Articles

Design, Synthesis, and Anti-inflammatory Properties of Orally Active 4-(Phenylamino)-pyrrolo[2,1-*f*][1,2,4]triazine p38α Mitogen-Activated Protein Kinase Inhibitors

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A novel structural class of p38 mitogen-activated protein (MAP) kinase inhibitors consisting of substituted 4-(phenylamino)-pyrrolo[2,1-*f*][1,2,4]triazines has been discovered. An initial subdeck screen revealed that the oxindole-pyrrolo[2,1-*f*][1,2,4]triazine lead **2a** displayed potent enzyme inhibition (IC_{50} 60 nM) and was active in a cell-based TNFα biosynthesis inhibition assay (IC_{50} 210 nM). Replacement of the C4 oxindole with 2-methyl-5-*N*-methoxybenzamide aniline **9** gave a compound with superior p38 kinase inhibition (IC_{50} 10 nM) and moderately improved functional inhibition in THP-1 cells. Further replacement of the C6 ester of the pyrrolo[2,1-*f*][1,2,4]triazine with amides afforded compounds with increased potency, excellent oral bioavailability, and robust efficacy in a murine model of acute inflammation (murine LPS-TNFα). In rodent disease models of chronic inflammation, multiple compounds demonstrated significant inhibition of disease progression leading to the advancement of 2 compounds **11b** and **11j** into further preclinical and toxicological studies.

Introduction

The cytokines TNFα and IL-1β are two of the predominant pro-inflammatory mediators associated with systemic inflammatory diseases such as rheumatoid arthritis (RA).[1] The use of protein therapeutics which target these cytokines is now the standard of care for the treatment of RA.[2] Extension of these therapies into additional indications, such as psoriasis and Crohn's disease, has increased the utility of the biologic approach to inflammatory disease management. However, the limitations of protein based therapies has stimulated significant research aimed at providing small molecule, orally bioavailable, anti-TNFα and anti-IL-1β agents.

p38 Mitogen-activated protein kinase (MAPK) has emerged as an attractive target for chemotherapeutic intervention for the treatment of RA and other inflammatory disorders.[3] Activation of p38, a serine threonine kinase consisting of 4 isoforms (α,β,γ, and δ), leads to the up-regulation of both TNFα and IL-1β.[4] Additionally, small molecule p38 blockade in humans dose-dependently inhibited exogenously induced TNFα production, providing validation of the pathway in humans.[5] Expression of the p38 MAPK isoforms varies across cell types of the immune system, and it is believed that the predominant isoform involved in inflammation is p38α.[6] Currently, there are several p38α inhibitors undergoing clinical trials for the treatment of RA (Figure 1).[7]

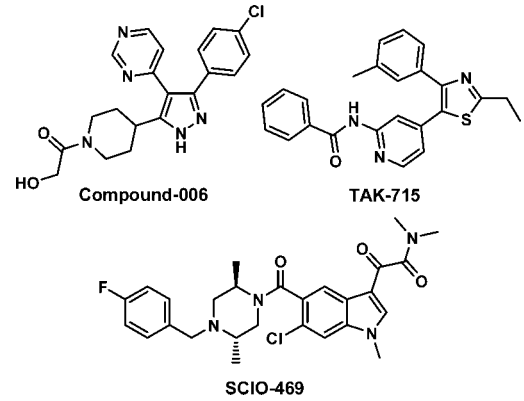

Figure 1. Examples of p38 MAPK inhibitors that have reached in-human studies.

We previously reported the in vitro and in vivo evaluation of 1,3,5-triaminotriazines (**1**, Figure 2) as p38α inhibitors.[8] Further screening of a focused deck of internal compounds revealed the pyrrolo[2,1-*f*][1,2,4]triazine oxindoles **2a** and **2b** as potent inhibitors of p38α with enzyme–inhibitory concentrations (IC_{50} values) of 60 and 80 nM, respectively. In a whole cell-based functional assay of lipopolysachharide (LPS) induced TNFα production, both compounds inhibited TNFα biosynthesis (**2a**, IC_{50} 210 nM; **2b**, IC_{50} 570 nM).

Substituted phenylaminopyrrolo[2,1-*f*][1,2,4]triazines have previously been used as a template for kinase inhibitor design,[9] and it was envisioned that analogs containing the 3-methyl-5-benzamido aniline of **1** coupled to a pyrrolo[2,1-*f*][1,2,4]triazine at C4 would provide an alternative class of p38 inhibitors. It is

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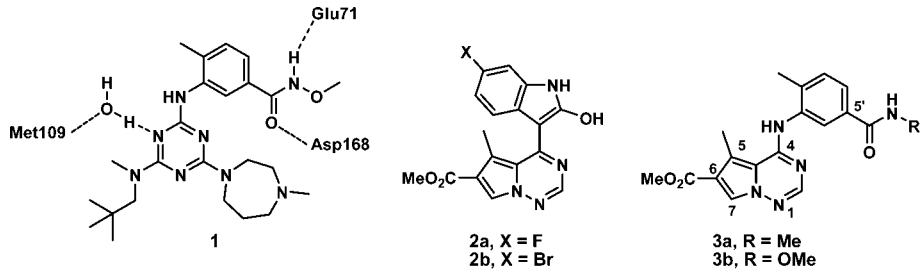


Figure 2. Discovery of the pyrrolo[2,1-*f*][1,2,4]triazine p38 inhibitors.

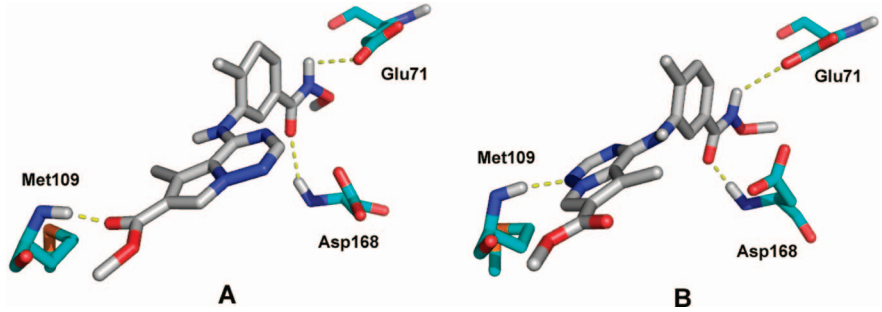


Figure 3. Proposed binding modes of **3b**.

noteworthy that the binding mode of the 1,3,5-triaminotriazine p38α inhibitors has been established via X-ray crystallography (Figure 2, compound **1** detail), revealing a hydrogen bond between Glu71 and the *N*-alkoxyamide NH (2.4 Å), in addition to a hydrogen bond between the backbone NH of Asp168 and the *N*-methoxyamide carbonyl (2.2 Å). A similar binding mode for the proposed pyrrolo[2,1-*f*][1,2,4]triazine p38α inhibitors (**3a**, **b**) can be envisioned; however, the critical Met109 interaction found in most p38α MAP kinase inhibitors is not obvious. Assuming that the aniline of **3b** binds in an identical pocket as **1**, two potential Met109 backbone hydrogen bond acceptors can be proposed: the C6 pendant carbonyl oxygen (**A**, Figure 3) or the pyrrolo[2,1-*f*][1,2,4]triazine core N1 (**B**, Figure 3). Molecular modeling suggested that both potential binding modes could be accessed with this class of inhibitors.

Compounds **3a** and **3b** were synthesized to test our initial hypothesis and were shown to inhibit p38α kinase with IC_{50} values of 220 and 1.1 nM, respectively. The more potent **3b** blocked LPS induced TNFα production with an IC_{50} of 160 nM, similar to the potency observed with the oxindole **2a**. When dosed orally in BALB/c mice at 30 mg/kg, **3b** failed to inhibit serum TNFα production following i.p. LPS administration (data not shown). The C6 ester was presumed to be a liability for in vivo efficacy, as predicted by the high rate of in vitro metabolism,[10] and efforts to stabilize this region of the molecule along with structure−activity relationship (SAR) studies aimed at increasing functional activity and oral efficacy were initiated.

Results and Discussion

Chemistry. Pyrrolo[2,1-*f*][1,2,4]triazine derivatives **3a–f**, **h**, and **i** were prepared using methods and materials previously described, as shown in Scheme 1.[11] Briefly, the 4-chloropyrrolo[2,1-*f*][1,2,4]triazines **4**, **12**, **13a**, and **13b** were reacted with various anilines to afford the C4 phenylaminopyrrolo[2,1-*f*][1,2,4]triazines (eq a and b). Additional analogs addressing the SAR at C6 were synthesized as outlined in Scheme 1. Amino-pyrrole **6** was synthesized via the electrophilic N-amination of pyrrole **5** with either *O*-(2,4-dinitrophenyl)hydroxylamine ($DnpONH_2$) or monochloramine.[12] Cyclization of **6** in refluxing formamide afforded the 3,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-4-one **7**, which was reacted with $POCl_3$ to give 4-chloropyrrolo[2,1-*f*][1,2,4]triazine **8**. Coupling with aniline **9** furnished **3g**, which was hydrolyzed to the corresponding acid **10** and converted to the amide analogs **11a–l** via standard amide bond forming conditions.

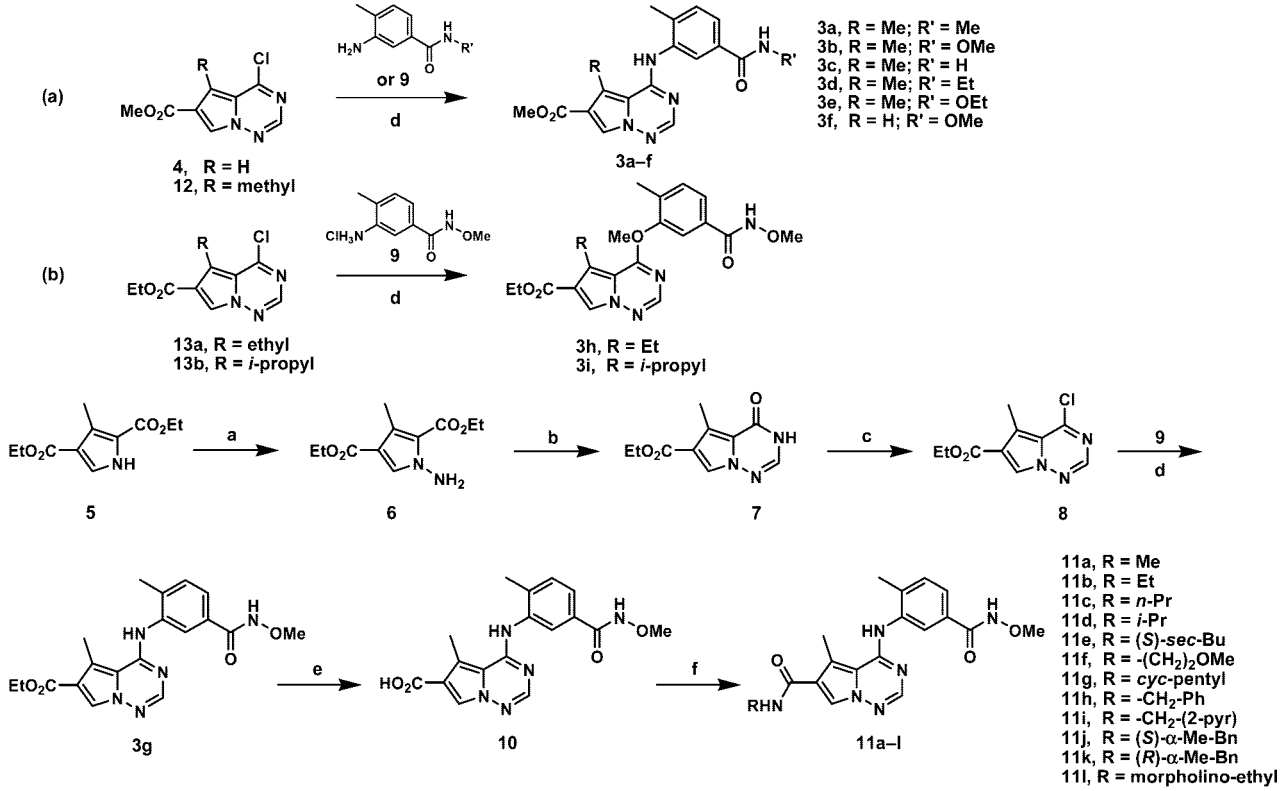
A small library of C6-aminopyrrolo[2,1-*f*][1,2,4]triazines was also prepared from acid **10** as outlined in Scheme 2. Reaction of **10** with diphenyl phosphoryl azide (DPPA) furnished the intermediate acyl azide, which was subjected to direct Curtius rearrangement in the presence of various alcohols to furnish the carbamate analogs **17a–d**. The *para*-methoxybenzyl carbamate **17d** was reacted with TFA to furnish the C6 amino analog **14**. Further reaction with acid anhydrides or ethyl isocyanate gave the reversed amides **15a–c** and urea **16**.

