Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5447–5454
Bioorganic & Medicinal Chemistry Letters

Pyrimidine benzamide-based thrombopoietin receptor agonists

Lawrence A. Reiter, Chakrapani Subramanyam, Emilio J. Mangual, Christopher S. Jones,* Marc I. Smeets, William H. Brissette, Sandra P. McCurdy, Paul D. Lira, Robert G. Linde, Qifang Li, Fangning Zhang, Amy S. Antipas, Laura C. Blumberg, Jonathan L. Doty, James P. Driscoll, Michael J. Munchhof, Sharon L. Ripp, Andrei Shavnya, Richard M. Shepard, Diana Sperger, Lisa M. Thomasco, Kristen A. Trevena, Lilli A. Wolf-Gouveia and Liling Zhang

Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA

Received 30 May 2007; revised 10 July 2007; accepted 10 July 2007
Available online 31 July 2007

Abstract—A series of pyrimidine benzamide-based thrombopoietin receptor agonists is described. The lead molecule contains a 2-amino-5-unsubstituted thiazole, a group that has been associated with idiosyncratic toxicity. The potential for metabolic oxidation at C-5 of the thiazole, the likely source of toxic metabolites, was removed by substitution at C-5 or by replacing the thiazole with a thiadiazole. Potency in the series was improved by modifying the substituents on the pyrimidine and/or on the thiazole or thiadiazole pendant aryl ring. In vivo examination revealed that compounds from the series are not highly bioavailable. This is attributed to low solubility and poor permeability.

Platelets, the key cellular component of blood clots, are produced from megakaryocytes, a large, polyploid cell with a multi-lobated nucleus.[1] Platelet formation, as well as the differentiation of multipotent hematopoietic bone marrow stem cells into megakaryocytes, is dependent on the hematopoietic growth factor thrombopoietin (TPO) which is constitutively produced in the liver. TPO induces this differentiation and the production of platelets from megakaryocytes through interaction with the cell surface thrombopoietin receptor (TPOr) which initiates an intracellular cascade involving the kinase JAK2 and the transcription factor STAT5. Normal levels of platelets range from 100,000 to 500,000/μL. A person is considered thromobocytopenic when platelet levels drop below 50,000/μL and at this level, the danger of uncontrollable bleeding arises. Thrombocytopenia can occur for a variety of reasons among which are impaired liver function, immune thrombocytopenia purpura (ITP), and cancer chemotherapy. Although each of these conditions can be treated with platelet transfusions, this is not typically done until platelet levels drop below 20,000/μL owing to the cost as well as the danger inherent in the transfusion of blood products. These conditions could, in principle, also be alleviated by treatment with exogenous TPO. However, unlike the other recombinant hematopoietic growth factors, erythropoietin (EPO) and granulocyte colony-stimulating factor (GCSF), development of TPO (recombinant or engineered) has not been successful, a key negative clinical finding being the production of neutralizing antibodies to an engineered rTPO protein. These antibodies cross-reacted with native TPO thereby leading to severe thrombocytopenia. Clearly, one approach to avoiding this problem would be to identify a low molecular weight compound that would induce TPOr signaling.

In general, the identification of low molecular weight compounds that induce signaling of cell surface receptors that are normally stimulated by a protein has not been particularly fruitful. However, in the case of the TPO receptor, a number of low molecular weight agonists have been reported.[2–7] One such agent has been studied in the clinic and has been reported to effectively increase platelet numbers in patients with ITP or receiving anti-viral treatment for hepatitis.[8] Our interest in the

Keywords: Thrombopoietin; Low molecular weight agonist; Small molecule agonist; Thrombocytopenia.
* Corresponding author. Tel.: +1 860 715 0516; e-mail: christopher.s.jones@pfizer.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.07.038

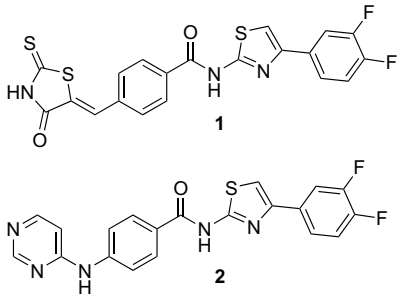


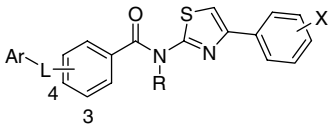
Figure 1. Lead molecules.

