	Means 394 SEM 96 %SE 24	Means 305 SEM 61 %SE 20
3 mg/kg; n = 8	Means 1118 * SEM 289 %SE 26	Means 927 * SEM 183 %SE 20	Means 546 SEM 90 %SE 16	Means 745 * SEM 143 %SE 20
30 mg/kg; n = 8	Means 4623 ***@ SEM 486 %SE 11	Means 3825 ***@ SEM 248 %SE 6	Means 6726 ***@ SEM 610 %SE 9	Means 4708 ***@ SEM 369 %SE 8
* p<0.01, *** p<0.0001 compared to vehicle (unpaired t-test) @ p<0.0001 compared to vehicle One-way ANOVA Dunnett's Multiple Comparison Test				

Recent Review Articles:

1. Schmitt, K. C.; Rothman, R. B.; Reith, M. E. A. *J. Pharmacol. Exp. Ther.* **2013**, *346* (1), 2−10.
2. Hoyer, D.; Bartfai, T. *Chem. Biodivers.* **2012**, *9* (11), 2367−87.
3. Schetz, J. A. *Mini-Rev. Med. Chem.* **2005**, *5* (6), 555−561.

2. NEGATIVE ALLOSTERIC MODULATORS FOR THE TREATMENT OF CNS DISORDERS

Title: 6,7-Dihydropyrazolo[l,5-*a*]pyrazin-4(5*H*)-one Compounds and Their Use as Negative Allosteric Modulators of mGluR2 Receptors

Patent Application Number: WO 2014/195311 A1 **Publication date:** 11 December 2014

Priority Application: EP 13170447.0 **Priority date:** 4 June 2013
EP 13173939.3 27 June 2013
EP 14166450.8 29 April 2014

Inventors: Van Gool, M. L. M.; Alonso-De Diego, S.-A.; Cid-Nunez, J. M.; Delgado-Gonzalez, O.; Decorte, A. M. A.; Macdonald, G. J.; Megens, A. A. H. P.; Trabanco-Suarez, A. A.; Garcia-Molina, A.; Andresgil, J. I.

Assignee Company: Janssen Pharmaceutica NV; Tumhoutseweg 30, B-2340 Beerse (BE)

Disease Area: CNS disorders **Biological Target:** The metabotropic glutamate receptor subtype 2 (mGluR2)

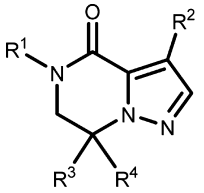
Summary: The invention in this patent application relates to 6,7-dihydropyrazolo[l,5-a]pyrazin-4(5*H*)-one derivatives represented generally by formula (I). These compounds are negative allosteric modulators (NAMs) of the metabotropic glutamate receptor subtype 2 (mGluR2) and may be useful for the prevention or treatment of CNS disorders.

Metabotropic glutamate receptors (mGluRs) are members of group C family of G-protein-coupled receptors (GPCRs). There are eight known subtypes (named mGluR1−8), which are distributed to various brain regions. They are also compiled into three subgroups based on their pharmacological and structural properties: Group-I (mGluR1 and mGluR5), Group-II (mGluR2 and mGluR3), and Group-III (mGluR4, mGluR6, mGluR7, and mGluR8). mGluRs are activated by binding to glutamate; the activated receptors play an important role in the modulation of synaptic transmission and neuronal excitability in the CNS system.

While both orthosteric and allosteric modulators of Group-II receptors (mGluR2 and mGluR3) are potentially useful for the treatment of various neurological disorders, antagonists and negative allosteric modulators in particular promise higher potential for the treatment of mood disorders and cognitive or memory dysfunctions. Studies have determined that inhibition of group-II mGluR receptors using either orthosteric antagonists or negative allosteric modulators enhances glutamatergic signaling. This effect is believed to produce antidepressant-like and procognitive effects. Additionally, studies have shown that treatment of mice with group-II mGluR orthosteric antagonists enhances signaling by growth factors such as brain derived neurotrophic factor (BDNF); these growth factors are critically involved in mediating synaptic plasticity. This effect is probably a contributor to both antidepressant and procognitive properties observed by these antagonists.

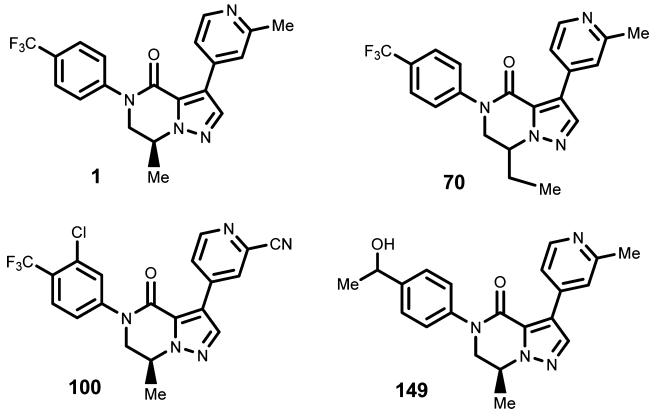
Therefore, inhibition of mGluRs of the group-II receptor family, particularly mGlu2, with negative allosteric modulators such as the compounds described in this patent application can potentially provide effective therapy for neurological disorders, including depression and cognitive or memory dysfunctions.

Important Compound Classes:



Formula (I)

Key Structures: The inventors reported the structures of 267 examples of formula (I) including the following compounds:



Biological Assay: The following assays were reported for testing the compounds of the invention:

- [^{35}S]GTPγS binding assay
- Reversal of the effect of the mGluR2 PAM JNJ-42153605 on scopolamine-induced hyperlocomotion
- V-maze test
- Reserpine interaction test in rats
- Ro-4-1284 interaction test in rats
- Reversal of LY-404039-induced decrease of palpebral opening in apomorphine-challenged rats
- Reversal of mGluR2-agonism in hippocampal brain slices

Biological Data: Some results from the [^{35}S]GTPγS binding assay reported for the representative examples of formula (I) are listed in the following table:

Measurement of mGluR2 negative allosteric modulatory activity using [^{35}S]GTPγS binding assay		
	GTPγS- hmGluR2 anGT pIC_{50}	GTPγS- hmGluR2 anGT E_{max}
Example **1**	8.05	106
Example **70**	7.1	106
Example **100**	8.16	109
Example **149**	<4.3	49

Recent Review Articles:

1. Celanire, S.; Duvey, G.; Poli, S.; Rocher, J.-P. *Annu. Rep. Med. Chem.* **2012**, *47*, 71−88.
2. Rocher, J.-P.; Bonnet, B.; Bolea, C.; Lutjens, R.; Le Poul, E.; Poli, S.; Epping-Jordan, M.; Bessis, A.-S.; Ludwig, B.; Mutel, V. *Curr. Top. Med. Chem.*; **2011**, *11* (6), 680−69.
3. Marino, M. J.; Conn, P. J. *Curr. Opin. Pharmacol.* **2006**, *6* (1), 98−102.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.