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The discovery and initial optimisation of pyrrole-2-carboxamides as inhibitors of p38α MAP kinase

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ABSTRACT

A novel pyrrole-2-carboxamide series of p38α inhibitors, discovered through the application of virtual screening, is presented. Following evaluation of activity, selectivity and developability properties of commercially available analogues, a synthesis program enabled rapid assessment of the series' suitability for further lead optimisation studies.

The p38α mitogen-activated protein kinase was first identified in human monocytes as the target for a class of cytokine suppressive anti-inflammatory compounds.[1] From its central position in the cell signalling pathway, p38α regulates the expression of many pro-inflammatory cytokines including IL-1, IL-6 and TNF-α. Inhibitors of p38α suppress the production of cytokines in vitro and have anti-inflammatory activity in vivo in models of rheumatoid arthritis (RA) and other diseases.[2]

Several compounds have progressed into clinical studies for RA, but so far their success has been limited.[3] Toxicity was the primary reason for failure, often because of liver, gastro-intestinal (GI) or neurological toxicity.[4,5] It is possible that these may be related to off-target effects, perhaps due to inhibition of other kinases, particularly for early examples where wider kinase selectivity was less thoroughly measured.[3] Results from two trials have been published recently. Pamapimod led to liver enzyme elevation and adverse events including infection, rash, dizziness and GI problems.[6] The highly selective VX702 was comparatively well tolerated and showed transient effects on biomarkers in the first few weeks of treatment, but disappointingly this was not sustained.[7] Nevertheless, at least seven phase II clinical trials of small-molecule p38α inhibitors are currently in progress or have recently completed for other indications, including pain, multiple myeloma, major depressive disorder, acute respiratory distress syndrome, chronic obstructive pulmonary disorder and acute cardiovascular diseases.[8] Therefore, selective and structurally distinct p38α inhibitors remain of interest. For instance, Pfizer reported ongoing development of a triazolopyridine series, and we recently presented the discovery of Losmapimod, a biaryl amide (Fig. 1).[9,10]

Kinase inhibitors frequently inhibit multiple protein kinases.[11] It has been our experience that rational, focused screening against a single kinase frequently yields hits, but these can often be more

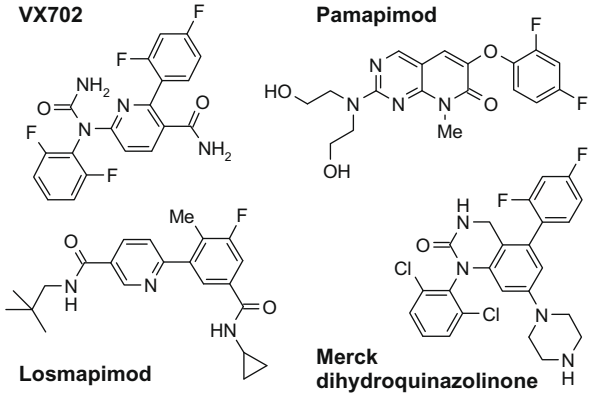

Figure 1. Structures of literature p38α inhibitors mentioned in the text.

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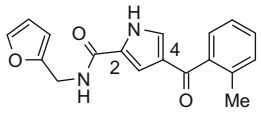
effective against kinases other than the intended target.[10b] Therefore, we have adopted an approach in which focused screening is directed towards the protein kinase family rather than individual targets.

Databases of commercially available compounds are used extensively in virtual screening and are a valuable resource for lead discovery. A database of millions of commercially available compounds offered by various suppliers has been assembled by GSK for this purpose. A search of this database was carried out using a 3D pharmacophore query intended to be generally applicable to kinases.[12] Selected pharmacophore hits were purchased and screened against a panel of protein kinases in duplicate at 10 μM compound concentration. Several examples of the pyrrole series, which is the subject of the rest of this report, showed sufficient p38α activity for progression to IC_{50} measurement.[13]

