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Novel triazolopyridylbenzamides as potent and selective p38α inhibitors

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ABSTRACT

A new class of p38α inhibitors based on a biaryl-triazolopyridine scaffold was investigated. X-ray crystallographic data of the initial lead compound cocrystallised with p38α was crucial in order to uncover a unique binding mode of the inhibitor to the hinge region via a pair of water molecules. Synthesis and SAR was directed towards the improvement of binding affinity, as well as ADME properties for this new class of p38α inhibitors and ultimately afforded compounds showing good in vivo efficacy.

The p38α mitogen-activated protein (MAP) kinase is an intracellular serine/threonine (Ser/Thr) kinase that is activated by a range of environmental stimuli such as TNFα, IL-1β and stress.[1,2] In its activated state, p38α phosphorylates a range of intracellular protein substrates that post-transcriptionally regulate the biosynthesis of TNFα and IL-1β. Excessive levels of TNFα and IL-1β are thought to be responsible for the progression of many inflammatory diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.[3–6] The proven ability of p38α MAP kinase to efficiently regulate both the release and the activity of such pro-inflamatory cytokines initially attracted numerous pharmaceutical companies and independent researchers into pursuing p38α inhibitors as novel anti-inflammatory drugs.[7] However, although initial preclinical results seemed to be very promising[8,9] resulting in the advancement of several candidates into the clinic,[10] recent reports on clinical trials performed with the most advanced compounds in rheumatoid arthritis have revealed limited efficacy.[11] Currently, the potential use of such molecules in other indications is under study.[12]

As part of ongoing efforts toward the discovery of novel p38α inhibitors,[13] we became interested in biaryl systems based on the tolyl amide motif (structure **A**, Fig. 1) which have been described in the literature as potent inhibitors of the p38α MAP kinase.[14] This hinge binding motif generally contains a nitrogen atom embedded in a fused bicyclic aromatic system which offers a direct interaction with the NH of Met109. At the other end of the biaryl system, the amide moiety presents two additional interactions with the corresponding carbonyl and NH units of Glu71 and Asp168, respectively. An additional interaction in the hinge region with the NH of Gly110 amide backbone has been described for several p38α inhibitors through a well documented 'Gly flip' which may be important in imparting the high levels of selectivity seen for such compounds.[15] The triazolopyridine inhibitor B (Fig. 1)[16] is reported to have such an interaction with the hinge region of p38α. In an effort to seek this double interaction in a novel series, a hybrid structure of A and B was devised (structure **C**, Fig. 1) and molecule **1** was synthesised as a representative example.[17,18]

It was satisfying to find that **1** showed good potency in the enzymatic assay (IC_{50} = 16 nM) and an X-ray co-crystal of **1** bound within p38α was obtained.[19] From this study, the presence of a 'Gly flip' was confirmed but, surprisingly, the key interactions between **1** and the hinge region of p38α were established through two molecules of water instead of direct ligand–protein interactions (Fig. 2). This novel binding mode clearly differs from that seen with other reported triazolopyridine-based p38α inhibitors[16] where direct interactions between the aromatic nitrogens of the triazolopyridine moiety and the amino acids of the hinge region are established (vide supra). The rigidity of the biarylamide system together with the two additional strong interactions of the benzamide

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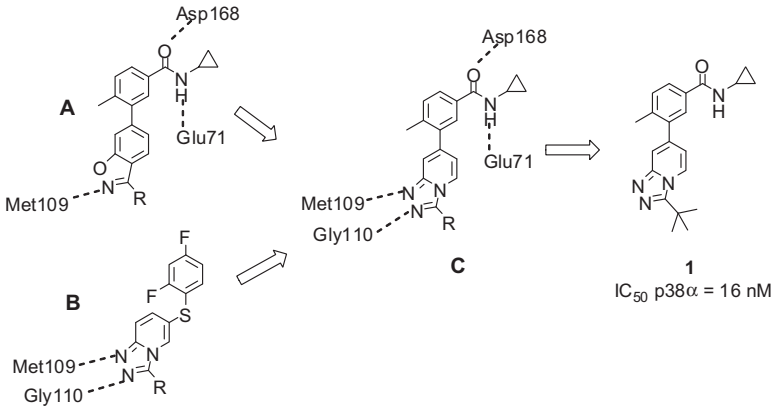


Figure 1. Design of triazolopyridylbenzamides **C**.

