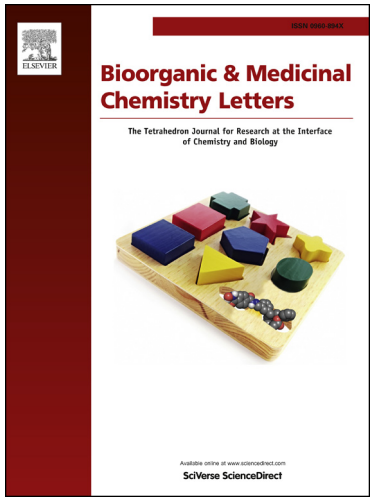


# Discovery of Aminoquinazoline Derivatives as Human $A_{2A}$ Adenosine Receptor Antagonists

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## Graphical Abstract

**Discovery of Aminoquinazoline Series as Human $A_{2A}$ Adenosine Receptor Antagonists**

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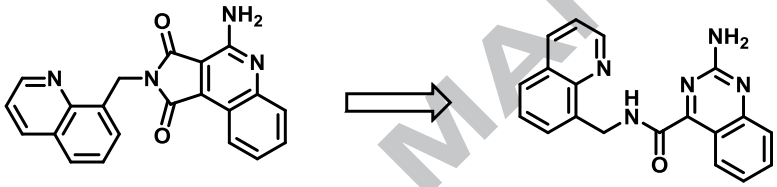


**1**
hA2A Ki = 0.6 nM
hA1 Ki = 1139 nM
Sol<1uM (PH 7)
rat catalepsy = 0% at 30 mg/kg

**4**
hA2A Ki = 1.1 nM
hA1 Ki = 90 nM
Sol 124 uM (PH 7)
rat catalepsy = -61% at 30 mg/kg

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# Discovery of Aminoquinazoline Derivatives as Human $A_{2A}$ Adenosine Receptor Antagonists

Gang Zhou,*[a] Amjad Ali,[a] Robert Aslanian,[b] Gioconda Gallo,[a] Timothy Henderson,[a] Tanweer Khan,[b] Rongze Kuang,[a] Guoqing Li,[b] Yeon-hee Lim,[a] Michael Lo,[a] Biju Purakkattle,[b] Manuel De Ruiz,[c] Andrew Stamford,[a] Pauline Ting,[a] Heping Wu,[a] Hongwu Wang,[b] Dong Xiao,[b] Tao Yu,[a] Yonglian Zhang[a]

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ABSTRACT

Novel bicyclic adenosine $A_{2A}$ antagonists with an aminoquinazoline moiety were designed and synthesized. The optimization of the initial lead compound based on *in vitro* and *in vivo* activity has led to the discovery of a potent and selective class of adenosine $A_{2A}$ antagonists. The structure-activity relationships of this novel series of bicyclic aminoquinazoline derivatives as adenosine $A_{2A}$ antagonists are described in detail.



Parkinson's disease (PD) is the most common movement disorder and is characterized by motor abnormalities such as bradykinesia, tremor, muscle rigidity, and postural instability.[1] Non-motor symptoms such as cognitive impairment and depression also occur in later stages of the disease. At the neurochemical level, PD is caused by progressive degeneration of dopamine (DA) neurons in key motor pathways such as the nigrostriatal pathway.[2] The standard of care is to increase dopaminergic transmission through the enhancement of DA release with the DA precursor L-Dopa or direct activation of DA $D_2/D_3$ receptors.[3] These agents are relatively effective, but are often accompanied by serious side effects, including dyskinesia, sedation and compulsive behavior. Moreover, the efficacy of current medications progressively decreases after chronic use.[4]

In recent years, adenosine $A_{2A}$ receptor have emerged as an alternative target for potential treatment of PD.[5] $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$ receptors belong to the family of G-protein-coupled receptors (GPCRs). Subtype $A_{2A}$ receptor which is coupled to stimulation of adenylyl cyclase activity and enhancement of the levels of cAMP, is a high-affinity receptor found in large amounts in the brain striatum.[6] Preclinical and clinical data strongly support the use of adenosine $A_{2A}$ receptor antagonists as a novel treatment of the motor complications of PD, both as monotherapy and as adjunctive therapy in combination with existing dopaminergic agents.[7] Clinical and preclinical evidence also suggests that adenosine $A_{2A}$ receptor antagonists are unlikely to be associated with many of the side effects associated with current therapies.[8] Currently, there are no drugs that treat the non-motor symptoms or block the progression of PD. There is evidence that $A_{2A}$ antagonists could address these unmet needs since they have pro-cognitive, anti-depressant and neuroprotective properties in animal models.[9] Collectively, these data indicate that a safe and well-tolerated $A_{2A}$ receptor antagonist will be a significant improvement over the current standard of PD care.