Compound **1** was the most potent from this set, with a pIC_{50} of 6.6 (mean, $n = 9$).[14] Because of this encouraging activity, and to explore the mechanistic activity in a cellular environment, compound **1** was tested in a human lung fibroblast assay measuring the inhibition of phosphorylation of Heat Shock Protein 27 (Hsp27), a downstream marker on the p38 pathway. It showed good activity with a pIC_{50} of 6.2 (mean, $n = 6$).[15]



1

Once the structural integrity of the initial hits had been confirmed by NMR, a ~1.9 Å resolution crystal structure of **1** in complex with p38α was obtained (Fig. 2).[16] The phenyl ring on the ketone at the pyrrole 4-position occupies the inner lipophilic pocket adjacent to the gatekeeper residue Thr106. The pyrrole NH donates a hydrogen-bond to the inner hinge acceptor backbone carbonyl of His107. In addition, a hydrogen-bond to the hinge at Met109 is formed from the carbonyl of the amide at the pyrrole 2-position. The amide NH in the 2-position and the ketone carbonyl in the 4-position interact with water molecules evident in the crystal structure. The methyl furan fills the outer lipophilic pocket near Ala111.

A further 120 available analogues were selected from the external suppliers compound database and screened against p38α. Whilst compounds allowing direct pairwise comparisons could not always be obtained, the SAR around the 120 tested compounds

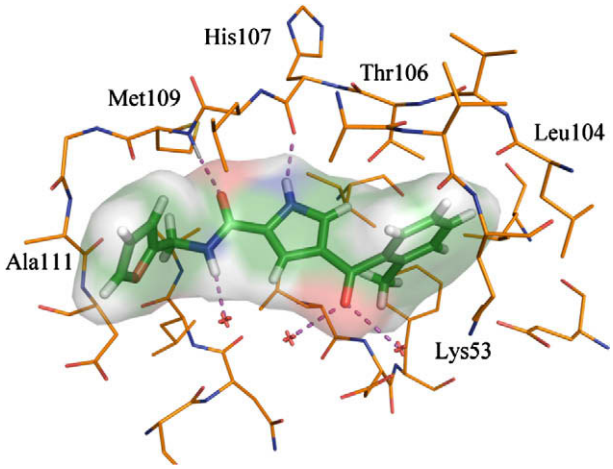
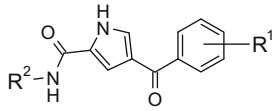
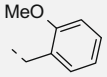
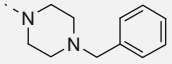


Figure 2. Crystal structure of **1** (green, with surface shaded) in complex with p38α (orange). Hydrogen-bonds to the inhibitor are shown as magenta dotted lines. Water molecules are represented by red crosses.

Table 1
Data for initial compounds **1–6**[13]



Compound	R^1	R^2	p38α pIC_{50}[14]
1	2-Methyl		6.6
2	2,6-Dichloro		6.1
3	4-Methoxy		<4.6
4	2-Methyl		6.5
5	2,6-Dichloro		5.7
6	2-Methyl		5.0

Values are means of at least three experiments.

nevertheless showed interpretable trends, some of which are exemplified in Table 1. Lipophilic *ortho*-substitution was preferred on the R^1 aryl ring (**1** and **2**), consistent with the geometry of the ketone to phenyl linker observed in the crystal structure. However, anything other than F or H in the *para* position resulted in greatly reduced potency (**3**). At the amide R^2 position, benzyl and benzyl-like substituents were the most potent, with a reasonable tolerance evident for substitution on the benzyl group, including at the *ortho* position (**4**). The benzyl group could also be replaced by small alkyl groups with only a small reduction in potency (**5**). More polar amine groups were less favoured however, with substituted secondary amines being the least potent (**6**), indicating a preference for a lipophilic group in the outer lipophilic subpocket of the site.

