Antagonists of the Human A_{2A} Adenosine Receptor. 4. Design, Synthesis, and Preclinical Evaluation of 7-Aryltriazolo[4,5-*d*]pyrimidines

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Received July 30, 2008

Antagonism of the human A_{2A} receptor has been implicated as a point of therapeutic intervention in the alleviation of the symptoms associated with Parkinson's disease. This is thought to occur, at least in part, by increasing the sensitivity of the dopaminergic neurons to the residual, depleted levels of striatal dopamine. We herein describe a novel series of functionalized triazolo[4,5-*d*]pyrimidine derivatives that display functional antagonism of the A_{2A} receptor. Optimization of these compounds has resulted in improvements in potency, selectivity, and the pharmacokinetic properties of key derivatives. These efforts have led to the discovery of **60** (V2006/BIIB014), which demonstrates strong oral activity in commonly used models of Parkinson's disease. Furthermore, this derivative has shown excellent preclinical pharmacokinetics and has successfully completed phase I clinical studies. This compound is presently undergoing further clinical evaluation in collaboration with Biogen Idec.

Introduction

Parkinson's disease is a neurodegenerative disorder that is characterized by symptoms affecting smooth and well controlled muscle movement. These symptoms often include postural changes, rigidity, a resting tremor, and a slowing of voluntary physical movement known as bradykinesia. Other symptoms often include sleep disturbance, depression, and an overall decline in cognition.[1,2] The disease results from degeneration of dopaminergic neurons in the substantia nigra, and the resultant decrease in interstitial dopamine levels leads to alterations in the activity of neural circuits within the basal ganglia that regulate movement.[3] Around 80% of these neurons need to be degraded before the clinical disease symptoms become apparent, making the condition more likely to manifest itself in the older population. The disease has an overall incidence of around 1 in 1000 in the general populous, but this incidence increases to around 1 in 100 in the over 60s.

Symptomatic treatment of the disorder centers around replacement of the depleted dopamine in the brain, generally by administration of the dopamine precursor levodopa (3,4-dihydroxy-L-phenylalanine).[4,5] Levodopa is decarboxylated in the brain to liberate dopamine and is generally coadministered with a non-brain-penetrant inhibitor of aromatic L-amino acid decarboxylase (commonly referred to as dopa decarboxylase) to reduce the incidence of peripheral side effects due to systemic production of dopamine. However, this treatment is far from ideal, as the drug suffers from erratic pharmacokinetics, leading to considerable problems related to the predictability of dosing. If too little drug is absorbed into the brain, insufficient levels of dopamine are achieved, and this leads to a premature re-emergence of symptoms, known as an "off episode". Alternatively, if too high a dose is administered to counteract poor brain permeation, the treatment can induce involuntary muscle movements (dyskinesias) or, in extreme circumstances, dystonia, a painful, involuntary spasm of muscles in various parts of the body that can be more debilitating than the underlying disease state. Dyskinesias occur in 68% of all Parkinson's disease patients after 5 years of levodopa treatment and have a considerable effect upon quality of life.[6] Furthermore, because of feedback inhibition, administration of increasing levels of exogenous levodopa results in a reduction in the endogenous formation of the compound (and thus endogenous dopamine). Administration of the therapy therefore eventually becomes counterproductive, requiring steadily increasing doses in order to retain efficacy.

These issues clearly highlight the urgent medical need for an alternative point of therapeutic intervention that can alleviate the symptoms of the disease while additionally offering predictable pharmacokinetics and a reduced incidence of side effects.

One such point of intervention appears to be antagonism of the adenosine A_{2A} receptor.[7] One of a family of four receptors (delineated A_1, A_{2A}, A_{2B}, and A_3), the A_{2A} receptor, is expressed in restricted locations within the CNS and exists primarily in the nucleus accumbens, olfactory tubercle, and the striatum, where it is often colocalized with the dopamine D_2 receptor.[8] Preclinical studies have demonstrated that administration of selective A_{2A} receptor antagonists can offset the effects of dopamine D_2 receptor antagonists in models of Parkinson's disease,[9] and coadministration experiments have demonstrated that such antagonists not only potentiate the therapeutic benefit of levodopa but also can reduce the incidence of induced dyskinesias compared to equivalent doses of levodopa alone.[10] Furthermore, recent studies suggest that monotherapy with A_{2A} antagonists alleviates motor disability symptoms in clinically relevant Parkinson's disease models in a manner that does not induce treatment-related dyskinesias.[11]

The exact role of the A_{2A} receptor in this context is presently unclear, but it is speculated that the A_{2A} and dopamine D_2 receptors form a heterodimeric receptor complex and antagonism of the A_{2A} receptor modulates the sensitivity of the D_2 receptor

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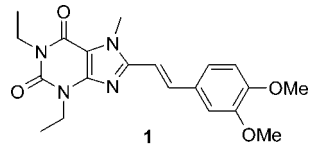
10.1021/jm800961g CCC: $40.75
Published on Web 12/10/2008

to what little dopamine remains in the striatum, perhaps by increasing the affinity of the D_2 receptor for dopamine.[12−16]

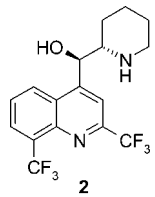
More recent evidence has suggested that adenosine antagonists may not provide purely symptomatic relief for patients with Parkinson's disease (in a manner akin to transmitter replacement therapies such as levodopa) but may also confer some neuroprotective effects, potentially slowing disease progression. Compelling experimental evidence suggests that blockade of the A_{2A} receptor in mice can confer protection against Parkinson's disease-like lesions caused by the administration of the potent neurotoxin MPTP.[17,18]

Given these findings, there has been considerable interest in developing well tolerated, orally bioavailable antagonists of this receptor. The most advanced of these studies appears to be KW-6002 **1**,[19] a xanthine derived antagonist that recently completed clinical trials for the alleviation of symptoms associated with Parkinson's disease.[20,21] However, this compound failed to meet its primary end-point in two out of three pivotal efficacy trials and approval was declined by the FDA in 2008.[22] Additional reports have highlighted further issues that may have implications for the clinical utility of this compound, including metabolic issues and poor photostability in both solid form and solution.[23,24]



1

We have recently revealed that the antimalarial compound mefloquine **2** is a potent and reasonably selective antagonist of the A_{2A} receptor. Additionally, we have described our efforts to optimize this compound, and a number of related series, in an effort to find a candidate compound with a suitable profile for clinical development.[25−27]



2

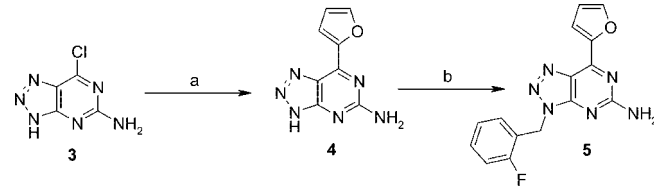
Though we could prepare derivatives that were potent or selective or displayed good oral bioavailability and promising pharmacokinetics, we had hitherto found that the parallel optimization of these properties was a considerable challenge. Herein, we describe our continued efforts in this area and, ultimately, the discovery of **60**, a small molecule with a profile appropriate for clinical evaluation.[28]

Chemistry

The synthetic routes used to prepare the derivatives used in this study are described in Schemes 1−13. The initial starting point for our work was the furyltriazolopyrimidine derivative **4**, which was prepared by palladium-mediated coupling of the known chlorotriazolopyrimidine **3**[29] and 2-tributylstannylfuran. This was further derivatized to give the 2′-fluorobenzyl derivative **5** by treatment with the corresponding benzyl bromide.

Alternative heterocyclic motifs were appended to the core scaffold using the methods described in Schemes 2 and 3 below. Palladium-mediated Suzuki coupling of 5-methylfuran-2-boronic acid and 2,6-diamino-4-chloro-5-nitropyrimidine **6**[30,31] gave the required bicyclic core, which was reduced to give the triamino

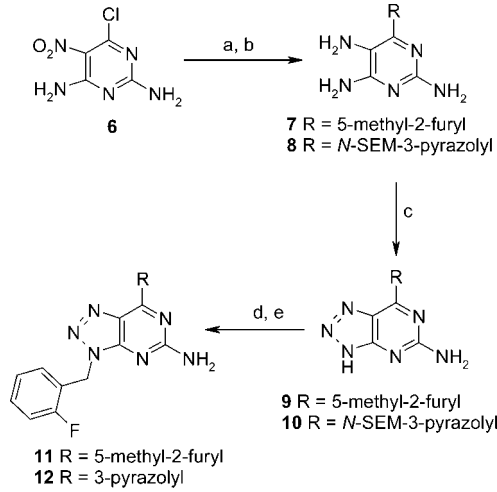
Scheme 1. Synthesis of the A_{2A} Receptor Antagonist **5**[a]



3 **4** **5**

[a] Reagents and conditions: (a) 2-(tributylstannyl)furan, $PdCl_2(PPh_3)_2$, NMP, 80 °C, 5 h, 65%; (b) NaH, 2-fluorobenzylbromide, DMF, room temp, 1 h, 22%.

Scheme 2. Synthesis of 7-Aryltriazolopyrimidine Analogues[a]



6

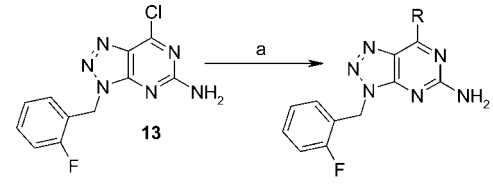
7 R = 5-methyl-2-furyl
8 R = *N*-SEM-3-pyrazolyl

9 R = 5-methyl-2-furyl
10 R = *N*-SEM-3-pyrazolyl

11 R = 5-methyl-2-furyl
12 R = 3-pyrazolyl

[a] Reagents and conditions: (a) arylboronic acid, $NaHCO_3$, THF, H_2O, $Pd(PPh_3)_4$, reflux, o/n, 42−72%; (b) $H_{2(g)}$, 10% Pd/C, MeOH, 40 °C, 4 h, ∼quant; (c) isoamyl nitrite, dioxane, 80 °C, 3.5 h, 48−77%; (d) NaH, 2-fluorobenzylbromide, DMF, room temp, 1 h, 47−51%. (e) For **12**, HCl, MeOH, room temp, 1 h, quant.

Scheme 3. Synthesis of 7-Aryltriazolopyrimidine Analogues[a]



13

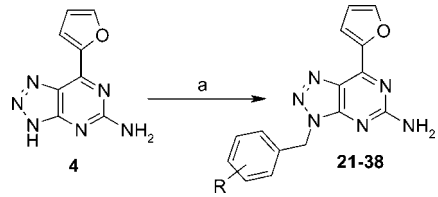
14 R = 2-thiazolyl
15 R = 4-methyl-2-thiazolyl
16 R = 5-Methyl-2-thiazolyl
17 R = 2-oxazolyl
18 R = 2-thienyl
19 R = 5-triazolyl
20 R = 5-thiazolyl

[a] Reagents and conditions. (a) For **14**−**17**: (i) heterocycle, *n*-BuLi, THF, −78 °C, then $ZnCl_2$; (ii) **13**, $Pd(PPh_3)_4$, reflux, 2−4 h, 2−35%. For **18**: **13**, thiophene-2-boronic acid, $NaHCO_3$, THF, H_2O, $Pd(PPh_3)_4$, reflux, 1 h, 51%. For **19**: (i) tributyl-1-(2-SEM)-1*H*-triazolyl-5-stannane, **13**, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 17 h; (ii) HCl, MeOH, room temp, 17 h, 10% over two steps. For **20**: tributylstannyl-5-thiazole, **13**, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 1 h, 56%.

derivative **7**. Cyclization to the triazolopyrimidine was effected with isoamyl nitrite, giving **9**. Treatment with 2-fluorobenzyl bromide yielded the desired target compound **11** (Scheme 2). Similarly, following deprotection, the 3-pyrazolyl derivative **12** could be accessed in a similar manner.

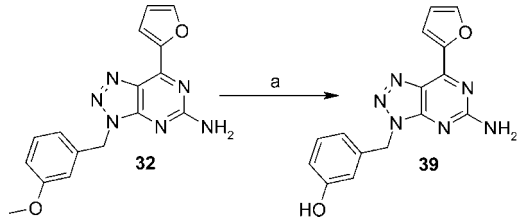
2-Thiazole derivatives were prepared from the functionalized core **13**[32] via a Negishi coupling with the appropriate arylzinc reagents to yield **14**−**16** (Scheme 3). A similar method allowed introduction of oxazole functionality, yielding **17**. Palladium-

Scheme 4. Synthesis of Functionalized 7-Aryltriazolopyrimidine A_{2A} Receptor Antagonists[a]



[a] Reagents and conditions: (a) NaH, 2-fluorobenzylbromide, DMF, room temp, 1 h, 4−40%.

Scheme 5. Synthesis of Phenoxy-7-aryltriazolopyrimidine A_{2A} Receptor Antagonist **39**[a]



[a] Reagents and conditions: (a) BBr_3, DCM, 0 °C, 72 h, 100%.

mediated coupling of thiophene-2-boronic acid allowed access to the 2-thienyl derivative **18**, and similarly, the corresponding triazole derivative **19** could be accessed via a Stille coupling, employing the appropriately protected heterocycle. The 5-thiazolyl variant was prepared by an analogous method, whereby the heterocycle was coupled to the functionalized chlorotriazolopyrimidine **13** using thiazolyl-5-tributylstannane, to give **20** (Scheme 3).

Benzyl derivatives were prepared by the methods detailed in Schemes 4−6. Treatment of the 2-furyltriazolopyrimidine scaffold **4** with the appropriate benzyl bromide gave the desired derivatives **21**−**38** in moderate yields. Though the alkylation protocol tended to generate a mixture of both the N-2 and N-3 functionalized regioisomers, in all cases the predominant N-3 functionalized derivative could be readily isolated.[33] Phenolic functionality was unmasked by treating the corresponding methoxy derivative **32** with small aliquots of boron tribromide in dichloromethane over 3 days to cleanly yield **39** (Scheme 5). The ester functionality present in **38** was hydrolyzed to reveal the acid **40** using sodium hydroxide and further derivatized to the amides **41**−**43** using carbonyldiimidazole in dimethylformamide (Scheme 6).