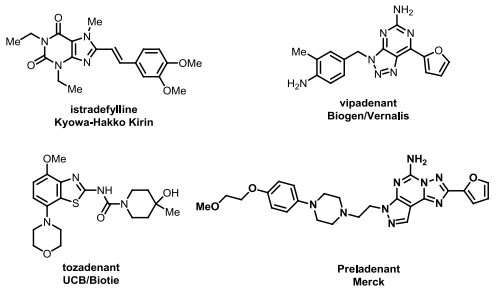



**Figure 1.** Selected examples of $A_{2A}$ receptor antagonists .

$A_{2A}$ antagonists have demonstrated efficacy in rodent and primate models of PD, with significant improvement in the side-effect profile related to both motor (e.g., dyskinesia) and non-motor (e.g., hallucinations) disturbances. A number of drug candidates from companies including Kyowa-Hakko, Merck (Schering-Plough) and Biogen have been advanced into clinical trials for treatment of PD; several representative examples are

showed in Figure 1.[10] The discovery of selective $A_{2A}$ receptor antagonists has also been disclosed in numerous reviews and publications.[11]

In our efforts to identify novel $A_{2A}$ receptor antagonists, a screening campaign of our in house collection led to several hit series. Among these hits was a series tricyclic leads exemplified by compounds **1** and **2** (Figure 2). Compound **1** was the most potent among its analogues, binding to the human $A_{2A}$ receptor with a Ki value of 0.6 nM with good selectivity over the human $A_1$ receptor.[12] Unfortunately, this series of compounds was inactive in an in vivo rat catalepsy assay due to poor oral pharmacokinetic (PK) properties.[12] Also, poor solubility of compounds in this series such as **1** and **2** made it difficult to further characterize these compounds. Consequently, a hit-to-lead optimization effort was undertaken with the aim of identifying a suitable replacement for the rigid tricyclic scaffold to improve water solubility, physicochemical properties and in vivo activity.

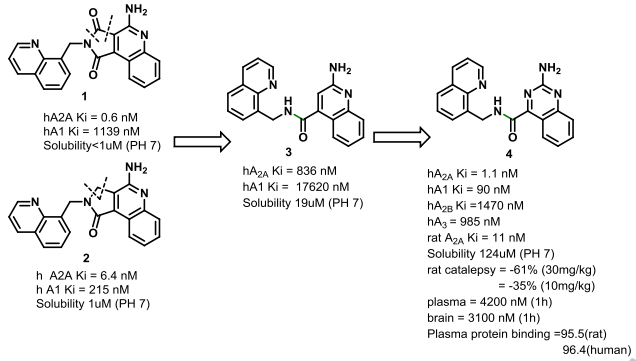
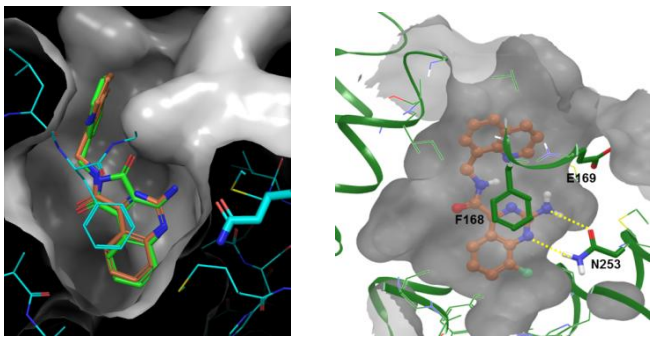



**Figure 2.** Lead structure design based on screening hits **1** and **2**

Through a strategy of fragmentation of the phthalimide and pyrrolidinone rings in structures **1** and **2**, aminoquinoline compound **3** was initially proposed to probe the effects of structure simplification. This modification significantly attenuated $hA_{2A}$ receptor affinity and selectivity versus the $hA_1$ receptor, although solubility was slightly increased. We believe the amide side chain in **3** might be positioned at wrong side for $A_{2A}$ binding. In theory, incorporation of nitrogen into the quinoline ring would restore the desired conformation of amide side chain. As a result, it led to the identification of the aminoquinazoline lead compound **4** which had good human and rat $A_{2A}$ potency and moderate to good $hA_1$, $hA_{2B}$, $hA_3$ selectivity. Water solubility and pharmacokinetic properties were dramatically improved with compound **4** (rat AUC = 1.6 uM.h @10 mg/kg, $T_{1/2}$ = 0.5h, permeability = 40 x $10^{-6}$ cm/s, $Cl_{rat/hu}$ = 12.8 / 34.8 µl /min/Mcells, non PGP substrate). Compound **4** also demonstrated a clean ancillary profile except for time-dependent inhibition (TDI) of 3A4 (3 fold at 30uM). Most importantly, good *in vivo* anti-cataleptic efficacy was observed after an oral dose of **4** in the haloperidol-induced catalepsy assay (−61% at 30 mg/kg @1h). [13]

