Bioorganic & Medicinal Chemistry 17 (2009) 6590–6605

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Antagonists of the human A_{2A} receptor. Part 6: Further optimization of pyrimidine-4-carboxamides

Roger J. Gillespie [a], Samantha J. Bamford [a], Alex Clay [b], Suneel Gaur [a], Tim Haymes [a], Philip S. Jackson [b], Allan M. Jordan [b,*], Burkhard Klenke [a], Stefania Leonardi [a], Jeanette Liu [a], Howard L. Mansell [a], Sean Ng [a], Mona Saadi [a], Heather Simmonite [b], Gemma C. Stratton [a], Richard S. Todd [a], Douglas S. Williamson [b], Ian A. Yule [a]

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

ARTICLE INFO

Article history:
Received 14 May 2009
Revised 28 July 2009
Accepted 31 July 2009
Available online 5 August 2009

Keywords:
Adenosine receptor
Parkinson's disease
Pyrimidine carboxamide

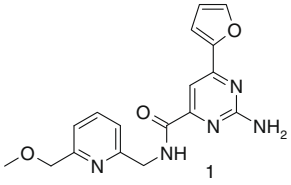
ABSTRACT

Antagonists of the human A_{2A} receptor have been reported to have potential therapeutic benefit in the alleviation of the symptoms associated with neurodegenerative movement disorders such as Parkinson's disease. As part of our efforts to discover potent and selective antagonists of this receptor, we herein describe the detailed optimization and structure–activity relationships of a series of pyrimidine-4-carboxamides. These optimized derivatives display desirable physiochemical and pharmacokinetic profiles, which have led to promising oral activity in clinically relevant models of Parkinson's disease.

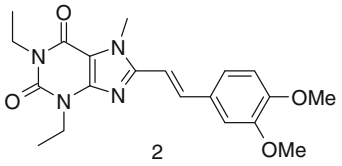
1. Introduction

The human adenosine receptor is a G-protein coupled receptor which is delineated into four distinct sub-types, designated A_1, A_{2A}, A_{2B} and A_3. The adenosine A_{2A} receptor plays an important role in regulating smooth and well co-ordinated movement, in part by moderating the activity of dopamine sensitive neurons in the striatum.[1] Degradation of these dopaminergic neurons gives rise to Parkinson's disease, in which the imbalance of neurotransmission results in the symptoms commonly associated with this condition, such as muscle rigidity, resting tremor and postural instability. There is strong, mounting evidence that adenosine A_{2A} receptor antagonists may provide a novel point of therapeutic intervention for Parkinson's disease by increasing the sensitivity of the dopaminergic neurons to the residual levels of striatal dopamine and restoring balance to the systems controlling muscle movement.[2]

We recently reported the discovery that pyrimidine carboxamide derivatives, typified by **1**, are potent antagonists of the human adenosine A_{2A} receptor subtype and possess good physiochemical and pharmacokinetic profiles.[3] With a K_i against the human A_{2A} receptor of 1.7 nM and a 25-fold selectivity against the A_1 receptor, compound **1** compares favourably with the clinically investigated KW-6002 **2**, which has recently completed Phase III clinical trials for the alleviation of symptoms associated with Parkinson's disease,[4,5] though **2** only met its primary end-point in one of three pivotal trials.[6]



1



2

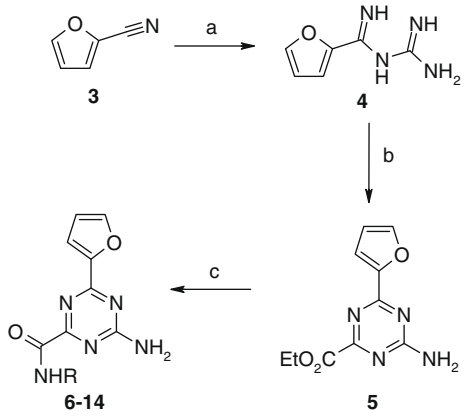
Herein, we report the further evaluation and elaboration of this interesting, highly ligand efficient lead.[7]

2. Results and discussion

The first modifications of **1** investigated were atom replacement analogues of the pyrimidine scaffold itself. We had previously performed detailed investigations into bicyclic scaffolds as adenosine receptor antagonists,[8–11] and we therefore wished to retain the monocyclic nature of our scaffold at this time. Our initial targets were the triazine class of compounds, exemplified by derivatives **6**–**14**, below. These were prepared from the commercial 2-furonitrile **3** as described in Scheme 1. Treatment with guanidine gave the intermediate **4**, albeit in low overall yield, which readily cyclized with diethyl oxalate to yield the key ethyl 2-furyltriazine carboxylate **5**. The desired amides **6**–**14** were then prepared via direct amidation.

* Corresponding author. Tel.: +44 01223 895555; fax: +44 01223 895556.
E-mail address: a.jordan@vernalis.com (A.M. Jordan).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.07.078



Scheme 1. Synthesis of 2-amino-6-furyl-triazine-4-carboxamides. Reagents and conditions: (a) guanidine HCl, NaOMe, MeOH, 30 °C, 8 h, 20%; (b) diethyl oxalate, NEt_3, reflux, 3 h, 75%; (c) amine, EtOH, reflux o/n, 34–75%.

Our initial choice of targets was guided by our earlier work in this series,[3] allowing a direct comparison of the two scaffolds. Data for these compounds are presented in Table 1.

The data in Table 1 demonstrated that *ortho*- and *meta*-substituted phenyl and pyridyl moieties gave potent A_{2A} antagonists with reasonable selectivity. A preference for 2- and 3-pyridyl over the 4-pyridyl conjoiner was also apparent. These general trends mirrored our earlier findings, though we noted that in almost all cases both potency and selectivity were diminished compared to our original pyrimidine carboxamide derivatives (e.g., **14** demonstrates a fivefold reduction in potency compared to the corresponding pyrimidine **1**). The only exception to this was **13** which, though it was roughly twofold more selective against the adenosine A_1 receptor than the corresponding aminopyrimidine, was also almost sevenfold less potent.

Given that increasing the nitrogen count of the scaffold had been detrimental to both potency and selectivity, we postulated that perhaps the corresponding pyridine scaffold may display an improved profile. To this end, we prepared **15**, the direct analogue of our most selective triazine, **13**.

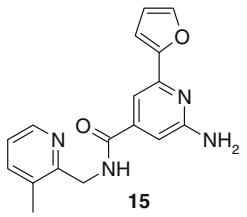
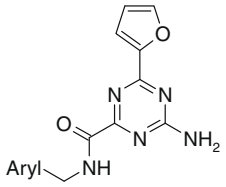


Table 1
Binding affinity data for triazine-4-carboxamide derivatives against human adenosine A_{2A} and A_1 receptors[22]



Compound	Aryl	A_{2A} K_i (nM)	A_1 K_i (nM)
6	2-Cl-Phenyl	4.9	41
7	2-Me-Phenyl	12.3	105
8	3-Me-Phenyl	7.5	103
9	2-OMe-Phenyl	6.5	202
10	2-Pyridyl	25	223
11	3-Pyridyl	88	409
12	4-Pyridyl	420	586
13	(3′-Methyl)-2-pyridyl	18.6	1112
14	(6′-Methoxymethyl)-2-pyridyl	8.8	595

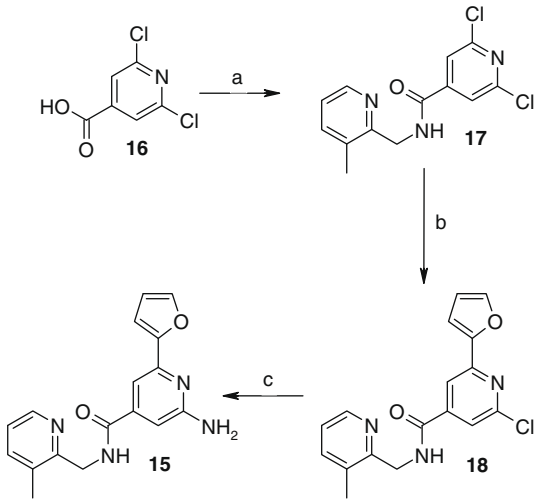
Preparation of this compound is detailed in Scheme 2. The amide **17** was formed from dichloroisonicotinic acid **16** using carbonyldiimidazole to effect the coupling. After Suzuki coupling with furan boronic acid to give the mono-arylated product **18**, the 2-chloro moiety was displaced with hydrazine and reduced with Raney Nickel to give the desired aminopyridine carboxamide **15**.

As detailed in Table 2, the pyridyl derivative **15** bound to the A_{2A} receptor with a K_i of 126 nM, some sevenfold less potent than the corresponding triazine **13** and 45-fold less potent than the associated aminopyrimidine **19**. Selectivity was also rather poor, only displaying a mediocre sevenfold difference in binding affinity over the A_1 receptor. Given these findings, no further work on these alternate scaffolds was undertaken and our further efforts focused upon optimization of the substituents around the aminopyrimidine core itself.

We were aware that, in some cases, the incorporation of a furan moiety can hypothetically lead to a potential metabolic liability.[12] However, we were also acutely aware that this heterocycle appeared to be a privileged moiety for both potency and selectivity in human A_{2A} receptor antagonists.[13] We therefore wished to determine whether the 2-furyl functionality could be replaced with alternate groups and still retain both potency and high levels of selectivity against the other adenosine receptor subtypes (Table 3).

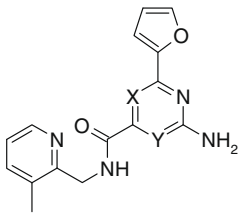
A series of around 20 aromatic and heteroaromatic derivatives were investigated as potential furan replacements, employing a limited subset of the two key 2-(aminomethyl)pyridine side chains found to be efficacious in our previous investigations. The synthesis of these compounds is detailed in Schemes 3–5 and data for a representative selection of these derivatives are presented in Table 3. The original furan compounds and corresponding 5-methylfuran derivatives were accessed from the commercial 2-amino-4,6-dichloropyrimidine **20**. Stille coupling selectively yielded the mono-arylated product **21**[14] and displacement of the chlorine at C-4 with sodium cyanide, followed by acidic hydrolysis, gave the key acid intermediate **23** which could be elaborated with a variety of amine substituents using solid-supported carbodiimide resin as the coupling agent.

Thiazole-containing derivatives were prepared as described in Scheme 4, from the appropriate commercial β-keto ester or by condensation of the appropriate 2-acetylthiazole with diethyl carbonate. Cyclization of this β-keto ester with guanidine yielded the



Scheme 2. Synthesis of 2-amino-6-furyl-pyridine-4-carboxamides. Reagents and conditions: (a) *N*,*N*′-carbonyldiimidazole, DMF, rt, 2 h then amine, rt, 3 h, 48%; (b) 2-furanboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, THF, reflux o/n, 31%; (c) hydrazine monohydrate, EtOH, 100 °C o/n then Raney Ni, H_2; (d) EtOH, rt, 3 h, 28%.

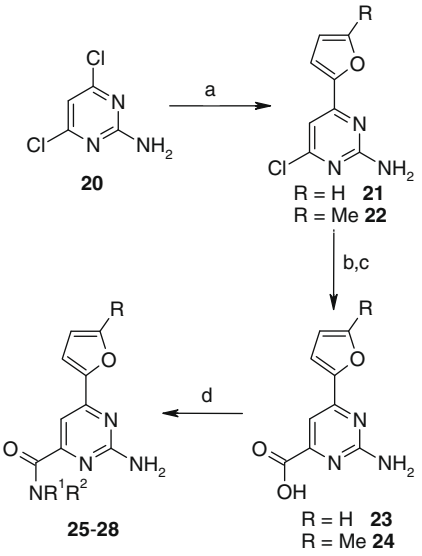
Table 2
Comparison of the binding affinities of the three scaffolds against human adenosine A_{2A} and A_1 receptors[12]



Compound	X	Y	A_{2A} K_i (nM)	A_1 K_i (nM)
15	CH	CH	126	921
19	CH	N	2.8	97
13	N	N	18.6	1112

corresponding 2-amino-4-hydroxypyrimidines **31** and **32**, which underwent chlorination with phosphorous oxychloride to give the 6-chloro derivatives **33** and **34**. This intermediate was converted to the desired carboxylic acid **35** and **36** by treatment with sodium cyanide and acidic hydrolysis, in a manner akin to that described in Scheme 3.

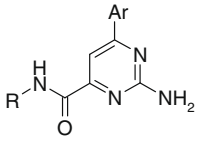
Non-heteroaromatic derivatives were accessed as detailed in Scheme 5, via a slightly shorter and more widely applicable route, from the known methyl-2-amino-6-hydroxypyrimidine-4-carboxylic acid ester **39**.[16] Cyclization of guanidine with sodium diethyloxaloacetate and esterification with methanol under acid catalysis gave the aminopyrimidine ester **39**. Chlorination of this intermediate proceeded smoothly to give the chloro ester **40**, but upon work-up generated a substantial quantity of the 2-amino-6-chloro-pyrimidine-4-carboxylic acid as a by-product, which

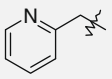
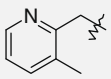


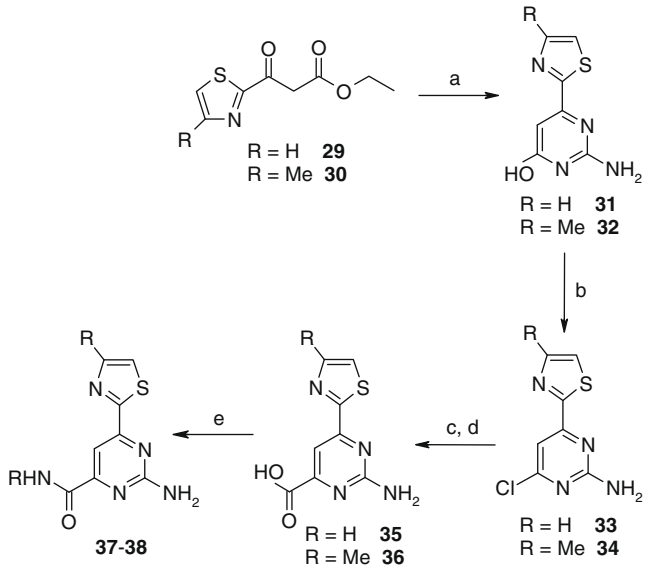
Scheme 3. Synthesis of 6-furylpyrimidines. Reagents and conditions: (a) Ar-$SnBu_3$, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 18 h, 57–63%; (b) NaCN, DABCO, DMSO, 6 days, rt, 10–77%; (c) H_2SO_4, rt, 2 h, 90%; (d) R^1R^2NH, PS-CDI, HOBt, DMF, rt, 24 h, 26–85%.

could be converted back to the 4-hydroxy ester **39** and recycled. Suzuki couplings with the desired boronic acids proceeded smoothly and the crude products from the coupling protocol were hydrolyzed to the corresponding carboxylic acids **41**–**56**, which could be isolated in acceptable purity simply by acidification of the aqueous liquors and filtration. Amine formation was effected in a parallel fashion by shaking overnight with hydroxybenzotria-

Table 3
Binding affinity data for furan replacement analogues against human adenosine A_{2A} and A_1 receptors[12]



Ar	R					
						
	Compound	A_{2A} K_i (nM)	A_1 K_i (nM)	Compound	A_{2A} K_i (nM)	A_1 K_i (nM)
2-Furyl	**25**	4.3	122	**26**	2.8	97
5-Me-2 Furyl	**27**	4	222	**28**	3	90
2-Thiazolyl		n/d		**37**	586	74
4-Me-2-thiazolyl	**38**	47	463		n/d	
Phenyl	**57**	14	66	**58**	6	38
2-F-phenyl	**59**	17	48	**60**	14	38
3-F-phenyl	**61**	18	38	**62**	9	31
2-Cl-phenyl	**63**	31	408	**64**	24	394
3-Cl-phenyl	**65**	31	40	**66**	23	56
2-Me-phenyl	**67**	49	1377	**68**	28	1208
3-Me-phenyl	**69**	18	67	**70**	9	94
4-Me-phenyl	**71**	36	118	**72**	16	83
2-MeO-phenyl	**73**	57	1242	**74**	30	720
3 MeO-phenyl	**75**	28	252	**76**	24	199
4-MeO-phenyl	**77**	153	478	**78**	155	276
2-Et-phenyl	**79**	92	>10,000	**80**	107	>10,000
2-EtO-phenyl	**81**	253	9171	**82**	107	7902
2-CN-phenyl	**83**	255	1670	**84**	123	1157
3-CN-phenyl	**85**	128	504	**86**	29	395
MeO-	**87**	3290	>10,000	**88**	2450	>10,000



Scheme 4. Synthesis of 6-thiazolylpyrimidines. Reagents and conditions: (a) guanidine carbonate, PhMe, EtOH, reflux, 40 h, 36%; (b) $POCl_3$, 120 °C, 3 h, 60%; (c) NaCN, DABCO, DMSO, 6 days, rt, 60–90%; (d) H_2SO_4, rt, 2 h, 90%; (e) R^1R^2NH, PS-CDI, HOBt, DMF, rt, 24 h, 14–60%.

zole, polymer-bound carbodiimide, DMAP and an excess of the desired amine. After filtration and concentration in vacuo, the desired amides (compounds **57**–**86**) were isolated by aqueous work-up, trituration from water and freeze-drying. The corresponding methoxy derivatives **87** and **88** were prepared in a similar manner, simply substituting the Suzuki coupling step for treatment with refluxing methanol.