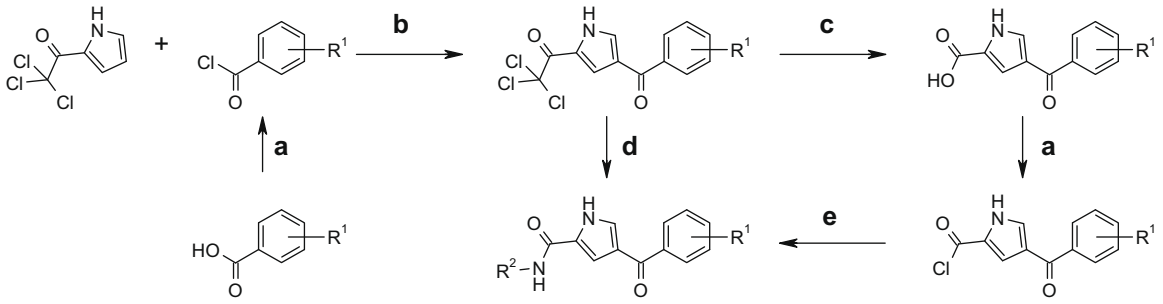
Despite the large number of purchased compounds screened, none were found showing better p38α potency than **1**. To build confidence in the series, **1** was profiled further.

The kinase selectivity of the series was excellent when screened against a wider kinase panel. For example, **1** had a $pIC_{50} < 5.5$ against every member of an in-house panel of 51 kinases, and showed no significant activity when screened at 10 μM against the Dundee University panel of 18 kinases.[17] In keeping with other compounds from this series, some p38β activity was present ($pIC_{50} = 5.2$), although for the series as a whole IC_{50}s were generally 10-fold lower than p38α. Furthermore, against a panel of 227 kinases at Ambit Biosciences, the only hits were p38α, p38β, JNK1 and JNK3.[18] However, JNK binding was weak, consistent with the low inhibition observed in internal assays measuring the catalytic activity of JNK1 ($pIC_{50} < 5$).

The wider developability properties were promising. Cytochrome P450 inhibition was low, for instance **1** had an IC_{50} of 15.8 μM against the 2C9 isoform and was less potent against others tested.[19]

In vivo rat PK was measured, showing the compound had moderate oral bioavailability ($F\% = 18$), with high clearance (56 ml/min/kg), short half-life (0.16 h) and low V_{DISS} (0.93 l/kg).[20]

With these encouraging data in hand a synthesis program was initiated to further explore the series. The array was prepared using chemistry shown in Scheme 1. 2-Trichloroacetylpyrrole was subjected to a Friedel–Crafts acylation with the appropriate acid chloride, formed from the carboxylic acid with thionyl chloride, to give the corresponding ketone. This was reacted directly



Scheme 1. Reagents and conditions: (a) DMA, $SOCl_2$, rt; (b) $AlCl_3$, chloroform, reflux; (c) NaOH (aq), rt; (d) primary and secondary amines, DMF, rt; (e) anilines, DMA, rt.

with primary and benzyl amines in DMF to give the desired amides. Anilines failed to react using this chemistry and so a different route was developed via the carboxylic acid, which could be rapidly obtained by treating the trichloroacetyl group with aqueous sodium hydroxide. This failed to react using common carboxylic acid coupling conditions, but in situ formation of the acid chloride using thionyl chloride, followed by addition of the anilines gave the desired amides.

SAR knowledge from other p38α compound classes was incorporated into the array design. Figure 3 shows an overlay between the p38α crystal structures of pyrrole-2-carboxamide **1** (green) and a Merck dihydroquinazolinone (magenta).[21] The back-pocket binding aryl group at the 4-position of the pyrrole superimposes well on the C-5 aryl group of the dihydroquinazolinone (circled area). In the dihydroquinazolinone series, aryl groups (in particular 2,4-difluorophenyl, 2-chlorophenyl and 2-chloro-4-fluorophenyl) were preferred C-5 substituents. These groups were included as 4-aryl substituents in the pyrrole series. Heterocycles and fused bicyclic systems were also prepared.

