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LcK Inhibitors and its analogues: A Review

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ABSTRACT

T-cells play an important role in the pathogenesis of many diseases. These include diseases with large commercial markets and also with significant unmet medical needs, such as rheumatoid arthritis and asthma in addition to those with smaller markets such as organ transplantation. Lck, one of eight members of the Src-family of tyrosine kinases, is activated following T cell stimulation and is required for T cell proliferation and IL-2 production. Inhibition of Lck has been a target to prevent lymphocyte activation and acute rejection. In this review we amass different functions and different moieties which act as an lck inhibitor for the treatment of different diseases. In addition we provide an analysis of the properties of these compounds that account for the specificity required for the inhibition of one of eleven highly similar kinases.

Key words Lck cell, Kinase, carcinoma, T-cells, inhibitors.

INTRODUCTION

Discovery of novel drugs targeting kinases, an important class of intracellular enzymes that play a critical role in signal transduction pathways controlling a variety of cellular functions, has become the focus of a large number of drug discovery programs in the pharmaceutical and biotech industry. The role of a kinase in signal transduction is to catalyze the transfer of the terminal phosphate group of ATP to an appropriate substrate leading to the activation of the substrate for its role in the next step of the signaling cascade. The substrate is often another kinase or a transcription factor. A large majority of kinase inhibitors are designed to inhibit the enzyme by binding at or near the ATP-binding site. Therefore, an inhibitor of one kinase is often found to inhibit other structurally related or unrelated kinases. This inherent promiscuity of kinase inhibitors calls for extensive profiling of the inhibitors either for driving structure-activity relationship (SAR) during lead optimization or for opportunistic discoveries. Lymphocyte

specific protein tyrosine kinase (Lck), a member of the Src family of non-receptor protein tyrosine kinases, is predominantly expressed in T-lymphocytes and natural killer cells [1,2]. Genetically modified mice with Lck mutations exhibit defects in T cell maturation and signaling [4,5]. These findings indicate that Lck inhibitors should inhibit T cell activation and therefore be useful therapies for T cell-mediated autoimmune diseases and graft rejection.

Functions

T cell development

Lck is involved in multiple aspects of T cell development including β chain rearrangement, differentiation into α/β or δ/γ T cells, and positive selection. Briefly, the developmental stages of a thymocyte in the thymus are: 1) A stem cell 2) A double negative (DN) cell (CD4-CD8-) in which the β chain rearranges and, if successful, the cell will express the pre-TCR with the associated CD3 chains. At this stage, the cell expresses both the α/β pre-TCR and the δ/γ TCR; different signal(s) received will cause the cell to commit to either the α/β or δ/γ T cell lineage [3]. At the double positive (DP) cell stage (CD4+CD8+), the α chain will rearrange. If this rearrangement is successful, the cell will express a TCR. 3) The cell will undergo positive selection and become a single-positive T cell. 4) After completing negative selection, the mature, naïve T cell will exit the thymus. Lck is first expressed in DN T cells and its expression continues into maturity.At the DN stage, Lck is required for successful β chain rearrangement and the subsequent expression of CD4 and CD8. Over expression of Lck in developing thymocyte causes a decrease in Vβ -Dβ rearrangement "while permitting normal juxtaposition of other TCR gene segments" [6]. In mice with deficient Lck, developing T-cells do not reach the DP stage and the α chain does not rearrange. Also during the DN stage, immunologists believe that a Lck-mediated signal is involved in the lineage commitment to α/β or δ/γ T cells [7,8] have found evidence that supports this hypothesis. They have shown that the pre-TCR (α/β), but not the δ/γ TCR, co localizes with Lck into glycolipid-enriched membrane domains without ligation. This phosphorylates and activates CD3ε and ZAP-70, which are involved in a subsequent signal cascade that may determine lineage commitment [8]. Later in T cell development, positive selection occurs to generate MHC restriction. Positive selection involves the interaction of MHC with the antigen receptor (TCR) and co-receptors such that only cells with the correct co-receptor survive. While the exact mechanism of positive selection is currently unknown, it is believed that Lck-mediated signals from the co-receptor are involved in the cell's development into a CD4+ or CD8+ T cell [7]. The current model suggests that the double-positive thymocyte down regulates both CD4 and CD8. Next, it re-expresses CD4. At this time, there are two possible signals that the cell could receive: if the TCR and CD4 bind to MHC class II and Lck-mediated signaling is sustained, the cell will become a CD4+ T cell; if the TCR binds MHC class I, the Lck-mediated signal will be interrupted because there is no CD8 expressed and the cell will become a CD8+ T cell [9]. The exact mechanism of positive selection and the role of Lck is currently under investigation.