In general, acceptable functionality around this region was limited. Though simple phenyl derivatives were tolerated without a considerable decrease in potency, selectivity across the majority of phenyl derivatives was greatly reduced. Only the *ortho*-methyl and *ortho*-methoxy derivatives maintained a reasonable degree of both potency and selectivity, though *meta*-substituents tended, in general, to be favoured in terms of absolute potency. Whilst the *ortho*-ethyl and *ortho*-ethoxy derivatives (compounds **79**–**82**) displayed reasonable to good selectivity against the A_1 receptor, potency against the A_{2A} receptor was diminished considerably.

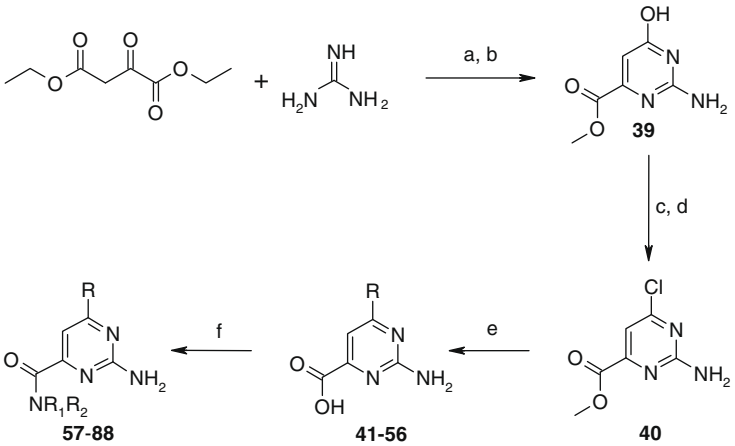
Previous reports had suggested that a simple methoxy derivative may be a potential mimic of the interactions afforded by the furan in other A_{2A} antagonists,[15–17] but this was found not to be the case in our particular series of derivatives (compounds **87** and **88**). Heteroaromatic furan replacements afforded a better overall profile in terms of potency and selectivity. Though the thiazole derivatives **37** and **38** showed some promise, the simple replacement of the furan with the 5-methylfuran gave compounds with similar levels of both potency and selectivity, whilst decreasing the potential risk of oxidative metabolism and covalent adduct formation.

The finding that the 2-ethylphenyl derivatives **79** and **80** and the 2-ethoxyphenyl derivatives **81** and **82** showed increased selectivity suggested to us that the steric encumbrance displayed by these derivatives may induce torsion around the biaryl linkage. We suggested that this conformational change may result in the observed enhancement of selectivity. However, we reasoned that steric encumbrance around the pendant aryl moiety may not be tolerated by the receptor, resulting in the observed reduction in potency. If this were the case, we suggested that similar torsions may be invoked by substitution at the C-5 of the pyrimidine ring, but that substitution of this area may be less affected by the spatial restraints imposed by the receptor.

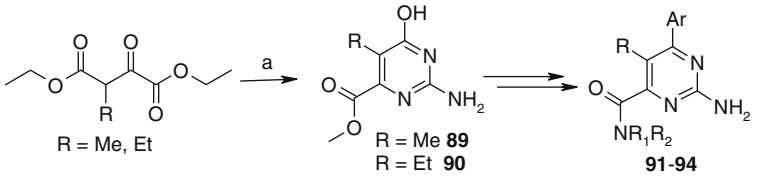
We therefore determined a limited series of compounds designed to investigate this phenomenon. These derivatives were prepared as described in Scheme 6. Formation of the desired alkyl diethyl oxaloaceate was accomplished according to literature methods,[18] in rather disappointing yields. These were then cyclized with guanidine to give the functionalized aminopyrimidine esters which were converted to the desired biaryl amides **91**–**94** in a similar manner to that outlined in Scheme 5.

It was immediately apparent from these results that this strategy had not delivered the anticipated increases in selectivity, certainly not rivaling the >100-fold selectivity exhibited by **79** (Table 4). Indeed, these compounds even failed to deliver the 35-fold and 70-fold selectivities displayed by the unsubstituted (and more synthetically tractable) derivatives **81** and **82**. Further studies in this area were therefore terminated.

An area which had received little attention at this point was the 2-amino functionality. Earlier studies within our laboratories on bicyclic adenosine A_{2A} antagonists had revealed that, whilst the amino functionality delivered good potency, it was by no means the only tolerated functionality in this region.[9] We therefore felt it prudent to investigate tolerances around this region, which had previously had an influence on the selectivities displayed by our compounds.

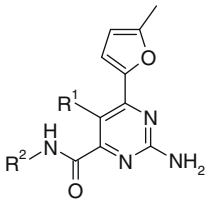


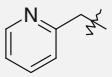
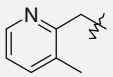
Scheme 5. Synthesis of substituted 6-phenylpyrimidine analogues. Reagents and conditions: (a) NaOH, H_2O, rt, 3.5 h, 78%; (b) MeOH, H_2SO_4, reflux, 18 h, 85%; (c) $POCl_3$, reflux, 3 h, 15%; (d) for **41**–**55**: $ArB(OH)_2$, $Pd(PPh_3)_4$, THF, $NaHCO_3$, then LiOH, 90 °C, 2 h; for **56**: MeOH, reflux, 18 h, 93%; (e) PS-DCC, HOBt, DMF, rt, 24 h, 2–74%.



Scheme 6. Synthesis of 5p-alkylpyrimidines. Reagents and conditions: (a) guanidine, NaOH, H_2O, rt, 3.5 h, 65–74%.

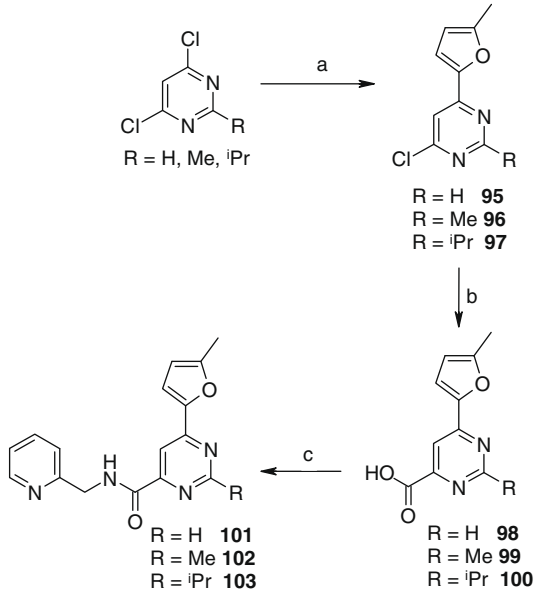
Table 4
Binding affinity data for analogues substituted at C-5, against human adenosine A_{2A} and A_1 receptors[12]



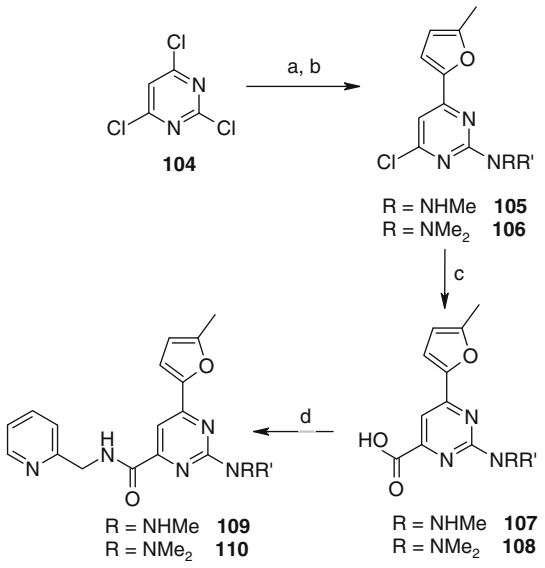
R^1	R^2					
						
	Compound	A_{2A} K_i (nM)	A_1 K_i (nM)	Compound	A_{2A} K_i (nM)	A_1 K_i (nM)
H	**27**	4	222	**28**	3	90
Me	**91**	12	314	**92**	155	576
Et	**93**	25	435	**94**	183	504

C-2 alkylated derivatives were prepared from the corresponding known dichloropyrimidines[19] as detailed in Scheme 7. Coupling with 5-methylfuran-2-boronic acid to give the biaryls **95**–**97** was followed by displacement of the 4-chloro moiety with sodium cyanide and hydrolysis to yield the corresponding acids **98**, **99** and **100**. Preparation of the desired amine was accomplished using hydroxybenzotriazole and polymer-bound carbodiimide (Scheme 8).

The corresponding 2-amino derivatives were prepared from 2,4,6-trichloropyrimidine **104** in a similar manner. Suzuki coupling with 5-methylfuran boronic acid and displacement of the 2-chloro moiety by refluxing with the requisite amine gave **105** and **106**. Conversion to the desired amide was then achieved in a manner analogous to that employed for the alkylated derivatives to yield **109**–**110**.



Scheme 7. Preparation of 2-alkylpyrimidine derivatives. Reagents and conditions: (a) 5-Me-furan boronic acid, $NaHCO_3$, $Pd(PPh_3)_4$, THF, reflux, 18 h, 39–48%; (b) NaCN, DABCO, NMP, 80 °C, 1.5 h, then cH_2SO_4, H_2O, reflux, 4 h, 70–98%; (c) 2-pyridylmethylamine, PS-DCC, HOBt, DMAP, DMF, rt, 16 h, 32–65%.



Scheme 8. Preparation of 2-aminopyrimidine derivatives. Reagents and conditions: (a) 5-Me-furan boronic acid, $NaHCO_3$, $Pd(PPh_3)_4$, THF, reflux, 18 h, 74%; (b) amine, MeOH, 80 °C, 30 min, 22–36%; (c) NaCN, DABCO, NMP, 80 °C, 1.5 h, then cH_2SO_4, H_2O, reflux, 4 h, 15–45%; (d) 2-pyridylmethylamine, PS-DCC, HOBt, DIPEA, DMF, rt, 16 h, 32–65%.

Unlike our previous experiences, it was apparent that small alkyl groups (compounds **102** and **103**) were not tolerated at this position, leading to a considerable decrease in activity. Furthermore, the dimethylamino functionality displayed by **110** was also detrimental to activity. This was a moiety which we had previously found to be efficacious,[10] perhaps indicating considerable steric restriction around this region or a requirement for a hydrogen bond donor in this position.

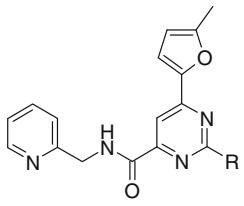
This data also challenges our earlier assumption that these systems bind to the receptor in a directly analogous manner to our earlier bicyclic derivatives,[3] given this marked inconsistency in the structure–activity relationships. Complete deletion of the amino functionality gave compound **101**, equally active with the mono-methylamino derivative **109**. This analogue was substantially more active than the dimethylamino derivative **110**, further indicating that a hydrogen bond donor, rather than a lone pair or other hydrogen bond acceptor was more important at this position. It was evident, however, that the simple C-2 amino functionality was optimal.

Our final point of investigation was the nature of the C-4 amide functionality. We had found previously that pyridyl-containing side-chains exhibited preferential properties in terms of solubility and biological activity and these, therefore, formed the main focus of our investigations.

A library of some 200 derivatives was prepared using the parallel methodology described in Scheme 5. These studies further highlighted that non-heteroaromatic derivatives at this point were detrimental, both in terms of potency and solubility.[20] It soon became clear that we had been extremely fortuitous with our initial choice of amines, as these proved to be amongst the most active investigated. Interestingly, the 6-(methoxymethyl)-pyridin-2-yl methylamine side chain displayed in **1**,[3] which had proven highly beneficial in our earlier studies on this template, proved to be considerably less effective in this system and was not considered for further evaluation, suggesting that the methylfuryl moiety forces a somewhat different binding orientation within the receptor (Table 5).

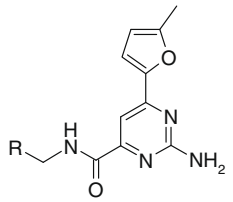
In general terms, we found that a nitrogen directly adjacent to the methylamine linker was highly favoured and that, alongside our original pyridine-containing derivatives, pyrroles, pyrazoles and imidazoles were also well tolerated. Selectivities of the derivatives against the other adenosine receptors and physiochemical properties could be influenced by substitution patterns around the heteroaromatic ring but, in some cases, this was accompanied by a moderate reduction of binding affinity at the A_{2A} receptor. A selection of the more active derivatives is described in Table 6.

Table 5
Binding affinity data for analogues substituted at C-2, against human adenosine A_{2A} and A_1 receptors[12]



Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)
27	NH_2	3.8	222
101	H	97	2545
102	Me	1117	4212
103	^{i}Pr	1725	1086
109	NHMe	63	151
110	NMe_2	1789	1401

Table 6
Binding affinity data for selected amide derivatives against human adenosine A_{2A} and A_1 receptors[12]



Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)
27	Pyridin-2-yl	4	222
28	3-Methyl-pyridin-2-yl	3.5	90
111	6-Methyl-pyridin-2-yl	2.5	133
112	3,6-Dimethyl-pyridin-2-yl	3	77.5
113	4,6-Dimethyl-pyridin-2-yl	9.5	57
114	5,6-Dimethyl-pyridin-2-yl	3	89
115	1-Methyl-1*H*-pyrrol-2-yl	2.5	172
116	Pyrrol-2-yl	2	270
117	1,5-Dimethyl-1*H*-pyrrol-2-yl	5	166
118	Imidazol-2-yl	1	368
119	1-Ethyl-1*H*-imidazol-2-yl	3.5	385
120	1-*n*-Propyl-1*H*-imidazol-2-yl	6	277
121	1-*Iso*propyl-1*H*-imidazol-2-yl	5.5	270
122	5-Methylisoxazol-3-yl	8.5	299
123	2-Methylthiazol-4-yl	6.5	72.5

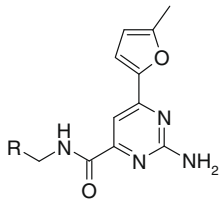
For those compounds showing 50-fold or greater selectivity over the A_1 receptor, selectivities against the other adenosine subtypes were also determined. Selected data for all four subtypes are detailed in Table 7. Though A_1 selectivity was acceptable and generally consistent at roughly 50–100-fold (except for the highly A_1-selective derivative **118**, which was found to be more than 350-fold selective), selectivities against the A_{2B} and A_3 receptors were found to be much higher. Indeed, values of 200-fold selectivity over the A_3 receptor and 1000-fold selectivity over the more closely related A_{2B} receptor were not uncommon in this series.

Encouraged by the selectivities observed, the optimized compounds described in Table 7 were investigated for their ability to reduce Parkinson's-like symptoms in the haloperidol-induced hypolocomotion (HaloLMA) assay. In this model, the symptoms of Parkinson's disease can be induced by using agents such as haloperidol, a dopamine receptor antagonist which blocks dopaminergic neurotransmission and thus mimics the degradation of striatal neurons observed in the disease.[21] Animals treated with this agent display an impairment of movement, mirroring that observed in patients. We therefore assessed the in vivo efficacy of our compounds by monitoring the reversal of the reduction in locomotor activity induced by haloperidol administration. Data from this assessment are detailed in Table 8.

Compound **27** and **116**, our first derivatives to undergo assessment, were found to be orally active and both derivatives reversed hypolocomotion induced by haloperidol at 10 mg/kg. Interestingly, though **116** was active in vivo, the closely related **118** was found to have no discernable activity when dosed orally at 10 mg/kg.

We speculated that the observed activities for **27**, **116** and **118** were being tempered by low brain penetration, potentially due to their low lipophilicity limiting permeability across cell membranes and we hoped that compounds **111** and **119**, with their slightly higher *c*Log *P*, would display improved CNS penetration. We anticipated that this would manifest itself in lower efficacious doses in the model, without hindering oral bioavailability. This was clearly not the case for **119**, which showed no improvement in activity, again being active at 10 mg/kg. However, **111** clearly had an improved profile, displaying activity in the model at just 1 mg/kg after oral dosing.