Alkylation with pyridylmethyl bromides failed to give the desired products in an acceptable manner, and for these problematic derivatives, an alternative route was devised. The starting aminopyrimidinone **44**[34] was treated with tosyl chloride to yield **45** and the tosylate moiety displaced in good yield with 2- and 3-pyridylmethylamine to incorporate the heterocyclic functionality. Hydrogenation of the nitro group and concomitant cyclization to the triazolopyrimidine with isoamyl nitrite yielded the desired pyridyl-functionalized derivatives **46** and **47** (Scheme 7).

Though the pyridyl derivatives required an alternative synthetic strategy as described above, the incorporation of other heteroaryl derivatives was more facile and the desired derivatives were readily prepared using the alkylation protocol detailed in Scheme 4, to give compounds **48**−**51** as described in Table 4.

Aromatic amino functionality on the pendent aromatic group was revealed by tin(II) chloride-mediated reduction of the corresponding nitro derivatives **35**−**37** to yield **52**−**54** (Scheme 8).

The homologated variant of **54**, **55**, was prepared as described in Scheme 9. Raney nickel catalyzed hydrogenation of 4-hydroxymethylbenzonitrile was followed by Boc protection of the resultant amine to give **56**. Bromination with carbon tetrabromide and triphenylphosphine proceeded smoothly to yield the benzyl bromide **57**, which could be coupled with the triazolopyrimidine scaffold **4** using the above methodology. Deprotection with hydrochloric acid in 1,4-dioxane afforded the desired compound.

Substituted 4-aminobenzylamine derivatives **58**−**60** were prepared via alkylation of the scaffold **4** with commercially available nitrobenzyl bromides, followed by reduction with tin(II) chloride. Where appropriate starting materials were not commercially available, such as for examples **61**−**64**, the prerequisite benzyl bromides prepared as detailed in the Experimental Section and outlined in Schemes 10−12. Conjugate Grignard addition to 4-nitrobenzyl bromide **65** followed by oxidative workup gave the substituted derivatives typified by **66**, in accordance with literature precedence for corresponding keto-functionalized nitrobenzene derivatives.[35] Standard alkylation of **4** with these derivatives was followed by reduction with tin(II) chloride, giving **61** and **62**. Synthesis of the 3-hydroxy-4-amino derivative **63** commenced from the commercially available 3-hydroxy-4-nitrobenzoic acid **69**, as detailed in Scheme 11. Boc protection of the alcohol to give **70** followed by transient esterification of the acid with isobutyl chloroformate and reduction with sodium borohydride gave the hydroxymethyl intermediate **71**, which was readily brominated with carbon tetrabromide and triphenylphosphine to yield **72**. After alkylation of the triazolopyrimidine scaffold under our standard conditions, reduction of the nitro moiety with tin(II) chloride proceeded with concomitant unmasking of the hydroxyl functionality to yield the desired derivative **63**. The N-methylated derivative **64** could also be accessed in an analogous manner, as detailed in Scheme 12.

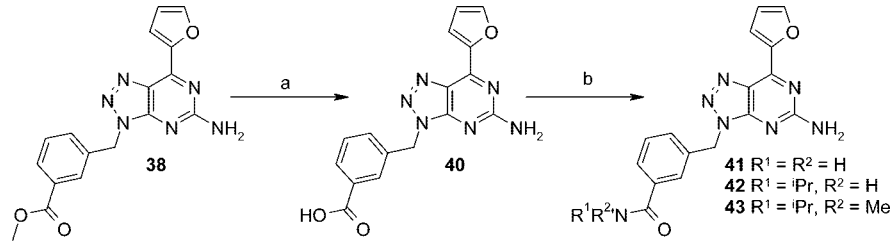
The *N*-acetyl derivative **77** was prepared from the commercially available *p*-acetamidobenzyl bromide in a manner analogous to that described in Scheme 4.

Pendent biaryl functionality was introduced via alkylation with the corresponding alkyl bromides, prepared by halogenation of the known, appropriately protected 5-methyl heterocycles[36] with *N*-bromosuccinimide, as described in Scheme 13.

Results and Discussion

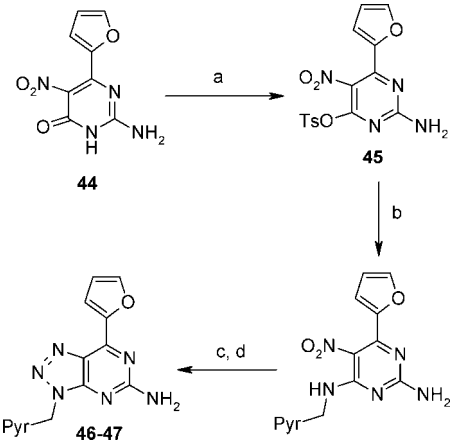
We have previously reported our efforts to optimize biaryl scaffolds as antagonists of the human A_{2A} receptor and, in particular, derivatives based upon pyrazolopyrimidine, pyrrolopyrimidine and purine cores.[27] To complement this work, we also wished to explore the triazolopyrimidine scaffold and therefore prepared the 7-furyltriazolopyrimidine core **4**. A comparison of the affinities of these related core structures is detailed in Table 1.[37] On first inspection, the triazolopyrimidine core did not appear particularly promising, with a marked reduction in binding affinity at the A_{2A} receptor compared to the pyrazolopyrimidine core **81**. However, activity and selectivity against the other subtypes of the human adenosine receptor were comparable with those of the purine and pyrrolopyrimidine cores **82** and **83**, respectively. Further investigations revealed that compound **4** was moderately active in the haloperidol-induced hypolocomotion assay (HaloLMA), a relatively simple

Scheme 6. Synthesis of Amido-7-aryltriazolopyrimidine A_{2A} Receptor Antagonists **41**−**43**[a]



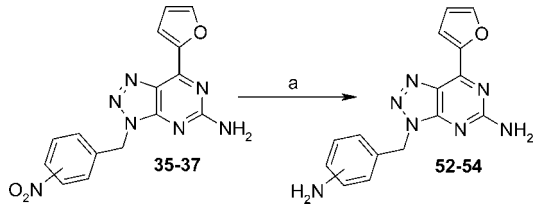
[a] Reagents and conditions: (a) NaOH, MeOH, reflux, 10 min, 98%; (b) CDI, DMF, room temp, 1 h, then amine, room temp, 16 h, 23−66%.

Scheme 7. Alternative Synthesis of Pyridyl-7-aryltriazolopyrimidine A_{2A} Receptor Antagonists **46** and **47**[a]



[a] Reagents and conditions: (a) *p*-TsCl, NEt_3, DCM, room temp, 1 h, 24%; (b) pyridylmethylamine, NEt_3, 1,2-dimethoxyethane, room temp, 16 h, 69−82%; (c) 1% Pd/C, $H_{2\ (g)}$, EtOH EtOAc, room temp, 1 h, quant; (d) isoamyl nitrite, 1,4-dioxane, 100 °C, 16 h, 46−50%.

Scheme 8. Synthesis of Amino-7-aryltriazolopyrimidine A_{2A} Receptor Antagonists **52**−**54**[a]



[a] Reagents and conditions: (a) $SnCl_2$, EtOH, HCl, 50 °C, 2 h, 45−92%.

yet robust model of the symptoms of Parkinson's disease.[38,39] Unlike the majority of the templates we had investigated in the course of our studies in this area, this derivative not only was active when dosed intraperitoneally but also demonstrated limited activity after oral administration. We therefore sought to optimize **4** in order to exploit this promising early sign of oral bioavailability.

Previous studies on the purines, pyrrolopyrimidines and pyrazolopyrimidines had demonstrated that incorporation of a benzyl substituent gave a considerable increase in activity while generally maintaining selectivity against the human A_1 receptor. This prior experience quickly led us to **5**. As with previous series, incorporation of the 2-fluorobenzyl moiety gave a substantial (70-fold) increase in binding affinity for the A_{2A} receptor and a useful doubling of selectivity against the A_1 receptor.

Aware that the furan displayed in our core scaffold was a potential site of oxidative metabolism[40,41] but also aware that this group appears to be a privileged moiety in compounds binding to the A_{2A} receptor,[42] we first sought to investigate whether alternative groups could be combined successfully with the triazolopyrimidine core without substantial reductions in receptor binding affinity.

As detailed in Table 2, it was apparent that a variety of small heteroaromatic groups could indeed be tolerated in this position. Most small aromatic heterocycles appeared to be tolerated except for those displaying an available N−H such as the 3-pyrazole (**12**) and the 4-triazole (**19**). Though the 3-pyrazolyl derivative **12** showed a marked reduction in binding affinity, it still retained activity in the HaloLMA assay after oral dosing at 30 mg kg^{-1}, the same in vivo efficacy demonstrated by the considerably more potent 2-thiazolyl derivative **14**. We speculated that this increased activity might be attributable to improved brain penetration, though further pharmacokinetic studies would be required to validate this hypothesis. However, given the obvious disconnect between receptor binding affinity activity in our efficacy model, we reasoned that the balance of physiochemical properties displayed by these compounds would be critical to attaining the ideal balance of in vitro potency, selectivity, oral bioavailability, and in vivo efficacy.

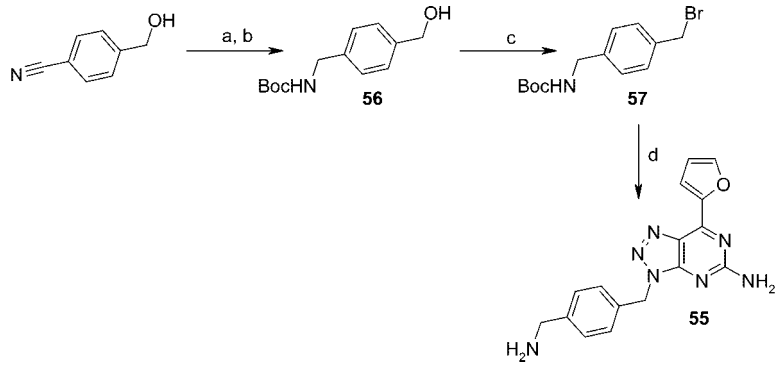
Of more immediate interest was the 2-methylfuran derivative **11**. Though this derivative was roughly equipotent with the furan derivative **5**, the compound displayed a substantial increase in oral activity in the HaloLMA assay, with a minimum effective dose of 3 mg kg^{-1}. Once again, it appeared that a small change in the structure of the compound had altered the physiochemical profile sufficiently to have a marked effect upon activity in the disease model. However, the substantial decrease in selectivity against both the A_1 and A_{2B} receptor subtypes precluded further optimization of this subseries at this time, and efforts focused upon the inherently more selective scaffold typified by **5**.

Given the dramatic increases in potency observed upon incorporation of the 2-fluorobenzyl substituent, attention was turned to the optimization of this position. Receptor binding data for a representative selection of analogues are presented in Table 3.

Removal of the 2-fluoro substituent yielded a slight improvement in potency (compound **21**), with little effect upon selectivity. Interestingly, complete removal of aromaticity in this position and incorporation of a cyclohexyl moiety gave only a moderate decrease in activity while maintaining a similar selectivity profile, perhaps indicating the group in this position is fulfilling an interaction that is predominantly hydrophobic in nature rather than partaking in a $\pi-\pi$ interaction with the receptor binding cavity.

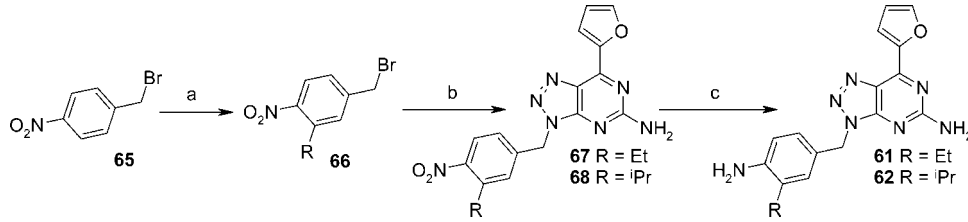
Difluorinated substituents appeared to be beneficial in terms of both binding affinity and overall selectivity profile, with **24** meeting our predefined selectivity criteria (≥50-fold selectivity against all three receptor subtypes) for the first time. This profile was also attained by the 2-methyl derivative **28**. In general terms,

Scheme 9. Synthesis of the Homologated 7-Aryltriazolopyrimidine A_{2A} Receptor Antagonist **55**[a]



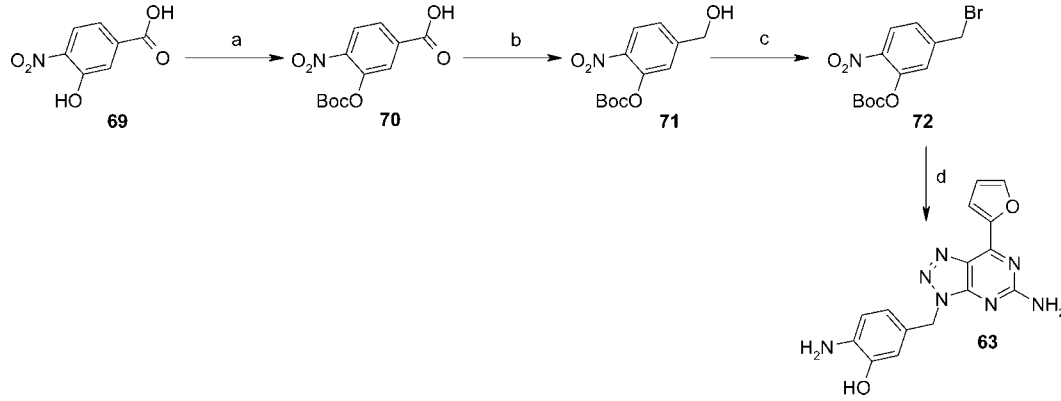
[a] Reagents and conditions: (a) Raney Ni, $H_{2(g)}$, EtOH, NEt_3, room temp, 16 h, 80%; (b) NEt_3, THF, room temp, 10 min, then di-*tert*-butyl dicarbonate, room temp, 90 min, 89%; (c) PPh_3, CBr_4, 0 °C, 1 h, 65%; (d) **4**, NaH, THF, 16 h, room temp, then HCl, 1,4-dioxane, MeOH, room temp, 16 h, 12%.

Scheme 10. Synthesis of Derivatized 7-Aryltriazolopyrimidine A_{2A} Receptor Antagonists **61** and **62**[a]



[a] Reagents and conditions: (a) alkylmagnesium chloride, THF, −70 °C, 1 h, then DDQ, room temp, 16 h, 16−40%; (b) **4**, NaH, THF, 16 h, room temp, 19−28%; (c) $SnCl_2$, EtOH, HCl, 50 °C, 2 h, 36−37%.