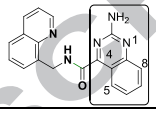


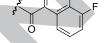
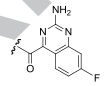
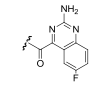
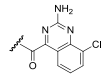
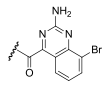
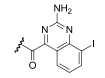
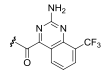
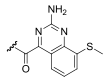
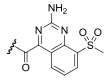
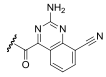
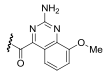
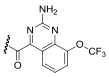
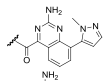
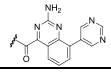

a b

**Figure 3.** (a) Pharmacophore model of lead compound **1**(green) and **4**(brown)**.** (b) Homology model of pharmacophore-based binding of **4** and $A_{2A}$ receptor.

Pharmacophore modeling with this new lead was conducted using conformational analysis and docking (Figure 3a).[14] This shows aminoquinazoline **4** has good alignment with tricyclic lead **1** in terms of hydrogen bond donor and acceptor features**.** Key elements of the plausible pharmacophore-based binding area are illustrated in a homology model (figure 3b); two key hydrogen bonds were proposed between aminoquinazoline **4** and Asn253 to form a hinge binding interaction. An intramolecular hydrogen bond between the amide NH and the quinazoline nitrogen locks the trans amide conformation. Further stabilization can be rationalized from aromatic π-π stacking of the bicyclic quinazoline core with Phe168 as well as possible cation-π interaction between partial positive charged N3 of aminoquinazoline with Phe186.

**Table 1.** Optimization of the Substitution on Aminoquinazoline **4**[a]



| Cpd # | R | Human $A_{2A}$ $K_i$ (nM) | human $A_1$ Ki (nM) | rat $A_{2A}$ $K_i$ (nM) | Rat catalapsy 1 h AUC (10mg/kg) |
|---|---|---|---|---|---|
| **5** |  | 0.5 | 12 | 1.3 | -74% (10 mg/kg) 2.4uM.h |
| **6** |  | 0.3 | 31 | 4.8 | -39% (10 mg/kg) 2.3uM.h |
| **7** |  | 4.4 | 346 | 8.7 | -55% (10 mg/kg) 0.8uM.h |
| **8** |  | 3.0 | 213 | 2.9 | -35% (30 mg/kg) NT |
| **9** |  | 0.7 | 10 | NT | NT |
| **10** |  | 3.1 | 33 | NT | -23% (10 mg/kg) 1.3 uM.h |
| **11** |  | 2.3 | 1299 | 57 | 0% (30 mg/kg) NT |
| **12** |  | 7.7 | 132 | 12 | 0% (30 mg/kg) 8.9uM.h |
| **13** |  | 86 | 4743 | 302 | NT |
| **14** |  | 24 | 337 | NT | NT |
| **15** |  | 0.2 | 6 | 0.6 | -31% (30 mg/kg) 0.8uM.h |
| **16** |  | 0.2 | 20 | 2.9 | 0% (30 mg/kg) NT |
| **17** |  | 1035 | 6037 | NT | NT |
| **18** |  | 160 | 6300 | NT | NT |

| | | | | | |
|---|---|---|---|---|---|
| **19** |  | 6.6 | 50 | NT | NT |
| **20** |  | 3.6 | 40 | NT | NT |

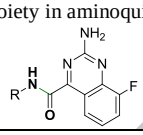
[a] Assay values are the average of at least two independent determinations.

SAR was focused on improving *in vitro* $hA_{2A}$ activity, *in vivo* potency andPK properties. Initial investigations were carried out by introducing substituents on the bicyclic quinazoline ring of **4**. Representative examples **(5-20)** for substitution on the bicyclic core (boxed) are summarized in Table 1. First, fluoro-substitutions at 6-, 7-, and 8- positions of quinazoline ring showed similar $A_{2A}$ binding affinity and $A_1$ selectivity (**5-7**). Compound **5** demonstrated good anti-cataleptic activity at the dose of 10 mg/kg (-74% @1h) and 10 fold lower dose (-30% @1h), as well as no CYP TDI effect.

