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Synthetic staurosporines via a ring closing metathesis strategy as potent JAK3 inhibitors and modulators of allergic responses

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ABSTRACT

The synthesis and biological evaluation of JAK3 based staurosporine compounds is described. The compounds are constructed completely de novo, and a ring closing metathesis strategy is used to assemble the sugar mimetic portion. These analogs show potent JAK3 activity against isolated enzyme and in T-cells. One analog (**32**) showed unique biological effects during in vitro and in vivo tests including inhibition of STAT5 phosphorylation, blockade of mast cell responses, and reduction of JAK3 based effects in mice models of allergic disease.

The Janus kinases (JAK's) are a small family of cytoplasmic receptor associated protein tyrosine kinases that play pivotal roles in cytokine mediated biological responses by activation of the latent forms of STATs (signal transducers and activators of transcription). Activated JAK's phosphorylate the intracellular domain of cytokine receptors creating docking sites for the STAT signaling proteins, and further phosphorylation by the JAK's of the STAT's takes place.[1] Among the four members (JAK1, JAK2, JAK3, and Tyk2), JAK3 is segregated to the hematopoietic cells due to restricted tissue expression.[2] JAK3 is abundantly expressed in lymphoid cells and has a crucial role in T-cell development and homeostasis of the immune system because of association with the common gamma chain (γc) of cytokine receptors. Disruption of JAK3 function results in quantitative and qualitative deficiencies in both B and T-cell compartments of the immune system of JAK3 deficient mice, and development of severe combined immunodeficiency (SCID) in humans with the JAK3 genetic aberration.[3] Our studies have shown that JAK3 is also a key regulator of IgE receptor-mediated mast cell responses.[4] Specifically, it has been shown that JAK3 knock out mast cells release substantially reduced amounts of inflammatory mediators upon IgE receptor crosslinking as compared to wild-type. Furthermore, JAK3 also plays a key role in mast cell dependent innate immune responses to gram-negative bacteria.[5] Inhibitors of JAK3 have shown utility in many different auto immune disorders, including allograft rejection during transplantation, acute lymphoblastic leukemia, type I diabetes, rheumatoid arthritis and allergic diseases.[6] Thus, targeting JAK3 may be helpful in the treatment and prevention of immune system based inflammatory diseases.

Currently, several potent JAK3 inhibitors have been identified. These include naphthyl ketones, oxindole derivatives, pyrimidine heterocycles, and pyrimidine based purines.[6] These inhibitors have been the focus of several reviews, and the two most notable developments have been the quinazoline WHIP-131 and the purine CP-690,550 (Fig. 1).[7,8] Both have shown JAK3 based activity in animal models of JAK3 related disease, including allograft rejection. Our effort focused on the staurosporine class of natural products. Staurosporine is a potent inhibitor of many kinases including JAK3.[9] Although both staurosporine and K-252a (Fig. 1) are broad spectrum protein kinase inhibitors, many of their derivatives have been found to selectively inhibit both serine/threonine and tyrosine protein kinase family members.[10] Furthermore, small modifications on these scaffolds can have dramatic effects on target specificity. In fact, synthetic and medicinal chemistry studies have provided many types of semi-synthetic derivatives, of which some have progressed through various stages of human clinical testing (Fig. 1; ruboxistaurin/LY-333531,[11] UCN-01,[12] PKC412,[13] lestaurtinib/CEP-701,[14] and CEP-1347[15]). Most notably, it was recently

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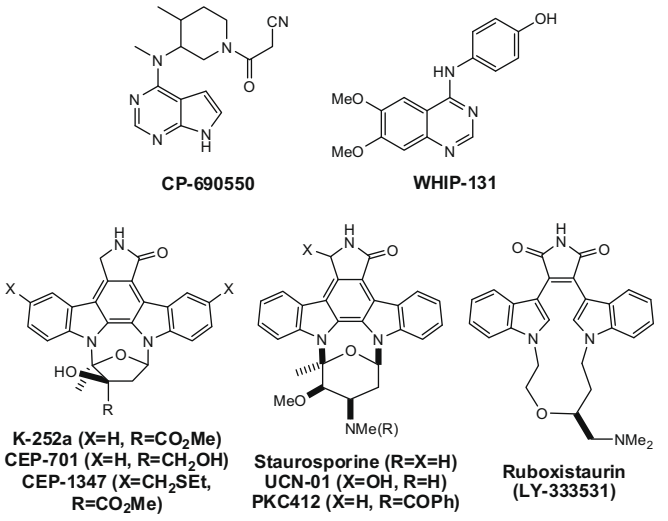