Scheme 11. Synthesis of Derivatized 7-Aryltriazolopyrimidine A_{2A} Receptor Antagonist **63**[a]

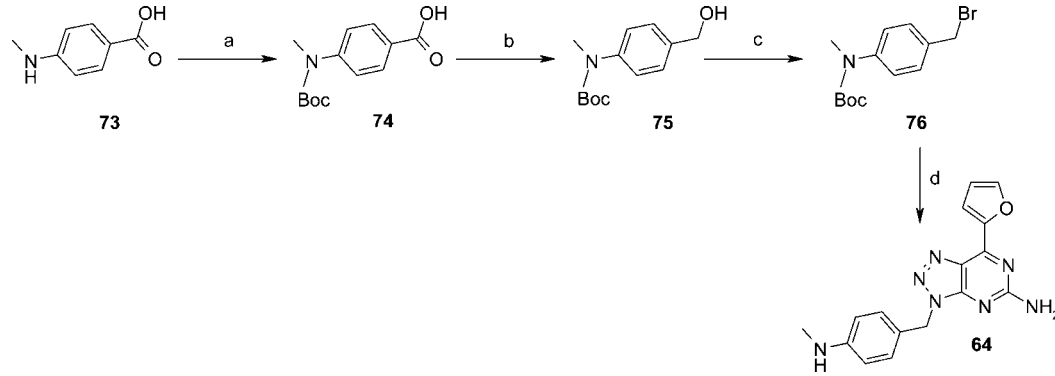


[a] Reagents and conditions: (a) di-*tert*-butyl dicarbonate, NEt_3, THF, room temp, 16 h, 83%; (b) isobutyl chloroformate, *N*-methyl morpholine, THF, 0 °C, 1 h, then $NaBH_4$, MeOH, −78 °C, 1 h, 86%; (c) PPh_3, CBr_4, 0 °C, 1 h, 86%; (d) **4**, NaH, THF, 16 h, room temp, 78%.

though a variety of substituents were tolerated in this series, meta-substituents tended to offer a better balance of potency and selectivity whereas para-substituents, such as those displayed in **34** and **37**, appeared to be less well tolerated. Additionally, though ester and amide functionality appeared to be tolerated (compounds **38** and **41**), the parent acid was some 80-fold less potent. This result suggested a preference for nonacidic functionality at this position, particularly given the tolerance for the isoelectronic nitro functionality (compound **36**). Though steric constraints may be an issue at the para-position and may contribute to the observed lack of tolerability discussed above, it would appear that this is much less of an issue at the meta-position, where even bulky amides such as **42** and, to a lesser extent, **43**, are well tolerated.

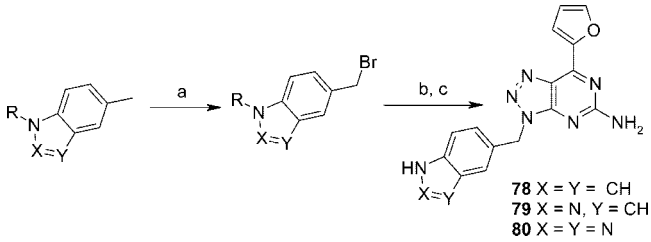
We were pleased to observe that, in general, metabolic stability of these derivatives appeared to be improved over our previously reported series. During our studies on the purine, pyrazolopyrimidines and pyrrolopyrimidine series,[27] we had observed that similar benzylated derivatives were susceptible to rapid metabolism by rodent liver microsomes, with turnover values after 30 min in the region of 95−99%. The corresponding functionalized triazolopyrimidines described above showed increased stability in this in vitro assay, demonstrating much more moderate turnover after 30 min. For example, compounds such as the ester **38** demonstrated a markedly reduced 35% turnover during this period under identical conditions. Unfortunately, in most cases, these derivatives failed to demonstrate any oral activity in the HaloLMA model when dosed at 30 mg kg^{-1}. We attributed this finding to the relatively low measured solubility of the compounds, which were in the 30−40 μM range,[43] and we therefore moved to address this issue by incorporation of heteroatoms in the pendent benzylic functionality, as detailed in Table 4.

Scheme 12. Synthesis of Derivatized 7-Aryltriazolopyrimidine A_{2A} Receptor Antagonist **64**[a]



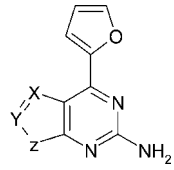
[a] Reagents and conditions: (a) di-*tert*-butyl dicarbonate, NEt_3, THF, reflux, 48 h, 69%; (b) (i) isobutyl chloroformate, *N*-methylmorpholine, THF, 0 °C, 1 h; (ii) $NaBH_4$, MeOH, −78 °C, then room temp, 2 h, 22%; (c) PPh_3, CBr_4, 0 °C, then room temp, 2 h, 43%; (d) **4**, NaH, THF, room temp, 16 h, then HCl, 1,4-dioxane, room temp, 2 h, 23%.

Scheme 13. Synthesis of 7-Aryltriazolopyrimidine A_{2A} Receptor Antagonists **78**−**80**[a]



[a] Reagents and conditions: (a) NBS, benzoyl peroxide, CCl_4, reflux, 16 h, 46−74%; (b) **4**, NaH, THF, room temp, 16 h, 14−27%. (c) For **78**: NaOMe, MeOH, reflux, 5 h, 74%. For **79**: HCl, 1,4-dioxane, methanol, room temp, 2 h, quant. For **80**: dimethylamine, methanol, reflux, 25 min, 30%.

Table 1. Comparison of Scaffold Binding Affinities at the Human Adenosine A_1 and A_{2A} Receptor Subtypes[a,37]



				K_i (nM)	
compd	X	Y	Z	A_{2A}	A_1
81	CH	N	N	48	647
82	N	CH	N	261	4951
83	CH	CH	N	242	2765
4	N	N	N	194	3624

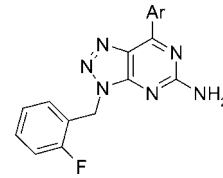
[a] All values are the mean of at least two separate assay determinations, and standard deviations for these values were generally within 20% of the mean value.

We were disappointed to find that the pyridyl-functionalized derivatives **46** and **47** failed to possess oral activity in the disease model, despite demonstrating a considerable increase in solubility (>250 μM) and a 2-fold increase in permeability in the Caco-2 model, compared to their nonheterocyclic counterparts. Interestingly, although the methylfuryl derivative **49** was inactive in this model, the corresponding 2-thienyl derivative **50** regained oral activity with a minimum effective dose of 30 mg kg^{-1}, though the slightly more potent regioisomer **51** did not.

Reduction of the nitrobenzyl functionality displayed in **35**−**37** gave the corresponding anilines **52**−**54**, which displayed a moderate 2-fold increase in solubility over their nitro precursors. The ortho- and meta-regioisomers showed a slight increase in potency, perhaps indicating the formation of an additional interaction with the receptor, but increased affinity was most dramatically observed in the para-regioisomer **45**, where binding affinity increased almost 20-fold compared to **37** while maintaining selectivity against the other receptor subtypes. Once again, this result suggests the existence of a sterically constrained region of the receptor in the vicinity of the para-substituent, where the less demanding amine functionality is more easily accommodated in the binding site and perhaps displays optimal geometry of interaction with the local receptor functionality. This view was further supported by data for the homologated aminomethyl derivative **55**, which was over 150-fold less potent at the A_{2A} receptor than the parent aniline **54**.

Though the thiophene-2-yl derivative **50** showed only limited activity after oral dosing, we were pleased to observe that the ortho-substituted aniline **52** displayed the anticipated increase in oral bioavailability. This was demonstrated by activity in the disease model, with a minimum effective dose of 10 mg kg^{-1}, despite similar receptor binding affinity. This finding is perhaps partly attributable to a moderate (3-fold) increase in permeability, given the comparable soubilities of these derivatives. However, the largely equipotent regioisomers **53** and **54** displayed a further increase in disease-relevant activity, demonstrating reversal of haloperidol-induced hypolocomotion in mice when dosed orally at just 1 mg kg^{-1}.

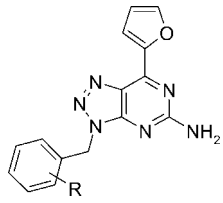
Table 2. Binding Affinities of 7-Aryl Variants at the Four Human Adenosine Receptor Subtypes[a,37]



		K_i (nM)			
compd	Ar	A_{2A}	A_1	A_{2B}	A_3
5	2-furyl	2.7	105	109	440
11	2-methylfuryl	2.1	19	6	260
12	3-pyrazolyl	239	1665	1778	1291
14	2-thiazolyl	8.5	553	271	2204
15	4-methyl-2-thiazolyl	2.2	203	53	1256
16	5-methyl-2-thiazolyl	8.5	86	199	338
17	2-oxazolyl	41	599	836	2108
18	2-thienyl	8.2	154	248	871
19	4-triazolyl	400	2965	1294	2806
20	5-thiazolyl	31	894	423	1779

[a] All values are the mean of at least two separate assay determinations, and standard deviations for these values were generally within 20% of the mean value.

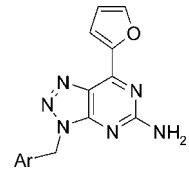
Table 3. Binding Affinities of N-3 Substituents at the Four Human Adenosine Receptor Subtypes[a,37]



		K_i (nM)			
compd	R	A_{2A}	A_1	A_{2B}	A_3
5	2-F	2.7	105	109	440
21	H	1.9	83	122	285
22	cyclohexyl	8.5	230	634	1138
23	2,3-diF	2.3	110	79	619
24	2,4-diF	2.0	118	226	1181
25	2,5-diF	2.2	98	128	450
26	2,6-diF	1.9	42	24	203
27	3-Cl	2.3	76	160	269
28	2-Me	3.0	183	282	341
29	3-Me	3.0	45	254	360
30	3-CF_3	2.2	100	259	736
31	2-OMe	5.4	319	741	340
32	3-OMe	1.8	77	643	563
33	3-CN	3.9	132	630	693
34	4-CN	73	738	885	1048
35	2-NO_2	6.6	400	383	168
36	3-NO_2	3.7	231	646	844
37	4-NO_2	28.0	769	440	1233
38	3-CO_2Me	4.1	105	907	1174
39	3-OH	4.0	314	10	491
40	3-CO_2H	832	4143	2110	3809
41	3-$CONH_2$	11.1	700	132	2576
42	3-CONH^{i}Pr	10.8	733	593	530
43	3-CON(Me)^{i}Pr	22	1133	937	2467

[a] All values are the mean of at least two separate assay determinations, and standard deviations for these values were generally within 20% of the mean value.

Table 4. Binding Affinities of N-3 Substituents with Enhanced Solubility at the Four Human Adenosine Receptor Subtypes[a,37]

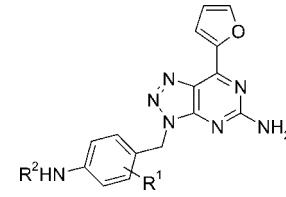


		K_i (nM)			
compd	R	A_{2A}	A_1	A_{2B}	A_3
46	2-pyridyl	12.0	1117	258	1075
47	3-pyridyl	14.5	931	225	1019
48	2-pyrazinyl	122	1166	1136	2224
49	2-furan-2-yl	8.8	77	192	240
50	thiophene-2-yl	2.3	117	88	123
51	thiophene-3-yl	1.9	78	164	136
52	2-anilino	2.0	63	123	302
53	3-anilino	2.5	131	270	792
54	4-anilino	1.5	190	46	752
55	4-aminomethyl	241	4909	916	>10000

[a] All values are the mean of at least two separate assay determinations, and standard deviations for these values were generally within 20% of the mean value.

In light of this oral efficacy, improved receptor binding affinity, and the better selectivity over the A_1 receptor, compound **54** was selected for further optimization. Given the effects we had noted previously, where increases in bioactivity had been associated with minor changes to the pharmacological profile of our compounds, we postulated that the overall profile of **54** could be improved by exploitation of functionality in the meta-position, given that this had already yielded interesting results as discussed above. Particularly, we reasoned that a slight increase in the log *D* of the chosen compound may facilitate an improvement in brain penetration and give rise to increased potency in the disease model. Results from these investigations are detailed in Table 5.

Table 5. Binding Affinities of Optimized N-3 Substituents with Enhanced Solubility at the Four Human Adenosine Receptor Subtypes[a,37]



			K_i (nM)			
compd	R^1	R^2	A_{2A}	A_1	A_{2B}	A_3
54	H	H	1.5	190	46	752
58	2-F	H	3.5	190	23	685
59	3-F	H	0.7	120	43	1071
60	3-Me	H	1.3	68	63	1005
61	3-Et	H	1.0	26	118	221
62	3-^{i}Pr	H	1.5	50	397	251
63	3-OH	H	1.6	249	84	1359
64	H	Me	1.6	40	181	636
77	H	Ac	116	2531	443	2380

[a] All values are the mean of at least two separate assay determinations, and standard deviations for these values were generally within 20% of the mean value.

Incorporation of fluorine initially appeared to be beneficial, with compound **50** displaying increased potency and adequate selectivity against other receptor subtypes. However, in the HaloLMA model, activity was only observed at 30 mg kg^{-1}. Small alkyl substituents were tolerated, and in all cases, binding affinity for the A_{2A} receptor was maintained or improved, albeit with a slight loss of subtype selectivity for the 3-ethyl and 3-isopropyl derivatives **61** and **62**. The phenolic derivative showed good receptor potency but failed to show activity in in vivo disease models, further confirming our hypothesis that small increases in log *D*, rather than a decrease, may be beneficial for brain penetration. As we had observed a large decline in activity upon incorporation of bulkier groups at the para-position in previous derivatives, we were somewhat surprised that N-methylation appeared to be well tolerated and compound **64** retained oral activity when dosed at 1 mg kg^{-1}, consistent with the parent compound **54**. In line with our expectations, the bulkier N-acetylated derivative **77** showed a marked decline in activity, suffering an 80-fold reduction in receptor affinity.

Of most interest from this exploration was the 3-methyl derivative **60**. Not only did this derivative show both a slight improvement in potency and enhanced selectivity against the A_{2B} receptor over the parent **54**, but when tested in the mouse and rat haloperidol-induced hypolocomotion model, this compound demonstrated a minimal effective dose of just 0.1 and 1 mg kg^{-1}, respectively (Figure 1). By comparison, in our hands, KW-6002 **1** demonstrated activity at 0.3 mg kg^{-1} in the mouse HaloLMA model (Figure 2) and 1 mg kg^{-1} in the corresponding rat model.

