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Review article

Drug design of Src Kinase inhibitor: An overview

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Key words: Drug discovery, Src Kinase inhibitors, BMS-354825.

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Abstract

Drug discovery for chemotherapeutic agent is making an extraordinary progress in the realm of advancing novel oncogenic protein kinase inhibitor lead compounds of varying chemical structure and biological mechanism. In the last 40 years, the first protein kinase, pp60src(Src), was discovered as a prototype of the new current superfamily of Ser/Thr, Tyr and dual-specificity protein kinases. In this review, we will highlight Src kinase inhibitors with respect to the structural biology, drug design, chemical diversity, and biological properties. This will help medicinal chemist to the design of more potent Src kinase inhibitors for resistive target protein in cancer.

Introduction

One of the most important respects for cancer drug discovery is the identification of key therapeutic targets for approaches focused on the ultimate objective to advance effective and safe- acting drugs. For this reasons, oncogenic protein kinase has been approved as promising therapeutic targets. There are many functional roles for protein kinase such as cell motility, growth, survival, differentiation, cell -cell interactions, and /or cell-matrix interaction have provided a basis for mechanism based approaches to create small – molecule inhibitors . On the past decade, an important progress has been established of protein kinase inhibitors and a new chemical entities have been approved by varying chemical and biological scope [1-20]. It is important to note that a few novel small molecules have enabled periclinal proof of concept studies as well as providing significant clinical candidate for cancer therapy [21-25].

From 300 cancer genes about 10% are protein kinases. On the last 25 years, they had identified the non-receptor tyrosine kinase, pp60src (Src) [26], the protein kinase complement of human genome sequence has been identified [27]. There are many cancers have been linked to somatic mutation of protein kinases, from which both receptor and non-receptor tyrosine kinase have been appeared as an important therapeutic target for cancer drug discovery.

Oncongenic of protein kinases in human are usually resulted from the fusion of the products from genomic rearrangement (e.g. chromosomal translocations, mutations, deletions), and over expression resulting from gene expression [10]. Such transformations typically resulted to enhance kinase activity, which then altered the downstream signal transduction. There are many cellular biology studies have been characterized a number of protein kinases in term of signal transduction pathways and in vivo phenotypes as related to cancer or other diseases (e.g., Src gene Gene knockout (KO) and osteopetrosis).

Src kinase inhibitor: Structural biology and drug design

Src kinase has catalytic and non-catalytic regulatory domains (i.e the SH3 and SH2 domains) which are functionally significant in signal transduction processes. The molecular basis of Src activation has been further elucidate by structural biology studies, including X-ray structures of full length Src (i.e. SH3-SH2-tyrosine kinase) [28–30]. These studies have shown that Src present in an assembled conformation, in active conformation by virtue of its SH3 and SH2 domains (Figure 1). The inactive conformation are formed by intramolecular binding of the SH2 with the C-terminal tail through phosphorylation of Tyr 527 as well as the intramolecular binding of the SH3 domain and a linker sequence between the SH2 domain and the N-terminal lobe of the tyrosine kinase. The defective intramolecular SH3 and SH2 interaction is considered to be involved in Src activation, with in the inactive conformation by intermolecular interaction with SH3, and/or SH2 cognate proteins, and followed by phosphorylation at Tyr-416 (kinase domain) and dephosphorylation at Tyr-527.

There are several X-ray structure of the Src kinase have been determined with respect to a number of small molecules complexes. For example AP23451, and AP23464 [31], CPG77675, and purvalanol [32], and a des-methyl analog of STI-571 (imatinib) [33].