The dihydroquinazolinone series has no analogous position to the pyrrole 2-carboxamide substituent. Figure 4 shows, however, how this carboxamide forms the hinge hydrogen-bond to Met109 in a similar way to the amide in the biaryl amide series (circled area).[10] In that series, aryl and benzyl substituted amide compounds gave the greatest enzyme potency, whilst alkyl substituents gave better all-round properties.[10c] Therefore anilines, benzylamines and small primary alkyl groups were used as pyrrole 2-position substituents. The X-ray structure showed that this substituent was partially exposed to solvent, so water solubilising groups were also included.

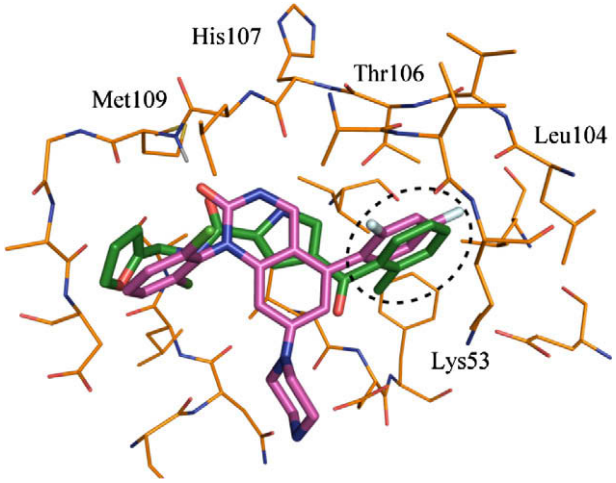


Figure 3. Overlaid X-ray structures of p38α (orange) complexed with **1** (green) and with a dihydroquinazolinone (magenta).

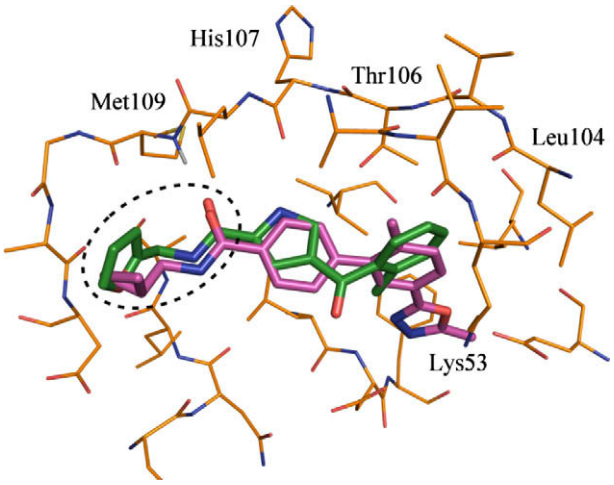


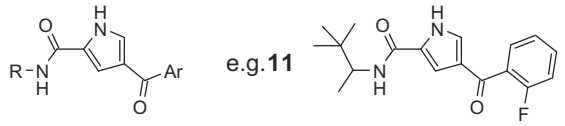
Figure 4. Overlaid X-ray structures of p38α (orange) complexed with 1 (green) and a biphenyl amide (magenta). [10c]

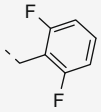
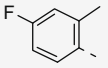
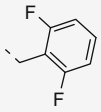
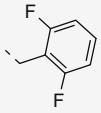
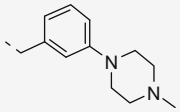
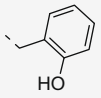
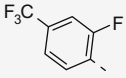
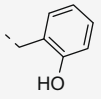
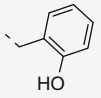
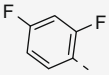
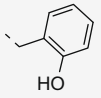
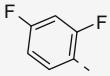
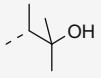
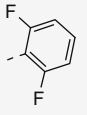
Data for selected compounds are summarised in Table 2. Changing the amide substituent of **1** to a 2,6-difluorobenzylamine (**7**) gave a marginal increase in potency but led to reduced activity in the pHsp27 assay. The addition of a 4-fluoro substituent to the aryl group was tolerated (**8**), giving similar potency to compound **7** in both assays. Changing the 2-methyl to a 2-fluoro (**9**) gave a 10-fold potency increase over compound **1**, but despite this had lower potency in the pHsp27 assay.