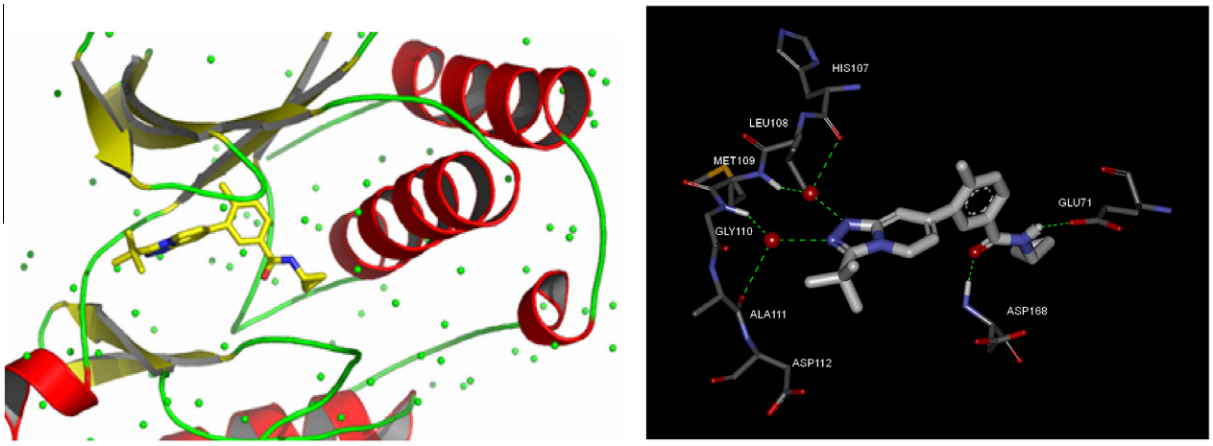
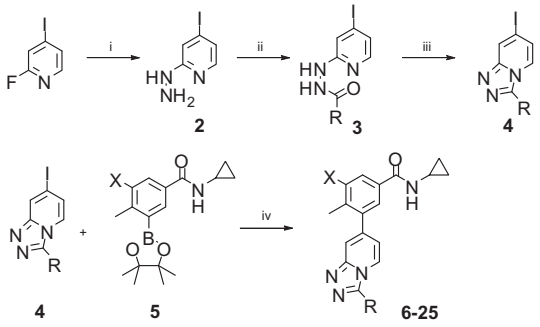


Figure 2. X-ray complex of **1** with p38α, showing a close-up of the key interactions between the triazolopyridine moiety and the hinge region via two water molecules (resolution 1.8 Å).

subunit with Glu71 and Asp168 increase the distance between the two nitrogens of the triazolopyridyl core and the hinge region, allowing for two water molecules to fit in this additional space in order to establish the observed binding interactions. To the best of our knowledge, this is the first described example in which two water molecules are involved in the interaction between a ligand and the hinge region of the p38α enzyme. As expected for this type of system, an almost perpendicular arrangement of the aromatic rings (torsion angle = 88°) is observed. Additionaly, the *tert*-butyl group of **1** lies in a hydrophobic pocket close to the solvent-exposed region.

Initial SAR effors were directed towards replacement of the *tert*-butyl moiety. Thus, a convergent synthesis was devised in order to rapidly access molecules containing different substituents at this position (Scheme 1). Treatment of commercially available 2-fluoro-4-iodopyridine with hydrazine hydrate followed by condensation with different carboxylic acids or acid chlorides afforded the corresponding hydrazides **3**. Cyclization of **3** with polymer supported triphenylphosphine in the presence of $TMSN_3$ and diethylazadicarboxylate (DEAD) proceeded smoothly to yield the corresponding triazolopyridine subunits **4**. A Suzuki-type cross coupling reaction of compounds of type **4** with boronates of type **5**[20] provided the corresponding triazolopyridylbenzamides **6–25**.

