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Discovery of novel 2-(aminoheteroaryl)-thiazole-5-carboxamides as potent and orally active Src-family kinase *p*56^{Lck} inhibitors

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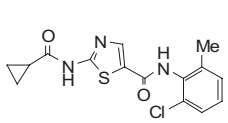
Abstract—A series of substituted 2-(aminoheteroaryl)-thiazole-5-carboxamide analogs have been synthesized as novel, potent inhibitors of the Src-family kinase *p*56^{Lck}. Among them, compound **2** displayed superior in vitro potency and excellent in vivo efficacy.

The tyrosine kinase *p*56^{Lck} has been shown to play a pivotal role in T cell development[1] and activation.[2] T cells that lack Lck or contain mutant Lck are unable to respond to stimulation via the TCR.[2a,3] Lck knockout mice or those with over expression of an Lck dominant negative show early arrest in thymocyte development.[1] Inhibition of Lck may be useful for the treatment of both chronic and acute T cell-mediated autoimmune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, transplant rejection and delayed hypersensitivity (DTH) reactions. Recent reviews have described several classes of Lck inhibitors and highlighted their therapeutic potential.[4]

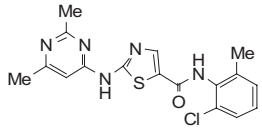
We recently reported the discovery of 2-(carboxamido)-thiazole-5-carboxamides, represented by **1**, as potent Lck inhibitors with modest cellular activity.[5] This paper describes our effort in the optimization of the in vitro potency of **1** which has led to the identification of compound **2** as a highly potent (K_i = 130 pM) and orally active Lck inhibitor (Fig. 1). In addition, compound **2** displays excellent activity against T cell proliferation (IC_{50} = 80 nM) and in vivo efficacy in a rodent rheumatoid arthritis model (rat adjuvant arthritis).

Our initial effort in the modification of **1** to improve its enzyme activity was focused on: (1) replacement of the cyclopropyl group with alkyl, aryl, and heterocyclic (including heteroaryl) groups of different sizes; and (2) replacement of the amide linker with other linkers such



1

$IC_{50\ (Lck)}$ = 35 nM
$IC_{50\ (T\ cell\ prolif.)}$ = 884 nM



2

$IC_{50\ (Lck)}$ = 1.2 nM
$Ki_{\ (Lck)}$ = 130 pM
$IC_{50\ (T\ cell\ prolif.)}$ = 80 nM

Figure 1. Activity for **1** and **2**.

Keywords: Lck inhibitor; *pan*-Src-family inhibitor.
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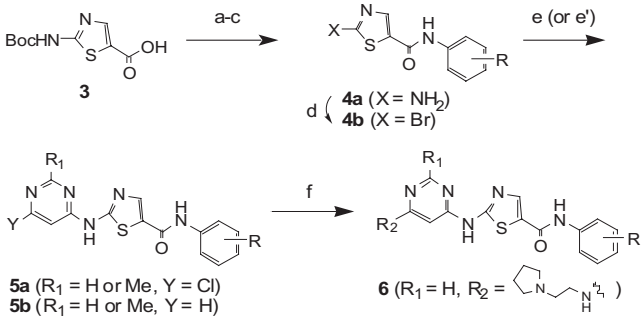
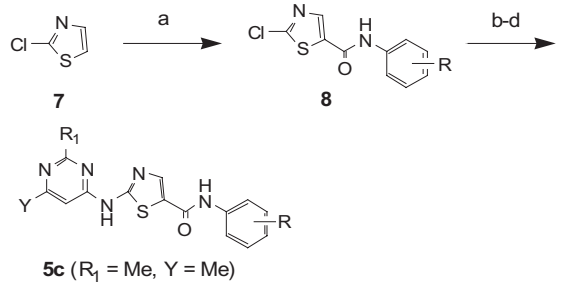
as carbamate or sulfonamide. Unfortunately, this approach led to little or no success. In most cases, subtle changes resulted in a >1000-fold drop in enzyme inhibitory activity.[6] While a few analogs displayed enzyme activity comparable to **1** (IC_{50} = 30–50 nM), none of them showed the desired level of cellular potency (<0.5 μM). Using a homology model of the $p56^{Lck}$ active site coupled with the observed SAR, we rationalized that while the carbonyl of the C_2-amide of **1** may not be involved in any active H-bonding interactions with the enzyme, its conformational rigidity directs the small cyclopropyl group into an optimal hydrophobic binding pocket. This optimal binding interaction derived from the small and rigid cyclopropyl amide was most likely disrupted when a larger alkyl or aryl group, a less conformational constrained group, or a sterically bulkier linker (such as a carbamate or a sulfonamide) were used. Accordingly, we turned our attention to a conformationally rigid 'amide mimic' as a possible replacement for the cyclopropyl amide of **1** and a heteroaryl amine appeared to be a suitable starting point to serve this purpose.

