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Antagonists of the human adenosine A_{2A} receptor. Part 3: Design and synthesis of pyrazolo[3,4-*d*]pyrimidines, pyrrolo[2,3-*d*]pyrimidines and 6-arylpurines

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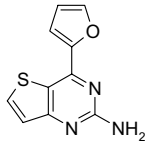
Abstract—A series of pyrazolo[3,4-*d*]pyrimidine, pyrrolo[2,3-*d*]pyrimidine and 6-arylpurine adenosine A_{2A} antagonists is described. Many examples were highly selective against the human A_1 receptor sub-type and were active in an in vivo model of Parkinson's disease.

Adenosine A_{2A} receptors play a role within the brain in regulating movement, and there is strong evidence that they may provide a novel therapy for the treatment of Parkinson's disease.[1,2] Further to the discovery that 4-arylthieno[3,2-*d*]pyrimidines such as compound **1** were potent adenosine A_{2A} receptor antagonists, selective over the A_1 receptor and demonstrated activity in a mouse haloperidol-induced hypolocomotion model of Parkinson's disease,[3–7] the SAR around other bicyclic heteroaromatic templates was explored.



1
A_{2A} K_i 14 nM
A_1 K_i 479 nM

The 4-(furan-2-yl)pyrazolo[3,4-*d*]pyrimidine **2** was selected as a starting point for further investigation and, encouragingly, this was found to have an A_{2A} K_i of 48 nM and was 13-fold selective over A_1 (Table 1).[8] 1-Benzyl substitution (compound **3**) increased potency at A_{2A} and selectivity over A_1, whilst retaining in vivo activity. Saturation of the phenyl ring of **3** or incorporation of heteroatoms (compounds **4**–**6**) was tolerated, but did not improve affinity significantly. Extension of the linker between the phenyl ring and pyrazole by one methylene group (compound **7**) was detrimental to A_{2A} potency, but further extension (compounds **8** and **9**) regained A_{2A} potency at the expense of A_1 selectivity. Elaboration of the 2-amino substituent was also explored, but its replacement with a 2-aminoethanol or 2-dimethylamino substituent (**10** and **11**) reduced A_{2A} potency.

Given the encouraging data on the benzyl analogue **3**, the effects of substitution around the phenyl ring were explored (Table 2). *Meta*-substitution with a range of electron-rich and deficient substituents was tolerated, with the 3-chlorobenzyl analogue **14** showing increased A_{2A} potency and selectivity over A_1. *Ortho*- and *para*-substitution was largely detrimental to the desired biological profile, although 2-fluoro substitution (compound **23**) was tolerated. Further work was

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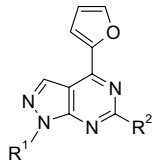
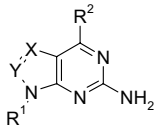
Table 1. Binding affinity and in vivo activity of pyrazolo[3,4-*d*]pyrimidines **2**–**11**



Compound	$\mathbf{R}^1$	R^2	A_{2A} K_i (nM)[8]	A_1 K_i (nM)[8]	HaloLMA activity[4–6]
2	H	NH_2	48	647	Active
3	Benzyl	NH_2	3	468	Active
4	Cyclohexylmethyl	NH_2	45	763	Active
5	Pyridin-3-ylmethyl	NH_2	28	1953	Active
6	Furan-2-ylmethyl	NH_2	36	709	Active
7	Phenethyl	NH_2	110	462	Inactive
8	3-Phenylpropyl	NH_2	4	17	Active
9	Benzylaminocarbonyl	NH_2	1	13	Active
10	Phenethyl	$NH(CH_2)_2OH$	135	175	Inactive
11	Phenethyl	NMe_2	1891	7255	—

Table 2. Binding affinity and in vivo activity of pyrazolo[3,4-*d*]pyrimidines **2**–**3** and **12**–**33**, and 9-substituted-6-(furan-2-yl)-9*H*-purin-2-ylamines **34**–**47**