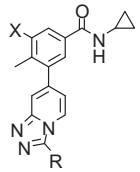
Biological results are presented in Table 1—both an enzymatic p38α binding assay as well as a LPS-induced TNFα production assay in human whole blood (hWB) were used to test compounds.[21] The compound which possessed an isopropyl substituent on the



Scheme 1. Reagents and conditions: (i) Hydrazine hydrate, EtOH, 48 h, rt (90%); (ii) RCOOH, EDC·HCl, Et_3N, HOBt, ACN or RCOCl, DIPEA, DCM, −78 °C (30–90%); (iii) PS-PPh_3, $TMSN_3$, DEAD (52–90%); (iv) $PdCl_2$dppf·DCM, Cs_2CO_3, dioxane, 90 °C, 6 h (8[R = CF_3]–94%).

triazolyl moiety (**7**) provided excellent inhibition in both the binding assay (IC_{50}: 29 nM) and the hWB assay (IC_{50}: 42 nM). Given this promising result other compounds possessing other alkyl or cycloalkyl susbtituents at this position were prepared and tested. As observed in Table 1, most substituents were well tolerated as ascertained from the binding assay and only the placement of larger groups such as the tetrahydropyranyl substituent (compounds **15** and **16**) resulted in a slight decrease in enzymatic potency. Substitution at this position with an aromatic ring resulted in compounds which showed both excellent enzymatic

Table 1
SAR around 3-substituted triazolopyridyl derivatives



Compound no.	X	R	p38α IC_{50}[a] (nM)	hWB TNFα IC_{50}[a] (nM)
A (Fig. 1, R = piperidine)	—	—	14 ± 1.4	98 ± 22
B (Fig. 1, R = *t*-Bu)	—	—	62 ± 16 [b]	143 ± 58
1	H	*t*Bu	16 ± 7.2	30 ± 2.2
6	F	*t*Bu	2 ± 0.9	48 ± 4.6
7	H	*i*Pr	27 ± 12	42 ± 23
8	F	*i*Pr	3 ± 0.1	115 ± 35
9	H		26 ±2.6	25 ± 3.5
10	F		6.7 ± 0.5	213 ± 7.8
11	H		12 ± 6.9	232 ± 63
12	F		0.64 ± 0.05	117 ± 31.3
13	H		20 ± 8.2	670 ± 358
14	F		1.9 ± 0.25	550 ± 490
15	H		56 ± 19	667 ± 50
16	F		30 ± 26	405 ± 106
17	H		6.3 ± 1.8	20 ± 1.7
18	F		1.6 ± 0.7	7.2 ± 4.9
19	H		38 ± 26	305 ± 51
20	F		0.83 ± 0.02	84 ± 7
21	H		43 ± 21	1056 ± 342
22	F		18 ± 0.04	257 ± 119
23	H	CF_3	853 ± 184	—
24	F	CF_3	85 ± 2.5	—
25	F		102 ± 71	1839 (1)

[a] IC_{50} values represent the mean ± standard deviation of two or more independent determinations except when indicated otherwise (between brackets).
[b] Literature reported binding affinity for compound **B**: p38α IC_{50} = 4.8 nM.[16a]

