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p38α Mitogen-Activated Protein Kinase Inhibitors: Optimization of a Series of Biphenylamides to Give a Molecule Suitable for Clinical Progression

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p38α MAP kinase is a key anti-inflammatory target for rheumatoid arthritis, influencing biosynthesis of pro-inflammatory cytokines TNFα and IL-1β at a translational and transcriptional level. In this paper, we describe how we have optimized a series of novel p38α/β inhibitors using crystal structures of our inhibitors bound to p38α, classical medicinal chemistry, and modeling of virtual libraries to derive a molecule suitable for progression into clinical development.

Introduction

Introduction of anticytokine biological therapies, for example, Etanercept, Infliximab, Adalimumab, and Anakinra, which specifically inhibit pro-inflammatory cytokines TNFα (tumor necrosis factor α[a]) and IL-1β (interleukin-1β), have resulted in significant progress in the treatment of rheumatoid arthritis (RA) patients who do not respond to current non-steroidal anti-inflammatories (NSAIDs) or current disease modifying antirheumatic drugs (DMARDs).[1] However, the administration of these biological therapies by injection or infusion is burdensome to patients and physicians. An oral therapy, such as a new, small molecule therapy would be a more convenient administration form. The serine/threonine kinase p38α has been identified as a key anti-inflammatory target, involved in the production of both TNFα and IL-1β,[2,3] and many pharmaceutical companies have pursued p38α inhibitors as an anti-inflammatory therapy.[4−7] To date, none of these molecules have progressed beyond clinical trials, as raised levels of liver enzymes associated with liver toxicity have been seen in some human trials and neurological effects in others.[8,9] Most of the earlier p38α inhibitors have relatively unselective kinase profiles or show inhibition of cytochrome p450 isoforms, either of which might be associated with the side effects seen in the clinic. In our earlier publications,[10−13] we described the optimization of a micromolar cross-screening hit to a small potent and selective p38α/β inhibitor **1** with an acceptable in vivo pharmacokinetic profile and activity in the rat peptidoglycan-polysaccharide reactivation (PG-PS)[14] and mouse collagen induced arthritis (CIA)[15−18] inflammation models. In this paper, we describe further optimization of **1**, by increasing potency in an assay to determine the inhibition of TNFα production in human whole blood (HWB) and improving the CYP450 profile resulting in a clinical candidate **2**, developed for treatment of rheumatoid arthritis (Figure 1). This molecule is currently also being clinically evaluated for other inflammatory indications including chronic obstructive pulmonary disease (COPD) and heart disease.

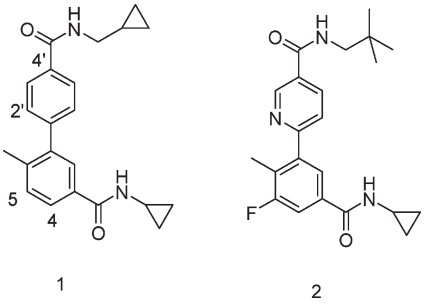

Figure 1. Lead molecule **1** and clinical candidate **2**.

Results and Discussion

Compound **1**, while selective for p38α/β and active in rat reactivation PG-PS (ED_{50} 0.02 mg/kg) and murine CIA (in which it totally prevented the progression of arthritis at 15 mg/kg/day) models, is weakly active in the HWB assay of inhibition of TNFα release and displays some potential liabilities against p450 isoform 2C9 (Table 1). Several potential causes of the low potency seen in the HWB assay have been considered; cellular penetration can only be a partial cause as the drop-off in activity from the enzyme to HWB is larger than that for the enzyme to the isolated human monocyte assay (PBMC). To try to understand this difference, a set of 48 compounds, from the biphenyl amide (BPA) and other chemical series, was profiled in PBMC and HWB assays using cells from the same donors. In addition, the physicochemical properties, CHI LogD (pH2, 7.4, 10.5),[19] human serum albumin (HSA) binding,[20] and solubility[21] were measured and further parameters calculated. Statistical models were

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[a] Abbreviations: MAP, kinase mitogen-activated protein kinase; TNFα, tumour necrosis factor alpha; IL-1β, Interleukin 1 beta; RA, rheumatoid arthritis; DMARD, disease modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory; PG-PS, peptidoglycan-polysaccharide; CIA, collagen induced arthritis; COPD, chronic obstructive pulmonary disease; PBMC, peripheral blood mononuclear cells; HWB, human whole blood; HSA, human serum albumin; LCMS, liquid chromatography−mass spectrometry.

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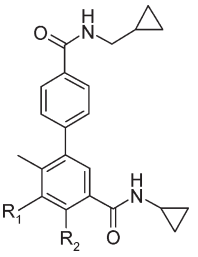
Table 1. Effect of Additional Substituents at the 5- and 4-Positions



compd	R_1	R_2	p38α FP pK_i (n)	PBMC pIC_{50} (n)	HWB pIC_{50} (n)	CYP450, 2C9, pIC_{50}
1	H	H	7.9 (11)	6.7 (24)	5.8 (22)	5.4
3	F	H	8.4 (6)	7.0 (13)	6.6 (12)	5.7
4	Cl	H	7.9 (2)	6.8 (2)	5.9 (2)	nd[a]
5	Me	H	7.0 (1)	nd[a]	nd[a]	nd[a]
6	H	F	6.9 (2)	nd[a]	nd[a]	nd[a]

[a] nd, not determined.

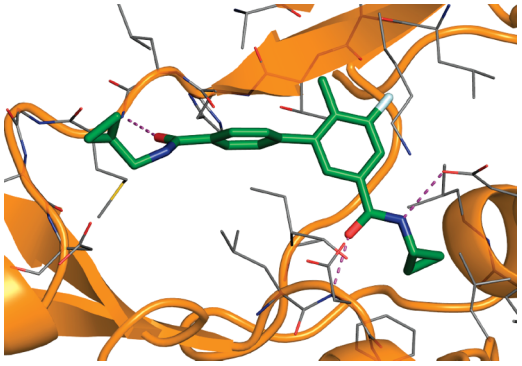


Figure 2. Compound **3** bound to p38α showing the fluorine binding in a small pocket formed by Leu 104 and Lys 53.

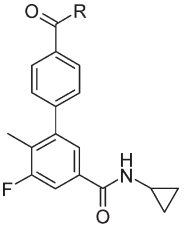
then generated on this data and tested by attempting to predict the drop-off for a further set of compounds. The models proved to be of limited predictive use, partially due to high interdonor variability for the cellular assays, and no unequivocal understanding was gained regarding factors affecting the relative PBMC and HWB potencies.

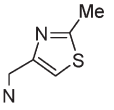
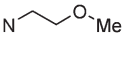
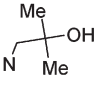
Comparison of crystal structures of **1** and a second series of in-house p38α inhibitors bound to p38α led to the introduction of a fluorine at the 5-position **3**, resulting in a 3-fold increase in p38α enzyme activity and a similar increase in PBMC potency but a 6-fold increase in HWB potency. Replacement of the fluorine by chlorine **4** gave no enhancement in potency in either the enzyme or cellular assays, and replacement by methyl **5** resulted in a 25-fold drop in enzyme potency. Shifting the fluorine to the 4-position **6**, which modeling had suggested would be equally valid, resulted in a 9-fold decrease in enzyme potency (Table 1).

These results can be explained by examination of a model of compound **3** bound to p38α, where it can be seen that the 5-substituent would bind in a lipophilic pocket formed by Leu 104 and Lys 53 (Figure 2). Fluorine appears to be optimal for the available space, with the larger chlorine and methyl groups causing unfavorable interactions due to the proximity to the protein. The lower affinity of **6** can also be explained by postulating that the 4-fluorine would be electrostatically unfavorable due to the close proximity of Glu71, approximately 2.2 Å by modeling.

Although **3** has improved HWB potency, it still has a potential cytochrome p450 liability at 2C9. To overcome this, a 2500-member virtual library was created, varying the 4′-amide. The amines had a wide variety of structural subtypes, as we knew from previous arrays that p38α has a wide tolerance in this area of the binding site.[10,11] The amines were chosen on molecular weight and by avoidance of reactive groups, with no bias from the current preferred groups. To this library, series specific predictors for oral bioavailability (high oral absorption − ACDlogD < 4 and CMR <12) and cytochrome p450 liability [negligible CYP2C9 inhibition − ACDlogD < 4 and ApK*a* > 10 (first acidic pK_a)], which had been generated from analysis of the SAR of previous examples of the series, were applied.[22] As the result of this, a set of cyclopropylmethyl replacements was chosen and further 87 analogues of **3** prepared. This resulted in a small set of molecules **7**−**10** with improved cytochrome p450 profiles and HWB pIC_{50} > 6.5 (Table 2).

Table 2. Results of the 4′-Amide Array Derived by a Virtual Array Process



Compound	R	p38α pKi (n)	HWB pIC_{50} (n)	CYP450, 2C9, pIC_{50}
7		7.8 (3)	6.5 (4)	4.9
8		8.0 (4)	7.1 (1)	<4
9		7.9 (4)	6.5 (1)	4.2
10		8.0 (2)	7.1 (7)	4.8

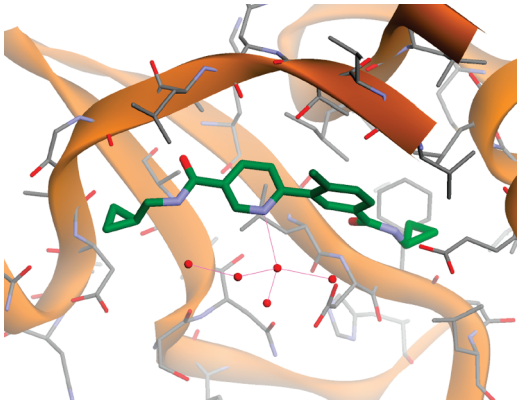


Figure 3. Compound **11** bound to p38α showing interaction of pyridine with network of conserved water molecules.

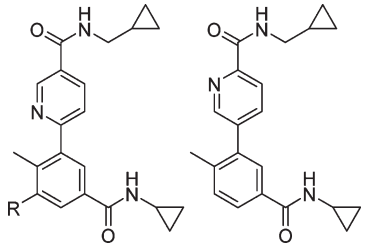


Figure 4. Structures **11**−**13**.

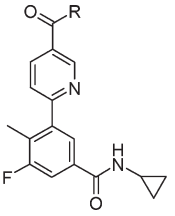
In work ongoing in parallel, comparison of several p38α crystal structures generated for this series suggested that a network of water molecules fills part of the site close to the 2′-position of the 1,4-substituted phenyl ring. This offered the possibility of obtaining favorable or at least tolerated interactions with these water molecules by the introduction of heteroatoms.

With this intention, a nitrogen was introduced into the 2′-position of the 1,4-substituted phenyl ring. The resulting compound **11** (Figure 4) displayed a similar p38α enzyme potency (pK_i 7.6, n = 9) to the phenyl analogue **1** (pK_i 7.9) and had a moderate potency in the HWB assay (pIC_{50} 6.5, n = 3). A crystal structure of **11** bound to p38α (Figure 3) clearly shows the interaction of the pyridine with the conserved water network. Compared with **3**, Tyr35 (not visible in Figure 3) has moved from a position packed across the front of the inhibitor to allow the pyridine nitrogen access to the water network, however this change appears to have little effect on p38α potency.