area was stimulated by the disclosure of a series of thiazolidine thiazoles that possess potent TPOr agonist activity.[9] The low molecular weight, potency, and overall simplicity made the series (represented by **1**, Fig. 1) an attractive starting point for a drug discovery effort. There were, however, structural features we wished to avoid, in particular the thiazolidinedione and the 2-amino-5-unsubstituted thiazole, both of which have been associated with idiosyncratic toxicity.[10]

To initiate our effort, we screened sub-sets of compounds from our files seeking to identify molecules that contain only one of the undesired groups. This effort led to the identification of **2**, which displayed agonist activity in a BaF3 cell reporter assay containing the human TPOr.[11] In concordance with the low molecular weight TPO agonists reported by other groups, **2** does not signal the murine TPOr or the other related hematopoietic receptors, EPOr and GCSFr. With the identification of this TPOr agonist, we began a detailed study of its SAR in an attempt to improve the potency of the series (**2**: EC_{50} 400 nM vs **1**: EC_{50} 28 nM) and to eliminate the second undesired structural feature, the 2-amino-5-unsubstituted thiazole.

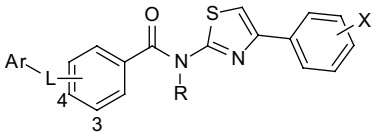
Owing to the facility with which 4-aryl-2-aminothiazoles can be synthesized through halogenation of substituted acetophenones and subsequent condensation with thiourea, we initially prepared a wide range of analogs of **2** containing various substituted pendant aryl rings.[12] The activity of these spans a range from ~30 nM to >10 μM (Table 1). Of the monosubstituted analogs (**4**–**18**), the most potent contain a relatively large, lipophilic group at C-3. A CF_3 group at C-4 also confers moderate potency. Larger lipophilic or polar groups at C-4 do not induce potent agonism nor does C-2 monosubstitution. Among the disubstituted analogs (**2**, **19**–**41**), the 2,3-disubstitution pattern yields the most potent agonists when the C-3 group is a relatively large lipophilic group, a finding consistent with data from the monosubstituted compounds. 2,4-Disubstitution is not quite as effective and 2,5-disubstitution does not yield potent agonists. 3,4-Disubstitution can lead to compounds of moderate potency. A 2,3,4-trisubstituted compound with a lipophilic C-3 group (**45**) is among the most potent analogs. Although further improvements in potency may have been attained through additional elaboration of the pendant aryl ring, we did not anticipate identifying significantly more potent compounds lying within molecular

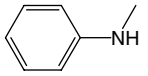
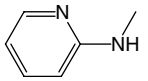
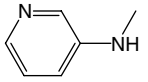
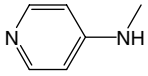
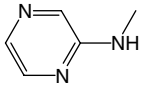
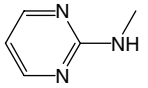
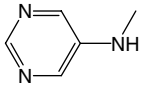
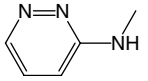
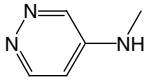
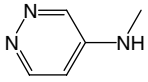
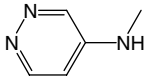
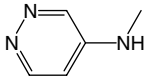
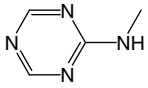
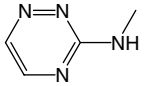
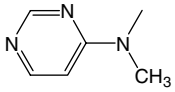
Table 1. Potency of substituted aryl analogs of **2** (EC_{50}s nM)



CPD	substituent	EC_{50}	clogP
3	H	3440	4.36
4	2-F	6850	4.51
5	2-Cl	9000	4.83
6	2-CF_3	>10000	5.26
7	3-F	>10000	4.51
8	3-Cl	3030	5.08
9	3-Br	645	5.23
10	3-CF_3	418	5.26
11	3-OCF_3	284	5.49
12	4-F	2560	4.51
13	4-Cl	568	5.08
14	4-CH_3	1200	4.86
15	4-CF_3	492	5.26
16	4-$OCHF_2$	>10000	4.83
17	4-OCF_3	>10000	5.49
18	4-NO_2	>10000	4.12
19	2,3-diF	415	4.59
20	2-F-3-Cl	612	5.23
21	2-F-3-Br	100	5.38
22	2-F-3-CF_3	60	5.41
23	2-F-3-ethyl	143	5.54
24	2-F-3-butyl	53	6.60
25	2-F-3-isobutyl	35	6.47
26	2-F-3-OCH_3	3130	4.40
27	2-F-3-OCF_3	32	5.51
28	2,3-diCl	1340	5.43
29	2,4-diF	173	4.66
30	2-F-4-Cl	232	5.23
31	2-F-4-CF_3	259	5.41
32	2,4-diCl	510	5.55
33	2,4-diCH_3	2260	5.06
34	2-F-5-CF_3	5190	5.41
35	2-OH-5-Cl	>10000	4.48
36	2-OCH_3-5-Cl	>10000	4.61
2	3,4-diF	403	4.59
37	3-F-4-CF_3	288	5.41
38	3-CF_3-4-F	104	5.41
39	3,4-diCl	347	5.68
40	3,4-diCH_3	784	5.31
41	2,6-diF	>10000	4.66
42	2-aza-3-CF_3	244	4.18
43	2,3,4-triF	84	4.66
44	2,3-diF-4-CF_3	87	5.48
45	2,4-diF-3-CF_3	33	5.55
46	2,6-diCl-4-CF_3	>10000	6.19

