Chapter

# The Role and Development of the Antagonist of Adenosine $A_{2A}$ in Parkinson's Disease

*Widya Dwi Aryati, Nabilah Nurtika Salamah, Rezi Riadhi Syahdi and Arry Yanuar*

## Abstract

Adenosine is a neuromodulator that regulates the body's response to dopamine and another neurotransmitter in the brain that is responsible for motoric, emotion, learning, and memory function. Adenosine is a G-protein-coupled receptor and has four subtypes, which are $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$. Adenosine $A_{2A}$ is located in the striatum of the brain. Antagonist interferes with GABA releasing, modulates acetylcholine and releases dopamine, and also facilitates dopamine receptor's signaling. Therefore, it can reduce motoric symptoms in Parkinson's disease. Adenosine $A_{2A}$ antagonist is also believed to have neuroprotective effects. Several compounds have been reported and have undergone clinical test as selective adenosine $A_{2A}$ antagonists, including istradefylline, preladenant, tozadenant, vipadenant, ST-1535, and SYN-115. Nonselective adenosine $A_{2A}$ antagonists from natural compounds are caffeine and theophylline.

**Keywords:** adenosine $A_{2A}$, selective adenosine $A_{2A}$ antagonists, Parkinson's disease, neuroprotective, natural compounds

## 1. Introduction

Adenosine is a neuromodulator that coordinates responses to dopamine and other neurotransmitters in areas of the brain responsible for motor function, mood, learning, and memory [1]. Adenosine consists of four receptor subtypes: $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$ belonging to the superfamily of G-protein-coupled receptor. Adenosine $A_1$ and $A_3$ receptors are coupled to inhibitory G proteins, while $A_{2A}$ and $A_{2B}$ receptors are coupled to stimulatory G proteins [2].

Adenosine $A_1$ receptor can be found in adipose tissue, heart muscle, and inflammatory cells. The receptor mostly expressed by the central nervous system such as neocortex, cerebellum, hippocampus, and dorsal horn of the spinal cord [3]. The pre- and postsynaptic nerve terminals, mast cells, airway smooth muscle, and circulating leukocytes are the places where adenosine $A_2$ receptor can be found. As the more widely dispersed receptor, adenosine $A_2$ is divided into two receptors on the basis of high- and low-affinity for adenosine, $A_{2A}$ and $A_{2B}$ [4]. Striatal neurons are where the adenosine $A_{2A}$ are highly enriched; however its lower levels can also be found in glial cells and neurons outside the striatum [5]. The adenosine $A_{2B}$ receptors are highly expressed in the gastrointestinal tract, bladder, lung, and on mast

cells. The most widely dispersed receptor is the $A_3$ receptor which can be found in the kidney, testis, lung, mast cells, eosinophils, neutrophils, heart, and the brain cortex [4].

Adenosine $A_{2A}$ receptors are found to be concentrates in GABAergic medium-sized spiny neurons in the dopamine-rich regions of the brain. The protein translated in the adenosine $A_{2A}$ is carried by many other tissues such as blood vessels, endothelial, lymphoid cells, smooth muscle cells, and several neurons in sympathetic and parasympathetic systems [6]. Therefore, the dispersion of adenosine $A_{2A}$ is not limited to the medium spiny neurons in the basal ganglia. It stimulates the modulation of cAMP production and increases the level of adenylyl cyclase. This receptor is essential in giving the medium of vasodilation of coronary arteries which then supports the combination of new blood vessels and giving protection for tissues from indirect inflammatory damage [7]. The role of the $A_{2A}$ in the brain includes influencing the activity within the indirect pathway of the basal ganglia. The $A_{2A}$ has complicated actions because it colocalizes and is physically combined with other unrelated G-protein-coupled receptors. Therefore, it can form heterodimers such as dopamine $D_2/A_{2A}$, and $D_3/A_{2A}$, cannabinoid $CB_1/A_{2A}$, and glutamate $mGluR5/A_{2A}$, as well as $CB_1/A_{2A}/D_2$ heterotrimers [7].