Table 7
Binding affinities of selected derivatives against all human adenosine receptor subtypes[12]



Compound	R	A_{2A} K_i (nM)	A_1 K_i (nM)	A_{2B} K_i (nM)	A_3 K_i (nM)
27	Pyridin-2-yl	4	222	1089	896
111	6-Methyl-pyridin-2-yl	2.5	133	3185	366
115	1-Methyl-1*H*-pyrrol-2-yl	2.5	172	2466	1150
116	Pyrrol-2-yl	2	270	>10,000	9090
118	Imidazo-2-yl	1	368	798	2104
119	1-Ethyl-1*H*-imidazol-2-yl	3.5	385	1304	741
121	1-*Iso*propyl-1*H*-imidazol-2-yl	5.5	270	1844	1627

Table 8
Minimum oral dose required for reversal of haloperidol-induced hypolocomotion in mice

Compound	HaloLMA activity (mg/kg)
27	10
111	1
115	10
116	10
118	>10
119	10

In vitro DMPK screening of **111** indicated low microsomal turnover across several species, with metabolism primarily attributable to the CYP450 1A2 isoform. The compound was screened for inhibition of common CYP isoforms and was found not to be an inhibitor of these enzymes at concentrations up to 10 μM. Plasma protein binding was also investigated and the compound found to be 84% bound. Pharmacokinetic analysis indicated the compound to have a reasonable terminal half-life of around 3 h and a plasma T_{max} of 15 min in rats. Clearance was found to be moderate at 1.95 L/h/kg, however given the promising in vivo efficacy after oral dosing, we were surprised to find a relatively low volume of distribution 0.7 L/kg and an oral bioavailability of just 3%. At this time, we have no data to suggest why the bioavailability of this derivative is so low, especially as other derivatives from this compound class, which display similar calculated and measured pharmacokinetic parameters, have shown bio-availabilities in the order of 90%.[3] Despite this, our compound clearly exhibits a beneficial profile once absorbed, given its observed potency in the HaloLMA model. Indeed, we speculate that this efficacy may be further enhanced through appropriate formulation strategies, which may allow improvements in the observed oral bio-availability.

In summary, we have described a series of soluble, low molecular weight antagonists of the human adenosine A_{2A} receptor. These derivatives show good to excellent selectivity against the other adenosine receptor subtypes. Iterative optimization of the scaffold has resulted in a number of highly potent compounds which display excellent in vitro activity. More importantly, these derivatives also show promising activity in a clinically validated model of Parkinson's disease and may, therefore, be of clinical relevance and utility.

3. Experimental

Flash chromatography was performed using pre-packed silica gel cartridges (Strata Si-1, 61 Å from Phenomenex, Cheshire UK, or IST Flash II, 54 Å from Argonaut, Hengoed UK). Thin layer chromatography was conducted with 5 × 10 cm plates coated with Merck Type 60 F_{254} silica gel to a thickness of 0.25 mm.

Microanalyses and high resolution mass spectrometry were performed by Medac Ltd, Egham, UK (http://www.medacltd.com). All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from the Sigma–Aldrich Chemical Company Ltd, and used without further drying. All compounds were >95% purity as determined by LC–MS (wavelength 220 nm) and by ^{1}H NMR, unless otherwise indicated. Where Cl or Br were present, expected isotopic distribution patterns were observed. Reactions that are specified as being carried out in a microwave oven were conducted in a Biotage Synthesizer, Biotage Initiator or CEM Explorer microwave.

3.1. Analytical chemistry procedures

3.1.1. LC–MS methods

The methods referred to in Section 2 are described in detail in the Supplementary data, which can be found in the online version of this article.

3.1.2. ^{1}H NMR

Proton NMR spectra were recorded on a 400 MHz Bruker spectrometer. Solutions were typically prepared in either deuterochloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with chemical shifts referenced to tetramethylsilane (TMS) as an internal standard. ^{1}H NMR data is reported indicating the chemical shift (δ), the integration (e.g., 1H), the multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets etc.) and the coupling constant (J) in Hz (app implies apparent coupling on broadened signals). Deuterated solvents were obtained from the Sigma–Aldrich Chemical Company or Fluorochem.

Mass spectra were acquired via loop injection on a Waters ZQ Mass Detector equipped with an Electrospray source operated in Positive/Negative Ion switching mode and a cone voltage of 25 V.

3.2. Biological assay protocols

3.2.1. Radioligand binding assay

Four cell lines, stably transfected to express human recombinant adenosine receptors (hA_1, A_{2A}, A_{2B} or A_3), were grown in Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% (v/v) foetal bovine serum, 1% (v/v) penicillin–streptomycin, 1% (v/v) L-glutamine, 1% (v/v) MEM non-essential amino acid solution and 10 μM sodium pyruvate. Cells were kept in a humidified incubator at 37 °C in 5% CO_2:95% air mixture, they were harvested

using a cell scraper and centrifuged at 1000*g* for 20 min. The resultant pellet was resuspended in Dulbecco's phosphate buffered saline and centrifuged at 1000*g* for 20 min. The pellet was then stored at −80 °C until use.

Frozen cells were reconstituted in 50 mM Tris HCl buffer (pH 7.5–8.0) containing 10 mM $MgCl_2$, 1 mM EDTA (A_{2B}, A_3 assays only) and 0.1 IU/mL adenosine deaminase using a Ultra-Turrax homogeniser. The resultant homogenate was kept for immediate use in the binding.

Binding assays were performed in a total volume of 250 μL, containing radioligand, membranes and additional drugs. Following 60 (A_{2B}, A_3) or 90 (A_1, A_{2A}) min incubation at 21 °C, assays were terminated by rapid filtration with GF/B filters (presoaked in 0.1% (w/v) polyethylenimine) using a Canberra Packard filtermate 196. The radioactivity was assessed using a Canberra Packard TopCount microplate scintillation counter.

3.2.2. Functional assay

Cells were plated out into black walled, clear bottom 96-well tissue culture plates at a density of 30,000 cells per well. This seeding density was sufficient to ensure that the cells formed a confluent monolayer after an overnight incubation. On the day of assay, cells were dye loaded by incubating for approximately 1 h with 4 μM Fluo-3-AM in ULTRA-CHO media supplemented with 20 mM HEPES and 2.5 mM probenecid, an inhibitor of anion exchange which prevents dye extrusion from the cells. Unincorporated dye was removed by four media changes using a Denley cell washer, which was programmed to leave 100 μL of a balanced salt solution (BSS: GIBCO 14065-049) containing 20 mM HEPES and 2.5 mM probenecid in each well.

The test compound was dissolved in 100% DMSO to a stock concentration of 3 mM, and diluted manually in BSS to produce the working stock solutions for use in the assay.

Background fluorescence readings were set to approximately 10,000 fluorescence units by altering the laser strength, with a typical laser setting being in the range of 0.4–0.8 W. Agonists were added at a rate of 70 μL/s following a 10 s baseline reading. For agonist studies 50 μL of agonist was added to each well for a final volume of 150 μL. For antagonist studies, 50 μL of a fixed concentration of antagonist was added manually to the cells 'off line' and incubated at 37 °C for 15 min. The final well volume following agonist application in this case was 200 μL. Agonist concentration–response curves were constructed in the absence and presence of varying concentrations of antagonist and the pA_2 value estimated by Schild analysis.

3.2.3. Haloperidol-induced hypolocomotion assay

All work reported in this manuscript was performed in accordance with Home Office regulations as detailed in the Animals (Scientific Procedures) Act 1986.

Female TO mice (25–30 g) and Sprague-Dawley rats (300–400 g) were used for all experiments. Animals were allowed free access to food and water, and were allowed at least 7 days to acclimatize after delivery before experimental use.

Liquid injectable haloperidol (1 mL Serenance ampoules from Baker Norton, Harlow, Essex, each containing haloperidol BP 5 mg) were diluted to a final concentration of 0.02 mg/mL for mice and 0.05 mg/mL for rats using saline. Mice were dosed at 10 mL/kg (final dose 0.2 mg/kg sc) and rats at 2 mL/kg (final dose 0.1 mg/kg sc). The test compound was prepared as an aqueous suspension in 1% methylcellulose.

1.5 h before testing, animals were administered haloperidol. The test compound was administered 15 min (mice) or 120 min (rat) prior to testing. The animals were then placed individually into clean, clear polycarbonate cages [20 (width) × 40 (length) × 20 (height) cm]. Horizontal locomotor activity is determined by placing the cages within a frame containing a 3 × 6 array of photocells linked to a computer, which tabulates beam breaks. Animals were left undisturbed to explore for 1 h, and the period of time spent active (assessed by beam breaks) served as a record of locomotor activity.

3.3. Synthetic procedures

3.3.1. Ethyl-2-amino-4-(2-furyl)-triazine-6-carboxylate 5

A solution of guanidine [prepared by treating NaOMe (0.58 g, 10.7 mmol) in MeOH (10 mL) with guanidine hydrochloride (0.51 g, 5.34 mmol)] was treated with 2-furonitrile (0.5 g, 5.37 mmol) over 30 min. The suspension was stirred at 30 °C for 8 h, filtered, and the filtrate was acidified with hydrochloric acid. The solid was filtered off to give *N*-aminoiminomethylfuran-2-carboximidamide hydrochloride **4** (0.20 g, 20%) as a cream solid which was used directly in the next step.

A solution of *N*-aminoiminomethylfuran-2-carboximidamide hydrochloride **4** (0.20 g, 1.06 mmol) and Et_3N (0.16 g, 1.60 mmol) in diethyl oxalate (2.15 g, 14.7 mmol) was heated under reflux for 3 h, allowed to cool, poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography [SiO_2; EtOAc–isohexane (1:1)] to give **5** (186 mg, 75%) as a white solid; NMR δ_H (400 MHz, DMSO) 1.25 (3H, t, *J* 7.2 Hz), 4.20 (2H, q, *J* 6.7 Hz), 6.73 (1H, dd, *J* 2.0, 3.2 Hz), 7.38 (1H, d, *J* 3.6 Hz), 8.19–7.90 (3H, m, *J* 1.2 Hz); *m*/*z* 235 $(M+1)^+$, 257 $(M+Na)^+$.

3.3.2. General amide synthesis for compounds 6–14

A suspension of ethyl 4-amino-6-(2-furyl)triazine-2-carboxylate **5** (0.150 g, 0.64 mmol) in EtOH (2.5 mL) was treated with the appropriate amine (0.83 mmol), refluxed overnight, cooled to room temperature and the resulting precipitate was filtered and washed with cold EtOH (2 × 2 mL) to give the desired amide derivative.

3.3.2.1. *N*-(2-Chlorobenzyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 6. Yield = 75%; IR ν_{max} (DR)/cm^{-1} 3477, 3377, 3308, 1741, 1686, 1624, 1558, 1415 and 1370; NMR δ_H (400 MHz, DMSO) 4.55 (2H, d, *J* 6.0 Hz), 6.74 (1H, dd, *J* 3.5 Hz, 2.0 Hz), 7.40–7.27 (3H, m), 7.47 (1H, dd, *J* 1.5 Hz, 7.0 Hz), 7.56 (1H, d, *J* 3.5 Hz), 7.96 (2H, br s), 7.98 (1H, d, *J* 1.0 Hz), 9.22 (1H, t, *J* 6.0 Hz). Anal. Calcd for $C_{15}H_{12}N_5O_2Cl$: C, 54.61; H, 3.67, N, 21.23. Found: C, 54.10; H, 3.39; N, 21.54; *m*/*z* 330.1 $(M+H)^+$, 352.1 $(M+Na)^+$; LC retention time 2.3 min. Method A.

3.3.2.2. *N*-(*ortho*-Tolyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 7. Yield = 75%; IR ν_{max} (DR)/cm^{-1} 3504, 3462, 3326, 1676, 1517, 1224, 1143, and 1078; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 4.46 (2H, d, *J* 6.1 Hz), 6.73 (1H, dd, *J* 1.8 Hz, 3.4 Hz), 7.20-7.14 (3H, m), 7.25 (1H, t, *J* 3.9 Hz), 7.53 (1H, d, *J* 0.7 Hz, 3.4 Hz), 7.94 (2H, br s), 7.97 (1H, d, *J* 0.75 Hz), 9.02 (1H, t, *J* 6.1 Hz); *m*/*z* 310.2 $(M+H)^+$, 332.2 $(M+Na)^+$; LC retention time 1.9 min. Method A.

3.3.2.3. *N*-(*meta*-Tolyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 8. Yield = 74%; IR ν_{max} (DR)/cm^{-1} 3462, 3308, 1670, 1636, 1542,1412, 1363, 1233, 1190, 1148, 1096 and 1065; NMR δ_H (400 MHz, DMSO) 2.29 (3H, s), 4.44 (2H, d, *J* 6.5 Hz), 6.74 (1H, dd, *J* 2.0 Hz, 3.5 Hz), 7.14–7.04 (3H, m), 7.22 (1H, d, *J* 7.5 Hz), 7.55 (1H, dd, *J* 1.0 Hz, 3.5 Hz), 7.93 (2H, br s), 7.97 (1H, d, *J* 1.0 Hz), 9.15 (1H, t, *J* 6.0 Hz); *m*/*z* 310.2 $(M+H)^+$, 332.2 $(M+Na)^+$; LC retention time 2.0 min. Method A.

3.3.2.4. *N*-(2-Methoxyphenyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 9. Yield = 65%; IR ν_{max} (DR)/cm^{-1} 3370, 3188, 2953, 2834, 1686, 1648, 1542, and 1247; NMR δ_H

(400 MHz, DMSO) 3.85 (3H, s), 4.45 (2H, d, *J* 6.0 Hz), 6.79 (1H, dd, *J* 1.5 Hz, 3.5 Hz), 6.92 (1H, dt, *J* 7.5 Hz, 1.0 Hz), 7.01(1H, d, *J* 7.5 Hz), 7.20 (1H, dd, *J* 1.5 Hz, 7.5 Hz), 7.26 (1H, t, *J* 8.0 Hz, 1.5 Hz), 7.53 (1H, d, *J* 3.5 Hz), 7.95 (2H, br s), 7.97 (1H, d, *J* 1.0 Hz), 8.98 (1H, t, *J* 6.0 Hz); *m*/*z* 326.2 $(M+H)^+$, 348.2 $(M+Na)^+$; LC retention time 1.7 min. Method A.

3.3.2.5. *N*-((Pyridin-2-yl)methyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 10. Yield = 74%; IR ν_{max} (DR)/cm^{-1}, 3301, 1697, 1633, 1518, 1224, 1189 and 1151; NMR δ_H (400 MHz, DMSO): 4.59 (2H, d, *J* 6.0 Hz), 6.75 (1H, dd, *J* 2.0, 3.5 Hz) 7.28 (1H, dd, *J* .1.0 Hz, 5.0), 7.35 (1H, d, *J* 7.5 Hz), 7.56 (1H, dd, *J* 1.0 Hz, 3.5 Hz), 7.77 (1H, dt, *J* 1.5 Hz, 7.5 Hz), 7.94 (2H, br s), 7.98 (1H, d, *J* 1.5 Hz), 8.53 (1H, d, *J* 4.0 Hz), 9.29 (1H, t, *J* 6.0 Hz). Anal. Calcd for $C_{14}H_{12}N_6O_2$: C, 56.75; H, 4.08, N, 28.35. Found: C, 55.37; H, 4.06; N, 28.10; *m*/*z* 297 $(M+H)^+$; LC retention time 2.3 min. Method B.

3.3.2.6. *N*-((Pyridin-3-yl)methyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 11. Yield = 72%; mp 216.2.–219.3 °C; IR ν_{max} (DR)/cm^{-1} 3453, 3308, 1633, 1537, 1227 and 1140; NMR δ_H (400 MHz, DMSO) 4.5 (2H, d, *J* 6.0 Hz), 6.75–6.73 (1H, m), 7.38–7.33 (1H, m), 7.55 (1H, dd, *J* 1.0 Hz, 3.5 Hz), 7.73 (1H, d, *J* 8.0 Hz), 7.94 (2H, br s), 7.97 (1H, d, *J* 1.0 Hz), 8.56 (1H, d, *J* 1.5 Hz), 8.47(1H, dd, *J* 2.0 Hz, 5.0 Hz), 9.3 (1H, t, *J* 6.0 Hz). Anal. Calcd for $C_{14}H_{12}N_6O_2$: C, 56.75; H, 4.08, N, 28.35. Found: C, 56.12; H, 4.06; N, 28.40; *m*/*z* 297.19 $(M+H)^+$; LC retention time 0.5 min. Method A.