Compound	X	Y	R^1	R^2	A_{2A} K_i (nM)[6]	A_1 K_i (nM)[6]	HaloLMA activity[4]
2	CH	N	H	Furan-2-yl	48	647	Active
3	CH	N	Benzyl	Furan-2-yl	3	468	Active
12	CH	N	3-Methylbenzyl	Furan-2-yl	3	252	Active
13	CH	N	2-Chlorobenzyl	Furan-2-yl	9	721	Inactive
14	CH	N	3-Chlorobenzyl	Furan-2-yl	1	206	Active
15	CH	N	3-Methoxybenzyl	Furan-2-yl	2	284	Active
16	CH	N	3-Methoxycarbonylbenzyl	Furan-2-yl	4	779	Active
17	CH	N	2-Nitrobenzyl	Furan-2-yl	26	1605	Inactive
18	CH	N	3-Nitrobenzyl	Furan-2-yl	4	497	Active
19	CH	N	4-Nitrobenzyl	Furan-2-yl	119	1610	Inactive
20	CH	N	2-Aminobenzyl	Furan-2-yl	8	320	Active
21	CH	N	3-Aminobenzyl	Furan-2-yl	4	123	Active
22	CH	N	3-Carboxybenzyl	Furan-2-yl	1322	6321	Inactive
23	CH	N	2-Fluorobenzyl	Furan-2-yl	4	264	Active
24	CH	N	2,6-Difluorobenzyl	Furan-2-yl	2	130	Active
25	CH	N	4-Trifluoromethylbenzyl	Furan-2-yl	6	47	Inactive
26	CH	N	4-Methylsulfonylbenzyl	Furan-2-yl	340	1126	Inactive
27	CH	N	2-Fluorobenzyl	Thiophen-2-yl	9	193	—
28	CH	N	2-Fluorobenzyl	Pyridin-2-yl	12	519	Active
29	CH	N	2-Fluorobenzyl	Pyrazol-3-yl	16	1642	Active
30	CH	N	2-Fluorobenzyl	Thiazol-2-yl	17	504	Inactive
31	CH	N	2-Fluorobenzyl	(1,2,4)Triazol-3-yl	71	1993	Active
32	CH	N	2-Fluorobenzyl	1-Methylimidazol-2-yl	1616	6219	Inactive
33	CH	N	2-Fluorobenzyl	Imidazol-2-yl	2086	4900	—
34	N	CH	H	Furan-2-yl	261	4951	Active
35	N	CH	Benzyl	Furan-2-yl	40	3324	Active
36	N	CH	3-Methylbenzyl	Furan-2-yl	6	1083	Active
37	N	CH	3-Chlorobenzyl	Furan-2-yl	8	984	Inactive
38	N	CH	3-Methoxybenzyl	Furan-2-yl	7	1680	Active
39	N	CH	3-Methoxycarbonylbenzyl	Furan-2-yl	45	1938	Inactive
40	N	CH	3-Nitrobenzyl	Furan-2-yl	85	3920	Inactive
41	N	CH	4-Nitrobenzyl	Furan-2-yl	372	5765	—
42	N	CH	3-Aminobenzyl	Furan-2-yl	23	4027	Active
43	N	CH	3-Carboxybenzyl	Furan-2-yl	4105	6470	—
44	N	CH	2-Fluorobenzyl	Furan-2-yl	5	1444	Active
45	N	CH	2,6-Difluorobenzyl	Furan-2-yl	3	612	Active
46	N	CH	4-Trifluoromethylbenzyl	Furan-2-yl	6	3288	Active
47	N	CH	4-Methylsulfonylbenzyl	Furan-2-yl	779	7628	—

undertaken to optimise the 4-(furan-2-yl) substituent of **23** since, in some compounds, this moiety is prone to oxidative metabolism, which can lead to the formation of reactive species capable of forming covalent adducts.[9] This iterative approach is complementary to database mining and molecular similarity approaches, which have been used to identify other classes of non-furan containing A_{2A} antagonists.[10] The resulting compounds **27**–**33** showed reduced affinity for A_{2A}, although the pyrazol-3-yl analogue **29** displayed increased A_1 selectivity, whilst retaining in vivo activity.