Compound **11** has an excellent rat DMPK profile, with oral bioavailability of 99%, low clearance (1.5 mL/mg/kg), and a long half-life (iv $T_{1/2}$ 3.0 h); additionally, the cytochrome p450 profile was improved over its phenyl analogue (2C9 pIC_{50} 4.4, 1A2, 2C19, 2D6, 3A4 pIC_{50} < 4). The isomeric pyridine with the nitrogen inserted into the 3′-position of **12** was prepared for comparison, and **12** shows substantially lower p38α potency (pKi 6.1, n = 3), which is surprising given that the pyridine in this position might be expected to help to rigidify the structure by forming an internal hydrogen bond to the NH of the amide.

The 5-fluorine used to enhance HWB potency in the biphenyl series was introduced into the 2′-pyridyl series. The resulting compound, **13**, combines HWB potency (pIC_{50} 7.1, n = 11) and a clean cytochrome p450 profile (pIC_{50} < 4.2 at all isoforms). p38α and p38β were inhibited with pK_i's of 8.1 and 7.6, respectively, and at least 100-fold selectivity was maintained against a panel of 33 kinases, including AKT1, ALK5, CDK2, EGFR, ErbB2, GSK3β, IKK2, IKK-ε, JNK3, LCK, PDGFR1B, PLK1, ROCK1, SRC, TIE2, and VEGFR2. The excellent oral bioavailability seen for **11** was maintained in the 5-*F* analogue (*F* > 95%, Clr 2.5 mL/min/kg, iv $T_{1/2}$ 1.9 h).

Table 3. Results of 4-Amide Arrays in the Pyridine Series



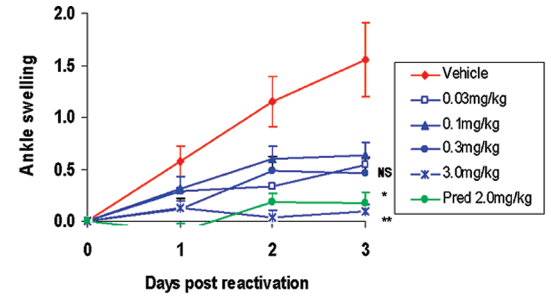
Compound	R	p38α pKi (n)	p38β pKi	PBMC pIC_{50} (n)	HWB pIC_{50} (n)	CYP450, 2C9, pIC_{50}	Rat DMPK Oral AUC (ng.hr/mL)
13		8.1 (7)	7.6	6.9 (11)	7.1 (11)	4.2	810 / 1300
14		8.1 (29)	7.5	6.8 (10)	7.3 (15)	4.5	360
15		8.1 (3)	nd[a]	7.2 (2)	7.7 (5)	4.4	50
16		8.1 (2)	nd[a]	nd[a]	7.6 (8)	4.4	8
2		8.1 (17)	7.6	7.0 (18)	7.6 (74)	4.5	220
17		7.9 (3)	nd[a]	7.6 (6)	7.6 (8)	4.4	23
18		8.2 (2)	nd[a]	nd[a]	8.2 (7)	4.5	6

[a] nd, not determined.

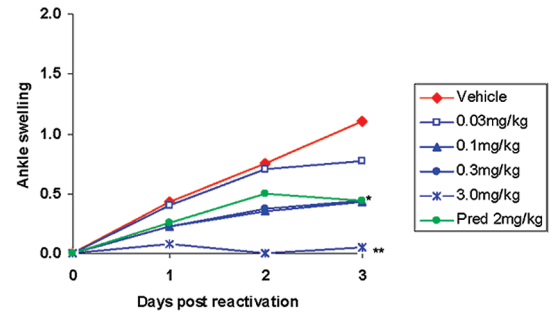
Reoptimization of the cyclopropylmethylamide moiety of **13**, by preparation of ca. 180 amides chosen as close analogues and also by the virtual library process described earlier, identified several further compounds that have increased potency and good cytochrome p450 profiles. The most interesting of these were ranked by oral AUC in rat cassette DMPK studies (Table 3). The additional α-methyl group on the amine in **15**, **16**, and **18** had a dramatic effect on the exposure, reducing the oral AUC from 360 ng·h/mL for isobutyl amide **14** to 8 ng·h/mL and 50 ng·h/mL, respectively, for the α-methylated enantiomers **15** and **16** (0.25 mg/kg dose). No further in vivo DMPK studies were performed on **15** and **16**, as the lower oral exposure was consistent with the in vitro clearance data generated in rat liver microsomes.

Compounds **13**, **14**, and **2** were profiled in the rat PG-PS reactivation model of arthritis; compound **14** generated a poor dose response curve and no ED_{50} was calculated, but **13** and **2** gave ED_{50}s of 0.1 mg/kg and 0.03 mg/kg, respectively (Figure 5). The rationale for the poor dose response for **14** in the PG-PS model is unclear, as the cassette DMPK profiles of **2** and **14** are very similar (**2**: Clr 9.2 mL/min/kg, iv $T_{1/2}$ 1.1 h, *F* 51%; **14**: Clr 6.4 mL/min/kg, iv $T_{1/2}$ 1.1 h, *F* 56%. Dosed at 0.25 mg/kg po and iv).

Compound **2** also demonstrated an analgesic effect in the rat PG-PS model, shown by increasing weight bearing on the



Compound **2** ED_{50} 0.03mg/kg



Compound **13** ED_{50} 0.1mg/kg

Figure 5. Effect of compounds **2** and **13** dosed orally twice daily on inflammation in the PG-PS reactivation arthritis model assessed by reduction in measured ankle swelling (mm). A comparison with prednisolone dosed at 2.0 mg/kg once daily is shown. * = $p < 0.05$ (Anova with posthoc planned comparisons, treatment vs control). ** = $p < 0.01$ (Anova with posthoc planned comparisons, treatment vs control).

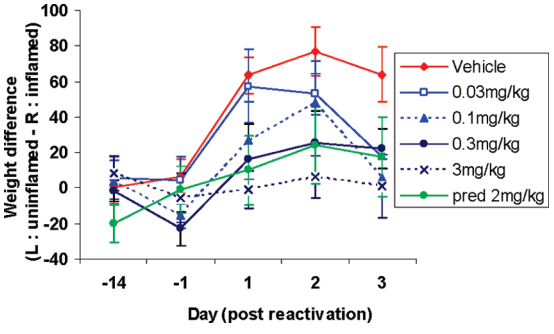


Figure 6. Effect of compound **2** on pain in the PG-PS reactivation arthritis model assessed by weight bearing.

injected paw on days 1 through 3 of the study, giving results equivalent to prednisolone (2 mg/kg) at a dose of 0.3 mg/kg (Figure 6).

In the murine CIA model, **2** showed dose related anti-inflammatory and joint protective activity, reducing clinical score, cellular influx into the synovial tissue and joint space, cartilage destruction, and new bone formation. At 20 mg/kg po bid, there was complete suppression of arthritis (Figure 7).

Further studies on compound **2** confirmed that, as well as being competitive with the fluorescent ATP-site ligand used to generate the SAR reported here, **2** was competitive with ATP in an assay measuring the catalytic activity of activated p38α with a K_i of 7.2. Compound **2** was profiled against a panel of 67 human kinases, using both in-house (pIC_{50} and % inhibition) and Dundee panel (% inhibition) screening. No significant

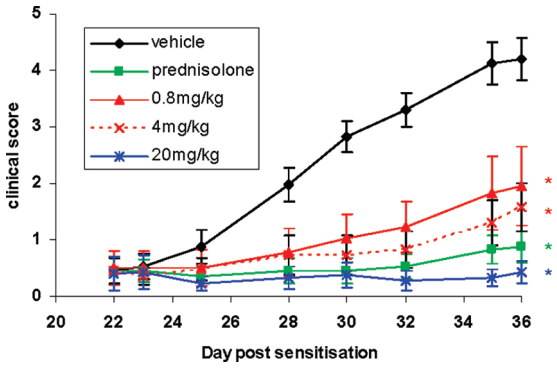


Figure 7. Inhibition of clinical score in the murine CIA model following 14 days of dosing with **2** (po bid), compared with prednisolone (3 mg/kg po once daily). * = $p < 0.05$ (Anova with posthoc planned comparisons, treatment vs control).

inhibition of these kinases including AKT1, ALK5, CDK2, EGFR, ErbB2, GSK3β, IKK2, IKK-ε, JNK3, LCK, PDGFR1B, PLK1, ROCK1, SRC, TIE2, and VEGFR2 was seen, and **2** has been shown to be highly selective for p38α/β. Compound **2** has an excellent p450 profile (pIC_{50} 2C9 4.5, 1A2, 2C19, 2D6, 3A4 ≤4.1) and moderate binding to rat and human serum albumen (96.0 and 94.9%, respectively). Compound **2** has acceptable pharmacokinetics in four species, rat (discrete data at 1 mg/kg po and iv: F 71%, iv $T_{1/2}$ 1.2 h, Clr 8.1 mL/mg/kg. and Vdss 0.9 mg/L), mouse (F 59%), dog (F 55%), and cynomolgus monkey (F 35%), with a desirably low level of brain exposure seen in the rat studies (brain:plasma ratio 0.1).

Conclusion

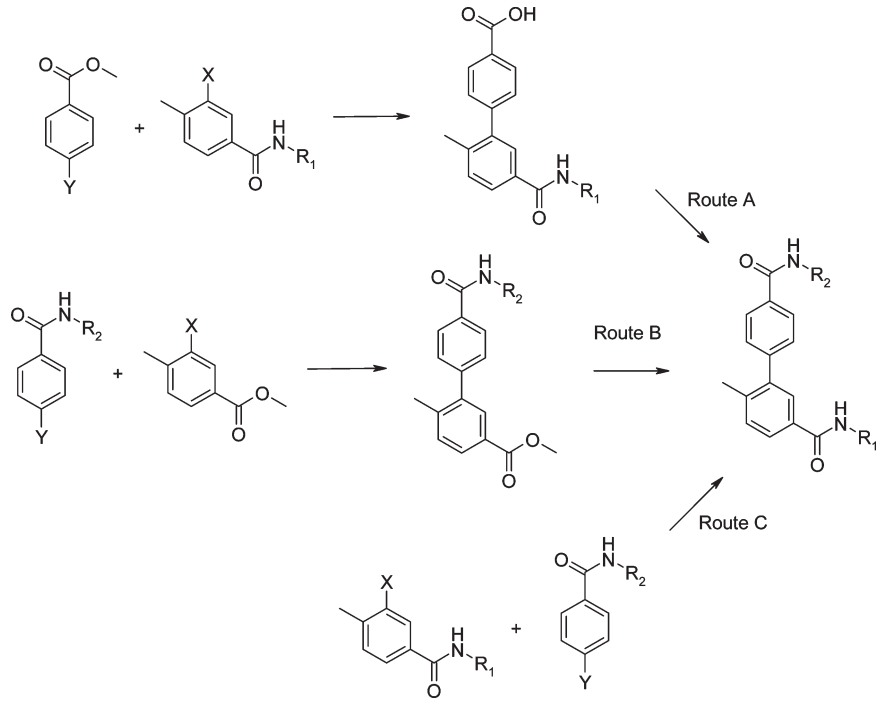
Using a combination of crystal structures of the biphenylamides bound to p38α, classical medicinal chemistry, array, and virtual array techniques, the BPA series has been optimized from an initial low potency cross-screening hit,[10] via a compound with high enzyme potency but suboptimal properties **1**, to a molecule suitable for clinical development **2**. This molecule has been developed for treatment of rheumatoid arthritis and is also currently being clinically evaluated for indications including COPD and heart disease

Chemistry. One of the advantages of the biphenylamide series of p38α inhibitors is their straightforward and flexible synthesis, either of the amide groups may be inserted in the final step or both amides may be prepared, and the biphenyl formed by a final Suzuki reaction (Scheme 1).