3.3.2.7. *N*-((Pyridin-4-yl)methyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 12. Yield = 71%; IR ν_{max} (DR)/cm^{-1} 3390, 1664, 1517, 1230, 993 and 799; NMR δ_H (400 MHz, DMSO) 4.50 (2H, d, *J* 6.0 Hz), 6.76–6.73 (1H, m), 7.57 (1H, d, *J* 1.0 Hz, *J* 3.5 Hz), 7.96 (2H, br s), 7.98 (1H, d, *J* 1.0 Hz), 8.51 (2H, d, *J* 6.0 Hz), 9.35 (1H, t, *J* 6.0 Hz), 7.31 (2H, d, *J* 6.0 Hz); *m*/*z* 297.2 $(M+H)^+$, 319.2 $(M+Na)^+$; LC retention time 1.8 min. Method B.

3.3.2.8. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 13. Yield = 34%; IR ν_{max} (DR)/cm^{-1} 3999, 3318, 1693, 1504, 1223, 1142, 1083 and 1008; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 4.63 (2H, d, *J* 5.0 Hz), 6.75 (1H, dd, *J* 1.5 Hz, 3.5 Hz), 7.26 (1H, dd, *J* 5.0 Hz, 7.5 Hz), 7.48 (1H, dd, *J* 1.0 Hz, 3.5 Hz), 7.63 (1H, d, *J* 7.0 Hz), 7.98–7.93 (2H, broad signal), 7.99(1H, d, *J* 1.0 Hz), 8.41 (1H, d, *J* 3.5 Hz), 9.24 (1H, t, *J* 5.0 Hz); *m*/*z* 311.1 $(M+H)^+$, 333.1$(M+Na)^+$; LC retention time 0.9 min. Method A.

3.3.2.9. *N*-((6-Methoxymethyl-pyridin-2-yl)methyl)-2-amino-4-(2-furyl)-1,3,5-triazine-6-carboxamide 14. Yield = 74%; mp 215.9–217.1 °C; IR ν_{max} (DR)/cm^{-1} 3300, 3122, 2917, 2827, 1690, 1633, 1593, 1511, 1409, 1331 and 1188; NMR δ_H (400 MHz, DMSO) 3.38 (3H, s), 4.50 (2H, s), 4.57 (2H, d, *J* 6.0 Hz), 6.75 (1H, dd, *J* 1.5 Hz, 3.5 Hz), 7.25 (1H, d, *J* 8.0 Hz), 7.31 (1H, d, *J* 7.5 Hz), 7.56 (1H, dd, *J* 1.0 Hz, 3.5 Hz), 7.79 (1H, t, *J* 7.5 Hz), 7.97(2H, br s), 7.99 (1H, d, *J* 1.0 Hz), 9.35 (1H, t, *J* 6.0 Hz). Anal. Calcd for $C_{16}H_{16}N_6O_3$: C, 56.47; H, 4.74, N, 24.68. Found: C, 55.60; H, 4.62; N, 24.72; *m*/*z* 341.2 $(M+H)^+$, 363.2 $(M+Na)^+$; LC retention time 3.5 min. Method B.

3.3.2.10. *N*-((6-Methoxymethyl-pyridin-2-yl)methyl)-2,6-dichloroisonicotinamide 17. A solution of 2,6-dichloroisonicotinic acid **16** (5.80 g, 30.2 mmol) in DMF (30 mL) was treated with *N*,*N*′-carbonyldiimidazole (5.39 g, 33.2 mmol), stirred at room temperature for 2 h, then treated with 2-aminomethyl-3-methylpyridine (4.42 g, 36.3 mmol). The reaction mixture was stirred at room temperature for 3 h, poured onto water (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated in vacuo and the resulting solid was triturated with EtOAC–isohexane (1:5) and filtered to give **17** (4.30 g, 48%) as a cream solid; NMR δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s), 4.67 (2H, d, *J* 4.0 Hz), 7.23 (1H, dd, *J* 8.0, 5.0 Hz), 7.56 (1H, d, *J* 8.0 Hz), 7.74 (2H, s), 8.45 (1H, d, *J* 5.0 Hz), 8.50 (1H, br s); *m*/*z* 296 $(M+H)^+$, 298 $(M+H)^+$.

3.3.2.11. *N*-((6-Methoxymethyl-pyridin-2-yl)methyl)-2-chloro-6-furyl-isonicotinamide 18. A solution of 2,6-dichloro-*N*-[(3-methyl)pyridyl]methyl pyridine-4-carboxamide **17** (1.20 g, 4.05 mmol) in THF (30 mL) was treated with 2 M aqueous Na_2CO_3 (7 mL), 2-furanboronic acid (544 mg, 4.86 mmol) and $Pd(PPh_3)_4$ (468 mg, 0.405 mmol) and refluxed with vigorous stirring under argon overnight. The mixture was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo and purified by chromatography [SiO_2; isohexane–EtOAc (2:1)] to give **18** (413 mg, 31%) as a cream solid; NMR δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s), 4.68 (2H, d, *J* 4.0 Hz), 6.58–6.56 (1H, m), 7.22–7.19 (2H, m), 7.54 (1H, d, *J* 8.0 Hz), 7.58 (1H, d, *J* 2.5 Hz), 7.62 (1H, d, *J* 1.5 Hz), 8.03 (1H, d, *J* 2.5 Hz), 8.47–8.44 (2H, m); *m*/*z* 328 $(M+H)^+$, 330 $(M+H)^+$.

3.3.2.12. *N*-((6-Methoxymethyl-pyridin-2-yl)methyl)-2-amino-6-furyl-isonicotinamide 15. A solution of 2-chloro-6-(2-furyl)-*N*-[(3-methyl)pyridyl] methylpyridine-4-carboxamide **18** (413 mg, 1.26 mmol) in EtOH (5 mL) and hydrazine monohydrate (5 mL) was stirred at 100 °C overnight, cooled to room temperature, poured onto water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give 2-(2-furyl)-6-hydrazino-*N*-[(3-methyl)-pyridyl]methylpyridine-4-carboxamide (400 mg) as a yellow oil. This was dissolved in EtOH (30 mL) and treated with Raney-Ni (approximately 200 mg), stirred under an hydrogen atmosphere for 3 h, filtered through Celite, concentrated in vacuo and purified by chromatography [SiO_2; EtOAc–isohexane–Et_3N (80:18:2)] to give **15** (110 mg, 28%) as a cream solid; mp 53.2–56.8 °C; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 4.57 (2H, d, *J* 5.0 Hz), 6.28 (2H, br s), 6.61 (1H, dd, *J* 3.5, 2.0 Hz), 6.79 (1H, d, *J* 1.0 Hz), 6.93–6.92 (1H, m), 7.22 (1H, dd, *J* 7.5, 4.5 Hz), 7.30 (1H, d, *J* 1.5 Hz), 7.59 (1H, dd, *J* 7.5, 1.0 Hz), 7.78–7.77 (1H, m), 8.36 (1H, d, *J* 4.5 Hz), 8.92 (1H, t, *J* 5.0 Hz); *m*/*z* 309 $(M+H)^+$; LC retention time 1.0 min. Method A.

3.3.2.13. 2-Amino-4-chloro-6-furyl-pyrimidine 21. A solution of 2-(tributylstannyl)furan (35.7 g, 100 mmol) in DMF (100 mL) was treated with 2-amino-4,6-dichloropyrimidine **20** (16.4 g, 100 mmol) and dichlorobis(triphenylphosphine)palladium(II) (3.51 g, 5.0 mmol). The suspension was stirred at 80 °C for 18 h, allowed to cool to room temperature and poured onto ice (400 g). The solid precipitate was filtered off, washed with water, dried in air, and the filtrate was extracted with EtOAc (300 mL), washed with water (100 mL), mixed with the solid precipitate and concentrated. The crude product was purified by chromatography [SiO_2; EtOAc–toluene (0:1–1:9–2:3)] and the material with R_f 0.23 (isopropyl ether) was triturated with isohexane to give **21** (11.1 g, 57%) as a yellow solid; mp 133–140 °C; NMR δ_H (400 MHz, DMSO) 6.70 (1H, q, *J* 2.0 Hz), 6.95 (1H, s), 7.16 (2H, br s), 7.27 (1H, d, *J* 3.6 Hz), 7.92 (1H, t, *J* 1.0 Hz).

3.3.2.14. 2-Amino-6-(2-furyl)pyrimidine-4-carboxylic acid 23. A solution of 2-amino-4-chloro-6-(2-furyl)pyrimidine **21** (9.78 g, 50.0 mmol) in DMSO (200 mL) was treated with sodium cyanide (14.7 g, 300 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.56 g, 5.0 mmol). The suspension was stirred for 4 days, and more DABCO (5.04 g, 45 mmol) and DMSO (100 mL) were

added. The suspension was stirred for a further 2 days, poured onto a mixture of ice (750 g) and water (750 mL), the crude product was filtered off, washed with water and MeCN, and dried in air to give 2-amino-6-(2-furyl)pyrimidine-4-carbonitrile (7.1 g, 77%) as a brown solid; mp 193–194 °C; NMR δ_H (400 MHz, DMSO) 6.74 (1H, q, *J* 1.6 Hz), 7.32 (2H, br s), 7.39 (1H, d, *J* 3.6 Hz), 7.43 (1H, s), 7.98 (1H, d, *J* 1.2 Hz); *m*/*z* 187 $(M+H)^+$.

A suspension of 2-amino-6-(2-furyl)pyrimidine-4-carbonitrile (7.06 g, 37.9 mmol) in water (30 mL) was treated carefully with concentrated sulfuric acid (30 mL), stirred at 100 °C for 2 h, allowed to cool to room temperature and poured onto a mixture of ice (150 g) and water (150 mL). After standing for 1 h the crude product was filtered off, washed with water and MeCN, and dried in air to give **15** (7.02 g, 90%) as a brown solid; NMR δ_H (400 MHz, DMSO) 6.71 (1H, dd, *J* 1.6, 3.6 Hz), 7.04 (2H, br s), 7.30 (1H, d, *J* 3.6 Hz), 7.36 (1H, s), 7.94 (1H, d, *J* 1.2 Hz).

The following compound was also prepared using the above methodology.

3.3.2.15. 2-Amino-6-(5-methyl-2-furyl)-pyrimidine-4-carboxylic acid 24. Yield = 91%, δ_H (400 MHz, DMSO); 2.38 (3H, s), 6.34 (1H, br d), 6.97 (2H, br s), 7.21 (1H, d, *J* 3.0 Hz), 7.30 (1H, s); *m*/*z* 241 $(M+H)^+$.

3.3.3. General method for amide couplings

A mixture of the appropriate acid (1.0 mmol), the desired amine (1.0 mmol), polymer supported carbodiimide (Argonaut Technologies, loading 1.38 mmol/g, 1.10 g, 1.5 mmol) and 1-hydroxybenzotriazole hydrate (203 mg, 1.5 mmol) in DMF (5 mL) was stirred at room temperature for 24 h. The mixture was filtered through a pad of Celite, washing through with EtOAc. The filtrate was washed successively with H_2O (10 mL), 2 M Na_2CO_3 (2 × 10 mL) and H_2O (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was dissolved in MeOH (1.0 mL), added dropwise with stirring to H_2O (2 mL) and the resulting precipitate filtered to give the amide.

Prepared using this methodology were:

3.3.3.1. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2′-furyl)-pyrimidine-4-carboxamide 25. Yield = 44%; NMR δ_H (400 MHz, DMSO) 4.62 (2H, d, *J* 6.0 Hz), 6.68–6.75 (1H, m), 6.94 (2H, s), 7.26–7.33 (2H, m), 7.35 (1H, d, *J* 7.5 Hz), 7.43 (1H, s), 7.78 (1H, dt, *J* 7.5, 1.5 Hz), 7.94 (1H, s), 8.54 (1H, d, *J* 4.5 Hz), 8.96 (1H, t, *J* 6.0 Hz).

3.3.3.2. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-furyl)-pyrimidine-4-carboxamide 26. Yield = 35%; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 4.63 (2H, d, *J* 5.0 Hz), 6.70–6.73 (1H, m), 7.01 (2H, s), 7.27 (1H, dd, *J* 7.5, 4.5 Hz), 7.31 (1H, d, *J* 3.5 Hz), 7.46 (1H, s), 7.64 (1H, dt, *J* 7.5, 1.0 Hz), 7.94–7.96 (1H, m), 8.41 (1H, dd, *J* 4.5, 1.0 Hz); retention time 1.50 min (Method B).

3.3.3.3. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 27. Yield = 60%; NMR δ_H (400 MHz, DMSO) 2.39 (3H, s), 3.74 (3H, s), 4.46 (2H, d, *J* 6.0 Hz), 6.33–6.34 (1H, m), 6.82–6.90 (5H, m), 7.20 (1H, d, *J* 3.0 Hz), 7.25 (1H, t, *J* 8.0 Hz), 7.36 (1H, s) and 8.76 (1H, t, *J* 6.5 Hz); *m*/*z* 309 $(M)^+$ retention time 1.19 min (Method A); HRMS found 308.1152. $C_{16}H_{14}N_5O_2$ ($[M-H]^-$) requires 308.1147.

3.3.3.4. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(5′-methyl-2′-furyl)-pyrimidine-4-carboxamide 28. Yield = 24%; NMR δ_H (400 MHz, DMSO) 2.32 (3H, s), 2.39 (3H, s), 4.62 (2H, d, *J* 5.0 Hz), 6.34 (1H, dd, *J* 1.0 Hz, 3.3 Hz), 6.99 (2H, br s), 7.22 (1H, d, *J* 3.3 Hz), 7.26 (1H, dd, *J* 4.8 Hz, 7.6 Hz), 7.39 (1H, s), 7.63 (1H, dd, *J* 0.6 Hz, 7.6 Hz), 9.06 (1H, t, *J* 5.0 Hz); *m*/*z* 324 $(M+H)^+$, retention time 1.88 min (Method C).

3.3.3.5. 4-Hydroxy-6-(2-thiazolyl)pyrimidine-2-amine 31. Guanidine carbonate (3.48 g, 19.32 mmol) was suspended in EtOH (100 mL) and toluene (20 mL) and 50 mL of the solvent was distilled off using a Dean and Stark apparatus. The suspension was cooled to 40 °C, treated with a solution of ethyl β-oxo-2-thiazolepropionate (7.7 g, 38.65 mmol) in EtOH (20 mL), refluxed for 40 h, cooled, treated with water (50 mL) and refluxed for 30 min. The suspension was cooled to 0 °C, treated with a solution of concd HCl (4 mL) in water (40 mL), stirred at 0 °C for 30 min and the resulting precipitate filtered, washed with water (2 × 25 mL) and MeCN (2 × 25 mL) and air dried to give **31** (2.7 g, 36%) as a yellow solid; IR ν_{max} (DR)/cm^{-1} 3188 br, 1664, 1609, 1460, 1437, 1376 and 1245; NMR δ_H (400 MHz, DMSO) 6.27 (1H, s), 6.79 (2H, br s), 7.90 (1H, d, *J* 3.2 Hz) and 7.98 (1H, d, *J* 3.2 Hz).

3.3.3.6. 4-Chloro-6-(2-thiazolyl)pyrimidine-2-amine 33. A suspension of the 4-hydroxy-6-(2-thiazolyl)pyrimidine-2-amine **31** (2.64 g, 13.6 mmol) in $POCl_3$ (30 mL) was heated at 120 °C for 3 h, cooled and concentrated in vacuo. The resulting brown solid was added to ice/water (200 g), basified with NH_4OH (8 mL), filtered and purified by chromatography [SiO_2; EtOAc–isohexane (2:3–1:0)] to give **33** (1.73 g, 60%) as a pale yellow solid; NMR δ_H (400 MHz, DMSO) 7.22 (1H, s), 7.40 (2H, br s), 8.01 (1H, d, *J* 3.2 Hz) and 8.07 (1H, d, *J* 3.2 Hz); *m*/*z* 213, 215 $(M+H)^+$.

This derivative was treated in a similar manner to the preparation of **21** and **22** above to give:

3.3.3.7. 2-Amino-6-(2-thiazolyl)-pyrimidine-4-carboxylic acid 35. Yield = 90%; *m*/*z* 223 $(M+H)^+$, retention time 0.50 min (Method B).

The following compound was also prepared using the above methodology:

3.3.3.8. 2-Amino-6-(4-methyl-2-thiazolyl)-pyrimidine-4-carboxylic acid 36. *m*/*z* 237 $(M+H)^+$, retention time 0.73 min (Method B).