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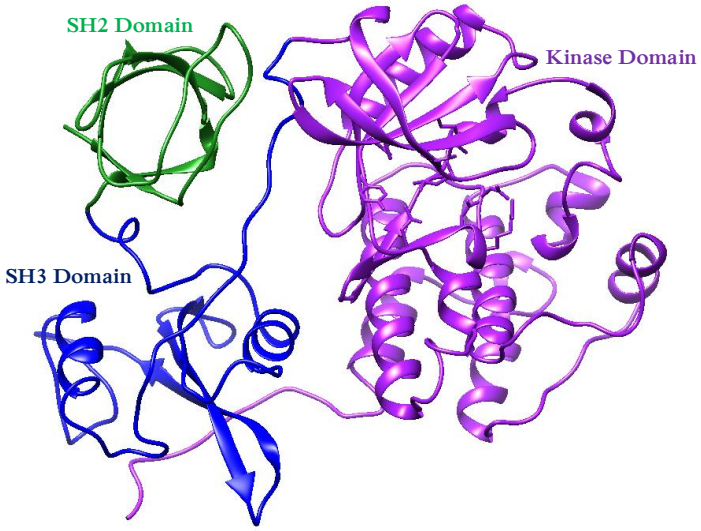


Figure 1. X-ray structure of Src SH3-SH2-tyrosine kinase pdb: 2SRC [111].

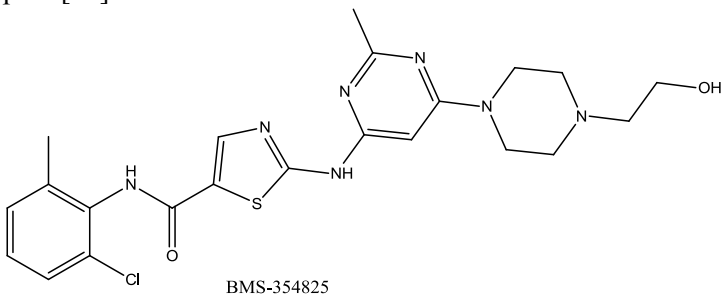
Finally, several studies had been performed to exploit protein engineering to mutate the ATP- binding pockets of protein kinase and enhance the selectivity for synthetic ATP inhibitors [66-68] using Src tyrosine kinase as prototype model . In summary, mutation of the conserved amino acid in the ATP binding pocket was created to made a new site that will increase the ability to accommodate synthetic ATP substrate analogue, [γ-^{32}P]-N^6- (benzyl)-ATP. This provided a set of enzyme-substrate to identify signal transduction pathways with respect to the identification of cellular substrate under deferent experimental conditions.

Src kinase inhibitor: Chemical diversity and biological properties

Several approaches had been used to design of Src kinase inhibitors [7, 24, 33-40] such as peptides, ATP template-related mimetic, substrate analogs, natural products, and unique small molecule resulted from biological screening of cooperate chemical collections, and /or combinatorial libraries, similar compounds from structure based denovo drug-design and virtual screening. The first and second generation of Src Tyrosine kinase inhibitors are usually worked through ATP competitive binding ligands for example, BMS-354825, bosutinib, AZM-475271, AZD-0530, SKI-606, PD180970, PD173955, PD166326, PP1, PP2, CGP-76030, CGP-77675, SU-6656, AP23464, AP23848 AP23846, AP23994, AP23451, and AP23588.
Nowadays, BMS-354825, AZD-0530, and SKI-606 are in clinical trials for Src tyrosine kinase -dependent cancers.

BMS-354825 (Pyrimidinylaminothiazole template-based inhibitor) (Dasatinib, Sprycel™)

Dasatinib (BMS-354825 is Src tyrosine kinase inhibitors with nanomolecular rang activity (IC_{50}=0.5 nM, Bcr-AbI kinase (IC50<1 nM), and KIT (IC50 < 1 nM), and it is also showed high activity against both PDGFR-β (IC50 = 28 nM) and EGFR (IC_{50} = 180 nM). Also it has been tested in vivo and in vitro against Src dependent cancer [41-46] . BMS-354825 bind with high affinity to the ATP binding pocket, the benzamide fragment binding to the hydrophobic specific pocket. BMS-354825 has been approved by FDA as a drug of choice for the treatment for CML. In addition Dasatinib (BMS-354825 has shown a highly potent activity against Src in prostatic cancer in terms of kinase activity, downstream signaling via FAK and Crk associated substrate (p130CAS), and related cellular functions (including cell adhesion, migration, and invasion). In 2017, Appel *et al.* had showed that dasatinib involved in delaying pain-related behaviour and conserves bone in a rat model of cancer-induced bone pain [47].