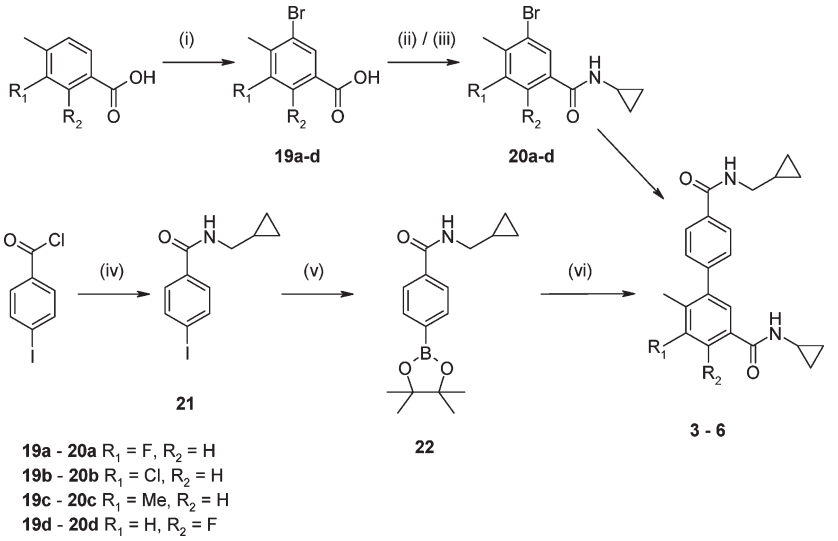
Compound **1** has been synthesized by a number of routes, one of which (route B) has previously been described.[12] Compounds **3**−**6** were prepared by route C, requiring the trisubstituted benzoic acids **19a**−**d** (Scheme 2). These were not available commercially, so they were synthesized by bromination of the disubstituted acids using bromine and iron powder. While this preparation is useable on a small scale, where there was a moderate and controllable exotherm, scale-up of **19a** required cooling due to a rapid temperature rise partway through the portionwise addition of the acid to the iron/bromine mixture. The resulting product contained two regioisomers, as had been seen in the small scale reaction, and also dibrominated material.

The 87 array compounds identified during the virtual array process were prepared by either route C, **7**, or by route A, which allowed facile variation of the 4′-amide, **8**−**10** (Scheme 3). To facilitate the larger arrays of amides, we wished to develop an improved synthesis of **20a** or preferably

Scheme 1. Biphenylamide Synthesis

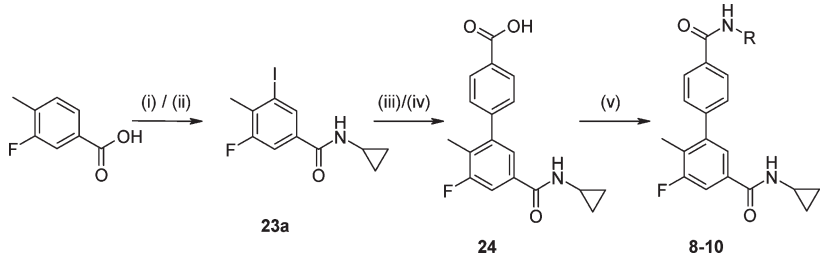


Scheme 2. Synthetic Route to Compounds **3**−**6**



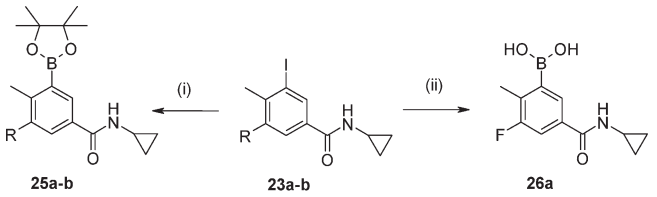
Reagents and conditions: (i) Br_2, Fe powder, rt (exothermic); (ii) $SOCl_2$, reflux; (iii) cyclopropylamine, Na_2CO_3, DCM, rt; (iv) cyclopropylmethylamine, Na_2CO_3, DCM, rt; (v) bispinnacolatodiboran, Pd(dppf)Cl_2, KOAc, DMF, 80 °C; (vi) $(Ph_3P)_4Pd$, 1 M $NaHCO_3$, IPA, 80 °C.

Scheme 3. 4-Amide Array Chemistry



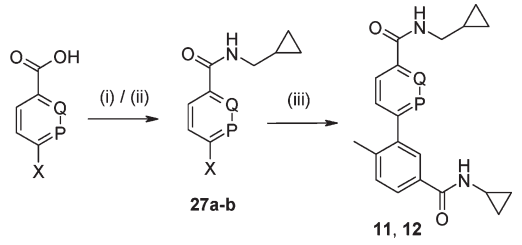
Reagents and conditions: (i) NIS, trifluoromethylsulfonic acid, −20 °C; (ii) $SOCl_2$ then cyclopropylamine, Na_2CO_3, DCM; (iii) {4-[(methyloxy)-carbonyl]phenyl}boronic acid, $(Ph_3P)_4Pd$, 1 M $NaHCO_3$, IPA, 80 °C; (iv) 2 M NaOH, MeOH; (v) RNH_2, HATU, DIPEA, DMF/DCM, rt.

Scheme 4. Synthesis of the Fluorinated Boronate Ester/Boronic Acid



Reagents and conditions: (i) bispinnacolatodiboran, $Pd(dppf)Cl_2$, KOAc, DMF, 80 °C; (ii) NaH, *n*-BuLi, $(iPrO)_3B$, THF, −75 °C.

Scheme 5. Preparation of Pyridine Analogues



Reagents and conditions: (i) $SOCl_2$ 80 °C; (ii) cyclopropylmethylamine, Na_2CO_3, DCM rt; (iii) **25b**, $(Ph_3P)_4Pd$, 1 M $NaHCO_3$, DMF, 90 °C.

the equivalent iodide **23a**, giving greater control of the halogenation reaction and improved regioselectivity. The bromination with iron and bromine was repeated at lower temperatures (0−30 °C), but these conditions gave little reaction. Various iodination conditions were assessed; iodine with concentrated nitric and sulfuric acid gave a controllable reaction but produced a mixture of isomers, and greatest regioselectivity was found with *n*-iodosuccinimide in trifluoromethylsulfonic acid. On a small scale, this chemistry was performed at 0 °C to give only the desired isomer and uniodinated material, but for generating larger quantities of material, reaction at −20 °C was found to give improved control of regioselectivity.

To avoid the toxicity issues associated with stannane chemistry for introduction of the 2′-pyridine, 3′-pyridine, and 2,6-pyrimidine, we desired the boronate esters **25a**−**b** or the equivalent boronic acid **26a**. These were readily prepared from the iodides, either by palladium chemistry or by lithiation and reaction with triisopropyl borate (Scheme 4).

The pyridines were then, simply prepared by Suzuki reaction of the boronate with an appropriate halopyridine (Scheme 5).

Pyridines **2** and **13**−**18** were prepared in a similar fashion from **25a** or **26a** and the appropriate chloronicotinamide.

Experimental Section

General Experimental Details. All commercial reagents and solvents were obtained from commercial sources and used without further purification. Unless otherwise specified, all reactions were performed under nitrogen. LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm × 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A) and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0.0−0.7 0% B, 0.7−4.2 min 0−100% B, 4.2−4.6 min 100% B, 4.6−4.8 min 100−0% B at a flow rate of 3 mL/min. The mass spectra were recorded on a Waters ZQ mass spectrometer using electrospray positive and negative mode (ES+ve and ES−ve). Unless otherwise specified, ^{1}H NMR spectra were recorded using a 400 MHz spectrometer and chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard. Purity of the tested compounds was of >95% using interpretation of a combination of LCMS and NMR data unless stated otherwise.

***N*^{3}-Cyclopropyl-*N*$^{4'}$-(cyclopropylmethyl)-5-fluoro-6-methyl-3,4′-biphenyldicarboxamide (3).** 3-Bromo-*N*-cyclopropyl-5-fluoro-4-methylbenzamide (**20a**, 90 mg, 0.34 mmol), *N*-cyclopropylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (**22**, 95 mg, 0.32 mmol), and tetrakis(triphenylphosphine)palladium (6.0 mg, 5.2×10^{-3} mmol) and aq sodium hydrogen carbonate (1M, 1.5 mL) were mixed in propan-2-ol (6 mL). The mixture was heated at 90 °C for 18 h. The cooled reaction was adsorbed onto silica under vacuum, and the residue was purified by chromatography on a silica cartridge (10 g) eluting with an ethyl acetate/cyclohexane gradient (0−75%). Appropriate fractions were reduced to dryness under vacuum and the residue triturated with diethyl ether to give the desired product (70 mg, 60%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.65 (t, J = 5.5 Hz, 1H), 8.53 (d, J = 4.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.64 (d, J=11.0 Hz, 1H), 7.60 (1H, s), 7.49 (d, J = 8.0 Hz, 2H), 3.18 (t, J = 6.0 Hz, 2H), 2.85 (1H, m), 2.17 (d, J = 2.0 Hz, 3H), 1.05 (1H, m), 0.70 (2H, m), 0.57 (2H, m), 0.45 (2H, m), 0.25 (2H, m). LCMS: MH^+ 367, retention time 3.06 min. Anal. Calcd for $C_{22}H_{23}FN_2O_2 \cdot 0.4H_2O$: C, 70.72; H, 6.42; N, 7.50. Found: C, 70.85; H, 6.19; N, 7.25.

3-Bromo-*N*-cyclopropyl-5-fluoro-4-methylbenzamide (20a). 3-Fluoro-4-methylbenzoic acid (460 mg, 3.0 mmol) was added to a stirred mixture of bromine (2.3 mL, 45 mmol) and iron powder (250 mg, 4.5 mmol) under nitrogen. The reaction was stirred at 20 °C for 4 h and then left to stand for 16 h. Sodium thiosulfate solution (200 mL) was added, and the product was extracted into ethyl acetate (3 × 150 mL). Ethyl acetate extracts were combined and evaporated under vacuum. The crude product (**19a**, mixture of isomers) was dissolved in DMF (7 mL). Cyclopropylamine (0.21 mL, 3.0 mmol), HOBT (410 mg, 3.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (580 mg, 3.0 mmol), and DIPEA (530 μL, 3.0 mmol) were added to the stirred solution. The reaction was stirred for 5 h at 20 °C. The solvent was evaporated under vacuum, and the residue was partitioned between ethyl acetate and water. The combined ethyl acetate extracts were washed sequentially with aq sodium hydrogen carbonate and hydrochloric acid (0.5M) and then dried (magnesium sulfate). The ethyl acetate was evaporated under vacuum, and the residue was purified by chromatography on a silica cartridge eluting with cyclohexane/ethyl acetate (6:1) to give the desired product (360 mg, 44%). ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H,), 7.39 (d, J = 9.5 Hz, 1H), 6.19 (bs, 1H), 2.88 (m, 1H), 2.36 (d, J = 2.5 Hz, 3H), 0.88 (m, 2H), 0.63 (m, 2H). LCMS: MH^+ 272/274, retention time 3.12 min. [When this reaction was repeated on 10 times the scale, with portionwise addition of the 3-fluoro-4-methylbenzoic acid (4.6 g, 30 mmol) to the iron/bromine mixture, ice cooling of the reaction was required part way through the addition due to a rapid exotherm.]

