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Antagonists of the human adenosine A_{2A} receptor. Part 1: Discovery and synthesis of thieno[3,2-*d*]pyrimidine-4-methanone derivatives

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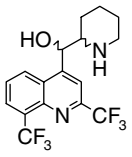
Abstract—The (−)-(11*R*,2′*S*)-enantiomer of the antimalarial drug mefloquine has been found to be a reasonably potent and moderately selective adenosine A_{2A} receptor antagonist. Further investigation of this compound has led to the discovery of a series of keto-aryl thieno[3,2-*d*]pyrimidine derivatives, which are potent and selective antagonists of the adenosine A_{2A} receptor. These derivatives show selectivity against the A_1 receptor. Furthermore, some of these compounds have been shown to have in vivo activity in a commonly used model, suggesting the potential for the treatment of Parkinson's disease.

Mefloquine (Lariam®) **1** is a clinically useful antimalarial compound, effective against multi-drug resistant strains of *Plasmodium falciparum*, the protozoan parasite responsible for infection.[1]



Mefloquine **1**

Although the agent is generally well tolerated, a number of reports of off-target effects have emerged which suggest that mefloquine is associated with infrequent but severe neuropsychiatric side effects. These include disturbed sleep, heightened anxiety, panic attacks, depression and psychosis.[2] The underlying mechanism for these effects is presently unknown.

In an effort to identify the off-target mechanisms involved, we studied mefloquine in a number of receptor binding and enzyme assays. Unexpectedly, out of 81 receptors and enzymes, strong binding was only observed to bovine striatal adenosine receptors.[3] Whilst adenosine receptor binding may, in part, explain some of the neuropsychiatric side effects associated with mefloquine, we were particularly interested in the apparent selectivity for adenosine A_{2A} receptors. Recent literature provides strong evidence that adenosine A_{2A} antagonists may be useful in the treatment of Parkinson's disease,[4] and several companies have now advanced selective antagonists of this receptor into clinical development.[5] We reasoned that mefloquine may therefore serve as a useful starting point for the design of novel adenosine A_{2A} antagonists.

Mefloquine is an asymmetric molecule, marketed as a racemic mixture of the two erythro enantiomers of α-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinoline-methanol. Our first goal was to determine the stereoselectivity of adenosine receptor binding. Chemical resolution methods, as reported in the literature,[6] provided the

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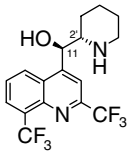
Table 1. Human adenosine receptor affinity of mefloquine enantiomers[8]

Compound	Stereochemistry	A_{2A} K_i (nM)	A_1 K_i (nM)
2	(11*R*,2′*S*)	61	255
3	(11*S*,2′*R*)	6553	14,044
4	(11*R*,2′*R*)	124	1221
5	(11*S*,2′*S*)	2534	8607

two erythro and two threo enantiomers, which were evaluated in binding studies at human adenosine receptors. (It is worthy of note, however, that the absolute stereochemistry described in the literature is incorrect and is the subject of a recent structural correction paper.[7]) As shown in Table 1, A_{2A} receptor affinity resides predominantly in enantiomers having 11*R* stereochemistry and in particular in the (−)-(11*R*,2′*S*) isomer 2.

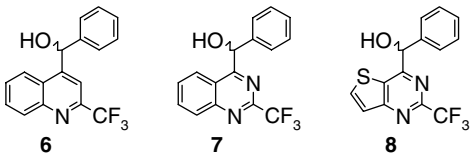


(11*R*, 2′*S*)-Mefloquine **2**

Despite extensive SAR studies of a series of related quinoline derivatives, we found it difficult to improve upon the overall profile of **2**, with the majority of modifications leading to diminished potency at the A_{2A} receptor. However, these studies highlighted two key findings. Firstly, we determined that the basic nitrogen of the piperidine ring was not explicitly required for potency. Secondly, it appeared that the piperidine ring itself appeared to be fulfilling a hydrophobic interaction with the receptor, which could be mimicked by the incorporation of a carbocyclic ring.[9]

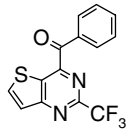
The next stage of our investigation was to assess the impact of altering the central scaffold. In particular, we considered it likely that the introduction of a central core with reduced lipophilicity, compared to quinoline, might lead to improved drug-like properties.

The introduction of an additional nitrogen atom into quinoline **6** (A_{2A} K_i 9524 nM, A_1 K_i 16,500 nM) led to quinazoline **7** (A_{2A} K_i 6493 nM, A_1 K_i > 100,000 nM). Investigation into changes in the A-ring of the biaryl system revealed that the thieno[3,2-*d*]pyrimidine scaffold (compound **8**) showed both improved potency at A_{2A} (A_{2A} K_i 3055 nM) and promising selectivity over A_1(K_i > 100,000 nM).