The pathways which give signals used by the $A_{2A}$ receptor depend on the location of the cell and tissue, the specific G protein which couples it, and the signaling in the cell. The brain also carries the $A_{2A}$ receptor in which it plays an important role in regulating the glutamate and releasing the dopamine [8]. In the striatopallidal neurons, dopamine $D_2$ receptors are colocalized with adenosine $A_{2A}$ receptors. Adenosine $A_{2A}$ receptor activity that mediates stimulation and $D_2$ receptors that mediate inhibition in the striatopallidal pathway are balanced [9]. The adenosine $A_{2A}$

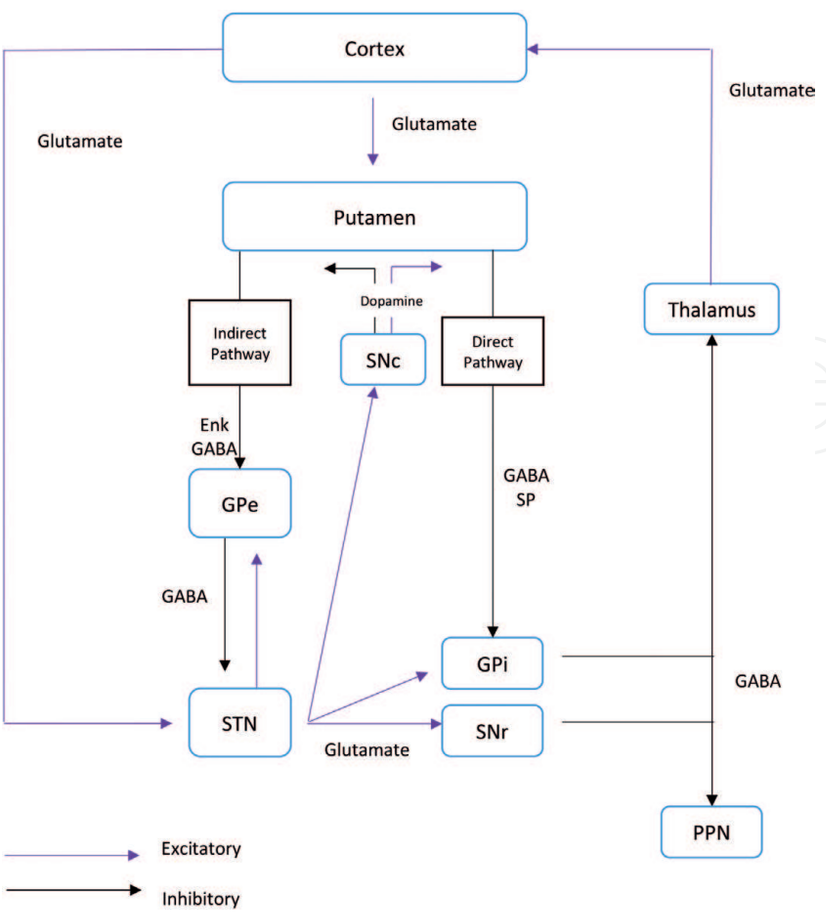


**Figure 1.**
*Basal ganglia circuitry in normal conditions.*

likely affects motor activity by acting at different levels of the basal ganglia network. The basal ganglia comprise the striatum (putamen), the globus pallidus externa (GPe), the globus pallidus interna (GPi), substantia nigra pars compacta (SNc), substantia nigra reticulata (SNr), and the subthalamic nucleus (STN). The striatum is represented by medium-sized spiny projection neurons (MSNs), accounting for almost 95% of striatal neurons and using γ-aminobutyric acid (GABA) as neurotransmitter. The GABAergic spiny neurons give rise to the two main striatal efferent circuits: the striatonigral and the striatopallidal pathway. The neurons of the striatonigral (direct) pathway contain the neuropeptide substance P and dynorphin and mainly express $D_1$ receptors; this pathway directly projects from the striatum to the GPi/SNr. The neurons of the striatopallidal (indirect) pathway containing the neuropeptide, enkephalin (ENK), predominantly express $D_2$ receptors; this circuit connects the striatum with the GPi/SNr via synaptic connections in the GPe and STN in **Figure 1**. Dopamine modulates motor coordination and fine movements by facilitating the action of the direct pathway on stimulatory $D_1$ receptors and by inhibiting indirect pathway function acting on inhibitory $D_2$ receptors [10].

The adenosine $A_{2A}$ receptor has agonists and antagonists of which the roles are potentiating and inhibiting, respectively. The $D_2$ receptor agonist has effects on motor activity, the releasing of neurotransmitter, and the expression of striatal of c-Fos, a factor of transcription which is used as neuronal activity's indirect marker [11]. The adenosine $A_{2A}$ receptor has a key role in regulating the striatal dopaminergic neurotransmission which produces substances that are valuable to treat neurological disorders that are relevant with dopaminergic dysfunction.