As we had observed that hydrophobic interactions between functionality at the N-3 position of the triazolopyrimidine core and the A_{2A} receptor appeared to be important, such as those described for **20**, we reasoned that cyclization of the pendent functionality displayed by **60**, while retaining a basic center in this region, may give rise to additional potency and further tailor

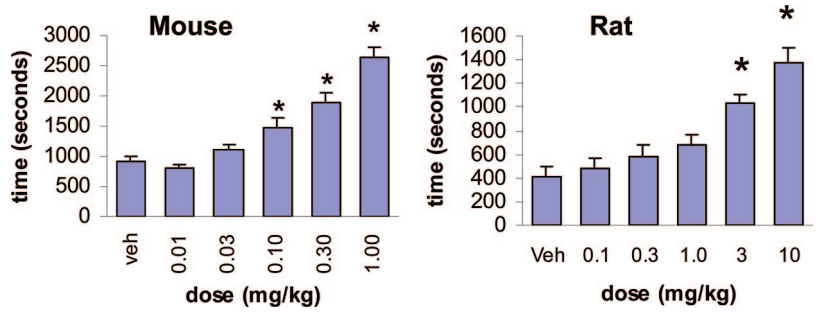


Figure 1. Reversal of haloperidol-induced hypolocomotion by compound **60** in mouse and rat (0.01−10 mg/kg po): (∗) $p < 0.05$ versus vehicle (+haloperidol alone) control. Shown are reversal of locomotor motor deficits in mice treated with the D_2 receptor antagonist haloperidol (0.2 mg/kg ip) by the A_{2A} receptor antagonist KW-6002. All doses are expressed as mg/kg ip. Behavioral scores represent time(s) spent active during a 60 min test session: (∗) $p < 0.05$ versus vehicle treatment group.

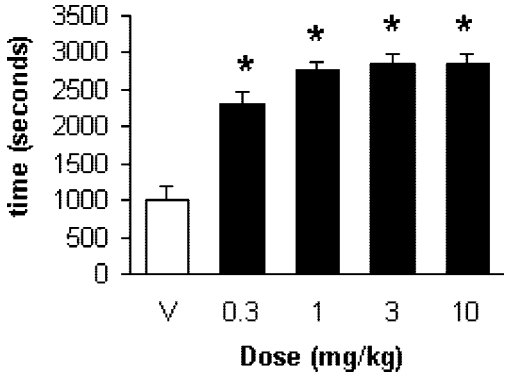
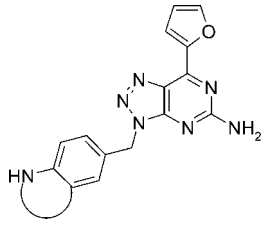


Figure 2. Reversal of haloperidol-induced hypolocomotion by compound **1** in mouse (0.3−10 mg/kg po): (∗) $p < 0.05$ versus vehicle (+haloperidol alone) control.

Table 6. Binding Affinities of Biaryl N-3 Substituents at the Four Human Adenosine Receptor Subtypes[a,37]



		K_i (nM)			
compd	heterocycle	A_{2A}	A_1	A_{2B}	A_3
78	5-indole	1.1	27	59	606
79	5-indazole	8.6	190	206	2433
80	5-benzotriazole	11.9	291	134	3013

[a] All values are the mean of at least two separate assay determinations, and standard deviations for these values were generally within 20% of the mean value.

the physiochemical properties of our derivatives in order to improve bioactivity. Indeed, cyclization of **60** to the corresponding indole derivative **78** provided a small increase in potency and generally retained biological activity in the HaloLMA model, showing efficacy when dosed orally at 1 mg kg^{-1}. However, this modification was clearly detrimental to subtype selectivity, giving a 2-fold decrease in selectivity against the A_1 receptor (Table 6).

Furthermore, incorporation of the corresponding indazole and benzotriazole moieties (compounds **79** and **80**, respectively) failed to restore selectivity against the A_1 receptor, and selectivities against the other two receptor subtypes were also diminished. Of more concern was the finding that neither of these two derivatives displayed oral activity in the HaloLMA model when dosed at 30 mg kg^{-1}. Given these results, further studies on similar biaryl substituents were suspended.

Table 7. Functional Activity of **60** at the Four Human Adenosine Receptor Subtypes[a,44]

	A_{2A}	A_1	A_{2B}	A_3
mean pA_2	9.2	7.0	7.5	5.8
K_A (nM)	0.58	95	31	1500

[a] All values are the mean of at least three separate determinations.

As **60** achieved our predetermined targets for potency, selectivity and oral bioactivity, further profiling of this derivative was undertaken. Assessment of the functional activity of the compound using a calcium mobilization-based FLIPR assay[44] demonstrated that **60** acted as a functional antagonist of the A_{2A} receptor and displayed potency and selectivity values against all the adenosine receptor subtypes, in good agreement with our radioligand binding assay (Table 7). This study also demonstrated that **60** was devoid of any intrinsic agonist activity at this receptor.

Though the compound was only moderately soluble at neutral pH, preparation of the dihydrochloride and dimesylate salts was straightforward, and these were found to display increased solubility, with measured solubilities of 18 and 36 mg mL^{-1}, respectively.

In vitro metabolic profiling demonstrated that **60** did not inhibit any of the major cytochrome P450 isoforms, reducing the risk of drug−drug interactions, and the compound itself was metabolized by multiple CYP450 isoforms. Permeability in the Caco-2 transwell system[45] was found to be good, at 11×10^{-6} cm s^{-1}, and **60** was not found to be a substrate for the PGP drug efflux transporter, unlike KW-6002 **1**, which displayed some PGP affinity in our hands. Plasma protein binding was found to be moderate, with an estimated 74−86% of the total plasma content bound.

Rat pharmacokinetics demonstrated an estimated half-life of 2−6 h and an oral bioavailability of ∼35%. A measured brain uptake of 57%[46] indicates good penetration of the compound from plasma into the brain, and when coupled with the T_{max} of 0.5 h, these properties undoubtedly contribute to the potent activity observed in the HaloLMA model.

To examine possible off-target effects, the compound was assessed in the CEREP wide binding screen[47] against 75 other targets. Other than the anticipated effects upon the A_{2A} and A_1 receptors, selectivities of greater than 500-fold were observed for all other targets investigated. Patch-clamp experiments at doses up to 30 μM (the maximal test concentration obtained in the assay protocol) demonstrated no activity greater than vehicle alone on the hERG potassium channel. Further safety pharmacology studies indicated that the compound was nonmutagenic,

showing activity in neither the Ames assay (three strains, ±S9) nor the mouse lymphoma assay in L5178Y cells. As the compound was known to be CNS-penetrant, potential behavioral effects were also investigated using the Irwin screen.[48] Despite dosing for 4 days at 100 mg kg^{-1}, a dose some 300-fold higher than the minimal effective dose in the HaloLMA assay, no overt signs of toxicity or behavioral changes were noted other than a slight, and expected, increase in locomotor activity.

In summary, these data demonstrate that **60** (V2006/BIIB014) displays an encouraging pharmacological, pharmacokinetic, and safety profile and the compound is presently undergoing phase II clinical trials as a potential treatment for the symptoms associated with Parkinson's disease, in collaboration with Biogen Idec. Further details of the preclinical and clinical development of this compound will be reported in due course.

Experimental Section

Flash chromatography was performed using prepacked silica gel cartridges (Strata Si-1, 61 Å from Phenomenex, Cheshire U.K., or IST Flash II, 54 Å from Biotage, Hertford, U.K.). 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. Proton NMR spectra were recorded on a 400 MHz Bruker spectrometer. Solutions were typically prepared in either deuterochloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) with chemical shifts referenced to tetramethylsilane (TMS) as an internal standard. Deuterated solvents were obtained from the Sigma-Aldrich Chemical Co. or Fluorochem. Microanalyses were performed by Medac Ltd., Egham, U.K. All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from the Sigma-Aldrich Chemical Co. Ltd. and used without further drying. All final compounds were >95% purity as determined by examination of both the LC chromatograms (wavelength 235 nm) and the ^{1}H NMR spectra, unless otherwise indicated. Where Cl or Br was present, expected isotopic distribution patterns were observed.

HPLC analysis conditions are described in detail in the Supporting Information, along with retention times and estimated purities of key derivatives.

7-(2-Furyl)-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 4. A solution of 7-chloro-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **3**[29] (570 mg, 3.34 mmol) in *N*-methyl-2-pyrrolidinone (4 mL) was treated with $PdCl_2(PPh_3)_2$ (117 mg, 0.17 mmol) and 2-(tributylstannyl)furan (1.05 mL, 1 mmol), stirred at 80 °C for 5 h, diluted with EtOAc, filtered through a silica pad, and concentrated in vacuo. The residue was triturated with diethyl ether and the title compound isolated as a yellow solid (438 mg, 65%). IR ν_{max} (Nujol)/cm^{-1} 3403, 3329, 3134, 2925, 1656, 1634, 1582, 1565, 1463 and 1377; NMR δ_H (400 MHz, DMSO) 6.83−6.87 (1H, m), 7.12 (2H, s), 7.89 (1H, d, *J* 3.1 Hz), 8.09−8.10 (1H, m), 15.52 (1H, s); m/z = 203 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 5. A solution of 7-(2-furyl)-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **4** (101 mg, 0.5 mmol) in DMF (2 mL), at 0 °C, was treated with NaH (20 mg, 60%, 0.5 mmol), stirred for 20 min, then treated with 2-fluorobenzyl bromide (60 μL, 0.5 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 h, quenched with water, extracted with EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography (EtOAc/heptane, 1:4, to EtOAc/heptane, 2:1) to give the title compound (34 mg, 22%) as a yellow solid. IR ν_{max} (Nujol)/cm^{-1} 3480, 3312, 3195, 3118, 2925, 2854, 1652, 1609, 1581, 1487, 1456, 1436, 1027, and 759; NMR δ_H (400 MHz, DMSO) 5.60 (2H, s), 6.84−6.86 (1H, m), 7.15−7.29 (3H, m), 7.32−7.43 (3H, m), 7.89 (1H, d, *J* 2.9 Hz), 8.12 (1H, s); m/z = 311 $[M + H]^+$.

6-(5-Methyl-2-furyl)pyrimidine-2,4,5-triamine 7. A solution of 6-chloro-5-nitropyrimidine-2,4-diamine[30] (10 g, 60% pure, 32 mmol) in THF (300 mL) was treated with saturated aqueous $NaHCO_3$ (75 mL), 5-methylfuran-2-boronic acid (7.33 g, 0.058 mol), and $Pd(PPh_3)_4$ (1 g, 0.865 mmol) and refluxed with vigorous stirring under argon overnight. The mixture was cooled to room temperature, diluted with EtOAc (400 mL) and water (300 mL), and filtered to remove insoluble material, and the filtrate was extracted with EtOAc (2 × 100 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo and the resulting solid triturated with dichloromethane and filtered to give the title compound (6 g, 72%) as a yellow solid: mp 196.3−196.9 °C; IR ν_{max} (Nujol)/cm^{-1} 3442, 3169, 2930, 1629, 1463, 1377, 1027, and 790; NMR δ_H (400 MHz, DMSO) 7.40 (2H, br s), 7.09 (2H, br s), 6.87 (1H, dd, *J* 0.5, 3.2 Hz), 6.26 (2H, dd, *J* 1.0, 3.3 Hz), and 2.28 (3H, s).

A suspension of this material (6.6 g, 29.6 mmol) and 10% Pd/C (0.66 g) in MeOH (100 mL) was heated at 40 °C under an atmosphere of H_2 for 3 h, cooled to room temperature, filtered through Celite, and concentrated in vacuo to give the title compound (5.8 g, 99%) as an off-white solid. IR ν_{max} (DR)/cm^{-1} 3333, 2237, 1634, 1458, 1237, 1025, 963, and 828; NMR δ_H (400 MHz, DMSO) 6.77 (1H, dd, *J* 0.5, 3.2 Hz), 6.21−6.17 (3H, m), 5.14 (2H, s), 4.21 (2H, s), and 2.35 (3H, s).

6-((1-(2-(Trimethylsilyl)ethoxymethyl)-1*H*-pyrazolyl-3-yl)pyrimidine-2,4,5-triamine 8. 8 was prepared as for compound **7**, using (1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrazolyl-3-boronic acid (2.32 g, 9.6 mmol), to give the nitrodiamine as a yellow solid (0.72 g, 42%). This material was hydrogenated as described above to give the title compound (0.32 g, 50%) which was carried forward immediately without further purification.

7-(5-Methyl-2-furyl)-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 9. A solution of 6-(5-methyl-2-furyl)pyrimidine-2,4,5-triamine **7** (5.8 g, 30.1 mmol) in dioxane (116 mL) was treated with isoamyl nitrite (4.1 mL, 30.5 mmol), heated at 80 °C for 3.5 h, and cooled to room temperature and the resulting precipitate was filtered, washed with dioxane (10 mL) and heptane (2 × 15 mL), then triturated with heptane and filtered to give the title compound (4.7 g, 77%) as a sandy solid: mp 291.8−292.0 °C; IR ν_{max} (DR)/cm^{-1} 3436, 3178, 1651, 1615, 1398, 1226, 1029 and 977; NMR δ_H (400 MHz, DMSO) 15.5−15.3 (1H, br s), 7.84 (1H, d, *J* 3.5 Hz), 7.07 (2H, br s), 6.48 (1H, dd, *J* 3.5, *J* 1.0 Hz), 2.44 (3H, s).

7-(1-(2-(Trimethylsilyl)ethoxymethyl)-1*H*-pyrazolyl-3-yl)-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 10. 10 was prepared as for compound **9** above, using crude 6-(1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrazolyl-3-yl)-pyrimidine-2,4,5-triamine **8** (0.64 g, 2 mmol) and other reagents scaled accordingly. Column chromatography (EtOAc/isohexane, 1:1) gave the title compound as a green solid (0.32 g, 48%) which was used immediately.