Figure 1. Small molecule JAK3 inhibitors, indole carbazole natural products and analogs.

shown that some of the anti-leukemic effects of the newly approved anti-cancer agent lestaurinib™ (CEP-701) are mediated through inhibition of the JAK2 enzyme pathway.[14] In these cases it is worth noting that most of these materials are derived semi-synthetically directly from the natural products through fermentation, isolation, and derivation chemistries. Staurosporine and K-252a have both been used extensively to map ATP binding sites of protein kinases through X-ray studies.[16] Natural product mimetics have the advantage of a high chance of target directed effects and have been estimated to be the basis for up to half of all new drugs in the past few decades.[17]

The overall goals of our efforts were to discover compounds that were more selective than staurosporine by modifying the natural products in three positions: the sugar portion, the pyrrolidinone ring, and also eventually on the indole ring. We devised an approach to allow the inclusion of eight, nine, and ten member carbocyclic chains via the ring closing metathesis reaction scheme, and we previously communicated some of this chemistry.[18] In principal, this would allow alkene type compounds to be produced, and also enable the ability to install oxygen functionality along the bottom portion. This strategy has been utilized in other natural product synthetic approaches.[19] In this Letter, we provide how we utilized this chemistry to discover a series of unique natural product analogs through further modification and derivatization reaction pathways which has resulted in the discovery of potent and selective JAK3 inhibitors.

Our route started from construction of the bisindole precursor natural products based on acryrubin and acryflavin A (Scheme 1). The *N*-methyl-maleimide precursor **2** was assembled according to previous methodology from 2,3-dichloromaleic anhydride (**1**). Alkylation sequences provide both symmetrical (**3**) and unsymmetrical (**4**) RCM precursors. As previously reported, these substrates were exposed to the Grubbs 1st generation catalyst (**I**, Fig. 2) to give the ring closed eight (**5**) and nine member (**6**) ring products. Elaboration to final products that included hydroxyl groups consisted of hydroboration, and oxidation, and maleimide hydrolysis to give mono hydroxyl eight (**7**) and nine (**8**) member ring appended products. Most notable with the nine member ring (**8**) was the formation of a single isomer resulting from oxidation at the carbon closer to the indole nitrogen. Osmylation followed by maleimide hydrolysis resulted in eight (**9**) and nine (**10**) ringed syn diols.

Continuing the maleimide chemistry (Scheme 2), we next turned our attention to a more elaborate sugar mimetic substitution. First, we installed a more labile protecting group which would

