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# Discovery and optimization of potent and selective functional antagonists of the human adenosine $A_{2B}$ receptor

Simon T. Bedford [a], Karen R. Benwell [a], Teresa Brooks [a], Ijen Chen [a], Mike Comer [b], Sarah Dugdale [b], Tim Haymes [b], Allan M. Jordan [a,*], Guy A. Kennett [b], Anthony R. Knight [b], Burkhard Klenke [b], Loic LeStrat [a], Angela Merrett [b], Anil Misra [b], Sean Lightowler [b], Anthony Padfield [b], Karine Poullennec [b], Mark Reece [b], Heather Simmonite [a], Melanie Wong [a], Ian A. Yule [b]

[a] Vernalis (R&D) Ltd, Granta Park, Cambridge, CB21 6GB, UK
[b] Vernalis (R&D) Ltd, 613 Reading Road, Winnersh, Wokingham, RG41 5UA, UK

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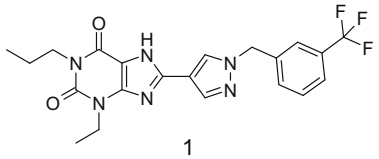
ABSTRACT

We herein report the discovery of a novel class of antagonists of the human adenosine A2B receptor. This low molecular weight scaffold has been optimized to offer derivatives with potential utility for the alleviation of conditions associated with this receptor subtype, such as nociception, diabetes, asthma and COPD. Furthermore, preliminary pharmacokinetic analysis has revealed compounds with profiles suitable for either inhaled or systemic routes of administration.



The human adenosine receptor is a G-protein coupled receptor which is delineated into four subtypes, namely the $A_1$, $A_{2A}$, $A_{2B}$ and $A_3$ receptors. Whilst the therapeutic roles of modulators of the $A_1$, $A_{2A}$ and $A_3$ receptor subtypes are comparatively well understood,[1] the role of such compounds targeting the $A_{2B}$ receptor in human disease is less clear. The limited information obtained thus far indicates that the receptor may play a role in diverse indications such as nociception,[2] diabetes,[3] cancer[4] and respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD).[5] However, our present understanding of the true role of the $A_{2B}$ receptor is complicated somewhat by the conflicting roles of the other adenosine receptor subtypes in these conditions. This lack of understanding is predominantly due to the paucity of low molecular weight adenosine $A_{2B}$ receptor antagonists which display appropriate functional subtype selectivity and pharmacokinetic properties.

Whilst this situation is gradually improving,[6] there is a need for compounds with appropriate properties which would allow a more thorough understanding of the implications of selective adenosine $A_{2B}$ receptor antagonism. The most advanced $A_{2B}$ antagonist in this respect appears to be the xanthine-based derivative CVT-6883 **1**,[7] which recently completed a Phase I clinical trial as a potential treatment for pulmonary disease.[8]



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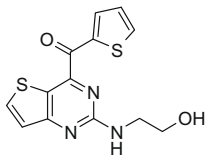
However, in our hands, this derivative suffered from a low volume of distribution and poor tissue penetration, limiting its application as a pharmacological tool. Alternate small molecule derivatives with appropriate physicochemical properties are therefore much needed to fully elucidate the potential therapeutic utility of this receptor subtype.

We recently described a series of thienopyrimidine derivatives which demonstrated antagonistic activity at the human adenosine $A_{2A}$ receptor. Some of these analogues, such as **2**, demonstrated moderate activity in models of Parkinson's disease.[9]



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* Corresponding author at present address: Paterson Institute for Cancer Research, Wilmslow Road, Manchester, M20 4BX, UK. Tel.: +44 (0) 161 446 8079; fax: +44 (0) 161 446 3109.
*E-mail address:* ajordan@picr.man.ac.uk (A.M. Jordan).