3-(2-Fluorobenzyl)-7-(5-methyl-2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 11. 11 was prepared as for compound **5** above, using 7-(5-methyl-2-furyl)-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **9** (0.09 g, 0.41 mmol) and other reagents scaled accordingly to give the title compound as a yellow solid (62 mg, 47%): mp 213.5−213.7 °C; IR ν_{max} (DR)/cm^{-1} 3300, 3218, 3098, 2957, 2927, 2744, 2368, 1645, 1602, 1570, 1537, 1508, 1490, 1438, 1328, and 1233; NMR δ_H (400 MHz, DMSO) 7.86 (1H, d, *J* 3.0 Hz), 7.43−736 (1H, m), 7.31 (2H, br s), 7.28−7.15 (3H, m), 6.50 (1H, dd, *J* 1.0, *J* 3.5 Hz), 5.68 (2H, s), and 2.45 (3H, s); m/z = 325 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(1*H*-pyrazol-3-yl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 12. 12 was prepared as for compound **9** above, using 7-(1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-pyrazolyl-3-yl)-1*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **10**. Following alkylation, the resultant bicyclic derivative was dissolved in methanol (2 mL), and hydrochloric acid (4 M solution in 1,4-dioxane, 1 mL) was added. Stirring at room temperature overnight resulted in the precipitation of a cream solid which was filtered and washed with cold diethyl ether to give the title compound (173 mg, 51%). IR ν_{max} (DR)/cm^{-1} 3282, 2852, 1630, 1368, 1120, 871, and 618; NMR δ_H (400 MHz, DMSO) 7.94 (1H, d, *J* 2.5 Hz), 7.45−7.36 (2H, m), 7.29−7.22 (2H, m), 7.21−7.16 (1H, m), and 5.71 (2H, s); m/z = 311 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(2-thiazolyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 14. A stirred solution of thiazole (0.10 mL, 1.43 mmol) in dry THF (5 mL) at −78 °C under argon was treated with *n*-BuLi (0.9 mL, 1.6 M in hexanes, 1.43 mmol), stirred for 30 min, treated with a solution of $ZnCl_2$ (1.8 mL, 1 M in Et_2O, 1.80 mmol), and allowed to warm gradually to room temperature. The mixture was treated with 7-chloro-3-(2-fluorobenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **13**[32] (200 mg, 0.714 mmol) and $Pd(PPh_3)_4$ (50 mg), refluxed for 2 h, and partitioned between saturated NH_4Cl (20 mL) and EtOAc (20 mL). The organic phase was dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography [SiO_2, isohexane/EtOAc (1:1)] to give the title compound (70 mg, 30%) as a cream solid: mp 225−230 °C; IR ν_{max} (DR)/cm^{-1} 3520, 3344, 1734, 1611, 1438, 1240, 996, 833, and 761; NMR δ_H (400 MHz, DMSO) 8.26 (1H, d, *J* 3.0 Hz), 8.15 (1H, d, *J* 3.0 Hz), 7.50−7.44 (2H, br s), 7.42−7.36 (1H, m), 7.29−7.21 (1H. m), 7.21−7.15 (1H, m), and 5.73 (2H, s); m/z = 328 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(4-methyl-2-thiazolyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 15. 15 was prepared as described for compound **14**, using 4-methylthiazole (0.27 mL, 3 mmol, 3 equiv) to give the compound as a pale-yellow solid after trituration from dichloromethane (94 mg, 29%): mp 265.7−26.2 °C; IR ν_{max} (DR)/cm^{-1} 3491, 3370, 3120, 1614, 1232, 972, 753, and 514; NMR δ_H (400 MHz, DMSO) 7.72 (1H, s), 7.51−7.43 (2H, s), 7.42−7.35 (1H, m), 7.30−7.14 (3H, m), 5.73 (2H, s), and 2.55 (3H, s); m/z = 342 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(5-methyl-2-thiazolyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 16. 16 was prepared as described for compound **14**, using 5-methylthiazole (0.20 mL, 3 mmol, 3 equiv) to give the compound as a pale-yellow solid after purification by column chromatography [SiO_2, isohexane/EtOAc (1:1)] (85 mg, 35%): mp 242.0−242.1 °C; IR ν_{max} (DR)/cm^{-1} 3513, 3294, 1570, 1234, 999, and 755; NMR δ_H (400 MHz, DMSO) 7.96 (1H, s), 7.46−7.34 (3H, m), 7.30−7.13 (3H, m), 5.72 (2H, s), and 2.60 (3H, s); m/z = 342 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(2-oxazolyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 17. 17 was prepared as described for compound **14**, using oxazole (0.14 g, 2 mmol, 2 equiv) to give the compound as a beige solid after purification by column chromatography [SiO_2, isohexane/EtOAc (1:1), then ethyl acetate] (6 mg, 2%). NMR δ_H (400 MHz, DMSO) 8.53 (1H, s), 7.69 (1H, s), 7.58 (2H, br s), 7.45−7.36 (1H, m), 7.29−7.22 (2H, m), 7.21−7.15 (1H, m), and 5.73 (2H, s); m/z = 312 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(2-thienyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 18. A stirred solution of 7-chloro-3*H*-[1,2,3]triazolo[4,5-d]pyrimidine-5-amine **13**[32] (0.2 g, 0.71 mmol), 2-thiophene boronic acid (0.27 g, 2.14 mmol), and $Pd(PPh_3)_4$ (0.1 g, 0.086 mmol) in THF (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL) was heated at reflux for 1 h, during which time the solution darkened to almost black. The mixture was cooled and partitioned between ethyl acetate and water and the organic phase separated, dried, and concentrated in vacuo. The resultant pale-yellow solid was triturated from isohexane/ethyl acetate, filtered, and dried to give the title compound as a yellow solid (0.12 g, 51%): mp 174.0−174.2 °C; IR ν_{max} (DR)/cm^{-1} 3473, 3317, 3188, 2740, 1736, 1648, 1243, 1004, and 752; NMR δ_H (400 MHz, DMSO) 8.68 (1H, dd, *J* 4.0, 1.5 Hz), 7.99 (1H, dd, *J* 5.0, 1.0 Hz), 7.43−7.35 (2H, m), 7.31−7.16 (5H, m), and 5.71 (2H, s); m/z = 327 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(5-triazolyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 19. To a stirred solution of (1-(2-(trimethylsilyl)ethoxymethyl)-1*H*-triazole (0.50 g, 2.50 mmol) in dry THF (10 mL) at −78 °C was slowly added *n*-butyllithium (1.7 mL, 1.6 M solution in hexanes, 2.7 mmol) and, after 30 min, tributyltin chloride (0.69 mL, 3.16 mmol). The mixture was allowed to warm slowly to room temperature and stirred for a further 1 h. After partitioning between ethyl acetate and water, the organic phase was dried (magnesium sulfate) and concentrated in vacuo. Column chromatography [SiO_2, isohexane/EtOAc (5:1)] gave the stannyltriazole as a clear oil. This oil (366 mg, 0.75 mmol) was redissolved in DMF and the chlorotriazolopyrimidine **13** (145 mg, 0.5 mmol) added. $PdCl_2(PPh_3)_2$ (35 mg) was added to this solution and the mixture shaken at 80 °C overnight. After cooling, the mixture was applied directly to a silica gel column and purified [eluting with isohexane/EtOAc (2:1)]. The resultant clear oil was redissolved in methanol (1 mL) and hydrochloric acid (4 M solution in 1,4-dioxane, 0.5 mL). After being stirred at room temperature overnight, the mixture was concentrated in vacuo and the residue triturated from diethyl ether to give the compound as an off-white solid (16 mg, 10%). NMR δ_H (400 MHz, DMSO) 8.84 (1H, br s), 7.46−7.35 (2H, m), 7.32−7.14 (4H, m), and 5.72 (2H, s); m/z = 312 $[M + H]^+$.

3-(2-Fluorobenzyl)-7-(5-thiazolyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 20. 20 was prepared as described for compound **4**, using 5-(tributlystannyl)thiazole (0.56 g, 1.5 mmol) and the chlorotriazolopyrimidine **13** with other reagents scaled accordingly and shaking for 1 h. This procedure gave the title compound as a yellow solid after trituration from diethyl ether (183 mg, 56%). IR ν_{max} (DR)/cm^{-1} 3479, 3289, 3169, 1597, 1502, 1226, 1119, 999, 880, and 757; NMR δ_H (400 MHz, DMSO) 9.43 (1H, s), 9.25 (1H, s), 7.48−7.34 (3H, m) 7.30−7.22 (2H, m), 7.21−7.15 (1H, m), and 5.72 (2H, s); m/z = 328 $[M + H]^+$.

General Alkylation Procedure. A solution of 7-(2-furyl)-1*H*-[1,2,3]triazolo[4,5-d]pyrimidine-5-amine **4** (101 mg, 0.5 mmol) in DMF (2 mL), at 0 °C, was treated with NaH (20 mg, 60%, 0.5 mmol), stirred for 20 min, then treated with the appropriate benzyl bromide (0.5 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 h, then quenched with water, extracted with EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography (EtOAc/heptane, 1:4, to EtOAc/heptane, 2:1)

The following derivatives were prepared using the above methodology.

3-Benzyl-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 21. Yield = 39%; IR ν_{max} (Nujol)/cm^{-1} 3499, 3316, 3193, 2946, 1651, and 1509; NMR δ_H (400 MHz, DMSO) 8.13−8.10 (1H, m), 7.90 (1H, d, *J* 3.5 Hz), 7.39−7.26 (7H, m), 6.87−6.84 (1H, m), and 5.67 (2H, s); m/z = 293 $[M + H]^+$. Anal. ($C_{15}H_{12}N_6O$) C, H, N.

3-Cyclohexylmethyl-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 22. Yield = 4%; IR ν_{max} (Nujol)/cm^{-1} 3316, 3193, 2926, 2851, 1637, 1508, and 1437; NMR δ_H (400 MHz, DMSO) 8.11−8.09 (1H, m), 7.89 (1H, dd, *J* 3.5, 1.0 Hz), 7.27 (2H, s), 6.86−6.83 (1H, m), 4.26 (2H, d, *J* 7.5 Hz), 2.04−1.90 (1H, m), 1.72−1.50 (5H, m), and 1.25−0.95 (5H, m); m/z = 299 $[M + H]^+$.

3-(2,3-Difluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 23. Yield = 20%; mp 188.8−188.9 °C; IR ν_{max} (Nujol)/cm^{-1} 3492, 3302, 3189, 2951, 1635, and 1505; NMR δ_H (400 MHz, DMSO) 8.14−8.10 (1H, m), 7.90 (1H, d, *J* 3.0 Hz), 7.47−7.32 (3H, m), 7.20 (1H, q, *J* 7.0 Hz), 7.05 (1H, t, *J* 7.0 Hz), 6.88−6.83 (1H, m), and 5.75 (2H, s); m/z = 329 $[M + H]^+$.

3-(2,4-Difluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 24. Yield = 15%; mp 207.0−207.4 °C; IR ν_{max} (Nujol)/cm^{-1} 3496, 3229, 3201, 3057, 2965, 2743, 1785, and 1615; NMR δ_H (400 MHz, DMSO) 8.13−8.10 (1H, m), 7.89 (1H, d, *J* 3.5 Hz), 7.40−7.27 (4H, m), 7.08 (1H, dt, *J* 8.5, 3.0 Hz), 6.87−6.84 (1H, m), and 5.66 (2H, s); m/z = 329 $[M + H]^+$.

3-(2,5-Difluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 25. Yield = 25%; mp 208.1−208.2 °C; IR ν_{max} (Nujol)/cm^{-1} 3347, 3199, 2981, 2932, 2764, 2719, 1660, and 1612; NMR δ_H (400 MHz, DMSO) 8.14−8.11 (1H, m), 7.90 (1H, d, *J* 3.5 Hz), 7.41−7.22 (4H, m), 7.15−7.09 (1H, m), 6.87−6.83 (1H, m), and 5.69 (2H, s); m/z = 329 $[M + H]^+$. Anal. ($C_{15}H_{10}F_2N_6O$) C, H, N.

3-(2,6-Difluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 26. Yield = 32%; mp 213.8 −213.9 °C; IR ν_{max} (DR)/cm^{-1} 3996, 3654, 3507, 3320, 2930, 2562, 2621, 1944, 1837, 1676, 1428, 1230, 1095, 1026, and 797; NMR δ_H (400 MHz, DMSO) 5.65 (2H, s), 6.81−6.86 (1H, m), 7.16 (2H, t, *J* 8.5 Hz), 7.31 (2H, s), 7.44−7.56 (1H, m), 7.86 (1H, dd, *J* 3.5, 1.0 Hz), 8.07−8.13 (1H, m); m/z = 329 $[M + H]^+$. Anal. ($C_{15}H_{10}N_6OF_2$) C, H, N.

3-(3-Chlorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 27. Yield = 19%; mp 209.9−210.1 °C; IR ν_{max} (DR)/cm^{-1} 3504, 3312, 3201, 2948, 1611, 1503, 1435, 1279, 1220, 1025, and 755; NMR δ_H (400 MHz, DMSO) 5.69 (2H, s), 6.82−6.87 (1H, m), 7.19−7.25 (1H, m), 7.33 (2H, s), 7.37−7.40 (3H, m), 7.90 (1H, d, *J* 3.5 Hz), 8.10−8.13 (1H, m); *m*/*z* = 328 [M + H]$^+$. Anal. ($C_{15}H_{11}N_6OCl$) C, H, N.

7-(2-Furyl)-3-(2-methylbenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 28. Yield = 9%; mp 218.0−218.1 °C; IR ν_{max} (DR)/cm^{-1} 3999, 3376, 3209, 2916, 2747, 2326, 1957, 1782, 1610, 1515, 1278, 1023, and 763; NMR δ_H (400 MHz, DMSO) 2.42 (3H, s), 5.64 (2H, s), 6.86 (1H, s), 6.91 (1H, d, *J* 7.5 Hz), 7.13 (1H, t, *J* 7.0 Hz), 7.17−7.26 (2H, m), 7.32 (2H, s), 7.90 (1H, d, *J* 3.5 Hz), 8.12 (1H, s); *m*/*z* = 307 [M + H]$^+$.

7-(2-Furyl)-3-(3-methylbenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 29. Yield = 20%; mp 187.3−187.7 °C; IR ν_{max} (DR)/cm^{-1} 3993, 3489, 3319, 3197, 2951, 2725, 2353, 1954, 1719, 1633, 1604, 1503, 1420, 1232, 1032, and 740; NMR δ_H (400 MHz, DMSO) 2.27 (3H, s) 5.62 (2H, s), 6.82−6.88 (1H, m), 7.02−7.16 (3H, m), 7.24 (1H, t, *J* 7.5 Hz), 7.33 (2H, s), 7.90 (1H, d, *J* 3.5 Hz), 8.12 (1H, s); *m*/*z* = 307 [M + H]$^+$.