Reasoning that the lower cellular activity might be related to solubility, a solubilising 4-(*N*-methylpiperazinyl)benzylamine substituent was introduced into the pyrrole 2-amide position (**10**). This resulted in a compound with excellent enzyme activity, but this did not translate into greater activity in the pHsp27 assay. This lower potency in the pHsp27 assay was a consistent trend with the benzylamine amides. However, when pinacolylamine was introduced (**11**, racemic), there was no drop-off between the enzyme and pHsp27 potency. This compares favourably with the most cell-active benzylamine (**12**), which still suffers a significant reduction from its enzyme potency. Compound **11** also showed inhibition of TNF-α release from LPS-stimulated PBMC cells with $pIC_{50} = 5.6$ (mean, $n = 5$) and from whole blood with $pIC_{50} = 6.5$ (mean, $n = 3$).[22]

Greatly reduced enzyme potency resulted when larger substituents were added at the 4-position of the aryl group (e.g. **13**). Similarly, the benzothiophene substituent was very weakly active (**14**). These results, along with compound **15**, confirmed the earlier hypothesis that the only 4-substituent small enough to be tolerated at this position was fluorine. Introducing polarity to the small alkyl amide substituent (e.g. **16**) resulted in reduced enzyme potency, consistent with the position of this group in the outer lipophilic pocket of p38α.

Table 2
p38α inhibition and pHsp27 human lung fibroblast cellular mechanistic assay data for compounds **7**–**17**



Compound	Ar	R	p38a	pHsp27
1			6.6	6.2
7			7.0	5.5
8			6.6	5.4
9			7.6	5.8
10			7.9	5.7
11			6.7	6.8
12			7.3	6.1
13			<4.6	NT
14			4.7	NT
15			7.5	5.9
16			5.9	NT
17			6.0	5.8[a]

plC_{50} values are mean of at least three experiments.
[a] n = 2 data only.

Anilides were also prepared at the pyrrole 2-amide position, but were generally less potent than the benzylamines and alkylamines (e.g. **17**). This is consistent with docking studies that predict that the inflexibility of the aniline results in a steric clash with the protein backbone around the Met109 residue.

In conclusion, we have presented a novel series for p38α discovered through the application of 3D pharmacophore virtual screening. Initial exploration and SAR optimisation resulted in lead compounds with good enzyme potency and excellent selectivity, as well as mechanistic and functional cellular assay potency resulting in a series suitable for further lead optimisation.