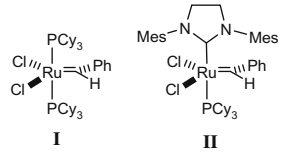
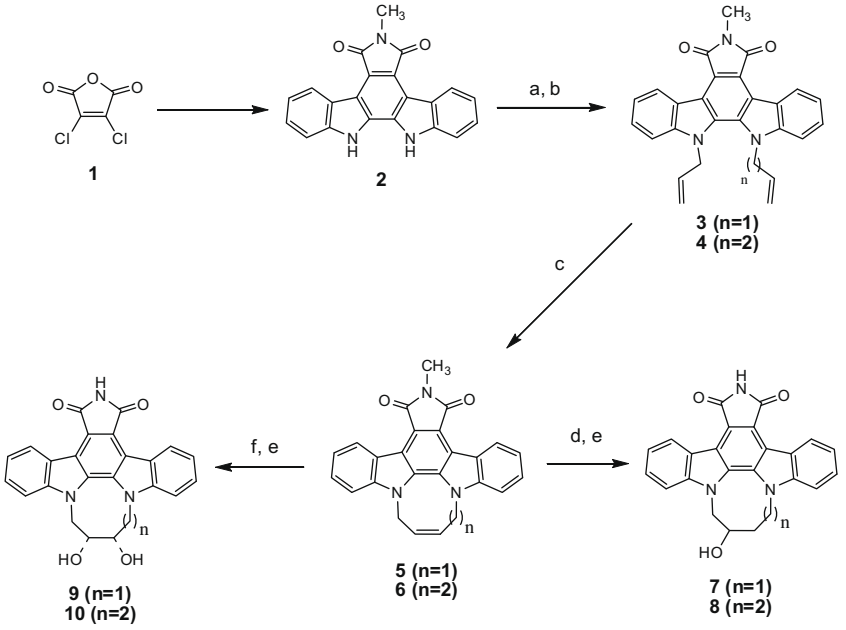
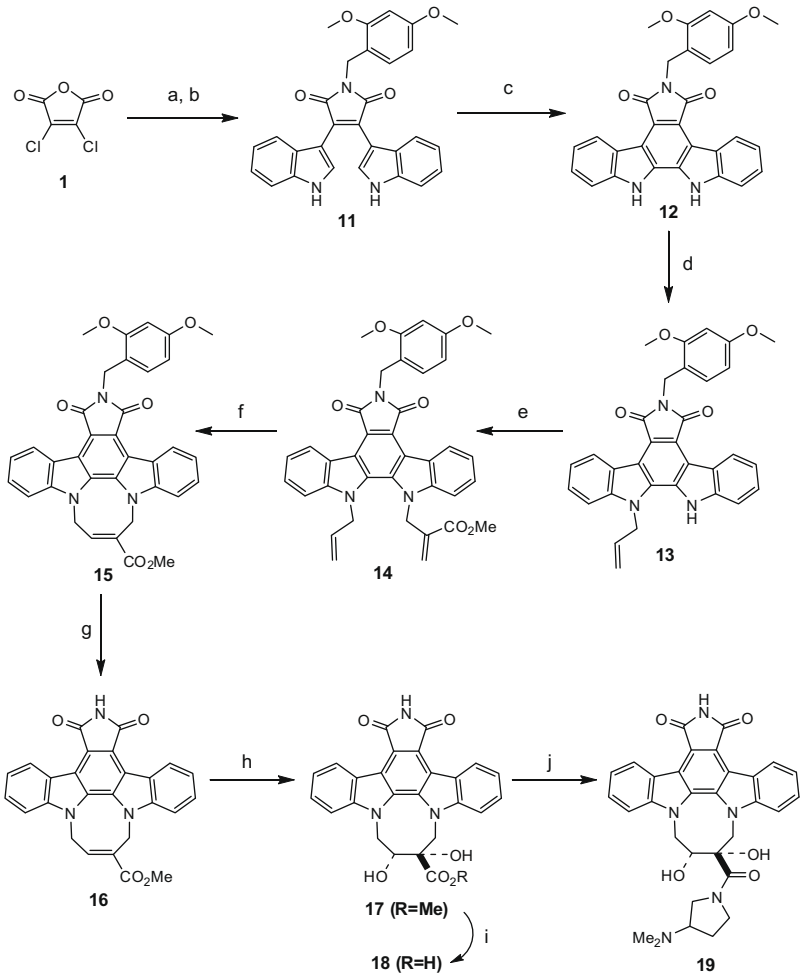


Figure 2. Ruthenium based olefin metathesis catalysts used in this study.



Scheme 1. Reagents and conditions: (a) Cs_2CO_3, allyl bromide, DMF, rt (83%); (b) 4-bromo-1-butene, DMSO, rt, (55%) then (a, 99%); (c) Grubbs I catalyst (**I**), DCM, rt, 85/96%; (d) (i) BH_3/THF, 0 °C–rt; (ii) H_2O_2, NaOH; (e) (i) NaOH, EtOH; (ii) HCl; (iii) HMDS, DMF, 90 °C; (f) $OsCl_3$, Me_3NO, $CHCl_3$/THF.



