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

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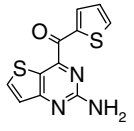
Abstract—We describe herein the discovery and development of a series of 4-arylthieno[3,2-*d*]pyrimidines which are potent adenosine A_{2A} receptor antagonists. These novel compounds show high degrees of selectivity against the human A_1, A_{2B} and A_3 receptor sub-types. Moreover, a number of these compounds show promising activity in vivo, suggesting potential utility in the treatment of Parkinson's disease.

Adenosine receptors comprise four distinct sub-types, designated A_1, A_{2A}, A_{2B} and A_3. In the brain, adenosine A_{2A} receptors are located primarily in the striatum, playing a key role in regulating movement. There is strong evidence that adenosine A_{2A} receptor antagonists may provide a novel therapy for the treatment of Parkinson's disease, with a lower risk of dyskinesias.[1]

We have previously reported that a series of thieno[3,2-*d*]pyrimidine ketones, typified by **1**, are potent adenosine A_{2A} receptor antagonists which show good selectivity over the A_1 receptor.[2] Furthermore, some of these compounds also demonstrate activity in vivo. Unfortunately, the compounds with the best in vivo activity in this series had relatively modest selectivity and it proved difficult to optimise both properties in the same molecule.

We herein report the further development of this series, leading to a novel class of biaryl A_{2A} antagonists which display high potency and selectivity against other adenosine receptor sub-types and, moreover, promising in vivo activity.



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The biaryl ketones were prepared by direct incorporation of the keto functionality via the reaction of a 2,4-dichlorothieno[3,2-*d*]pyrimidine with the appropriate aryl aldehyde in the presence of *N*,*N*-dimethylimidazolium iodide and sodium hydride.[3] A significant byproduct was often isolated from this reaction which, following analysis, was shown to be the directly coupled biaryl derivative **2**, lacking the keto linkage, as shown in Scheme 1.

Initial testing indicated that, like their keto counterparts, these compounds showed good A_{2A} receptor binding affinity[4] with some selectivity over A_1. These data suggested that this series warranted further investigation.

Initially, a small series of 4-(2-thienyl) analogues, as detailed in Table 1, were prepared and evaluated.

Encouraged by these preliminary results, an investigation of SAR around the 4-aryl group was undertaken. Since the initial results indicated that the 2-ethyl and 2-dimethylamino substituents provided the best binding affinity and selectivity, these groups were chosen as the

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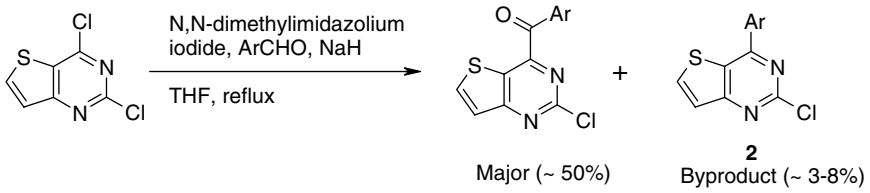
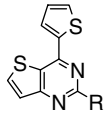


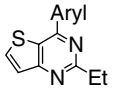
Scheme 1. Formation of biaryl derivatives with representative isolated yields.

Table 1. Initial 2-position SAR



Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)	HaloLMA activity[5]
3	Cl	391	2041	Inactive
4	Et	69	1466	Inactive
5	OMe	444	1590	Inactive
6	NHEt	154	813	Inactive
7	NMe_2	55	1963	Inactive
8	$NH(CH_2)_2OH$	172	401	Active

Table 2. 2-Ethylthieno[3,2-*d*]pyrimidines: 4-aryl SAR



Compound	Aryl	A_{2A} K_i (nM)	A_1 K_i (nM)	HaloLMA activity[5]
4	2-Thienyl	69	1466	Inactive
9	2-Furyl	30	3205	Active
10	3-Furyl	681	10000	n/d
11	2-Thiazolyl	1.6	388	Active
12	2-(4-Methyl-thiazolyl)	2.1	413	Active
13	2-Imidazolyl	142	5525	Active
14	2-Triazoyl	779	4938	n/d[a]
15	2-Pyridyl	13	917	Active
16	2-(6-Methyl-pyridyl)	12	1273	Inactive

[a] n/d, not determined.