Since 8-fluoro substituted aminoquinazoline **5** had an improved profile, we investigated other substituents in place of fluorine at the 8-position (**8-18**). The majority of these didn't show any advantage in terms of A2A affinity and selectivity except analog **11**, which was inactive in the rat catalepsy assay at an oral dose of 30 mg/kg. Heteroaryl substituted analogs **17–18** had greatly decreased $A_{2A}$ affinity. Disubstituted compounds **19-20** didn't produce any further improvement over monosubstituted analogs.

We also discovered that alkylation of the amide NH or the aminoquinazoline $NH_2$ led to a complete loss of affinity at $hA_{2A}$ receptors (data not shown). Because the amide NH appeared to be important to $hA_{2A}$ affinity our explorations were mainly focused on optimization of the amide N-substituent to improve potency and selectivity (Table 2).

**Table 2.** SAR on the amide moiety in aminoquinazoline series[a]

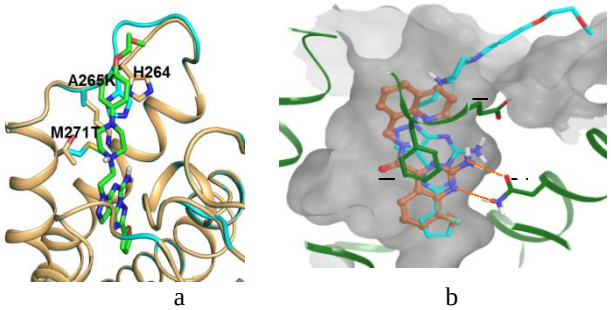


| # | R | $hA_{2A}$ $K_i$ (nM) | $hA_1$ Ki (nM) | # | R | $hA_{2A}$ $K_i$ (nM) | $hA_1$ Ki (nM) |
|---|---|---|---|---|---|---|---|
| **21** |  | 5.4 | 83 | **22** |  | 45.0 | 170 |
| **23** |  | 8.4 | 112 | **24** |  | 13.6 | 116 |
| **25** |  | 14 | 600 | **26** |  | 160 | 559 |
| **27** |  | 6.7 | 57 | **28** |  | 126 | 524 |
| **29** |  | 10.1 | 90 | **30** |  | 7.6 | 213 |
| **31** |  | 20 | 103 | **32** |  | 21.5 | 135 |
| **33** |  | 25 | 281 | **34** |  | 3.1 | 24 |
| **35** |  | 8.2 | 54 | **36** |  | 1.8 | 5.4 |
| **37** |  | 927 | 10000 | **38** |  | 26.7 | 78 |
| **39** |  | 6.7 | 84 | **40** |  | 15.0 | 78 |

[a] Assay values are the average of at least two independent determinations.

Results in Table 2 show that compounds with monocyclic substituents (**21-26**) led to a substantial loss in $hA_{2A}$ receptor affinity compared to the quinoline **5**. Introduction of alkyl group at the benzylic position showed differentiation towards $A_{2A}$ receptor binding as depicted by compounds **27** and **28.** Replacement of the quinoline ring with naphthalene **29**, tetrahydroquinoline **30**, dihydrobenzodioxane **31**, or benzomorpholine **32** resulted in reduced *in vitro* affinity. The quinoline ring was also substituted by 5, 6-fused bicyclic rings (**33-36**), in which certain ring replacements were tolerated with a slight loss of $hA_{2A}$ receptor affinity and a drop in selectivity versus the $hA_1$ receptor as shown by benzoimidazole **34** and isoindolinone **36.** Furthermore, nitrogen-walking around the quinoline ring (**37-39**) and changing the substitution pattern as shown in compounds **40** failed to provide any improvement.

The challenge remained to achieve $A_1$ selectivity in the aminoquinazoline series. Comparison of the proposed binding conformations to the A1 and A2A receptors of **5** and preladenant were analyzed to achieve better understanding of A1 selectivity. Structural modeling has shown that the majority of differences between the $A_{2A}$ and $A_1$ receptors are in the extracellular loop (ECL) region (blue color in figure 3a).[14] The ECL3 loop, where the tail of preladenant is proposed to bind, is one residue shorter in $A_1$ than $A_{2A}$, leading to a possible conformational difference in this area. In addition, at the top of the ligand binding pocket, there are three residue differences between the two receptors; L167E, A265K and M271T in the $A_1$ receptor (Figure 4a). On the other hand, there is minimal difference at the lower half of the ligand binding pocket. Therefore, structural modifications of compound **5** designed to bind in a region corresponding to the binding site of the extended tail of preladenent could have a higher possibility of achieving $A_1$ selectivity (Figure 3b).