6 **7** **8**

These compounds were prepared by the reduction of the corresponding keto-precursors (see below for details). During the routine screening of these intermediates, compound **9**, the keto-precursor of **8**, was shown to have a K_i of 90 nM at the A_{2A} receptor, a dramatic 35-fold improvement, though selectivity over the A_1 receptor was reduced somewhat, to 15-fold.



9

This finding prompted further investigation, and a series of arylketone analogues of **9** were prepared and evaluated. A representative selection of these derivatives is described in Table 2. Pleasingly, these highly active compounds were now both achiral and synthetically easier to access than the corresponding hydroxyl conjoiners.

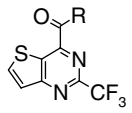
Gratifyingly, low nanomolar potencies and reasonable selectivities were observed in a number of compounds in this series. The most potent compounds arose by the replacement of the phenyl group in compound **9** with the 5-membered, electron-rich groups thiophene and furan, as in compounds **14**, **16**, **17** and **18**. A corresponding reduction in affinity associated with the use of pyridyl substituents, as in compounds **10**, **11** and **12**, supports the hypothesis that electron-rich groups are favoured in this position.

Based on these data, the 2-thienyl substituent in compound **14** was selected as a fixed substituent in efforts towards the optimisation of the C-2 substituent. The results from these studies are described in Table 3.

The data in Table 3 show that a range of C-2 substituents are tolerated and provide compounds with good A_{2A} potency. A reasonable degree of selectivity for A_{2A} over A_1 is maintained by small alkyl and some alkylamino substituents.

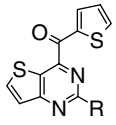
As part of our investigation into the potential of this class of compound as anti-Parkinsonian agents, we

Table 2. Binding affinity of 2-trifluoromethylthieno[3,2-*d*]pyrimidin-4-yl aryl ketones[8]



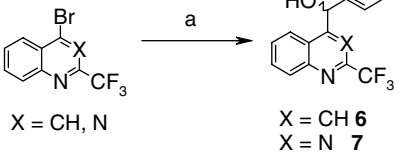
Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)
9	Phenyl	92	1364
10	2-Pyridyl	5737	17,514
11	3-Pyridyl	435	4475
12	4-Pyridyl	1384	14,454
13	2-Pyrrolyl	118	3474
14	2-Thienyl	11	430
15	3-Thienyl	56	4216
16	2-Furyl	33	471
17	3-Furyl	30	316
18	5-Methyl-2-furyl	22	295
19	2-Thiazolyl	335	5462

Table 3. Binding affinity of 2-substituted thieno[3,2-*d*]pyrimidin-4-yl 2-thienyl ketones[8]

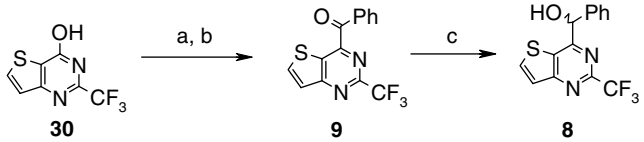


Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)
14	CF_3	11	430
20	Me	29	487
21	Et	16	400
22	OMe	80	710
23	NH_2	23	181
24	NH–NH_2	60	33
25	NHEt	25	107
26	NMe_2	49	1458
27	NHBn	25	1733
28	$NH(CH_2)_2OH$	4.3	14
29	$NH(CH_2)_3OH$	8.1	32

tested a selection of compounds in vivo in the haloperidol-induced hypolocomotion model in mice.[10] In this model, the reduction in locomotor activity induced by the D_2 antagonist haloperidol can be reversed by the subsequent administration of an adenosine A_{2A} antagonist. This model can be used as a measure of A_{2A} antagonist effects in vivo. In this assay, a number of thieno[3,2-*d*]pyrimidine analogues showed modest in vivo effects. In particular, compounds **24**, **25**, **28** and **29** were shown to be active following intraperitoneal administration at 30 mg/kg.



Scheme 1. Reagents and conditions: (a) Et_2O, *n*-BuLi, −78 °C, 15 min, then PhCHO, −78 °C, 1 h then rt, 51–77%.



Scheme 2. Reagents and conditions: (a) $POCl_3$, reflux, 2 h, 35%; (b) PhCHO, *N*,*N*-dimethylimidazolium iodide, NaH, THF, reflux, 15 min, 21%; (c) $NaBH_4$, MeOH, rt, 1 h, 27%.