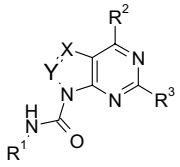
Despite many pyrazolo[3,4-*d*]pyrimidine examples showing in vivo activity following intraperitoneal administration, none were active when given orally. Modification of the core template of this series to a purine was investigated, with a view to obtaining orally active compounds. The 6-arylpurine **34** had weaker binding affinity for A_{2A} (K_i 261 nM) than compound **2**, but had similar selectivity over A_1 (K_i 4951 nM). Additionally, **34** caused reversal of haloperidol-induced hypolocomotion in mice dosed at 10 mg/kg ip and, encouragingly, at 1 mg/kg po.

As with the pyrazolo[3,4-*d*]pyrimidine examples, benzylic substitution (compound **35**) at the 9-position of compound **34** was beneficial to affinity for the A_{2A} receptor and also selectivity over A_1. This compound was also active in vivo when dosed at 30 mg/kg ip, but inactive when administered orally at the same dose. In comparison with the analogous pyrazolo[3,4-*d*]pyrimidine **3**, however, compound **35** was 13-fold less potent against A_{2A}. Further studies were carried out to optimize compound **35**. These augment the work of Kiselgof et al.,[11] published subsequent to our patent disclosure.[12] Appropriate substitution on the phenyl ring led to increased potency, with some examples displaying affinity for A_{2A} at a similar level to their pyrazolo[3,4-*d*]pyrimidine counterparts, as well as greater selectivity over A_1. The 2,6-difluorophenyl analogue **45** was the most potent example in this sub-series (A_{2A} K_i 3 nM, A_1 K_i 612 nM). Whilst several analogues were active in vivo following ip administration, the 3-aminobenzyl analogue **42** was the only example which showed in vivo efficacy, when dosed orally at 30 mg/kg.

With the intention of further optimising the in vivo profile of the 6-arylpurine series, it was noted that the urea analogue **9** of the pyrazolo[3,4-*d*]pyrimidine series had an A_{2A} K_i of 1 nM and was 13-fold selective over A_1. The analogous 6-arylpurine compound **48** was synthesised, and was found to have a very similar level of potency for A_{2A} and selectivity over A_1 (Table 3). The phenyl analogue **49** had a similar in vitro profile to the unsubstituted compound **34**, but the introduction of an extra two methylene spacers (**50**) led to improved selectivity over A_1 and incorporation of an (*S*)-α-methylbenzyl substituent (**51**) enhanced A_{2A} potency whilst maintaining >100-fold selectivity over A_1. A range of heteroaryl and substituted phenyl analogues (**53**–**58**) was shown to be highly potent at A_{2A}, selective for A_1 and active in vivo when dosed ip. Additionally, compounds **53**, **54** and **56** were shown to be orally active in vivo at 30, 10 and 30 mg/kg, respectively.

SAR at the 6-position of the purine ring was investigated, with the furan-2-yl ring of compound **48** being replaced with thiophen-2-yl, phenyl or thiazol-5-yl groups

Table 3. Binding affinity and in vivo activity of pyrazolo[3,4-*d*]pyrimidine **9** and 6-aryl-9*H*-purin-9-ylcarboxamides **48**–**65**