7-(2-Furyl)-3-(3-trifluoromethylbenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 30. Yield = 7%; IR ν_{max} (Nujol)/cm^{-1} 3379, 3336, 3208, 1655, 1604, 1513, 1456, 1325, 11687, 1124, 1025, and 755; NMR δ_H (400 MHz, DMSO) 5.79 (2H, s), 6.83−6.88 (1H, m), 7.36 (2H, s), 7.53 (1H, d, *J* 7.5 Hz), 7.60 (1H, t, *J* 7.5 Hz), 7.67−7.76 (2H, m), 7.91 (1H, d, *J* 3.5 Hz), 8.13 (1H, s); *m*/*z* = 361 [M + H]$^+$. Anal. ($C_{16}H_{11}F_3N_6O$) C, H, N.

7-(2-Furyl)-3-(2-methoxybenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 31. 31 was prepared using Cs_2CO_3 (1 equiv) in place of sodium hydride. Yield = 25%; mp 212.1−214.3 °C; IR ν_{max} (DR)/cm^{-1} 4007, 3474, 3323, 3199, 2934, 2747, 2105, 1647, 1603, 1492, 1245, 1028, and 754; NMR δ_H (400 MHz, DMSO) 3.82 (3H, s), 5.60 (2H, s), 6.78−6.93 (3H, m), 7.05 (1H, d, *J* 8.5 Hz), 7.24−7.38 (3H, m), 7.90 (1H, d, *J* 3.0 Hz), 8.12 (1H, s); *m*/*z* = 323 [M + H]$^+$.

7-(2-Furyl)-3-(3-methoxybenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 32. Yield = 40%; IR ν_{max} (Nujol)/cm^{-1} 3327, 3207, 2924, 2854, 1650, 1602, 1583, 1566, 1513, and 1487; NMR δ_H (400 MHz, DMSO) 3.72 (3H, s), 5.63 (2H, s), 6.80 (1H, d, *J* 7.5 Hz), 6.85−6.89 (3H, m), 7.26 (1H, t, *J* 7.5 Hz), 7.33 (2H, s), 7.90 (1H, d, *J* 3.5 Hz), 8.11 (1H, s); *m*/*z* = 323 [M + H]$^+$; Anal. ($C_{16}H_{14}N_6O_2$) C, H, N.

3-(3-Cyanobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 33. Yield = 15%; IR ν_{max} (Nujol)/cm^{-1} 3490, 3307, 3189, 2230, 1959, 1728, 1642, 1611, 1583, 1565, 1463, 1377, 1283, 1234, 1030, and 761; NMR δ_H (400 MHz, DMSO) 5.75 (2H, s), 6.82−6.89 (1H, m), 7.35 (2H, s), 7.57−7.59 (2H, m), 7.79−7.81 (2H, m), 7.91 (1H, d, *J* 3.5 Hz), 8.12 (1H, s); *m*/*z* = 318 [M + H]$^+$. Anal. ($C_{16}H_{11}N_7O$) C, H, N.

3-(4-Cyanobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 34. Yield = 13%; mp 292.3−292.4 °C; IR ν_{max} (DR)/cm^{-1} 3324, 3207, 2098, 1602, 1527, 1352, 1024, and 813; NMR δ_H (400 MHz, CDCl3) 8.10 (1H, d, *J* 3.0 Hz), 7.79 (1H, d, *J* 1.5 Hz), 7.64 (2H, d, *J* 8.5 Hz), 7.49 (2H, d, *J* 8.5 Hz), 6.71 (1H, dd, *J* 3.5, 1.5 Hz), 5.71 (2H, s), and 5.38 (2H, br s); *m*/*z* = 318 [M + H]$^+$.

7-(2-Furyl)-3-(2-nitrobenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 35. Yield = 21%; IR ν_{max} (Nujol)/cm^{-1} 3374, 3311, 3202, 1636, 1606, 1586, 1530, 1511, 1465, 1439, 1377, and 1343; NMR δ_H (400 MHz, DMSO) 6.03 (2H, s), 6.86−6.89 (1H, m), 6.98 (1H, d, *J* 7.5 Hz), 7.36 (2H, s), 7.60−7.73 (2H, m), 7.92 (1H, d, *J* 3.5 Hz), 8.14 (1H, s), 8.2 (1H, d, *J* 8.0 Hz); *m*/*z* = 338 [M + H]$^+$. Anal. ($C_{15}H_{11}N_7O_3$) C, H, N.

7-(2-Furyl)-3-(3-nitrobenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 36. Yield = 9%; mp 221.0−221.1 °C; IR ν_{max} (Nujol)/cm^{-1} 3470, 3310, 3191, 3144, 2924, 2854, 1642, 1610, 1521, 1463, and 1354; NMR δ_H (400 MHz, DMSO) 5.85 (2H, s), 6.87 (1H, s), 7.37 (2H, s), 7.63−7.73 (2H, m), 7.91 (1H, d, *J* 2.8 Hz), 8.13 (1H, s), 8.18 (1H, s), 8.20 (1H, s); *m*/*z* = 338 [M + H]$^+$. Anal. ($C_{15}H_{11}N_7O_3$) C, H, N.

7-(2-Furyl)-3-(4-nitrobenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 37. Yield = 14%; mp 240.9−241.1 °C. IR ν_{max} (DR)/cm^{-1} 4010, 3629, 3499, 3313, 3196, 2946, 2733, 2447, 1943, 1638, 1528, 1420, 1351, 1222, 1025, and 960. NMR δ_H (400 MHz, DMSO) 5.85 (2H, s), 6.84−6.89 (1H, m), 7.36 (2H, s), 7.50 (2H, dt, *J* 8.5, 2.0 Hz), 7.92 (1H, dd, *J* 3.5, 1.0 Hz), 8.12−8.14 (1H, m), 8.22 (2H, dt, *J* 9.0, 2.0 Hz); *m*/*z* = 338 [M + H]$^+$. Anal. ($C_{15}H_{11}N_7O_3$) C, H, N.

Methyl 3-(5-Amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)methylbenzoate 38. Yield = 21%; IR ν_{max} (Nujol)/cm^{-1} 3405, 3328, 3211, 3155, 2925, 2854, 1719, 1603, 1577, 1463, 1023, and 731; NMR δ_H (400 MHz, DMSO) 3.84 (3H, s), 5.76 (2H, s), 6.85−6.87 (1H, m), 7.33−7.38 (2H, s), 7.50−7.59 (2H, m), 7.89−7.92 (3H, s), 8.12−8.13 (1H, m); *m*/*z* = 351 [M + H]$^+$. Anal. ($C_{17}H_{14}N_6O_3$) C, H, N.

7-(2-Furyl)-3-(3-hydroxybenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 39. A solution of 7-(2-furyl)-3-(3-methoxybenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **32** (119 mg, 0.37 mmol) in dichloromethane (20 mL) at 0 °C was treated with boron tribromide (1 M in dichloromethane, 8.8 mL, 8.8 mmol) portionwise over 3 days, concentrated in vacuo, and isolated by filtration to give the title compound (114 mg, 100%) as a yellow solid. IR ν_{max} (Nujol)/cm^{-1} 3451, 3206, 2361, 2261, 1655, 1604, 1459, 1378, 1195, 1028, and 774; NMR δ_H (400 MHz, DMSO) 5.57 (2H, s), 6.57−6.63 (1H, m), 6.65−6.74 (2H, m), 6.83−6.88 (1H, m), 7.14 (1H, t, *J* 7.5 Hz), 7.91 (1H, d, *J* 3.0 Hz), 8.12 (1H, d, *J* 1.0 Hz); *m*/*z* = 309 [M + H]$^+$.

3-(5-Amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl-methyl)benzoic Acid 40. A solution of methyl 3-(5-amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)methylbenzoate **38** (771 mg, 2.2 mmol) in MeOH (20 mL) was treated with aqueous NaOH (2 M, 2 mL, 4 mmol), refluxed for 10 min, cooled, acidified with aqueous HCl (1M), filtered, and dried to give the title compound (723 mg, 98%) as a white solid. IR ν_{max} (Nujol)/cm^{-1} 3324, 3206, 1698, 1650, and 1611; NMR δ_H (400 MHz, DMSO) 13.56−12.46 (1H, s), 8.13−8.11 (1H, s), 7.92−7.84 (3H, m), 7.56−7.31 (3H, m), 6.87−6.85 (1H, m), and 7.74 (2H, s); *m*/*z* = 337 [M + H]$^+$.

3-(5-Amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl-methyl)benzamide 41. A suspension of 3-(5-amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-ylmethyl)benzoic acid **40** (168 mg, 0.5 mmol) in DMF (1 mL) was treated with carbonyl diimidazole (81 mg, 0.5 mmol), stirred at room temperature for 1 h, and treated with ammonium hydroxide (1 mL) and the mixture stirred at room temperature for 16 h. The reaction mixture was cooled, diluted with water (3 mL), and filtered to give the title compound (111 mg, 66%) as a cream solid. IR ν_{max} (Nujol)/cm^{-1} 3324, 1644, 1491, and 1417; NMR δ_H (400 MHz, DMSO) 8.12 (1H, s), 7.98−7.93 (1H, s), 7.91 (1H, d, *J* 3.0 Hz), 7.81 (1H, d, *J* 6.5 Hz), 7.77 (1H, s), 7.47−7.29 (5H, m), 6.86 (1H, s), and 5.77−5.68 (2H, m); *m*/*z* = 336 [M + H]$^+$.

The following amides were prepared using the above methodology, employing the appropriate amines.

3-(5-Amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl-methyl)-*N*-isopropylbenzamide 42. Yield = 58%; IR ν_{max} (Nujol)/cm^{-1} 3298, 2972, 1635, and 1418; NMR δ_H (400 MHz, DMSO) 8.21 (1H, d, *J* 7.5 Hz), 8.12 (1H, s), 7.91 (1H, d, *J* 3.0 Hz), 7.82−7.74 (2H, m), 7.48−7.29 (4H, m), 6.86 (1H, s), 5.71 (2H, s), 4.13−4.01 (1H, m), and 1.13 (6H, d, *J* 6.5 Hz); *m*/*z* = 378 [M + H]$^+$.

3-(5-Amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl-methyl)-*N*-isopropyl-*N*-methylbenzamide 43. Yield = 23%; IR ν_{max} (Nujol)/cm^{-1} 3480, 3322, 3202, 283, 1608, and 1506; NMR δ_H (400 MHz, DMSO) 8.12 (1H, s), 7.90 (1H, d, *J* 3.5 Hz), 7.47−7.25 (5H, m), 6.87−6. 84 (1H, m), 5.72 (2H, s), 3.77−3.61 (1H, s), 2.76 (3H, s), 1.10 (3H, s), and 0.99 (3H, s); *m*/*z* = 392 [M + H]$^+$.

(2-Amino-6-(2-furyl)-5-nitropyrimidin-4-yl) 4-Methylbenzenesulfonate 45. A suspension of 2-amino-6-(2-furyl)-5-nitropyrimidine-4(1*H*)-one **44**[34] (1.00 g, 4.50 mmol) in dichloromethane (50 mL) was treated with triethylamine (0.941 mL, 6.75 mmol) and *p*-toluenesulfonyl chloride (944 mg, 4.95 mmol), stirred for 1 h,

diluted with dichloromethane (50 mL), washed with 2 M HCl (20 mL), dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography [SiO_2, isohexane/EtOAc (2:1)] to give the title compound (410 mg, 24%) as a yellow solid. NMR δ_H (400 MHz, $CDCl_3$) 7.95 (2H, d, *J* 8.5 Hz), 7.59−7.57 (1H, m), 7.39 (2H, d, *J* 8.5 Hz), 7.23−7.21 (1H, m), 6.59−6.51 (1H, m), 5.39 (2H, br s), 2.48 (3H, s).

7-(2-Furyl)-3-(2-pyridylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 46. A solution of (2-amino-6-(2-furyl)-5-nitropyrimidin-4-yl) 4-methylbenzenesulfonate **45** (478 mg, 1.27 mmol) in dimethoxyethane (15 mL) was treated with triethylamine (0.531 mL, 3.81 mmol) and 2-pyridinemethylamine (0.393 mL, 3.81 mmol), stirred for 16 h, and poured into water (100 mL), and the resulting solid was filtered to give 6-(2-furyl)-5-nitro-N^4-(2-pyridylmethyl)pyrimidine-2,4-diamine (275 mg, 69%) as a yellow solid. NMR δ_H (400 MHz, $CDCl_3$) 8.70−8.58 (2H, m), 7.70−7.66 (1H, m), 7.55−7.54 (1H, m), 7.28 (1H, d, *J* 8.0 Hz), 7.24−7.20 (1H, m), 7.07−7.06 (1H, m), 6.54−6.52 (1H, m), 5.26 (2H, br s), and 4.83 (2H, d, *J* 5.0 Hz)

A mixture of this material and 10% Pd/C (92 mg, 0.086 mmol) in EtOH (30 mL) and EtOAc (10 mL) was stirred under a hydrogen atmosphere for 1 h, filtered through Celite, and concentrated in vacuo. The resulting yellow oil was dissolved in 1,4-dioxane (25 mL), treated with isoamyl nitrite (0.109 mL, 0.815 mmol), stirred at 100 °C for 6 h, cooled to room temperature, filtered through Celite, concentrated in vacuo, and triturated with Et_2O to give the title compound (110 mg, 46%) as a yellow solid: mp 196.9−197.1 °C; IR ν_{max} (DR)/cm^{-1} 3448, 3321, 3200, 1649, 1616, 1509, 1488; NMR δ_H (400 MHz, DMSO) 8.49−8.47 (1H, m), 8.12−8.11 (1H, m), 7.91 (1H, d, *J* 3.5 Hz), 7.81−7.77 (1H, m), 7.34−7.30 (1H, m), 7.27 (2H, br s), 7.24 (1H, d, *J* 8.0 Hz), 6.86−6.85 (1H, m), 5.77 (2H, s); m/z = 294 $[M + H]^+$.

