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Studies on adenosine A_{2a} receptor antagonists: comparison of three core heterocycles

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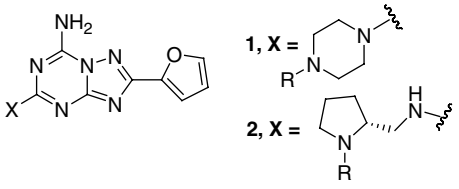
Abstract—Piperazine and (*R*)-2-(aminomethyl)pyrrolidine derivatives of [1,2,4]triazolo[1,5-*a*][1,3,5]triazine have recently been shown to be potent and selective adenosine A_{2a} receptor antagonists. We have replaced the triazolotriazine core structure with two different heterocyclic cores. One of these, the one deriving from [1,2,4]triazolo[1,5-*c*]pyrimidine, appears to be particularly effective and selected analogs from this series have been shown to be orally active in a mouse catalepsy model of Parkinson's disease.

The adenosine receptors represent an intriguing set of therapeutic targets since they are distributed throughout the body and are responsible for numerous biological functions. These seven *trans*-membrane G-protein-coupled receptors (GPCRs) have been divided into four different subtypes: A_1, A_{2a}, A_{2b}, and A_3.[1,2] Both selective agonists, as well as antagonists, of these four adenosine receptors are being intensively investigated.[3] The A_{2a} receptors are expressed widely in the striatum[4] and they can modulate the striatal output through the regulation of GABA and acetylcholine release.[5] Selective adenosine A_{2a} receptor antagonists have been shown to improve motor disabilities in rodent and primate models of Parkinson's disease.[6] KW-6002 is a xanthine-based adenosine A_{2a} receptor antagonist that is currently being evaluated in human clinical trials for the treatment of Parkinson's disease.[7] Our laboratory has been involved for some time with the identification of adenosine A_{2a} receptor antagonists that are nonxanthine-based. Our efforts have led to the recent disclosure regarding a piperazine series of [1,2,4]triazolo[1,5-*a*][1,3,5]triazines as potent and selective adenosine A_{2a} receptor antagonists (general structure **1**).[8] Further optimization by our group has also resulted in the successful replacement of the piperazine moiety with (*R*)-2-(aminomethyl)pyrrolidine (general structure **2**).[9] One of the drawbacks with both of these series, however, has been their low oral bioavailability. In order to address this issue, we have begun to modify the heterocyclic core.



A number of fused heterobicyclic templates are currently being examined as the central structural motif of potential A_{2a} receptor antagonists and some of these are illustrated in Figure 1 (structures **3**–**7**).[10–13] Numerous substituents have now been installed onto each of these core heterocyclic templates. However, there has not been a direct comparison between some of these

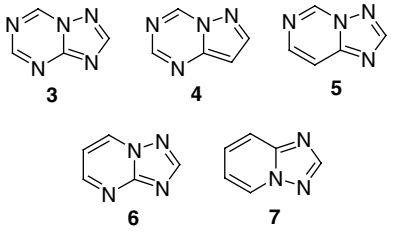


Figure 1.

Keywords: A_{2a} antagonists; Catalepsy; Parkinson's disease.
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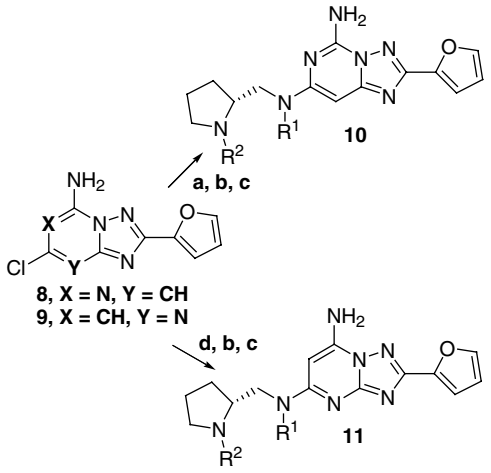


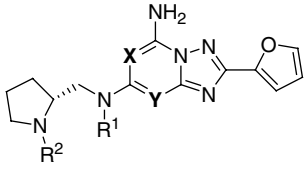
Scheme 1. Reagents and conditions: (a) **8**, CsF, DMSO, 110 °C; for R^1 = H, (*R*)-2-(aminomethyl)pyrrolidine was used; for R^1 = Me, (*R*)-2-(methylaminomethyl)pyrrolidine was used. (b) 25% TFA in CH_2Cl_2. (c) R^2CHO, $Na(OAc)_3BH$, CH_2Cl_2; or R^2CH_2Cl, CH_3CN. (d) **9**, CsF, DMSO, 110 °C; for R^1 = H, (*R*)-2-(aminomethyl)pyrrolidine was used; for R^1 = Me, (*R*)-2-(methylaminomethyl)pyrrolidine was used.