***N*-Cyclopropylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (22).** *N*-(Cyclopropylmethyl)-4-iodobenzamide (**21**, 800 mg, 2.7 mmol), bispinnacolatodiboron (740 mg, 2.9 mmol), potassium acetate (1.2 g, 12 mmol), and $Pd(dppf)Cl_2$ (50 mg, 0.07 mmol) were mixed in DMF (10 mL) and heated at 80 °C overnight. The cooled reaction was adsorbed onto silica and purified by chromatography on a silica cartridge (10 g), eluting with an ethyl acetate/cyclohexane gradient (0−100%). The appropriate fractions were reduced to dryness under vacuum and the residue triturated with diethyl ether to give the desired product as a white solid (550 mg, 69%). ^{1}H NMR (DMSO-d_6) δ 8.63 (t, J = 5.7 Hz, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 3.13 (t, J = 6.3 Hz, 2H), 1.30 (s, 12H), 1.04 (m, 1H), 0.41 (m, 2H), 0.22 (m, 2H).

***N*-(Cyclopropylmethyl)-4-iodobenzamide (21).** 4-Iodobenzoic acid (1.0 g, 4.0 mmol) in thionyl chloride (3.0 mL, 41 mmol) was heated at 100 °C for 30 min. The excess thionyl chloride was evaporated under vacuum and the residue dissolved in DCM (10 mL). Cyclopropylmethylamine (0.35 mL, 4.0 mmol) and sodium carbonate (2.0 g, 19 mmol) were added to the solution and the reaction left at ambient temperature for 2 h. The reaction was filtered, the residue washed with DCM, and the combined filtrate and washings reduced to dryness under vacuum. The resulting material was triturated with diethyl ether to give the desired product as a white solid (850 mg, 71%). ^{1}H NMR (DMSO-d_6) δ 8.61 (t, J = 5.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 3.11 (t, J = 6.5 Hz, 2H), 1.00 (m, 1H), 0.41 (m, 2H), 0.21 (m, 2H). LCMS: MH$^+$ 302, retention time 2.98 min.

5-Chloro-N^3-cyclopropyl-$N^{4\prime}$-(cyclopropylmethyl)-6-methyl-3,4′-biphenyldicarboxamide (4). 3-Bromo-5-chloro-*N*-cyclopropyl-4-methylbenzamide (**20b**, 30 mg, 2:1 mixture with 3-chloro-*N*-cyclopropyl-4-methylbenzamide), *N*-cyclopropylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (**22**, 28 mg, 0.09 mmol), tetrakis(triphenylphosphine)palladium (1.0 mg, 0.87 × 10^{-3} mmol), and aq sodium hydrogen carbonate (1M, 0.5 mL) were mixed in propan-2-ol (2 mL) and heated at 90 °C under nitrogen for 24 h. The reaction was adsorbed onto silica under vacuum, the residue purified by chromatography on a silica cartridge (5 g) eluting with an ethyl acetate/cyclohexane gradient (0−100%). The product fractions were reduced to dryness under vacuum and the residue recrystallized from ethyl acetate to give the desired product as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.65 (t, J = 5.5 Hz), 1H), 8.57 (d, J = 4.5 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 3.18 (t, J = 6.0 Hz, 2H), 2.86 (m, 1H), 2.27 (s, 3H), 1.05 (m, 1H), 0.69 (m, 2H), 0.57 (m, 2H), 0.45 (m, 2H), 0.25 (m, 2H). LCMS: MH$^+$ 383/385, retention time 3.27 min.

3-Bromo-5-chloro-*N*-cyclopropyl-4-methylbenzamide (20b). 3-Bromo-5-chloro-4-methylbenzoic acid (**19b**, 310 mg, 2:1 mixture with 3-chloro-4-methylbenzoic acid) was mixed with thionyl chloride (3.0 mL, 41 mmol) and the mixture heated at 90 °C for 2.5 h. The excess thionyl chloride was evaporated under vacuum, and the residue was dissolved in DCM (7.5 mL). Cyclopropylamine (0.20 mL, 2.9 mmol) and sodium carbonate (∼500 mg) were added to the solution and the reaction stirred for 2 h at room temperature. The reaction was filtered, the residue washed with DCM, and the combined filtrate and washings were reduced to dryness under vacuum and the resulting solid triturated with cyclohexane. The resulting white solid was adsorbed onto silica under vacuum and purified by chromatography on a silica cartridge (10 g), eluting with an ethyl acetate/cyclohexane gradient (0−50%). The product fractions were reduced to dryness under vacuum to give a mixture of 3-bromo-5-chloro-*N*-cyclopropyl-4-methylbenzamide and 3-chloro-*N*-cyclopropyl-4-methylbenzamide (2:1). 3-Bromo-5-chloro-*N*-cyclopropyl-4-methylbenzamide ^{1}H NMR (DMSO-d_6) δ 8.61 (d, J = 3.5 Hz 1H), 8.03 (s, 1H), 7.90 (s, 1H), 2.85 (m, 1H), 2.49 (s, 3H), 0.70 (m, 2H), 0.58 (m, 2H). LCMS: MH$^+$ 288/290/292, retention time 3.28 min.

3-Bromo-5-chloro-4-methylbenzoic acid (19b). 3-Chloro-4-methylbenzoic acid (270 mg, 1.6 mmol) was added in portions to a mixture of bromine (1.0 mL, 20 mmol) and iron powder (45 mg, 0.81 mmol) and the reaction stirred in a sealed vial for 28 h. The reaction mixture was poured into aq sodium thiosulfate and extracted with ethyl acetate. The combined extracts were washed with brine, dried (magnesium sulfate), and the solvent evaporated under vacuum. The residue was redissolved in ethyl acetate, filtered, and the filtrate reduced to dryness under vacuum to give a mixture of 3-bromo-5-chloro-4-methylbenzoic acid and 3-chloro-4-methylbenzoic acid (320 mg, 2:1). 3-Bromo-5-chloro-4-methylbenzoic acid ^{1}H NMR (DMSO-d_6) δ 8.02 (d, J = 1.5 Hz, 1H), 7.89 (d, J = 1.5 Hz, 1H), 2.51 (s, 3H). LCMS: [M − H]$^-$ 247/249/251, retention time 3.73 min.

N^3-Cyclopropyl-$N^{4\prime}$-(cyclopropylmethyl)-5,6-dimethyl-3,4′-biphenyldicarboxamide (5). 3-Bromo-*N*-cyclopropyl-4,5-dimethylbenzamide (**20c**, 30 mg, 0.11 mmol), *N*-cyclopropylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (**22**, 28 mg, 0.09 mmol), tetrakis(triphenylphosphine)palladium (1.0 mg, 0.87 × 10^{-3} mmol), and aq sodium hydrogen carbonate (1M, 0.5 mL) were mixed in propan-2-ol (2 mL) and heated at 90 °C under nitrogen for 24 h. The reaction was adsorbed onto silica under vacuum, and the residue was purified by chromatography on a silica cartridge (10 g) and eluted with an ethyl acetate/cyclohexane gradient (0−100% ethyl acetate). The product fractions were reduced to dryness under vacuum, and the residue was recrystallized from ethyl acetate to give the desired product as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.62 (t, J = 5.5 Hz, 1H), 8.38 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.67 (s, 1H), 7.52 (s, 1H), 7.41 (d, J = 8.5 Hz, 2H), 3.18 (t, J = 6.0 Hz, 2H), 2.84 (m, 1H), 2.34 (s, 3H), 2.14 (s, 3H), 1.05 (m, 1H), 0.68 (m, 2H), 0.56 (m, 2H), 0.45 (m, 2H), 0.25 (m, 2H). LCMS: MH$^+$ 363, retention time 3.06 min.

3-Bromo-*N*-cyclopropyl-4,5-dimethylbenzamide (20c). 3-Bromo-4,5-dimethylbenzoic acid[23] (**19c**, 200 mg, 0.87 mmol) was mixed with thionyl chloride (2.0 mL, 27 mmol) and the mixture heated at 90 °C for 2.5 h. The excess thionyl chloride was evaporated under vacuum, and the residue was dissolved in DCM (5 mL). Cyclopropylamine (0.2 mL, 2.9 mmol) and sodium carbonate (∼300 mg) were added to the solution and the reaction stirred for 2 h at room temperature. The reaction was filtered, the filtrate reduced to dryness under vacuum, and the residue triturated with diethyl ether. The resulting solid was dissolved in acetone/methanol and adsorbed onto silica under vacuum. The residue was purified by chromatography on a silica cartridge (5 g) eluting with an ethyl acetate/cyclohexane gradient (0−50% ethyl acetate) to give the desired product. ^{1}H NMR (DMSO-d_6) δ 8.44 (d, J = 4.0 Hz, 1H), 7.87 (s, 1H), 7.64 (s, 1H), 2.83 (m, 1H), 2.34 (s, 6H), 0.69 (m, 2H), 0.57 (m, 2H). LCMS: MH$^+$ 268/270, retention time 3.05 min.

N^3-cyclopropyl-$N^{4\prime}$-(cyclopropylmethyl)-4-fluoro-6-methyl-3,4′-biphenyldicarboxamide (6). 5-Bromo-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (**20d**, 30 mg, 0.11 mmol), *N*-cyclopropylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzamide (**22**, 28 mg, 0.09 mmol), tetrakis(triphenylphosphine)palladium (1.0 mg, 0.87 × 10^{-3} mmol), and aq sodium hydrogen carbonate (1M, 0.5 mL) were mixed in propan-2-ol (2 mL) and heated at 90 °C under nitrogen for 24 h. The reaction was adsorbed onto silica under vacuum, and the residue was purified by chromatography on a silica cartridge (5 g) eluting with an ethyl acetate/cyclohexane gradient (0−100% ethyl acetate). The product fractions were reduced to dryness under vacuum and the residue recrystallized from ethyl acetate to give the desired product as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.63 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 4.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 11.5 Hz, 1H), 3.17 (t, J = 6.5 Hz, 2H), 2.83 (m, 1H), 2.26 (s, 3H), 1.05 (m, 1H), 0.69 (m, 2H), 0.54 (m, 2H), 0.45 (m, 2H), 0.25 (m, 2H). LCMS: MH$^+$ 367, retention time 2.97 min.