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In our routine binding protocols, many of these derivatives displayed good subtype selectivity against the other adenosine receptors, including the $A_{2B}$ receptor subtype. However, screening these derivatives against the four human adenosine receptors in a fluorometric calcium mobilization assay[10] demonstrated that a small subset displayed moderate functional antagonism of the adenosine $A_{2B}$ receptor and, in contrast to their binding affinities, were roughly equipotent when compared to their functional antagonism of the $A_{2A}$ receptor. These derivatives generally contained a small alkyl or alkylamino substituent at C-2 and to fully investigate the utility of this effect at the $A_{2B}$ receptor, a series of derivatives were prepared. Data from a selection of these compounds is shown in Table 1.

Small alkyl and alkylamino moieties gave only moderate activity against the $A_{2B}$ receptor and generally failed to yield notable improvements in receptor subtype selectivity. The only notable exception to this was the α-methyl benzylamine derivative **10**, which gave a considerable increase in potency compared to the parent **9**, alongside a modest 2.5-fold selectivity over the $A_{2A}$ receptor. However, whilst most benzylamine derivatives showed a loss of potency (data not shown), the introduction of a more electron deficient pyridyl group gave a considerable increase in potency and, in the case of **12**, almost 20-fold functional selectivity over the $A_{2A}$ receptor subtype. Both N-methylation (**17**) and conversion of the pyridylmethylamine to the corresponding nicotinamide (**14**) were detrimental to activity, as was homologation of the alkyl chain (**15, 16**). However, the combination of the α-methyl substituent and the pyridyl moiety (to give **18** and **19**) gave a useful 2–3-fold increase in potency, albeit with a small reduction in subtype selectivity.

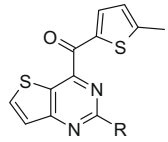
In parallel with these studies, the nature of the aromatic moiety at C-4 was also investigated. Data for representative derivatives are given in Table 2. Whilst a variety of heterocyclic and phenyl ring systems yielded moderate activity, only the 3-pyridyl derivative **29**, the 5-thiazoloyl **25** and the 5-methyl-2-thienyl derivative **12** maintained some selectivity against the adenosine $A_{2A}$ receptor.

However, the derivatives described in Tables 1 and 2 suffered somewhat with poor physicochemical properties, particularly regarding their aqueous solubility, which hampered further studies. In an attempt to alleviate this, we investigated the placement of potentially solubilizing moieties around the core thienopyrimidine scaffold. Substitution of the 7-position of the thienopyrimidine proved detrimental to functional antagonism of the $A_{2B}$ receptor, whilst offering no improvement in receptor subtype selectivity (data not shown). However, considerably better results were observed with substitution at the adjacent 6-position (Table 3). Surprisingly in this case, the use of the 5-methyl-2-thieno moiety at C-4, which had previously given a helpful increase in selectivity against the $A_{2A}$ receptor, now had the opposite effect, diminishing efficacy at the $A_{2B}$ receptor and restoring efficacy at the $A_{2A}$ subtype. We therefore returned to the 2-thienyl moiety, which restored both potency and some degree of selectivity. However, this data highlighted the delicate nature of the observed selectivities between the two receptor subtypes.

Our findings demonstrated that only small substituents were tolerated at the C-6 position. Interestingly, the introduction of amino moieties not only gave a small increase in solubility but also yielded a considerable increase in selectivity against the $A_{2A}$ receptor, with the methylamino derivative **33** now displaying both single-digit nanomolar antagonist efficacy and an almost 300-fold difference in functional activity at the two receptor subtypes.