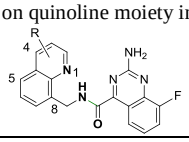

a b

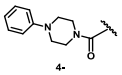
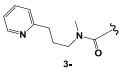
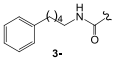
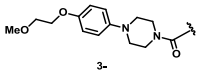
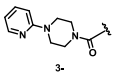
**Figure 4.** (a) Homology model of preladenant in the $A_{2A}$ (cyan) and $A_1$ (brown) receptor binding pockets. (b) Homology model comparison of aminoquinazoline **5** and preladanant.

Guided by this hypothesis**,** efforts to improve $A_1$ selectivity were therefore largely concentrated on extension of the quinoline moiety in compound **5** to reach the ECL3 loop. A series of targets with substitution at the 3 and 4 positions of quinoline ring of **5** were synthesized, with the 3 position predicted to be the preferred position based on modeling. Selected biological data are collated in Table 3. To our disappointment, substitutions at the 3-position were not well tolerated; A2a binding affinity was significantly decreased as the substituent size increased as shown by compounds **41-44**. Subsequently, substitution was shifted to the 4- position of the quinoline ring with an amide linker, as shown by compounds **45** and **46,** which led to a 10-fold loss of $hA_{2A}$ receptor affinity and a slightly improvement in selectivity

versus the $hA_1$ receptor. Gratifyingly, bulkier and more extended substituents exemplified by compounds **47-49** retained potent $A_{2A}$ affinity and demonstrated moderately improved selectivity over $A_1$, revealing a promising trend towards improved $A_1$ selectivity.

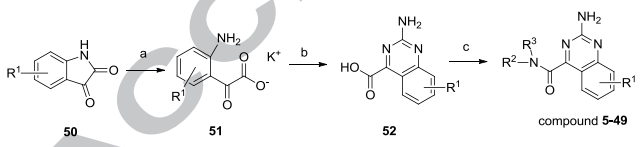
**Table 3.** SAR of substitution on quinoline moiety in lead **5**[a]



| # | R | Human $A_{2A}$ $K_i$ (nM) | Human $A_1$ Ki (nM) | rat $A_{2A}$ $K_i$ (nM) |
|---|---|---|---|---|
| **41** | 4-OMe | 15.2 | 69 | 1.3 |
| **42** | 4-OEt | 73.2 | 252 | NT |
| **43** | 4-OBu | 245 | 748 | NA |
| **44** |  | 1536 | 6003 | NT |
| **45** |  | 12.0 | 210 | NT |
| **46** |  | 6.9 | 160 | NT |
| **47** |  | 4.4 | 160 | NT |
| **48** |  | 4.8 | 120 | 11.4 |
| **49** |  | 2.7 | 110 | 12.5 |

[a] Assay values are the average of at least two independent determinations.

The general synthesis of aminoquinazoline compounds **4-49** from the readily available bicyclic isatin intermediate **50** is outlined in Scheme 1. Under basic condition, isatin **50** was hydrolyzed to amino acid potassium salt **51**, which were then subjected to a cyclization reaction with guanidine to generate aminoquinazoline carboxylic acid **52**. Standard amide formation with the corresponding amine yielded the final products **4-49**.




**Scheme 1**. Reagents and conditions: (a) $K_2CO_3$, $H_2O$-$CH_3CN$, 40°C; (b) guanidine, NaOEt, MeOH, heat; (c) amine, HATU, DIPEA, $CH_2Cl_2$ or DMF.

In conclusion, novel bicyclic adenosine $A_{2A}$ antagonists with an aminoquinazoline core have been discovered. Systematic SAR investigations have optimized the original lead compound **1** into compound **5**.[15] Compound **5** exhibit much improved solubility, excellent in vitro activity and moderate selectivity over A1 receptors, was active in an in vivo rat catalepsy assay at a low dose with minimal off-target issues. As a general tendency, these series of compounds displayed low selectivity toward the $hA_1$ receptor; however, it was possible to identify compounds with selectivity over the $hA_1$ receptor based on a modeling analysis. Further research results of this series will be disclosed in the future.

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15. Compound **5:** $^{1}$H NMR (CDCl3, 400 MHz) δ 9.38 (m, 1H), 9.01(m, 1H), 8.44 (d, *J*=3.2 Hz, 1H), 8.03 (d, *J*=6.4 Hz, 1H), 7.94 (d, *J*=6.4 Hz, 1H), 7.77 (d, *J*=3.2 Hz, 1H), 7.57 (m, 2H), 7.17 (m,1H), 5.17(d, J=5.8Hz, 2H); MS (ESI) $[M+1]^{+}$ 347.9.