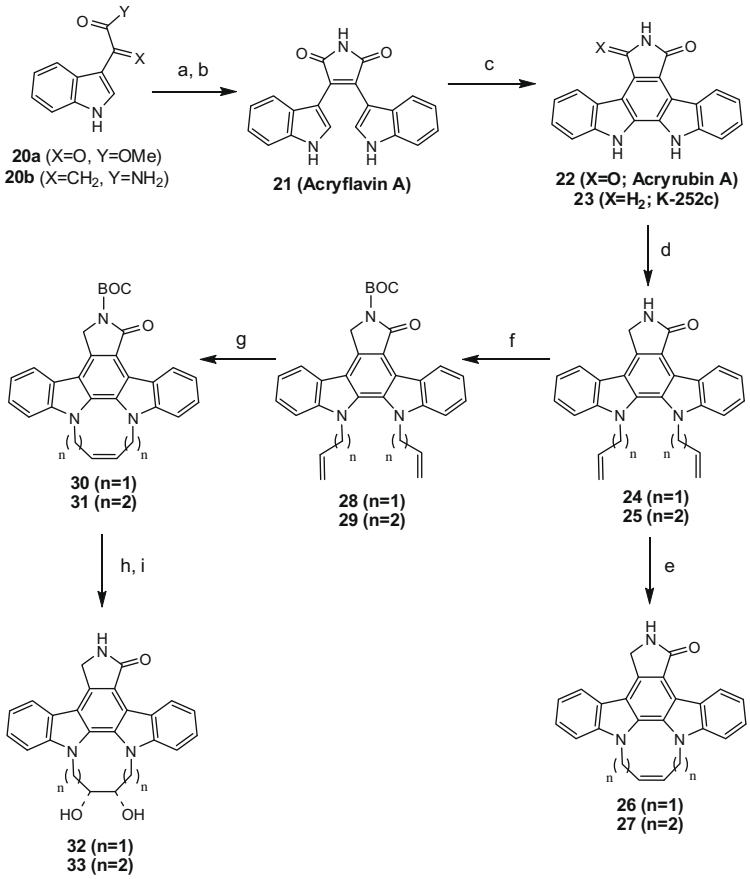
Scheme 2. Reagents and conditions: (a) AcOH, 80 °C, 18 h, 2,4-$(MeO)_2PhCH_2NH_2$, (87%); (b) indole, EtMgBr, Et_2O, THF, reflux, 24 h (56%); (c) DDQ, *p*-TsOH (cat.), $PhCH_3$, 1,4-dioxane (100%); (d) NaH, THF, allyl bromide, −50 °C to rt (51%); (e) Cs_2CO_3, methyl-(2-bromomethyl)-acrylate, DMF, 96%; (f) Grubbs **II** catalyst (**II**, 0.125 equiv), μwave, 150 °C, $ClCH_2CH_2Cl$, 30 min (59–74%); (g) TFA, anisole, reflux, 71%; (h) $OsCl_3$, Me_3NO, THF/$CHCl_3$, H_2O, 81%; (i) LiOH, THF (75%); (j) HOBt, DIPEA, EDAC, 3-(diemthylamino)-pyrrolidine, DMF (45%).

allow the installation of more sensitive functionality on the bottom portion. The 2,4-dimethoxy-bis-indole precursor **12** was synthesized by a similar sequence that was used for **2**. First, 2,3-dichloromaleimide (**1**) was converted to the bisindole compound **11** in two steps, followed by oxidation with DDQ. Selective alkylation was carried out by low temperature allylation to give **13**. Alkylation with bromomethyl acrylate gave **14**. Reaction with the Grubbs 2nd generation catalyst (**II**, Fig. 2) using microwave irradiation conditions we developed for this substrate gave a good yield of the corresponding acrylate gave the corresponding ring closed product **15**. Next, we removed the maleimide 2,4-dimethoxybenzyl protecting group utilizing acidic conditions to give **16**. We then performed dihydroxylation with osmium trichloride to give **17**. Hydrolysis of the ester gave dihydroxy-carboxylic acid **18**. Finally, amide bond formation could be completed to form secondary amide **19**.

The pyrrolidinone chemistry began with the synthesis of the staurosporine alglycon **23** (Scheme 3). Components of this synthesis were previously reported, and begin by condensation of indole precursors **20a** and **20b** to give Acrirubin A (**21**). Next, oxidation with palladium chloride was followed by Clemmenson reduction with tin metal to give **23**. Allylation was carried to out to give bis-allyl compound **24**. In a similar fashion, bis-1-butenyl chains were attached (**25**) but required microwave irradiation. At this stage, ring closing metathesis was performed directly with **I** to give eight (**26**) and ten member (**27**) cis-alkenyl ring systems. Alternatively, nitrogen protection with a *t*-butyl carbonate group (**28** and **29**), was followed by ring closing metathesis with **I** (**30** and **31**). Dihydroxylation with osmium trichloride followed by BOC deprotection gave the eight (**32**) and ten (**33**) member syn diols.