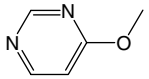
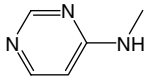
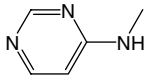
Table 2. TPOr potency of azine analogs of **22** and related compounds



CPD		Ar-L	Method[a]	Attachment point	R	X	BaF3 EC_{50} (μM)
47	Benzene		A	4	H	2-F-3-CF_3	>10 (0.060)[b]
48	2-Aminopyridine		B	4	H	2-F-3-CF_3	2.2 (0.060)[b]
49	3-Aminopyridine		B	4	H	2-F-3-CF_3	8.6 (0.060)[b]
50	4-Aminopyridine		B	4	H	2-F-3-CF_3	0.40 (0.060)[b]
51	2-Aminopyrazine		C	4	H	2-F-3-CF_3	7.9 (0.060)[b]
52	2-Aminopyrimidine		C	4	H	2-F-3-CF_3	7.7 (0.060)[b]
53	5-Aminopyrimidine		C	4	H	2-F-3-CF_3	0.32 (0.060)[b]
54	3-Aminopyridazine		D	4	H	2-F-3-CF_3	>10 (0.060)[b]
55	4-Aminopyridazine		D	4	H	4-Cl	1.6 (0.57)[b]
56	4-Aminopyridazine		D	4	H	2,4-DiF	0.55 (0.17)[b]
57	4-Aminopyridazine		D	4	H	2-F-3-CF_3	0.12 (0.060)[b]
58	4-Aminopyridazine		D	4	H	3-CF_3-4-F	0.40 (0.10)[b]
59	2-Amino-1,3,5-triazine		C	4	H	2-F-3-CF_3	0.54 (0.060)[b]
60	3-Amino-1,2,4-triazine		A	4	H	2-F-3-CF_3	>10 (0.060)[b]
61	*N*-Methylated link		E	4	H	2-F-3-CF_3	>10

(*continued on next page*)

Table 2 (*continued*)

CPD		Ar-L	Method[a]	Attachment point	R	X	BaF3 EC_{50} (μM)
62	Ether link		F	4	H	2-F-3-CF_3	>10
63	*N*-Methyl amide		G	4	CH_3	2-F-3-CF_3	>10
64	3-Subst. analog		H	3	H	3,4-DiF	>10

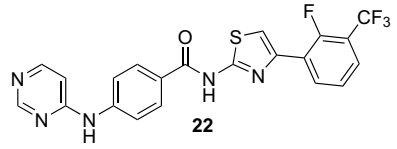
[a] See Ref. 13 for synthetic methods.
[b] Activity of corresponding 4-aminopyrimidine analog.

weight and clog *P* constraints for drug-like properties. Notably, the most potent analogs have clog *P*s > 5.5.

Although the pyrimidine group was not of any particular concern with regard to potential toxicity or other issues, we did investigate whether it could be replaced with other azines (Table 2).[13] Of this set (mostly bearing a 2-F-3-CF_3-phenyl substituent on the thiazole), only the 4-aminopyridazine analogs (**55**–**58**) approach the potency of the corresponding 4-aminopyrimidines. We also observed that alkylating the nitrogen linking the pyrimidine and benzene rings (**61**), replacing this nitrogen with an oxygen (**62**), methylating the amide group (**63**), or altering the point of attachment of the 4-aminopyrimidine moiety (**64**) all abolish agonist activity.