The heteroaryl aminothiazole-5-carboxamides described in this report were synthesized as depicted in Schemes 1 and 2. In Scheme 1, the acid **3**[5] was coupled to an appropriate aniline via the acid chloride intermediate. Removal of the Boc protecting group provided the intermediate **4a**. Amine **4a** was then coupled to an appropriately activated heteroaryl core (for illustration, 4,6-dichloro-2-methylpyrimidine was used in Scheme 1, where R_1 = Me and X = Cl) to afford the corresponding analog **5a**. Alternatively, the conversion of amine **4a** to bromide **4b** followed by coupling with an aminoheterocycle (in this case, 2-methyl-4-chloropyrimidine was used) in the presence of a base afforded **5b** (R_1 = Me and X = H). If desired, **5a** (Y = Cl) could be further homologated to give **6** (R_2 = amines). For illustration, 2-aminoethylpyrrolidine was used in this coupling reaction as shown in Scheme 1 (step **f**).



Scheme 1. Synthesis of C_2-heteroaromatic aminothiazole derivatives: (a) $(COCl)_2$, cat. DMF, THF; (b) $ArNH_2$, *i*-Pr_2NEt, THF; (c) TFA, CH_2Cl_2; (d) $NaNO_2$, CuBr; (e) 4,6-dichloro-2-methylpyrimidine, NaH, THF; (e′) 4-amino-6-chloro-2-methylpyrimidine, NaH (or NaHMDS); (f) 1-(2-hydroxyethyl)piperazine, neat, 80 °C.

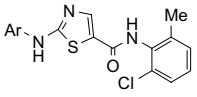


Scheme 2. Synthesis of C_2-heteroaromatic aminothiazole derivatives: (a) *n*-BuLi, ArN=C=O, −78 °C; (b) *p*-MeO-$C_6H_4CH_2Cl$, NaH, THF; (c) 4-amino-2-methylpyrimidine, NaH, THF; (d) TFA, anisole, TfOH.

Alternatively, deprotonation of 2-chlorothiazole **7**[7] using *n*-butyl lithium followed by quenching with commercially available arylisocyanates at −78 °C gave rise to 2-chloro-5-carboxamidothiazoles **8** in excellent yield (>90%). Protection of the amide **8** with the *p*-methoxybenzyl (PMB) bromide and reaction with an appropriate aminoheteroaryl, such as 4-amino-2,6-dimethylpyrimidine in the presence of a base, followed by the removal of the PMB protecting group similarly gave analog **5c** (where R_1 = Y = Me) in excellent overall yield (>95%), as shown in Scheme 2. Since the C_2-chlorothiazole **8** is significantly less reactive than the C_2-bromothiazole **4b**, protection of the amide in **8** prior to the coupling with aminoheterocycles is necessary to minimize the undesired cross coupling side reaction. In general, this route is complementary, and sometimes superior to the first one described in Scheme 1, especially when a properly activated heterocycle cannot be obtained readily.

Since our previous SAR[5] in this series of inhibitors demonstrated that 2-chloro-6-methyl aniline was an optimal pharmacophore for excellent Lck binding affinity, this particular aniline was used throughout our SAR studies. For simplicity, data on only a limited set of analogs are presented in Tables 1–3 to describe the SAR.

Table 1. 2-Arylaminothiazole-5-carboxamide SAR (compounds **1**, **9**–**14**)

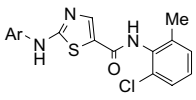


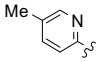
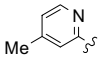
Compds	Ar	Lck (enzyme)[b] IC_{50}, nM[a]	T Cell Prolif.[b] IC_{50}, nM[a]
1	na	35	884
9		0.6	210
10		1.2	140
11		6.7	870
12		10	270
13		4	350
14		374	–

[a] Values throughout are mean of three experiments, standard deviation ±10%.