Compound	X	Y	R^1	R^2	R^3	A_{2A} K_i (nM)[8]	A_1 K_i (nM)[8]	HaloLMA activity[4–6]
9	CH	N	Benzyl	Furan-2-yl	NH_2	1	13	Active
48	N	CH	Benzyl	Furan-2-yl	NH_2	1	17	Active
49	N	CH	Phenyl	Furan-2-yl	NH_2	206	4960	Active
50	N	CH	Phenethyl	Furan-2-yl	NH_2	6	624	Active
51	N	CH	(*S*)-1-Phenylethyl	Furan-2-yl	NH_2	2	231	Active
52	N	CH	(*R*)-1-Phenylethyl	Furan-2-yl	NH_2	26	1856	Inactive
53	N	CH	Thiophen-2-ylmethyl	Furan-2-yl	NH_2	1	28	Active
54	N	CH	Furan-2-ylmethyl	Furan-2-yl	NH_2	2	170	Active
55	N	CH	4-Fluorobenzyl	Furan-2-yl	NH_2	1	70	Active
56	N	CH	3-Methylbenzyl	Furan-2-yl	NH_2	1	26	Active
57	N	CH	4-Methylbenzyl	Furan-2-yl	NH_2	1	76	Active
58	N	CH	2-Chlorobenzyl	Furan-2-yl	NH_2	1	26	Active
59	N	CH	Benzyl	Thiophen-2-yl	NH_2	13	127	Inactive
60	N	CH	Benzyl	Phenyl	NH_2	17	60	Active
61	N	CH	Benzyl	Thiazol-5-yl	NH_2	56	835	Active
62	N	CH	Benzyl	Furan-2-yl	OMe	8	534	—
63	N	CH	Benzyl	Furan-2-yl	SMe	13	547	Inactive
64	N	CH	Benzyl	Furan-2-yl	NMe_2	23	748	Inactive
65	N	CH	Benzyl	Furan-2-yl	Me	102	2726	—

(**59**–**61**). In all cases, potency at A_{2A} and selectivity over A_1 was reduced. Replacement of the 2-amino group of compound **48** with OMe, SMe, NMe_2 or Me (**62**–**65**) was detrimental to A_{2A} potency, but gave enhanced selectivity over A_1.

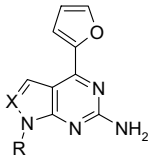
Selected pyrrolo[2,3-*d*]pyrimidine analogues were also prepared, allowing comparison with the direct analogues in the pyrazolo[3,4-*d*]pyrimidine series (Table 4). Examples **66** and **67** showed that replacement of N-2 with CH resulted in a significant drop in potency at A_{2A}, along with a smaller drop in selectivity over A_1.

Pyrazolo[3,4-*d*]pyrmidines were prepared using the following methodology.[13] 4-Chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamine **68**[14] underwent Boc-protection and then arylation with 2-(tributylstannyl)furan in the presence of bis(triphenylphospine)palladium(II) dichloride, followed by deprotection to afford compound **2** (Scheme 1). Subsequent treatment with sodium hydride, followed by a benzyl or alkyl bromide, afforded compounds **3**–**8**, **12**–**19** and **23**–**26** as largely the desired N1-substituted regioisomer.[15] Reduction of the nitrobenzyl analogs **17** and **18** with tin(II) chloride afforded the aminobenzyl analogs **20** and **21**, respectively, and hydrolysis of the methyl ester **16** afforded the carboxylic acid **22**. The benzyl urea **9** was synthesized by treatment of 4-(furan-2-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamine **2** with benzyl isocyanate and 4-dimethylaminopyridine.