The synthesis of a related series, in which the C5′ carboxamide is converted to a carbamate, is outlined in Scheme 3. Reaction of chloride **8** with 3-nitro-6-methyl aniline gave **18**, which was hydrolyzed and coupled with *n*-propylamine to furnish **19**. Compound **19** was reduced to the C5′ amine **20** and reacted with chloroformates or acid chlorides to give compounds **21a–f**. Alternatively, reaction of 4-chloropyrrolotriazine **12** and ethyl 3-amino-4-methylphenylcarbamate **22** furnished the methyl ester **23**. Subsequent hydrolysis afforded **24**, which was reacted with various amines to provide the analogs **22g–i**.

In Vitro Pharmacology and SAR. Subsequent to the discovery of **3b**, the synthesized pyrrolo[2,1-*f*][1,2,4]triazine analogs were screened and optimized for inhibition of human p38α MAP kinase. Compounds with significant enzyme inhibition (IC_{50} < 50 nM) were then evaluated in a cell-based functional assay, where the inhibition of LPS induced TNFα biosynthesis in human peripheral blood mononuclear cells (PBMCs) was determined.

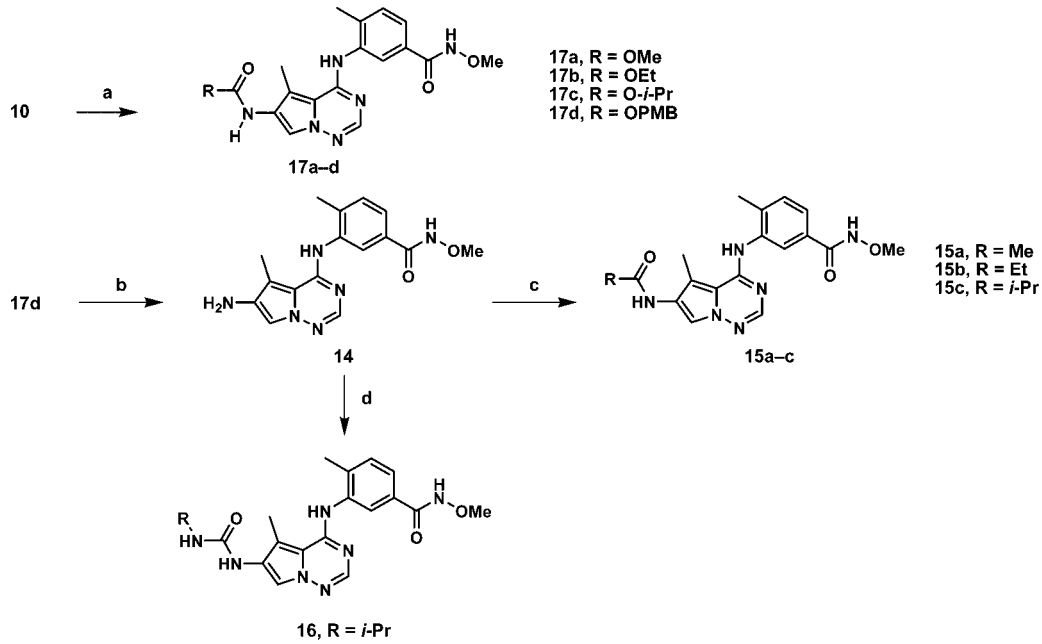
The original C4 phenylaminopyrrolo[2,1-*f*][1,2,4]triazine analogs, **3a** and **3b**, provided the framework for establishing a more potent and orally efficacious series. Table 1 summarizes the C5′ SAR at the outset of our effort. Generation of the primary amide **3c** resulted in an 80-fold decrease in p38α

Scheme 1[a]



[a] Reagents and conditions: (a) $DnpONH_2$ or NH_2Cl, NaH, DMF, 85%; (b) formamide, 165 °C, 89%; (c) $POCl_3$, 110 °C, 3 h, 94%; (d) DMF, DIPEA, 55 °C, 12−18 h; (e) 1 N NaOH, THF, 55 °C; (f) R-NH_2 or R-NH_3Cl, EDC, HOBt, DMF, DIPEA, rt.

Scheme 2[a]

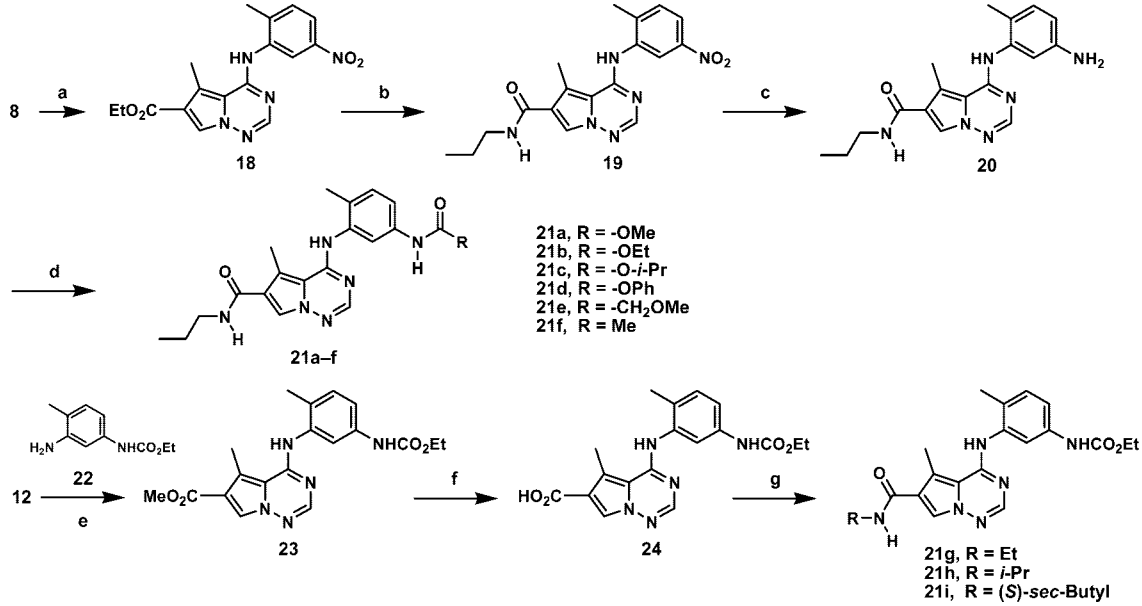


[a] Reagents and conditions: (a) (i) DPPA, TEA, dioxane, 60 °C (ii) ROH, 80 °C; (b) TFA, CH_2Cl_2, 93%; (c) $(RCO)_2O$, CH_2Cl_2, TEA; (d) R−N=C=O, CH_2Cl_2, TEA.

inhibition relative to **3b** and only a slight increase relative to methyl amide **3a**. The C5′ ethyl amide **3d** had minimal p38α inhibition whereas the *N*-ethoxyamide **3e** was slightly less potent than **3b** in both enzyme and cell-based assays.

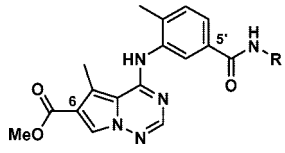
While fixing the C5′ substituent as the *N*-methoxy amide, SAR studies were initiated at C5 and C6 of the pyrrolo[2,1-*f*][1,2,4]triazine core. As shown in Table 2, removal of the C5 methyl group (**3f**) resulted in a 40-fold decrease in enzyme inhibition with a corresponding loss of functional activity relative to **3b**. Interestingly, the C6 ethyl ester **3g** was equipotent to **3b** in the enzyme inhibition assay and ∼4.5-fold more potent in the LPS−TNFα cell-based assay. This moderate increase in cellular potency suggested that larger alkyl groups or more lipophilic substitution at C6 leads to compounds with improved

Scheme 3[a]



[a] Reagents and conditions: (a) 3-nitro-6-methyl aniline, DIPEA, DMF, 55 °C, 86%; (b) (i) 1 N NaOH, THF, MeOH (ii) propyl amine, DMF, EDC, HOBt, 93%; (c) H_2, 10% Pd/C, MeOH, 95%; (d) ROC(O)Cl, CH_2Cl_2, DIPEA; (e) DMF, DIPEA, 55 °C, 81%; (f) 1 N NaOH, THF, MeOH, 65 °C; (g) RNH_2 or RNH_3Cl, EDC, HOBt, DMF DIPEA, rt.

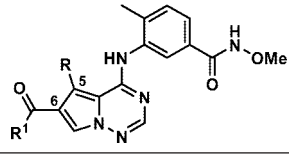
Table 1. Effect of the C5′-Substituent on Enzymatic and Cellular Activity



		IC_{50} (nM)	
cmpd	R	p38α[a]	TNFα[b]
3a	Me	220	>5000
3b	−OMe	1.1	160
3c	H	78	>2000
3d	Et	24%[c]	
3e	−OEt	4.0	380

[a] Compounds were assayed in triplicate unless otherwise noted. Variability around the mean value was <50%. [b] $n = 1$ determination. [c] Percent inhibition at 1 μM ($n = 1$).

Table 2. Effect of the C5 and C6 Substituent on Enzymatic and Cellular Activity

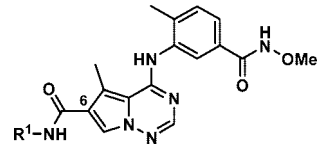


			IC_{50} (nM)	
cmpd	R	R^1	p38α[a]	TNFα[b]
3b	Me	−OMe	1.1	160
3f	H	−OMe	42	>2000
3g	Me	−OEt	0.9	37
3h	Et	−OEt	61%[c]	
3i	*i*-Pr	−OEt	63%[c]	

[a] Compounds were assayed in triplicate unless otherwise noted. Variability around the mean value was <50%. [b] $n = 1$ determination. [c] Percent inhibition at 1 μM ($n = 1$).

cellular potency. Increasing the size of the C5 substituent (**3h**, **i**) resulted in significantly decreased enzyme inhibition.

Table 3. Effect of the C6-Substituent on Enzymatic and Cellular Activity

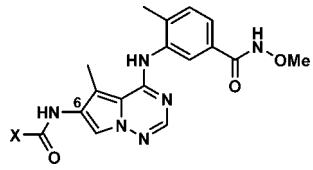


		IC_{50} (nM)	
cmpd	R^1	p38α[a]	TNFα[b]
11a	Me	23	580
11b	Et	3.1[c]	61[d]
11c	*n*-Pr	0.9	30
11d	*i*-Pr	10	41
11e	(*S*)-*sec*-Bu	3.0	<2.0
11f	$-(CH_2)_2-OMe$	2.2	140
11g	*cyc*-pentyl	8.0	43.0
11h	$-CH_2-Ph$	0.4	9.6
11i	$-CH_2-$(2-pyr)	1.2	2.4
11j	(*S*)-α-Me-benzyl	2.2	10
11k	(*R*)-α-Me-benzyl	180	>1000
11l	morpholino-ethyl	8.0	72

[a] Compounds were assayed in triplicate unless otherwise noted. Variability around the mean value was <50%. [b] Compounds were typically assayed in duplicate. Assay variability was measured using a standard control, <60%. [c] $n = 5$ determinations. [d] $n = 6$ determinations.