We then tested our compounds against the JAK3 enzyme along with staurosporine (Table 1). The SAR showed several trends. The maleimide derivatives had slightly better potency compared to the pyrrolidinones (**9** vs **32**). In all cases, the alglycon portion adds significant potency to the molecule resulting in up to 60-fold better potencies compared to the alglycon (K-252c). The dihydro-deoxy derivatives (**26** and **27**) showed activity better than K-252c and one derivative (**16**) was comparable to staurosporine, while the ring opened material lost almost all activity (**24**). The mono-hyrdroxyl (**7** and **8**) and diol chains (**9**, **10**, **32**, and **33**) showed equal or even greater activity (**17**) than staurosporine. Although the carboxymethyl group, which is also present on the natural product K-252a, seems to add some potency on these analogs (**17** versus **9**), the hydroxyl function seems to add equal and even more potency (**26** vs **32**). The diol functionality tolerates other substitutions such as a carboxylic acid (**18**) and a carboxamide (**19**) without much change in potency.

A computer based modeling study of one of the analogs (**32**) showed typical interactions of an ATP competitive inhibitor (Fig. 3).[20] Compound **32** was docked into a homology model of



Scheme 3. Reagents and conditions: (a) $PdCl_2$, DMF, 90 °C, (70%); (b) Sn°, HCl(conc.), THF, (86%); (d) allyl bromide, Cs_2CO_3, DMF, rt (72%); (d) 4-bromo-1-butene, Cs_2CO_3, AcCN, microwave, 150 °C (40%); (e) Grubbs I catalyst (**I**, 0.25 equiv.), Cl_2CH_2, reflux, 40 hrs., (55% for **26**, 31% for **27**); (f) (tBuOCO)$_2$O, MTBD, DMAP, THF, (83%); (g) Grubbs I catalyst (**I**, 0.125 equiv.), Cl_2CH_2, rt, (85%); (h) $OsCl_3$, Me_3NO, THF/$CHCl_3$, H_2O, (91%); (i) TFA, rt (67%).

Table 1
Janus kinase 3 (JAK3) enzyme and jurkat cell activity for derivatives and staurosporine

Compound	JAK3 IC_{50}[a] (nM)	IL2-stimulated jurkat cells IC_{50}[b] (nM)	Resting jurkat cells IC_{50}[b] (nM)
Staurosporine	6	71	311
7	5	160	5670
8	8	2860	>10,000
9	3	48	>10,000
10	9	227	>10,000
16	7	575	>10,000
17	1	23	>10,000
18	9	222	>10,000
19	15	57	1600
23	61	—	—
24	>200	—	—
26	39	111	>10,000
27	39	432	~10,000
32	6	98	~10,000
33	12	45	616

[a] JAK3 enzyme inhibition was measured by inhibition of phosphorylation of biotinylated substrate in 96 well format.
[b] Cell assays measuring JAK3 versus non-JAK3 inhibtory effects when stimulated by interleukin-2 (IL-2).

JAK3 generated from HCK sequence interchanging. The pyrrolidinone forms a donor acceptor complex with the backbone region with NH-O bonds to the Glu903 and Leu905 residues. The diol alglycon forms hydrogen bonding to the Arg953 residue in the flap region. The backbone interaction is consistent with the X-ray crystal structure determination of AFN491 with JAK3 and our own findings after docking staurosporine, while the Arg953 binding is a new interaction.[21]

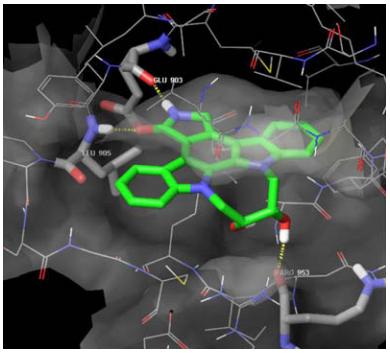


Figure 3. Compound **32** docked into the ATP site of JAK3.

Since JAK3 plays a key role in the proliferation of T-cells through IL-2 mediated signaling,[1–3] we hypothesized that a JAK3 inhibitor would inhibit clonogenic growth of JAK3-expressing human T-cells. In order to test this hypothesis, we exposed test compounds to resting or IL-2 stimulated Jurkat cells (Table 1) and their anti-proliferative effect was assessed. Most of these compounds showed modest to potent inhibition when the JAK3 based pathway is stimulated by IL-2, while showing little effect on resting cells ($\geqslant$10,000 nM). In contrast, staurosporine shows lower selectivity in this assay (fourfold—71 nM vs 311 nM). The potency of inhibition in the IL2-Jurkat cell assay was mainly dependent upon the

alglycon portion. In general, the potencies increased relative to the increase in number of oxygen atoms in the molecule (**17** vs **32** vs **26**). The diols (**9**, **10**, **17**, **19**, **32**, and **33**) had the lowest IC_{50} values in this assay (<100 nM), with equal or more potency than staurosporine in the IL-2 stimulated cells. Most notable were the compounds (**9**, **17**, **26**, and **32**) that were potent in the IL-2 stimulated pathway (<100 nM) and retained high selectivity (>100-fold) versus the non-stimulated Jurkat cells (>10,000 nM).