T cell activation

A T cell is activated when the TCR and the co-receptor bind the antigen peptide: MHC complex, which causes the TCR complexes cluster and triggers an intracellular signal cascade. In T cell activation, the binding of the co-receptors CD4 or CD8 to MHC class II or class I, respectively, increases the sensitivity of T cells to antigen. The TCR complex includes the TCR (α and β chains), CD3 (δ, γ, and two ε chains), and two ζ chains [7]. TCR signaling initially involves two

Src-family kinases, Lck and Fyn. When antigen is recognized, the TCR complexes cluster. Clustering brings Lck, which is associated with the cytoplasmic domain of the co-receptor, to its targets in the TCR complex. Lck phosphorylates immunoreceptor tyrosine-based activation motifs (ITAMs) on the cytoplasmic domains of the ζ and the CD3 δ, γ, and ε chains of the TCR complex. The SH2 domains of the protein-tyrosine kinase ZAP-70 subsequently bind to the phosphorylated ζ chain. Upon binding, ZAP-70 is activated and propagates the signal cascade. Ultimately, the signal cascade results in the activation of the transcription factors NFAT, AP-1, and NFκB in the nucleus and the T cell is activated.

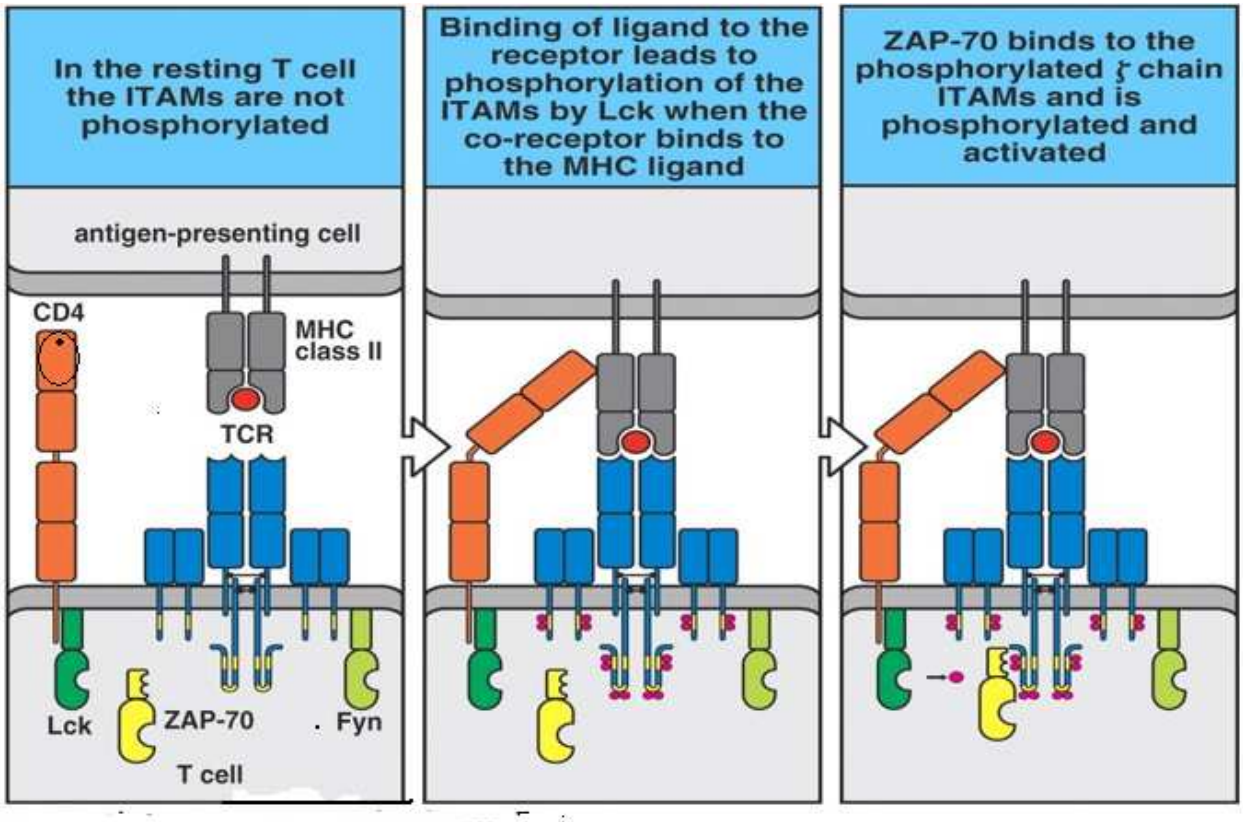