As stated previously, the lack of in vivo efficacy of **3b** was presumed to be due to the presence of the potentially labile C6 methyl ester and it was anticipated that the ethyl ester **3g** would encounter a similar fate upon oral dosing. Therefore, a series of C6 amides were prepared. As shown in Table 3, the C6 methyl amide **11a** was 20-fold less potent in the p38α enzyme inhibition assay relative to **3b**, whereas the ethyl amide **11b** (IC_{50} 3.1 nM) had increased p38α inhibition.[13] Additionally, **11b** was a potent inhibitor of LPS-induced TNFα release in cells (IC_{50} 61 nM). These results parallel the previous observation that increased lipophilicity at C6 increases cellular potency (e.g., **3b** to **3g**). For example, the propyl and (*S*)-*sec*-butyl amides (**11c–e**) displayed significant p38α enzyme inhibition ($IC_{50} \leq 10$ nM) and in the LPS−TNFα assay, and **11c** and

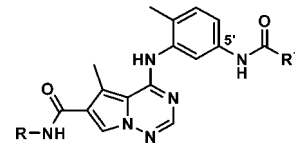
Table 4. Effect of the C6-Amino Substituent on Enzymatic and Cellular Activity



cmpd	X	IC$_{50}$ (nM) p38α[a]	IC$_{50}$ (nM) TNFα[b]
15a	Me	3.6	190
15b	Et	13	530
15c	*i*-Pr	13	120
16	−NH−*i*-Pr	12	>2000[c]
17a	−OMe	3.3	100
17b	−OEt	1.5	26
17c	−O−*i*-Pr	1.2	110

[a] Compounds were assayed in triplicate unless otherwise noted. Variability around the mean value was <50%. [b] Compounds were typically assayed in duplicate. Assay variability was measured using a standard control, <60%. [c] $n = 1$.

Table 5. Effect of the C5′-Amino Substituent on Enzymatic and Cellular Activity



cmpd	R	R^1	IC$_{50}$ (nM) p38α[a]	IC$_{50}$ (nM) TNFα[b]
21a	*n*-Pr	−OMe	15	150
21b	*n*-Pr	−OEt	5.5	69
21c	*n*-Pr	−O−*i*-Pr	680	
21d	*n*-Pr	−OPh	32%[c]	
21e	*n*-Pr	−CH_2OMe	20	43
21f	*n*-Pr	−Me	230	
21g	Et	−OEt	4.7	72
21h	*i*-Pr	−OEt	7.7	110
21i	(*S*)-*sec*-Bu	−OEt	5.6	47

[a] Compounds were assayed in triplicate unless otherwise noted. Variability around the mean value was <50%. [b] Compounds were typically assayed in duplicate. Assay variability was measured using a standard control, <60%. [c] Percent inhibition at 1 μM ($n = 1$).

11d were nearly equipotent and comparable in activity to **11b**. In the PBMC TNFα assay, **11e** was highly potent, (IC$_{50}$ < 2 nM) and represented the most active compound prepared in this series. Incorporation of an ether linkage in the C6 amide chain (**11f**) was less tolerated in the functional assay, whereas large alkyl groups (**11g**), benzyl amides (**11h**, **j**, **k**), and pyridyl amides (**11i**) were tolerated in both the biochemical and cellular assays. Interestingly, the (*R*)-α-methylbenzamide, **11k**, was shown to be 60-fold less potent in the enzyme inhibition assay and over 200-fold less active in the functional assay relative to the enantiomeric **11j**. The ability of p38α kinase to discriminate between enantiomeric pairs of small molecule inhibitors has been well established.[14] More importantly, the chiral discrimination has been associated with the orientation of the chiral group proximal to the Met109 binding site. It was therefore proposed that the C4-phenylaminopyrrolo[2,1-*f*][1,2,4]triazine based p38α MAP kinase inhibitors were binding to p38α via a hydrogen bond between the C6 amide carbonyl and the backbone NH of Met109 (Figure 3, binding mode A). This binding mode would allow for the positioning of the C6 substituent out to the enzyme protein surface exposed to the solvent (water) interface. As a further test of this binding model, C6 substituents containing a basic, solubilizing group were prepared. As seen with the morpholino ethyl amide **11l**, this substitution allows for significant p38α enzyme inhibition (IC$_{50}$ 8 nM) and reasonable functional inhibition in cells (IC$_{50}$ 72 nM).

It was anticipated that reversing the C6 carboxamide to the C6 aminopyrrolo[2,1-*f*][1,2,4]triazines would provide additional analogs containing a Met109 hydrogen bond acceptor. As shown in Table 4, the C6 reversed amide analogs (**15a**–**c**), the urea (**16**), and the carbamates (**17a**–**c**) provided an additional series with p38α enzyme inhibition SAR trends similar to those observed in Table 3. Evaluation of compounds **15a**–**c** in the LPS−TNFα PBMC assay revealed that cellular potency was significantly less than the p38α enzyme inhibition. A more pronounced disconnect between enzyme and functional inhibition was observed for **16**, presumably an indication of poor cellular permeability. Analogous to the corresponding amide SAR, the ethyl and isopropyl carbamates **17b** and **17c** had excellent enzyme inhibition and acceptable functional activity.

Having identified the C6 amide as an optimal substituent, C5′ reversed amide anilines were investigated. As shown in Table 5, small alkoxy groups (R′ = OMe, OEt) inhibited p38α kinase with moderate inhibition of LPS induced TNFα in PBMCs. Larger C5′ substitutions reduced enzyme inhibition (**21c**, **d**). Interestingly, the methoxyacetyl analog **21e** had moderate activity in both the enzyme and PBMC assays, whereas removal of the chain oxygen (**21f**) significantly decreased enzyme inhibition. The smaller C5′ ethyl carbamate present in **21b** was then used to find matched substitutions at C6. As shown in examples **21g**–**i**, significant potency enhancements relative to **21b** were not observed.

Subsequent to the recognition of the C6 amide carbonyl as the potential Met109 hydrogen bond acceptor, X-ray structures of **11b** and **11j** bound to unphosphorylated p38α were obtained confirming the proposed binding mode in addition to revealing several key binding interactions (Figure 4). As previously hypothesized, Glu71 and Asp168 form hydrogen bonds with the C5′ hydroxamate NH (1.61 Å) and carbonyl (1.77 Å), respectively, with **11j**. Additionally, the Asp168 carboxyl group forms a bridging hydrogen bond via water with N3 of the pyrrolo[2,1-*f*][1,2,4]triazine core and Lys53. As suggested by the observed SAR, Met109 forms a hydrogen bond (1.6–1.7 Å) with the pendant C6 amide carbonyl oxygen for both **11b** and **11j**. Two hydrophobic interactions are also evident from these structures. The C4 aniline occupies the typical hydrophobic pocket accessed by most reported p38α kinase inhibitors and the C6 substituent orients along a hydrophobic surface near the hinge region of the enzyme. Much of the experimentally observed SAR can be rationalized from these structures. Larger C5 substitutions (ethyl, *iso*-propyl, Table 2, **3g** and **h**) are not allowed due to disfavored steric interactions along the His107−Thr106 region surface. Additionally, the broader array of allowed substitution at C6 is due to the orientation of these substituents relative to the solvent exposed protein surface.

Kinase Selectivity Profile for Select Analogs. Advanced compounds (**11b**–**e**, **j**, **21b**) were screened against a panel of kinases (e.g., EMT, LCK, Zap70, IKK-β2, HER-1/2, PKA/C, KDR) for potential off target liabilities. The compounds tested exhibited >2000-fold selectivity for p38α against the various kinases tested, whereas these compounds were less selective against p38β (e.g., **11b** p38β IC$_{50}$ 15 nM). In a broader selectivity screen encompassing G-protein coupled receptors, ion channels and various transporters, these compounds did not demonstrate any off-target interactions when tested at 10 μM concentrations.

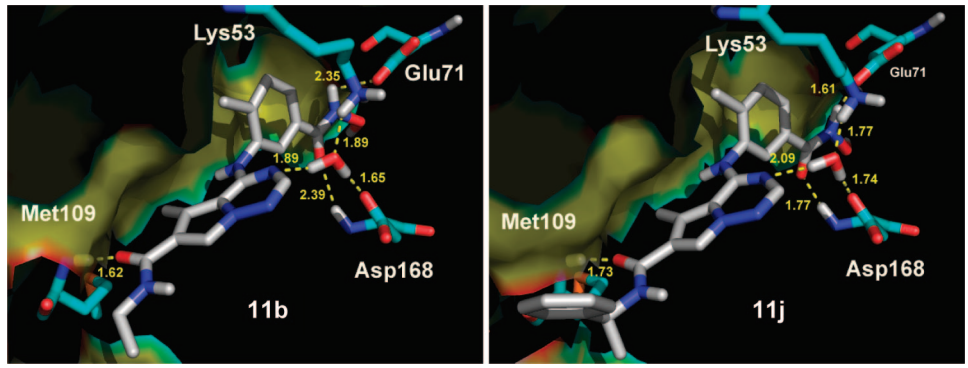


Figure 4. X-ray cocrystal structure of **11b** and **11j** with p38α.

Table 6. Inhibition of Circulating TNFα in LPS Challenged Mice

entry	cmpd	dose[a] (mg/kg)	dosing interval (min)	percent inhib[b]
1	**11b**	10	−30	80 ± 10[c]
2	**11j**	10	−30	95 ± 6
3	**11b**	2	−120	61 ± 13[d]
4	**11c**	2	−120	60 ± 23
5	**11d**	2	−120	65 ± 11
6	**11e**	2	−120	50 ± 30
7	**11i**	2	−120	62 ± 23
8	**17b**	2	−120	na[e]
9	**21b**	2	−120	66 ± 21

[a] Using PEG 300 as the vehicle, 6–8 mice per group. [b] Maximum percent inhibition relative to vehicle group; >50% inhibition is considered active in this study. Variability is expressed as ± standard error of the mean (SEM) for the individual animals in each study unless otherwise noted. [c] Average of 8 separate studies. [d] Average of 10 separate studies. [e] na = not active.

In Vivo Anti-inflammatory Efficacy and Pharmacokinetics. A murine model of acute inflammation (LPS induced serum TNFα production) was used as a primary screen of oral efficacy for advanced compounds with favorable in vitro pharmacological profiles (Table 6). A single 10 mg/kg dose of **11b** provided an 80% reduction in circulating TNFα (entry 1). Similarly, **11j** provided >90% reduction of TNFα production (entry 2). In a dose response study, **11b** demonstrated an ED_{50} of 0.3–1 mg/kg when dosed 30 min prior to LPS challenge. Extending the dosing interval prior to LPS challenge (2 vs 0.5 h), in addition to reducing the compound dose (2 vs 10 mg/kg) provided a reasonable (61%, entry 3) reduction in serum TNFα levels using **11b**. Other analogs were then screened under these conditions. As shown in Table 6, additional C6 amides (entries 4–7) exhibited similar efficacy to **11b**. The C6 ethyl carbamate **17b** (entry 8) was not efficacious in this model, whereas the C5′ ethyl carbamate **21b** (entry 9) was highly efficacious.

Prior to evaluation in a chronic RA disease model, several C6 amido pyrrolo[2,1-*f*][1,2,4]triazine p38α inhibitors were evaluated in 4 h of oral exposure studies in rats. As shown in Table 7, moderate to high levels of systemic drug exposure was observed for compounds of similar (**11b**, **c**) and varying (**11d**–**11j**) C6 substitution. A partial explanation for the reduced exposure at 0.5 h of **11b** is the lower intrinsic permeability of **11b** relative to other compounds as measured in a Caco-2 permeability assay (20 nm/s for **11b** vs 58 nm/s for **11c** and 131 nm/s for **11j**). The C5′ carbamate **21b** had reduced drug exposure relative to the C6 amide analogs and was not evaluated further. Incubation of several analogs in rat and human liver microsomes indicated that low (rat) to moderate (human) levels of parent drug would be metabolized in the liver.