Introduction of substituents to the 4-aminopyrimidine revealed that substitution at C-2 is not tolerated while substituents at C-6 could be varied quite widely yielding some analogs more potent than **22** (Table 3).[14] Notably, incorporation of hydrophilic groups allowed for potency improvements without raising the clog *P*, for example, the *N*-azetidin-3-ol analog **75** is both ~6-fold more potent and somewhat less lipophilic. Combining this pyrimidine substituent with a 2-F-3-OCF_3 phenyl substituent on the thiazole yielded the most potent analog in the series, **76** (Fig. 2).

Metabolic oxidation of 2-aminothiazoles is known to lead to ring opening and production of thiourea derivatives that have the potential for hepatotoxicity unless a blocking substituent at C-5 is present.[10] Accordingly, we explored two strategies in order to reduce this risk: (1) introducing a substituent at C-5, and (2) replacing the thiazole with isomeric thiazoles[15] or alternative heterocycles: thiadiazoles,[16,17] pyrazoles,[18,19] isothiazoles[20]



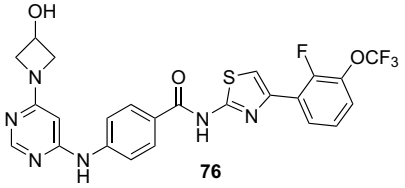
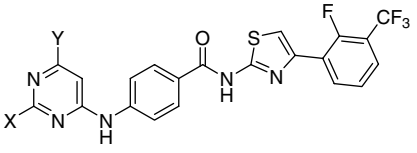


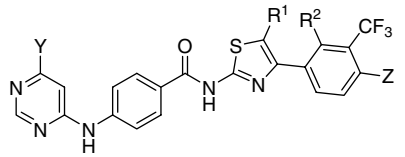
Figure 2. Key thiazole agonists.

Table 3. SAR of substituted 4-aminopyrimdine derivatives



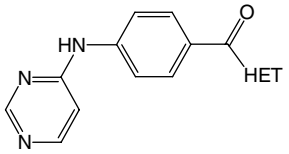
Compound	X	Y	EC_{50} (μM)	clog *P*
22	H–	H–	0.060	5.41
65	CH_3–	H–	>10	5.91
66	H–	CH_3–	0.043	5.91
67	CH_3–	CH_3–	>10	6.40
68	H–	CH_3O–	0.038	6.35
69	H–	$(CH_3)_2N$–	0.054	6.31
70	H–	CH_3CH_2NH–	0.13	6.75
71	H–	$HOCH_2CH_2N$–	0.065	5.45
72	H–	$HOCH_2CH_2N(CH_3)$–	0.022	5.57
73	H–	$CH_3OCH_2CH_2N(CH_3)$–	0.084	6.34
74	H–	*N*-Azetidine	0.023	5.87
75	H–	*N*-3-Azetidinol	0.009	5.29

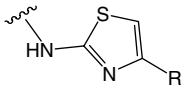
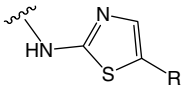
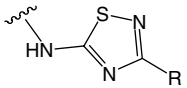
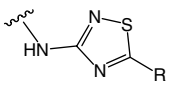
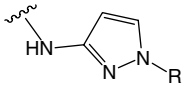
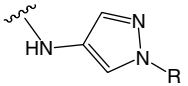
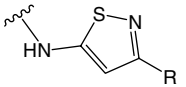
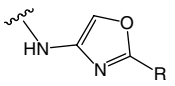
Table 4. SAR of 5-substituted 2-aminothiazoles



Compound	Y	R^1	R^2	Z	EC_{50} (μM)
22	H–	H–	F–	H–	0.060
38	H–	H–	H–	F–	0.10
69	$(CH_3)_2N$–	H–	F–	H–	0.054
77	H–	CH_3–	F–	H–	0.54
78	H–	CH_3–	H–	F–	0.18
79	$(CH_3)_2N$–	CH_3–	H–	F–	0.045
80	$(CH_3)_2N$–	Cl–	H–	F–	0.011
81	H–	$–CH_2O$–		H–	0.14
82	H–	$–CH_2CH_2O$–		H–	0.027