Figure 1. Activation of T cell signal cascade. The mature, naïve T cell is activated once the TCR and co-receptors bind to the peptide:MHC complex. The TCR complexes cluster allowing Lck to phosphorylate the ITAMs on the cytoplasmic domains of the TCR complex molecules. Subsequently, ZAP-70 binds to the phosphorylated ITAMs on the ζ chain and is activated to propagate the signal.

Diseases & Drugs/ Treatments

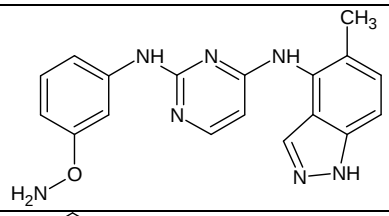
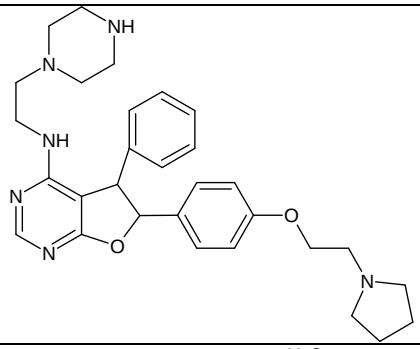
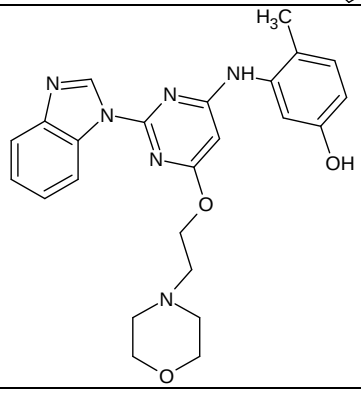
There are many diseases and conditions that involve T cell abnormalities including rheumatoid arthritis, asthma, organ transplantation, multiple sclerosis, inflammatory bowel diseases, type 1 diabetes, systemic lupus erythematosus, psoriasis [10], Hereditary Haemochromatosis [11], leukemia, Hodgkin lymphomas, neuroblasts, and others [12]. Research into some of these T cell-related conditions/diseases has not shown any connection between Lck and the pathogenesis of the disease. For instance, research to this date indicates that Lck abnormalities most likely do not play a major role in type 1 diabetes [13]. However, Lck impairments have been shown to contribute to the pathogenesis of other T cell-related diseases. Discovery of Lck-related diseases and conditions is important because drug treatments that inhibit Lck may improve the safety of