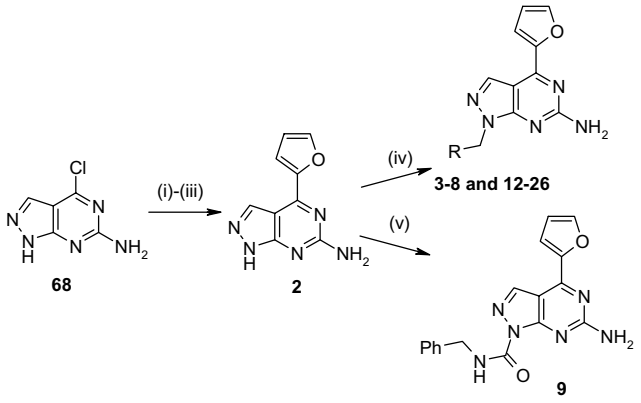
An alternative synthetic strategy (Scheme 2) involved hydrolysis of 5-amino-1-phenethyl-1*H*-pyrazole-4-carbonitrile **69**[16] with sulfuric acid, followed by cyclocondensation of the resulting acid with urea and treatment with phenylphosphonic dichloride, which afforded 4,6-dichloro-1-phenethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **70**. Subsequent arylation with 2-(tributylstannyl)furan in the presence of bis(triphenylphospine)palladium(II) dichloride afforded compound **71**. The 6-Cl of **71** underwent displacement by primary and secondary amines to afford **10** and **11**.

Scheme 3 outlines the synthesis of compounds **27**–**33**. 4-Chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-ylamine **68** was treated with sodium hydride, followed by 1-bromo-

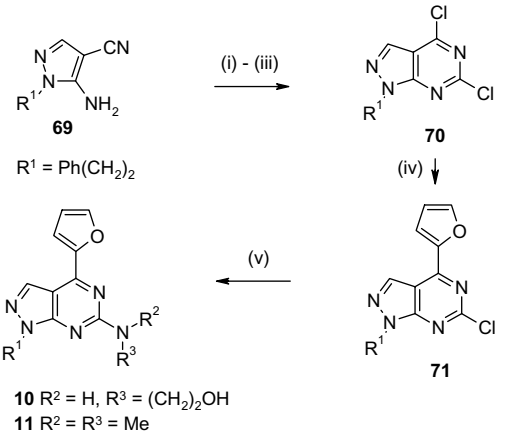
Table 4. Comparison of in vitro binding activity and in vivo activity of pyrazolo[3,4-*d*]pyrmidines **2** and **23**, and pyrrolo[2,3-*d*]pyrimidines **66** and **67**



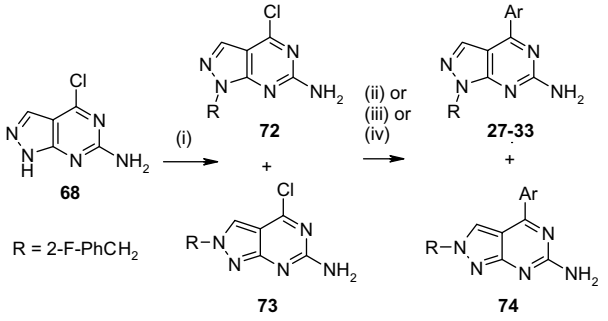
Compound	R	X	A_{2A} K_i (nM)[8]	A_1 K_i (nM)[8]	HaloLMA activity[4–6]
2	H	N	48	647	Active
66	H	CH	242	2765	Active
23	2-Fluorobenzyl	N	4	264	Active
67	2-Fluorobenzyl	CH	16	709	—



Scheme 1. Reagents and conditions: (i) Boc_2O, Et_3N, DMAP, DMF, rt, 23%; (ii) 2-(tributylstannyl)furan, $PdCl_2(PPh_3)_2$, DMF, rt, 99%; (iii) $Me_2NH_{(aq)}$ (40% w/v), Δ, 70%; (iv) NaH, DMF, 0 °C; RCH_2Br, rt, 34–100%; (for **20** and **21**) $SnCl_2{\cdot}2H_2O$, concd HCl, EtOH, 50–70 °C, 94%; (for **22**) 1 M $NaOH_{(aq)}$, MeOH, Δ, 95%; (v) $PhCH_2NCO$, DMAP, DMF, rt, 24%.