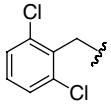
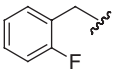
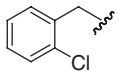
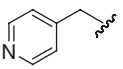
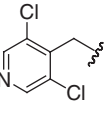
templates using a standard set of substituents. In our preliminary assessment, we selected the [1,2,4]triazolo[1,5-*c*]pyrimidine and [1,2,4]triazolo[1,5-*a*]pyrimidine templates (core structures **5** and **6**, respectively) since these two bicyclic systems bore close resemblance to our previous template **3**. We also selected (*R*)-2-(aminomethyl)pyrrolidine as the diamino component since analogs bearing it have not been reported with the two triazolopyrimidine templates.

Scheme 1 illustrates how compounds of the general structure **10** and **11** were obtained. In order to synthesize analogs having the [1,2,4]triazolo[1,5-*c*]pyrimidine core structure **10**, the chloro intermediate **8**[12] was used. This compound was fairly resistant to direct replacement with amines, even at elevated temperature. However, upon addition of CsF to the DMSO reaction mixture, direct displacement of the chloride took place readily at 110 °C.[14] After removal of the Boc group, the resulting amine could then be alkylated or subjected to a reductive amination to obtain compounds of the general structure **10**. In order to prepare analogs having the [1,2,4]triazolo[1,5-*a*]pyrimidine core structure **11**, chloride **9**[12] was used. The same type of manipulation could then be carried out to install the desired capping group R.

Table 1 lists the analogs that were made for the preliminary comparison between the three different heterocyclic core structures. The dichloro derivative **12** had an A_{2a} K_i of 18 nM. The equivalent analogs in the two triazolopyrimidyl core templates (**13** and **14**) were significantly less potent. Compound **13** was about 17-fold less active and compound **14** was about 36-fold less active. We then selected compound **15**, which was 3-fold more potent against A_{2a} than compound **12**. When the equivalent analogs bearing the two different triazolopyrimidyl core templates were prepared (**16** and **17**), a similar increase in A_{2a} binding affinity was observed.

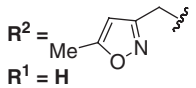
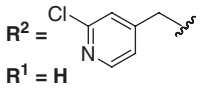
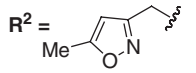
Table 1.



	General structure **2**, X = N,Y = N	General structure **10**, X = N,Y = CH	General structure **11**, X = CH,Y = N
R^2 =  R^1 = H	**12** A_{2a} K_i = 18 nM A_1 K_i > 250 nM	**13** A_{2a} K_i = 312 nM A_1 K_i = nd	**14** A_{2a} K_i = 659 nM A_1 K_i = nd
R^2 =  R^1 = H	**15** A_{2a} K_i = 6 nM A_1 K_i > 250 nM	**16** A_{2a} K_i = 127 nM A_1 K_i = nd	**17** A_{2a} K_i = 187 nM A_1 K_i = nd
R^2 =  R^1 = H	**18** A_{2a} K_i = 39 nM A_1 K_i > 250 nM	**19** A_{2a} K_i = 192 nM A_1 K_i = nd	**20** A_{2a} K_i = 148 nM A_1 K_i = nd
R^2 =  R^1 = H	**21** A_{2a} K_i = 37 nM A_1 K_i > 250 nM	**22** A_{2a} K_i = 100 nM A_1 K_i = nd	**23** A_{2a} K_i = 112 nM A_1 K_i = nd
R^2 =  R^1 = H	**24** A_{2a} K_i = 60 nM A_1 K_i > 250 nM	**25** A_{2a} K_i = 366 nM A_1 K_i = nd	**26** A_{2a} K_i = 397 nM A_1 K_i = nd

(*continued on next page*)

Table 1 (*continued*)

	General structure **2**, X = N,Y = N	General structure **10**, X = N,Y = CH	General structure **11**, X = CH,Y = N
R^2 =  R^1 = H	**27** A_{2a} K_i = 25 nM A_1 K_i > 250 nM	**28** A_{2a} K_i = 57 nM A_1 K_i > 250 nM	**29** A_{2a} K_i = 44 nM A_1 K_i > 250 nM
R^2 =  R^1 = H	**30** A_{2a} K_i = 4 nM A_1 K_i > 250 nM	**31** A_{2a} K_i = 10 nM A_1 K_i > 250 nM	**32** A_{2a} K_i = 79 nM A_1 K_i > 250 nM
R^2 =  R^1 = CH_3	**33** A_{2a} K_i = 12 nM A_1 K_i > 250 nM	**34** A_{2a} K_i = 19 nM A_1 K_i > 250 nM	**35** A_{2a} K_i = 11 nM A_1 K_i > 250 nM

For the A_{2a} receptor, membranes were prepared from rat brain tissues and the radioligand binding assay was performed using [^{3}H]ZM-241385. For the A_1 receptor, membranes were prepared from rat cerebral cortex and the radioligand binding assay was performed using [^{3}H]DPCPX. As a control for these radioligand binding assays, we routinely used SCH-58261, which had an A_{2a} K_i of 37 nM and an A_1 K_i of 390 nM. K_i values were calculated from binding curves generated from the mean of three determinations, with variation in individual values of <15%. K_i values for the A_{2b} and A_3 receptors were not determined.