Table 5. Replacements for the 2-amino-4-arylthiazole



	A 2-Amino-4-arylthiazoles	B 2-Amino-5-aryl-thiazoles	C 5-Amino thiadiazoles	D 3-Amino thiadiazole	E 3-Amino pyrazoles	F 4-Amino pyrazoles	G 5-Amino isothiazole	H 4-Amino oxazoles
	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)	BaF3 EC_{50} (μM)
R / HET→ ↓								
Ph	**3** 3.4	—	**85** 1.6	—	—	—	**102** >10	—
4-Cl–Ph	**13** 0.578	—	—	—	—	—	**103** >10	—
2,4-DiF–Ph	**29** 0.17	—	**86** 1.3	—	—	—	—	—
3,4-DiF–Ph	**2** 0.40	—	**87** 0.72	**94** >10	—	—	—	—
3,4-DiCl–Ph	**39** 0.35	—	**88** 4.4	—	—	**99** >10	—	—
2-F-3-CF_3–Ph	**22** 0.060	**83** >10	**89** 1.5	**95** >10	**97** 1.4	**100** >10	—	**104** 7.9
3-CF_3-4-F–Ph	**38** 0.10	**84** 6.7	**90** 0.41	—	**98** 2.0	**101** >10	—	**105** 2.3
3-F-4-CF_3–Ph	**37** 0.29	—	**91** >10	—	—	—	—	—
3-OCF_3–Ph	**11** 0.28	—	**92** >10	—	—	—	—	—
2-F-3-OCF_3–Ph	**27** 0.032	—	**93** 0.97	**96** >10	—	—	—	—

or oxazoles.[21] Of these only C-5 substituted thiazoles (Table 4) and 5-amino-3-aryl-[1,2,4]-thiadiazoles (Table 5, Column C) displayed agonist activity on the order of the parent series. The other replacements proved to be significantly less active.

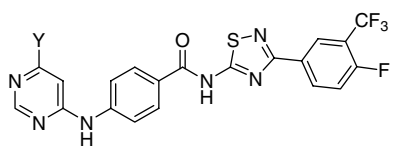
Although introduction of a methyl group at C-5 of the thiazole ring reduced activity in the 2-F-3-CF_3-phenyl series (**77** vs **22**), such substitution is tolerated in the 4-F-3-CF_3 series yielding an analog only slightly less potent than the corresponding C-5 unsubstituted derivative (**78** vs **38**). The 4-dimethylaminopyrimidine analogs **79**and **80** emerged as the most potent agonists in this series. Fusing a ring between the thiazole and phenyl groups, as in **81** and **82**, also served to block C-5 of the thiazole. These compounds both displayed good agonist activity.

Within the 5-amino-3-aryl-[1,2,4]-thiadiazoles, we observed that the 2-F-3-CF_3 and 2-F-3-OCF_3 analogs (**89** and **93**) are not particularly potent. However, the 4-F-3-CF_3 analog **90** is active and only slightly less potent than the corresponding 2-amino-4-arylthiazole **38**.

Further optimization of potency and physical properties (i.e., clog *P*) in the 5-amino-3-aryl-[1,2,4]-thiadiazole series was achieved by introduction of C-6 substituents onto the pyrimidine (Table 6). The most potent analog is the *N*-azetidin-3-ol analog **110**. Notably, inclusion of hydrophilic side chains on the pyrimidine lowered the clog *P*s of many of these analogs to <5.

Although activity in the BaF3 reporter assay was deemed to be a good indicator of inherent potency, to better assess agonist activity, the ability of some of the more potent analogs to induce BaF3 cell proliferation was determined (Table 7). All of these compounds induced proliferation with a ~20- to 100-fold shift in EC_{50}s over the reporter assay, a shift attributed to protein binding in the proliferation assay. Further substantiation of agonist activity was obtained by the compounds' ability to induce proliferation of human $CD34^+$ cells—a multipotent progenitor cell that will differentiate into a megakaryocyte in the presence of TPOr signaling in a CFU_{MEG} colony assay.

Table 6. SAR of substituted 4-aminopyrimdine thiadiazoles



Compound	Y	EC_{50} (μM)	clog *P*
90	H–	0.41	4.73
105	$(CH_3)_2N$–	0.043	5.64
106	$HOCH_2CH_2N$–	0.030	4.78
107	$HOCH_2CH_2N(CH_3)$–	0.22	4.90
108	$CH_3OCH_2CH_2N(CH_3)$–	0.13	5.66
109	*N*-Azetidine	0.081	5.19
110	*N*-3-Azetidinol	0.013	4.61
111	$(HOCH_2CH_2CH_2)_2N$–	0.071	4.88
112	$\pm HOCH_2CH(OH)N(CH_3)N$–	0.029	4.62

Table 7. Cell proliferation of key compounds

Compound	BaF3 reporter EC_{50} (μM)	BaF3 proliferation EC_{50} (μM)	CFU_{MEG} proliferation EC_{50} (μM)
22	0.060	1.4	0.34
76	0.007	0.29	—
69	0.054	8.5	—
74	0.023	0.71	0.13
75	0.009	0.34	—
79	0.045	1.6	—
80	0.011	1.1	—
82	0.027	1.3	—
110	0.013	1.0	—
111	0.071	1.4	—