The rat adjuvant induced arthritis (RAA) disease model was then incorporated into the compound efficacy evaluation paradigm. Accordingly, compounds were evaluated at 10 mg/kg, bid, in this disease model (Figure 5). Interestingly, compounds

Table 7. Rat Exposure Data Following Oral Administration (10 mg/kg) of Select Compounds[a]

cmpd	plasma level (0.5 h, μM)[b]	AUC[c] (μM·h)	RLM[d]	HLM[e]
11b	0.8	0.7	100	69
11c	6.6	2.1	82	83
11d	3.8	3.7		
11e	4.3	9.2	96	62
11i	3.4	2.8		
11j	2.1	2.1	90	72
21b	0.4	0.7		

[a] Vehicle: 9/0.5/0.5 water/EtOH/Tween 80. [b] Average of 2 rats. [c] $AUC_{0\text{-}4h}$, average of 2 rats. [d] Rat liver microsome incubation, percent remaining of parent drug at 10 min, ($n = 1$). [e] Human liver microsome incubation, percent remaining of parent drug at 10 min, ($n = 1$).

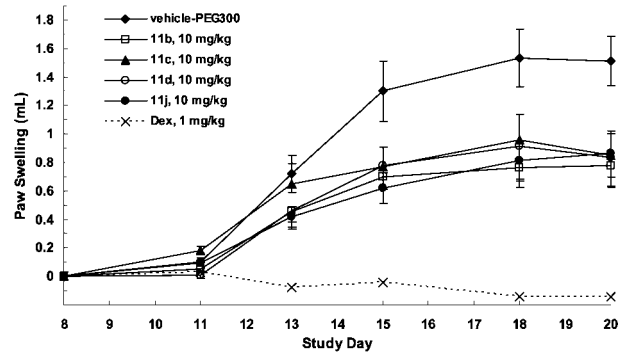


Figure 5. Efficacy in the rat adjuvant arthritis model (6–8 mice per group). Terminal paw measurements (mean ± SEM) were as follows: **11b**, 0.78 ± 0.15 mL; **11c**, 0.85 ± 0.0.15 mL; **11d**, 0.83 ± 0.20 mL; **11j**, 0.86 ± 0.16 mL; vehicle, 1.5 ± 0.17 mL.

11b, **c**, **d**, and **j** inhibited disease progression equally in this model and the statistical significance between compounds was not observed. Compounds **11e** and **11i** were not efficacious in this model.

Subsequently, a discrete pharmacokinetic analysis in mice of **11b**, **11c**, and **11j** was performed in an effort to further differentiate these advanced compounds and as a precursor to chronic studies in mice (Table 8). All compounds had good to excellent oral bioavailability and drug exposure over the time course of the study. Moderate to high clearance was observed for all compounds tested.

C6 amido pyrrolo[2,1-*f*][1,2,4]triazine analogs **11b**, **11c**, and **11j** were then evaluated in the mouse collagen induced arthritis (mCIA) disease model. As can be seen in Figure 6, **11b** provided significant reduction in the measured outcome of disease progression relative to the vehicle group when dosed orally at 3 mg/kg, bid (49% reduction). Compound **11c** demonstrated reduced efficacy relative to **11b** in the mouse CIA model at an

Table 8. Discrete Pharmacokinetic Properties of Compounds 11b, 11c, and 11j in Mice[a]

PK parameter	11b	11c	11j
% F_{po}	79	97	34
C_{max} (μM)[b]	3.1 ±0.6	18 ±1.9	3.7±1.8
T_{max} (h)	0.25	0.25	0.5
$t_{1/2}$ (h)	2.2	2.5	1.2
MRT (h)	1.4	1.0	0.8
CL (mL/min/kg)	93	28	31
V_{SS} (L/kg)	7.6	1.6	1.5
AUC_{0-8h} (μM·h)	3.6	13	3.8

[a] Vehicle: 9/0.5/0.5 water/EtOH/Tween 80; dose 5 mg/kg i.v., 10 mg/kg p.o.; 3 mice per group. [b] Average ± SEM.

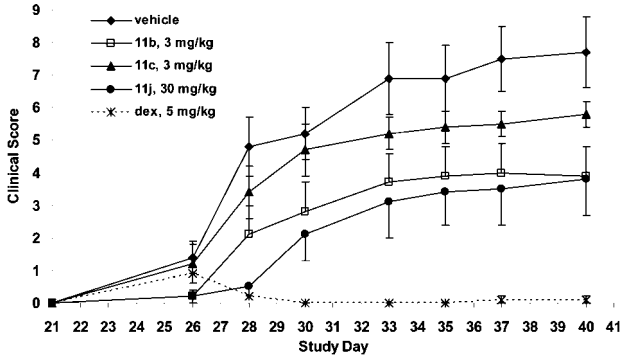


Figure 6. Efficacy in mouse collagen induced arthritis (6–8 mice per group). Compounds **11b** and **11j** achieved statistically significant reduction in clinical score ($p < 0.05$, Kruskall-Wallis test) vs vehicle (PEG300 or Tween80/EtOH/water 90/5/5). Compound **11b** was dosed as the monomethanesulfonic acid salt; **11c** was dosed as the mono-bisulfate salt; **11j** was dosed as the monohydrochloride salt. All doses were adjusted to the free base equivalent. The study is inclusive of two separate experiments in which the vehicle and dexamethazone controls were nearly identical.

equivalent dose (3 mg/kg, 29% reduction) which was not statistically significant relative to the vehicle control. Compound **11j** provided 54% reduction in the measured clinical score albeit at 30 mg/kg, bid.

Conclusions

A focused screening effort identified the oxindole-pyrrolo[2,1-*f*][1,2,4]triazines (**2a**, **b**) as novel p38 MAPK inhibitors. Replacement of the C4 oxindole with a substituted aniline yielded potent p38α inhibitors. The C5′ alkoxy amide substitution was found to be important for achieving significant enzyme inhibition and whole cell functional activity. SAR studies at C6—which included a survey of amide-, reversed amide-, urea-, and carbamate-linked pyrrolo[2,1-*f*][1,2,4]triazines—led to compounds with oral efficacy in multiple rodent models of inflammation. The combined in vitro pharmacology, in vivo efficacy, and suitable pharmacokinetics of **11b** and **11j** resulted in the selection of both compounds for advanced preclinical studies in higher species. As will be described separately,[15] the results of these studies prompted the nomination of amide **11b** as a candidate for clinical development.

Experimental Section

Chemistry. All nonaqueous reactions were carried out under an argon or nitrogen atmosphere at room temperature, unless otherwise noted. All commercial reagents and anhydrous solvents were purchased from Aldrich and were used without further purification or distillation, unless otherwise stated. Analytical thin layer chromatography (tlc) was performed on EM Science silica gel 60 F_{254} (0.25 mm). Compounds were visualized by UV light and/or stained with either *p*-anisaldehyde, potassium permanganate, or cerium molybdate solutions followed by heating. Flash column chromatography was performed on EM Science silica gel 60 (particle size of 40−63 μm). Analytical high pressure liquid chromatography (HPLC) and LC-MS analyses were conducted using Shimadzu LC-10AS pumps and a SPD-10AV UV–vis detector set at 220 nm with the MS detection performed with a Micromass Platform LC spectrometer. Analytical HPLC analyses were performed using one of the following conditions: (column A) YMC S5 ODS, 4.6 × 50 mm, 4 min gradient, 10% MeOH/water/0.2% H_3PO_4 to 90% MeOH/water/0.2% H_3PO_4, 4 mL/min flow rate; (column B) Chromalith Speedrod, 4.6 × 50 mm, 4 min gradient, 10% MeOH/water/0.2% H_3PO_4 to 90% MeOH/water/0.2% H_3PO_4, 4 mL/min flow rate; (column C) YMC S5 ODS, 4.6 × 50 mm, 4 min gradient, 10% MeOH/water/0.1% TFA to 90% MeOH/water/0.1% TFA, 4 mL/min flow rate; or (column D) Phenomenex Phenom-Prime, 4.6 × 30 mm, 2 min gradient, 10% MeOH/water/0.1% TFA to 90% MeOH/water/0.1% TFA, 4 mL/min flow rate. Preparative reverse phase (RP) HPLC was performed using two Shimadzu LC-8A pumps, a SPD-10AV UV–vis detector set at 220 nm, and a YMC C18 ODS-A 5 μm, 20 × 100 mm column (eluting at 20 mL/min with a 12 min gradient of 0–100% B where solvent A = 10% MeOH/90% H_2O/0.1% TFA and solvent B = 90% MeOH/10% H_2O/0.1% TFA).

NMR (^{1}H and ^{13}C) spectra were recorded on one of the following instruments: JEOL GSX-500 MHz, or Bruker ARX-400 MHz spectrometers and calibrated using an internal reference. High-resolution mass spectra (HMRS) were recorded on a JEOL SX102 mass spectrometer. Elemental analyses were performed by Robertson Microlit Laboratories, and the results obtained are within ±0.4% of the theoretical values.

Methyl 4-(2-methyl-5-(methylcarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3a). Representative Procedure for the Preparation of an *m*-Amino-*N*-substituted Benzamide Intermediate and Subsequent Coupling To Methyl 4-Chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate. To a solution of 3-nitro-4-methyl benzoyl chloride (19.9 g, 100 mmol) in CH_2Cl_2 (115 mL) at 0 °C was added methylamine (100 mmol, 100 mL, 2 M in THF), and the reaction mixture was allowed to warm to room temperature. Stirring was continued for 1 h, and then, a second aliquot of methylamine was added (20 mL, 20 mmol) and the reaction mixture was allowed to stir overnight. The volatile solvents were removed on a rotovap, and the residue was suspended in ethanol (100 mL) and treated with NaOH (0.1 N, 200 mL) to quench the remaining acid halide. The reaction mixture was neutralized with 1 N HCl, and the volatile solvents were removed on a rotovap. Additional water (200 mL) was added, and the resulting solids were stirred rapidly for 2 h and then filtered and rinsed with water to give methyl 3-nitro-4-methyl benzamide (17.2 g, 89% yield).

To a solution of methyl 3-nitro-4-methyl benzamide (6.0 g, 30.9 mmol) in EtOH (150 mL) was added 10% Pd-C (380 mg, wet), and the reaction placed under a H_2 atmosphere (43 psi) on a Parr shaker for 3 h. The reaction solution was filtered through celite. This step was repeated on an additional 6 g, and the filtrates were combined and concentrated in vacuo. EtOH (150 mL) was added to slurry the solids, and concentrated HCl (5.4 mL, 65 mmol) was added dropwise; the slurry was then stirred overnight. The slurry was then cooled to ∼5 °C, and the solids were collected by filtration to give methyl 3-amino-4-methyl benzamide hydrochloride (9.52 g, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (br s, 2H), 8.40 (s, 1H), 7.68 (s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 2.64 (d, J= 4.4 Hz, 3H), 2.25 (s, 3H); Anal. RP-HPLC t_R = 0.23 min (column A, purity 99.5%); MS (ESI) m/z 165.10 $(M + H)^+$.

To a solution of methyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4] triazine-6-carboxylate **12** (13.4 mg, 0.059 mmol) in DMF (0.25 mL) was added methyl 3-amino-4-methyl benzamide (9.8 mg, 0.59 mmol), and the reaction mixture stirred at room temperature for 18 h. The solution was filtered, and the filtrate was dissolved in

MeOH and purified by preparative HPLC to afford **3a** (10.3 mg, 37% yield, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.95 (s, 1H), 7.72 (s, 2H), 7.45 (m, 1H), 3.89 (s, 3H), 2.92 (s, 6H), 2.36 (s, 3H); Anal. RP-HPLC t_R = 3.17 min (column A, purity 99.4%); HRMS for $C_{18}H_{19}N_5O_3$, $(M + H)^+$ calcd 354.1566, found 354.1572.

***N*-Methoxy-3-amino-4-methyl benzamide hydrochloride (9).** A mixture of commercially available 3-amino-4-methylbenzoic acid (100 g, 0.66 mol) and *N*-(*tert*-butoxycarbonyl)anhydride (150 g, 0.68 mol) in THF (1000 mL) was slowly heated to 50 °C overnight. The resulting mixture was cooled to rt, and the solvent was removed on a rotary evaporator. The resulting solids were triturated with hexanes and dried in vacuo to afford 151 g (91%) of the crude BOC-protected aniline as a light pink solid.