The following two derivatives were prepared from **35** and **36**, respectively, using the general amide coupling method outlined above.

3.3.3.9. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-thiazolyl)-pyrimidine-4-carboxamide 37. Yield = 60%; NMR δ_H (400 MHz, DMSO) 2.39 (3H, s), 4.48 (2H, d, *J* 6.5 Hz), 6.33–6.34 (1H, m), 6.82 (2H, s), 7.20 (1H, d, *J* 3.5 Hz), 7.28–7.33 (2H, m), 7.35 (1H, s), 7.37–7.39 (2H, m) and 8.93 (1H, t, *J* 6.5 Hz); *m*/*z* 344 $(M+H)^+$, retention time 1.27 min (Method A).

3.3.3.10. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(4-methyl-2-thiazolyl)-pyrimidine-4-carboxamide 38. Yield = 14%; IR ν_{max} (DR)/cm^{-1} 3569, 3470, 3348, 2924, 1671, 1622, 1451, 1346, 1226, 1138, 854 and 737; NMR δ_H (400 MHz, DMSO) 2.34 (3H, d, *J* 1.0 Hz), 2.47 (3H, d, *J* 1.0 Hz), 4.73 (2H, d, *J* 6.0 Hz), 7.16–7.17 (3H, m), 7.58 (1H, s), 7.71 (1H, s) and 9.22 (1H, t, *J* 6.0 Hz); *m*/*z* 347 $(M+H)^+$.

3.3.3.11. 2-Amino-6-phenylpyrimidine-4-carboxylic acid 41. Ethyl-2-amino-6-chloropyrimidine-4-carboxylate (0.2 g, 1.07 mmol) (prepared according to the literature method[17]) and phenyl boronic acid (0.16 g, 1.3 mmol) were dissolved in THF (10 mL) and saturated aqueous sodium bicarbonate (1.6 mL) added. Nitrogen was bubbled through the resultant solution for 5 min then tetrakis(triphenylphosphine) palladium(0) added (0.04 g) and the mixture refluxed under nitrogen overnight. The crude mixture was then treated with aqueous lithium hydroxide (1 M, 1 mL) and heated at 90 °C for 2 h. The mixture was concentrated to dryness in vacuo and partitioned between ethyl acetate and water. The

aqueous layer was then acidified to pH 1 with 2 N hydrochloric acid. The resultant solids were obtained by centrifugation and decantation of the liquors and drying overnight in vacuo to give the acid as a white powder (0.17 g, 72%) which was used in the next step without additional purification; *m*/*z* 216 $(M+H)^+$; retention time 1.60 min (Method C).

The following intermediates were also synthesized by this method.

3.3.3.12. 2-Amino-6-(2-fluorophenyl)pyrimidine-4-carboxylic acid 42. *m*/*z* 234 $(M+H)^+$.

3.3.3.13. 2-Amino-6-(3-fluorophenyl)pyrimidine-4-carboxylic acid 43. NMR δ_H (400 MHz, DMSO) 7.13 (2H, br s), 7.39 (1H, m), 7.56 (1H, m), 7.60 (1H, s), 7.93 (1H, d, *J* 10.0 Hz), 7.98 (1H, d, *J* 8.0 Hz), 13.52 (1H, br s).

3.3.3.14. 2-Amino-6-(2-chloropheny)pyrimidine-4-carboxylic acid 44. *m*/*z* 250 $(M+H)^+$; retention time 1.71 min (Method C).

3.3.3.15. 2-Amino-6-(3-chlorophenyl)pyrimidine-4-carboxylic acid 45. *m*/*z* 250 $(M)^+$; retention time 1.83 min (Method C).

3.3.3.16. 2-Amino-6-(2-methylphenyl)pyrimidine-4-carboxylic acid 46. *m*/*z* 230 $(M+H)^+$; retention time 1.69 min (Method C).

3.3.3.17. 2-Amino-6-(3-methylphenyl)pyrimidine-4-carboxylic acid 47. *m*/*z* 230 $(M+H)^+$; retention time 1.77 min (Method C).

3.3.3.18. 2-Amino-6-(4-methylphenyl)pyrimidine-4-carboxylic acid 48. *m*/*z* 230 $(M+H)^+$; retention time 1.75 min (Method C).

3.3.3.19. 2-Amino-6-(2-methoxyphenyl)pyrimidine-4-carboxylic acid 49. *m*/*z* 246 $(M+H)^+$, retention time 1.01 min (Method A).

3.3.3.20. 2-Amino-6-(3-methoxyphenyl)pyrimidine-4-carboxylic acid 50. *m*/*z* 246 $(M+H)^+$; retention time 1.69 min (Method C).

3.3.3.21. 2-Amino-6-(4-methoxyphenyl)pyrimidine-4-carboxylic acid 51. NMR δ_H (400 MHz, DMSO) 3.84 (3H, s), 6.93 (2H, br s), 7.07 (2H, d, *J* 9.0 Hz), 7.51 (1H, s), 8.10 (2H, d, *J* 8.5 Hz); *m*/*z* 246 $(M+H)^+$.

3.3.3.22. 2-Amino-6-(2-ethyl)pyrimidine-4-carboxylic acid 52. *m*/*z* 244 $(M)^+$; retention time 1.80 min (Method C).

3.3.3.23. 2-Amino-6-(2-ethoxyphenyl)pyrimidine-4-carboxylic acid 53. *m*/*z* 260 $(M)^+$; retention time 1.72 min (Method C).

3.3.3.24. 2-Amino-6-(2-cyanophenyl)-pyrimidine-4-carboxylic acid 54. *m*/*z* 241 $(M+H)^+$; retention time 0.79 min (Method C).

3.3.3.25. 2-Amino-6-(3-cyanophenyl)-pyrimidine-4-carboxylic acid 55. *m*/*z* 241 $(M+H)^+$; retention time 1.64 min (Method C).

3.3.3.26. 2-Amino-6-methoxy-pyrimidine-4-carboxylic acid 56. 2-Amino-6-chloro-pyrimidine-4-carboxylic acid methyl ester **40** (500 mg, 2.67 mmol) was dissolved in methanol (25 mL) under the addition of 4 N hydrochloric acid in 1,4-dioxan (0.5 mL) and heated to reflux for 18 h. The solvents were evaporated under reduced pressure and the white residue was taken up in water. Saturated aqueous sodium hydrogen carbonate solution was added until pH 8 was reached and a white precipitate formed. This was filtered off, rinsed with diethyl ether and dried. Yield = 93%; NMR δ_H (400 MHz, DMSO) 3.81 (3H, s), 3.85 (3H, s), 6.49 (1H, s), 7.01 (2H, br s); *m*/*z* 184 $(M+H)^+$; retention time 1.60 min (Method C).

This white solid was suspended in water (10 mL) and 2 N aqueous lithium hydroxide solution (5 mL). After 10 min, the starting material had dissolved completely and 2 N hydrochloric acid (5 mL) was added. A white precipitate formed which was filtered off, rinsed with water and dried to give **56**. Yield = 98%; *m*/*z* 170 $(M+H)^+$; retention time 0.37 min (Method C).

The following derivatives were prepared from **56**, using the previously described coupling general amide coupling method.

3.3.3.27. *N*-((Pyridin-2-yl)methyl)-2-amino-6-phenyl-pyrimidine-4-carboxamide 57. Yield = 27%; NMR δ_H (400 MHz, $CDCl_3$) 4.63 (2H, d, *J* 6.0 Hz), 6.99 (2H, br s), 7.30 (1H, m), 7.36 (1H, d, *J* 7.8 Hz), 7.53 (1H, d, *J* 2.2 Hz), 7.54 (2H, d, *J* 1.7 Hz), 7.62 (1H, s), 7.79 (1H, dt, *J* 1.7 Hz, 4.2 Hz), 8.13 (2H, m), 8.54 (1H, m), 9.03 (1H, t, *J* 6.0 Hz); *m*/*z* 306 $(M+H)^+$, retention time 2.03 min (Method C).

3.3.3.28. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-phenyl-pyrimidine-4-carboxamide 58. Yield = 16%; NMR δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s), 4.63 (2H, d, *J* 5.9 Hz), 7.07 (2H, br s), 7.27 (2H, dd, *J* 4.8 Hz, 7.5 Hz), 7.52 (1H, d, *J* 1.8 Hz), 7.54 (2H, d, *J* 1.8 Hz), 7.65 (1H, s), 8.13 (2H, m), 8.42 (1H, d, *J* 3.9 Hz), 9.12 (1H, t, *J* 5.9); *m*/*z* 320 $(M+H)^+$, retention time 1.98 min (Method C).

3.3.3.29. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2-fluorophenyl)-pyrimidine-4-carboxamide 59. Yield = 74%; NMR δ_H (400 MHz, DMSO) 4.63 (2H, d, *J* 6.0 Hz), 7.03 (2H, br s), 7.30 (1H, m), 7.37 (3H, m), 7.53 (1H, d, *J* 3.0 Hz), 7.58 (1H, m), 7.78 (1H, td, *J* 1.8 Hz, 7.7 Hz), 8.02 (1H, td, *J* 1.8 Hz, 7.7 Hz), 8.55 (1H, d, *J* 5.0 Hz), 9.01 (1H, t, *J* 6.0 Hz); *m*/*z* 324 $(M+H)^+$, retention time 1.20 min (Method A).

3.3.3.30. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-fluorophenyl)pyrimidine-4-carboxamide 60. Yield = 55%; NMR δ_H (400 MHz, DMSO) 9.09 (1H, t, *J* 5.0 Hz), 8.42 (1H, dm, *J* 5.0 Hz), 8.03 (1H, td, *J* 7.7, 1.8 Hz), 7.64 (1H, d, *J* 7.5 Hz), 7.59 (1H, m), 7.56 (1H, d, *J* 2.5 Hz), 7.37 (2H, tm, *J* 8.8 Hz), 7.28 (1H, dd, *J* 4.5, 3.0 Hz), 7.10 (2H, br s), 4.63 (2H, d, *J* 5.0 Hz), 2.33 (3H, s); *m*/*z* 338 $(M+H)^+$, retention time 2.16 min (Method A).

3.3.3.31. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(3-fluorophenyl)-pyrimidine-4-carboxamide 61. Yield = 25%; NMR δ_H (400 MHz, DMSO) 4.64 (2H, d, *J* 6.0 Hz), 7.02 (2H, br s), 7.30 (1H, dd, *J* 5.0 Hz, 7.5 Hz), 7.38 (2H, m), 7.58 (1H, td, *J* 6.0 Hz, 8.0 Hz), 7.65 (1H, s), 7.78 (1H, td, *J* 1.8 Hz, 7.6 Hz), 7.93 (1H, dm, *J* 10.5 Hz), 7.98 (1H, dm, *J* 7.5 Hz), 8.54 (1H, dm, *J* 5.5 Hz), 9.01 (1H, t, *J* 6.0 Hz); *m*/*z* 324 $(M+H)^+$, retention time 2.25 min (Method A).

3.3.3.32. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(3-fluorophenyl)pyrimidine-4-carboxamide 62. Yield = 16%; NMR δ_H (400 MHz, DMSO) 2.34 (3H, s), 4.64 (2H, d, *J* 5.0 Hz), 7.09 (2H, br s), 7.27 (1H, dd, *J* 7.5, 4.5 Hz), 7.39 (1H, td, *J* 2.8 Hz, 8.5 Hz), 7.58 (1H, td, *J* 6.0 Hz, 8.0 Hz), 7.64 (1H, dm, *J* 7.5 Hz), 7.68 (1H, s), 7.94 (1H, dm, *J* 10.3 Hz), 7.99 (1H, dm, *J* 8.0 Hz), 8.42 (1H, dm, *J* 5.0 Hz), 9.09 (1H, t, *J* 4.8 Hz); *m*/*z* 338 $(M+H)^+$, retention time 3.78 min (Method A).

3.3.3.33. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2-chlorophenyl)-pyrimidine-4-carboxamide 63. Yield = 5%; NMR δ_H (400 MHz, DMSO) 4.62 (2H, d, *J* 6.0 Hz), 7.07 (2H, br s), 7.30 (1H, qd, *J* 1.1 Hz, 6.0 Hz), 7.33 (1H, s), 7.36 (1H, d, *J* 7.8 Hz), 7.48 (2H, m), 7.62 (2H, m), 7.77 (1H, dt, *J* 1.8 Hz, 7.5 Hz), 8.53 (1H, ddd, *J* 0.8 Hz, 1.6 Hz, 5.6 Hz), 9.02 (1H, t, *J* 6.0 Hz); *m*/*z* 340 $(M+H)^+$, retention time 2.03 min (Method C).

3.3.3.34. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-chlorophenyl)pyrimidine-4-carboxamide 64. Yield = 17%; NMR δ_H (400 MHz, DMSO) 2.31 (3H, s), 4.64 (2H, d, *J* 4.9 Hz), 7.15 (2H, br

s), 7.27 (1H, dd, *J* 4.8 Hz, 7.7 Hz), 7.35 (1H, s), 7.49 (2H, m), 7.63 (3H, m), 8.41 (1H, dd, *J* 1.0 Hz, 5.0 Hz), 9.10 (1H, t, *J* 4.9 Hz); *m*/*z* 354 $(M+H)^+$, retention time 2.11 min (Method C).

3.3.3.35. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(3-chlorophenyl)-pyrimidine-4-carboxamide 65. Yield = 5%; NMR δ_H (400 MHz, DMSO) 4.62 (2H, d, *J* 6.0 Hz), 7.07 (2H, br s), 7.30 (1H, qd, *J* 1.1 Hz, 6.0 Hz), 7.33 (1H, s), 7.36 (1H, d, *J* 7.8 Hz), 7.48 (2H, m), 7.62 (2H, m), 7.77 (1H, dt, *J* 1.8 Hz, 7.5 Hz), 8.53 (1H, ddd, *J* 0.8 Hz, 1.6 Hz, 5.6 Hz), 9.02 (1H, t, *J* 6.0 Hz); *m*/*z* 340 $(M+H)^+$, retention time 2.03 min (Method C).

3.3.3.36. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(3-chlorophenyl)pyrimidine-4-carboxamide 66. Yield = 8%; NMR δ_H (400 MHz, DMSO) 2.35 (3H, s), 4.63 (2H, d, *J* 4.9 Hz), 7.13 (2H, br s), 7.27 (1H, dd, *J* 4.9 Hz, 7.5 Hz), 7.62 (3H, m), 7.68 (1H, s), 8.09 (1H, dt, *J* 1.4 Hz, 7.7 Hz), 8.19 (1H, t, *J* 1.7 Hz), 8.41 (1H, d, *J* 3.7 Hz), 9.10 (1H, t, *J* 4.9 Hz); *m*/*z* 354 $(M+H)^+$, retention time 2.36 min (Method C).

3.3.3.37. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(ortho-tolyl)pyrimidine-4-carboxamide 67. Yield = 36%; NMR δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s), 4.62 (2H, d, *J* 5.9 Hz), 6.97 (2H, br s), 7.18 (1H, s), 7.33 (5H, m), 7.42 (1H, m), 7.78 (1H, dt, *J* 1.8 Hz, 7.7 Hz), 8.54 (1H, m), 9.03 (1H, t, 5.9 Hz); *m*/*z* 320 $(M+H)^+$, retention time 2.06 min (Method C).

3.3.3.38. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(ortho-tolyl)pyrimidine-4-carboxamide 68. Yield = 45%; NMR δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s), 2.37 (3H, s), 4.63 (2H, d, *J* 5.9 Hz), 7.05 (2H, br s), 7.21 (1H, s), 7.28 (2H, m), 7.32 (1H, d, *J* 0.7 Hz), 7.35 (1H, m), 7.43 (1H, m), 7.64 (1H, m), 8.41 (1H, dd, *J* 1.0 Hz, 4.8 Hz), 9.10 (1H, t, *J* 5.9 Hz); *m*/*z* 334 $(M+H)^+$, retention time 2.12 min (Method C).

3.3.3.39. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(meta-tolyl)pyrimidine-4-carboxamide 69. Yield = 11%; δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s), 4.63 (2H, d, *J* 5.9), 6.96 (2H, br s), 7.35 (4H, m), 7.61 (1H, s), 7.77 (1H, dt, *J* 1.8 Hz, 7.7 Hz), 7.91 (1H, d, *J* 7.7 Hz), 7.96 (1H, br s), 8.54 (1H, d, *J* 4.3 Hz), 9.02 (1H, t, *J 5.9 Hz); m/z* 320 $(M+H)^+$, retention time 2.18 min (Method C).