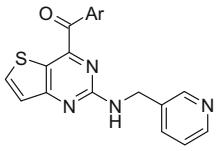
Whilst these findings were of interest, limited solubility was still an issue with these derivatives. We believed this was attributable to the high degree of crystallinity and planarity of these com-

**Table 1**
Functional receptor antagonism data for initial thienopyrimidines[11]



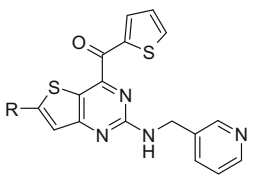
| Compound | R | $A_{2B}$ $IC_{50}$ (nM) | $A_{2A}$ $IC_{50}$ (nM) |
|---|---|---|---|
| **3** | –H | 5376 | 6685 |
| **4** | –Me | >10,000 | 7847 |
| **5** | –Et | 3672 | 3852 |
| **6** | $-NH_2$ | 758 | 220 |
| **7** | –NHEt | 1259 | 126 |
| **8** | $-NHCH_2$-cyclohexyl | >10,000 | >10,000 |
| **9** | –NHBn | 5577 | 7146 |
| **10** | $-NHCH(CH_3)Ph$ | 414 | 1077 |
| **11** | $-NHCH_2$(2-pyridyl) | 43 | 186 |
| **12** | $-NHCH_2$(3-pyridyl) | 55 | 990 |
| **13** | $-NHCH_2$(6-pyrimidinyl) | 92 | 116 |
| **14** | –NHCO(3-pyridyl) | 287 | 161 |
| **15** | $-NH(CH_2)_2$(2-pyridyl) | 944 | 351 |
| **16** | $-NH(CH_2)_2$(3-pyridyl) | 450 | 177 |
| **17** | $-NMeCH_2$(3-pyridyl) | 4142 | 2271 |
| **18** | –NHCH(Me)(2-pyridyl) | 19 | 118 |
| **19** | –NHCH(Me)(3-pyridyl) | 17 | 99 |

**Table 2**
Functional receptor antagonism data for C-4 ketoaryl derivatives[11]



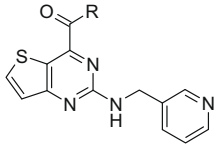
| Compound | Ar | $A_{2B}$ $IC_{50}$ (nM) | $A_{2A}$ $IC_{50}$ (nM) |
|---|---|---|---|
| **12** | 5-Methyl-2-thienyl | 55 | 990 |
| **20** | 5-Chloro-2-thienyl | 487 | 1541 |
| **21** | 5-Methyl-2-furyl | 468 | 1252 |
| **22** | 2-Thienyl | 18 | 51 |
| **23** | 3-Thienyl | 148 | 405 |
| **24** | 2-Thiazolyl | 176 | 732 |
| **25** | 5-Thiazolyl | 148 | 1715 |
| **26** | Phenyl | 511 | 1619 |
| **27** | 4-Methylphenyl | 215 | 442 |
| **28** | 4-Methoxyphenyl | 1295 | 637 |
| **29** | 3-Pyridyl | 109 | 1168 |
| **30** | 4-Pyridyl | 869 | 1942 |

**Table 3**
Functional receptor antagonism data for C-6 substituents[11]



| Compound | R | $A_{2B}$ $IC_{50}$ (nM) | $A_{2A}$ $IC_{50}$ (nM) |
|---|---|---|---|
| **22** | –H | 18 | 51 |
| **31** | –Cl | 16 | 62 |
| **32** | $-NH_2$ | 32 | >10,000 |
| **33** | –NHMe | 3.5 | 965 |
| **34** | –NHEt | 19 | 2485 |
| **35** | $-NMe_2$ | 39 | 1417 |

**Table 4**
Functional receptor antagonism data for 4-amide derivatives[11]



| Compound | R | $A_{2B}$ $IC_{50}$ (nM) | $A_{2A}$ $IC_{50}$ (nM) |
|---|---|---|---|
| **36** | –NHMe | 495 | 7107 |
| **37** | –NHEt | 120 | 2516 |
| **38** | –NH$^{i}$Pr | 309 | 2610 |
| **39** | –NH$^{c}$Pr | 256 | 710 |
| **40** | –NH$^{c}$Hexyl | 571 | 3093 |
| **41** | Pyrrolidine | 189 | 6136 |

pounds, as evidenced by their high melting points.[12] (For example, **33** has a melting point in excess of 240 °C.)