To the above solid was added EDC (127 g, 0.66 mol), HOBt (90 g, 0.66 mol), and DMF (1000 mL), and the resulting mixture was stirred at rt for 30 min followed by addition of methoxyamine hydrochloride (55 g, 0.66 mol). After stirring for 10 min, the mixture was cooled using an ice bath. DIPEA (250 mL, 1.4 mol) was added at such a rate so as to maintain the internal reaction temperature below 25 °C. After the addition was complete, the ice bath was removed and the reaction was stirred overnight at rt. The reaction mixture was partitioned between 0.5 L of water and 1.5 L of EtOAc, and the resulting layers were separated. The aqueous portion was extracted with additional EtOAc (3 × 400 mL), and the combined organic extracts were washed with water (3 × 300 mL), cold 0.5 N aqueous HCl (2 × 400 mL), and water (500 mL). The product was then extracted with cold 0.5 N aqueous NaOH (3 × 300 mL), and the combined basic aqueous extracts were neutralized to pH = 8 by a slow addition of cold 0.5 N aqueous HCl. The resulting solid which precipitated was collected by filtration and washed with cold water. The wet solid was decolorized in hot EtOH with activated charcoal to give 106 g of white solid as the BOC-protected *N*-methoxyamide intermediate.

To a slurry of the above solid (91 g, 0.32 mol) in 1,4-dioxane (400 mL) at rt was added a 4 M solution of HCl in dioxane (400 mL), and the resulting mixture was stirred at rt overnight. Diethyl ether (1000 mL) was added, and the precipitated solid was collected by filtration and triturated with a hot EtOH/H_2O mixture (4:1 v/v). Drying the resulting solid in vacuo afforded *N*-methoxy-3-amino-4-methyl benzamide hydrochloride **9** (53 g, 76% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (br s, 1H), 9.00 (br s, 2H), 7.59 (s, 1H), 7.41 (br d, 1H), 7.30 (br d, 1H), 3.70 (s, 3H), 2.31 (s, 3H); Anal. RP-HPLC t_R = 0.36 min (column A, purity 99.5%).

Methyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3b). This compound was prepared according to the procedure outlined as in **3a** from *N*-methoxy-3-amino-4-methyl benzamide hydrochloride **9**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 7.82 (s, 1H), 7.68 (m, 2H), 7.45 (m, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.91 (s, 6H), 2.35 (s, 3H); Anal. RP-HPLC t_R = 3.20 min (column A, purity 98.7%); HRMS for $C_{18}H_{19}N_5O_4$, $(M + H)^+$ calcd 370.1515, found 370.1510.

Methyl 4-(2-methyl-5-carbamoyl-phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3c). This compound was prepared according to the procedure outlined as in **3a** from commercially available 3-amino-4-methylbenzamide. ^{1}H NMR (500 MHz, CD_3OD) δ 7.90 (br s, 1H), 7.71 (m, 2H), 7.42 (m, 2H), 3.86 (s, 3H), 2.87 (s, 3H), 2.31 (s, 3H); Anal. RP-HPLC t_R = 3.06 min (column A, purity 97.4%); HRMS for $C_{17}H_{17}N_5O_3$, $(M + H)^+$ calcd 340.1410, found 340.1405.

Methyl 4-(2-methyl-5-(ethylcarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3d). This compound was prepared according to the procedure outlined as in **3a** starting with ethyl 3-amino-4-methylbenzamide.[16] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.92 (s, 1H), 7.83 (br s, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 3.81 (s, 3H), 3.40 (dq, J = 7.1 Hz, 2H), 2.87 (s, 3H), 2.30 (s, 3H), 1.18 (m, 3H); Anal. RP-HPLC t_R = 3.31 min (column A, purity 98.1%); HRMS for $C_{19}H_{21}N_5O_3$, $(M + H)^+$ calcd 368.1723, found 368.1725.

Methyl 4-(2-methyl-5-(ethoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3e). This compound was prepared according to the procedure outlined as in **3a** from *N*-ethoxy-3-amino-4-methylbenzamide. ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (s, 1H), 7.80 (s, 1H), 7.62 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 3.91 (t, J = 7.1 Hz, 2H), 3.76 (s, 3H), 2.80 (s, 3H), 2.24 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H); Anal. RP-HPLC t_R = 3.30 min (column A, purity 97.2%, 254 nm); HRMS for $C_{19}H_{21}N_5O_4$, $(M + H)^+$ calcd 384.1672, found 384.1675.

Methyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3f). This compound was prepared using the general coupling procedure using **9** and methyl 4-chloro-pyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate **4**.[17] ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, J = 1.4 Hz, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.28 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 2.23 (s, 3H); Anal. RP-HPLC t_R = 2.97 min (column A, purity 95.0%); HRMS for $C_{17}H_{17}N_5O_4$, $(M + H)^+$ calcd 356.1359, found 356.1375.

Ethyl 4-oxo-5-methyl-1,4-dihydropyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (7). A solution of the amino pyrrole **6** (51.0 g, 212 mmol) in formamide (400 mL) was heated at 120 °C for 20 h. The reaction mixture was cooled and then poured into a rapidly stirring solution of ice−water (2 L) to precipitate the product. The solids were collected by filtration and washed with water (2 × 50 mL) and ether (150 mL) to furnish **7** (41.6 g, 89% yield) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 7.89 (s, 1H), 7.85 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz) δ 163.8, 155.5, 140.4, 123.7, 123.2, 118.1, 114.4, 60.0, 14.6, 11.4; Anal. RP-HPLC t_R = 3.19 min (column A, purity 99%); HRMS for $C_{10}H_{11}N_3O_3$, $(M + H)^+$ calcd 222.0879, found 222.0876.

Ethyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (8). A solution of **7** (41.8 g, 189 mmol) in $POCl_3$ (400 mL) was heated at 100 °C for 20 h. The reaction mixture was cooled, diluted with dichloromethane (200 mL), poured into ice-cold sat. aqueous $NaHCO_3$-dichloromethane (1500−500 mL), and stirred rapidly to ensure quenching of the excess $POCl_3$. The solution was filtered through celite, the layers were separated, and the aqueous layer was extracted with dichloromethane (500 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford **8** (42.4 g, 94% yield) as a tan yellow solid which was used without further purification.

Ethyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3g). To a solution of **9** (41.2 g, 190 mmol) in DMF (230 mL) was added DIPEA (33.1 mL, 180.7 mmol, 0.95 equiv), and the reaction vessel was heated to 55 °C. Solid ethyl 4-chloro-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (**8**) (45.6 g, 190 mmol) was added in several portions over 10 min, and the flask was rinsed with DMF (150 mL) and added to the reaction. The reaction was heated for 10 h at 55 °C and cooled to rt. The mixture was then poured into 1.5 L water diluted to 2.2 L with ice slowly over 10 min. The pH was adjusted to 6, and the solids were stirred for 1 h. The solids were filtered, washed with water (2 × 200 mL), and dried on the filter to give 71.9 g of the crude ester. The solid was then suspended in MeCN (450 mL) and heated with stirring (rotovap) at 50 °C for 1 h. The mixture was cooled and filtered to give 64.2 g product (>99% purity). These solids were then dissolved in hot ethanol (2.8 L), and decolorizing carbon was added (6.4 g) and heated at reflux for 15 min. The mixture was then filtered through a pad of celite, and the reaction flask was rinsed with hot ethanol (1 L). The solution was then concentrated to ~1 L of ethanol by distillation upon which the product started to crystallize out of solution at a volume of 2.5 L. The solution was cooled and placed in a cold room with stirring for 40 h. The solids were filtered and rinsed with 1/1 EtOH/Et_2O (500 mL) to give **3g** (58.5 g, 80% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, rotameric) δ 9.55 (br s, 1H), 8.09 (br s, 1H), 7.93 (s, 2H), 7.82 (s, 1H), 7.44 (m, 1H), 7.22 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 2.88 (s, 3H), 2.29 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); Anal. RP-HPLC t_R =

3.51 min (column A, purity 96.1%); HRMS for $C_{19}H_{21}N_5O_4$, $(M + H)^+$ calcd 384.1671, found 384.1672; Anal. calcd C, 59.52; H, 5.52; N, 18.26; found C, 59.44; H, 5.61; N, 18.19.

Ethyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-ethylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3h). This compound was prepared using the general coupling procedure from **9** and ethyl 4-chloro-5-ethylpyrrolo[2,1-f][1,2,4]triazine-6-carboxylate **13a**.[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.34 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.54 (d, $J = 7.1$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.20 (s, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 3.89 (s, 3H), 3.32 (q, $J = 7.7$ Hz, 2H), 2.93 (s, 3H), 1.40 (m, 6H); Anal. RP-HPLC t_R = 3.72 min (column A, purity 96.6%); HRMS for $C_{20}H_{23}N_5O_4$, $(M + H)^+$ calcd 398.1824, found 398.1822.

Ethyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-*iso*-propylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (3i). This compound was prepared using the general coupling procedure from **9** and ethyl 4-chloro-5-iso-propylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate **13b**.[18] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (br s, 2H), 7.82 (s, 1H), 7.45 (br s, 2H), 7.27 (m, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 3.81 (s, 3H), 1.97 (s, 3H), 1.50 (d, $J = 6.6$ Hz, 6H), 1.33 (t, $J = 7.2$ Hz, 3H); Anal. RP-HPLC t_R = 3.96 min (column A, purity 91.3%); HRMS for $C_{21}H_{25}N_5O_4$, $(M + H)^+$ calcd 412.1985, found 412.1995.

4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (10). To a suspension of **3g** (10.5 g, 27.8 mmol) in THF (110 mL) was added 1N NaOH (110 mL, 110 mmol), and the reaction vessel was heated at 55 °C for 16 h. The reaction mixture was cooled, filtered through a medium porosity fritted funnel, and concentrated to remove the THF. 1 N HCl was added to adjust the pH to ~5–6, and the crude acid was stirred for several hours and then filtered. The solids were washed with water (2 × 200 mL) and then IPA/Et_2O (1/1, 200 mL) and dried to give the crude acid which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6, rotameric) δ 12.5 (br s, 1H), 11.68 (m, 1H), 8.79 (s, 1H), 7.20–8.05 (m, 5H), 3.69 (s, 3H), 2.84 (s, 3H), 2.25 (s, 3H); Anal. RP-HPLC t_R = 2.72 min (column A, purity 98.2%); HRMS for $C_{17}H_{17}N_5O_4$, $(M + H)^+$ calcd 356.1359, found 356.1349.

***N*-Methyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (11a).** To a solution of **10** (40 mg, 0.11 mmol), HOBt (19 mg, 0.12 mmol), EDC (24 mg, 0.12 mmol), and methylamine hydrochloride (15 mg, 0.22 mmol) in DMF was added DIPEA (0.069 mL, 0.39 mmol), and the solution was stirred for 2 h. The reaction was concentrated and purified via preparative HPLC to furnish **11a** (40 mg, 74% yield, TFA salt) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (br s, 1H), 8.75 (br s, 1H), 7.38–8.05 (m, 6H), 3.70 (s, 3H), 2.79 (s, 3H), 2.75 (s, 3H), 2.22 (s, 3H); Anal. RP-HPLC t_R = 2.31 min (column A, purity 92.1%); HRMS for $C_{18}H_{20}N_6O_3$, $(M + H)^+$ calcd 369.1675, found 369.1682.