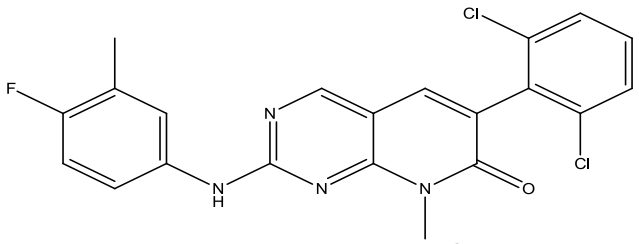


BMS-354825

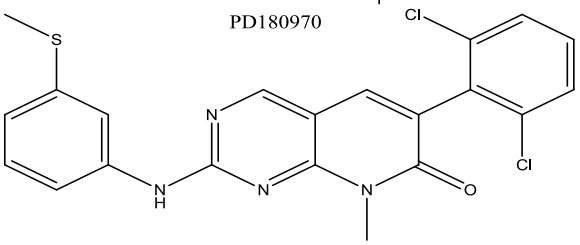
Pyridopyrimidinone template-based inhibitors (PD180970, PD173955 and PD166326)

Pyridopyrimidinone template-based inhibitors have been determined to be highly active against Src and AbI kinase with different selectivities against Platelet-derived growth factor receptor (PDGFR), Fibroblast growth factor receptor (FGFR), EGFR, and Kit kinases [48-58]. PD173955 had shown anticancer activity against both MDA-MB-468 breast cancer cell lines and also it has shown antimiotic activity against Src and Yea kinases, which have roles in cellular progression through the initial phase of mitosis in vitro studies had shown that PD173955 had high potent anticancer activity against Abl (IC_{50} = 2.2 nM) in CML. PD166326 has shown antileukemic activity through inhibition of Bcr-Abl tyrosine kinase inhibitors and several Bcr-AbI mutant in both invitro and in vivo studies . PD166326 was shown to prolong the survival of mice with imatinib -resistant CML. The problem with PD173955 is their limited solubility in aqueous environments which makes them less desirable for medical applications.PD180970 has shown anticancer activity by blocking Stat5 signaling and induces the apoptosis in Bcr-AbI cell line. Adding to that, PD180970 had shown high antiproliferative activity against several mutant BCR-AbI except T315I.
Finally, NJ-26854165 inhibits the proliferation and triggers cell death in a p53-independent manner in various BCR/ABL-expressing cells, which include primary leukemic cells from patients with CML blast

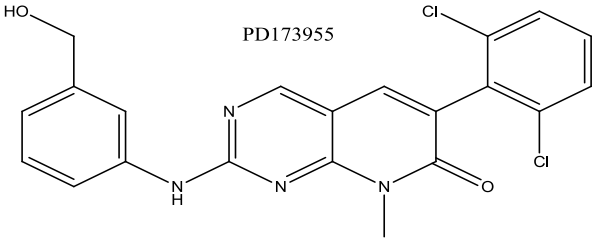
crisis and cells expressing the Imatinib-resistant T315I BCR/ABL mutant. The response to JNJ-26854165 is associated with the down regulation of BCR/ABL dependently of proteosome activation. Moreover, combining JNJ-26854165 and tyrosine kinase inhibitor (TKI) Imatinib or PD180970 leads to a synergistic effect. [59].