[b] For detailed assay conditions, see Ref. 17.

Table 2. 2-Arylaminothiazole-5-carboxamide SAR (compounds **15**–**21**)



Compds	Ar	Lck (enzyme)[b] IC_{50}, nM[a]	T cell prolif.[b] IC_{50}, nM[a]
15		<1	106
16		1.1	156
17		0.5	85
18		7.3	365
19		4	140
2		1 (K_i = 130 pM)	80
20		50	—
21		2	883

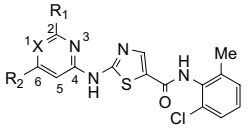
[a] Values throughout are mean of three experiments, standard deviation ±10%.
[b] For detailed assay conditions, see Ref. 17.

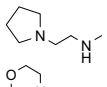
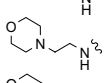
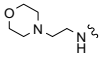
Replacement of the 2-cyclopropylamido functionality of **1**[6] with a simple aniline resulted in a significant gain (>30-fold) of enzyme potency, as demonstrated by compound **9** in Table 1. This dramatic enhancement of enzyme activity was also reflected in the cellular based assay. Compound **9** showed a 4-fold improvement of IC_{50} against T cell proliferation over **1**. Exchange of aniline in **9** with 2-aminopyridine essentially retained in vitro potency (**10**). However, similar substitution using the regio-isomeric 3- and 4-aminopyridines led to the loss of intrinsic activities (**11** and **12**). To investigate if basicity played a significant role in the enhancement of intrinsic activity, the 3-aminopyridazine analog **13** was prepared. The activity of **13** is between that of **10** and **11**, a result consistent with the observation that the 2-pyridyl substituent is more potent than the 3-pyridyl substituent and that basicity does not play a significant role in the binding affinity.[8] Finally, replacing the aniline of **9** with a cyclohexyl amine (**14**) is detrimental to the activity. The more than 400-fold loss of enzyme activity clearly indicates a steric restriction in this region, consistent with the observation that the C_2-cyclobutyl amide, a very close analog of **1**, is less active against Lck.[6]

Our next effort focused on developing the SAR with respect to the substitution pattern on the 2-amino-heteroaromatic ring system of **10**. While 2- or 3-methyl-aminopyridyl analogs (**15** and **16**) were equipotent to **10**, the 4- and 5-methyl substitution (**17** and **18**) resulted in reduction of activity (5- to 7-fold). In addition, appropriate disubstitution was tolerated (**19** and **2** vs **10**). Switching pyridine to pyrimidine led to a dramatic result: while the 4,6-dimethyl-2-aminopyrimidine analog **2** displayed excellent intrinsic potency, its regio-isomer **20** was substantially less potent, indicating the geometric preference of polar heteroatoms in the small hydrophobic pocket (vide infra). Interestingly, the corresponding di-substituted aniline was tolerated with respect to enzyme binding but a considerable drop in cellular activity was observed (**21** vs **9**) (Table 2).

Further optimization was focused on the enhancement of the cellular activity of **2**. This was achieved via the introduction of solubility-enhancing side chains[9] containing polar and weakly basic groups onto the

Table 3. 2-Arylaminothiazole-5-carboxamide SAR (compounds **2**, **22**–**25**)



Compds	X	R_1	R_2	Lck (enzyme)[b] IC_{50}, nM[a]	T cell prolif.[b] IC_{50}, nM[a]
2	N	Me	Me	1 (K_i = 130 pM)	80
22	N	H		0.4 (K_i = 60 pM)	19
23	N	H		4	17
24	N	H		<1	3
25	CH		H	<1	6
26	CH		H	<1	11
CsA				NA	50

[a] Values throughout are mean of three experiments, standard deviation ±10%.
[b] For detailed assay conditions, see Ref. 17.