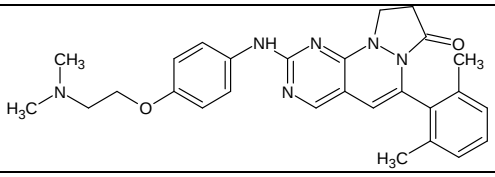
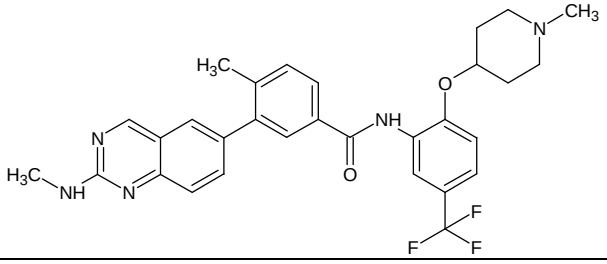
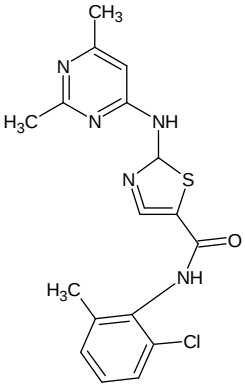
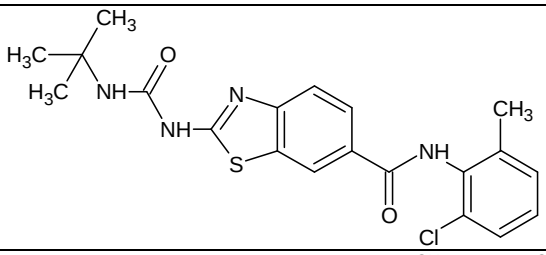
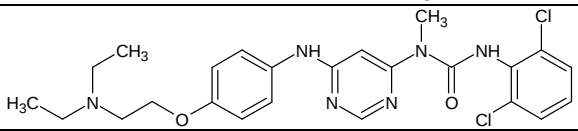
treatment for T-cell-driven diseases because Lck expression is restricted to lymphoid cells [10]. A number of human diseases are caused by abnormalities at the LCK locus [12]. One example is T-cell acute lymphoblastic leukemia, which is caused by the translocation (1;7) (p34;q34) with the TCRB gene. As a second example, LCK abnormalities are involved in the severe combined immunodeficiency (SCID) phenotype, which includes defects in cellular and humoral immunity. Mice either lacking Lck or expressing dominant-negative mutations in Lck showed SCID-like phenotypes that included T-cell developmental defects [12]. Similarly, in an infant with severe SCID symptoms, selective CD lymphopenia, and lack of CD28 expression on CD8+ T cells, Lck was spliced such that it lacked the exon 7 kinase encoding domain [14]. A final example of a Lck-associated genetic condition is the autosomal recessive disease Hereditary Haemochromatosis (HH). The disease is associated with increased iron absorption and, in some cases, low numbers of CD8+ T cells in the periphery. HH patients also show a decrease in CD8-Lck specific activity that contributes to the pathogenesis and is not corrected by iron depletion [11]. Other T-cell-associated diseases involve inhibition of Lck activity by various mechanisms. For instance, in Hodgkin's lymphoma and other tumors, there is decreased cellular immunity because of impaired CD4+ T cell activation. It has been suggested that the elevated levels of prostaglandin E (2) that are associated with Hodgkin's lymphoma inhibits CD4+ T cell function by inactivating Lck [15]. Lck function is also impaired in people infected with the human immunodeficiency virus (HIV) and contributes to the pathogenesis of HIV, which is characterized by a depletion of CD4+ T cells. The HIV-encoded proteins Tat and Nef and the gp120 envelope gene product are involved in the associated T cell dysfunctions [16]. The Nef protein of the human immunodeficiency virus type 1 (HIV-1) is required for the progression of HIV and for the maintenance of high viral loads; HIV strains that lack Nef do not progress to AIDS [17]. Nef expression has been shown to cause depressed Lck kinase activity, which impaired Lck-mediated signaling events [16]. More recently, it has been shown that Nef triggers the internalization and degradation of CD4 primarily by disrupting the CD4-Lck complex [17]. Specifically, a proline rich region in the N-terminal of the Nef protein binds to the SH3 domain of Lck to disrupt the CD4-Lck interaction [18]. Currently, anti-HIV treatments are targeting a limited number of HIV proteins, so the development of new HIV drugs may increase treatment success [17] have shown that synthetic guanidine alkaloids of the batzelladine and crambescidin families can disrupt Nef-Lck interaction to inhibit HIV. The role of Lck in inducing apoptosis has been utilized for cancer treatments and immunosuppressive drugs. Anticancer drugs and irradiation induce apoptosis of human lymphocytes and lymphoma cells via the mitochondrial apoptosis pathways [19] found that Lck is essential for apoptosis induction by the drugs Doxorubicin, Paclitaxel, and 5-Fluorouracil. Lck is necessary for the early steps of the mitochondrial apoptosis signaling cascade, specifically the alteration of mitochondrial function and the activation of caspases [19]. Lck regulates these events by controlling the expression of the Bcl-2 protein Bak. Lck also plays a key role in drug resistance; T cells that are Lck deficient are resistant to anticancer drugs, but are still capable T cell death mediated by death receptors [20]. A range of immunosuppressive drugs that induce apoptosis of lymphocytes can suppress harmful immune responses. Rosmerinic acid (RosA) is an immunosuppressive drug derived from herbal plants that induces apoptosis via the mitochondrial pathway. The effect of RosA is Lck-dependent, requiring the SH2 domain of Lck but not the Lck kinase activity, and independent of the Fas/Fas ligand interaction. Due to the requirement for Lck, RosA is expected to have selectivity towards Lck-containing cells, specifically T and NK (natural killer) cells. Thus, RosA may be a future treatment for T cell-mediated pathologic conditions such as rheumatoid arthritis,