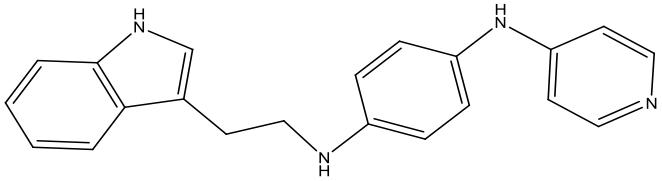
PD180970



PD173955



PD166326

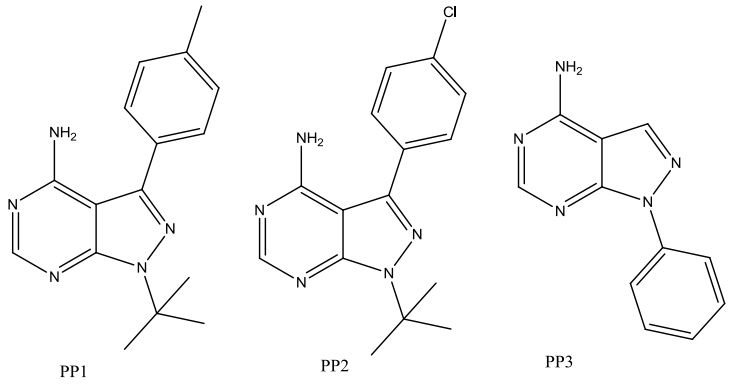


JNJ-26854165

Pyrazolopyrimidine template-based inhibitors [PP1 and PP2]

PP1, and it is chemically analogues PP2 have been determined to be highly activity against ZAP-70, JAK2, EGF-R, and PKA kinases[60-69]. PP1 has been approved to be Src inhibitors and its roles in VEGF-mediated angiogenesis and vascular permeability, Src- driven human breast cancer cell lines with respect to both heregulin-dependent or independent growth, Src-related, collagen type-I-induced E-cadherin down-regulation and consequent effects on both metastatic and proliferation properties. PP1 and PP2 have been showed to be effective against kinase stem cell factor (SCF) receptor c-Kit. In addition, PP1 has shown to inhibit the mutant constitutively active forms of c-kit kinase (D814V and D814Y) that are known to be presented in mast cell disorders.

Finally, PP3 was identified as a negative control for the Src family protein tyrosine kinase inhibitor PP2 [70], and inhibit the EGFR kinase activity (IC50=2.7μM) [71,72].

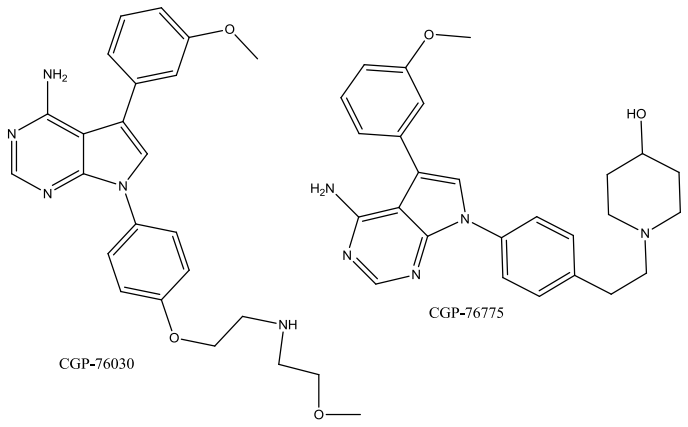


PP1 PP2 PP3

Pyrrolopyrimidine template-based inhibitors (CGP-76030 and CGP-76775)

Pyrrolopyrimidine template-based inhibitors (CGP-76030 and CGP-76775) [73–76] were first described as potent and selective inhibitors of Src tyrosine kinase in both in vivo and in vitro study in comparative to animal models of osteoporosis, and subsequently in cancer cell lines (e.g leukemia and pancreatic). Recently, CGP76030 has been founded to overcome the imatinib resistance [77].

CGP-76775 inhibited osteoclasts, and reduce the growth, adhesion, motility, and invasion in PC3 prostatic cancer. Furthermore, CGP-76775 has determined to inhibit the Bcr-AbI tyrosine kinase, and several imatinib-resistant Bcr-Abl mutants (except for T315I). Bcr-AbI blocked the propagation in invito and increased the survival of Bcr-Abl-driven B-cell acute lymphoblastic leukemia mice.