2-amino-heteroaromatic rings of **19** and/or **2**. Using a parallel synthetic approach outlined in Scheme1 (step **f**), analogs with sub-nanomolar activities against Lck and single digit nanomolar inhibitory activities against T cell proliferation were identified (Table 3). With the exception of **23**, incorporation of side chains bearing polar groups at the C_6 position of **2** in general led to compounds with better Lck affinity relative to the corresponding parent and, more significantly, a substantial boost (4- to 25-fold) in cellular potency (**22** and **24**). A similar result was also observed in the 2-aminopyridine series. Analogs containing (*S*)-methyl-piperazine (**25**) and morpholino-2-ethylamine (**26**) side chains at the C_2 position (numbering according to the structure shown in Table 3) also displayed superior cell potency in comparison to their parent compound **10**. The increased in vitro potency of **22** and **24–26** as compared to **2** and **10** can be attributed, at least in part, to the enhanced aqueous solubility since our modeling studies indicate that these side chains are pointed toward the solvent front.[10]

In contrast to the in vitro assays, the physiological level of ATP in intracellular settings is thought significantly higher and may approach 500 μM or above. Such a change in ATP concentration can potentially generate a drastic reduction in binding affinity for any ATP-competitive inhibitors. To gain insight into the change of magnitude in binding affinity against Lck, compound **2** was further tested at a higher ATP concentration. Not surprisingly, in the presence of 1 mM ATP, compound **2** displayed a significant loss in binding affinity toward the enzyme, with an IC_{50} of 5.5 ± 0.1 μM and a K_i value of 247 ± 94 nM ($n = 2$).

The improvement of physicochemical properties derived from the incorporation of polar side chains and/or the enhancement of cell permeability are unlikely to be the sole contributing factors for the superior cellular potency observed for compounds **22–26**. To ensure that this extraordinary level of cellular potency was not associated with a cytotoxic effect, analogs within this series, including **22**, were routinely assayed for cytotoxicity in an Alamar Blue Assay. In general, compounds such as **22** and closely relate related analogs showed no sign of cytotoxicity to Jurkat (T) and Ramos (B) cells. To put the superior T cell potency of these analogs into perspective, cyclosporine A (CsA), a potent anti-inflammatory drug on the market, was used as a comparator ($IC_{50(T\ cell\ prolif.)} = 50$ nM, Table 3). Cyclosporin A suppresses the T cell proliferation by inhibiting the phosphatase activity of calcineurin on NFAT, thereby preventing its translocation to the nucleus and suppressing IL-2 mRNA transcription. On the other hand, inhibition of Lck by compounds such as **22** blocks the signal transduction cascade considerably upstream of calcineurin, presumably suppressing the activities of signaling molecules from multiple pathways. In addition, compounds in this series potently inhibit several other kinases (vide infra), thus profound suppression of T cell proliferation may also be due to an additive or synergistic effect of inhibiting multiple kinase activities and/or signaling pathways.

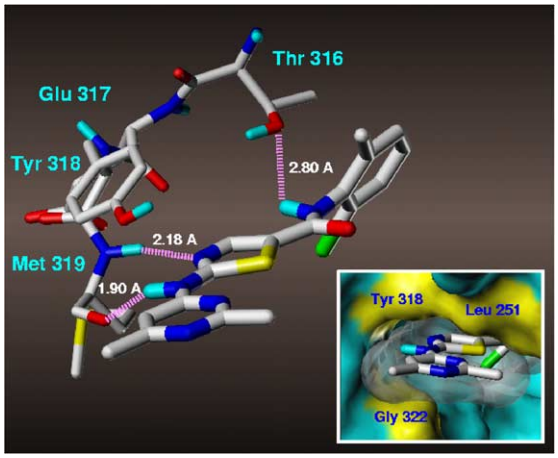
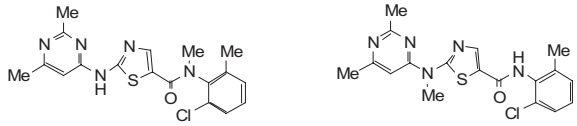


Figure 2. Proposed binding interactions of **2** with Lck kinase domain. Van der Waals surfaces are shown (inset) illustrating the fit of the pendant pyrimidine ring in the hydrophobic cleft of the binding site.



27 $IC_{50\ (Lck)} = 277$ nM

28 $IC_{50\ (Lck)} = 2{,}345$ nM

Figure 3. Enzyme activity of **27** and **28.**

The proposed binding mode for **2** is consistent with that previously published for **1** in the ATP binding pocket.[5] This is illustrated in Figure 2 using a model of the $p56^{Lck}$ ATP binding site based on the published structure.[11] The H-bonding donor/acceptor system at Met319/aminothiazole appears to play a central role in orientation of the ligand, with the deep hydrophobic pocket occupied by the angular 2-chloro-6-methylaniline ring. In addition, there is a likelihood that some interaction occurs between the Thr316 hydroxyl acting as a H-bond acceptor and the carboxamide NH as these groups are modeled to about 2.8 Angstroms of each other. *N*-substitution of **2** with a methyl functionality led to dramatic loss of enzyme binding affinity (**27** and **28**, Fig. 3) relative to its parent. In addition, the pendant 2,6-dimethyl-2-amino pyrimidine ring occupies a relatively narrow hydrophobic cleft created by Leu251, Tyr318 and Gly322 (Fig. 2, inset). This feature may explain the added affinity of the pendant ring series as such burial of hydrophobic surfaces for both the ligand and protein is energetically favored in aqueous solution.