5-Bromo-*N*-cyclopropyl-2-fluoro-4-methylbenzamide (20d). 5-Bromo-2-fluoro-4-methylbenzoic acid (**19d**, 180 mg, 0.77 mmol) was mixed with thionyl chloride (2.0 mL, 27 mmol) and the mixture heated at 90 °C for 2 h. The excess thionyl chloride was evaporated under vacuum, and the residue was dissolved in DCM (5 mL). Cyclopropylamine (0.10 mL, 1.4 mmol) and sodium carbonate (∼300 mg) were added to the solution and the reaction stirred for 2 h at room temperature. The reaction was filtered, the residue washed with DCM, and the combined filtrate and washings reduced to dryness under vacuum. The residue was recrystallized from cyclohexane to give the desired product as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 7.71 (d, J = 6.8 Hz, 1H), 7.36 (d, J = 10.8 Hz, 1H), 2.81 (m, 1H), 2.36 (s, 3H), 0.69 (m, 2H), 0.55 (m, 2H). LCMS: MH$^+$ 272/274, retention time 2.88 min.

5-Bromo-2-fluoro-4-methylbenzoic Acid (19d). 2-Fluoro-4-methylbenzoic acid[24] (240 mg, 1.6 mmol) was added in portions to a mixture of bromine (1.0 mL, 20 mmol) and iron powder (60 mg, 1.1 mmol) and the reaction stirred in a sealed reacti-vial

at room temperature for 25 min. The reaction was poured into aq sodium thiosulfate and extracted with ethyl acetate (×2). The combined extracts were washed with brine, dried (magnesium sulfate), and the solvent evaporated under vacuum. The residue was recrystallized from cyclohexane to give the desired product as a white solid (180 mg, 48%). ^{1}H NMR (DMSO-d_6) δ 13.44 (bs, 1H), 7.98 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 11.5 Hz, 1H), 2.39 (s, 3H). LCMS: $[M - H]^-$ 231/233, retention time 3.37 min.

N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4\prime}$-(tetrahydro-2-furanylmethyl)-3,4′-biphenyldicarboxamide (7). *N*-Cyclopropyl-3-fluoro-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (**25a**, 30 mg, 0.10 mmol), 4-bromo-*N*-(tetrahydro-2-furanylmethyl)-benzamide (**28**, 27 mg, 0.10 mmol), tetrakis(triphenylphosphine)-palladium (7.0 mg, 6.1×10^{-3} mmol), and aq sodium hydrogen carbonate (1M, 0.45 mL) were mixed in propan-2-ol (2 mL) and heated at 90 °C under nitrogen for 18 h. The reaction was filtered, the residue washed with DCM, and the combined filtrate and washings reduced to dryness. The resulting material was purified by chromatography on a silica cartridge (8 g) eluting with ethyl acetate/cyclohexane (1:2, then 1:1 and 3:1). Appropriate fractions were reduced to dryness under vacuum to give the desired product (17 mg, 45%). ^{1}H NMR (DMSO-d_6) δ 8.64 (t, J = 5.5 Hz, 1H), 8.53 (d, J = 4.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 10.5 Hz, 1H), 7.60 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 4.00 (m, 1H), 3.79 (q, J = 7.0 Hz, 1H), 3.64 (q, J = 7.0 Hz, 1H), 3.36 (m partially obscured by water, 2H), 2.85 (m, 1H), 2.17 (s, 3H), 1.95−1.77 (m, 3H), 1.63 (m, 1H), 0.70 (m, 2H), 0.57 (m, 2H). LCMS: MH^+ 396, retention time 3.01 min.

4-Bromo-*N*-(tetrahydro-2-furanylmethyl)benzamide (28). A solution of 4-bromobenzoyl chloride (500 mg, 2.3 mmol) in DCM (5 mL) was treated with sodium carbonate (290 mg) and (tetrahydro-2-furanylmethyl)amine (230 mg, 2.3 mmol) and the mixture stirred at ambient temperature under nitrogen for 16 h. The reaction was filtered, and the solid was washed with DCM. The combined filtrate and washings were filtered through an aminopropyl ion exchange cartridge and the filtrate evaporated under vacuum to give the desired product as a white solid (280 mg, 42%). ^{1}H NMR (DMSO-d_6) δ 8.63 (t, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 3.96 (m, 1H), 3.77 (q, J = 7.5 Hz, 1H), 3.62 (q, J = 7.4 Hz, 1H), 3.30 (m, 2H), 1.94−1.75 (m, 3H), 1.59 (m, 1H). LCMS: MH^+ 284/286, retention time 2.66 min. Purity 85%.

N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4\prime}$-[(2-methyl-1,3-thiazol-4-yl)methyl]-3,4′-biphenyldicarboxamide (8). A solution of 5′-[(cyclopropylamino)carbonyl]-3′-fluoro-2′-methyl-4-biphenylcarboxylic acid (**24**, 310 mg, 1.0 mmol) in DMF (4.2 mL) was treated with HATU (400 mg, 1.05 mmol) and diisopropylethylamine (450 μL, 2.0 mmol). After 10 min, 200 μL of this mixture was added to 200 μL of a solution of [(2-methyl-1,3-thiazol-4-yl)-methyl]amine (260 mg, 0.2 mmol) in DMF (2 mL). The reaction was left at ambient temperature for 16 h before the solvents were evaporated under vacuum. The residue was dissolved in chloroform, loaded onto an aminopropyl ion exchange cartridge (0.5 g), the cartridge washed with chloroform, and the basic material eluted with ethyl acetate/methanol (9:1). The combined chloroform fractions were reduced to dryness to give the desired compound. ^{1}H NMR (600 M Hz, DMSO-d_6) δ 9.11 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 4.0 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 10.0 Hz, 1H), 7.60 (s, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.22 (s, 1H), 4.55 (d, J = 6.0 Hz, 2H), 2.85 (m, 1H), 2.64 (s, 3H), 2.17 (s, 3H), 0.70 (m, 2H), 0.57 (m, 2H). LCMS: MH^+ 424, retention time 2.95 min.

5′-[(Cyclopropylamino)carbonyl]-3′-fluoro-2′-methyl-4-biphenylcarboxylic acid (24). A mixture of *N*-cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide (**23a**, 0.85 g, 2.7 mmol), {4-[(methyloxy)carbonyl]phenyl}boronic acid (0.48 g, 2.7 mmol), tetrakis-(triphenylphosphine)palladium (0.31 g, 0.27 mmol), and aq sodium hydrogen carbonate (1M, 13 mL) in propan-2-ol (28 mL) was heated at 90 °C for 22 h under nitrogen. The solvents were evaporated under vacuum and the residue treated with methanol (35 mL) and sodium hydroxide (5 mL) at 50 °C for 2 h. The mixture was reduced to dryness under vacuum and the residue dissolved in ethyl acetate water (1:1, 60 mL). The solution was acidified to pH2 with hydrochloric acid (2M), the layers separated, and the aqueous extracted with ethyl acetate (30 mL). The combined organic phases were washed with water, dried (magnesium sulfate), and reduced to dryness under vacuum. The residue was dissolved in ethyl acetate (30 mL), extracted with sodium hydroxide (2M, 2 × 50 mL), and the aqueous phase acidified to pH 1 and extracted with ethyl acetate (3 × 30 mL). The combined organics were dried (magnesium sulfate) and reduced to dryness under vacuum. The resulting solid was dried under vacuum for 2 h to give the desired product (0.28 g, 34%). ^{1}H NMR (MeOD) δ 8.11 (d, J = 8.3 Hz, 2H), 7.55 (m, 2H), 7.46 (d, J = 8.0 Hz, 2H), 2.84 (m, 1H), 2.20 (s, 3H), 0.78 (m, 2H), 0.62 (m, 2H). LCMS: MH^+ 314, retention time 3.08 min.

***N*-Cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide (23a).** 3-Fluoro-5-iodo-4-methylbenzoic acid (**29**, 220 g, 0.77 mol) in thionyl chloride (270 mL, 3.70 mol) was heated at 100 °C for 3 h. The excess thionyl chloride was evaporated under vacuum and the residue azeotroped with DCM (×2). The resulting acid chloride was dissolved in DCM (200 mL) and the solution added slowly to a cold (ice/water bath), stirred suspension of cyclopropylamine (110 mL, 1.6 mol) and sodium carbonate (220 g, 2.0 mol) in DCM (500 mL). The reaction was stirred overnight at ambient temperature, diluted with DCM, and washed with water (×2). The combined aqueous washings were extracted with DCM, the DCM fractions combined, dried (sodium sulfate), and partially concentrated under vacuum. The resulting suspension was allowed to stand for 3 h and the solid isolated by filtration, washed with DCM, and dried to give the desired product (184 g). A further batch of the desired product (11 g) was obtained by evaporation of the solvent from the mother liquor and recrystallization of the residue from DCM (150 mL). A final batch of the desired product (30 g) was prepared by chromatography of the mother liquor on a silica cartridge (800 g) eluting with DCM and then ethyl acetate/DCM (5:95). Total yield (225 g, 92%). ^{1}H NMR (600 M Hz, $CDCl_3$) δ 7.93 (s, 1H), 7.42 (d, J = 9.6 Hz, 1H), 6.42 (bs, 1H), 2.88 (m, 1H), 2.38 (s, 3H), 0.87 (m, 2H), 0.64 (m, 2H). LCMS: MH^+ 320, retention time 3.23 min.

3-Fluoro-5-iodo-4-methylbenzoic acid (29). 3-Fluoro-4-methylbenzoic acid (180 g, 1.2 mol) in trifluoromethanesulfonic acid (1.1 L) was cooled to −20 °C. *n*-Iodosuccimide (270 g, 1.2 mol) was added in portions over 75 min maintaining a temperature of −18 to −19 °C. The reaction was stirred at −20 °C for 4 h, further NIS (55 g, 0.24 mol) added, and the reaction stirred overnight at −20 °C. NIS (19 g, 84 mmol) was added to the reaction and stirring continued for 24 h. The reaction was warmed up to −5 °C and the suspension poured into ice (3 kg) and 10% sodium thiosulfate solution. The aqueous suspension was filtered, and the solid was washed with water and partially dried. The solid was partitioned between ethyl acetate (5 L) and 10% sodium thiosulfate solution (1.5 L) and the organic phase washed with sodium thiosulfate solution. The combined aqueous phases were extracted with ethyl acetate (2 L); the organic phases were combined, dried (sodium sulfate), and concentrated under vacuum to ca. 600 mL. The slurry was allowed to stand for 4 h, the solid filtered off, washed with ethyl acetate, and dried to give the desired product (215 g, 65%). ^{1}H NMR (250 M Hz, $CDCl_3$) δ 10.76 (bs, 1H), 8.34 (s, 1H), 7.72 (d, 1H), 2.45 (s, 3H). LCMS: $[M - H]^-$ 279, retention time 3.75 min.

N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4\prime}$-[2-(methyloxy)ethyl]-3,4′-biphenyldicarboxamide (9). A solution of 5′-[(cyclopropylamino)-carbonyl]-3′-fluoro-2′-methyl-4-biphenylcarboxylic acid (**24**, 0.31 g, 1.0 mmol) in DMF (4.2 mL) was treated with HATU (0.40 g, 1.1 mmol) and diisopropylethylamine (450 μL, 2.0 mmol). After 10 min, 200 μL of this mixture was added to 200 μL of a solution of 2-methoxyethylamine (150 mg, 0.20 mmol) in DMF (2 mL). The reaction was left at ambient temperature for 16 h before the solvents

were evaporated under vacuum. The residue was dissolved in chloroform, loaded onto an aminopropyl ion exchange cartridge (0.5 g), the cartridge washed with chloroform, and the basic material eluted with ethyl acetate/methanol (9:1). The combined chloroform fractions were reduced to dryness to give the desired compound. ^{1}H NMR (DMSO-d_6) δ 8.61 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 4.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 11.0 Hz, 1H), 7.59 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 3.49−3.44 (4H, m), 3.28 (s, 3H), 2.17 (d, J = 2.0 Hz, 3H), 0.70 (m, 2H), 0.57 (m, 2H). LCMS: MH$^+$ 371, retention time 2.81 min, purity 88%.