As further proof of selectivity, three of the most potent JAK3 inhibitors (Table 2; **16**, **17**, and **32**) were tested against other protein tyrosine kinases known to be involved in T-cell and mast cell signaling (e.g., SYK, Zap70, MK2, and LCK). We found our analogs had a high level of selectivity for JAK3 from 30 to greater than 1000-fold against these other kinases. Although not definitive, these findings further suggest that the activity seen in the Jurkat assay is due to JAK3 inhibition.

We then selected the most potent diol compound **32** for further biological characterization. Because JAK3 is required for the activation and phosphorylation of STAT5 in T-cells following IL-2 stimulation,[1–3] we hypothesized that a JAK3 inhibitor would inhibit phosphorylation of STAT5 in T-cells. The T-cells were incubated with differing amounts of compound **32** and STAT5 phosphorylation was assessed by western blot analysis after cell lysis. As we expected, compound **32** inhibited STAT5 phosphorylation with an IC_{50} of 689 nM. The observed 100-fold decrease in potency over the isolated enzyme assay could be due to several factors, but is not unprecedented.

We next examined the effect of this JAK3 inhibitor on IL-2 induced phytohematoglutinin stimulated T-cell (PHA blast T-cells) proliferation. The T-cells were incubated with increasing concentrations of the compound and T-cell proliferation was assessed by a ^{3}H-thymidine assay. In this assay the compound exhibited an IC_{50} of 100 nM (Table 3). Because JAK3 also plays a key role in IgE as well as bacteria mediated mast cell responses,[5,6] we examined the effect of the JAK3 inhibitor **32** on LPS induced TNFα and IgE/antigen induced mast cell degranulation. Compound **32** potently inhibited LPS induced TNF-α release with an IC_{50} value of 18 nM and IgE/antigen induced hexosaminidase (granule associated enzyme) release with an IC_{50} value of 55 nM. These results suggest that compound is a potent inhibitor of JAK3 based signaling pathways in different cell types.

We then tested compound **32** in mice models of allergy and asthma. We examined the effect of this compound on anti-ovalbumin (OVA) IgE production and OVA induced airway inflammation and airway-responsiveness. Immunoglobin E (IgE) is a known biomarker of and cause of allergic responses, including increased mast cell chemotaxis, and is the basis for the recently approved monoclonal antibody therapeutic.[22] It has been postulated that IgE production is regulated mainly through the JAK3 pathway by B cells. Furthermore, mice with a JAK3 deficiency (JAK3 knockout) fail to produce sufficient levels of IgE. To examine the effect of compound **32** on ovalbumin induced IgE production, mice were challenged intraperitoneally with ovalbumin (OVA) and two doses of compound **32**. Quantization of plasma IgE levels was performed by ELISA analysis.[24] As shown in Figure 4, compound **32** caused 15% (10 mg/kgi.p.) and ~70% (30 mg/kgi.p.) reduction in OVA induced IgE production in mice.

Asthma is a chronic inflammatory condition of the lung. Mast Cells, T-cells and dendritic cells play a key role in the pathogenesis of the disease[23]. JAK3 happens to be a key regulator of functional responses in these cells. We therefore, next examined the effect of compound **32** on airway inflammations and airway hyperresponsiveness in a mouse model of allergic asthma.[24] When compound **32** was tested in a mouse model of asthma (30 mg/kg ip dose), two effects were observed. First, a 54% reduction in eosinophils and neutrophils was observed in the broncheovular lavage fluid. Second, a greater than 90% reduction was observed in methacoline induced airway constriction (Fig. 5). These results show that compound **32** could be useful in both the acute and chronic phases of asthma.

In summary, we have presented the synthesis and evaluation of novel staurosporine based JAK3 inhibitors. These compounds have potent activity against the isolated enzyme, and also against JAK3 induced pathways in T-cells. Several compounds showed reasonable selectivity when tested against other immune system related

Table 2
Five enzyme protein kinase panel.