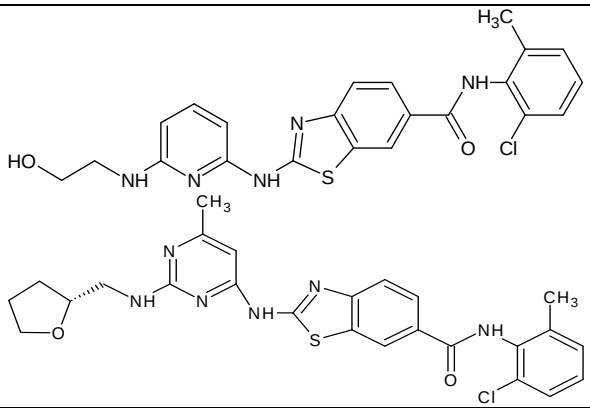
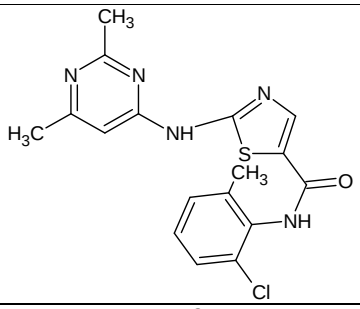
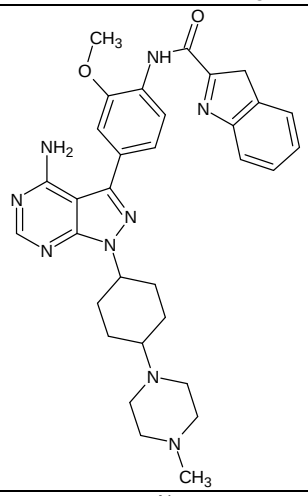
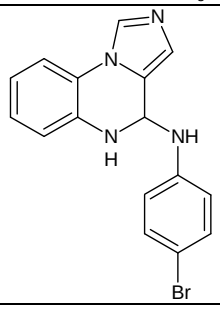
T cell leukemia, and transplant rejections. If RosA were proven to be an effective treatment for these conditions, it would be an improvement over drugs that are currently used for rheumatoid arthritis and transplant rejections because current drugs kill all leukocytes (T cells, macrophages, and monocytes). Also, because RosA apoptosis is independent of activation induced T cell death (ACID) and Fas/FasL interaction, RosA may be used in treating rheumatoid arthritis patients with AICD and Fas/FasL apoptosis-resistant T cells [21].