N^3-cyclopropyl-5-fluoro-$N^{4\prime}$-(2-hydroxy-2-methylpropyl)-6-methyl-3,4′-biphenyldicarboxamide (10). 5′-[(Cyclopropylamino)carbonyl]-3′-fluoro-2′-methyl-4-biphenylcarboxylic acid (**24**, 50 mg, 0.16 mmol), HATU (61 mg, 0.16 mmol), 1-amino-2-methyl-2-propanol (21 mg, 0.24 mmol), and diisopropylethylamine (31 μL, 0.18 mmol) were mixed in DMF (2 mL) and stirred at ambient temperature under nitrogen for 24 h. A further aliquot of 1-amino-2-methyl-2-propanol (10 mg, 0.12 mmol) was added and stirring continued for 24 h. The reaction was reduced to dryness under vacuum and purified by chromatography on a silica cartridge (10 g) eluting with an ethyl acetate/cyclohexane gradient (50−100%) and then methanol/ethyl acetate (1−3%). Appropriate fractions were reduced to dryness, to give the desired compound (35 mg, 57%). ^{1}H NMR (DMSO-d_6) δ 8.53 (d, J = 4.0 Hz, 1H), 8.34 (t, J = 6.0 Hz, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 10.5 Hz, 1H), 7.60 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 4.58 (s, 1H), 3.29 (d, J = 6.0 Hz, 2H), 2.85 (m, 1H), 2.17 (d, J = 2.5 Hz, 3H), 1.12 (s, 3H), 0.70 (m, 2H), 0.57 (m, 2H). LCMS: MH$^+$ 385, retention time 2.73 min.

6-(5-Cyclopropylcarbamoyl-2-methyl-phenyl)-*N*-cyclopropylmethyl-nicotinamide (11). 6-Chloro-*N*-cyclopropylmethylnicotinamide (**27a**, 26 mg, 0.10 mmol), *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (**25b**, 30 mg, 0.10 mmol), aq sodium carbonate (2N, 0.5 mL), and tetrakis-(triphenylphosphine)palladium (4.0 mg, 3.5 x10^{-3} mmol) were heated at 90 °C in DMF (1 mL) for 3 h. The reaction was adsorbed onto silica and purified by chromatography on a silica cartridge (5 g), eluting with an ethyl acetate/cyclohexane gradient (0 to 100%), and then acetone. The solvent was evaporated from the product fractions under vacuum and the residue triturated with diethyl ether to give the desired product as a cream solid. ^{1}H NMR (DMSO-d_6) δ 9.11 (s, 1H), 8.84 (t, J = 5.5 Hz, 1H), 8.48 (d, J = 4.0 Hz, 1H), 8.31 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.88 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 3.20 (t, J = 6.5 Hz, 2H), 2.86 (m, 1H), 2.37 (s, 3H), 1.06 (m, 1H), 0.69 (m, 2H), 0.57 (m, 2H), 0.46 (m, 2H), 0.26 (m, 2H). LCMS: MH$^+$ 350, retention time 2.70 min

***N*-Cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (25b).** *N*-Cyclopropyl-3-iodo-4-methylbenzamide (**23b**, 1.1 g, 3.6 mmol), bis(pinnacolato)diboron (1.9 g, 7.3 mmol), potassium acetate (1.8 g, 18 mmol), and Pd(dppf)Cl$_2$ (55 mg, 75 × 10^{-3} mmol) were heated at 85 °C in DMF (30 mL) for 4.5 h. The cooled reaction was adsorbed onto silica and purified by chromatography on a silica cartridge (10 g), eluting with an ethyl acetate/cyclohexane gradient (0 to 100%). The solvent was evaporated from the product fractions under vacuum and the residue triturated with cyclohexane to give the desired product as a beige solid (650 mg, 59%). ^{1}H NMR (DMSO-d_6) δ 8.40 (d, J = 4.0 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.76 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 2.82 (m, 1H), 2.48 (s, 3H), 1.30 (s, 12H), 0.66 (m, 2H), 0.56 (m, 2H).

***N*-Cyclopropyl-3-iodo-4-methylbenzamide (23b).** 3-Iodo-4-methylbenzoic acid (1.0 g, 3.8 mmol) was heated at 80 °C in thionyl chloride (10 mL, 140 mmol) for 2 h. The reaction was allowed to cool to room temperature and the excess thionyl chloride evaporated under vacuum. The residue was dissolved in DCM (10 mL), and cyclopropylamine (0.32 mL, 4.6 mmol) and sodium carbonate (2.0 g) were added to the solution. The reaction was stirred at room temperature for 18 h, filtered, and the filtrate reduced to dryness under vacuum. The residue was triturated with diethyl ether to give *N*-cyclopropyl-3-iodo-4-methylbenzamide as a white solid (1.1 g, 96%). ^{1}H NMR (DMSO-d_6): δ 8.46 (d, J = 4.0 Hz, 1H), 8.24 (d, J = 1.5 Hz, 1H), 7.74 (dd, J = 7.8 Hz, J = 1.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 2.82 (m, 1H), 2.38 (s, 3H), 0.67 (m, 2H), 0.55 (m, 2H).

6-Chloro-*N*-cyclopropylmethylnicotinamide (27a). 6-Bromonicotinic acid (1.5 g, 7.6 mmol) was heated at 100 °C in thionyl chloride (5.0 mL, 69 mmol) for 2 h. The excess thionyl chloride was evaporated under vacuum and residue was dissolved in DCM (15 mL), and sodium carbonate (1.5 g) was added to the mixture followed by slow addition of cyclopropylmethylamine (2.0 mL). The reaction was stirred at room temperature overnight, filtered, and the residue washed with DCM (30 mL) and then ethyl acetate (30 mL). The combined filtrate and washings were reduced to dryness under vacuum. The residue was purified by dissolving in DCM, applying to a silica cartridge and eluting with ethyl acetate. The solvent was evaporated from the eluent fractions under vacuum and the residue further dried under vacuum to give 6-chloro-*N*-cyclopropylmethylnicotinamide as a white solid (1.2 g, 62%). ^{1}H NMR (DMSO-d_6) δ 8.83 (m, 2H), 8.25 (dd, J = 8.3 Hz, J = 2.5 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 3.15 (t, J = 5.8 Hz, 2H), 1.02 (m, 1H), 0.44 (m, 2H), 0.24 (m, 2H).

5-{5-[(Cyclopropylamino)carbonyl]-2-methylphenyl}-*N*-(cyclopropylmethyl)-2-pyridinecarboxamide (12). 5-Bromo-*N*-(cyclopropylmethyl)-2-pyridinecarboxamide (**27b**, 44 mg, 0.27 mmol) and *N*-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (**25b**, 50 mg, 0.17 mmol), aq sodium carbonate (2N, 1 mL), and tetrakis(triphenylphosphine)palladium (6 mg, 5.2 × 10^{-3} mmol) were heated at 80 °C in DMF (3 mL) for overnight. The reaction was diluted with ethyl acetate, dried (magnesium sulfate), and the solution filtered through a silica cartridge (5 g). The cartridge was washed with further ethyl acetate and the combined filtrate and washings reduced to dryness under vacuum. The residue was triturated with diethyl ether to give the desired product. ^{1}H NMR (DMSO-d_6) δ 9.03 (d, J = 2.0 Hz, 1H), 8.82 (t, J = 5.5 Hz, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.44 (d, 4.5 Hz, 1H), 8.21 (d, J = 2.5 Hz, d), 7.80 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 3.17 (t, J = 6.5 Hz, 2H), 2.84 (m, 1H), 2.27 (s, 3H), 1.05 (m, 1H), 0.67 (m, 2H), 0.55 (m, 2H), 0.44 (m, 2H), 0.23 (m, 2H). LCMS: MH$^+$ 350, retention time 2.62 min

5-Bromo-*N*-(cyclopropylmethyl)-2-pyridinecarboxamide (27b). 5-Bromo-2-pyridinecarboxylic acid (51 mg, 0.25 mmol) was heated in thionyl chloride (1.0 mL, 14 mmol) at 85 °C for 2 h. The excess thionyl chloride was evaporated under vacuum, and the residue was dissolved in DCM (2 mL) and treated with cyclopropylmethylamine (0.10 mL) and potassium carbonate (200 mg). The reaction was stirred at room temperature for ~2 h and then left to stand for 72 h. The reaction was filtered and the residue washed with DCM (~2 mL). The combined filtrate and washings (pale-yellow solution) were reduced to dryness under a stream of nitrogen. The residual gum was triturated with diethyl ether, filtered, and the filtrate diluted with cyclohexane. The solvents were evaporated under vacuum to give the desired product as cream-colored waxy solid (44 mg, 68%). ^{1}H NMR (DMSO-d_6) δ 8.81 (bt, 1H), 8.77 (d, J = 2.3 Hz, 1H), 8.24 (dd, J = 8.3 Hz, J = 2.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 3.16 (t, J = 6.5 Hz, 2H), 1.05 (m, 1H), 0.42 (m, 2H), 0.24 (m, 2H). LCMS: MH$^+$ 255/257, retention time 2.83 min.

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-(cyclopropylmethyl)-3-pyridinecarboxamide (13). 6-Chloro-*N*-(cyclopropylmethyl)-3-pyridinecarboxamide (**27a**, 26 mg, 0.10 mmol), *N*-cyclopropyl-5-fluoro-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (**25a**, 32 mg, 0.10 mmol), tetrakis(triphenylphosphino)palladium (2.0 mg, 1.7 × 10^{-3} mmol), and aq sodium hydrogen carbonate (1M, 0.5 mL) were mixed in propan-2-ol (2 mL) and heated at reflux for 18 h. The cooled reaction was diluted with ethyl acetate and applied to

a silica cartridge (5 g), the cartridge was washed with ethyl acetate and the combined filtrate and washings reduced to dryness under vacuum. The residual glass was dissolved in ethyl acetate/methanol and applied to an SCX-2 ion exchange cartridge. The product was eluted with 0.88 ammonia/ethyl acetate/methanol, the solvents evaporated under vacuum, and the residue triturated with diethyl ether/cyclohexane to give the desired product as a white solid (18 mg, 49%). ^{1}H NMR (DMSO-d_6) δ 9.14 (d, J = 1.5 Hz, 1H), 8.87 (t, J = 5.5 Hz, 1H), 8.58 (d, J = 3.5 Hz, 1H), 8.35 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 7.78 (s, 1H), 7.75−7.69 (m, 2H), 3.21 (t, J = 6.0 Hz, 2H), 2.87 (m, 1H), 2.27 (s, 3H), 1.08 (m, 1H), 0.71 (m, 2H), 0.60 (m, 2H), 0.48 (m, 2H), 0.28 (m, 2H). LCMS: MH$^+$ 368, retention time 2.81 min. Anal. Calcd. for $C_{21}H_{22}FN_2O_2$: C, 68.65; H, 6.04; N, 11.44. Found: C, 68.32; H, 6.01; N, 11.17.