2-substituent for most compounds in this evaluation. The results obtained are shown in Tables 2 and 3.

It was apparent from these data that, in both series, a 2-thiazolyl group offered a significant advantage over other heteroaryl groups in the 4-position and provided a number of highly potent and selective analogues, several of which showed promising in vivo activity. Based on these data, the 2-thiazolyl group was selected as the 4-aryl substituent for a further round of optimisation of the C-2 substituent, as described in Table 4.

These data showed that, with a 2-thiazolyl substituent in place at the C-4 position, a wide range of C-2 substituents are tolerated and provide a series of highly potent and selective A_{2A} antagonists. Potency and selectivity over A_1 is particularly good where the C-2 substituent is a small lipophilic group such as alkyl or dialkylamino as in compounds **11**, **24**, **36** and **37**. Although good A_{2A} receptor affinity is retained in compounds containing larger alkylamino substituents, for example, compound **40**, selectivity is poorer. Compound **38**, containing a bulkier *tert*-butyl substituent, shows a similar in vitro binding profile to analogues containing smaller alkyl groups, but is inactive in vivo. It is likely that the increased lipophilicity and higher log *D* of this compound have a detrimental effect on the pharmacokinetic profile.

A number of the most promising candidates were examined for selectivity against the adenosine A_{2B} and A_3 receptor sub-types, using methods previously described.[4] These data, detailed in Table 5, demonstrate that these compounds show excellent selectivity for A_{2A} over both the A_{2B} and A_3 receptors, alongside the previously observed selectivity over the A_1 sub-type. It is particularly noteworthy that excellent binding affinity and selectivity can be achieved in molecules with very low molecular weight (e.g., compound **11**, M_{Wt} 247).

The functional activity of these compounds was determined in cells by assessing Ca^{2+} mobilisation using a Fluorescence Imaging Plate Reader (FLIPR).[6] All the compounds tested were found to be functional antagonists of the A_{2A} receptor and exhibited no appreciable agonist activity ($EC_{50} \gg 10$ μM).

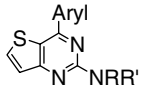
As illustrated in the tables, a number of compounds in this class were active in vivo in reversing haloperidol-induced hypolocomotion in mice. For example, compound **37**, a potent and selective A_{2A} antagonist, showed significant efficacy when dosed ip at 30 mg kg^{-1} or sc at 10 mg kg^{-1}.

The compounds employed in these studies were prepared as described below.[7] Compound **3** was prepared as described in Scheme 2. Cyclisation of 3-aminothiophene-2-carboxylate methyl ester **43** with urea gave diol **44**, the chlorination of which yielded 2,4-dichlorothieno[3,2-*d*]pyrimidine **45**. The treatment of **45** with thiophene-2-boronic acid under standard Suzuki coupling conditions then gave regioselective access to the desired C-4 substituted regioisomer **3**.[8]

Similarly, the cyclisation of 3-aminothiophene-2-carboxamide **46** with propionic anhydride, followed by chlorination with phosphorous oxychloride yielded 4-chloro-2-ethylthieno[3,2-*d*]pyrimidine **47**. Suzuki coupling with thiophene-2-boronic acid gave **4**.