The topology of G-protein-coupled receptor is displayed in the structure of the adenosine $A_{2A}$ receptor. These receptors have a central core which consists of seven

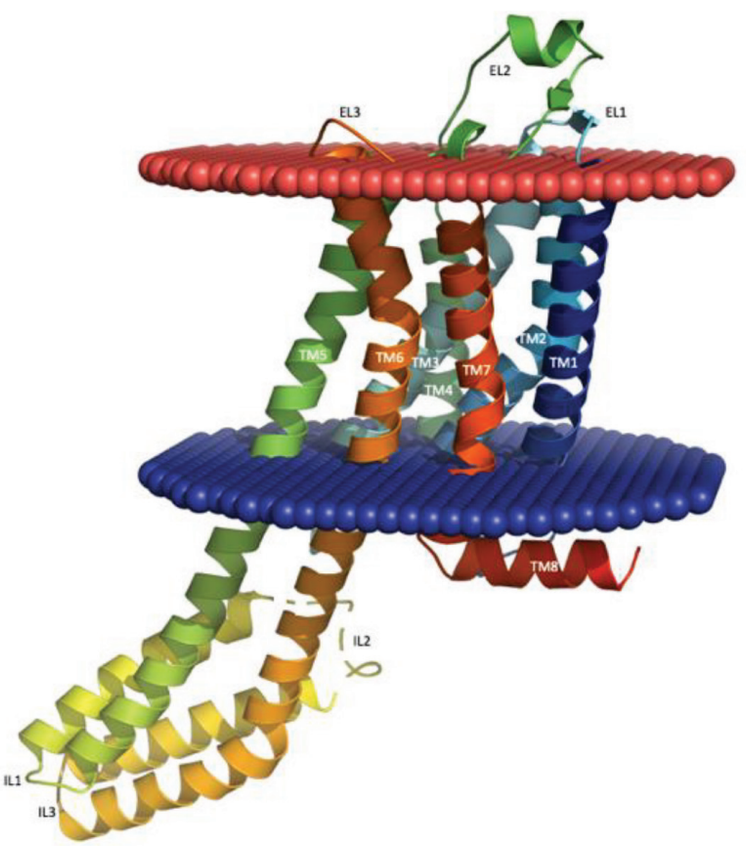


**Figure 2.**
*Crystal structure of the adenosine $A_{2A}$ receptor (4EIY) shown in the membrane structure. The extracellular and intracellular parts of the membrane are shown in red and blue beads, respectively. The disorder residues of intracellular loop (IL2) are modeled in dashed line.*

transmembrane helices (7TM). Each of the TM is mainly α-helical and consists of 20–27 amino acids. Three intracellular (IL1, IL2, and IL3) and three extracellular (EL1, EL2, and EL3) loops connect each of the TM domain. A short helix TM8 runs parallel to the cytoplasmic surface of the membrane. The adenosine $A_{2A}$ receptor has differences in length and N-terminal extracellular domain function, their domain of C-terminal intracellular, and their loops of intracellular/extracellular. These differences are shown in **Figure 2**.

## 2. The role of adenosine $A_{2A}$ in Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disorder in the brain, marked by motoric symptoms [12]. The motoric symptoms in PD are resting tremor, rigidity, bradykinesia, and postural disorder. Besides motoric symptoms, PD also has non-motoric symptoms such as depression, hallucination, sleeping disorder, and decreasing cognitive and sensory functions. The main pathological characteristic of PD is the loss of dopaminergic neurons in *substantia nigra pars compacta*, a region in the brain that controls all the body movement and forms the dopamine. The development of PD also includes the formation of Lewy body, a deposit of cytoplasmic, eosinophilic neuronal inclusions, composed of the presynaptic protein α-synuclein [13, 14].

The current therapy of PD is targeted at dopamine replacement, thereby decreasing the motor symptoms. It includes precursor of dopamine (levodopa), dopamine agonists [15, 16] monoamine oxidase type B (MAO-B) inhibitors [17], and catechol-O-methyltransferase (COMT) inhibitors [17, 18]. These agents produce undesirable side effects such as on-off effects, hallucinations, and dyskinesia. These effects get more severe as the treatment continued. The efficacy of these agents is also decreasing as the disease progressed [19].