***N*-Cyclopropyl-5-fluoro-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-benzamide (25a).** *N*-Cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide (**23a**, 6.0 g, 19 mmol), bispinnacolatodiboron (7.2 g, 28 mmol), potassium acetate (9.2 g, 94 mmol), and Pd(dppf)Cl$_2$ (150 mg, 0.20 mmol) were mixed in anhydrous DMF (130 mL) and heated at 90 °C for 19 h. The cooled reaction was adsorbed onto silica and purified by chromatography on silica cartridges (40 g × 2) eluting with ethyl acetate/cyclohexane (10 then 15%). The product fractions were combined the solvents evaporated under vacuum. The residue was recrystallized from cyclohexane to give the desired product as a white solid (3.0 g, 54%). ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.60 (d, J = 11.8 Hz, 1H), 6.32 (bs, 1H), 2.89 (m, 1H), 2.49 (d, J = 2.3 Hz, 3H), 1.36 (s, 12H), 0.88 (m, 2H), 0.65 (m, 2H).

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (2). 6-Chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (**30**, 560 mg, 2.3 mmol), *N*-cyclopropyl-5-fluoro-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (**25a**, 790 mg, 2.5 mmol), tetrakis(triphenylphosphine)palladium (30 mg, 0.025 mmol), and aq sodium hydrogen carbonate (1M, 3 mL) were mixed in propan-2-ol (10 mL) and heated at 90 °C for 18 h. The propan-2-ol was evaporated, the residue dissolved with ethyl acetate, applied to an SCX-2 ion exchange cartridge (10 g), and the cartridge washed with ethyl acetate and then methanol. The product was eluted from the cartridge with 0.880 ammonia/ethyl acetate/methanol and the solvents evaporated in vacuo. The residue was triturated with diethyl ether to give the desired product as a white solid (500 mg, 57%). The combined ethyl acetate and methanol washings were reduced to dryness in vacuo, the residue was dissolved in a mixture of acetone and methanol and applied to an SCX-2 ion exchange cartridge (10 g), and the cartridge was washed with methanol and eluted with 0.880 ammonia/methanol. The basic fraction was reduced to dryness in vacuo to give a second batch of the desired product as a white solid (200 mg, 22%). ^{1}H NMR (DMSO-d_6): δ 9.11 (d, J = 1.5 Hz, 1H), 8.63 (t, J = 6.0 Hz, 1H), 8.56 (d, J = 4.0 Hz, 1H), 8.33 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.76 (s, 1H), 7.73−7.68 (m, 2H), 3.16 (d, J = 6.5 Hz, 2H), 2.86 (m, 1H), 2.26 (d, J = 2.0 Hz, 3H), 0.93 (s, 9H), 0.70 (m, 2H), 0.58 (m, 2H). LCMS: MH$^+$ 384, retention time 3.01 min. Anal. Calcd. for $C_{22}H_{26}FN_3O_2$: C, 68.9; H, 6.80; F, 4.95; N, 11.0. Found: C, 68.8; H, 6.72; F, 5.03; N, 10.82.

6-Chloro-*N*-(2,2-dimethylpropyl)-3-pyridinecarboxamide (30). 6-Chloro-3-pyridinecarboxylic acid (500 mg, 3.1 mmol) in thionyl chloride (3.5 mL, 48 mmol) was heated at 100 °C for 1.5 h. The excess thionyl chloride was evaporated under vacuum and the solid residue dissolved in DCM (20 mL). This mixture was treated with 2,2-dimethylpropylamine (1.0 mL, 16 mmol) and sodium carbonate (1.7 g, 16 mmol) and stirred for 15 h at ambient temperature. The reaction was filtered and the solvent evaporated to give the title compound (840 mg, quant). ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 2.3 Hz, 1H), 8.61 (bt, 1H), 8.25 (dd, J = 8.3 Hz, J = 2.5 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 3.12 (d, J = 6.3 Hz, 2H), 0.90 (s, 9H).

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-(2-methylpropyl)-3-pyridinecarboxamide (14). Compound **14** was prepared as for **2** using 6-chloro-*N*-(2-methylpropyl)-3-pyridinecarboxamide (**31**). ^{1}H NMR (DMSO-d_6) δ 9.11 (d, J = 1.5 Hz, 1H), 8.74 (t, J = 6.0 Hz, 1H), 8.56 (d, J = 4.0 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 2.5 Hz, 1H), 7.76 (s, 1H), 7.73−7.68 (m, 2H), 3.13 (t, J = 6.5 Hz, 2H), 2.85 (m, 1H), 2.26 (d, J = 2.0 Hz, 3H), 1.87 (m, 1H), 0.92 (d, J = 7.0 Hz), 0.70 (m, 2H), 0.58 (m, 2H). LCMS: MH$^+$ 370, retention time 2.86 min. Anal. Calcd. for $C_{21}H_{24}FN_3O_2$: C, 68.27; H, 6.55; N, 11.37. Found: C, 68.10; H, 6.52; N, 11.31.

6-Chloro-*N*-(2-methylpropyl)-3-pyridinecarboxamide (31). Compound **31** was prepared in a similar manner to **30**, using 2-methylpropylamine. ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 2.0 Hz, 1H), 8.73 (bt, 1H), 8.23 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 3.09 (t, J = 6.0 Hz, 2H), 1.84 (m, 1H), 0.89 (d, J = 6.8 Hz, 6H).

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-[(1*R*)-1,2-dimethylpropyl]-3-pyridinecarboxamide (15). 6-Chloro-[(*R*)-(−)-3-methyl-2-butyl]nicotinamide (**32**, 100 mg, 0.44 mmol), {5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}boronic acid (**26a**, 100 mg, 0.42 mmol), tetrakis(triphenylphosphine)-palladium (10 mg, 8.7×10^{-3} mmol), and aq sodium hydrogen carbonate (4 mL) were mixed in propan-2-ol (8 mL) and heated at 90 °C under nitrogen for 18 h. The solvents were evaporated from the cooled reaction under vacuum and the residue dissolved as far as possible in ethyl acetate. The solution was applied to an SCX-2 ion exchange cartridge (10 g) and the cartridge washed with ethyl acetate. The product was eluted with 0.880 ammonia/methanol and the solvents evaporated under vacuum. The residue was redissolved in ethyl acetate and filtered through a silica cartridge (0.5 g). The filtrate was reduced to dryness under vacuum and the residue triturated with diethyl ether to give the desired compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.10 (d, J = 1.0 Hz, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.43 (d, J = 8.0 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 7.76 (s, 1H), 7.72−7.68 (m, 2H), 3.88 (m, 1H), 2.86 (m, 1H), 2.26 (d, J = 1.5 Hz, 3H), 1.79 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 6H), 0.70 (m, 2H), 0.57 (m, 2H). LCMS: MH$^+$ 384, retention time 2.93 min.

6-Chloro-[(*R*)-(−)-3-methyl-2-butyl]nicotinamide (32). 6-Chloro-3-pyridinecarboxylic acid (3.0 g, 19 mmol) in thionyl chloride (8.0 mL, 110 mmol) was heated at 90 °C for 2 h. The excess thionyl chloride was removed under vacuum and the residue dissolved in DCM (30 mL). A portion (5 mL) of this mixture was treated with (*R*)-(−)-3-methyl-2-butylamine (0.50 mL), sodium carbonate (1.0 g), and DCM (5 mL). The reaction was stirred at ambient temperature overnight, filtered, and the filtrate reduced to dryness under vacuum. The residue was further dried under vacuum to give the desired product as a solid. ^{1}H NMR (DMSO-d_6) δ 8.82 (d, J = 2.5 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.24 (dd, J = 8.3 Hz, J = 2.5 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 3.83 (m, 1H), 1.76 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.89 (dd, J = 6.8 Hz, J = 2.3 Hz, 6H). LCMS: MH$^+$ 227/229, retention time 2.60 min.

{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}boronic Acid (26a). A stirred solution of *N*-cyclopropyl-3-fluoro-5-iodo-4-methylbenzamide (**23a**, 0.50 g, 1.6 mmol) in THF (20 mL) was treated with sodium hydride (60% in mineral oil, 120 mg, 3.1 mmol). The mixture was cooled to −75 °C and *n*-butyl lithium (1.6 M in hexanes, 9.8 mL, 16 mmol) added slowly maintaining the temperature below −62 °C. Triisopropylborate (4.3 mL, 19 mmol) was added dropwise over 10 min, maintaining the temperature below −65 °C, and the mixture was stirred at −75 °C for 4 h and then allowed to warm to ambient temperature overnight. The reaction was recooled to −75 °C and quenched with water (20 mL). The mixture was allowed to warm to ambient temperature and stirred for 30 min. The mixture was concentrated and the residue partitioned between ethyl acetate and saturated ammonium chloride. The aqueous phase was extracted with ethyl acetate (×2), the combined organic phases dried (sodium sulfate), and the solvent evaporated under vacuum. The residue was dissolved in ethyl acetate and the

solvent re-evaporated, and the residue was dissolved in DCM and applied to a silica column. The column was eluted with an ethyl acetate/cyclohexane gradient (50−100%) and then with methanol. Appropriate fractions were reduced to dryness under vacuum to give the desired compound (270 mg, 73%). ^{1}H NMR (MeOD) δ 7.58 (s, 1H), 7.39 (d, J = 10.6 Hz, 1H), 2.82 (m, 2H), 2.31 (s, 3H), 0.79 (m, 2H), 0.63 (m, 2H). LCMS: MH$^+$ 238, retention time 2.20 min.

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-[(1*S*)-1,2-dimethylpropyl]-3-pyridinecarboxamide (16). 6-Chloro-[(*S*)-(+)-3-methyl-2-butyl]nicotinamide (**33**, 100 mg, 0.44 mmol), {5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}boronic acid (**26a**, 100 mg, 0.42 mmol), tetrakis(triphenylphosphine)-palladium (10 mg, 8.7×10^{-3} mmol), and aq sodium hydrogen carbonate (4.0 mL) were mixed in propan-2-ol (8 mL) and heated at 90 °C under nitrogen for 18 h. The solvents were evaporated from the cooled reaction under vacuum and the residue dissolved as far as possible in ethyl acetate. The solution was applied to an SCX-2 ion exchange cartridge (10 g) and the cartridge washed with ethyl acetate. The product was eluted with 0.880 ammonia/methanol and the solvents evaporated under vacuum. The residue was redissolved in ethyl acetate and filtered through a silica cartridge (0.5 g). The filtrate was reduced to dryness under vacuum and the residue triturated with diethyl ether to give the desired compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.10 (s, 1H), 8.57 (d, J = 3.5 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 2.5 Hz, 1H), 7.76 (s, 1H), 7.72−7.68 (m, 2H), 3.88 (m, 1H), 2.86 (m, 1H), 2.26 (d, J = 1.5 Hz, 3H), 1.79 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 7.0 Hz, 6H), 0.70 (m, 2H), 0.58 (m, 2H). LCMS: MH$^+$ 384, retention time 2.93 min.