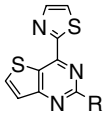
The methoxy derivative **5** and the amino derivatives **6**–**8** were prepared via the 2-chloro precursor **3**, by heating

Table 3. 2-Aminothieno[3,2-*d*]pyrimidines: 4-aryl SAR



Compound	Aryl	NRR′	A_{2A} K_i (nM)	A_1 K_i (nM)	HaloLMA activity[5]
7	2-Thienyl	NMe_2	55	1963	Inactive
17	Benzo-thiophene-2-yl	NMe_2	1326	1255	n/d
18	2-Furyl	NH_2	14	479	Active
19	2-Furyl	NHMe	40	568	Active
20	2-Furyl	NHEt	58	375	Active
21	2-Furyl	NMe_2	60	2197	Active
22	2-Furyl	$NH(CH_2)_2OH$	203	868	Inactive
23	3-Furyl	NMe_2	748	3467	n/d
24	2-Thiazoyl	NMe_2	2.3	366	Active
25	2-Thiazoyl	NH_2	35	675	Active
26	2-(4-Methyl-thiazolyl)	NMe_2	1.3	303	Active
27	2-(5-Methyl-thiazolyl)	NMe_2	5.7	908	Inactive
28	2-(4,5-Dimethyl-thiazolyl)	NMe_2	6.6	254	Inactive
29	2-Imidazolyl	NMe_2	299	5768	Active
30	2-(1-Methyl-imidazolyl)	NMe_2	14	1095	Inactive
31	4-Pyrazoyl	NMe_2	3079	5513	n/d
32	2-Pyridyl	NMe_2	26	1588	n/d
33	2-(5-Methyl-pyridyl)	NMe_2	19	1260	Inactive
34	2-Pyrazinyl	NMe_2	81	990	Inactive

Table 4. 4-(Thiazol-2-yl)thieno[3,2-*d*]pyrimidines: 2-position SAR



Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)	HaloLMA activity[5]
11	Et	1.6	388	Active
24	NMe_2	2.3	366	Active
35	Cl	20	615	n/d
36	*iso*-Propyl	1.4	208	Active
37	Cyclopropyl	3.3	259	Active
38	*tert*-Butyl	3.1	240	Inactive
39	NH_2	35	675	Active
40	$NH(CH_2)_2OH$	18	57	Active
41	*N*-(*S*)-Prolinol	2.8	14	Active
42	*N*-(*R*)-Prolinol	3.6	250	Active

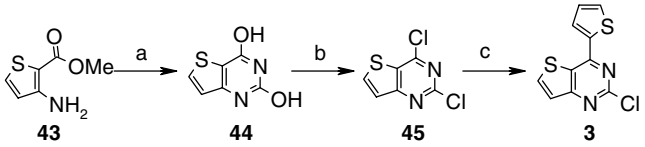
Table 5. Binding affinity for selected compounds at all four human adenosine receptor sub-types[5]

Compound	A_{2A} K_i (nM)	A_1 K_i (nM)	A_{2B} K_i (nM)	A_3 K_i (nM)
11	1.6	388	721	1813
24	2.3	366	1560	1759
36	1.4	208	865	476
37	3.3	259	910	945
41	2.8	14	2479	456

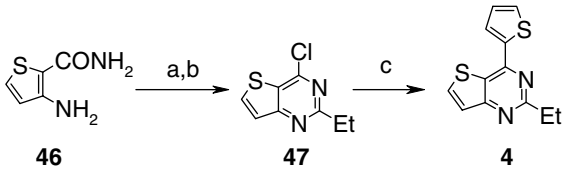
with sodium methoxide or the required amine in *N*-methyl pyrrolidone, respectively (Scheme 4).

Compounds **9**–**16** were prepared in the manner outlined in Scheme 5. 4-Chloro-2-ethylthieno[3,2-*d*]pyrimidine **47** was coupled with a variety of heterocycles under Stille, Suzuki or Negishi conditions to yield the desired biaryl systems.