Selectivity over other kinases is an important factor for consideration when developing a chronically administered therapeutic agent. As a representative analog in this series, compound **2** was screened against in-house kinase panels and the relevant selectivity data is shown in Table 4. In general, excellent selectivity is observed for **2** against the receptor tyrosine and serine/threonine kinases whereas no selectivity against the Src-family kinases (Fyn, Src, Hck, Blk, and Fgr) or JAK3

Table 4. Kinase selectivity profile for compound **2**

Kinase	**Enzyme** IC_{50}, μM[a]	Kinase	**Enzyme** IC_{50}, μM[a]
Lck	0.001	JAK3	0.006
Fyn	0.001	CDK2	>25
Src	<0.001	CDK4	>25
Hck	0.002	FGFR1	>10
Blk	0.001	KDR	>10
Fgr	<0.001	HER2	5.2

[a] Values throughout are mean of three experiments, standard deviation ±10%.

was observed, presumably due to the high sequence homology within their ATP binding sites.

Compound **2** was selected as a prototype from this series of Lck inhibitors for further evaluation. The in vivo pharmacokinetic profile of **2** was determined in rats. Upon single doses of 10 mpk iv and po, **2** showed a T_{max} at 1 h with peak plasma exposure of 2 μM (C_{max}). Both plasma half life ($T_{1/2}$) and the mean residence time (MRT) of **2** are approximately 4 h. The volume of distribution (Vss) is 12 L/kg, indicating that significant partitioning of **2** into the tissues can be expected. The rate of plasma clearance (Cl) is moderate at 29 mL/min/kg, giving the oral bioavailability of **2** as 65% in rats. In addition, compound **2** displayed a 93.6% plasma protein binding in mouse.

Studies have shown that T cells plays an important role in the pathogenesis of rheumatoid arthritis (RA).[12] Recent clinical investigation in RA patients using a modulator of T cell co-stimulation (CTLA4-Ig) demonstrated significant improvement of signs and symptoms of rheumatoid arthritis as well as the health-related quality of life,[13] suggesting that a strategy of targeting T cell responses could lead to therapeutic benefits for RA patients. *pan*-Src-family kinase inhibitors could potentially provide benefit in the rat adjuvant arthritis model by action on Src-family kinases in multiple cell types. The inhibition of Lck and Fyn would be expected to block T cell activation. In addition, macrophages are believed to play an important role in the rat adjuvant arthritis model. Many Fc-γ receptor-induced functional responses and signaling events have been reported to be diminished or delayed in macrophages from mice deficient in the Src-family kinases Hck, Fgr, and Lyn, including immunoglobulin (Ig)G-coated erythrocyte phagocytosis and the respiratory burst.[14] The same macrophages have also been reported to have impaired integrin-mediated signal transduction, altered cytoskeletal structure and reduced motility.[15] Taken together, *pan*-Src-family kinase inhibition might therefore contribute to efficacy in an in vivo model by inhibiting responses of T cells and macrophages beyond the inhibition of T cell responses that would be expected from an Lck-specific inhibitor. Based on its encouraging in vitro potency and PK profile in rats, we evaluated **2** in a rat adjuvant arthritis model (Fig. 4). In this model, male Lewis rats were immunized with complete Freund's adjuvant at the base of the tail. Hind paw volumes were measured by volume displacement plethysmometry

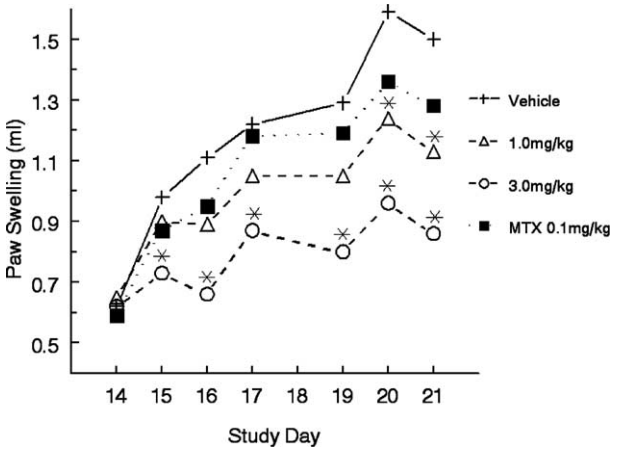


Figure 4. Rat adjuvant arthritis studies using **2**.