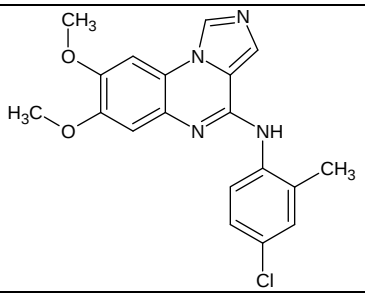
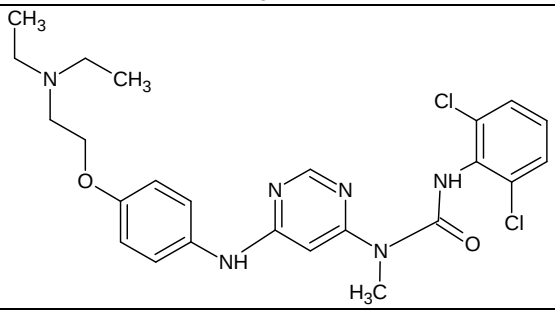
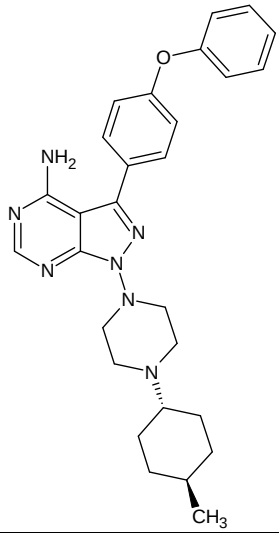
Types of Lck inhibitor

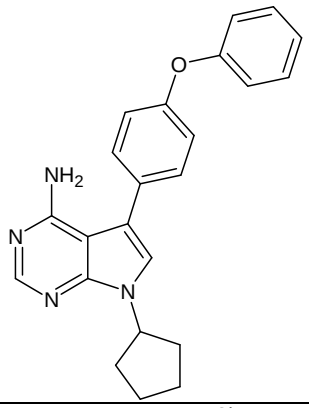
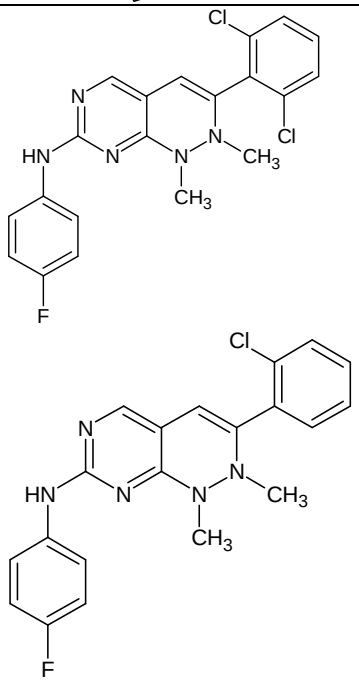
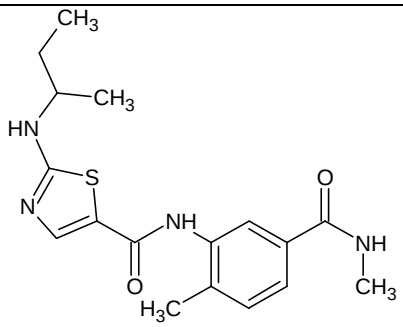
The lymphocyte-specific kinase (Lck), belonging to the Src family of tyrosine kinases, is expressed in T cells and natural killer (NK) cells and is responsible for the activation of and signaling through the T-cell receptor. Activation of this cascade results in the up regulation of inflammatory cytokines such as IL-2 and interferon (IFN)-γ, and ultimately in the activation and proliferation of T lymphocytes to generate an immune response. Therefore, inhibition of Lck is likely to elicit an immunosuppressive effect that could be useful in the treatment of T-cell-mediated diseases like rheumatoid arthritis, inflammatory bowel disease, psoriasis, and organ graft rejection [22]. A large number of compounds are reported to be potent inhibitors of Lck.