Throughout our investigations we noted the low solubility of the compounds in both organic and aqueous media. Since low solubility can significantly impact the absorption of a compound, we assessed a number of compounds for oral bioavailability in rats. Compound **22**, which has thermodynamic solubility of <1 μg/mL, is only 10% bioavailable after dosing in a standard methyl cellulose formulation. Other compounds from the series show even lower bioavailabilities, thiazole **76** only 3% and thiadiazole **109** <2%. Both of these have thermodynamic solubilities <1 μg/mL. A more soluble thiadiazole **111**, having a thermodynamic solubility of 56 μg/mL, was also found to have low bioavailability, <1%.

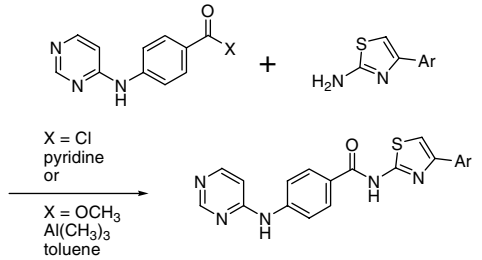
The latter finding in particular suggested that issues other than solubility may be responsible for the observed low bioavailability. Attempts to assess the permeability of compounds from the series in in vitro permeability assays were thwarted by their low solubility and we therefore resorted to in vivo experiments. Thus, **22** was solubilized in a PEG-400 formulation and dosed intraduodenally. The bioavailability was 11%, essentially the same as when the compound was dosed orally in a standard formulation. Additionally, **76** was formulated in a solubility-enhancing spray dried dispersion that increased its solubility to ~85 μg/mL, but when dosed orally, it was only slightly more bioavailable (6%) than when dosed in a standard formulation. These experiments indicated that in addition to low solubility, the absorption of compounds from the series was hindered by low permeability. This combination of low solubility with poor permeability constituted a significant obstacle, one likely to impede the identification of an orally bioavailable TPOr agonist from this series.

In conclusion, we have described the identification and development of a series of pyrimidine benzamides as low molecular weight agonists of the TPOr. Our goals for the series pertaining to potency (BaF3 EC_{50}s < 50 nM) and the removal of undesired chemical features of the lead molecule were achieved. Compounds from the series were shown to induce proliferation of human $CD34^+$ progenitor cells into megakaryocytes.

However, the physical properties of compounds in the series posed a significant obstacle to further development.

References and notes

1. Szilvassy, S. J. *Expert Opin. Biol. Ther.* **2006**, *6*, 983.
2. Duffy, K. J.; Darcy, M. G.; Delorme, E.; Dillon, S. B.; Eppley, D. F.; Erickson-Miller, C. L.; Giampa, L.; Hopson, C. B.; Huang, Y.; Keenan, R. K.; Lamb, P.; Leong, L.; Liu, N.; Miller, S. G.; Price, A. T.; Rosen, J.; Shah, R.; Shaw, A. N.; Smith, H.; Stark, K. C.; Tian, S.-S.; Tyree, C.; Wiggall, K. J.; Zhang, L.; Luengo, J. I. *J. Med. Chem.* **2001**, *44*, 3730.
3. Duffy, K. J.; Shaw, A. N.; Delorme, E.; Dillon, S. B.; Erickson-Miller, C.; Giampa, L.; Huang, Y.; Keenan, R. M.; Lamb, P.; Liu, N.; Miller, S. G.; Price, A. T.; Rosen, J.; Smith, H.; Wiggall, K. J.; Zhang, L.; Luengo, J. I. *J. Med. Chem.* **2002**, *45*, 3573.
4. Duffy, K. J.; Price, A. T.; Delorme, E.; Dillon, S. B.; Duquenne, C.; Erickson-Miller, C.; Giampa, L.; Huang, Y.; Keenan, R. M.; Lamb, P.; Liu, N.; Miller, S. G.; Rosen, J.; Shaw, A. N.; Smith, H.; Wiggall, K. J.; Zhang, L.; Luengo, J. I. *J. Med. Chem.* **2002**, *45*, 3576.
5. Erickson-Miller, C. L.; DeLorme, E.; Tian, S.-S.; Hopson, C. B.; Stark, K.; Giampa, L.; Valoret, E. I.; Duffy, K. J.; Luengo, J. L.; Rosen, J.; Miller, S. G.; Dillon, S. B.; Lamb, P. *Exp. Hematol.* **2005**, *33*, 85.
6. Safonov, I. G.; Heerding, D. A.; Keenan, R. M.; Price, A. T.; Erickson-Miller, C. L.; Hopson, C. B.; Levin, J. L.; Lord, K. A.; Tapley, P. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1212.
7. Nakamura, T.; Miyakawa, Y.; Miyamura, A.; Yamane, A.; Suzuki, H.; Ito, M.; Ohnishi, Y.; Ishiwata, N.; Ikeda, Y.; Tsuruzoe, N. *Blood* **2006**, *107*, 4300.
8. Revill, P.; Serradell, N.; Bolos, J. *Drugs Future* **2006**, *31*, 767.
9. (a) Takemoto, H.; Takayama, M.; Shiota, T. Eur. Patent 1 207 155; (b) Eur. Patent 1 354 880.
10. Kalgutkar, A. S.; Gardner, I.; Obach, R. S.; Shaffer, C. L.; Callegari, E.; Henne, K. R.; Mutlib, A. E.; Dalvie, D. K.; Lee, J. S.; Nakai, Y.; O'Donnell, J. P.; Boer, J.; Harriman, S. P. *Curr. Drug Metab.* **2005**, *6*, 161.
11. Reiter, L. A.; Linde, R. G., II WO 2006033005.
12. Analogs of **2** (Table 1) were prepared by acylation of the requisite 2-amino-4-arylthiazole with 4-(pyrimidin-4-ylamino)benzoyl chloride or in a trimethylaluminum-mediated reaction, with methyl 4-(pyrimidin-4-ylamino)benzoate.



