

A_{2A} Receptor Antagonists May Potentially Treat Parkinson's Disease

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Title: Heterobicyclo-Substituted-[1,2,4]Triazolo[1,5-c]quinazolin-5-amine Compounds for Treatment of Central Nervous System Disorder

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Disease Area: Central nervous system diseases, in particular Parkinson's disease **Biological Target:** A_{2A}-receptor

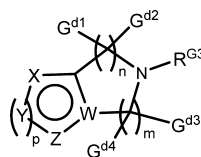
Summary: The invention in this patent application relates to heterobicyclo-substituted [1,2,4]triazolo[1,5-c]quinazolin-5-amine derivatives represented generally by formula (I). These compounds are A_{2A} receptor antagonists and may be useful for the treatment of several central nervous system diseases, including, but not limited to, Parkinson's disease.

Adenosine is an endogenous purine nucleoside that modulates several physiological functions in the cardiovascular system, the central nervous system, the respiratory system, and the kidney. It also acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets. Adenosine activities are mediated by four different membrane specific G-protein-coupled receptors known as A₁, A_{2A}, A_{2B}, and A₃. Researchers have identified several adenosine analogues that act as antagonists of the A₁, A_{2A}, A_{2B}, and A₃ receptors. Selective antagonists of the A_{2A} receptor are of particular pharmacological importance because they possess antidepressant properties and stimulate cognitive functions while displaying reduced level of side effects. Most importantly, A_{2A} receptor antagonists have shown a promise as a treatment for Parkinson's disease.

Parkinson's disease is linked to the progressive degeneration of the nigrostriatal dopaminergic pathway, which causes the loss of fine motor control or motor impairment in patients. Current therapies include replacing dopamine either directly through stimulation of the postsynaptic D₂ receptors or indirectly by inhibiting its metabolism using monoamine oxidase type B (MAO-B) or catechol-O-methyltransferase (COMT). However, the long-term administration of these therapies is often associated with some adverse effects such as motor complications that may become progressively more severe with continued treatment.

Studies have shown that A_{2A} receptors are present in high density in the basal ganglia known to be important in controlling movement. Several highly selective A_{2A} antagonists have been discovered and clinical studies have demonstrated their efficacy in improving motor symptoms associated with neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin. Hence A_{2A} receptor antagonists can potentially offer a useful treatment to alleviate the motor impairment symptoms associated with these diseases. Selective A_{2A} receptor antagonists represent a promising potential for treating or managing the progression of several central nervous system diseases, including, but not limited to, Parkinson's disease. The promise of a new treatment for this disabling disease increases the need for the discovery of novel potent inhibitors of the A_{2A} receptor. The compounds described in this patent application address this need.

Important Compound Classes:



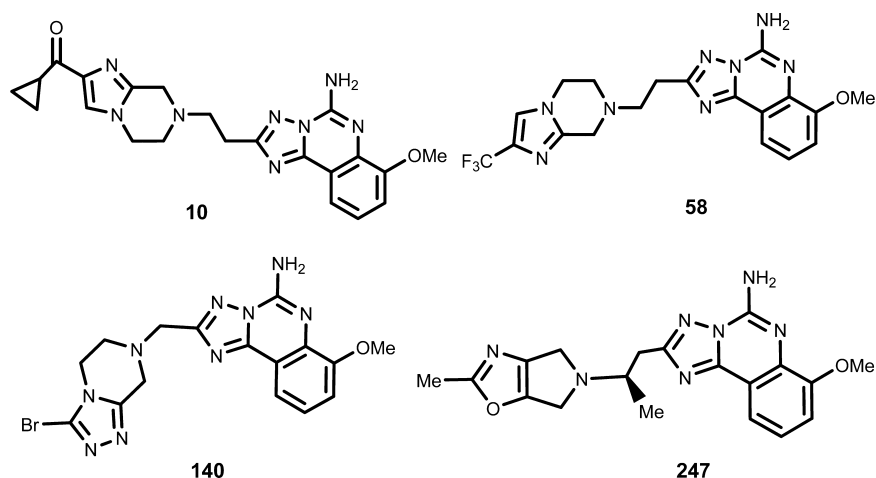
Formula (I)

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Key Structures:

The inventors described the synthesis and structures of 248 examples of formula (I) compounds. The following are representative examples:



Biological Assay:

A_{2A} Activity of Compounds of the Invention

Biological Data:

The inventors reported the EC_{50} data from the A_{2A} activity assay for all 248 examples. The EC_{50} values obtained from the above representative examples are listed in the following table:

A_{2A} Activity of representative examples			
Compound	EC_{50} (nM)	Compound	EC_{50} (nM)
10	1.2	58	0.9
140	103.8	247	0.2

Claims:

Claims 1–12:

Claim 13:

Claim 14:

Claim 15:

Claim 16–17:

Claim 18:

Composition of matter, variations of formula (I)

Composition of matter, 216 specific examples listed by chemical names

Pharmaceutical composition

Use of compounds as medicine

Use of compounds for treatment or prevention of a central nervous system disorder

Use of compounds for treatment or prevention of movement disorder associated with Parkinson's disease

Recent Review Articles:

1. Pinna, A. *CNS Drugs* **2014**, *28* (5), 455–474.
2. Perez-Lloret, S.; Merello, M. *Expert Opin. Pharmacother.* **2014**, *15* (8), 1097–1107.
3. Hickey, P.; Stacy, M. *Curr. Neurol. Neurosci. Rep.* **2012**, *12* (4), 376–385.
4. Armentero, M. T.; Pinna, A.; Ferre, S.; Lanciego, J. L.; Mueller, C. E.; Franco, R. *Pharmacol. Ther.* **2011**, *132* (3), 280–299.

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Notes

The authors declare no competing financial interest.