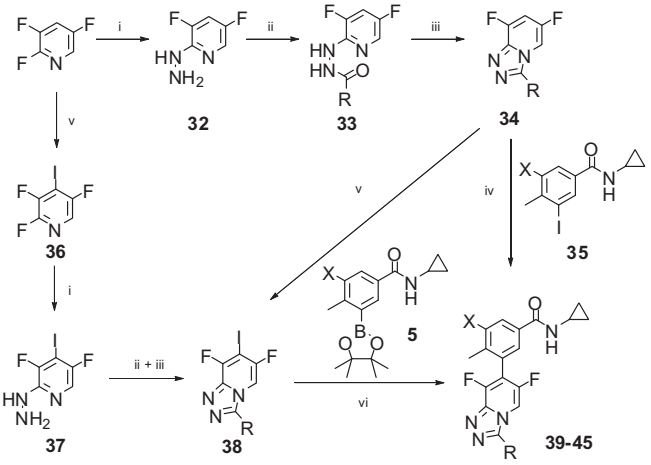
as well as hWB activity as observed with compounds **17** and **18**. In the particular case of the chloropyridyl substituent a wider variability is observed and significant differences are observed between the benzamide **19** and the *meta*-fluoro substituted benzamide **20** in both assays. When this effect of the different substitution at the *meta*-position of the benzamide subunit is examined more thoroughly (H vs F) a clear trend is observed in all the examples where binding affinity is increased up to one order of magnitude with fluorine substitution. However, this improved affinity is not translated into the hWB assay, where, in general, more erratic results were obtained resulting in apparently illogical trends. In some instances a one order of magnitude loss in potency is seen (compounds **9** and **10**) whereas in other examples the potency is maintained (compounds **1** and **6**) or even increased (compounds **17** and **18**).[22] Measurements of protein plasma binding (PPB) and permeability for compounds **1** (X = H) and **6** (X = F) were performed in order to assess whether this might provide an explanation for the potency difference between both assays (PPB rat/human (%): 61/58 for **1** and 79/84 for **6**; Caco2 (AB/BA) Papp (10^{-6} cm/s): 15/18 for **1** and 27/23 for **6**). However, data obtained for both compounds does not account for the potency differences observed. It is also noticeable that, when stronger electron-withdrawing groups are placed at this position (compounds **23** and **24**) a marked enzymatic potency loss is observed, probably due to an electronic effect on the triazolopyridyl core by debilitating the hydrogen bond interaction of the nitrogens to the two water molecules.

Given that compounds possessing a *tert*-butyl substituent were potent in both the binding and hWB assays (compounds **1** and **6**) it was decided to maintain two of the methyl groups of the *tert*-butyl substituent and replace the third methyl by more polar substituents to examine both the tolerance and effects on the biological potencies (Table 2). The placement of a primary amine at this position (compound **26**) resulted in a slight decrease in enzymatic potency

compared to analogue **6**. However, enzymatic potency could be maintained upon introduction of a bulky tertiary amine (NMe_2, Compound **29**) at this position. Compound **27** containing an alcohol in this position also kept enzymatic activity whereas the sulfonamide derivative **30** proved to be equipotent to the primary amine **26**. When the amine was transformed into the acetamide derivative **28** a 10-fold loss in activity was observed. Unfortunately, all these substitutions proved to be detrimental in the hWB assay and a significant potency drop was generally observed with all compounds. Only in the case of the compound with the NMe_2 substituent **29** was cellular potency somewhat maintained.

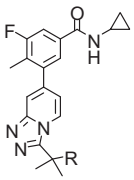
Related to the above compounds, and in order to explore substitution at the triazolopyridyl core, a series of (6,8)-difluorinated triazolopyridyl derivatives were also prepared by the synthetic route described in Scheme 2. In an analogous manner to the previous central core, treatment of commercially available trifluoropyridine with hydrazine hydrate followed by condensation with the corresponding acid or its chloride derivative provided the hydrazide precursor **33** to the triazolopyridine motif **34**. The cyclization step was performed either using $POCl_3$ or polymer supported triphenylphosphine in the presence of $TMSN_3$ and diethylazadicarboxylate (DEAD) to yield the desired difluorinated central core **34**. Coupling to the upper benzamide part of the molecule could be accomplished either by reaction of the correponding organozinc derivative of the triazolopyridyl unit (preparared in situ from the corresponding lithiated derivative) with the iodobenzamide derivate **35**,[20] or by a boron-mediated coupling of the iodotriazolopyridyl moiety **38** with the boronate ester of the benzamide unit **5**.[20] Iodo derivative **38** was prepared by trapping of the afore mentioned lithited intermediate with iodine or, alternatively, by preparation of the iodide derivative **36** from trifluoropyridine and subsequent hydrazide formation and cyclization as depicted in Scheme 2.