7-(2-Furyl)-3-(3-pyridylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 47. 47 was prepared as described for compound **46** from **44** using 3-pyridinemethylamine (0.357 mL, 3.51 mmol) and other reagents scaled accordingly, to give the compound as a yellow solid (103 mg, 50%). IR ν_{max} (DR)/cm^{-1} 3326, 3211, 2956, 2856, 1641, 1612, 1507, 1491; NMR δ_H (400 MHz, $CDCl_3$) 8.77−8.76 (1H, m), 8.58−8.56 (1H, m), 8.08 (1H, d, *J* 3.5 Hz), 7.78 (1H, m), 7.75−7.72 (1H, m), 7.29−7.25 (1H, m), 6.71−6.69 (1H, m), 5.68 (2H, s), 5.37 (2H, br s); m/z = 294 $[M + H]^+$. Anal. ($C_{14}H_{11}N_7O$) C, H, N.

The following derivative was also prepared using the general alkylation methodology outlined above.

7-(2-Furyl)-3-(2-pyrazinylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 48. Yield = 16%; mp 129.1−131.0 °C; IR ν_{max} (DR)/cm^{-1} 3993, 3470, 3310, 3197, 1610, 1508, 1420, 1239, 1002, and 796; NMR δ_H (400 MHz, DMSO) 8.74 (1H, d, *J* 1.5 Hz), 8.61 (1H, d, *J* 2.5 Hz), 8.57−8.54 (1H, m), 8.13−8.11 (1H, m), 7.91 (1H, d, *J* 3.5 Hz), 7.31 (2H, br s), 6.86 (1H, dd, *J* 3.5, 2.0 Hz), and 5.88 (2H, s); m/z = 295 $[M + H]^+$.

7-(2-Furyl)-3-(2-furylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 49. Yield = 18%; IR ν_{max} (Nujol)/cm^{-1} 3495 and 3304; NMR δ_H (400 MHz, DMSO) 8.14−8.12 (1H, m), 7.90−7.88 (1H, dd, *J* 1.0, 3.5 Hz), 7.64−7.62 (1H, dd, *J* 1.0, 2.0 Hz), 7.43−7.37 (2H, s), 6.87−6.84 (1H, dd, *J* 1.5, 3.5 Hz), 6.51−6.48 (1H, dd, *J* 1.0, 3.5 Hz), 6.46−6.44 (1H, dd, *J* 2.0, 3.5 Hz), and 5.67−5.65 (2H, s); m/z = 283 $[M + H]^+$. Anal. ($C_{13}H_{10}N_6O_2$) C, H, N.

7-(2-Furyl)-3-(2-thienylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 50. Yield = 11%; mp 204.1−204.2 °C; IR ν_{max} (DR)/cm^{-1} 3490, 3321, 3200, 2923, 2711, 2490, 1749, 1605, 1502, 1376, 1272, 1034, and 761; NMR δ_H (400 MHz, DMSO) 5.83 (2H, s), 6.83−6.86 (1H, m), 7.01 (1H, dd, *J* 5.0, 3.5 Hz), 7.16 (1H, dd, *J* 3.5, 1.0 Hz), 7.34 (2H, s), 7.48 (1H, dd, *J* 5.0, 1.5 Hz), 7.89 (1H, d, *J* 3.5 Hz), 8.09−8.12 (1H, m); m/z = 299 $[M + H]^+$.

7-(2-Furyl)-3-(3-thienylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 51. Yield = 11%; mp 215.8−216.9 °C; IR ν_{max} (Nujol)/cm^{-1} 3482 and 3305; NMR δ_H (400 MHz, DMSO) 8.13−8.11 (1H, m), 7.91−7.89 (1H, d, *J* 3.5 Hz), 7.55−7.52 (1H, dd, *J* 3.0, 5.0 Hz), 7.42−7.40 (1H, m), 7.39−7.34 (2H, s), 7.11−7.08 (1H, dd, *J* 1.5, 5.0 Hz), 6.87−6.85 (1H, dd *J* 1.5, 3.5 Hz), and 5.66−5.64 (2H, s); m/z = 299 $[M + H]^+$. Anal. ($C_{13}H_{10}N_6OS$) C, H, N.

3-(2-Aminobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 52. A solution of 7-(2-furyl)-3-(2-nitrobenzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine **35** (472 mg, 1.4 mmol) in EtOH (10 mL) at 50 °C was treated with a solution of $SnCl_2$ (947 mg, 4.2 mmol) in concentrated HCl (1.6 mL), stirred for 2 h, cooled, diluted with water, basified to pH 10 (5 M, NaOH), and filtered to give the title compound (287 mg, 67%) as an off-white solid. IR ν_{max} (Nujol)/cm^{-1} 3489, 3313, 3191, 1638, 1603, 1505, 1460, and 1378; NMR δ_H (400 MHz, DMSO) 5.27 (2H, s), 5.47 (2H,s), 6.50 (1H, t, *J* 7.5 Hz), 6.67−6.78 (2H, m), 6.86 (1H, s), 7.01 (1H, t, *J* 7.0 Hz), 7.36 (2H, s), 7.90 (1H, d, *J* 3.0 Hz), 8.12 (1H, s); m/z = 308 $[M + H]^+$.

Similarly prepared were the following compounds.

3-(3-Aminobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 53. 53 was prepared from compound **36**. Yield = 92%; mp 259.8−259.9 °C; IR ν_{max} (Nujol)/cm^{-1} 3452, 3367, 3318, 3185, 3142, 2922, 1651, 1602, 1514, 1463, and 1377; NMR δ_H (400 MHz, DMSO) 5.09 (2H, s), 5.49 (2H, s), 6.35 (1H, s), 6.41 (1H, d, *J* 7.5 Hz), 6.45 (1H, d, *J* 8.0 Hz), 6.85−6.86 (1H, m), 6.96 (1H, t, *J* 8.0 Hz), 7.30 (2H, s), 7.90 (1H, d, *J* 3.5 Hz), 8.11 (1H, s); m/z = 308 $[M + H]^+$. Anal. ($C_{15}H_{13}N_7O$) C, H, N.

3-(4-Aminobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 54. 54 was prepared from compound **37**. Yield = 45%; mp 240.3−240.4 °C. IR ν_{max} (DR)/cm^{-1} 3320, 3198, 2929, 1610, 1505, 1438, 1280, 1233, 1028, 956, and 759; NMR δ_H (400 MHz, DMSO) 5.85 (2H, s), 6.84−6.89 (1H, m), 7.36 (2H, s), 7.50 (2H, dt, *J* 8.5, 2.0 Hz), 7.92 (1H, dd, *J* 3.5, 1.0 Hz), 8.12−8.14 (1H, m), 8.22 (2H, dt, *J* 9.0 Hz); m/z = 308 $[M + H]^+$.

3-(4-Aminomethylbenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 55. 4-Hydroxymethylbenzonitrile (1.33 g, 10 mmol) and ammonium hydroxide (1 mL) were dissolved in ethanol (20 mL), and catalytic Raney nickel was added. The reaction vessel was evacuated, placed under an atmosphere of hydrogen, then shaken at room temperature overnight. After filtration through Celite and concentration in vacuo, the resultant off-white solid (1.10 g, 80%) was redissolved in THF and triethylamine (1.12 mL, 8 mmol) added. After stirring at room temperature for 10 min, di-*tert*-butyl dicarbonate (1.84 g, 8 mmol) was added and the reaction stirred for a further 90 min. The reaction mixture was then partitioned between saturated aqueous ammonium chloride solution and ethyl acetate, and the organic phase was separated, dried (magnesium sulfate), and concentrated to dryness to give the N-protected benzyl alcohol **56** as a white solid (1.70 g, 89%) which was used without further purification. NMR δ_H (400 MHz, DMSO) 7.35 (1H, t, *J* 6.0 Hz), 7.24 (2H, d, *J* 8.0 Hz), 7.17 (2H, d, *J* 8.0 Hz), 5.13 (1H, t, *J* 5.7 Hz), 4.46 (2H, d, *J* 5.7 Hz), 4.08 (2H, d, *J* 6.0 Hz)

This material (1.65 g, 6.96 mmol) was then mixed with triphenylphosphine (2.19 g, 10.4 mmol) in dichloromethane (50 mL) at 0 °C and treated portionwise with CBr_4 (3.46 g, 10.4 mmol), stirred for 1 h, concentrated in vacuo, and purified by chromatography [SiO_2, isohexane/EtOAc (5:1)] to give the corresponding protected bromide **57** (1.35 g, 65%). NMR δ_H (400 MHz, DMSO) 7.41 (1H, br t), 7.38 (2H, d, *J* 8.0 Hz), 7.21 (2H, d, *J* 8.0 Hz), 4.68 (2H, s), 4.11 (2H, d, *J* 6.2 Hz), 1.39 (9H, s)

Alkylation of the triazolopyrimidine **4** with this material (600 mg, 2 mmol) under our standard procedure described above was followed by dissolution in methanol (30 mL) and addition of hydrochloric acid (4 M solution in 1,4-dioxane). After stirring at room temperature overnight, the resultant mixture was concentrated to dryness and triturated from diethyl ether to yield the title compound as a yellow solid (57 mg, 12%): mp >300 °C dec; IR ν_{max} (DR)/cm^{-1} 2903, 2030, 1606, 1464, 1033, 779, and 589; NMR δ_H (400 MHz, DMSO) 8.30 (2H, br s), 8.14 (1H. s), 7.92 (1H, d, *J* 3.5 Hz), 7.46 (2H, d, *J* 8.0 Hz), 7.32 (2H, d, *J* 8.0 Hz), 6.92−6.84 (1H, m), 5.69 (2H, s), and 4.04−3.96 (2H, m); m/z = 322 $[M + H]^+$.

The following were prepared via alkylation of the furyltriazolopyrimidine **4** with commercially available substituted 4-nitrobenzyl

bromides, followed by reduction with tin(II) chloride, as per compound **53**.

3-(4-Amino-2-fluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 58. Yield = 17%; NMR δ_H (400 MHz, DMSO) 8.11−8.09 (1H, m), 7.89−7.86 (1H, dd, *J* 1.0, 3.5 Hz), 7.32−7.27 (2H, s), 7.22−6.95 (1H, t, *J* 9.0 Hz), 6.85−6.83 (1H, dd, *J* 2.0, 3.5 Hz), 6.35−6.29 (2H, m), 5.48−5.46 (2H, s), and 5.46−5.44 (2H, s); m/z = 326 $[M + H]^+$.

3-(4-Amino-3-fluorobenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 59. Yield = 57%; mp >200 °C dec; IR ν_{max} (DR)/cm^{-1} 2816, 2004, 1660, 1507, 1427, 1277, 1030, 746, and 524; NMR δ_H (400 MHz, DMSO) 8.15−8.12 (1H, m), 7.91 (1H, d, *J* 3.5 Hz), 7.14 (1H, d, *J* 12.0 Hz), 7.06−6.94 (2H, m), 6.86 (1H, dd, *J* 3.5, 2.0 Hz), and 5.57 (2H, s); m/z = 326 $[M + H]^+$.

3-(4-Amino-3-methylbenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 60. Yield = 63%; mp 245.3−246.1 °C; IR ν_{max} (DR)/cm^{-1} 4010, 3406, 3320, 3198, 2929, 2746, 1608, 1507, 1414, 1285, 1022, and 753; NMR δ_H (400 MHz, DMSO) 2.00 (3H, s), 4.86 (2H, s), 5.42 (2H, s), 6.54 (1H, d, *J* 8.0 Hz), 6.82−6.85 (1H, m), 6.90 (1H, dd, *J* 8.0, 2.0 Hz), 6.92−6.95 (1H, m), 7.29 (2H, s), 7.88 (1H, d, *J* 3.5 Hz), 8.09−8.12 (1H, m); m/z = 322 $[M + H]^+$. Anal. ($C_{16}H_{15}N_7O$) C, H, N.

3-(4-Amino-3-ethylbenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 61. A solution of 4-nitrobenzyl bromide **65** (2.16 g, 10 mmol) in THF (40 mL) at −70 °C was treated dropwise with ethylmagnesium chloride (5 mL, 2 M in Et_2O, 10 mmol), stirred for 1 h, treated with DDQ (2.5 g, 11 mmol), and stirred at room temperature for 16 h. The reaction mixture was poured into water (10 mL), extracted with EtOAc (2 × 10 mL), dried ($MgSO_4$), concentrated in vacuo, and filtered. The resulting solid was purified by chromatography [SiO_2, EtOAc/hexane (1:9)] to give the benzyl bromide (968 mg, 40%) as an orange oil which was used without further purification. NMR δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 8.3 Hz), 7.37 (1H, s), 7.35 (1H, d, *J* 8.3 Hz), 4.47 (2H, s), 2.92 (2H, q, *J* 7.5 Hz), and 1.30 (3H, t, *J* 7.5 Hz).

Alkylation and tin(II) chloride reduction using the standard procedures described above gave the title compound (100 mg, 6% over two steps) as a cream powder. IR ν_{max} (DR)/cm^{-1} 3427, 3318, 3201, 2966, 1605, 1503, 1415, 1281, 1027, and 762; NMR δ_H (400 MHz, DMSO) 1.08 (3H, t, *J* 7.0 Hz), 2.39 (2H, q, *J* 7.0 Hz), 4.91 (2H, s), 5.44 (2H, s), 6.54 (1H, d, *J* 8.0 Hz), 6.80−9.62 (2H, m), 6.97 (1H, s), 7.34 (2H, s), 7.89 (1H, s), 8.12 (1H, s); m/z = 336 $[M + H]^+$. Anal. ($C_{17}H_{17}N_7O$) C, H, N.

3-(4-Amino-3-isopropylbenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 62. 62 was prepared as for **61** using isopropylmagnesium chloride to give the title compound as an orange oil (505 mg, 10%). IR ν_{max} (DR)/cm^{-1} 3480, 3379, 3199, 2958, 2761, 2104, 1879, 1776, 1659, 1516, 1439, 1334, 1024, 762, and 575; NMR δ_H (400 MHz, DMSO) 1.10 (6H, d, *J* 7.0 Hz), 2.92 (1H, sept, *J* 6.5 Hz), 4.93 (2H, s), 5.44 (2H, s), 6.54 (1H, d, *J* 8.0 Hz), 6.80−6.88 (2H, m), 7.09 (1H, d, *J* 2.0 Hz), 7.34 (2H, s), 7.88 (1H, d, *J* 3.5 Hz), 8.10−8.13 (1H, m); m/z = 350 $[M + H]^+$. Anal. ($C_{18}H_{19}N_7O$) C, H, N.