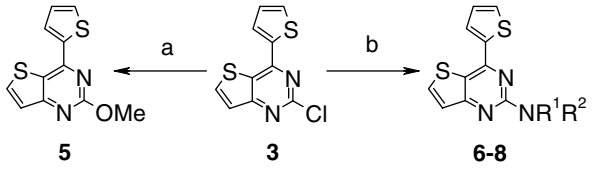
The amino derivatives **17**–**34** were also prepared by palladium or zinc-mediated coupling employing 2,4-dichlo-



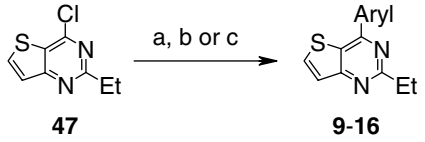
Scheme 2. Reagents and conditions: (a) urea, 200 °C, 4 h, 83%; (b) $PhPOCl_2$, 170 °C, 2 h, 66%; (c) $Pd(OAc)_2$, PPh_3, THF, rt, 5 min then thiophene-2-boronic acid, satd aq $NaHCO_3$, reflux, 4 h, 94%.



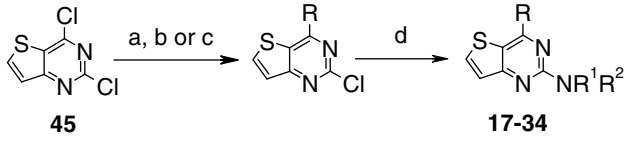
Scheme 3. Reagents and conditions: (a) (i) propionic anhydride, $PhCH_3$, NEt_3, reflux, 1.5 h, 82%; (ii) NaOH, reflux, 4 h, 100%; (b) $POCl_3$, reflux, 2.5 h, 72%; (c) $Pd(OAc)_2$, PPh_3, THF, rt, 5 min then thiophene-2-boronic acid, satd aq $NaHCO_3$, reflux, 4 h, 36%.



Scheme 4. Reagents and conditions: (a) sodium methoxide, reflux, 18 h, 95%; (b) NHR^1R^2, NMP, 90 °C, 16 h, 42–77%.



Scheme 5. Reagents and conditions: (a) (compound **9**) $PdCl_2(PPh_3)_2$, DMF, Ar–$SnBu_3$, rt, 16 h, 56%; (b) (compound **10**) $Pd(OAc)_2$, PPh_3, THF, rt, 5 min then aryl boronic acid, satd aq $NaHCO_3$, reflux, 4 h, 36–52%; (c) (compounds **11**–**16**); (i) heterocycle, THF, *n*-BuLi, −78 °C, 15 min then $ZnCl_2$, Et_2O, −78 °C to rt; (ii) **47**, $Pd(PPh_3)_4$, reflux, 17 h, 37–65%.



Scheme 6. Reagents and conditions: (a) (compounds **17**–**22**, **32** and **33**) $PdCl_2(PPh_3)_2$, DMF, Ar–$SnBu_3$, rt, 16 h, 31–67%; (b) (compound **23**) $Pd(OAc)_2$, PPh_3, THF, rt, 5 min then aryl boronic acid, satd aq $NaHCO_3$, reflux, 4 h, 33%; (c) (compounds **24**–**31** and **34**); (i) heterocycle, THF, *n*-BuLi, −78 °C, 15 min then $ZnCl_2$, Et_2O, −78 °C to rt; (ii) **45**, $Pd(PPh_3)_4$, reflux, 17 h, 22–87%; (d) NHR^1R^2, NMP, 90 °C, 16 h, 13–100%.

rothieno[3,2-*d*]pyrimidine **45**. Coupling with the desired heterocycle under Suzuki, Stille or Negishi conditions was followed by the displacement of the 2-Cl with the relevant amine, in the manner illustrated in Scheme 6.

Compounds **36**–**42** were all prepared via methodology similar to the preparation of **11**, **24** and **25**.[7]

In summary, 4-arylthieno[3,2-*d*]pyrimidines, serendipitously discovered as byproducts in the preparation of a related compound series, have been shown to display strong functional antagonism of the human A_{2A} receptor. Optimisation of this series has led to A_{2A} antagonists with low nM affinity and a high degree of selectivity over other adenosine receptor sub-types. Moreover, a number of these compounds show promising activity in vivo suggesting that they may have potential for the treatment of Parkinson's disease. The further evolution of this series is reported in the following communication.[9]

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