Because of the undesirable side effects of dopamine replacement therapy, the non-dopaminergic therapy is continuously being explored. One of the approaches is selective adenosine $A_{2A}$ antagonist [20, 21]. Adenosine $A_{2A}$ receptors are found mainly in the striatum of rat [22, 23], which has similar distribution with the human brain [24, 25]. In the striatum, adenosine $A_{2A}$ receptors are colocalized with dopamine $D_2$ receptors. These two receptors have opposite effect on motoric function [26]. The activation of adenosine $A_{2A}$ receptors will inhibit the signaling of dopamine $D_2$ receptors, and conversely, the inhibition of signaling of adenosine $A_{2A}$ receptors will increase the activation of dopamine $D_2$ receptors, therefore facilitating dopamine $D_2$-mediated responses [11]. The inhibition of adenosine $A_{2A}$ receptors showed motoric improvement in animal models of PD [27–30]. This also has desirable effect on long-term levodopa treatment such as decreasing the dyskinesia and increasing the therapeutic effect on levodopa [31, 32].

## 3. Adenosine $A_{2A}$ receptor antagonist as a neuroprotective

For years, adenosine-dopamine interactions have been investigated in order to observe their relevance for treatment of central nervous system (CNS) disorders [33]. It is assumed that adenosine $A_1$ receptors ($A_1$Rs) play an important role in neuroprotection as their activation at the onset of neuronal injury has shown to reduce brain damage in adult animal model. Vice versa, their blockade aggravates the damage. In other hand, adenosine $A_2$ receptors ($A_{2A}$Rs) are shown to be upregulated in harmful brain conditions, and their blockade shows brain neuroprotection in studied animals [34]. The blockade of $A_{2A}$Rs alleviates the long-term

burden of brain disorders in different neurodegenerative conditions, namely, ischemia, epilepsy, and Parkinson's and Alzheimer's disease, through its control on neuronal cell death [35].

$A_{2A}$Rs have been shown to be viable in serving as alternative non-dopaminergic strategy of Parkinson's disease treatment because of their limited distribution in the striatum and the intense interaction between adenosine and dopamine receptors in the brain. $A_{2A}$Rs antagonists were shown to improve motor function in different animal models (primates and rodents), alone or co-administered with dopaminomimetic drugs, levodopa, or dopamine agonists [35]. Based on rigorous preclinical animal studies, istradefylline (KW6002) has shown its promising ability to increase motor activity in PD of the advanced stage in clinical phase IIB trial [36]. It became the first therapeutic agent developed to target $A_{2A}$Rs, and other similar compounds will be available in near future [37].

The recent meta-analysis (n = 6) suggested that 20 mg of istradefylline improves unified Parkinson's disease ranking scale (UPDRS) III. Meanwhile at 40 mg per day, istradefylline could alleviate off time and motor symptoms derived from Parkinson's disease [38]. Phase 3 study (613 randomized patients), done by Isaacson et al. concluded that greater reduction from baseline in total hours off time/day were shown at all-time points for istradefylline 20 and 40 mg/day, compared to placebo. However, future development is needed as the study has not yet reached statistical significance [39].

In the case of Parkinson's disease, microglia has been suggested to be the most likely cell type to be targeted by $A_{2A}$Rs antagonists [40]. In vitro and in vivo studies showed that local neuroinflammation make glial cells (especially microglial cells) particularly sensitive to $A_{2A}$R modulation [41]. Previous research done by Gao and Phillis is the first study to demonstrate nonselective $A_{2A}$R antagonist action in reducing cerebral ischemic injury in the gerbil, following global forebrain ischemia [42]. After that, many studies have reported the neuroprotective of $A_{2A}$R antagonists in different models of ischemia [43].