Biological results for compounds **39–45** are presented in Table 3. As before, when compounds were tested against the binding and whole blood assays, a poor correlation existed. For example, although very small structural differences exist between compounds **1** and **39**, results from the whole blood assay differ by over an order of magnitude (31 vs 516 nM) whereas in the case of compounds **6** and **4** the difference is only threefold (48 vs 110 nM). It was also noted that with these difluorinated derivatives the fluorine atom on the *meta* position of the benzamide subunit was pivotal in order to optimize enzymatic activity—compare compound **39** (IC_{50} = 49 nM) with the fluorinated derivative **40** (IC_{50} = 6 nM),—and for this reason this fluorine was kept for all the other derivatives prepared in this series. Again, the *tert*-butyl group



Scheme 2. Synthetic sequence used to access 6,8-difluorotriazolopyridylbenzamides with different substitution at the triazolopyridyl ring. Reagents and conditions: (i) Hydrazine hydrate, EtOH, 48 h, rt (85%); (ii) RCOOH, EDC·HCl, Et_3N, HOBt, ACN or RCOOH, HATU, DIEA DMF, or RCOCl, DIPEA, DCM, −78 °C (60–100%); (iii) $POCl_3$ or PS-PPh_3, $TMSN_3$, DEAD (52–90%); (iv) LiHMDS (1 M in hexanes), $ZnCl_2$, $Pd(PPh_3)_4$, (25–58%); (v) LiHMDS (1 M in hexanes), I_2, THF (40–53%); (vi) $PdCl_2$dppf·DCM, Cs_2CO_3, dioxane, 90 °C, (25–60%); (vii) LDA, I_2, THF (84%).

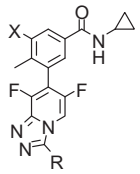
Table 2
Effect of polar substituents attached to the geminal dimethyl substituent



Compound no.	R	p38α IC_{50}[a] (nM)	hWB TNFα IC_{50}[a] (nM)
26	NH_2	15.4 ± 4.6	177 ± 72
27	OMe	9.4 ± 5	278 ± 156
28	NHAc	253 ± 90	—
29	NMe_2	1.7 ± 0.5	84 ± 10
30	NHMs	17 ± 2	1110 ± 417
31	OH	3.1 ± 1.2	105 ± 2

[a] IC_{50} values represent the mean ± standard deviation of two or more independent determinations.

Table 3
6,8-Difluorotriazolopyridyl derivatives



Compound no.	X	R	p38α IC_{50} (nM)[a]	hWB TNFα IC_{50} (nM)[a]
39	H	*t*Bu	49 ± 11	516 ± 55
40	F	*t*Bu	6.2 ± 0.8	116 ± 45
41	F	*i*Pr	6.7 ± 3.7	467 ± 225
42	F		10 ± 4.5	1466 ± 597
43	F		23 ± 3.5	>5000
44	F		12 ± 8.1	822 ± 278
45	F		15 ± 5.1	124 ± 26

[a] IC_{50} values represent the mean ± standard deviation of two or more independent determinations.

appeared to be the optimal susbstituent in filling the lipophilic pocket at the 3-position of the triazolopyridine. Although enzymatic potency was maintained for compounds with other substituents such as isopropyl or cyclopropyl (**41** and **42**), there were inexplicable drops in potency in the functional assay. An aromatic substituent as well as a polar amino group were also incorporated in the 3-position in order to see the effect and, whilst keeping good binding affinities, such compounds provided very poor values in the hWB assay (compounds **43** and **44**). Interestingly, replacement of the NH_2 by its dimethylamino derivative led to a significant gain in potency in the hWB assay whilst maintaining binding affinity (**45** vs **44**). Thus, although good binding affinities were obtained from this difluorotriazolopyridyl derivatives, hWB values were again completely unpredictable.

Table 4
In vitro profiles of selected derivatives

Compound no.	Rat/Human metabolism[a] (+NADPH)	Caco-2 (AB/BA) P_{app}[b] (10^{-6} cm/s)	Cytotoxicity CHO IC_{50}[c] (μM)	Rat/Human PPB (%)
1	<5/<5	15/18	50% @ 200 μM	61/58
6	<5/<5	27/23	107	79/84
40	<5/6	41/25	33% @ 200 μM	75/79

[a] % turnover after a 30 min incubation period at 37 °C of a 5 μM solution of test compound with hepatic microsomes (1 mg/mL).
[b] Passive permeability through a Caco-2 monolayer determined using 12.5 μM test compound.
[c] For assay details see Ref. 13b.