(Ugo Basile, Italy). Fourteen days after adjuvant immunization, rats with clinical signs of disease were randomized into treatment groups (n = 8/group). Compound **2** was administered orally twice daily at 1.0 or 3.0 mg/kg and compared to the once daily methotrexate (MTX) treated group at 0.1 mg/kg. As shown in Figure 2, compound **2** showed a dose-dependent inhibition of paw swelling in this animal model of rheumatoid arthritis. At 3.0 mg/kg, treatment with **2** slowed disease progression significantly ($p > 0.05$; Student's test) when compared to the vehicle treatment group within the first 24 h after administration was initiated. The 1.0 mg/kg dose level was less efficacious, but still demonstrated significant inhibition of paw swelling after one week of treatment. In contrast to the vehicle control rats which showed loss of body weight due to disease progression, rats that received **2** appeared healthy and actually gained weight over the course of treatment.

In summary, we have identified a series of novel 2-(aminoheteroaryl)thiazole-5-carboxamide analogs, represented by compound **2**, as potent Lck inhibitors with superior T cell activity over CsA. Compound **2** displayed a pharmacokinetic profile suitable for oral administration and demonstrated excellent in vivo efficacy comparable to the known anti-inflammatory drug methotrexate in a rodent inflammation model. Additional characterization of **2** and related analogs from this series will be reported in due course.[16]

Acknowledgements

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References and notes

1. (a) Molina, T. J.; Kishihara, K.; Siderovski, D. P.; van Ewijk, W.; Narendran, A.; Timms, E.; Wakeham, A.; Paige, C. J.; Hartman, K.-U.; Veilette, A.; Davison, D.; Mak, T. W. *Nature* **1992**, *357*, 161; (b) Levin, S. D.;