Amide formation by these methods was also a key step in the preparation of other analogs.

13. The anilide and azine analogs (Table 2) were prepared by the following methods: *Method A*—(1) *N*-(4-(2-fluoro-3-(trifluoromethyl)phenyl)thiazol-2-yl)-4-iodobenzamide was prepared by acylation of requisite thiazoleamine with 4-iodobenzoyl chloride; (2) the requisite amine was coupled to the iodide by the procedure of Yin et al. (Ref. 22); *Method B*—(1) the requisite amine was coupled to *tert*-butyl 4-bromobenzoate by the method of Yin et al. Ref. 22; (2) TFA; (3) $SOCl_2$; (4) reaction with requisite thiazoleamine in pyridine; *Method C*—(1) the requisite amine was reacted with *tert*-butyl 4-fluorobenzoate in the presence of potassium *tert*-butoxide in DMF, (2) TFA, (3) $SOCl_2$, (4) reaction with requisite thiazoleamine in pyridine; *Method D*—(1) the requisite chloride was coupled to *tert*-butyl 4-aminobenzoate by the procedure of Yin et al. (Ref. 22), (2) TFA, (3) $SOCl_2$, (4) reaction with requisite thiazoleamine in pyridine; *Method E*—(1) methyl 4-(pyrimidin-4-ylamino)benzoate was methylated with methyl iodide and sodium hydride, (2) the methylated product was condensed with the requisite thiazoleamine in a trimethylaluminum-mediated reaction; *Method F*—(1) 4,6-dichloropyrimidine was coupled with methyl 4-hydroxybenzoate in DMF in the presence of cesium carbonate, (2) the ester was coupled with the requisite thiazoleamine in a trimethylaluminum-mediated reaction, (3) H_2–Pd/C; *Method G*—(1) 4-bromo-*N*-(4-(2-fluoro-3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide was alkylated with methyl iodide and sodium hydride, (2) the methylated product was coupled to 4-aminopyrimidine by the procedure of Yin et al. (Ref. 22); *Method H*—3-bromo-*N*-(4-(2-fluoro-3-(trifluoromethyl)phenyl)thiazol-2-yl)benzamide was coupled to 4-aminopyrimidine by the procedure of Yin et al. (Ref. 22).
14. C-6 Amino substituted pyrimidines (Table 3) were prepared in four steps: (1) 4,6-dichloropyrimidine was coupled with 4-aminobenzoic acid in the presence of concd hydrochloric acid in acetone, (2) $SOCl_2$, (3) reaction with requisite thiazoleamine in pyridine, (4) coupling with requisite amine in NMP at 100 °C.
15. 2-Amino-5-arylthiazoles (Table 5, Column B) were prepared in six steps: (1) 2-aminothiazole was protected with di-*tert*-butyl dicarbonate, (2) the thiazole ring was brominated with bromine in potassium acetate buffered acetic acid, (3) the carbamate was protected with 4-methoxybenzylchloride in the presence of DBU, (4) the bromide was coupled with the requisite arylboronic acid using $Pd(Ph_3P)_4$ and Cs_2CO_3 in dioxane, (5) the amine protection was removed with neat refluxing TFA, (6) the aminothiazole was acylated with 4-(pyrimidin-4-ylamino)benzoyl chloride.
16. 5-Amino-3-arylthiadiazoles (Table 5, Column C) were prepared in four steps: (1) the requisite benzonitrile was converted to the amidine with lithium hexamethyldisilazane according to the method of Thurkauf et al. (Ref. 23), (2) the amidine was converted to the aminothiadiazole by treatment with potassium thiocyanate and bromine according to the procedure of Goerdeler et al. (Ref. 24), (3) the aminothiadiazole was acylated in a trimethylaluminum-mediated reaction with methyl 4-(pyrimidin-4-ylamino)benzoate.
17. 3-Amino-5-arylthiadiazoles (Table 5, Column D) were prepared in four steps: (1) the amino group of 3-amino-5-methylthio[1,2,4]thiadiazole was protected as the dimethylformamidine with dimethylformamide dimethylacetal, (2) the aryl group was introduced using the requisite arylboronic acid employing the procedure of Liebeskind et al. (Ref. 25), (3) the amine protection was removed with *p*-toluenesulfonic acid in methanol, (4) the aminothiadiazole was acylated in a trimethylaluminum-mediated reaction with methyl 4-(pyrimidin-4-ylamino)benzoate.
18. 3-Amino-1-arylpyrazoles (Table 5, Column E) were prepared in two steps: (1) the aminopyrazoles were prepared from the requisite hydrazine by the procedure of Ege et al. (Ref. 26), (2) the aminopyrazoles were acylated with (pyrimidin-4-ylamino)benzoyl chloride.