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that is indicated by the progressive loss of memory and other cognitive functions, leading to dementia [44, 45]. Adenosine can control and integrate cognition and memory [46]. Both $A_1$Rs and $A_{2A}$Rs, mainly located in synapses, control the release of neurotransmitters which are involved in memory or other cognitive processes [34, 47]. Methylxanthine was discovered to act as nonselective adenosine receptors antagonist. Caffeine, the most famous methylxanthine found in common beverages, is the most widely consumed psychoactive drug. Maia and de Mendonca presented the first epidemiological data showing that the incidence of AD is inversely proportioned with coffee consumption [48]. Several other studies also show this inverse relationship [49–51]. Animal models also shown that caffeine intake may be beneficial for AD. In a study, a 6-month period of 0.3 g/L caffeine intake alleviated the cognitive deficits found in AD transgenic mice (APPsw). Furthermore, these mice culture neurons showed the reduced production of $A\beta_{1–40}$ and $A\beta_{1–42}$ peptides [52]. $A_{2A}$Rs antagonists and/or caffeine prophylactic and long-term neuroprotective process are suggested to be based on inhibition of reactive oxygen species activity, tau pathology, and Aβ production by neuronal cells [53].

$A_{2A}$Rs antagonist may also serve as antidepressants, as observed in animal model of antidepressants screening test done by El-Yacoubi et al. [54, 55]. In both tests, $A_{2A}$Rs antagonists prolong escape-directed behavior. Additionally, potential role as antidepressants was also observed in attenuated behavioral despairs displayed in both tests [55]. The relation between adenosine and depression in preclinical models was obtained from the genetic manipulation model of $A_{2A}$R. Genetic depletion of $A_{2A}$Rs resulted in antidepressant-like phenotype in animal models [55]. The

$A_{2A}$Rs blockade also relieves stress-induced early hippocampal modifications [56]. However, the effect of adenosine neuromodulation system in depression is complex, as it has the ability to modulate several other neurotransmission systems [35].

As addressed in previous paragraphs, $A_{2A}$R emerges as potential target candidate in various disorders. This is majorly caused by its unique interaction with D2 receptors, a major psychoactive drug target. Important roles of $A_{2A}$R were also observed in its robust neuroprotective activity, in which it mainly acts in the normalization of glutaminergic synapses, the control of mitochondria-induced apoptosis, and the control of neuroinflammation [35].

## 4. Current sources of the adenosine $A_{2A}$ antagonist

The treatment of PD currently focuses on symptom management with dopaminergic therapy, such as dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) (in combination with peripheral decarboxylase inhibitors) and dopamine agonists [57]. Although L-DOPA is beneficial in patients with PD, with time, the span of the effect is shortened), the response becomes less probable, and involuntary muscle movements or, in a severe situation, dystonia can emerge [57]. These problems highlight the urgent medical need for an alternative mode of therapeutic intervention that can relieve the symptoms of the disorder while also allowing a decrease in the occurrence of side effects.

Among the non-dopaminergic therapies investigated for the treatment of PD, the adenosine $A_{2A}$ receptor antagonists show very convincingly for two main reasons: their selective and restricted localization in the basal ganglia circuitry and their interaction with dopaminergic receptors. In another word, inhibition of the interaction of adenosine with the $A_{2A}$ receptor may provide a potential treatment for PD.