***N*-Ethyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (11b). Representative Procedure for the Preparation of the C6 Amides 11b–11l.** A solution of **10** (49 g, 139 mmol), HOBt (20.5 g, 152 mmol), EDC (29.2 g, 152 mmol), and ethylamine hydrochloride (22.6 g, 277 mmol) in DMF (225 mL) was stirred for 30 min. DIPEA (48.2 mL, 277 mmol) was added, and the mixture was stirred for 8 h. Water was added (1.35 L), and the mixture was stirred overnight to precipitate the product. The solids were filtered, washed with water (2 × 200 mL), and dried on a filter to give a tan solid which was slurried in hot EtOH (200 mL), cooled, and filtered to give the crude amide. A total of 63.3 g of the above crude solids were dissolved in hot ethanol/water (7/1, 1.7 L), decolorizing carbon was added, and the mixture was heated at reflux for 15 min. The mixture was then filtered through a pad of celite, and the reaction flask was rinsed with hot ethanol (2 × 200 mL). The solution was cooled slowly and allowed to stir overnight. The vessel was then cooled in an ice bath for 3 h, and the solids were filtered and rinsed with ice cold ethanol (100 mL) and water (200 mL) to give 47.5g of **11b** (77% recovery) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (m, 2H), 7.72 (s, 1H), 7.65 (app d, $J = 6.9$ Hz, 1H), 7.45 (d, $J = 7.5$ Hz, 1H), 3.83 (s, 3H), 3.41 (q, $J = 7.2$ Hz, 2H), 2.86 (s, 3H), 2.36 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); Anal. RP-HPLC t_R = 2.57 min (column A, purity 99.2%); HRMS for $C_{19}H_{22}N_3O_6$, $(M + H)^+$ calcd 383.1832, found 383.1829; Anal. Calcd C, 59.67; H, 5.79; N, 21.97; found: C, 59.42; H, 5.83; N, 22.00.

***N*-*n*-Propyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (11c).** ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 7.78 (m, 3H), 7.54 (d, $J = 6.6$ Hz, 1H), 3.72 (s, 3H), 3.24 (m, 2H), 2.82 (s, 3H), 2.33 (s, 3H), 1.57 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H); Anal. RP-HPLC t_R = 2.88 min (column A, purity 95.2%); HRMS for $C_{20}H_{24}N_6O_3$, $(M + H)^+$ calcd 397.1988, found 397.1995.

***N*-*iso*-Propyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (11d).** ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (s, 1H), 7.77 (s, 1H), 7.62 (m, 2H), 7.41 (d, $J = 8.0$ Hz, 1H), 4.10 (m, 1H), 3.71 (s, 3H), 2.76 (s, 3H), 2.27 (s, 3H), 1.16 (d, $J = 6.6$ Hz, 6H); Anal. RP-HPLC t_R = 2.77 min (column A, purity 97.5%); HRMS for $C_{20}H_{24}N_6O_3$, $(M + H)^+$ calcd 397.1988, found 397.1987.

***N*-(*S*)-*sec*-Butyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11e).** ^{1}H NMR (400 MHz, CD_3OD, rotameric) δ 8.08 (m, 1H), 7.88 (m, 1H), 7.73 (m, 2H), 7.53 (m, 1H), 4.05 (m, 1H), 3.83 (s, 3H), 2.88 (s, 3H), 2.35 (s, 3H), 1.61 (m, 2H), 1.25 (m, 3H), 1.01 (m, 3H); Anal. RP-HPLC t_R = 3.05 min (column A, purity 99.4%); HRMS for $C_{21}H_{26}N_6O_3$, $(M + H)^+$ calcd 411.2145, found 411.2161.

***N*-(2-Methoxyethyl)-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11f).** ^{1}H NMR (500 MHz, CD_3OD, TFA salt) δ 7.93 (s, 1H), 7.82 (br s, 1H), 7.62 (m, 2H), 7.42 (d, $J = 7.7$ Hz, 1H), 3.80 (s, 3H), 3.56 (app dd, $J = 14.3$, 2.7 Hz, 4H), 3.39 (s, 3H), 2.83 (s, 3H), 2.32 (s, 3H); Anal. RP-HPLC t_R = 2.09 min (column A, purity 96.4%); HRMS for $C_{20}H_{24}N_6O_4$, $(M + H)^+$ calcd 413.1937, found 413.1926.

***N*-Cyclopentyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11g).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.37 (s, 1H), 7.88 (s, 3H), 7.69 (s, 1H), 7.52 (m, 1H), 7.30 (m, 1H), 7.22 (s, 1H), 5.92 (d, $J = 7.1$ Hz, 1H), 4.39 (q, $J = 7.0$ Hz, 1H), 3.90 (s, 3H), 2.86 (s, 3H), 2.37 (s, 3H), 2.10 (m, 2H), 1.74 (m, 2H), 1.51 (m, 2H); Anal. RP-HPLC t_R = 3.15 min (column A, purity 98%); HRMS for $C_{22}H_{26}N_6O_3$, $(M + H)^+$ calcd 423.2145, found 423.2154.

***N*-Benzyl-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11h).** ^{1}H NMR (500 MHz, CD_3OD, TFA salt) δ 7.99 (m, 1H), 7.91 (m, 1H), 7.36 (m, 7H), 7.23 (m, 1H), 4.55 (s, 2H), 3.80 (s, 3H), 2.85 (s, 3H), 2.33 (s, 3H); Anal. RP-HPLC t_R = 2.85 min (column A, purity 98.6%); HRMS for $C_{24}H_{24}N_6O_3$, $(M + H)^+$ calcd 445.1988, found 445.1981.

***N*-(Pyridin-2-ylmethyl)-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11i).** ^{1}H NMR (500 MHz, CD_3OD) δ 8.49 (d, $J = 4.4$ Hz, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.83 (m, 1H), 7.72 (s, 1H), 7.65 (m, 1H), 7.47 (m, 2H), 7.33 (m, 1H), 4.67 (s, 2H), 3.80 (s, 3H), 2.86 (s, 3H), 2.34 (s, 3H); Anal. RP-HPLC t_R = 1.58 min (column A, purity 92.4%); HRMS for $C_{23}H_{23}N_7O_3$, $(M + H)^+$ calcd 446.1941, found 446.1933.

***N*-((*S*)-1-Phenylethyl)-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11j).** ^{1}H NMR (500 MHz, CD_3OD) δ 8.02 (br s, 1H), 7.41 (s, 1H), 7.70 (s, 1H), 7.62 (m, 1H), 7.40 (m, 2H), 7.33 (t, $J = 7.7$ Hz, 2H), 7.22 (t, $J = 7.2$ Hz, 1H), 5.21 (q, $J = 7.6$ Hz, 1H), 3.79 (s, 3H), 2.80 (s, 3H), 2.32 (s, 3H), 1.55 (d, $J = 7.2$ Hz, 3H); Anal. RP-HPLC t_R = 2.95 min (column A, purity 99.8%); HRMS for $C_{25}H_{26}N_6O_3$, $(M + H)^+$ calcd 459.2145, found 459.2139.

***N*-((*R*)-1-Phenylethyl)-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11k).** ^{1}H NMR (500 MHz, CD_3OD, TFA salt) δ 8.06 (br s, 1H), 7.84 (s, 1H), 7.65 (m, 2H), 7.44 (d, $J = 7.7$ Hz, 1H), 7.41 (m, 2H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 1H), 5.22, (q,

$J = 7.2$ Hz, 1H), 3.79 (s, 3H), 2.81 (s, 3H), 2.35 (s, 3H), 1.55 (d, $J = 7.2$ Hz, 3H); Anal. RP-HPLC $t_R = 2.81$ min (column A, purity 97%); HRMS for $C_{25}H_{26}N_6O_3$, $(M + H)^+$ calcd 459.2145, found 459.2135.

***N*-(2-Morpholinoethyl)-4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (11l).** ^{1}H NMR (500 MHz, CD_3OD, TFA salt) δ 7.95 (br s, 1H), 7.76 (s, 1H), 7.61 (m, 2H), 7.42 (d, $J = 7.7$ Hz, 1H), 4.10 (br m, 4 H), 3.80 (s, 3H), 3.75 (t, $J = 6.0$ Hz, 2H), 3.40 (t, $J = 6.1$ Hz, 2H), 3.29 (br m, 4H), 2.87 (s, 3H), 2.31 (s, 3H); Anal. RP-HPLC $t_R = 1.39$ min (column A, purity 96.9%); HRMS for $C_{23}H_{29}N_7O_4$, $(M + H)^+$ calcd 468.2359, found 468.2351.

4-Methoxybenzyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ylcarbamate (17d). Representative Procedure for the Preparation of 4-Alkyl 4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ylcarbamates (17a–d). To a suspension of **10** (330 mg, 0.93 mmol) and 4 Å molecular sieves in dioxane (15 mL) at 50 °C was added TEA (323 μL, 2.3 mmol) and diphenyl phosphoryl azide (503 μL, 2.3 mmol). The reaction mixture was stirred for 1.5 h at which point *p*-methoxy benzyl alcohol (1.16 mL, 9.3 mmol) was added, and the reaction temperature was increased to 80 °C for 2 h. The reaction was cooled, diluted with EtOAc, and filtered. After concentrating, the residue was purified via flash chromatography (75% EtOAc/hexane) to afford 4-methoxybenzyl4-(2-methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ylcarbamate **17d** (150 mg, 33% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.39 (m, 1H), 7.91 (s, 2H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.35 (m, 3H), 6.92 (m, 2H), 6.42 (s, 1H), 5.17 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 2.49 (s, 3H), 2.38 (s, 3H); Anal. RP-HPLC $t_R = 2.86$ min (column A, purity 98%); MS (ESI) *m*/*z* 491.30 $(M + H)^+$.

4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-amine (14). Carbamate **17d** (150 mg) was dissolved in dichloromethane (10 mL), and TFA was added (0.5 mL) The mixture was stirred at rt for 30 min and concentrated to give the crude amine **14** (126 mg, 93% yield) as a brown oil which was used without further purification.

4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-acetamide (15a). Representative Procedure for the Conversion of 14 To the Amides 15a–c and Urea 16. To a suspension of **14** (20 mg, 0.06 mmol) in dichloromethane (3 mL) was added TEA (26 μL, 0.18 mmol) followed by acetic anhydride (10 mg, 0.1 mmol) and the reaction mixture was stirred for 3 h. Water (2 mL) was added, and the product was extracted with dichloromethane (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to an oil which was purified via flash chromatography (33% EtOAc/hexane) to give **15a** (5 mg, 23% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (m, 2H), 7.67 (m, 2H), 7.41 (m, 1H), 3.81 (s, 3H), 2.58 (s, 3H), 2.34 (s, 3H), 2.20 (s, 3H); Anal. RP-HPLC $t_R = 1.60$ min (column A, purity 94%); MS (ESI) *m*/*z* 369.23 $(M + H)^+$.

4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-propylamide (15b). ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 7.88 (s, 1H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.72 (s, 1H), 7.75 (d, $J = 7.9$ Hz, 1H), 3.81 (s, 3H), 2.62 (s, 3H), 2.49 (q, $J = 7.5$ Hz, 2H), 2.38 (s, 3H), 1.33 (t, $J = 7.4$ Hz, 3H); Anal. RP-HPLC $t_R = 2.33$ min (column A, purity 96%); HRMS for $C_{19}H_{22}N_6O_3$, $(M + H)^+$ calcd 383.1826, found 383.1816.

4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-*iso*-butyramide (15c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.72 (s, 1H), 7.48 (m, 2H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.24 (m, 1H), 5.50 (br s, 1H), 3.74 (s, 3H), 2.71 (m, 1H), 2.56 (s, 3H), 2.33 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H); Anal. RP-HPLC $t_R = 2.50$ min (column A, purity 96.4%); HRMS for $C_{20}H_{24}N_6O_3$, $(M + H)^+$ calcd 397.1988, found 397.1977.

4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-*iso*-propylurea (16). ^{1}H NMR (500 MHz, CD_3OD) δ 7.81 (br s, 1H), 7.74 (br s, 1H), 7.50 (m, 2H), 7.31 (d, $J = 8.2$ Hz, 1H), 3.80 (m, 1H), 3.71 (s, 3H), 2.42 (s, 3H), 2.23 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H); Anal. RP-HPLC $t_R = 2.58$ min (column A, purity 97.5%); HRMS for $C_{20}H_{25}N_7O_3$, $(M + H)^+$ calcd 412.2097, found 412.2089.

Methyl 4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ylcarbamate (17a). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1H), 7.66 (m, 1H), 7.43 (m, 1H), 7.23 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.53, (s, 3H), 2.33 (s, 3H); Anal. RP-HPLC $t_R = 2.38$ min (column A, purity 98%); HRMS for $C_{18}H_{20}N_6O_4$, $(M + H)^+$ calcd 385.1624, found 385.1614.