In an effort to alleviate this issue, we investigated the effect of disrupting the co-planar arrangement of the biaryl ketone system. Alkyl, aminoalkyl and aminoacyl derivatives at C-4 all proved highly detrimental to antagonistic efficacy (data not shown), indicating a requirement for the keto-moiety at this position. However, reversal of the amide moiety of the aminoacyl derivatives to maintain the position of the aryl carbonyl led to a series of moderately potent and selective amide derivates. A selection of these amides are shown in Table 4.

Whilst the *N*-ethyl derivative **37** displayed the best potency, the pyrrolidine derivative **41** offered the best overall balance of potency and selectivity, being 30-fold more efficacious at the $A_{2B}$ receptor compared to the $A_{2A}$ receptor. More importantly, this simple replacement displayed a marked increase in measured aqueous solubility, in excess of 500 μM at both pH 1 and pH 6.8, compared to 14.5 μM for compound **12** at pH 1.

Having previously observed a useful increase in selectivity upon incorporating an α-methyl moiety in earlier derivatives, we investigated whether the selectivity of **41** could be further improved in a similar way. As detailed in Table 5, incorporation of this moiety to give the racemic compound **42** gave a 15-fold increase in potency and a corresponding sixfold increase in selectivity. Separation of the enantiomers of **42** indicated that the (*R*)-isomer **43** was essentially devoid of efficacy at the $A_{2B}$ receptor, with most activity residing in the (*S*)-isomer **44** (Table 5).

Given the interesting data obtained so far for both **44** and **33**, further studies were undertaken to assess in more detail the overall profile of these derivatives.

Though only displaying moderate 26-fold selectivity against the $A_{2A}$ receptor, **44** demonstrated good selectivity against both the $A_1$ and $A_3$ receptor subtypes, with functional selectivities greater than 500-fold in both cases. The solubility of this compound offered a reasonable pharmacokinetic profile after oral dosing in rats, with a $t_{1/2}$ of 2.3 h and an oral bio-availability of 84%. Whilst moderate clearance was observed (2.6 L/h/kg), the volume of distribution was reasonable, at 3.9 L/kg in rats. Furthermore, **44** displayed good cellular permeability in a Caco-2 assay of 33 cm/s × $10^6$ and moderate (85%) binding to human plasma proteins. The compound also showed no adverse effects in a hERG patch clamp assay at 30 μM and a cell panel screen demonstrated no cellular toxicity at 40 μM in a range of both normal and tumor cell lines. These tolerability studies were also supported by a micro-Ames study, which observed no toxicity at 100 μM in two bacterial strains, ±rat liver S9 fraction.[13] Pleasingly, the compound also showed no notable effects in an Irwin behavioral study,[14] with no evidence of $A_{2A}$ receptor mediated effects (such as alteration of locomotor activity) after oral dosing at 50 mg $kg^{-1}$ in mice.[15]

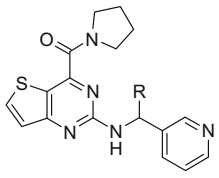
Although somewhat hindered by its limiting aqueous solubility, **33** demonstrated strong antagonism of the $A_{2B}$ receptor, though selectivity against the other human adenosine receptors was diminished compared to **44**. Despite greater than 400-fold functional selectivity against the $A_{2A}$ receptor, selectivities against the $A_1$ and $A_3$ subtypes were somewhat diminished, at 85-fold and 20-fold, respectively.

A more detailed examination of the pharmacokinetics of **33** revealed poor oral bio-availability of just 2% and a short half-life in rats of 0.93 h after iv dosing. Though these properties preclude oral dosing, when coupled with the high melting point of the solid, they may make the compound appropriate for an inhaled route of administration. Furthermore, given the compound displays a moderate volume of distribution of 2.2 L/kg, high human plasma protein binding, moderate clearance of 1.7 L/h/kg and rapid elimination, **33** would seem to be ideally suited for an inhaled route of administration and would be expected to display minimal levels of systemic exposure.