Scheme 2. Reagents and conditions: (i) 9 M $H_2SO_{4(aq)}$, 60 °C, 47%; (ii) $CO(NH_2)_2$, 180 °C, quant.; (iii) $PhPOCl_2$, 165 °C, 23%; (iv) 2-(tributylstannyl)furan, $PdCl_2(PPh_3)_2$, DMF, rt, 99%; (v) (for **10**) $HO(CH_2)_2NH_2$, NMP, 100 °C, 57%; (for **11**) $Me_2NH_{(aq)}$ (40% w/v), *i*-PrOH, Δ, 67%.



Scheme 3. Reagents and conditions: (i) NaH, DMF, 0 °C; 1-bromomethyl-2-fluorobenzene, 0 °C to rt, 34%; (ii) (for **27**), $ArB(OH)_2$, $Pd(PPh_3)_4$, satd $NaHCO_{3(aq)}$, THF, Δ, 20%; (iii) (for **28**) 2-bromopyridine, *n*-BuLi, THF, −78 °C; 1 M $ZnCl_2$ in Et_2O, −78 °C to rt; **72** and **73** (as 1:1 mixture), $Pd(PPh_3)_4$, Δ, 19%; (iv) (for **30** and **32**) ArH, *n*-BuLi, THF, −78 °C; 1 M $ZnCl_2$ in Et_2O, −78 °C to rt; **72** and **73** (1:1 mixture), $Pd(PPh_3)_4$, Δ, 19–21%; (iv) (for **29**, **31** and **33**) *N*-SEM-ArH, *n*-BuLi, THF, −78 °C; 1 M $ZnCl_2$ in Et_2O, −78 °C to rt; **72** and **73** (1:1 mixture), $Pd(PPh_3)_4$, Δ, 2 h, 31%; 4 M HCl in 1,4-dioxane, rt, 23–40%.

methyl-2-fluorobenzene, to give a 1:1 mixture of N1 and N2 benzylated derivatives **72** and **73**. This mixture then underwent a range of Suzuki couplings with an aryl boronic acid or Negishi couplings with an aryl zinc reagent. The desired N1-benzylated regiosomers **27**–**33** were then isolated from the undesired N2-benzylated regioisomers of type **74**.[15]

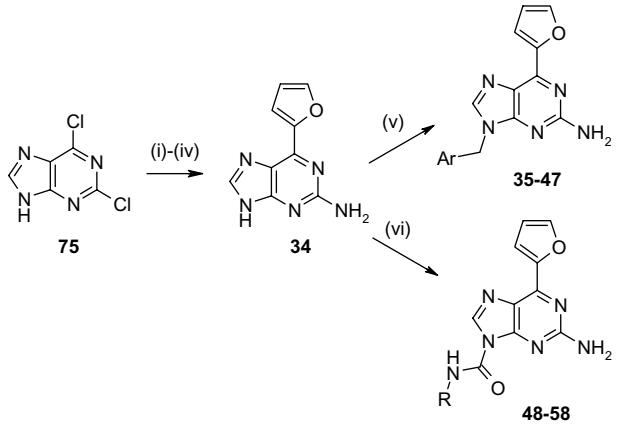
6-Aryl purines were prepared as follows.[12] 2,6-Dichloropurine **75**[17] underwent Boc-protection followed by 6-arylation with 2-(tributylstannyl)furan (Scheme 4). Displacement of the 2-Cl with veratrylamine followed by TFA deprotection afforded compound **34**. Alkylation of **34** with a benzyl bromide afforded compounds **35**–**41** and **44**–**47**. Reduction of the 3-nitrobenzyl analogue **40** with tin(II) chloride afforded the aniline **42**, and basic hydrolysis of the methyl ester **39** afforded the carboxylic acid **43**. Treatment of compound **34** with the appropriate isocyanate afforded ureas **48**–**58**.

THP-protection of 2-amino-6-chloropurine **76**, followed by Suzuki or Stille arylation and then deprotection, afforded compounds of type **77**, which underwent treatment with benzyl isocyanate to afford ureas **59**–**61** (Scheme 5).