Ethyl 4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ylcarbamate (17b). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (br s, 1H), 7.81 (br s, 1H), 7.53 (m, 2H), 7.32 (br d, 1H), 4.20 (q, $J = 7.0$ Hz, 2H), 3.79 (s, 3H), 2.53 (s, 3H), 2.33 (s, 3H), 1.32 (t, $J = 6.9$ Hz, 3H); Anal. RP-HPLC $t_R = 2.66$ min (column A, purity 99%); HRMS for $C_{19}H_{22}N_6O_4$, $(M + H)^+$ calcd 399.1781, found 399.1771.

Isopropyl 4-(2-Methyl-5-(methoxycarbamoyl)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-ylcarbamate (17c). ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (s, 1H), 7.72 (br s, 1H), 7.53 (m, 2H), 7.32 (d, $J = 7.9$ Hz, 1H), 4.88 (q, $J = 6.6$ Hz, 2H), 3.71 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H); Anal. RP-HPLC $t_R = 2.87$ min (column A, purity 98.5%); HRMS for $C_{20}H_{24}N_6O_4$, $(M + H)^+$ calcd 413.1937, found 413.1930.

Ethyl 4-[(2-Methyl-5-nitro)phenylamino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (18). To a solution of chloride **8** (4.0 g, 16.7 mmol) in DMF (50 mL) was added 2-methyl-5-nitro aniline (2.8 g, 18.4 mmol), and the reaction mixture was stirred for 48 h. Water (200 mL) was added slowly via addition funnel, and the resulting suspension was adjusted to pH 7 with $NaHCO_3$ (sat. aq.). The resulting precipitate was stirred for 2 h, filtered, and washed with water (2 × 25 mL) to afford **18** (5.09 g, 86% yield) as a pale tan solid. ^{1}H NMR (400 MHz, CD_3OD, rotameric) δ 8.57 (s, 1H), 8.17 (m, 1H), 8.07 (s, 1H), 7.81 (m, 2H), 4.37 (m, 2H), 2.95 (s, 3H), 2.44 (s, 3H), 1.41 (m, 3H); Anal. RP-HPLC $t_R = 4.04$ min (column A, purity 96.6%); MS (ESI) *m*/*z* 356.19 (M + H).

***N*-*n*-Propyl-4-[(2-methyl-5-nitro)phenylamino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (19).** To a solution of **18** (825 mg, 2.32 mmol) in THF (2 mL) and MeOH (1 mL) was added 1 N NaOH (6 mL), and the reaction mixture was heated at 60 °C for 24 h. The reaction mixture was then cooled and concentrated to remove the organic solvents. The pH of the solution was adjusted to ~6 with 1 N HCl, and the resulting solids were filtered, washed successively with water, and dried to afford the crude acid which was used without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.4 (br s, 1H), 7.55–7.86 (m, 5H), 2.79 (s, 3H), 2.28 (s, 3H); Anal. RP-HPLC $t_R = 3.40$ min (column A, purity 98%); MS (ESI) *m*/*z* 328.1 $(M + H)^+$.

To a solution of the above acid (2.32 mmol) in DMF (6 mL) was added HOBt (345 mg, 2.6 mmol) and EDC (489 mg, 2.6 mmol), and the resulting mixture was stirred at rt for 1 h. *n*-Propylamine (0.38 mL, 6.4 mmol) was added, and the reaction was stirred for an additional 4 h. Water was added (25 mL) to precipitate the product, and the solids were stirred rapidly for 10 min, filtered, and washed with additional water (2 × 10 mL). The collected solids were purified via column chromatography (33% EtOAc/hexanes) to give **19** (0.79 g, 93% yield, 2 steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.92 (m, 2H), 7.71 (s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.25 (m, 1H), 5.82 (br m, 1H), 3.34 (q, $J = 6.7$ Hz, 2H), 2.86 (s, 3H), 2.41 (s, 3H), 1.58 (m, 2H), 1.16 (t, $J = 7.5$ Hz, 3H); MS (ESI) *m*/*z* 369.3 $(M + H)^+$.

***N*-*n*-Propyl-4-[(2-methyl-5-amino)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (20).** A solution of **19** (794 mg, 2.16 mmol) and 10% Pd/C (250 mg, wet) in MeOH (20 mL) wad degassed and backfilled with hydrogen gas. The reaction was maintained under a hydrogen atmosphere for 2 h with stirring at which time the reaction solution was filtered and concentrated to give **20** (691 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.23 (s, 1H), 7.06 (d, $J = 8.1$ Hz, 1H), 6.53 (dd, $J = 8.1, 2.2$ Hz, 1H), 5.86 (br m, 1H), 3.43 (q, $J = 6.6$ Hz, 2H), 2.91 (s, 3H), 2.27 (s, 3H), 1.68 (m, 2H), 1.02 (t, $J = 7.3$ Hz, 3H); Anal. RP-HPLC $t_R = 2.39$ min (column A, purity 98%); MS (ESI) *m*/*z* 339.2 $(M + H)^+$.

***N*-*n*-Propyl-4-[(2-methyl-5-methylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21a). Representative Procedure for the Conversion of 20 to the Carbamates (21a–d).** To a solution of **20** (25.2 mg, 0.075 mmol) in dichloromethane (250 μL) was added DIPEA (14.3 μL, 0.082 mmol) followed by methyl chloroformate (6.4 μL, 0.082 mmol). The reaction was stirred for 1 h, and then, IPA was added (1 mL). The resulting solids were collected on a filter and washed with cold IPA (1 mL) to afford, after drying, **21a** (20.1 mg, 68% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, rotameric) δ 9.64 (s, 1H), 8.56 (s, 1H), 8.09 (m, 2H), 7.78 (s, 1H), 7.52 (m, 1H), 7.31 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 3.65 (s, 3H), 3.18 (m, 2H), 2.79 (s, 3H), 2.12 (s, 3H), 1.51 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); Anal. RP-HPLC t_R = 2.94 min (column A, purity 96.6%); HRMS for $C_{20}H_{24}N_6O_3$, $(M + H)^+$ calcd 397.1988, found 397.1955.

***N*-*n*-Propyl-4-[(2-methyl-5-ethylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21b).** ^{1}H NMR (400 MHz, DMSO-d_6, rotameric) δ 9.62 (br s, 1H), 8.57 (br s, 1H), 8.08 (m, 2H), 7.78 (s, 1H), 7.59 (m, 1H), 6.89–7.32 (m, 2H), 4.11 (app q, J = 7.1 Hz, 2H), 3.18 (app q, J = 6.5 Hz, 2H), 2.80 (s, 3H), 2.12 (s, 3H), 1.52 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); Anal. RP-HPLC t_R = 3.16 min (column A, purity 99.5%); HRMS for $C_{21}H_{26}N_6O_3$, $(M-H)^+$ calcd 409.1988, found 409.2006; Anal. calcd C, 61.45; H, 6.38; N, 20.47; found C, 61.39; H, 6.46; N, 20.49.

***N*-*n*-Propyl-4-[(2-methyl-5-*iso*-propylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21c).** ^{1}H NMR (500 MHz, DMSO-d_6, rotameric) δ 9.52 (br s, 1H), 8.56 (br s, 1H), 8.07 (m, 2H), 7.77 (s, 1H), 7.60 (m, 1H), 7.16–7.31 (m, 2H), 4.86 (m, 1H), 3.17 (m, 2H), 2.79 (s, 3H), 2.11 (s, 3H), 1.51 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H), 0.90 (t, J = 7.2 Hz, 3H); Anal. RP-HPLC t_R = 3.38 min (column A, purity 94.9%); HRMS for $C_{22}H_{28}N_6O_3$, $(M + H)^+$ calcd 425.2301, found 425.2307.

***N*-*n*-Propyl-4-[(2-methyl-5-phenylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21d).** ^{1}H NMR (500 MHz, DMSO-d_6, rotameric) δ 10.23 (br s, 1H), 8.57 (s, 1H), 8.10 (s, 1H), 8.07 (t, J = 5.5 Hz, 1H), 7.79 (s, 1H), 7.44 (s, 1H), 7.43 (t, J = 6.3 Hz, 2H), 7.35 (m, 1H), 7.23 (m, 3H), 3.18 (m, 2H), 2.80 (s, 3H), 2.15 (s, 3H), 1.51 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); Anal. RP-HPLC t_R = 3.46 min (column A, purity 91.5%); HRMS for $C_{25}H_{26}N_6O_3$, $(M + H)^+$ calcd 459.2145, found 459.2136.

Ethyl 3-Amino-4-methylphenylcarbamate (22). To a solution of 3-nitro-4-methyl aniline (2.0 g, 13.1 mmol) in dichloroethane (40 mL) wad added ethyl chloroformate (1.38 mL, 14.4 mmol) followed by DIPEA (2.3 mL, 14.4 mmol). The reaction was stirred for 12 h and then poured into a separatory funnel containing water (75 mL) and dichloromethane (50 mL). The layers were separated, and the organic layer was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to an oil. The product was purified via column chromatography (20% EtOAc/hexanes) to furnish ethyl-3-nitro-4-methyl phenyl carbamate (2.39 g, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 2.3 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.32 (s, 1H), 6.74 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.59 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); Anal. RP-HPLC t_R = 3.37 min (column A, purity 97.8%); MS (ESI) m/z 225.13 $(M + H)^+$.

To a solution of ethyl-3-nitro-4-methyl phenyl carbamate (1.33 g, 5.9 mmol) in MeOH (30 mL) was added 5% Pd/C (480 mg, wet), and the reaction vessel was evacuated and backfilled with hydrogen gas. The reaction was maintained under a hydrogen atmosphere for 2 h with stirring at which time the reaction solution was filtered and concentrated to give **22** (1.15 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (m, 2H), 6.46 (dd, J = 8.0, 2.1 Hz, 1H), 6.36 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.42 (br s, 2H), 2.04 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); Anal. RP-HPLC t_R = 1.43 min (column A, purity 98.7%).

Methyl 4-(2-Methyl-5-(ethoxycarbonylamino)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (23). This compound was prepared according to the procedure outlined for compound **18** starting from chloride **12** (248 mg, 1.1 mmol) and ethyl 3-amino-4-methylphenylcarbamate **22** (235 mg, 1.2 mmol) to provide **23** (339 mg, 81% yield). ^{1}H NMR (500 MHz, DMSO-d_6, rotameric) δ 9.62 (s, 1H), 8.73 (s, 1H), 8.09 (s, 1H), 7.81 (m, 1H), 7.55 (m, 1H), 7.31 (m, 1H), 7.17 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.33 (s, 3H), 2.82 (s, 3H), 2.11 (s, 3H), 1.24 (m, 3H); Anal. RP-HPLC t_R = 3.51 min (column A, purity 98%); MS (ESI) m/z 384.23 $(M + H)^+$.

4-(2-Methyl-5-(ethoxycarbonylamino)phenylamino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid (24). To a solution of **23** (290 mg, 0.59 mmol) in THF (2 mL) and MeOH (2 mL) was added 1 N NaOH (1.77 mL, 1.77 mmol), and the reaction mixture was heated at 55 °C for 24 h. The reaction mixture was then cooled and concentrated to remove the organic solvents. The pH of the solution was adjusted to ~6 with 1 N HCl, and the resulting solids were filtered, washed successively with water, and dried to afford the crude acid **24** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6, rotameric) δ 9.60 (s, 1H), 8.23 (s, 1H), 7.66 (m, 2H), 7.20 (m, 2H), 4.10 (m, 2H), 2.88 (s, 3H), 2.14 (s, 3H), 1.24 (br m, 3H); Anal. RP-HPLC t_R = 3.07 min (column A, purity 98.5%); MS (ESI) m/z 370.28 $(M + H)^+$.