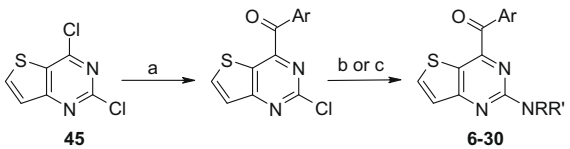
The synthesis of the compounds employed in this study is described below.[16,17] Compounds **3**–**5** were synthesized as previously described.[9] Derivatives **6**–**30** were prepared from the known dichloropyrimidine **45**.[9] An *Umpolung* coupling of this core with an aldehyde in the presence of *N*,*N*-dimethylimidazolium iodide[18] gave the corresponding mono-chloro scaffolds which were converted to the desired derivatives either by refluxing with the corresponding amine or, in the case of the amide **14**, via a Buchwald coupling (Scheme 1).

Thienopyrimidines bearing a substituent at C-6 were prepared in a similar way, from the trichlorothienopyrimidine scaffold **49** (Scheme 2). Nitration of dione **4** gave a mixture of 6- and 7-mono nitrated products, which were readily separated. Treatment of **8** with $PhPOCl_2$ not only introduced the 2,4-dichloro substitution but simultaneously effected the ipso nitro-chloro exchange at the C-6 position providing the trichlorinated scaffold **9** in good yield. Exploiting the differential reactivity of the three chloro moieties allowed stepwise installation of the keto-aryl moiety, followed by introduction of the 3-picolylamine side chain at C-2 to give **31**.

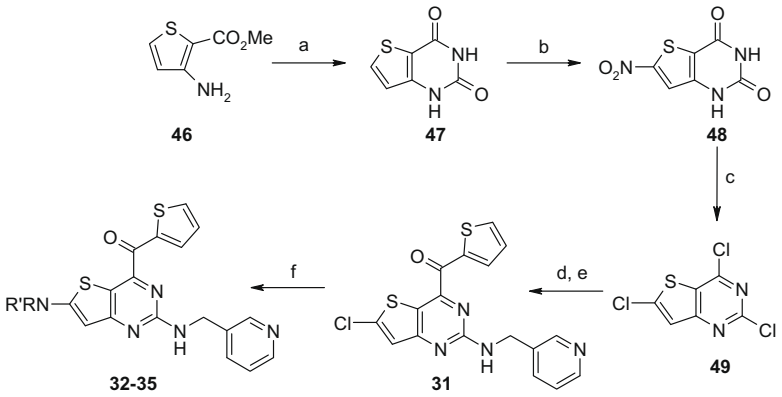
**Table 5**
Functional receptor antagonism data for the optimization of the C-4 amide scaffold[11]



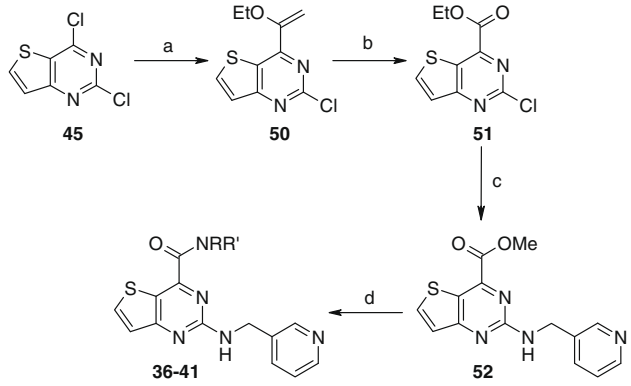
| Compound | R | $A_{2B}$ $IC_{50}$ (nM) | $A_{2A}$ $IC_{50}$ (nM) |
|---|---|---|---|
| **41** | H | 189 | 6136 |
| **42** | *rac*-Me | 13 | 2347 |
| **43** | (*R*)-Me | 3073 | 6760 |
| **44** | (*S*)-Me | 18 | 468 |