6-Chloro-[(*S*)-(+)-3-methyl-2-butyl]nicotinamide (33). Compound **33** was prepared in a similar manner to **32**, using (*S*)-(+)-3-methyl-2-butylamine. ^{1}H NMR (DMSO-d_6) δ 8.82 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 8.5 Hz, 1H), 8.24 (dd, J = 8.3 Hz, J = 2.3 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 3.83 (m, 1H), 1.75 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.89 (dd, J = 6.9 Hz, J = 2.4 Hz, 6H). LCMS: MH$^+$ 227/229, retention time 2.60 min.

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-[(1*R*)-1,2,2-trimethylpropyl]-3-pyridinecarboxamide (17). 6-Chloro-*N*-[(1*R*)-1,2,2-trimethylpropyl]-3-pyridinecarboxamide (**34**, 100 mg, 0.42 mmol), {5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}boronic acid (**26a**, 100 mg, 0.42 mmol), tetrakis(triphenylphosphine)palladium (10 mg, 8.7×10^{-3} mmol), and aq sodium hydrogen carbonate (4.0 mL) were mixed in propan-2-ol (8 mL) and heated at 90 °C under nitrogen for 18 h. The solvents were evaporated from the cooled reaction under vacuum and the residue dissolved as far as possible in ethyl acetate. The solution was applied to an SCX-2 ion exchange cartridge (10 g) and the cartridge washed with ethyl acetate. The product was eluted with 0.880 ammonia/methanol and the solvents evaporated under vacuum. The residue was redissolved in ethyl acetate and filtered through a silica cartridge (0.5 g). The filtrate was reduced to dryness under vacuum and the residue triturated with diethyl ether to give the desired compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.09 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.32−8.26 (m, 2H), 7.76 (s, 1H), 7.72−7.68 (m, 2H), 4.02 (m, 1H), 2.86 (m, 1H), 2.27 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.93 (s, 9H), 0.70 (m, 2H), 0.57 (m, 2H). LCMS: MH$^+$ 398, retention time 3.05 min.

6-Chloro-*N*-[(1*R*)-1,2,2-trimethylpropyl]-3-pyridinecarboxamide (34). Compound **34** was prepared in a similar manner to **32**, using (*R*)-3,3-dimethyl-2-butylamine. ^{1}H NMR (DMSO-d_6) δ 8.80 (d, J = 2.5 Hz, 1H), 8.26−8.21 (m, 2H), 7.63 (d, J = 8.5 Hz, 1H), 3.96 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H). LCMS: MH$^+$ 241/243, retention time 2.77 min.

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-*N*-[(1*S*)-1,2,2-trimethylpropyl]-3-pyridinecarboxamide (18). 6-Chloro-*N*-[(1*S*)-1,2,2-trimethylpropyl]-3-pyridinecarboxamide (**35**, 100 mg, 0.42 mmol), {5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}boronic acid (**26a**, 100 mg, 0.42 mmol), tetrakis(triphenylphosphine)palladium (10 mg, 8.7×10^{-3} mmol), and aq sodium hydrogen carbonate (1M, 4.0 mL) were mixed in propan-2-ol (8 mL) and heated at 90 °C under nitrogen for 18 h. The solvents were evaporated from the cooled reaction under vacuum and the residue dissolved as far as possible in ethyl acetate. The solution was applied to an SCX-2 ion exchange cartridge (10 g) and the cartridge washed with ethyl acetate. The product was eluted with 0.880 ammonia/methanol and the solvents evaporated under vacuum. The residue was redissolved in ethyl acetate and filtered through a silica cartridge (0.5 g). The filtrate was reduced to dryness under vacuum and the residue triturated with diethyl ether to give the desired compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 9.09 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 4.0 Hz, 1H), 8.32−8.26 (m, 2H), 7.76 (s, 1H), 7.72−7.68 (m, 2H), 4.02 (m, 1H), 2.86 (m, 1H), 2.27 (d, J = 1.5 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H), 0.93 (s, 9H), 0.70 (m, 2H), 0.58 (m, 2H). LCMS: MH$^+$ 398, retention time 3.05 min.

6-Chloro-*N*-[(1*S*)-1,2,2-trimethylpropyl]-3-pyridinecarboxamide (35). Compound **35** was prepared in a similar manner to **32**, using (*S*)-3,3-dimethyl-2-butylamine. ^{1}H NMR (DMSO-d_6) δ 8.80 (d, J = 2.5 Hz, 1H), 8.26−8.21 (m, 2H), 7.63 (d, J = 8.3 Hz, 1H), 3.96 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H). LCMS: MH$^+$ 241/243, retention time 2.79 min.

Protein Crystallography Method. The crystal structure of human unphosphorylated p38α with compound **11** was determined by closely following methodology previously described.[10] More specificially in this case an apo-crystal was soaked (and simultaneously cryoprotected) with compound **11** at 0.25 mM for ∼2 days in soaking buffer containing 10% glycerol prior to data collection at 100 K (using an Oxford Cryostream). The X-ray diffraction data were collected on an in-house Rigaku-MSC RuH2R rotating anode X-ray generator with a RAXIS IV++ image-plate detector. The data were processed with HKL data processing package[25] and CCP4 program suite[26] and the structure solved using the native p38 coordinates (PDB entry 1WFC) as the initial model in refinement by REFMAC.[27] The final R factor and R-free achieved for the complex were 18.1% and 24.9%, respectively and the coordinates have been deposited in the PDB as entry 3iph.

p38α Kinase Assay, Fluorescence Polarization Method. Fluorescence polarization assays used GST-tagged p38α (activated using MKK6 and repurified) and an ATP-competitive rhodamine-green labeled fluoroligand (2-(6-amino-3-imino-3*H*-xanthen-9-yl)-5-{[({4-[4-(4-Cl-3-hydroxyphenyl)-5-(4-pyridinyl)-1*H*-imidazol-2yl]phenyl}methyl)amino]carbonyl}benzoic acid). These components were dissolved in a buffer of final composition 62.5 mM Hepes, pH 7.5, 1.25 mM CHAPS, 1 mM DTT, 12.5 mM $MgCl_2$, with final concentrations of 12 nM of p38α and 5 nM fluoroligand. Then 30 μL of this mixture were added to wells containing 1 μL of test compound (0.28 nM−16.6 μM) and incubated for 30−60 min at room temperature. Fluorescence anisotropy was read in a Molecular Devices Acquest (excitation 485 nm/emission 535 nm). The Cheng−Prusoff equation (Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108), $K_i = IC_{50}(1 + ([S]/K_m))$, was used to calculate K_i from determined IC_{50} for activity assays. To calculate K_i from determined IC_{50} for fluorescence polarization assays a modification of the Cheng−Prusoff equation was used (Cheng, H. C. *Pharmacol. Res.* **2005**, *50*, 21−40). $K_i = IC_{50}(1 + ((n[E])/K_d))$ where n is the fraction of enzyme competent to bind fluoroligand. K_i values for 381 compounds in the fluorescence polarization assay correlate with those from an activity assay with $r^2 = 0.9$.

Cytokine Production in Human PBMC. PBMC were prepared from heparinized human blood from normal volunteers by centrifugation on hystopaque at 1000*g* for 30 min. The cells were collected from the interface, washed by centrifugation (1300*g*, 10 min) and resuspended in assay buffer (RPMI1640 containing 10% fetal calf serum, 1% L-glutamine, and 1% penicillin/streptomycin) at 5×10^5 cells/mL. Then 100 μL cells were added to microtiter wells containing 0.5 or 1.0 μL of an appropriately diluted compound solution. After the assay plates had been incubated for 1 h at 37 °C, 5% CO_2, 25 μL of

LPS (1 ng/mL final) was added and the samples incubated at 37 °C, 5% CO_2 for a further 20 h. The supernatant was removed and the concentrations of TNFα determined by enzyme linked immunosorbant assay (ELISA) or using a multiplex bead technology (Luminex) or antibody complex and electrochemiluminescence (Igen).

Cytokine Production in Human Whole Blood. Heparinized blood drawn from normal volunteers was dispensed (100 μL) into microtiter plate wells containing 0.5 or 1.0 μL of an appropriately diluted compound solution. After 1 h incubation at 37 °C, 5% CO_2, 25 μL of LPS solution in RPMI 1640 (containing 1% L-glutamine and 1% penicillin/streptomycin) was added (50 ng/mL final). The samples were incubated at 37 °C, 5% CO_2 for 20 h, 100−150 μL physiological saline (0.138% NaCl) was added, and diluted plasma was collected using a Platemate or Biomek FX liquid handling robot after centrifugation at 1300*g* for 10 min. Plasma TNFα content was determined by enzyme linked immunosorbant assay (ELISA) or using a multiplex bead technology (Luminex).

TNFα ELISA. Human TNFα was assayed using a commercial assay kit (AMS Biotechnology 211-90-164-40) according to the manufacturer's instructions but with TNFα calibration curves prepared using Pharmingen TNFα (cat. no. 555212).

LUMINEX Assay. First, 45 μL of luminex assay buffer (PBS/1%BSA/0.025% Triton X-100) was added to 96-well microtiter Millipore filter plates (MABVN1210) followed by 5 μL of HWB or PBMC supernatant. Then 50 μL of Luminex microspheres coated in a primary antibody against human TNFα (1×10^5 beads/mL) were added and the plates were shaken and then incubated at 4 °C overnight in the dark. Standard curves for TNFα were present on each plate (0−2000 pg/mL for TNFα). Plates were then washed under low vacuum filtration and 50 μL/well of diluted biotinylated secondary antibodies added. The plates were shaken for 1 h at room temperature, washed, and then 50 μL/well of streptavidin phycoerythrin added (Zymed 15-4301) at 0.25 μg/mL. The plates were shaken for 30 min in the dark, and after a final wash, the beads were resuspended in 120 μL of Sheath fluid (BioRad cat. no. 171-000055) and the plates read on the BioRad multiplex reader.

Data Analysis. TNFα concentrations were determined from standard curves, and IC_{50}s were generated from percent inhibition values using nonlinear least-squares curve fitting, in general with a four-parameter logistic model using Activity Base.

CYP450 Assay. The inhibition of recombinant CYP450 mediated *O*-dealkylase metabolism of pro-fluorescent probe substrates was assessed in a fluorimetric assay with the following recombinant human cytochrome P450′s coexpressed in *Escherichia coli* with human NADPH reductase (Bactosomes, CYPEX UK), CYP2C9 with the substrate 7-methoxy-4-trifluoromethylcoumarin-3-acetic acid (FCA), CYP1A2 with the substrate ethoxyresorufin (ER), CYP2D6 with the substrate 4-methylaminomethyl-7-methoxycoumarin (MMMC), CYP2C19 with the substrate 3-butyryl-7-methoxycoumarin (BMC), and CYP3A4 with the substrates 7-benzyloxyquinolone (7BQ) and diethoxyfluorescein (DEF). Compounds were incubated at a starting concentration of 5 mM in <2% MeOH. The concentration range for the IC_{50} determination assay was 0.1−100 uM (spread over nine points) and included a 0.2 mM NADPH regeneration system.

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Supporting Information Available: NMR spectrum for compound **2**, pharmacokinetic protocols for rat cassette, rat discrete, and cynomolgus monkey studies, rat PG-PS model protocol, murine CIA protocol, poster giving further information about modeling used in generation of virtual arrays. This material is available free of charge via the Internet at http://pubs.acs.org.

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