Anderson, S. J.; Forbush, K. A.; Perlmutter, R. M. *EMBO J.* **1993**, *12*, 1671.
2. (a) Strauss, D. B.; Weiss, A. *Cell* **1992**, *70*, 585; (b) Chan, A. C.; Desai, D. M.; Weiss, A. *Annu. Rev. Immunol.* **1994**, *12*, 555.
3. Karnitz, L.; Sutor, S. L.; Torigoe, T.; Reed, J. C.; Bell, M. P.; McKean, D. J.; Leibson, P. J.; Abraham, R. T. *Mol. Cell Biol.* **1992**, *12*, 4521.
4. (a) Kamens, J. S.; Ratnofsky, S. E.; Hirst, G. C. *Curr. Opin. Invest. Drugs* **2001**, *2*, 1213; (b) Dowden, J.; Ward, S. G. *Exp. Opin. Ther. Patents* **2001**, *11*, 295; (c) Boschelli, D. H.; Boschelli, F. *Drugs Future* **2000**, *25*, 717; (d) Susa, M.; Teti, A. *Drug News Perspect.* **2000**, *13*, 169.
5. Wityak, J.; Das, J.; Moquin, R. V.; Shen, Z.; Lin, J.; Chen, P.; Doweyko, A. M.; Pitt, S.; Pang, S.; Shen, D. R.; Fang, Q.; de Fex, H. F.; Schieven, G. L.; Kanner, S. B.; Barrish, J. C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4007.
6. Unpublished results: Lck enzyme activity (IC_{50}) of other C_2-carboxaminothiazole-5-carboxamide analogs: *n*-propyl amide (>12.5 μM), *n*-butyl amide (2.8 μM), 1-methylcyclopropyl amide (>12.5 μM) and cyclobutyl amide (>12.5 μM).
7. Mclean, J.; Muir, G. D. *J. Chem. Soc.* **1942**, 383.
8. A similar trend of SAR was also observed in the 2-aminobenzothiazole-5-carboxamate series in our lab and reported previously. For reference, see: Das, J.; Moquin, R. V.; Lin, J.; Liu, C.; Doweyko, A. M.; de Fex, H. F.; Fang, Q.; Pang, S.; Pitt, S.; Shen, D. R.; Schieven, G. L.; Barrish, J. C.; Wityak, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2587.
9. (a) Palmer, B. D.; Trumpp-Kallmeyer, S.; Fry, D. W.; Nelson, J. M.; Showalter, H. H. D.; Denny, W. A. *J. Med. Chem.* **1997**, *40*(10), 1519–1529; (b) Thompson, A. M.; Murray, D. K.; Dlliott, W. L.; Fry, D. W.; Nelson, J. A.; Showalter, H. H. D.; Roberts, B. J.; Vincent, P. W.; Denny, W. A. *J. Med. Chem.* **1997**, *40*(24), 3915–3925; (c) Rewcastle, G. W.; Murray, D. K.; Elliott, W. L.; Fry, D. W.; Howard, C. T.; Nelson, J. M.; Roberts, B. J.; Vincent, P. W.; Showalter, H. H. D.; Winters, R. T.; Denny, W. A. *J. Med. Chem.* **1998**, *41*(5), 742–751.
10. This part of the modeling work will be discussed in a separate paper.
11. (a) Yamaguchi, H.; Hendrickson, W. A. *Nature* **1996**, *384*, 484; (b) Zhu, X.; Kim, J. L.; Newcomb, J. R.; Rose, P. E.; Stover, D. R.; Toledo, L. M.; Zhao, H.; Morgenstern, K. A. *Structure* **1999**, *7*, 651.
12. (a) Falta, M. T.; Kotzin, B. L. In *T Cells in Arthritis*; van den Berg, W. B., Firestein, G. S. T., Eds.; Birkhauser: Basel, Switzerland, 1998; pp 201–231; (b) Korganow, A.-S. J. H.; Mangialaio, S.; Duchatelle, V.; Pelanda, R.; Martin, T.; Degott, C.; Kikutani, H.; Rajewsky, K.; Pasquali, J.-L.; Benoist, C.; Mathis, D. *Immunity* **1999**, *10*(4), 451–461.
13. Kremer, J. M.; Westhovens, R.; Leon, M.; Di Giorgio, E.; Alten, R.; Steinfeld, S.; Russell, A.; Dougados, M.; Emery, P.; Nuamah, I. F.; Williams, G. R.; Becker, J.-C.; Hagerty, D. T.; Moreland, L. W. *New Engl. J. Med.* **2003**, *349*(20), 1907–1915.
14. Fitzer-Attas, C. J.; Lowry, M.; Crowley, M. T.; Finn, A. J.; Meng, F.; DeFranco, A. L.; Lowell, C. A. *J. Exp. Med.* **2000**, *191*(4), 669–682.
15. Suen, P. W.; Ilic, D.; Caveggion, E.; Berton, G.; Damsky, C. H.; Lowell, C. A. *J. Cell Sci.* **1999**, *112*(Pt 22), 4067–4078.
16. For a report on compound **2** and its related analogs used as anti-cancer agents, see: Lombardo, L. J.; Lee, F. Y.; Chen, P.; Norris, D.; Barrish, J. C.; Behnia, K.; Castaneda, S.; Cornelius, L. A. M.; Das, J.; Doweyko, A. M.; Fairchild, F.; Hunt, J. T.; Inigo, I.; Johnston, K.; Kamath, A.; Kan, D.; Klei, H.; Marathe, P.; Pang, S.; Peterson, R.; Pitt, S.; Schieven, G. L.; Schmidt, R. J.; Tokarski, J.; Wen, M.-L.; Wityak, J.; Borzilleri, R. M. *J. Med. Chem.*, submitted for publication.
17. Chen, P.; Doweyko, A. M.; Norris, D.; Gu, H. H.; Spergel, S. H.; Das, J.; Moquin, R. V.; Lin, J.; Wityak, J.; Iwanowicz, E. J.; McIntyre, K. W.; Shuster, D. J.; Behnia, K.; Chong, S.; de Fex, H.; Pang, S.; Pitt, S.; Shen, D. R.; Thrall, S.; Stanley, P.; Kocy, O. R.; Witmer, M. R.; Kanner, S. B.; Schieven, G. L.; Barrish, J. C. *J. Med. Chem.* **2004**, *47*, 4517–4529.