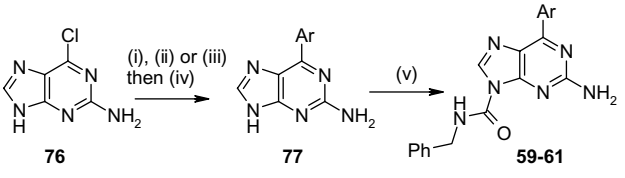
2,6-Dichloropurine **75** underwent Boc- or SEM-protection and subsequent arylation with 2-(tributylstannyl)furan to give intermediates **78** or **79** (Scheme 6). 2-Chloro displacement, followed by deprotection and subsequent treatment with benzyl isocyanate afforded **62**–**65**.

4-(Furan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-2-ylamines **66** and **67** were prepared as follows (Scheme 7).[18] 2,4-Dichloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **80**[19] underwent Boc-protection and then 4-arylation with 2-(tributylstannyl)furan to give compound **81**. Displacement of the 2-chloro substituent of **81** with veratrylamine, followed by treatment with trifluoracetic acid, gave compound **66**. Compound **67** could be prepared by benzylation of **80**, followed by arylation to give intermediate **82** and then subsequent amine displacement and treatment with trifluoracetic acid.

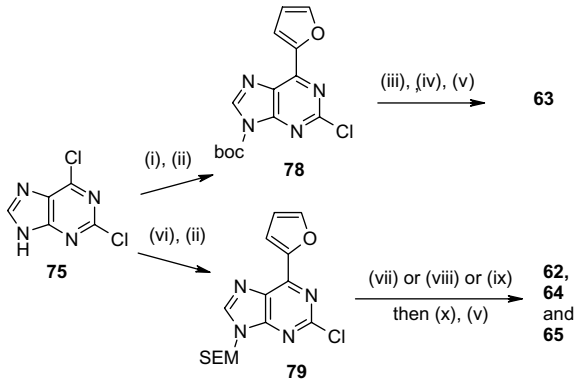
In conclusion, a series of pyrazolo[3,4-*d*]pyrimidine, pyrrolo[2,3-*d*]pyrimidine and 6-arylpurine adenosine A_{2A} antagonists was described. Many examples were highly



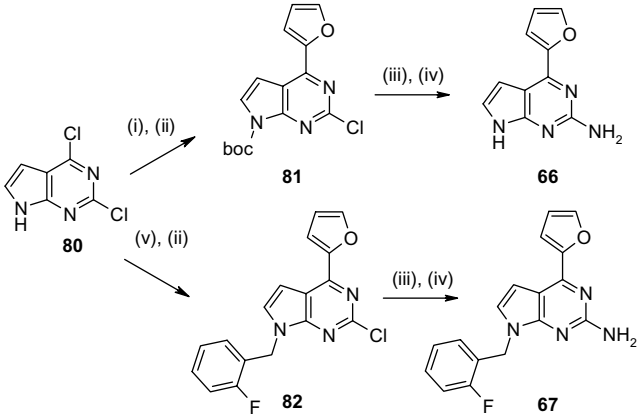
Scheme 4. Reagents and conditions: (i) Boc_2O, Et_3N, DMAP, THF, rt, quant.; (ii) 2-(tributylstannyl)furan, $PdCl_2(PPh_3)_2$, DMF, 96%; (iii) veratrylamine, NMP, 120 °C, 50%; (iv) CF_3CO_2H, 60 °C, 57%; (v) NaH, DMF, 0 °C; $ArCH_2Br$, 20–88%; (for **42** only) $SnCl_2{\cdot}2H_2O$, concd HCl, EtOH, 50 °C, 22%; (for **43** only) 1 M $NaOH_{(aq)}$, MeOH, Δ, 95%; (vi) RNCO, DMAP, DMF, 65 °C, 28–97%.