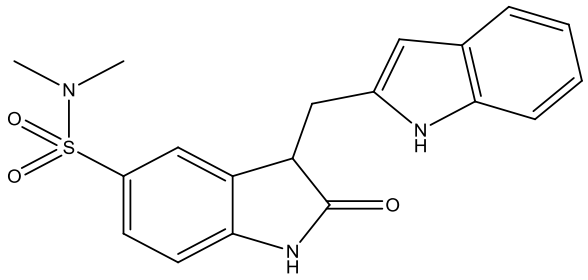


CGP-76030 CGP-76775

Indolinone template-based inhibitor (SU-6656)

Indolinone template-based inhibitor (SU-6656) is an effective inhibitor of Src kinase, and it is also a potent inhibitor of PDGF-stimulated DNA synthesis and Myc induction in a fibroblast cell line [78-81]. SU-6656 has also been used to estimate the role of Src and Ras-ERK signal transduction in Src-transformed cells with respect to Rac1, similar implicating Vav2, and Tiam1 as

downstream effectors of Src to modulate Rac1-dependent pathways. In endothelial cells, SU-6656 is an effective in increasing radiation-induced apoptosis and vascular endothelium destruction, co-administration of SU-6656 before fractionated irradiation have increased the radiation induced destruction of blood vessels within the cancer cell as well as delay it is growth. Recently, (SU6656) had been shown to reduce EGFR phosphorylation and downstream signaling which resulted in the inhibition of the OVA-induced inflammatory cell influx in broncho alveolar lavage fluid (BALF), perivascular and peribronchial inflammation, fibrosis, goblet cell hyper/metaplasia and airway hyper-responsiveness [82].

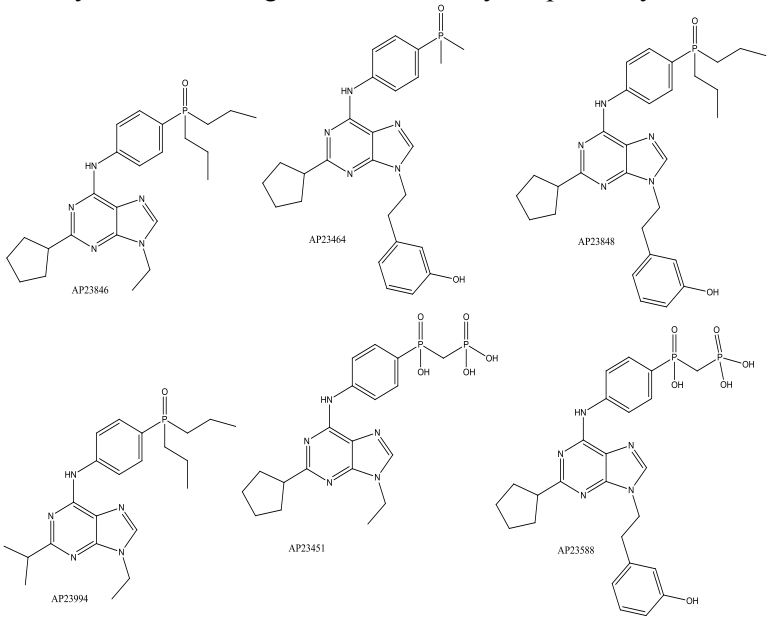


SU-6656

Purine template-based inhibitors (AP23464, AP23848, AP23846, AP23994, AP23451, and AP23588)

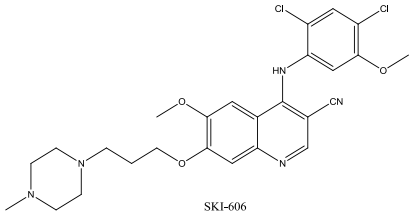
Purine template-based inhibitors (AP23464, AP23848, AP23846, AP23994, AP23451, and AP23588) [7, 24, 34, 37-39, 83–90] are highly potent anticancer activity with IC_{50} range from 1-10 nM. AP23464 has been used to examine the functional relationship of Src and FAK in adhesion turnover combined with the migration of colon cancer cells, providing proof of concept and correlating Src tyrosine kinase as a key therapeutic target. Specifically, Src kinase dependent phosphorylation of FAK in colon cancer cells was determined to associate cell migration with cell matrix adhesion turnover. AP23846 has been used to estimate the ovarian cancer cell by comparing the cancer growth with Src-dependent inhibition to enhance the cytotoxicity of docetaxel in both chemoresisitant and chemosenstive ovarian cancer cell lines. Recently, AP23846 had been to reduces vascular endothelial growth factor and interleukin-8 expression in human solid tumor cell lines and abrogates downstream angiogenic processes [96].