The synthesis of the compounds employed in this study is described below.[11] 4-Bromo-2-trifluoromethyl-quinoline was prepared by the adaptation of literature procedures.[12] Compound **6** was readily accessed by the lithiation of the corresponding quinoline followed by reaction with benzaldehyde to give the racemic benzyl alcohol as depicted in Scheme 1. Similarly, compound **7** was prepared from the corresponding 4-bromoquinazoline.

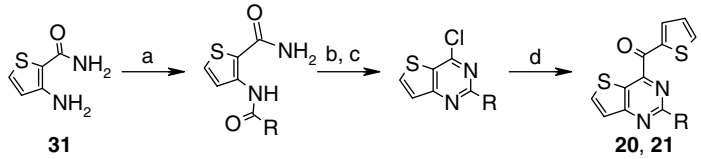
Compound **8** was prepared from 4-hydroxythienopyrimidine **30**.[13] Chlorination with phosphorous oxychloride was followed by aldehyde incorporation catalysed by *N*,*N*-dimethylimidazolium chloride,[14] to give the keto-aryl compound **9**. The alcohol was then obtained by facile reduction with sodium borohydride (Scheme 2).

Compounds **10**–**19** were prepared in a manner similar to compound **9** in Scheme 2, by employing the appropriate aldehyde.

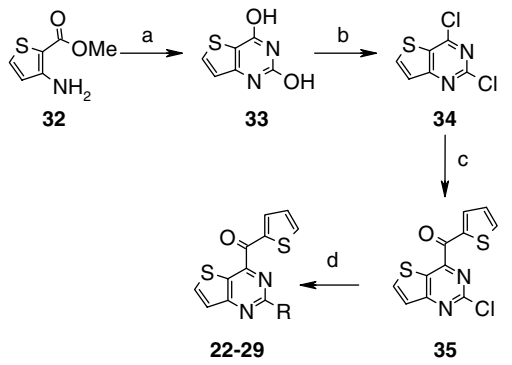
The C-2 alkyl derivatives **20** and **21**, detailed in Table 3, were prepared in a related manner, though the precursor 2-alkyl-4-chlorothienopyrimidines required bespoke synthesis from aminothiophene **31**, as detailed in Scheme 3. *N*-Acylation of **31** with the appropriate alkyl anhydride introduced the desired aliphatic moiety and the resultant *bis*-amide was cyclised under basic conditions then converted to the corresponding 4-chlorothienopyrimidine with phosphorous oxychloride. The thiophene ketone moiety was then introduced via the aforementioned *N*,*N*-dimethylimidazolium iodide-mediated coupling.[14]

The methoxy derivative **22** was prepared from methyl 3-aminothiophene-2-carboxylate **32**, as shown in Scheme 4. Cyclisation with urea gave the dihydroxy thienopyrimidine **33**, which was converted to the *bis*-chloro derivative **34** using phenylphosphonic dichloride. Again, aldehyde incorporation was mediated by *N*,*N*-dimethylimidazolium chloride[14] to yield the keto-aryl compound **35** and the displacement of the 2-chloro was achieved with a refluxing solution of sodium methoxide. Similarly, the amino derivatives **23**–**29** were prepared by treating **35** with the appropriate amine in refluxing ethanol.

In summary, we report herein the discovery of a novel class of adenosine A_{2A} antagonists. Through iterative medicinal chemistry, we have demonstrated that 4-keto-



Scheme 3. Reagents and conditions: (a) $(RCO)_2O$, $PhCH_3$, NEt_3, reflux, 1.5 h, 80–82%; (b) NaOH, reflux, 4 h, 100%; (c) $POCl_3$, reflux, 4 h, 72–92%; (d) thiophene-2-carboxaldehyde, *N*,*N*-dimethylimidazolium iodide, NaH, THF, reflux, 15 min, 54–66%.



Scheme 4. Reagents and conditions: (a) Urea, 200 °C, 4 h, 83%; (b) $PhPOCl_2$, 170 °C, 2 h, 66%; (c) thiophene-2-carboxaldehyde, *N*,*N*-dimethylimidazolium iodide, NaH, THF, reflux, 15 min, 46%; (d) (compound **22**) sodium methoxide, reflux, 18 h, 90%; (e) (compounds **23**–**29**) NHR^1R^2, EtOH, reflux, 2 h, 37–68%.

arylthieno[3,2-*d*]pyrimidine derivatives show strong antagonism of the human adenosine A_{2A} receptor and selectivity against the A_1 receptor. Furthermore, some of these compounds have demonstrated activity in a commonly used in vivo model predictive of potential utility for the treatment of Parkinson's disease.

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