3-(4-Amino-3-hydroxybenzyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 63. A solution of 3-hydroxy-4-nitrobenzoic acid **69** (1.83 g, 10 mmol) in THF (10 mL) was treated with Et_3N (3.4 mL, 24 mmol) and di-*tert*-butyl dicarbonate (2.40 mL, 11 mmol) and the mixture stirred at room temperature for 16 h. The reaction mixture was poured into 10% citric acid solution (20 mL), extracted with EtOAc (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give the protected benzoic acid **70** (2.36 g, 83%) as a cream solid. IR ν_{max} (Nujol)/cm^{-1} 2985, 1772, 1717, and 1592; NMR δ_H (400 MHz, DMSO) 13.85 (1H, s), 8.26 (1H, d, *J* 8.5 Hz), 8.04 (1H, dd, *J* 8.5, 2.0 Hz), 7.98 (1H, d, *J* 2.0 Hz), and 1.49 (9H, s).

The acid (2.26 g, 8 mmol) and *N*-methylmorpholine (1.85 mL, 16.8 mmol) in THF (20 mL) at 0 °C were treated with isobutyl chloroformate (1.09 mL, 8.4 mmol), and the mixture was stirred for 1 h. The mixture was added to a cooled (−78 °C) solution of $NaBH_4$ (605 mg, 16 mmol) in MeOH (16 mL) and stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc (20 mL), washed with saturated $NaHCO_3$ (10 mL) and 10% citric acid solution (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give *tert*-butyl (5-hydroxymethyl-2-nitrophenyl)carbonate **71** (1.36 g, 86%) as a cream solid. This material was then combined with triphenylphosphine (2.13 g, 8.25 mmol) in dichloromethane (50 mL) at 0 °C and treated portionwise with CBr_4 (3.36 g, 10.11 mmol), stirred for 1 h, concentrated in vacuo, and purified by chromatography [SiO_2, isohexane/EtOAc (3:1)] to give the corresponding protected bromide **72** as a yellow oil (961 mg, 58%). NMR δ_H (400 MHz, $CDCl_3$) 8.09 (1H, d, *J* 8.4 Hz), 7.41 (1H, dd, *J* 8.4, 2.0 Hz), 7.34 (1H, d, *J* 2.0 Hz), 4.47 (2H, s), and 1.58 (9H, s).

Alkylation of the furyl triazolopyrimidine **4** (899 mg, 4.55 mmol) with this material (989 mg, 2.52 mmol) gave 415 mg (32%) of a yellow solid. Tin(II) chloride reduction of this material (226 mg, 0.5 mmol), as described above, gave the title compound as a brown solid (126 mg, 78%): mp 239.6−239.8 °C; IR ν_{max} (Nujol)/cm^{-1} 3323, 2936, 2733, 1772, 1734, 1609, 1508, and 1282; NMR δ_H (400 MHz, DMSO) 9.07 (1H, s), 8.13−8.11 (1H, m), 7.89 (1H, d, *J* 3.5 Hz), 7.34 (2H, s), 6.87−6.84 (1H, m), 6.59−6.50 (3H, m), 5.41 (2H, s), and 4.57 (2H, s); m/z = 324 $[M + H]^+$.

7-(2-Furyl)-3-(4-(*N*-methylamino)benzyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 64. To a stirred solution of 4-(methylamino)benzoic acid **73** (5 g, 33.1 mmol) in THF (30 mL) was added diisopropylethylamine (14.4 mL, 36.4 mmol) and di-*tert*-butyl dicarbonate (8.36 mL, 36.4 mmol) and the mixture stirred at reflux for 48 h. After cooling, the mixture was diluted with ethyl acetate and washed sequentially with an aqueous solution of citric acid (10% w/v), water, and brine, then dried (magnesium sulfate) and concentrated in vacuo to give the N-protected benzoic acid **74** as a cream solid (5.87 g, 69%). NMR δ_H (400 MHz, DMSO) 12.78 (1H, s), 7.89 (2H, d, *J* 8.6 Hz), 7.41 (2H, 2H, d, *J* 8.6 Hz), 3.22 (3H, s), 1.41 (9H, s)

This material was redissolved in THF (50 mL) and cooled to 0 °C before *N*-methylmorpholine (5.06 mL, 46 mmol) and isobutyl chloroformate (3.02 mL, 23.25 mmol) were added. After the mixture was stirred at 0 °C for 15 min, a cooled (−78 °C) solution of sodium borohydride (1.75 g, 46 mmol) in methanol (30 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature and was stirred for a further 2 h. The reaction mixture was diluted with ethyl acetate and washed sequentially with an aqueous solution of citric acid (10% w/v), saturated aqueous sodium bicarbonate solution, water, and brine, then dried (magnesium sulfate) and concentrated in vacuo to give the benzyl alcohol **75** as a clear, dark-orange oil (1.21 g, 22%). NMR δ_H (400 MHz, DMSO) 7.27 (2H, d, *J* 8.5 Hz), 7.21 (2H, d, *J* 8.5 Hz), 5.16 (1H, t, *J* 5.7 Hz), 4.46 (2H, d, *J* 5.7 Hz), 3.15 (3H, s), 1.38 (9H, s)

This material was then mixed with triphenylphosphine (2.01 g, 7.67 mmol) in dichloromethane (10 mL) at 0 °C. The resultant solution was treated portionwise with CBr_4 (2.20 g, 6.64 mmol), warmed to room temperature, and stirred for 2 h. After concentration in vacuo, column chromatography [SiO_2, heptane/EtOAc (10:1)] yielded the corresponding protected bromide **76** (669 mg, 43%). NMR δ_H (400 MHz, DMSO) 7.40 (2H, d, *J* 8.5 Hz), 7.25 (2H, d, *J* 8.5 Hz), 4.69 (2H, s), 3.17 (3H, s), 1.39 (9H, s)

Alkylation of the furyltriazolopyrimidine **4** (200 mg, 1 mmol) with this material (654 mg, 2.20 mmol) proceeded as per the standard methodology described above. A portion of the resultant material (82 mg, 0.19 mmol) was dissolved in a mixture of 1,4-dioxane (5 mL) and hydrochloric acid (4 M solution in 1,4-dioxane, 0.07 mL, 0.28 mmol). After being stirred at room temperature overnight, the reaction mixture was concentrated in vacuo and the resultant yellow solid washed with cold diethyl ether to yield the title compound (17 mg, 23%). NMR δ_H (400 MHz, DMSO) 8.14−8.12 (1H, m), 7.92−7.89 (1H, dd, *J* 1.0, 3.5 Hz), 7.35−7.31 (2H, d, *J* 8.5 Hz), 7.28−7.16 (2H, s), 6.88−6.85 (1H, dd, *J* 1.5, 3.5 Hz), 5.66−5.64 (2H, s), and 2.82−2.80 (3H, s); m/z = 322 $[M + H]^+$.

***N*-(4-(5-Amino-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-ylmethyl)phenyl)acetamide 77. 77** was prepared via alkylation with the corresponding commercial benzyl bromide as described above,

to give the title compound as a cream powder (42 mg, 6%): mp 253.6−254.0 °C; IR ν_{max} (DR)/cm^{-1} 3320, 1611, 1414, 1315, 1255, 1026, and 767; NMR δ_H (400 MHz, DMSO) 2.01 (3H, s), 5.59 (2H, s), 6.84−6.88 (1H, m), 7.22 (2H, d, *J* 8.5 Hz), 7.36 (2H, s), 7.54 (2H, d, *J* 8.5 Hz), 7.90 (1H, d, *J* 3.5 Hz), 8.11−8.14 (1H, m), 9.97 (1H, s); $m/z = 350$ $[M + H]^+$.

7-(2-Furyl)-3-(5-indolylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 78. To a stirred solution of *N*-Boc-5-methylindole (2.15 g, 9,.15 mmol) in carbon tetrachloride (100 mL) was added *N*-bromosuccinimide (1.63 g, 9.15 mmol) and benzoyl peroxide (75%, 295 mg, 0.9 mmol). The mixture was refluxed for 1 h, then cooled and concentrated, and the residues were purified by chromatography [SiO_2, isohexane/EtOAc (30:1)] to give the protected bromomethylindole as a colorless oil (2.10 g, 74%). NMR δ_H (400 MHz, $CDCl_3$) 8.10 (1H, br d, *J* 7.5 Hz), 7.60 (1H, d, *J* 3.6 Hz), 7.58 (1H, d, *J* 1.7 Hz), 7.35 (1H, dd, *J* 1.7 Hz, 8.6 Hz), 6.54 (1H, d, *J* 3.6 Hz), 4.63 (2H, s), 1.66 (9H, s)

Alkylation of the furyltriazolopyrimidine **4** (404 mg, 2 mmol) with this material (682 mg, 2.2 mmol) under the conditions described above gave a yellow solid (121 mg, 14%) which was dissolved in methanol (5 mL) and treated with sodium methoxide (39 mg, 0.73 mmol), and the mixture was refluxed for 5 h. After concentration to half of the original volume and washing with water, evaporation to dryness gave the title compound as a cream solid (63 mg, 74%): mp 226.8−227.4 °C; IR ν_{max} (DR)/cm^{-1} 3475, 3320, 2739, 1645, 1506, 1223, 1008, and 778; NMR δ_H (400 MHz, DMSO) 11.14 (1H, br s), 8.14−8.10 (1H, m), 7.90 (1H, d, *J* 3.5 Hz), 7.50 (1H, s), 7.40−7.31 (4H, m), 7.09 (1H, dd, *J* 8.0, 1.5 Hz), 6.85 (1H, dd, *J* 3.5, 1.5 Hz), 6.43−6.38 (1H, m), and 5.70 (2H, s); $m/z = 332$ $[M + H]^+$.

7-(2-Furyl)-3-(5-indazolylmethyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 79. 79 was prepared via alkylation of the furyltriazolopyrimidine 4 (404 mg, 2 mmol) with *N*-THP-5-bromomethylindazole[36] (740 mg, 2.5 mmol). After alkylation, the resultant solid (226 mg, 27%) was dissolved in a mixture of MeOH (5 mL) and hydrochloric acid (4 M solution in 1,4-dioxane, 1 mL, 0.25 mmol) and the reaction mixture was stirred at room temperature overnight. After concentration in vacuo, the resulting solid was triturated with ether, filtered, and dried to give the title compound (196 mg, quant) as a yellow solid: mp >300 °C dec; IR ν_{max} (DR)/cm^{-1} 3100, 1662, 1465, 1281, 1032, 782, and 592; NMR δ_H (400 MHz, DMSO) 8.16−8.13 (1H, m), 8.07 (1H, s), 7.92 (1H, d, *J* 3.5 Hz), 7.68 (1H, s), 7.54 (1H, d, *J* 8.5 Hz), 7.35 (1H, dd, 8.5, 1.5 Hz), 6.87 (1H, dd, *J* 3.5, 2.0 Hz), and 5.76 (1H, s); $m/z = 333$ $[M + H]^+$.

3-(1*H*-Benzotriazol-5-ylmethyl)-7-(2-furyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-amine 80. A mixture of 5-methyl-1*H*-benzotriazole (Acros Chemicals) (666 mg, 5 mmol) in THF (20 mL) was treated with NaH (60% dispersion, 200 mg, 5 mmol), stirred at room temperature for 10 min, treated with di-*tert*-butyl dicarbonate (115 mg, 5 mmol), and stirred overnight. The mixture was treated with saturated $NaHCO_3$ solution (10 mL), extracted with EtOAc (2 × 10 mL), dried ($MgSO_4$), filtered through a plug of SiO_2, and concentrated in vacuo to give *tert*-butyl 5-methylbenzotriazole-1-carboxylate (as a mixture with the 6-methyl regioisomer) (1.08 g, 92%) as a colorless oil. NMR δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* 8.4 Hz), 7.87 (1H, s), 7.28 (1H, dd, *J* 7.6 Hz, 1.2 Hz), 2.56 (2H, s), 1.76 (9 H, s)

A solution of the protected benzotriazole (as a mixture with the 6-methyl regioisomer) (1.08 g, 4.63 mmol), benzoyl peroxide (112 mg, 0.46 mmol), and *N*-bromosuccinimide (0.76 g, 4.63 mmol) in CCl_4 (25 mL) was refluxed overnight, cooled, filtered, concentrated in vacuo, and purified by chromatography [SiO_2, isohexane/EtOAc (10:1)] to give the protected bromomethylbenzotriazole (666 mg, 46%) (as a mixture with the 6-bromomethyl regioisomer) as a colorless oil. NMR δ_H (400 MHz, DMSO) 8.21 (1H, d, *J* 8.6 Hz), 8.14 (1H, s), 7.64 (1H, d, *J* 8.6 Hz), 4.98 (2H, s), 1.71 (9H, s)

A solution of the furyltriazolopyrimidine **4** (404 mg, 2 mmol) in DMF (4 mL) was treated with NaH (60% dispersion, 80 mg, 2 mmol), stirred at room temperature for 10 min, treated with a solution of the protected bromomethylbenzotriazole (as a mixture with the 6-bromomethyl regioisomer) (624 mg, 2 mmol) in DMF (2 mL), and stirred overnight. The mixture was concentrated in vacuo and purified by chromatography [SiO_2, isohexane/EtOAc (2:1)] to give the alkylated triazolopyrimidine (135 mg, 24%) (as a mixture with the 6-substituted regioisomer) as a white solid which was dissolved in a mixture of MeOH (5 mL) and THF (5 mL). The solution was treated with 40% aqueous dimethylamine (0.176 mL, 1.56 mmol), refluxed for 25 min, and concentrated in vacuo and the resulting solid triturated with ether, filtered, triturated with MeOH, filtered, and dried to give the title compound as a single regioisomer (31 mg, 30%) as a yellow solid: mp >300 °C dec; IR ν_{max} (DR)/cm^{-1} 3212, 1607, 1438, 1212, 1029, and 770; NMR δ_H (400 MHz, DMSO) 15.74 (1H, br s), 8.13 (1H, s), 7.91 (1H, d, *J* 3.5 Hz), 7.80 (2H, br s), 7.54−7.30 (3H, s), 6.86 (1H, dd, *J* 4.0, 2.0 Hz), and 5.85 (2H, s); $m/z = 334$ $[M + H]^+$.

Acknowledgment. We thank Tim Haymes, Heather Simmonite, and Loic LeStrat for analytical support. We also thank Douglas Williamson and Karen Benwell for helpful comments during the preparation of this manuscript.

Supporting Information Available: Details of biological protocols, tables of elemental analysis results, and chromatographic data, including methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM800961G