Compound	JAK3[b]	IC_{50}[a] (nM)			
		SYK	Zap70	MK2[b]	LCK
16	7	>1000	>1000	540	>1000
17	1	>1000	>1000	>1000	300
32	6	300	200	>1000	>1000

[a] Enzyme assays were measured as inhibition of phosphorylatin of biotinylated substrate in 96 well format.
[b] Values for K-252a: JAK3—6 nM; MK2—9 nM.

Table 3
Outcome of JAK3 dependent in vitro assays performed on compound **32**

Bioassay	IC_{50} (nM)
STAT5 phosphorylation western blot in T-cells	689
IL2 induced PHA blast T-cell replication	100
LPS induced TNF-α release from mast cells	18
Inhibition of hexosaminidase release from IgE stimulated mast cells	55

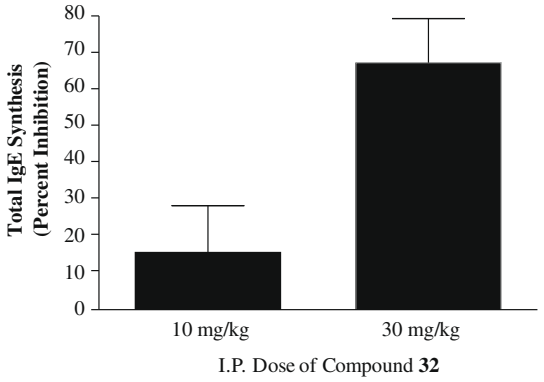


Figure 4. Effect of compound **32** on plasma IgE levels in a mouse model of ovalbumin (OVA) induced IgE synthesis.

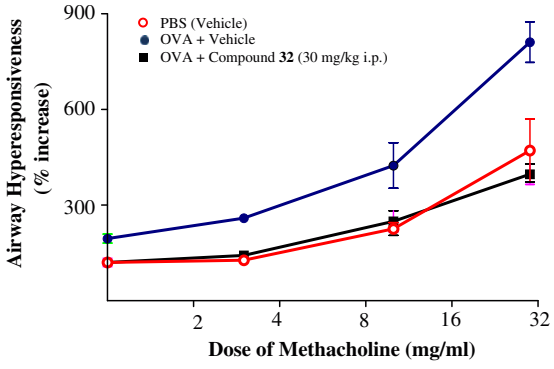


Figure 5. Reduction in airway hyper responsiveness by compound **32** in a mouse model of ovalbumin (OVA) induced asthma at the 30 mg/kg ip dose.

kinases. One compound (**32**) showed broader activity in other biological systems and cell lines. This compound showed inhibition of the JAK3 phosphorylation substrate STAT5 in T-cells and potent activity in mast cells preventing chemotaxis. Furthermore, it showed potent activity in vivo lowering biomarkers of increased JAK3 activity, including IgE and asthmatic responses.

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Supplementary data

Supplementary data (synthetic procedures and characterization data for most compounds are provided, along with procedures for the some biological assays and animal experiments) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.039.