S. No	Name	Structure	Comments
1	anilinopyrimidine		It has been reported to inhibit Lck with IC50=19 nM with a selectivity of 3- to 30-fold against Btk, Lyn, Syk, and Txk and is proposed to bind in the ATP site of Lck **(23).**
2	2,3-diaryl-furopyrimidines		This Compound inhibited Lck with IC50=98 nM and inhibited anti-CD3/CD-28-induced secretion of IL-2 in T cells isolated from human peripheral blood lymphocytes with IC50=430 nM. The X-ray structure in Lck indicated that the compound binds in the ATP. site and that the C-H at the 2-position donates an H-bond to the carbonyl of Glu317**.(24)**
3	benzimidazole-substituted aniline pyrimidines		Compound 20 inhibited Lck with IC50=3 nM and inhibited phorbol myristate acetate (PMA)-induced IL-2 production in Jurkat T cells with IC50=54 nM **(25).**

4	pyrimidopyrazine derivative		It is reported to be a potent Lck inhibitor with IC50=2 nM **(26).** The cellular activity (IL-2 inhibition in T cells), selectivity against other Src family of kinases.
5	2-amino-6-aryl-quinazoline derivative		It is a potent Lck inhibitor (IC50=0.5 nM) that is not selective against other members of Src family kinases, p38, and VEGFR2 **(27).** In a human whole blood assay, 24 inhibited the anti-CD3/CD28 antibody-induced IL-2 production with IC50=113 nM. Compound 24 had a desirable pharmacokinetic profile in rats (%F=55) and was orally efficacious in reducing serum levels of IL-2 in BALB/c mice with ED50=22 mg/kg purinergic Signaling.
6	2-amino-6-carboxamidobenzothaizoles		2-amino-5-carboxamidothiazoles were identified as inhibitors of Lck. Structure–activity studies demonstrate the structural requirements for potent Lck activity. Cyclopropylamide 11d is a potent Lck inhibitor having submicromolar activity in a PBL proliferation assay**.(28)**
7	BMS-354825		It is marketed kinase inhibitor drug for the treatment of chronic myelogenous leukemia (CML), is a potent, selective, and ATP-competitive inhibitor of Lck and other Src family kinases (IC50=1 nM for hLck) **(29)**
8	BMS-243117		A series of structurally novel benzothiazoles based small molecule inhibitors of p56lck were prepared to elucidate their Structure–activity relationships (SARs), selectivity and cell activity in the T-cell proliferation assay. BMS-243117 (compound 2) is Identified as a potent, and selective Lck inhibitor with good cellular activity(IC 50=1.1 mM) against T-cell proliferation. **(30)**
9	Anilinopyrimidine urea		It inhibited Lck with IC50=87 nM and inhibited the hind paw swelling by 63% upon oral administration twice a day at 25 mg/kg in an adjuvant-induced arthritis model in rats. **(31)**