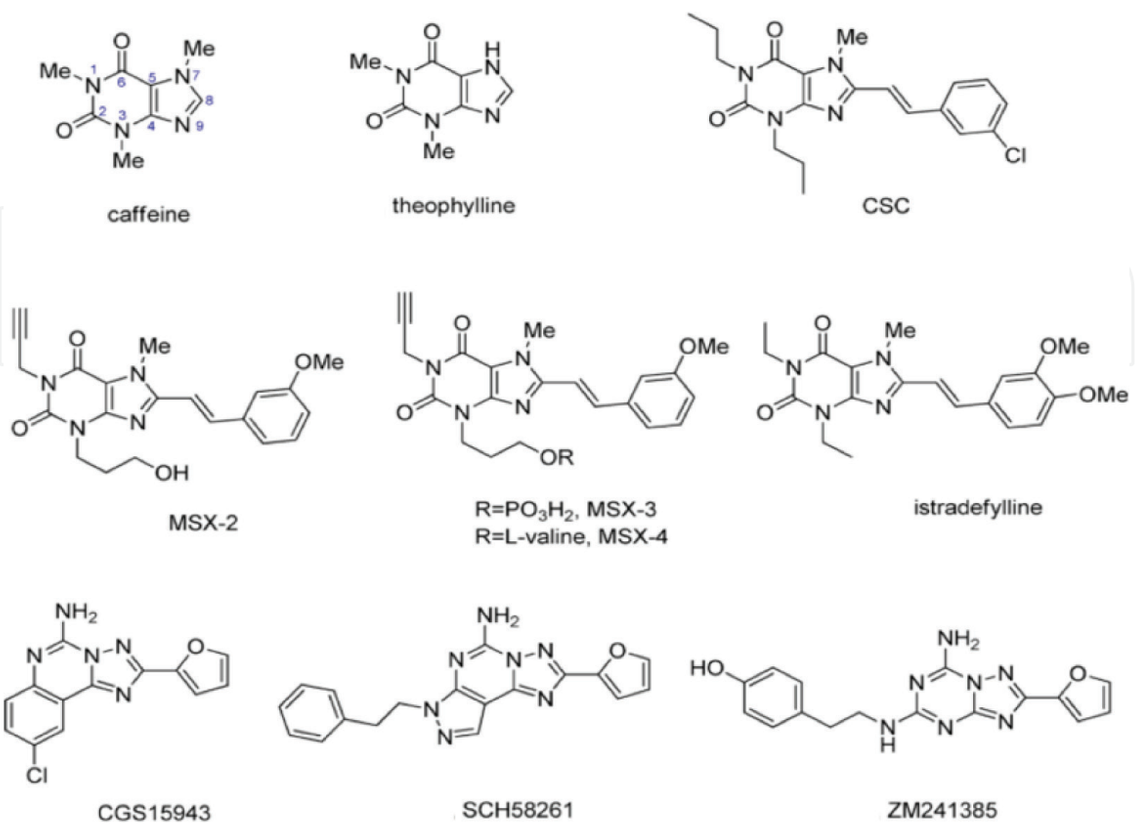


**Figure 3.**
*Adenosine $A_{2A}$ inhibitors.*

Many highly selective $A_{2A}$ antagonists, both xanthine and non-xanthine derivatives, have been created, and some of them are being investigated as treatment for subjects with PD in various stage of clinical trials (**Figure 3**) [7, 19, 58–61]. Caffeine as a xanthine derivate is developed as a lead compound for the design of antagonist of adenosine $A_{2A}$ receptor [62]. Experimental model using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism is known to be an evidence that caffeine have a protective effect in Parkinson's disease [36, 63]. Some $A_{2A}$ antagonists have progressed to clinical trials by various pharmaceutical companies including istradefylline [59], PBS-509, ST1535 and its metabolite ST4206, tozadenant, V81444, preladenant, and vipadenant [64]. Several studies of novel series of 2-aminoimidazo[4,5-b]pyridine-derivatives [65], arylindenopyrimidine [66], and bicyclic aminoquinazoline derivatives [67] as adenosine $A_{2A}$ antagonists are reported.

Various computational methods were used to study neuroprotective effect from adenosine $A_{2A}$ antagonists such as pharmacophore model [68], QSAR, molecular docking [69–71], and molecular dynamics [72, 73]. Orally bioavailable adenosine $A_{2A}$ receptor antagonists have been studied for its QSAR and pharmacokinetics properties [74].

The study of structure-kinetics relationship (SKR) is done as a complement to a SAR analysis at the adenosine $A_{2A}$ receptor. The series of 24 triazolotriazine derivatives showing a similar binding kinetics to the putative antagonist ZM241385 (4-(2-((7-amino-2-(furan-2-yl)-[1,2,4]triazolo[1,5-a][1,3,5]triazin-5-yl)amino) ethyl)phenol) revealed minor affinity changes, although they varied substantially in their dissociation rates from the receptor [75].

## 5. Future direction of drug discovery of Parkinson's disease

Various studies have been conducted in the discovery of Parkinson's drugs against the target $A_{2A}$ receptors. The discovery of drugs assisted by computers has accelerated in obtaining lead compounds. Apparently, this method takes a lot of consideration before entering the preclinical and clinical phases. It is because this computational method is more able to describe the answer in preparing the next design. This method can also make various predictions of activities that are difficult to do in the absence of chemical compounds before they are synthesized. In silico prediction of various pharmacokinetic parameters and toxicity can also be done faster. All of these things can provide a better picture of getting a cure for Parkinson's disease.

## 6. Conclusions

$A_{2A}$ receptors emerge as potential target candidate in various disorders, caused by its unique interaction with D2 receptors, a major psychoactive drug target. Various studies have been conducted in the discovery of Parkinson's drugs against the target $A_{2A}$ receptors. In silico study brings a new approach of study with $A_{2A}$ receptors.

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## Conflict of interest

The authors declare that they have no conflict of interest or involvement with any organization of affiliation.



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