References and notes

1. Ihle, J.; Kerr, I. M. *Trends Genet.* **1995**, *11*, 69.
2. (a) Nosaka, T.; van Deursen, J. M. A.; Tripp, R. A.; Thierfelder, W. E.; Witthuhn, B. A.; McMikle, A. P.; Doherty, P. C.; Grosveld, G. C.; Ihle, J. N. *Science* **1995**, *270*, 800; (b) Thomis, D. C.; Gurniak, C. B.; Tivol, E.; Sharpe, A. H.; Berg, L. J. *Science* **1995**, *270*, 794.
3. (a) Villa, A.; Sironi, M.; Macchi, P.; Matteucci, C.; Notarangelo, L. D.; Vezzoni, P.; Mantovani, A. *Blood* **1996**, *88*, 817; (b) Buckley, R. H.; Schiff, R. I.; Schiff, S. E.; Markert, M. L.; Williams, L. W.; Harville, T. O.; Roberts, J. L.; Pucks, J. M. *J. Pediatr.* **1997**, *130*, 378.
4. Malaviya, R.; Uckun, F. M. *Biochem. Biophys. Res. Commun.* **1999**, *257*, 807.
5. Malaviya, R. M.; Navara, C.; Uckun, F. M. *Immunity* **2001**, *18*, 313.
6. Papageorgiou, A. C.; Wikman, L. E. K. *Trends Pharm. Sci.* **2004**, *25*, 558.
7. Sudbeck, E. A.; Liu, X. P.; Narla, R. K.; Mahajan, S.; Ghosh, S.; Mao, C.; Uckun, F. M. *Clin. Cancer Res.* **1999**, *5*, 1569.
8. Changelian, P. S.; Flanagan, M. E.; Ball, D. J.; Kent, C. R.; Magnuson, K. S.; Martin, W. H.; Rizzuti, B. J.; Sawyer, P. S.; Perry, B. D.; Brissette, W. H.; McCurdy, S. P.; Kudlacz, E. M.; Conklyn, M. J.; Elliott, E. A.; Koslov, E. R.; Fisher, M. B.; Strelevitz, T. J.; Yoon, K.; Whipple, D. A.; Sun, J.; Munchhof, M. J.; Doty, J. L.; Casavant, J. M.; Blumenkopf, T. A.; Hines, M.; Brown, M. F.; Lillie, B. M.; Subramanyam, C.; Chang, S. P.; Milici, A. J.; Beckius, G. E.; Moyer, J. D.; Su, C.; Woodworth, T. G.; Gaweco, A. S.; Beals, C. R.; Littman, B. H.; Fisher, D. A.; Smith, J. F.; Zagouras, P.; Magna, H. A.; Saltarelli, M. J.; Johnson, K. S.; Nelms, L. F.; Etages, S. G. D.; Hayes, L. S.; Kawabata, T. T.; Finco-Kent, D.; Baker, D. L.; Larson, M.; Si, M. S.; Paniagua, R.; Higgins, J.; Holm, B.; Reitz, B.; Zhou, Y.-J.; Morris, R. E.; O'Shea, J. J.; Borie, D. C. *Science* **2003**, *302*, 875.
9. Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535.
10. Sanchez, C.; Mendez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007.
11. *Drug News Perspect.* **2003**, *16*, 691.
12. Fuse, E.; Kuwabara, T.; Sparreboom, A.; Sausville, E. A.; Figg, W. D. *J. Clin. Pharmacol.* **2005**, *45*, 394.
13. Fabbro, D.; Ruetz, S.; Bodis, S.; Pruschy, K.; Csermak, K.; Man, A.; Campochiaro, P.; Wood, J.; Reilly, T. O.; Meyer, T. *Anti-Cancer Drug Des.* **2000**, *15*, 17.
14. Hexner, E. O.; Serdikoff, C.; Jan, M.; Swider, C. R.; Robinson, C.; Yang, S.; Angeles, T.; Emerson, S. G.; Carroll, M.; Ruggeri, B.; Dobrzanski, P. *Blood* **2008**, *111*, 5663.
15. Mucke, H. A. M. *I. Drugs* **2003**, *6*, 377.
16. (a) Schiering, N.; Knapp, S.; Marconi, M.; Flooco, M. M.; Cui, J.; Perego, R.; Rusconi, L.; Cristiani, C. *Proc. Natl. Acad. Sci.* **2003**, *100*, 12654; (b) Bartlett, S.; Beddard, G. S.; Jackson, R. M.; Kayser, V.; Kilner, C.; Leach, A.; Nelson, A.; Oledzki, P. R.; Parker, P.; Reid, G. D.; Warriner, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 11699.
17. Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022.
18. Wilson, L. J.; Yang, C.; Murray, W. M. *Tetrahedron Lett.* **2007**, *48*, 7399.
19. Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
20. Compound **32** was docked into JAK3 using the docking program Glide (Glide, Schrodinger, 1500 S.W. First Ave., Suite 1180, Portland, OR 97201). The molecular mechanism calculations were done with MacroModel (MacroModel, Schrodinger, 1500 S.W. First Ave., Suite 1180, Portland OR 97201), using OPLS2001 force field. The effect of aqueous solution was treated by GB/SA model. Polak-Ribiere conjugate gradient method was used for energy minimization, and the derivative convergence criterion was set at 0.05 KJ/A-Mol.
21. Boggon, T. J.; Li, Y.; Manley, P. W.; Eck, M. J. *Blood* **2005**, *106*, 996.
22. Omalizumb/Xolair™ Casale, T. B. *Drugs of Today* **2004**, *40*, 367.
23. Hanissian, S. H.; Geha, R. S. *Immunity* **1997**, *6*, 379.
24. Malaviya, R.; Chen, C. L.; Navara, C.; Malaviya, R.; Liu, X. P.; Keenan, M.; Waurzyniak, B.; Uckun, F. M. *J. Pharm. Exp. Therap.* **2000**, *295*, 912.