3.3.3.40. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(meta-tolyl)pyrimidine-4-carboxamide 70. Yield = 42%; NMR δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s), 2.40 (3H, s), 4.64 (2H, d, *J* 5.9 Hz), 7.05 (2H, br s), 7.27 (2H, dd, *J* 4.7 Hz, 7.6 Hz), 7.36 (2H, m), 7.64 (1H, s), 7.91 (1H, d, *J* 7.6 Hz), 7.96 (1H, br s), 8.42 (1H, dd, *J* 0.9 Hz, 4.7 Hz), 9.11 (1H, t, *J* 5.9 Hz); *m*/*z* 334 $(M+H)^+$, retention time 2.26 min (Method C).

3.3.3.41. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(para-tolyl)pyrimidine-4-carboxamide 71. Yield = 25%; NMR δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s), 4.63 (2H, d, *J* 6.0 Hz), 6.94 (2H, br s), 7.30 (4H, m), 7.59 (1H, s), 7.80 (1H, dt, *J* 1.9 Hz, 3.4 Hz), 8.03 (2H, d, *J* 7.8 Hz), 8.53 (1H, m), 9.01 (1H, t, *J* 6.0 Hz); *m*/*z* 320 $(M+H)^+$, retention time 2.17 min (Method C).

3.3.3.42. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(para-tolyl)pyrimidine-4-carboxamide 72. Yield = 18%; NMR δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s), 2.38 (3H, s), 4.62 (2H, d, *J* 6.0 Hz), 7.02 (2H, br s), 7.27 (1H, dd, *J* 4.8 Hz, 7.4 Hz), 7.32 (2H, d, *J* 8.2 Hz), 7.62 (1H, s), 7.64 (1H br s), 8.04 (2H, d, *J* 8.2 Hz), 8.41 (1H, d, *J* 3.8 Hz), 9.11 (1H, t, *J* 6.0 Hz); *m*/*z* 334 $(M+H)^+$, retention time 2.25 min (Method C).

3.3.3.43. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2-methoxyphenyl)-pyrimidine-4-carboxamide 73. Yield = 68%; δ_H (400 MHz, DMSO); 3.86 (3H, s), 4.62 (2H, d, *J* 6.0 Hz), 6.84 (2H, br s), 7.07 (1H, td, *J* 7.5, 1.0 Hz), 7.18 (1H, d, *J* 8.0 Hz), 7.30 (1H, m), 7.36 (1H, d, *J* 8.0 Hz), 7.48 (1H, tdm, *J* 2.0 Hz, 7.5 Hz), 7.64 (1H, s), 7.78 (1H, td, *J* 2.0 Hz, 7.5 Hz), 7.83 (1H, dd, *J* 2.0 Hz, 7.5 Hz), 8.98 (1H, t, *J* 5.7 Hz), 8.54 (1H, dm, *J* 5.0 Hz); *m*/*z* 336 $(M+H)^+$, retention time 1.01 min (Method A).

3.3.3.44. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-methoxyphenyl)pyrimidine-4-carboxamide 74. Yield = 72%; NMR δ_H (400 MHz, DMSO) 2.33 (3H, s), 3.87 (3H, s), 4.62 (2H, d, *J* 5.0 Hz), 6.91 (2H, br s), 7.08 (1H, td, *J* 1.0 Hz, 7.5 Hz), 7.18 (1H, d, *J* 7.5 Hz), 7.27 (1H, dd, *J* 5.0 Hz, 7.5 Hz), 7.48 (1H, m), 7.64 (1H, dd, *J* 1.0 Hz, 7.5 Hz), 7.67 (1H, s), 7.83 (1H, dd, *J* 1.8 Hz, 7.8 Hz), 8.42 (1H, dd, *J* 1.0 Hz, 5.0 Hz), 9.06 (1H, t, *J* 5.0 Hz); *m*/*z* 350 $(M+H)^+$, retention time 1.81 min (Method A).

3.3.3.45. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(3-methoxyphenyl)pyrimidine-4-carboxamide 75. Yield = 5%; NMR (400 MHz, DMSO) δ_H 3.84 (3H, s), 4.62 (2H, d, *J* 5.9 Hz), 7.00 (2H, br s), 7.12 (1H, dd, *J* 1.7 Hz, 7.6 Hz), 7.29 (1H, dd, *J* 0.6 Hz, 4.8 Hz), 7.36 (1H, d, *J* 7.9 Hz), 7.44 (1H, t, *J* 7.9 Hz), 7.61 (1H, s), 7.66 (2H, m), 7.77 (1H, dt, *J* 1.7 Hz, 7.6 Hz), 8.53 (1H, dd, *J* 0.6 Hz, 4.8 Hz), 9.03 (1H, t, 5.9 Hz); *m*/*z* 336 $(M+H)^+$, retention time 2.07 min (Method C).

3.3.3.46. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(3-methoxyphenyl)pyrimidine-4-carboxamide 76. Yield = 5%; NMR δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s), 3.84 (3H, s), 4.62 (2H, d, *J* 5.9 Hz), 7.07 (2H, br s), 7.11 (1H, dd, *J* 1.5 Hz, 8.1 Hz), 7.27 (1H, dd, *J* 4.6 Hz, 7.5 Hz), 7.44 (1H, t, *J* 8.0 Hz), 7.63 (1H, s), 7.66 (2H, m), 7.68 (1H, dt, J 1.3 Hz, 7.5 Hz), 8.41 (1H, dd, *J* 1.0 Hz, 4.6 Hz), 9.11 (1H, t, *J* 5.9 Hz); *m*/*z* 350 $(M+H)^+$, retention time 2.03 min (Method C).

3.3.3.47. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(4-methoxyphenyl)pyrimidine-4-carboxamide 77. Yield = 47%, NMR δ_H (400 MHz, DMSO); 3.84 (3H, s), 4.63 (2H, d, *J* 5.5 Hz), 6.86 (2H, br s), 7.07 (2H, d, *J* 9.0 Hz), 7.30 (1H, m), 7.36 (1H, d, *J* 7.5 Hz), 7.58 (1H, s), 7.78 (1H, m), 8.11 (2H, d, *J* 8.5 Hz) 8.55 (1H, br d), 8.98 (1H, br t); *m*/*z* 336 $(M+H)^+$, LC retention time 1.40 min (Method A).

3.3.3.48. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(4-methoxyphenyl)pyrimidine-4-carboxamide 78. Yield = 23%, NMR δ_H (400 MHz, DMSO) 2.34 (3H, s), 3.84 (3H, s), 4.63 (2H, d, *J* 5.0 Hz), 6.93 (2H, br s), 7.06 (2H, d, *J* 9.0 Hz), 7.27 (1H, m), 7.60 (1H, s), 7.63 (1H, br d), 8.11 (2H, d, *J* 9.0 Hz), 8.41 (1H, br d), 9.07 (1H, br t); *m*/*z* 350 $(M+H)^+$, retention time 2.57 min (Method A).

3.3.3.49. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2-ethylphenyl)-pyrimidine-4-carboxamide 79. Yield = 21%; NMR δ_H (400 MHz, DMSO) 1.08 (3H, t, *J* 7.5 Hz), 2.73 (2H, q, *J* 7.5 Hz), 4.62 (2H, d, *J* 5.8 Hz), 6.96 (2H, br s), 7.15 (1H, s), 7.36 (5H, m), 7.59 (1H, m), 7.78 (1H, td, *J* 1.8 Hz, 7.7 Hz), 8.54 (1H, d, *J* 4.2 Hz), 9.01 (1H, t, *J* 5.8 Hz); *m*/*z* 334 $(M+H)^+$, retention time 2.14 min (Method C).

3.3.3.50. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-ethylphenyl)pyrimidine-4-carboxamide 80. Yield = 27%; NMR δ_H (400 MHz, DMSO) 1.07 (3H, t, *J* 7.4 Hz), 2.33 (3H, s), 2.72 (2H, q, *J* 7.4 Hz), 4.62 (2H, d, *J* 5.0 Hz), 7.03 (2H, br s), 7.17 (1H, s), 7.35 (4H, m), 7.64 (1H, dd, J 0.8 Hz, 7.5 Hz), 8.41 (1H, dd, *J* 0.8 Hz, 3.7 Hz), 9.09 (1H, t, *J* 5.0 Hz); *m*/*z* 348 $(M+H)^+$, retention time 2.25 min (Method C).

3.3.3.51. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2-ethoxyphenyl)pyrimidine-4-carboxamide 81. Yield = 22%; NMR δ_H (400 MHz, DMSO) 1.35 (3H, t, *J* 7.0 Hz), 3.32 (2H, s), 4.14 ((2H, q, *J* = 7.0 Hz), 4.62 (2H, d, *J* = 5.9 Hz), 6.84 (2H, br s), 7.06 (1H, t, *J* 7.4 Hz), 7.15 (1H, d, *J* 8.3 Hz), 7.29 (1H, dd, *J* 5.2 Hz, 7.4 Hz), 7.35 (1H, d, *J* 7.8 Hz), 7.45 (1H, td, *J* 1.7 Hz, 7.8 Hz), 7.78 (1H, td, *J* 1.7 Hz, 7.8 Hz), 7.81 (1H, s), 7.88 (1H, dd, *J* 1.7 Hz, 7.8 Hz), 8.54 (1H, d, *J* 4.7 Hz), 8.97 (1H, t, *J* 5.9 Hz); *m*/*z* 350 $(M+H)^+$, retention time 2.10 min (Method C).

3.3.3.52. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-ethoxyphenyl)pyrimidine-4-carboxamide 82. Yield = 25%; NMR δ_H (400 MHz, DMSO) 1.36 (3H, t, *J* 6.8 Hz), 2.32 (3H, s), 4.15 (2H, q, *J* 6.8 Hz), 4.63 (2H, d, *J* 4.9 Hz), 6.91 (2H, br s), 7.06 (1H, td, *J* 0.9 Hz, 7.8 Hz), 7.15 (1H, d, *J* 8.3 Hz), 7.26 (1H, dd, *J* 4.9 Hz, 7.5 Hz), 7.45 (2H, m), 7.26 (2H, m), 7.84 (1H, s), 7.90 (1H, dd, *J* 1.8 Hz, 6.7 Hz), 9.01 (1H, t, *J* 4.9 Hz); *m*/*z* 364 $(M+H)^+$, retention time 2.18 min (Method C).

3.3.3.53. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(2-cyanophenyl)-pyrimidine-4-carboxamide 83. Yield = 2%; NMR δ_H (400 MHz, MeOD) 4.72 (2H, d, *J* 0.7 Hz), 7.33 (1H, dd, *J* 0.5 Hz, 3.9 Hz), 7.43 (1H, d, *J* 7.8 Hz), 7.63 (1H, s), 7.67 (1H, td, *J* 1.2 Hz, 6.7 Hz), 7.80 (2H, m), 7.91 (2H, m), 8.51 (1H, dd, *J* 0.7 Hz, 4.0 Hz); *m*/*z* 331 $(M+H)^+$, retention time 1.87 min (Method C).

3.3.3.54. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(2-cyanophenyl)-pyrimidine-4-carboxamide 84. Yield = 4%; NMR δ_H (400 MHz, MeOD) 3.29 (3H, t, *J* 1.6 Hz), 4.71 (2H, s), 7.24 (1H, dd, *J* 4.8 Hz, 6.6 Hz), 7.63 (1H, s), 7.65 (2H, m), 7.78 (1H, td, *J* 1.6 Hz, 7.8 Hz), 7.90 (2H, m), 8.37 (1H, d, *J* 4.8 Hz); *m*/*z* 344 $(M+H)^+$, retention time 1.91 min (Method C).

3.3.3.55. *N*-((Pyridin-2-yl)methyl)-2-amino-6-(3′-cyanophenyl)-pyrimidine-4-carboxamide 85. Yield = 16%; NMR δ_H (400 MHz, $CDCl_3$) 4.63 (2H, d, *J* 5.9 Hz), 7.22 (2H, br s), 7.29 (1H, dd, *J* 1.1 Hz, 7.5 Hz), 7.34 (1H, d, *J* 8.2 Hz), 7.74 (1H, s), 7.77 (2H, m), 8.18 (1H, dt, *J* 1.4 Hz, 6.5 Hz), 8.45 (1H, m), 8.54 (1H, m), 8.58 (1H, m), 9.05 (1H, t, 5.9 Hz); *m*/*z* 331 $(M+H)^+$, retention time 2.01 min (Method C).

3.3.3.56. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-(3′-cyanophenyl)-pyrimidine-4-carboxamide 86. Yield = 24%; NMR δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s), 4.64 (2H, d, *J* 5.9 Hz), 7.19 (2H, br s), 7.27 (1H, dd, *J* 4.9 Hz, 7.5 Hz), 7.64 (1H, d, *J* 7.5 Hz), 7.74 (1H, t, *J* 7.8 Hz), 7.76 (1H, s), 8.01 (1H, d, *J* 7.8 Hz), 8.41 (1H, d, *J* 3.9 Hz), 8.47 (1H, d, *J* 8.1 Hz), 8.59 (1H, br s), 9.13 (1H, t, *J* 5.9 Hz); *m*/*z* 345 $(M+H)^+$, retention time 2.07 min (Method C).

3.3.3.57. *N*-((Pyridin-2-yl)methyl)-2-amino-6-methoxy-pyrimidine-4-carboxamide 87. Yield = 55%; NMR δ_H (400 MHz, DMSO) 3.86 (3H, s), 4.57 (2H, d, *J* 5.9 Hz), 6.52 (1H, s), 6.84 (2H, br s), 7.28 (2H, m), 7.34 (1H, br s), 7.75 (1H, dt, *J* 7.7 Hz), 8.52 (1H, m), 8.84 (1H, t, *J* 5.9 Hz); *m*/*z* 260 $(M+H)^+$, retention time 1.53 min (Method C).

3.3.3.58. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-6-methoxy-pyrimidine-4-carboxamide 88. Yield = 16%; NMR δ_H (400 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.5, 7.2 Hz), 2.4 (3H, s), 2.76 (2H, q, *J* 7.3 Hz), 4.51 (2H, d, *J* 6.1 Hz), 6.32 (1H, dd, *J* 1.0, 2.4 Hz), 6.62 (2H, br s), 7.03 (1H, d, *J* 3.3 Hz), 7.27 (1H, m), 7.37 (1H, d, *J* 7.8 Hz), 7.77 (1H, m), 8.51 (1H, m), 9.06 (1H, br t, *J* 6.1 Hz); *m*/*z* 338 $(M+H)^+$, retention time 1.91 min (Method C).

3.3.3.59. Methyl-2-amino-6-hydroxy-5-methyl-pyrimidine-4-carboxylate 89. Diethyl oxalopropionate (9.56 g, 47.3 mmol) was dissolved in 2.5 M aqueous sodium hydroxide solution (20 mL). Guanidine carbonate (4.26 g, 23.64 mmol) was added to the solution which was then heated to 100 °C for 18 h. The reaction mixture was cooled to room temperature and acidified to pH 2 with 2 M hydrochloric acid. The white precipitate was then filtered off and dried, then suspended in methanol (100 mL). Concentrated sulfuric acid (98%, 15 mL) was slowly added, upon which the reagent dissolved completely. The solution was heated to reflux for 24 h, then cooled to room temperature and carefully neutralized with aqueous ammonia (Sp. Gr. 1.18, 40 mL). Methanol was removed under reduced pressure and the residue filtered off and dried.

Yield = 65%; δ_H (400 MHz, DMSO) 1.83 (s, 3H), 3.77 (s, 3H), 6.52 (br s, 2H), 11.13 (br s, 1H); *m*/*z* 184 $(M+H)^+$, retention time 0.74 min (Method C).

This crude solid was suspended in phosphorous oxychloride (20 mL) and heated to reflux for 2 h. The reaction was cooled to room temperature, evaporated in vacuo and the residue was poured onto saturated aqueous solution of sodium hydrogen carbonate (90 mL). The product was extracted into 2-butanone (2 × 50 mL) and adsorbed onto sorbent granules. Purification was carried out by flash chromatography on 20 g silica gel, eluting with hexane–ethyl acetate (1:1) to give **89** as a white solid.

Yield = 49%; δ_H (400 MHz, $CDCl_3$) 2.13 (3H, s), 3.86 (3H, s), 7.19 (2H, br s); *m*/*z* 202 $(M+H)^+$, retention time 1.56 min (Method C).

The following intermediate was also synthesized by this method.

3.3.3.60. Methyl-2-Amino-5-ethyl-6-hydroxy-pyrimidine-4-carboxylate 90. Yield = 74%; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.4 Hz), 2.23 (2H, q, *J* 7.3 Hz), 3.77 (3H, s), 6.55 (2H, br s), 11.10 (1H, br s); *m*/*z* 216 $(M+H)^+$, retention time 2.01 min (Method C).