Acknowledgements

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References and notes

1. Lee, J.; Laydon, J.; McDonnell, P.; Gallgher, T.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M.; Heys, J.; Landvatter, S.; Strickler, J.; McLaughlin, M.; Siemens, I.; Fisher, S.; Livi, G.; White, J.; Adams, J.; Young, P. *Nature* **1994**, *372*, 739.
2. Goldstein, D. M.; Gabriel, T. *Curr. Top. Med. Chem.* **2005**, *5*, 1017.
3. Goldstein, D. M.; Kuglstatter, A.; Lou, Y.; Soth, M. J. *J. Med. Chem.* **2010**, *53*, 2345.
4. Genovese, M. C. *Arthritis Rheum.* **2009**, *60*, 317.
5. Sweeney, S. E. *Nat. Rev. Rheum.* **2009**, *5*, 475.
6. Cohen, S. B.; Cheng, T. T.; Chindalore, V.; Damjanov, N.; Burgos-Vargas, R.; DeLora, P.; Zimany, K.; Travers, H.; Caulfield, J. P. *Arthritis Rheum.* **2009**, *60*, 335.
7. Damjanov, N.; Kauffman, R. S.; Spencer-Green, G. T. *Arthritis Rheum.* **2009**, *60*, 1232.
8. Available from: http://clinicaltrials.gov, February 2010.
9. 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.
10. (a) Walker, A.; Aston, N.; Bamborough, P.; Buckton, J.; Edwards, C.; Holmes, D.; Jones, K.; Patel, V.; Smee, P.; Somers, D.; Vitulli, G. *J. Med. Chem.* **2009**, *52*, 6257; (b) Angell, R. M.; Bamborough, P.; Cleasby, A.; Cockerill, S. G.; Jones, K. L.; Mooney, C. J.; Somers, D. O.; Walker, A. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 318; (c) Angell, R. M.; Angell, T. D.; Bamborough, P.; Brown, D.; Brown, M.; Buckton, J. B.; Cockerill, S. G.; Edwards, C. D.; Jones, K. L.; Longstaff, T.; Smee, P. A.; Smith, K. J.; Somers, D. O.; Walker, A. L.; Willson, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 324; (d) Angell, R. M.; Aston, N. M.; Bamborough, P.; Buckton, J. B.; Cockerill, S. G.; deBoeck, S. J.; Edwards, C. D.; Holmes, D. S.; Jones, K. L.; Laine, D. I.; Patel, S.; Smee, P. A.; Smith, K. J.; Somers, D. O.; Walker, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4428; (e) Angell, R. M.; Angell, T. D.; Bamborough, P.; Bamford, M. J.; Chung, C.; Cockerill, S. G.; Flack, S. S.; Jones, K. L.; Laine, D. I.; Longstaff, T.; Ludbrook, S.; Pearson, R.; Smith, K. J.; Smee, P. A.; Somers, D. O.; Walker, A. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4433.
11. Paolini, G. V.; Shapland, R. H. B.; van Hoorn, W. P.; Mason, J. S.; Hopkins, A. L. *Nat. Biotechnol.* **2006**, *24*, 805.
12. The pharmacophore was constructed manually from a crystal structure of a non-selective kinase inhibitor (unpublished results) complexed with cyclin-dependent kinase 2. Hydrogen-bonding and aromatic interactions between the inhibitor and conserved residues of the ATP-binding site acids were included in the pharmacophore query. The distance tolerances of the resulting model were set loosely in order to be suitable for multiple protein kinases. Searching was carried out using Catalyst (Accelrys Inc., www.accelrys.com). All molecules identified from the external suppliers' database in this way were passed through proprietary in silico developability filters before being clustered and examined visually in order to make a final selection.
13. Compounds **1**–**6** were sourced from Bionet (Key Organics Ltd, www.keyorganics.net).
14. Recombinant full length human p38α was expressed in *E. coli* as an N-terminal 6-His-tagged fusion protein and activated by incubation with MKK6 (Millipore, Dundee, UK) in the presence of ATP and stored frozen in aliquots at −80 °C. Its activity was assessed using a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. Briefly, p38α (typically 0.1–0.2 nM final) diluted in assay buffer (12.5 mM HEPES, pH 7.4, with 1 mM DTT) was added to wells of a black, shallow 384-well plate (Greiner Bio-One, Stroudwater, Gluocester, UK) containing various concentrations of compound or DMSO vehicle (less than 2% v/v final). The reaction was initiated by the addition of biotinylated recombinant ATF2 (residues 19–96) substrate (0.4 nM final), ATP (125 μM final) and 5 mM $MgCl_2$ final in 12.5 mM HEPES buffer as above to a total volume of 6 μl. The reaction was incubated for 120 min at room temperature and then terminated by the addition of stop reagent (3 μl) containing 60 mM EDTA and detection reagents in buffer (40 mM HEPES, pH 7.4, 150 mM NaCl and 0.3% w/v BSA). Detection reagents comprise antiphosphothreonine-71ATF2 monoclonal antibody at 0.35 nM final concentration (Cell Signalling Technology, Beverly Massachusetts, USA) labelled with W-1024 europium chelate (Perkin-Elmer, Turku, Finland) and allophycocyanin-labelled streptavidin at 258 nM final concentration (Prozyme, San Leandro, California, USA). The reaction mixture (9 μl total volume) was further incubated for at least 60 min at room temperature. The degree of phosphorylation of ATF2 was measured using a suitable time-resolved fluorimeter such as a Rubystar (BMG, Aylesbury, Buckinghamshire, UK) or Envision (Perkin-Elmer Ltd, Seer Green, Beaconsfield, UK) as a ratio of specific 665 nm energy transfer signal to reference europium 620 nm signal.