10	BMS-350751 BMS-358233		2-aminopyridyl analogue 2 (BMS-350751) Lck IC50 = 0.5 Lck Ki = 900pM T-cell Prolif IC50 = 475 nM and 2-aminopyrimidinyl analogue 3 (BMS-358233) as highly potent Lck inhibitors in vitro with excellent activity in a T-cell proliferation assay.Lck IC50 = 1Nm Lck Ki = 540pM T-cell Prolif IC50 = 262nM **(32)**
11	2-(aminoheteroaryl)-thiazole-5-carbox amide		A series of substituted 2-(aminoheteroaryl)-thiazole-5-carboxamide analogs have been synthesized as novel, potent inhibitors of the Src-family kinase p56Lck. Among them, compound 2 displayed superior in vitro potency and excellent in vivo efficacy. Lck IC50 = 1.2Nm Lck Ki = 130Pm, T-cell Prolif = 80nM. **(33)**
12	A-420983		The pyrazolo[3,4-d]pyrimidine A-420983 (compound 7) as a potent inhibitor of lck. A-420983 exhibits oral efficacy in animal models of delayed-type hypersensitivity and organ transplant rejection. Lck = 0.037. **(34)**
13	1,5-imidazo quinoxalines		1,5-imidazoquinoxalines as inhibitors of Lck with excellent potency (IC50s<5 nM) as well as good cellular activity against T-cell proliferation (IC50s<1 mM). Structure–activity studies demonstrate the requirement for the core heterocycle in addition to an optimal 2,6-disubstituted aniline group. **(35)**

14	Aniline (imidazo quinoxaline		A series of anilino(imidazoquinoxaline) analogues bearing solubilizing side chains at the 6- and 7-positions of the fused phenyl ring has been prepared and evaluated for inhibition against Lck enzyme and of T-cell proliferation. Significant improvement of the cellular activity was achieved over the initial lead, compound 2. **(36)**
15	N-4,6-pyrimidine-N-alkyl-N0-phenyl urea		N-4,6-pyrimidine-N-alkyl-N0-phenyl urea scaffold is described. Many of these compounds showed low-nanomolar inhibition of lck kinase activity as well as IL-2 synthesis from Jurkat cells. One of these analogs, 7i, was shown to be orally efficacious by in vivo testing in a rat adjuvant-induced arthritis study. **(37)**
16	Pyrrolo [2,3-d] pyrimidines		Pyrrolo[2,3-d]pyrimidines was synthesized and evaluated as inhibitors of Lck. Lck accommodates a diverse set of substituents at N-7. Altering the substituent at N-7 provided compound 13, an orally available lck inhibitor which inhibited TCR mediated IL-2production after oral dosing. **(38)**
17	Para-substituted 3-phenyl pyrazolo pyrimidines		Para-substituted 3-phenyl pyrazolopyrimidines was synthesized and evaluated as inhibitors of Lck. The nature of the substitution affected enzyme selectivity and potency for Lck, src, kdr, and tie-2. The para-phenoxyphenyl analogue 2 is an orally active lck inhibitor with a bioavailability of 69% and exhibits an extended duration of action in animal models of T cell Inhibition. **(39)**

18	Pyrrolo [2,3-d] pyrimidines containing a 5-(4-phenoxyphenyl)		Pyrrolo[2,3-d]pyrimidines containing a 5-(4-phenoxyphenyl) substituent are novel, potent and selective inhibitors of Lck in vitro. Exploration of C-6 position of the pyrrolo[2,3-d] pyrimidine and the terminal phenyl group structure activity relationship (SAR) is detailed. Compound 1 is orally active in animal models. **(40)**
19	1. Tri-cyclic derivatives of 1,2-dihydro-pyrimido[4,5-c]pyridazines 2.		Tri-cyclic derivatives of 1,2-dihydro-pyrimido[4,5-c]pyridazines 1 and 2. The most potent analogs disclosed showed low nanomolar activity for the inhibition of Lck kinase. **1** R= Cl; lck IC50 = 3.2 μM **2** R=H; inactive. **(41)**
20	BMS-640994		A novel structural class of p38a MAP kinase inhibitors has been identified via iterative SAR studies of a focused deck screen hit. Optimization of the lead series generated 6e, BMS-640994, a potent and selective p38a inhibitor that is orally efficacious in rodent models of acute and chronic inflammation. **(42)**

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