Using the methods described above, these intermediates were converted to:

3.3.3.61. *N*-((Pyridin-2-yl)methyl)-2-amino-5-methyl-6-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 91. Yield = 30%; δ_H (400 MHz, DMSO) 2.30 (3H, s), 2.37 (3H, s), 4.51 (2H, d, *J* 6.1 Hz), 6.33 (1H, dd, *J* 0.9 Hz, 2.4 Hz), 6.62 (2H, br s), 7.04 (1H, d, *J* 3.3 Hz), 7.27 (1H, m), 7.37 (1H, d, *J* 7.8 Hz), 7.77 (1H, m), 8.51 (1H, m), 9.06 (1H, br t, 1H, *J* 6.1 Hz); *m*/*z* 324 $(M+H)^+$, retention time 1.76 min (Method C).

3.3.3.62. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-5-methyl-6-(5′-methyl-2′-furyl)-pyrimidine-4-carboxamide 92. Yield = 36%; δ_H (400 MHz, DMSO) 2.34 (3H, s), 2.35 (3H, s), 2.37 (3H, s), 4.54 (2H, d, *J* 5.2 Hz), 6.32 (1H, dd, *J* 1.0 Hz, 2.4 Hz), 6.61 (2H, br s), 7.04 (1H, d, *J* 3.4 Hz), 7.22 (1H, dd, *J* 2.7 Hz, 4.8 Hz), 7.60 (1H, m), 8.36 (1H, dd, *J* 1.0 Hz, 3.7 Hz), 8.85 (1H, br t, *J* 5.2 Hz); *m*/*z* 338 $(M+H)^+$, retention time 1.78 min (Method C).

3.3.3.63. *N*-((Pyridin-2-yl)methyl)-2-amino-5-ethyl-6-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 93. Yield = 16%; δ_H (400 MHz, DMSO) 1.09 (3H, t, *J* 7.5 Hz), 2.4 (3H, s), 2.76 (2H, q, *J* 7.3 Hz), 4.51 (2H, d, *J* 6.1 Hz), 6.32 (1H, dd, *J* 1.0 Hz, 2.4 Hz), 6.62 (2H, br s), 7.03 (1H, d, *J* 3.3 Hz), 7.27 (1H, m), 7.37 (1H, d, *J* 7.8 Hz), 7.77 (1H, m), 8.51 (1H, m), 9.06 (1H, br t, *J* 6.1 Hz); *m*/*z* 338 $(M+H)^+$, retention time 1.91 min (Method C).

3.3.3.64. *N*-((3-Methyl-pyridin-2-yl)methyl)-2-amino-5-ethyl-6-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 94. Yield = 23%; δ_H (400 MHz, DMSO) 1.10 (3H, t, *J* 7.3 Hz), 2.35 (3H, s), 2.37 (3H, s), 2.83 (2H, q, *J* 7.0 Hz), 4.54 (2H, d, *J* 5.3 Hz), 6.31 (1H, dd, *J* 0.9 Hz, 2.4 Hz), 6.61 (2H, br s), 7.02 (1H, d, *J* 3.3 Hz), 7.22 (1H, dd, *J* 2.7 Hz, 4.8 Hz), 7.60 (1H, d, *J* 7.0 Hz), 8.35 (1H, m), 8.83 (1H, br t, *J* 5.3 Hz); *m*/*z* 352 $(M+H)^+$, retention time 1.96 min (Method C).

3.3.3.65. 6-(5-Methyl-2-furyl)pyrimidine-4-carboxylic acid 98. A solution of 4,6-dichloropyrimidine (9.78 g, 50.0 mmol) in DMSO (200 mL) was treated with sodium cyanide (14.7 g, 300 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.56 g, 5.0 mmol). The suspension was stirred for 4 days, and more DABCO (5.04 g, 45 mmol) and DMSO (100 mL) were added. The suspension was stirred for a further 2 days, poured onto a mixture of ice (750 g) and water (750 mL), the crude product was filtered off, washed with water and MeCN, and dried in air to give the carbonitrile, which was suspended in water (30 mL) was treated carefully with concentrated sulfuric acid (30 mL), stirred at 100 °C for 2 h, allowed to cool to room temperature and poured onto a mixture of ice (150 g) and water (150 mL). After standing for 1 h the crude product was filtered off, washed with water and MeCN, and dried in air to give the pyrimidine acid (7.02 g, 90%) as a brown solid. Yield = 98%; NMR δ_H (400 MHz, DMSO) 2.43 (3H, s), 6.37 (1H, d, *J* 2.5 Hz), 7.40 (1H, d, *J* 2.5 Hz), 8.04 (1H, s), 9.16 (1H, s); *m*/*z* 205 $(M+H)^+$, retention time 1.55 min (Method C).

The following derivatives were also made using the method detailed above.

3.3.3.66. 2-Methyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxylic acid 99. Yield = 70%; NMR δ_H (400 MHz, DMSO) 2.68 (3H, s), 3.18 (3H, s), 6.42 (1H, d, *J* 3.3 Hz), 7.44 (1H, d, *J* 3.3 Hz) and 7.94 (1H, s).

3.3.3.67. 2-Isopropyl-6-(5-methyl-2-furyl)pyrimidine-4-carboxylic acid 100. Yield = 93%; NMR δ_H (400 MHz, $CDCl_3$) 1.39 (6H, d, *J* 6.9 Hz), 2.45 (3H, s), 3.28 (1H, sept, *J* 6.9 Hz), 6.23 (1H, d, *J* 3.3 Hz), 7.33 (1H, d, *J* 3.4 Hz) and 8.14 (1H, s); *m*/*z* 247 $(M+H)^+$, retention time 2.14 min (Method C).

The desired amines were synthesized from the above derivatives and the appropriate amine, using the general amide coupling method, to give:

3.3.3.68. 6-(5-Methyl-2-furyl)-N-(2-pyridylmethyl)pyrimidine-4-carboxamide 101. Yield = 65%; NMR δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s), 4.75 (2H, d, *J* 5.5 Hz), 6.16 (1H, d, *J* 3.4 Hz), 7.20 - 7.16 (2H, m), 7.28 (1H, d, *J* 7.8 Hz), 7.64 (1H, td, *J* 7.7, 1.8 Hz), 8.26 (1H, s), 8.57 - 8.55 (1H, m), 8.95 (1H, br s) and 9.07 (1H, s); *m*/*z* 295 $(M+H)^+$, retention time 2.04 min (Method C).

3.3.3.69. *N*-(2-Pyridylmethyl)-2-Methyl-6-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 102. Yield = 35%; NMR δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s), 2.70 (3H, s), 4.75 (2H, d, *J* 5.8 Hz), 6.14 (1H, d, *J* 3.4 Hz), 7.18–7.16 (2H, m), 7.31 (1H, d, *J* 7.8 Hz), 7.64 (1H, td, *J* 7.7, 1.8 Hz), 8.08 (1H, s), 8.57 - 8.55 (1H, m) and 8.88 (1H, br s); *m*/*z* 309 $(M+H)^+$, retention time 2.15 min (Method C).

3.3.3.70. *N*-(2-Pyridylmethyl)-2-Isopropyl-6-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 103. Yield = 32%; NMR δ_H (400 MHz, $CDCl_3$) 1.40 (6H, d, *J* 6.9 Hz), 2.44 (3H, s), 3.27 (1H, sept, *J* 6.9 Hz), 4.84 (2H, d, *J* 5.8 Hz), 6.21 (1H, d, *J* 3.3 Hz), 7.26–7.24 (2H, m), 7.40 (1H, d, *J* 7.8 Hz), 7.72 (1H, td, *J* 7.7, 1.6 Hz), 8.16 (1H, s), 8.63 (1H, d, *J* 4.3 Hz) and 9.05 (1H,br s); *m*/*z* 337 $(M+H)^+$, retention time 2.63 min (Method C).

3.3.3.71. [4-Chloro-6-(5-methylfuran-2-yl)-pyrimidin-2-yl]-methylamine 105. A mixture of 2,4,6-trichloropyrimide (**104**) (5.50 g, 30 mmol), 5-methylfuran-2-boronic acid, methyl ester (4.91 g, 30 mmol), saturated aqueous sodium hydrogencarbonate (30 mL) and tetrahydrofuran (30 mL) was degassed with a stream of nitrogen for 10 min. Palladium(0) tetrakis(triphenylphosphine) (1.73 g, 1.5 mmol) was then added, and the reaction mixture was heated at reflux under a nitrogen atmosphere for 18 h. The reaction mixture was then cooled and partitioned between dichloromethane and water. The organic phase was separated and the aqueous phase extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was subjected to silica-gel column chromatography [hexane then hexane–EtOAc (9:1) as eluent]. The eluted material, obtained as a pale-yellow solid (5.08 g, 74%), was identified as 2,4-dichloro-6-(5-methylfuran-2-yl)-pyrimidine; NMR δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s), 6.22–6.23 (1H, m), 7.30–7.31 (1H, m) and 7.47 (1H, s).

To a solution of 2,4-dichloro-6-(5-methylfuran-2-yl)-pyrimidine (2) (0.70 g, 3.07 mmol) in methanol (5 mL) was added a 2 N solution of methylamine in ethanol (2 mL, 4 mmol). The reaction mixture was heated at 80 °C for 30 min, cooled and then evaporated. The residual material was subjected to silica-gel column chromatography [hexane then hexane–EtOAc (0–10%) as eluent] to give **105** as a white solid (0.17 g, 22%); NMR δ_H (400 MHz, CD_3OD) 2.38 (3H, s), 2.93 (3H, s), 6.22–6.23 (1H, m), 6.83 (1H, s) and 7.12–7.13 (1H, m); MS (ES+) *m*/*z* $(M+H)^+$ 224 (100).

3.3.3.72. 2-Methylamino-6-(5-methylfuran-2-yl)-pyrimidine-4-carboxylic acid 107. A solution of [4-chloro-6-(5-methylfuran-2-yl)-pyrimidin-2-yl]-methylamine **105** (0.17 g, 0.76 mmol), sodium cyanide (0.22 g, 4.56 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.09 g, 0.76 mmol) in 1-methyl-2-pyrrolidinone (6 mL) was heated at 80 °C for 1.5 h. The reaction mixture was cooled, poured onto an ice-water mixture and the resulting precipitate was filtered. The residue was washed with dichloromethane–methanol, and the resulting solution was evaporated to a brown solid. The material was subjected to silica-gel column chromatography [hexane–EtOAc (0–10%) as eluent] to give the nitrile as a white solid (0.073 g, 45%), which was contaminated with 1-methyl-2-pyrrolidinone; NMR δ_H (400 MHz, CD_3OD) (inter alia) 2.40 (3H, s), 2.93 (3H, s), 6.26–6.27 (1H, m), 7.16 (1H, s) and 7.21–7.22 (1H, m); *m*/*z* $(M+H)^+$ 215.

A solution of 2-methylamino-6-(5-methylfuran-2-yl)-pyrimidine-4-carbonitrile (0.073 g, 0.34 mmol) in water and (4 mL) and concentrated sulfuric acid (4 mL) was heated at reflux for 4 h. The reaction mixture was then cooled and poured onto ice but did not solidify. The material could not be extracted into ethyl acetate, owing to its zwitterionic nature. The solution was introduced onto an acidic ion-exchange column (Isolute® Flash SCX-2). The column was eluted with dichloromethane–methanol, followed by 1 N ammonia–methanol, yielding XX as a pale brown solid (0.08 g, *quant.*); NMR δ_H (400 MHz, CD_3OD) 2.39 (3H, s), 2.99 (3H, s), 6.21–6.22 (1H, m), 7.11–7.12 (1H, m) and 7.33 (1H, s); *m*/*z* $(M+H)^+$ 234.

3.3.3.73. *N*-(Pyridin-2-ylmethyl)-2-Methylamino-6-(5-methylfuran-2-yl)-pyrimidine-4-carboxamide 109. A mixture of 2-methylamino-6-(5-methylfuran-2-yl)-pyrimidine-4-carboxylic acid **107** (0.080 g, 0.34 mmol), 2-(aminomethyl)pyridine (0.074 g, 0.68 mmol), polymer supported carbodiimide (0.86 g, 1.04 mmol), 1-hydroxybenzotriazole (0.07 g, 0.52 mmol) and *N*,*N*′-diisopropylethylamine (0.09 mL, 0.52 mmol) in dimethyl formamide (5 mL) was stirred at ambient temperature. After 16 h, the reaction mixture was filtered through Celite, and the filtrate was partitioned between water and ethyl acetate. The organic phase was separated, and the aqueous phase was twice re-extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting syrup was subjected to silica-gel column chromatography [hexane–EtOAc (0–100%) gradient] to give a yellow gum, which was subjected to preparative LC–MS, giving XX as an off-white solid (0.01 g, 9%); NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.02 (3H, s), 4.71 (2H, s), 6.23–6.24 (1H, m), 7.16 (1H, d, *J* 3.5 Hz), 7.32 (1H, dd, *J* 7.5 and 5.5 Hz), 7.42 (1H, d, *J* 7.5 Hz), 7.46 (1H, s), 7.78–7.83 (1H, m) and 8.50 (1H, d, *J* 4.5 Hz); MS (ES+) *m*/*z* $(M+H)^+$ 324.

3.3.3.74. [4-Chloro-6-(5-methylfuran-2-yl)pyrimidin-2-yl]-dimethylamine 106. A mixture of (4,6-dichloropyrimidin-2-yl)dimethylamine (3.32 g, 17.3 mmol), 5-methylfuran-2-boronic acid methyl ester (2.66 g, 17.3 mmol), saturated aqueous sodium hydrogencarbonate (15 mL) and tetrahydrofuran (15 mL) was degassed with a stream of nitrogen for 10 min. Palladium(0) tetrakis(triphenylphosphine) (1.00 g, 0.87 mmol) was then added, and the reaction mixture was heated at reflux under a nitrogen atmosphere for 18 h. The reaction mixture was then cooled and partitioned between dichloromethane and water. The organic phase was separated and the aqueous phase twice extracted with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was subjected to silica-gel column chromatography [hexane then hexane–EtOAc (9:1) as eluent], giving **106** as a pale-yellow solid (1.46 g, 36%); NMR δ_H (400 MHz, CD_3OD) 2.38 (3H, s), 3.17 (6H, s), 6.20–6.22 (1H, m), 6.76 (1H, s) and 7.10–7.11 (1H, m); m/z $(M+H)^+$ 238 (100%).

3.3.3.75. 2-Dimethylamino-6(5-methylfuran-2-yl)-pyrimidine-4-carboxylic acid, lithium salt 108. A solution of [4-chloro-6-(5-methylfuran-2-yl)pyrimidin-2-yl]dimethylamine **106** (1.44 g, 6.06 mmol), sodium cyanide (1.78 g, 36.35 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.68 g, 6.06 mmol) in dimethyl sulfoxide (50 mL) was stirred at ambient temperature for 3 days. The reaction mixture was poured onto an ice-water mixture and the resulting precipitate was filtered; the residue was obtained a brown solid (1.40 g). The material was subjected to silica-gel column chromatography [hexane–EtOAc (10:1) as eluent], yielding 2-dimethylamino-6-(5-methylfuran-2-yl)-pyrimidine-4-carbonitrile as a yellow solid (0.68 g, 49%); NMR δ_H (400 MHz, CD_3OD) 2.40 (3H, s), 3.20 (6H, s), 6.25–6.26 (1H, m), 7.11 (1H, s) and 7.21–7.22 (1H, m); m/z $(M+H)^+$ 229.

2-Dimethylamino-6-(5-methylfuran-2-yl)-pyrimidine-4-carbonitrile (0.68 g, 2.98 mmol) in 6 M hydrochloric acid (40 mL) and tetrahydrofuran (10 mL) were heated at reflux for 6 h. The reaction mixture was evaporated and the residue subjected to ion-exchange column chromatography (Isolute® Flash SCX-2). The column was eluted with dichloromethane–methanol, followed by 1 N ammonia–methanol. The eluted material (0.42 g) was identified as a mixture of the desired product (**108**) and its methyl ester. This material was diluted with methanol (15 mL) and water (15 mL) and treated with lithium hydroxide (0.072 g, 1.81 mmol). The reaction mixture was stirred at ambient temperature for 1 h. The resulting precipitate was filtered, and the residue dried in vacuo to afford **108** as a white solid (0.15 g, 30%); NMR δ_H (400 MHz, CD_3OD) 2.38 (3H, s), 3.23 (6H, s), 6.19–6.20 (1H, m), 7.08–7.09 (1H, m) and 7.31 (1H, s); m/z $(M+H)^+$ 248.