19. 4-Amino-1-arylpyrazoles (Table 5, Column F) were prepared in three steps: (1) the requisite 1-arylpyrazole was nitrated by the procedure of Khan et al. (Ref. 27), (2) the nitro group was reduced with ammonium formate in the presence of Pd/C, (3) the aminopyrazole was acylated with (pyrimidin-4-ylamino)benzoyl chloride.
20. 5-Amino-3-arylisothiazoles (Table 5, Column G) were prepared in four steps: (1–3) the requisite 5-amino-3-arylisothiazoles were prepared from the corresponding benzonitriles by reaction with the anion of acetonitrile, conversion to the thioamide with hydrogen sulfide and then oxidation with iodine as described by Heckler (Ref. 28), (4) the aminoisothiazole was acylated with (pyrimidin-4-ylamino)benzoyl chloride.
21. 4-Amino-2-aryloxazoles (Table 5, Column H) were prepared in seven steps: (1–2) the requisite carboxylic acid was converted to the corresponding oxazoline and then oxidized by the method of Phillips et al. (Ref. 29), (3) the oxazole ester was saponified under standard conditions as described by Shafer et al. (Ref. 30), (4–5) a Curtius rearrangement in *tert*-butanol and subsequent acylation with 4-iodobenzoyl chloride was effected as described by Redies et al. (Ref. 31), (6) the BOC group was removed with magnesium perchlorate according to the procedure of Stafford et al. (Ref. 32), (7) the pyrimidine amine was coupled to the iodide by the procedure of Yin et al. (Ref. 22).

22. Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.
23. Thurkauf, A.; Hutchison, A.; Peterson, J.; Cornfield, L.; Meade, R.; Huston, K.; Harris, K.; Ross, R. C.; Gerber, K.; Ramabhadran, T. V. *J. Med. Chem.* **1995**, *38*, 2251.
24. Goerdeler, J.; Wember, K.; Worsch, G. *Chem. Ber.* **1954**, *87*, 57.
25. Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.
26. Ege, G.; Hermann, F. *J. Het. Chem.* **1982**, *19*, 1265.
27. Khan, M. A.; Lynch, B. M.; Hung, Y.-Y. *Can. J. Chem.* **1963**, *41*, 1540.
28. Heckler, R. E. EP 0 129 407.
29. Phillips, A. J.; Uto, Y.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.
30. Shafer, C. M.; Molinski, T. F. *Heterocycles* **2000**, *53*, 1167.
31. Redies, F.; Redies, B.; Turk, D.; Gille, Ch. DE 2 459 380.
32. Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873.