15. Hsp27 phosphorylation in human lung fibroblast cells was measured as described in Ref. 10e.
16. An *apo* crystal of unphosphorylated human p38α (expressed, purified and crystallized as previously described, Ref. 10b) was soaked with 1 mM **1** for 40 h and cryoprotected as before. X-ray diffraction data were collected in-house on a Rigaku-MSC MicroMax007 rotating anode generator with a MarResearch Mar345 image plate detector mounted on a Mar-dtb. The data were processed and the structure solved as in Ref. 10b. The final *R*-factor and *R*-free achieved for the complex were 23.2% and 29.7%, respectively. Coordinates have been deposited in the PDB as entry 3MPT. Figures were produced using Pymol (DeLano, W.L., DeLano Scientific, Palo Alto CA, USA. http://www.pymol.org).
17. Available from: http://www.kinase-screen.mrc.ac.uk/.
18. Assays were carried out by Ambit Biosciences, San Diego. The ability of compounds to compete with the binding of the human kinase (expressed as fusion to T7 bacteriophage) to immobilized ATP-site probe ligands was determined as previously described, see: Fabian, M. A.; Biggs, W. H., III; Treiber, D. K.; Atteridge, C. E.; Azimioara, M. D.; Benedetti, M. G.; Carter, T. A.; Ciceri, P.; Edeen, P. T.; Floyd, M.; Ford, J. M.; Galvin, M.; Gerlach, J. L.; Grotzfeld, R. M.; Herrgard, S.; Insko, D. E.; Insko, M. A.; Lai, A. G.; Lélias, J.-M.; Mehta, S. A.; Milanov, Z. V.; Velasco, A. M.; Wodicka, L. M.; Patel, H. K.; Zarrinkar, P. P.; Lockhart, D. J. *Nat. Biotechnol.* **2005**, *23*, 329. Compounds were screened at 10 μM. Binding was only detected for p38α, p38β, JNK1 and JNK3 (% of binding remaining relative to DMSO control was 0.7%, 17%, 12% and 34%, respectively).
19. CYP450 inhibition was carried out as described in Ref. 10d.
20. Pharmacokinetic parameters in male CD rats were determined following intravenous (iv) and oral (po) administration at 1 mg/kg. Compound was administered as a solution in DMSO/PEG200/sterile water (1:7:2 v/v/v), 1 ml/kg (iv) and 4 ml/kg (po). Blood was collected over a 7-h time period. Plasma was prepared following centrifugation and compound extracted from 50 μl plasma using protein precipitation with acetonitrile. Samples were evaporated under nitrogen and re-suspended in 200 μl of 20:80 acetonitrile/water. Analysis was performed using LC–MS/MS on the API365 with a 3 min fast gradient comprising 0.1% formic acid in water and 0.1% formic acid in acetonitrile (mobile phases), 30 μl injection volume, flow rate 0.8 ml/min and Luna C18 column (50 × 2.1 mm, 5 μm). Pharmacokinetic data was generated using a non-compartmental approach.
21. Stelmach, J. E.; Liu, L.; Patel, S. B.; Pivnichny, J. V.; Scapin, G.; Singh, S.; Hop, C. E.; Wang, Z.; Cameron, P. M.; Nichols, E. A.; O'Keefe, S. J.; O'Neill, E. A.; Schmatz, D. M.; Schwartz, C. D.; Thompson, C. M.; Zaller, D. M.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 277.
22. TNF-α release from LPS-stimulated PBMC cells and whole blood was carried out as previously described, see: Christopher, J. A.; Bamborough, P.; Alder, C.; Campbell, A.; Cutler, G. J.; Down, K.; Hamadi, A.; Jolly, A. M.; Kerns, J. K.; Lucas, F. S.; Mellor, G. W.; Miller, D. D.; Morse, M. A.; Pancholi, K. D.; Rumsey, W.; Solanke, Y. E.; Williamson, R. *J. Med. Chem.* **2009**, *52*, 3098.