**Scheme 1.** Reagents and conditions: (a) aryl-2-carboxaldehyde, *N*,*N*-dimethylimidazolium iodide, NaH, THF, reflux, 5 h, 33–83%; (b) (for compounds **3**–**13** and **15**–**30**) NHRR', EtOH, reflux, 18 h, 8–80%; (c) (For amide compd **14**), nicotinamide, $NaO^{t}Bu$, $Pd(OAc)_2$, xantphos, 1,4-dioxane, water, reflux, 24 h, 44%.



**Scheme 2.** Reagents and conditions: (a) urea, 180 °C, 5 h, 94%; (b) $HNO_3$, $H_2SO_4$, rt, 20 min, 61% (as a 2:1 mixture of the 6- and 7-regioisomers); (c) $PhPOCl_2$, 180 °C, 4 h, 45%; (d) thiophene-2-carboxaldehyde, *N*,*N*-dimethylimidazolium iodide, NaH, THF, reflux, 3 h, 72%; (e) 3-picolylamine, *n*-BuOH, 100 °C, 2 h, 38%; (f) amine, DMA, sealed tube, 150 °C, 1 h, 10–68%.



**Scheme 3.** Reagents and conditions: (a) (1-ethoxyvinyl)-tributylstannane, $K_2CO_3$, $PdCl_2(PPh_3)_2$, 1,4-dioxane, 100 °C, 30 min, 65%; (b) $NaIO_4$, $KMnO_4$, 1,4-dioxane, water, 4 h, 54%; (c) (i) 3-picolylamine, NMP, 130 °C, 6 h; (ii) CHCl, 100 °C, 14 h; (iii) $SOCl_2$, MeOH, 60 °C, 2 h, 57% over three steps; (d) NHRR′, 1,4-dioxane, reflux, 1 h, 7–88%.

More forcing conditions were then required to install the desired functionality at the C-6 position to yield derivatives **32**–**35**.

Preparation of the C-4 amide derivatives **36**–**44** was somewhat less facile. A Stille coupling introduced an ethoxyvinyl moiety at C-4 to yield **50**, which could be oxidized to the corresponding ester **51** under modified Lemieux conditions with catalytic potassium permanganate and sodium periodate as re-oxidant.[19] Introduction of the 3-picolylamine side chain at C-2 gave concomitant, partial formation of the amide at C-4, via displacement of ethoxide. This necessitated hydrolysis of the amide and re-esterification of the resultant acid with thionyl chloride and methanol to give **52**. Though slightly inefficient, efforts to circumvent this issue were unsuccessful. However, this process could be performed without intermediate purification and proceeded in reasonable overall yield. Finally, formation of the C-4 amides by refluxing with the appropriate amines yielded the desired derivatives **36**–**41**.

The racemic derivative 42 and the single enantiomers 43 and 44 described in Table 5 were also prepared as described in Scheme 3, employing racemic 2-(3-pyridyl)ethylamine in step (c), followed by resolution by chiral HPLC. The stereochemical identity of each isomer was later confirmed by repeating the synthesis on a small scale using the known enantiopure amines.[20]

In summary, we report herein the discovery of a novel class of adenosine $A_{2B}$ antagonists. These low molecular weight compounds display promising functional activity and selectivity against the other subtypes of adenosine receptors. Their differing physicochemical profiles offer the possibility of administration via inhalation or oral, systemic dosing and, as such, may offer potential therapeutic options for the treatment of respiratory disorders such as asthma or COPD. Moreover, these agents may offer useful pharmacological tools to further elucidate the role of the adenosine $A_{2B}$ receptor in human disease conditions.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.08.040.

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