Table 5
Pharmacokinetic properties of selected derivatives in Wistar rats[a,b]

Compound no.	iv (1 mg/kg)				po (10 mg/kg)		
	$t_{1/2}$ (h)	AUC (ng h/ml)	Cl (ml/min/kg)	V_{ss} (l/kg)	C_{max} (μg/ml)	AUC (ng h/ml)	F (%)
1	3.4	2119	7.8	2	2595	19402	93
6	3.8	2668	6.5	1.3	2581	17750	66
40	3.3	8012	2.3	0.57	3471	38561	50

[a] Mean values ($n = 2$).
[b] Formulations: iv: 40% PEG + 0.4% HCl 1 N; po: 0.5% methylcellulose + 0.1% Tween 80.

Table 6
Pharmacokinetic properties of selected derivatives in Beagle dogs[a]

Compound no.	iv (1 mg/kg)				po (1 mg/kg)		
	$t_{1/2}$ (h)	AUC (ng h/ml)	Cl (ml/min/kg)	V_{ss} (l/kg)	C_{max} (ng/ml)	AUC (ng h/ml)	F (%)
1	2.5	1688	9.9	1.7	215	1262	75
6	3.5	2767	6.2	1.6	—	—	—
40	7.3	6438	2.7	1.6	185	5055	79

[a] Mean values ($n = 2$).

Compounds **1**, **6** and **40** were chosen for further profiling since they exhibited the most balanced potencies in the enzymatic and whole blood assays. The in vitro metabolism in hepatic microsomes, permeability in a Caco-2 cell line and cytotoxicity in a Chinese hamster ovarian (CHO) cell line were performed for the selected compounds and results are shown in Table 4. Additionally, all three compounds show a moderate ppb value in both rat and human in vitro assays.

Very low metabolism was observed in both rat and human microsomes and the Caco-2 permeation studies indicated all three compounds should not present permeability issues. In terms of intrinsic toxicity of the compounds, none of them showed significant cytotoxicity (Table 4) towards CHO cells. In addition (data not shown) none of the compounds showed any significant inhibition of the major human cytochrome isoforms (1A2, 3A4, 2C9, 2C19, 2D6) at concentrations below 25 μM. The compounds were also tested in a kinase selectivity panel,[23] the most significant findings being the inhibition of c-Raf ($IC_{50} = 3.2$ μM) for **1**, Ret ($IC_{50} = 2$ μM) for **40** and c-Raf and Ret for **6** (66% at 10 μM—for each kinase, respectively).

The pharmacokinetic profiles of the three selected analogues were determined in the rat (Table 5). Compounds **1** and **6** showed a moderate clearance and also a moderate volume of distribution. However, compound **40** had a significantly lower clearance and volume of distribution. As a result all three molecules showed a half life of approximately 3.5 h. In addition, all three compounds displayed good oral exposure, bioavailabilities being greater than 50% in all cases.

The pharmacokinetic profiles in dog were also evaluated for compounds **1**, **6** and **40** (see Table 6). The volume of distribution was moderate and similar for all three compounds (1.6–1.7 l/kg). In line with the results from the rat pharmacokinetic studies, compound **40** showed a significantly lower clearance compared to the other compounds, resulting in an increased half-life of 7.3 h in dog compared with $t_{1/2} = 3.5$ and 2.5 h for compounds **6** and **1**, respectively.

To assess in vivo pharmacological activity, compounds **1** and **40** were evaluated in an LPS-induced endotoxemia rat model for their ability to inhibit TNFα release. In this model, compounds were dosed orally 1 h prior to LPS administration and the amount of TNFα in plasma was measured 1.5 h later (coinciding with peak TNFα production). Both compounds potently inhibited the release of TNFα with ED_{50}'s of 0.26 and 1.36 mg/kg, respectively. In addition, the efficacy of both compounds in inhibiting the course of rat adjuvant-induced arthritis was evaluated. In this model, arthritis was induced by the inoculation of complete Freund's adjuvant in the left hind paw of the rat. Compounds **1** or **40** were administered daily (oral administration) during the last 10 days of the protocol. Monitoring of right paw volume revealed that both compounds were efficacious at inhibiting paw oedema with an average inhibition of 60% and 67% at 3 mg/kg, respectively (see also Ref. 24).