However, both were still significantly less potent against A_{2a} than the corresponding triazolotriazine core template. We then prepared the three sets of compounds shown **18**–**26**. Again, the equivalent analogs bearing the two different triazolopyrimidyl core templates were consistently less active against A_{2a}. However, the magnitude of the loss was not as great, and only a 3–6-fold loss of A_{2a} binding affinity was observed.

In a previous disclosure regarding the triazolotriazine derivatives of the general structure **2**, we found that capping groups that were 1, 3 relative to the benzylic attachment point afforded some of the best A_{2a} binding affinity.[9] We then compared the triazolotriazine **27** with compounds **28** and **29**. Here, we were pleased to find that there was only a minor loss in A_{2a} binding affinity when the triazolotriazine core was switched to the corresponding triazolopyrimidine template. The chloropyridine analog **30** has previously been identified as a particularly potent and selective adenosine A_{2a} receptor antagonist.[9] When this capping group was installed onto the [1,2,4]triazolo[1,5-*c*]pyrimidyl template, the resulting compound **31** was only about 2-fold less active. The corresponding [1,2,4]triazolo[1,5-*a*]pyrimidyl analog **32** was, however, considerably less active against A_{2a}. Finally, we have previously observed that methylation of the (*R*)-2-(aminomethyl)pyrrolidine, as in **33**, afforded slightly more potent A_{2a} antagonists (compare **27** and **33**). We have found a similar trend with the two triazolopyrimidine templates (compare the two pairs **28/34** and **29/35**). In this initial assessment, we also looked at the selectivity level and found that analogs deriving from the two triazolopyrimidines were still fairly selective over the adenosine A_1 receptor (at least 20-fold).

All the compounds listed in Table 1 were evaluated in a mouse catalepsy model of Parkinson's disease. In this model, mice were administered subcutaneously with 3 mg/kg of haloperidol in order to induce catalepsy. A test compound was then given orally and the compound's ability to reverse these Parkinson's-like symptoms was analyzed by the bar test.[15] Of all the compounds shown in Table 1, only compounds **30**, **31**, and **34** showed anti-cataleptic activity at 10 mg/kg when administered orally. Figure 2 summarizes the mouse data for compounds **30**–**32** and it illustrates a very compelling trend in favor of the triazolopyrimidine series **10**. Compound **30** was indeed active at 10 mg/kg; but as shown in Figure 2, the anti-cataleptic activity was not as significant as that displayed by compound **31**. Compound **32**, with the alternative triazolopyrimidine core, was essentially ineffective at 10 mg/kg po. This trend was again repeated with compounds **33**–**35**. Of the three compounds shown in this set, only compound **34** showed oral activity at 10 mg/kg.

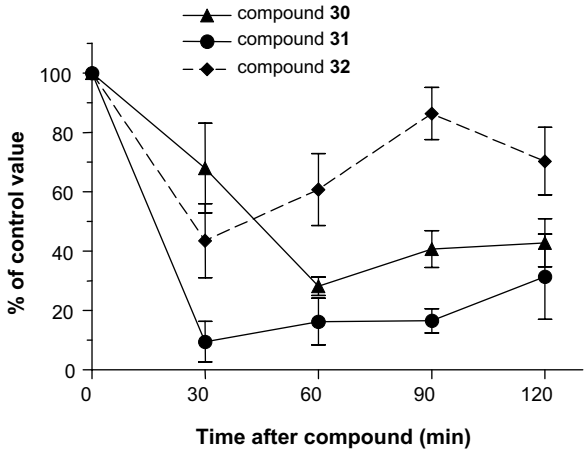


Figure 2. CD-1 mice (25–30 g) were injected subcutaneously with 3 mg/kg of haloperidol in order to induce catalepsy. Test compounds, formulated as the hydrochloride salts, were dosed orally at 10 mg/kg. The data represent the mean of six animals per group. Catalepsy was measured as the time in seconds until the animal removed at least one forepaw from the bar, with a maximum value of 120 s per test. Values for each animal in the drug-treated groups were expressed as the percentage of the mean value for the vehicle-treated control group at that time point.

In summary, we have provided for the first time a direct comparison between the three different heterocyclic

templates. Among the three cores, [1,2,4]triazolo[1,5-*a*]-[1,3,5]triazine (general structure **2**) in general afforded compounds with the best A_{2a} binding affinity. On the other hand, [1,2,4]triazolo[1,5-*c*]pyrimidine, as in the general structure **10**, appeared to give compounds with better oral efficacy in the mouse catalepsy model. A more thorough evaluation of the structure–activity relationship and the pharmacokinetic properties within the [1,2,4]triazolo[1,5-*c*]pyrimidine series is currently underway. These results will be disclosed in due course.

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