Scheme 5. Reagents and conditions: (i) 3,4-dihydro-2*H*-pyran, 1 M HCl in Et_2O, DMF, 60 °C, 78%; (ii) (for **59** and **60**) $ArB(OH)_2$, $Pd(PPh_3)_4$, satd $NaHCO_{3(aq)}$, THF, Δ, 51–72%; (iii) (for **61**) $ArSnBu_3$, $Pd(PPh_3)_2Cl_2$, DMF, 80 °C, 75%; (iv) Amberlyst, MeOH, Δ; NH_3, MeOH, rt, 72–89%; (v) $PhCH_2NCO$, DMAP, DMF, 70 °C, 76–87%.



Scheme 6. Reagents and conditions: (i) Boc_2O, Et_3N, DMAP, THF, rt, quant.; (ii) 2-(tributylstannyl)furan, $PdCl_2(PPh_3)_2$, DMF, 96%; (iii) NaSMe, NMP, 110 °C, 61%; (iv) 4 M HCl in 1,4-dioxane, 1,4-dioxane, rt, 87%; (v) $PhCH_2NCO$, DMAP, THF, DMF, 35–82%; (vi) SEMCl, NaH, THF 0 °C to rt, 78%; (vii) (for **62**) MeONa, MeOH, Δ, 67%; (viii) (for **64**) $NHMe_2$, *i*-PrOH, Δ, 86%; (ix) (for **65**) Me_3Al, $Pd(PPh_3)_4$, $Cl(CH_2)_2Cl$, Δ, 30%; (x) 1 M TBAF in THF, THF, Δ, 43–76%.



Scheme 7. Reagents and conditions: (i) Boc_2O, Et_3N, DMAP, THF, rt, 52%; (ii) 2-(tributylstannyl)furan, $PdCl_2(PPh_3)_2$, DMF, rt, 61%; (iii) veratrylamine, NMP, 100 °C, 88%; (iv) CF_3CO_2H, 50 °C, 51%; (v) NaH, DMF, 0 °C; 1-bromomethyl-2-fluorobenzene, rt, 76%.

Table 5. Comparison of binding affinity and in vivo activity (following ip and po dosing) of selected 6-arylpurines

Compound	A_{2A} K_i (nM)[8]	A_1 K_i (nM)[8]	HaloLMA activity[4–6]	
			MED (mg/kg) ip	MED (mg/kg) po
34	261	4951	10	1
42	23	4027	10	30
53	1	28	≪30	30
54	2	170	<30	10
56	1	26	1	30

selective against the human A_1 receptor sub-type and showed efficacy in a mouse haloperidol-induced hypolocomotion model of Parkinson's disease, following ip administration. 6-Arylpurines **42**, **53**, **54** and **56** showed efficacy in this model following oral administration, but each had an MED greater than that for the parent purine **34** (Table 5). In comparison with **34**, the urea and benzyl derivatives are more lipophilic and, although rat PK studies showed good brain penetration, they had low oral bioavailability. Studies also showed that the urea side-chains were vulnerable to cleavage in vivo, and so these compounds were not progressed further. Subsequent work in this area will be disclosed in due course.

References and notes

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15. In ^{1}H NMR spectroscopic studies of compounds **3**–**8** and **12**–**33**, there was no nuclear Overhauser enhancement (nOe) of the signals pertaining to the protons of the benzyl substituent, following irradiation of the pyrazole 3-H. For compounds of type **74**, which were isolable during the synthesis of compounds **27**–**33**, nOe of the signal pertaining to the protons of the benzylic methylene group was observed upon irradiation of the pyrazole 3-H, thus confirming N2 benzyl substitution in compounds of type **74** and, indirectly, confirming that benzylation had occurred at N1 of **3**–**8** and **12**–**33**. Comparison of ^{1}H and ^{13}C NMR data for compounds **3**–**8** and **12**–**33** and that for compounds **10** and **11**, which were prepared from the unambiguously N1-substituted pyrazole **69**, further supported the structural assignment.
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