***N*-Ethyl-4-[(2-methyl-5-ethylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21g). Representative Procedure for the Coupling of 24 with an Amine for the Preparation of 21g–i.** To a solution of acid **24** (25 mg, 0.07 mmol) in DMF was added HOBt (10.1 mg, 0.075 mmol) and EDC (14.3 mg, 0.075 mmol), and the mixture was stirred for 30 min. Ethyl amine hydrochloride (11.4 mg, 0.14 mmol) was added followed by DIPEA (24.4 μL, 0.14 mmol), and the reaction mixture was stirred for 2 h. Water (1 mL) was added to precipitate the product, and the solids were stirred for 2 h, filtered, and dried under high vacuum to afford **21 g** (18.0 mg, 66% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.88 (br s, 1H), 7.65 (br m, 2H), 7.28 (m, 1H), 7.21 (m, 1H), 4.16 (app q, J = 7.0, 2H), 3.37 (app q, J = 7.5 Hz, 2H), 2.81 (s, 3H), 2.20 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H); Anal. RP-HPLC t_R = 2.89 min (column A, purity 96%); HRMS for $C_{20}H_{24}N_6O_3$, $(M + H)^+$ calcd 397.1988, found 397.1992.

***N*-*iso*-Propyl-4-[(2-methyl-5-ethylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21h).** ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (br s, 1H), 7.68 (m, 2H), 7.31 (m, 1H), 7.23 (m, 1H), 4.16 (m, 2H), 2.81 (s, 3H), 2.22 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.25 (s, 3H), 1.24 (s, 3H); Anal. RP-HPLC t_R = 3.06 min (column A, purity 97.4%); HRMS for $C_{21}H_{26}N_6O_3$, $(M + H)^+$ calcd 411.2145, found 411.2146.

***N*-(*S*)-*sec*-Buytl-4-[(2-methyl-5-ethylcarbamoyl)aminophenyl]-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (21i).** ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (br s, 1H), 7.65 (m, 2H), 7.30 (m, 1H), 7.25 (m, 1H), 4.16 (q, J = 7.4 Hz, 2H), 4.00 (m, 1H), 2.98 (m, 2H), 2.81 (s, 3H), 2.22 (s, 3H), 1.58 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); Anal. RP-HPLC t_R = 3.25 min (column A, purity 94.1%); HRMS for $C_{22}H_{28}N_6O_3$, $(M + H)^+$ calcd 425.2301, found 425.2305.

***N*-*n*-Propyl 4-(2-methyl-5-(methoxyacetamido)phenylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (21e).** This compound was prepared via the acylation of **20** with 2-methoxyacetyl chloride using the general procedure outlined for **21a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 8.39 (s, 1H), 7.91 (m, 2H), 7.63 (m, 2H), 7.29 (m, 1H), 7.03 (m, 1H), 3.80 (s, 2H), 3.19 (s, 3H), 2.62 (s, 3H), 1.97 (s, 3H), 1.36 (m, 2H), 0.73 (m, 3H); Anal. RP-HPLC t_R = 2.84 min (column A, purity 95.9%); HRMS for $C_{21}H_{26}N_6O_3$, $(M + H)^+$ calcd 411.2145, found 411.2145.

***N*-*n*-Propyl 4-(2-methyl-5-(acetamido)phenylamino)-5-methylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide (21f).** This compound was prepared via the acylation of **20** with acetylchloride using the general procedure outlined for **21a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.94 (s, 1H), 8.54 (s, 1H), 8.07 (m, 2H), 7.75 (m, 2H), 7.40 (m, 1H), 7.19 (m, 1H), 3.18 (m, 2H), 2.80 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H), 1.51 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); Anal. RP-HPLC t_R = 2.74 min (column A, purity 95%); LRMS for $C_{2o}H_{24}N_6O_2$, $(M + H)^+$ calcd 381.45, found 381.23.

p38 Kinase Assay. The assays were performed in V-bottomed 96-well plates. For both assays, the final assay volume was 60 μL

which was from three 20-μL additions of enzyme, substrates (myelin basic protein (MBP) and ATP), and test compounds in assay buffer (50 mM Tris pH 7.5, 10 mM $MgCl_2$, 50 mM NaCl, and 1 mM DTT). Bacterially expressed, activated p38α was preincubated with test compounds for 10 min prior to the initiation of reaction by adding substrates. The plates were incubated at room temperature for 45 min. The reaction was terminated by adding 5 μL of 0.5 M EDTA to each well. The reaction mixture was aspirated onto a prewetted filtermat using a Skatron Micro96 cell harvester (Skatron) and then washed with PBS. The filtermat was dried in a microwave oven for 1 min, coated with a layer of MeltilLex A scintillation wax (PerkinElmer), and counted on a Microbeta scintillation counter (Model 1450, PerkinElmer). The data were analyzed using Prizm nonlinear least-squares regression (GraphPad Software). The final concentrations of reagents in the assays were [ATP], 1 μM; [[γ-^{33}P]ATP]], 3 nM; [MBP] (Sigma, M1891), 2 μg/well; [p38], 15 ng/well; [DMSO], 0.3%.

LPS-Induced TNFα Production in THP-1 Cells. Human monocytic THP-1 cells, obtained from ATCC, were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum. Cells (40 000 cells in 80 μL) were added to wells of 96-well flat-bottomed plates. Tested compounds (10 μL) or vehicle (1% DMSO final) was added to cells. Subsequently, LPS (Sigma, No. L7261; 10 μL /well) was added to the cells for a final concentration of 1 μg/mL. Plates were incubated overnight at 37 °C and 5% CO_2. Supernatant (50 μL/well) was harvested for an ELISA assay. TNFα was captured by an antihuman TNFα antibody (R&D, No. MAB610) which was preabsorbed in high binding EIA plates (Costar, No. 3590). Captured TNF was recognized by a biotinylated antihuman TNF polyclonal antibody (R&D, No. BAF210). Streptavidin conjugated with peroxidase was added to each well, and the activity of peroxidase was quantitated by a peroxide substrate kit (Pierce, Nos. 34062 and 34006).

LPS-Induced TNFα Production in Human PBMC. Human PBMCs were isolated from whole blood collected from healthy donors. Blood was diluted into RPMI 1640 (Life Technologies) containing 2.5 mM EDTA (Life Technologies) and 10 μg/mL polymyxin (Sigma) and, then, underlaid with ficoll (Accurate Scientific Co.) and centrifuged at 600*g* for 25 min. The interface was collected, and cells were washed twice and resuspended in RPMI, 10% FBS. Cells were then distributed (200 μL/well) into 96-well tissue culture treated plates (Falcon) at 1×10^6 cells/mL in RPMI, 10% FBS. Test compounds were added to appropriate wells and incubated with cells for 30 min. Cells were then stimulated by the addition of lipopolysaccharide (LPS, BioWhittaker), with a final concentration of 25 ng/mL, and incubated for 6 h at 37 °C, 5% CO_2. The cell supernatants were removed and assayed for TNFα by ELISA (R&D Systems).

Inhibition of TNFα Release in Mice. BALB\c female mice, 6–8 weeks of age, were obtained from Harlan Laboratories and maintained ad libitum on water and standard rodent chow (Harlan Teklad). Mice were acclimated to ambient conditions for at least 1 week prior to use. For oral dosing, the compounds were prepared in a solution of 100% polyethylene glycol (MW 300), and a dosing volume of 0.2 mL per mouse was administered by gavage 30 or 120 min prior to LPS injection (0.1 mL of LPS suspended at 10 μg/mL in PBS, administered ip). Blood samples were obtained 90 min after LPS injection. Serum was separated from clotted blood samples by centrifugation (5 min, 5000*g*, room temperature) and analyzed for levels of TNFα by ELISA assay (R&D Systems) according to the manufacturer's directions. Results are shown as mean percent inhibition of $n = 6$–8 mice per treatment group. All studies were performed using **11b** as a positive control and as a measure of model variability. All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee.

Rat and Human Liver Microsome Stability. Rat microsomes were purchased from XenoTech (Kansas City, KS). The human microsomes were purchased from In Vitro Technology (Baltimore, MD) and were pooled from 10 individual donors. The rates of oxidative metabolism were measured in triplicate under the following conditions: compound, 3 μM final concentration; final microsomal protein concentration approximately 1 mg/mL; NADPH 1 mM; pH 7.4 potassium phosphate buffer, 56 mM. Incubations were performed at 37 °C and were initiated by the addition of the substrate. Aliquots (100 μL) of the incubation were quenched at 0, 10, 20, 30, and 40 min by the addition of 1 volume of acetonitrile. Results from 10-min incubations were used for the rate calculations. Samples were analyzed by the LC/MS/MS assay for the amount of the drug remaining at any time point. The percent metabolized was calculated based on the disappearance of the parent compound.

Rat Adjuvant Arthritis. Male Lewis rats (Harlan, 175–200 g) were immunized sc at the base of the tail with 0.1 mL complete Freund's adjuvant containing 10 mg/mL *Mycobacterium butyricum*. Seven days later, baseline (predisease) measurements of hind paw volume were determined by volume displacement plethysmometry (Ugo Basile, Italy). Compound was administered orally in 1 mL PEG 300 bid beginning on day 11. Paw volume measurements were repeated 3 times/week for the remainder of the study. Data are presented as the summed increase in volume (expressed in mL) above baseline for each rat's two hind paws. Dexamethasone (1 mg/kg) was used as a positive control.

Mouse Collagen Induced Arthritis. DBA/1LacJ male mice 6–8 weeks (The Jackson Laboratory, Bar Harbor, ME) were immunized subcutaneously on day 0 and day 21 with 200 μg bovine type II collagen in a 0.1 mL RIBI adjuvant system (RAS) with monophosphoryl lipid A (RIBI ImmunoChem Research, Hamilton, Montana). Following the day 21 booster, mice were monitored daily for the development paw inflammation. On day 26, the animals were randomly assigned to a treatment group and treatment (po, bid) was initiated immediately. Clinical paw scores for all four paws were summed for each mouse and mean ± SD was calculated for each treatment group. Dexamethasone (5 mg/kg) was used as a positive control.

Clinical Scoring. Each paw was visually scored by the following criteria: 0 = normal; 1 = one (or more) joints inflamed on digits; 2 = inflammation of plantar surface of paw and paw thickness increased; 3 = ankylosis of ankle joint (significantly reduced hock joint motion on flexion/extension).

Crystal Structure of p38 MAP Kinase. Recombinant p38α MAP Kinase with an N-terminal $(His)_5$-affinity tag was expressed in *E. coli* and purified by sequential Q-Sepharose FF, His-Trap HP Ni^{2+}-affinity, and Superdex 200 size exclusion chromatography. Purified $(His)_5$-p38α, at 2 mg/mL in 25 mM Tris (pH 7.5), 50 mM NaCl, 5% glycerol, 0.5 mM EDTA, 2 mM DTT, was combined with a 5-fold molar excess of inhibitor from a 50 mM stock in DMSO, incubated at 20 °C for 1 h, and ultrafiltered (10 kDa cutoff) to a retentate protein concentration of 10 mg/mL. Cocrystals of $(His)_5$-p38α **11j** inhibitor complexes grew spontaneously in hanging drop vapor-diffusion trials conducted at 4 °C with drops containing 1 μL of concentrated protein−inhibitor complex mixed with an equal volume of reservoir solution (50 mM Mes pH 6.0, 4% PEG 3350, 5 mM $MgSO_4$). More perfect crystals of **11j** and **11b** were obtained using a cat whisker to streak clear drops with microseeds from crushed cocrystals of $(His)_5$-p38α and **11j**. Prior to data collection, the crystals were slowly transferred to a stabilization solution (5% glycerol, 30% PEG 3350, 50 mM Mes pH 6.0, 50 mM NaCl) and then flash frozen in liquid nitrogen. Data were collected at the IMCA-CAT beamline ID-17 at the Advanced Photon Source, Argonne, IL, reduced with the programs DENZO and SCALEPACK,[19] and refined by with the program autoBuster (Global Phasing, Ltd., Cambridge, U.K.). The final crystallographic refinement statistics are summarized in the Supporting Information. Details of the data collection, reduction, and refinement will be presented elsewhere.[20]

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Supporting Information Available: Table of HPLC purity analysis or combustion analysis of key compounds and final X-ray crystallographic refinement statistics. This material is available free of charge via the Internet at http://pubs.acs.org.

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