The filtrate was evaporated to afford an off-white solid (0.334 g, 68%), which was also identified as largely the desired product **108**.

3.3.3.76. *N*-(Pyridin-2-ylmethyl)-2-Dimethylamino-6-(5-methyl-furan-2-yl)-pyrimidine-4-carboxamide 110. A mixture of 2-dimethylamino-6(5-methylfuran-2-yl)-pyrimidine-4-carboxylic acid, lithium salt **108** (0.100 g, 0.41 mmol), 2-(aminomethyl)-pyridine (0.088 g, 0.82 mmol), polymer supported carbodiimide (1.51 g, 1.81 mmol), 1-hydroxybenzotriazole (0.24 g, 1.81 mmol) and *N*,*N*′-diisopropylethylamine (0.07 mL, 0.41 mmol) in dimethyl formamide (5 mL) was stirred at ambient temperature. After 16 h, the reaction mixture was evaporated. The residue was subjected to silica-gel column chromatography [hexane–EtOAc (0–100%) as eluent]. The eluted material was subjected to preparative LC–MS to give a white solid (0.028 g, 26%); NMR δ_H (400 MHz, CD_3OD) 2.39 (3H, s), 3.26 (6H, s), 4.71 (2H, s), 6.22–6.23 (1H, m), 7.14 (1H, d, *J* 3.5 Hz), 7.29–7.32 (1H, m), 7.42 (1H, s), 7.80 (1H, dt, *J* 7.5, 7.5 and 2.0 Hz) and 8.49–8.51 (1H, m); m/z $(M+H)^+$ 338.

Derivatives **111–123** were prepared from the 2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxylic acid **24** using the general amide synthesis method outlined above.

3.3.3.77. *N*-(6-Methyl-pyridin-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 111. Yield = 44%; NMR δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s), 2.48 (3H, s), 4.55 (2H, d, *J* 6.0 Hz), 6.34–6.35 (1H, m), 6.88 (2H, s), 7.14 (2H, t, *J* 8.0 Hz), 7.21 (1H, d, *J* 23.0 Hz), 7.37 (1H, s), 7.65 (1H, t, *J* 7.5 Hz), 8.92 (1H, t, *J* 6.0 Hz); m/z 324 $(M+H)^+$; LC retention time 1.86 min. (Method C); HRMS found 346.1283. $C_{17}H_{17}N_5O_4Na$ ($[M+Na]^+$) requires 346.1279.

3.3.3.78. *N*-(3,6-Dimethyl-pyridin-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 112. Yield = 11%; NMR δ_H (400 MHz, DMSO) 2.26 (3H, s), 2.39 (3H, s), 2.50 (3H, s), 4.54 (2H, d, *J* 4.8 Hz), 6.98 (2H, br s), 7.11 (1H, d, *J* 7.7 Hz), 7.21 (1H, d, *J* 3.3 Hz), 7.39 (1H, s), 7.51 (1H, d, *J* 7.7 Hz), 9.11 (1H, t, *J* 4.8 Hz); m/z 338 $(M+H)^+$, retention time 1.77 min (Method C).

3.3.3.79. *N*-(4,6-Dimethyl-pyridin-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 113. Yield = 22%; NMR δ_H (400 MHz, DMSO) 2.25 (3H, s), 2.39 (3H, s), 2.43 (3H, s), 4.51 (2H, d, *J* 6 Hz), 6.35 (1H, dd, *J* 3 and 1 Hz), 6.93 (2H, br s), 6.95 (1H, s), 6.35 (1H, s), 7.22 (1H, d, *J* 3 Hz), 7.37 (1H, s) and 8.91 (1H, t, *J* 6 Hz); LC retention time 1.64 min (Method C); m/z $(M+H)^+$ 338.

3.3.3.80. *N*-(5,6-Dimethyl-pyridin-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 114. Yield = 44%, NMR δ_H (400 MHz, DMSO); 2.22 (3H, s), 2.39 (3H, s), 2.43 (3H, s), 4.52 (2H, d, *J* 6.0 Hz), 6.34 (1H, br d), 6.88 (2H, br s), 7.06 (1H, d, *J* 8.0 Hz), 7.21 (1H, br d), 7.36 (1H, s), 7.48 (1H, d, *J* 7.5 Hz), 8.87 (1H, br t); m/z 338 $(M+H)^+$, LC retention time 4.57 min (Method E).

3.3.3.81. *N*-(1-Methyl-1H-pyrrol-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 115. Yield = 52%; NMR δ_H (400 MHz, DMSO) 2.39 (3H, s), 4.50 (2H, d, *J* 6.0 Hz), 6.33–6.34 (1H, m), 6.82 (2H, s), 7.06–7.17 (3H, m), 7.21 (1H, d, *J* 3.5 Hz), 7.35 (1H, s), 7.35–7.41 (1H, m) and 8.91 (1H, t, *J* 6.5 Hz); m/z 312 $(M+H)^+$; HRMS found 310.1294. $C_{16}H_{16}N_5O_2$ ($[M-H]^-$) requires 310.1304.

3.3.3.82. *N*-(Pyrrol-2-ylmethyl)-2-amino-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 116. Yield = 59%; NMR δ_H (400 MHz, DMSO); 2.39 (3H, s), 4.43 (2H, d, *J* 6.0 Hz), 5.94 (1H, m), 5.96 (1H, br m), 6.34 (1H, d, *J* 2.5 Hz), 6.67 (1H, m), 6.88 (2H, br s), 7.20 (1H, d, *J* 3.5 Hz), 7.36 (1H, s), 8.31 (1H, br t), 10.73 (1H, br, s); m/z 298 $(M+H)^+$, retention time 4.97 min (Method D); HRMS found 296.1156. $C_{15}H_{14}N_5O_2$ ($[M-H]^-$) requires 296.1147.

3.3.3.83. *N*-(1,5-Dimethyl-1*H*-pyrrol-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 117. Yield = 5%; IR ν_{max} (DR)/cm^{-1} 3329, 3219, 2939, 1628, 1521, 1217, 1129, 1023, 860 and 777; NMR δ_H (400 MHz, DMSO) 2.39 (3H, s), 3.80 (3H, s), 4.43 (2H, d, *J* 6.0 Hz), 6.15 (1H, d, *J* 2.0 Hz), 6.33–6.34 (1H, m), 6.87 (2H, s), 7.20 (1H, d, *J* 3.5 Hz), 7.36 (1H, s), 7.60 (1H, d, *J* 2.0 Hz) and 8.48 (1H, t, *J* 6.0 Hz); m/z 313 $(M+H)^+$.

3.3.3.84. *N*-(Imidazo-2-ylmethyl)-2-amino-(5-methyl-2-furyl)-pyrimidine-4-carboxamide 118. Yield = 24%, NMR δ_H (400 MHz, DMSO); 2.39 (3H, s), 4.52 (2H, d, *J* 2.5 Hz), 6.34 (1H, d, *J* 2.5 Hz), 6.91 (2H, br s), 6.94 (2H, s), 7.21 (1H, d, *J* 3.0 Hz), 7.37 (1H, s), 8.62 (1H, br t); m/z 299 $(M+H)^+$, LC retention time 2.19 min (Method D); HRMS found 297.1113. $C_{14}H_{13}N_9O_2$ ($[M-H]^-$) requires 297.1100.

3.3.3.85. *N*-(1-Ethyl-1*H*-imidazol-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 119. Yield = 46%; NMR δ_H (400 MHz, DMSO); 1.28 (3H, t, *J* 7.3 Hz), 2.39 (3H, s), 4.00 (2H, q, *J* 7.3 Hz), 4.57 (2H, d, *J* 5.5 Hz), 6.34 (1H, dd, *J* 1.0 Hz, 3.5 Hz), 6.85 (1H, d, *J* 1.0 Hz), 6.93 (2H, br s), 7.18 (1H, d, *J* 1.0 Hz), 7.21 (1H, d, *J* 3.5 Hz), 7.37 (1H, s), 8.61 (1H, t, *J* 5.5 Hz); *m*/*z* 327 $(M+H)^+$, retention time 0.72 min (Method F) and 3.59 min (Method G); HRMS found 325.1425. $C_{16}H_{17}N_6O_2$ ($[M-H]^-$) requires 325.1413.

3.3.3.86. *N*-(1-*n*-Propyl-1*H*-imidazol-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 120. Yield = 30%, NMR δ_H (400 MHz, DMSO); 0.83 (3H, t, *J* 7.3 Hz), 4.68 (2H, m), 2.39 (3H, s), 3.92 (2H, t, *J* 7.3 Hz), 4.57 (2H, d, *J* 5.5 Hz), 6.34 (1H, d, *J* 2.5 Hz), 6.85 (1H, d, *J* 1.0 Hz), 6.93 (2H, br s), 7.16 (1H, d, *J* 1.0 Hz), 7.21 (1H, d, *J* 3.0 Hz), 7.37 (1H, s), 8.61 (1H, br t); *m*/*z* 341 $(M+H)^+$, LC retention time 1.63 min (Method E).

3.3.3.87. *N*-(1-Isopropyl-1*H*-imidazol-2-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 121. Yield = 8%, NMR δ_H (400 MHz, DMSO); 1.34 (6H, d, *J* 6.5 Hz), 2.39 (3H, s), 4.52 (1H, m), 4.59 (2H, d, *J* 5.5 Hz), 6.34 (1H, br d), 6.87 (1H, br d), 6.94 (2H, br s), 7.21 (1H, d, *J* 3.0 Hz), 7.28 (1H, br d), 7.37 (1H, s), 8.61 (1H, br t); *m*/*z* 341 $(M+H)^+$, LC retention time 1.51 min (Method E); HRMS found 341.1719. $C_{17}H_{21}N_6O_2$ ($[M-H]^-$) requires 341.1726.

3.3.3.88. *N*-(5-Methylisoxazol-3-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 122. Yield = 84%; IR ν_{max} (DR)/cm^{-1} 3324, 3183, 1686, 1540, 1359, 1220, 1136 and 1021; NMR δ_H (400 MHz, DMSO) 2.40 (3H, s), 6.35–6.36 (1H, m), 6.96 (2H, br s), 7.15 (1H, t, *J* 7.4 Hz), 7.25 (1H, d, *J* 3.6 Hz), 7.37–7.42 (3H, m), 7.79 (2H, d, *J* 7.2 Hz) and 10.22 (1H, s); *m*/*z* 295 $(M+H)^+$; LC retention time 2.02 min (Method C).

3.3.3.89. *N*-(2-Methylaminothiazol-4-ylmethyl)-2-amino-(5-methyl-2-furyl)pyrimidine-4-carboxamide 123. Yield = 31%, NMR δ_H (400 MHz, DMSO); 2.39 (3H, s), 2.64 (3H, s), 4.54 (2H, d, *J* 6.0 Hz), 6.34 (1H, br d), 6.88 (2H, br s), 7.20 (1H, d, *J* 3.0 Hz), 7.26 (1H, s), 7.36 (1H, s), 8.66 (1H, br t); *m*/*z* 330 $(M+H)^+$, LC retention time 2.20 min (Method E).vv

Acknowledgements

We wish to thank Lynne Barratt, Sarah Denny, Sean Lightowler, Angela Merritt, Anil Mirsa, Anthony Padfield and Daniel Selwood for undertaking the biological assessment of the derivatives described in these studies.

Supplementary data

Supplementary data (purity information, analytical methods and NMR spectra of key derivatives) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.07.078.

References and notes

1. Xu, K.; Bastia, E.; Schwarzschild, M. *Pharmacol. Ther.* **2005**, *105*, 267.
2. Bara-Jimenez, W.; Sherzai, A.; Dimitrova, T.; Favit, A.; Bibbiani, F.; Gillespie, M.; Morris, M. J.; Mouradian, M. M.; Chase, T. N. *Neurology* **2003**, *61*, 293.
3. Gillespie, R. J.; Bamford, S. J.; Guar, S.; Jordan, A. M.; Lepiniere, J.; Mansell, H. L.; Stratton, G. C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2664.
4. Rabasseda, X.; Sorbera, L. A.; Martin, L.; Leeson, P. A.; Castaner, J. *Drugs Future* **2001**, *26*, 20.
5. LeWitt, P. A.; Guttman, M.; Tetrud, J. W.; Tuire, P. J.; Mori, A.; Chaikin, P.; Sussman, N. M. *Ann. Neurol.* **2008**, *63*, 295.
6. http://www.kyowa-kirin.co.jp/english/news/kyowa/er080228_01.html; http://www.kyowa-kirin.co.jp/english/news/2009/e20090115_01.htm.
7. Gillespie, R. J.; Todd, R. S.; Stratton, G. C.; Jordan, A. M. PCT Int. Appl. WO2005079801, 2005; Gillespie, R. J.; Williamson, D. S. PCT Int. Appl. WO2005079800, 2005.
8. Gillespie, R. J.; Adams, D. R.; Benwell, K.; Bebbington, D.; Cliffe, I. A.; Dawson, C. E.; Dourish, C. T.; Fletcher, A.; Giles, P. R.; Gaur, S.; Jordan, A. M.; Knight, A. R.; Knutsen, L. J. S.; Lawrence, A.; Lerpiniere, J.; Misra, A.; Porter, R. H. P.; Pratt, R. M.; Shepherd, R.; Upton, R.; Ward, S. E.; Weiss, S. M.; Williamson, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2916.
9. Gillespie, R. J.; Cliffe, I. A.; Dawson, C. E.; Dourish, C. T.; Gaur, S.; Giles, P. R.; Jordan, A. M.; Knight, A. R.; Lawrence, A.; Lerpiniere, J.; Misra, A.; Pratt, R. M.; Todd, R. S.; Upton, R.; Weiss, S. M.; Williamson, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2920.
10. Gillespie, R. J.; Cliffe, I. A.; Dawson, C. E.; Dourish, C. T.; Gaur, S.; Jordan, A. M.; Knight, A. R.; Lerpiniere, J.; Misra, A.; Pratt, R. M.; Roffey, J.; Stratton, G. C.; Upton, R.; Weiss, S. M.; Williamson, D. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2924.
11. Gillespie, R. J.; Bamford, S. J.; Botting, R.; Comer, M.; Denny, S.; Gaur, S.; Griffin, M.; Jordan, A. M.; Knight, A. R.; Lerpiniere, J.; Leonardi, S.; Lightowler, S.; McAteer, S.; Merrett, A.; Misra, A.; Padfield, A.; Reece, M.; Saadi, M.; Selwood, D. L.; Stratton, G. C.; Surry, D.; Todd, R.; Tong, X.; Ruston, V.; Upton, R.; Weiss, S. M. *J. Med. Chem.* **2009**, *52*, 33.
12. For additional details of K_i determination, see: Weiss, S. M.; Benwell, K.; Cliffe, I. A.; Gillespie, R. J.; Knight, A. R.; Lerpiniere, J.; Misra, A.; Pratt, R. M.; Revell, D.; Upton, R.; Dourish, C. T. *Neurology* **2003**, *61*, S101. All values are the mean of at least two separate values.
13. Broughton, H. B.; Watson, I. A. *J. Mol Graphics Modell.* **2004**, *23*, 51.
14. Dixon, J. A.; Nagarathnam, D.; Zhang, L.; Wang, C.; Yi, L.; Chen, Y.; Chen, J.; Bear, B. R.; Brands, M.; Hillisch, A.; PCT Int. Appl. WO2006099231, 2006; Nagarathnam, D.; Dumas, J.; Hatoum-Mokdad, H.; Boyer, S.; Pluempe, H. PCT Int. Appl. WO2003062227, 2003.
15. Richardson, C. M.; Gillespie, R. J.; Williamson, D. S.; Jordan, A. M.; Fink, A.; Knight, A. R.; Sellwood, D. M.; Misra, A. *Bioorg. Med. Chem Lett.* **2006**, *16*, 5993.
16. Kiselgof, E.; Tulshian, D. B.; Arik, L.; Zhang, H.; Fawzi, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2119.
17. Davies, G. D.; Baiocchi, F.; Robins, R. K.; Cheng, C. C. *J. Org. Chem.* **1961**, 2755.
18. Flohr, A.; Norcross, R. D. U.S. Pat. Appl. 2004204584, 2004.
19. Emerson, D. W.; Titus, R. L.; Gonzalez, R. M. *J. Org. Chem.* **1991**, *56*, 5301; Emerson, D. W.; Titus, R. L.; Gonzalez, R. M. *J. Org. Chem.* **1990**, *55*, 3572.
20. Gershon, H.; Braun, R.; Scala, A.; Rodin, R. *J. Med. Chem.* **1964**, *7*, 808.
21. Data not shown.
22. Bezard, E.; Imbert, C.; Gross, C. E. *Rev. Neurosci.* **1998**, *9*, 71.