In conclusion, a novel class of p38α inhibitors has been identified from a structure-based design. The X-Ray co-crystal structure of compound **1** bound in the p38α enzyme revealed an unprecedented binding mode in which the inhibitor interacts indirectly with the hinge region of the kinase via a pair of water molecules. An extensive SAR study around compound **1** led to the discovery of two compounds (**6** and **40**) which showed potent inhibition of TNFα production both in vitro (whole blood assay) and in vivo, good overall kinase selectivity and excellent pharmacokinetic properties. Compounds **1** and **40** also demonstrated significant anti-inflammatory activity in a rat model of arthritis.

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16. (a) Jerome, K. D.; Rucker, P. V.; Xing, L.; Shieh, H. S.; Baldus, J. E.; Selness, S. R.; Letavic, M. A.; Braganza, J. F.; McClure, K. F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 469; For related triazolopyridine scaffolds showing 'Gly flip' see also: (b) McClure, K. F.; Abramov, Y. A.; Laird, E. R.; Barberia, J. T.; Cai, W.; Carty, T. J.; Cortina, S. R.; Danley, D. E.; Dipesa, A. J.; Donahue, K. M.; Dombroski, M. A.; Elliot, N. C.; Gabel, C. A.; Han, S.; Hynes, T. R.; LeMotte, P. K.; Mansour, M. N.; Marr, E. S.; Letavic, M. A.; Pandit, J.; Ripin, D. B.; Sweeney, F. J.; Tan, D.; Tao, Y. *J. Med. Chem.* **2005**, *48*, 5728; (c) McClure, K. F.; Letavic, M. A.; Kalgutkar, A. S.; Gabel, C. A.; Audoly, L.; Barberia, J. T.; Braganza, J. F.; Carter, D.; Carty, T. J.; Cortina, S. R.; Dombroski, M. A.; Donahue, K. M.; Elliot, N. C.; Gibbons, C. P.; Jordan, C. K.; Kuperman, A. V.; Labasi, J. M.; LaLiberte, R. E.; McCoy, J. M.; Naiman, B. M.; Nelson, K. L.; Nguyen, H. T.; Peese, K. M.; Sweeney, F. J.; Taylor, T. J.; Trebino, C. E.; Abramov, Y. A.; Laird, E. R.; Volberg, W. A.; Zhou, J.; Bach, J.; Lombardo, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4339.
17. Compounds in this manuscript were first described in the Almirall patent application: Vidal, B.; Eastwood, P.; González, J.; Esteve, C.; PCT Int. Appl. WO2008107125, 2008.
18. During the course of this work a patent application resulting from an independent study describing triazolopyridylbenzamides as p38α inhibitors was published: see WO2008045393, 2008.
19. Coordinates and structure factors for the complex of p38α with **1** have been deposited in the RCSB Protein Data Bank (RSCB id code-rscb065714; PDB id code-3S3I).
20. Syntheses of boronate **5** and iodobenzamide **35** are described in Ref. 17.
21. Full details of all biological assays used in this article can be found in Refs. 13a,e.
22. Although compounds **17** and **18** were the most promising in the series in terms of potency, they were discarded as they delivered several adducts in the GSH assay (4% and 10%, respectively).
23. Compounds were tested against a panel of 55 kinases: Compounds were assayed at Upstate Ltd at single inhibitor concentrations of 10 μM in duplicate using ATP concentrations corresponding to the K_m values of the appropriate kinases.
24. For full details of in vivo experiments performed on compounds **1** and **40** see: Balagué C.; Pont, M.; Prats, N.; Godessart, N. *Br. J. Pharmacol.* **2012**, 165 (Epub ahead of print).