AP23994 is an analogue of AP23846, it was effective to decline the tumor burden in ovarian cancer models (SKOV3ip1 and HeyA8 MDR), compared to the controls one. The in vivo studies observed that the combination therapy with docetaxel has synergistically declined the tumor growth and tumor production of vascular endothelial growth factor and interleukin, and affected antiangiogenic production by declining the micro vessel density, vascular permeability. Another study has shown that AP23846 has declined cellular metastasis in pancreatic adenocarcinoma cells and angiogenesis for implanted tumor cells. AP23451 is a potent Src kinase inhibitor [IC50=8nM). It is a novel bone-targeted, significantly reduce the osteoclast activity by declining the osteoclast formation and osteoclast-dependent bone resorption in both in vivo and invitro study (0.1–1 μM). AP23451 is a dose-dependent interfere with bone resorption hypercalcemia and ovariectomy – induced bone loss. The administration of AP23451 to mice injected with MDA-231 breast cancer cells effectively inhibit the metastasis and induced osteolysis like the bisphosphonate zoledronic (Zometa™). In addition, it is significantly decline the tumor mass inside the bone marrow cavities in contrast to zoledronic acid. AP23588 is a potent a bone targeted Src kinase inhibitor which has been founded to act as anti-resorptive and anabolic properties in vitro with respect to declining osteoclast activity and stimulating osteoblast activity, respectively.



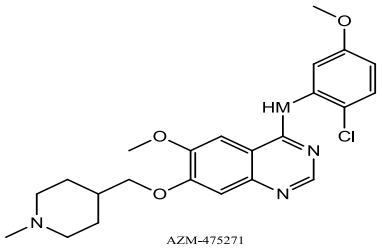
Quinoline template-based inhibitor SKI-606 (Bosutinib)

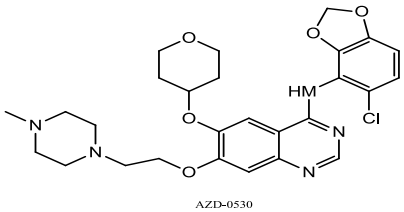
SK-606 [91-95] has been determined to be effective Src kinase inhibitor (IC_{50}= 1.1 nM), and AbI kinase inhibitor (IC_{50}= 1nM). In addition, this compound has selectivity inhibit Src over non-Src family kinase and inhibit Src-dependent cell proliferation (IC_{50} = 100 nM). SKI-606 is an orally active drug in s.c. colon tumor xenograft models, declined Src autophosphorylation (Tyr418) in HT29 and Colo205 tumors. SKI-606 was shown to inhibit Colo205, HCT116, and DLD1 tumor growth upon twice a daily administration, and inhibit HT29 tumor growth upon once daily administration so that SKI-606 is the drug of choice for the treatment of colorectal cancer. SKI-606 is in phase II clinical trails. Recently, SKI-606 (bosutinib) has been founded to suppresses migration and invasion of human breast cancer cells [96].

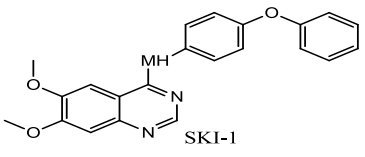


Quinazoline template-based inhibitors AZM475271 (M475271) and AZD0530

Quinazoline template-based inhibitors AZM475271 and AZD0530 [97-102] are potent Src tyrosine kinase inhibitors and have been used to inhibit the tumor growth in Src transformed 3T3 tumor xenograft mice at doses 6 mg/kg po once daily. In in vivo study, AZM475271 has provided to be used as Src kinase inhibitor for pancreatic cancer invasion and metastasis. The combination therapy between AZM475271 with gemcitabine has shown to highly potent anticancer and antimetastic activity. In studies involving lung adenocarcinoma cells, AZM475271 has been shown to decline growth, metastasis, and VEGF-mediated neovascularization resulting on inhibition the subcutaneous growth and lung metastasis. AZD0530 [101, 102] is a highly potent, selective of Src kinase inhibitor with good pharmacokinetic properties (orally active). It is inhibiting the tumor growth in Src-transformed 3T3-fibroblast xenograft models. AZD0530 is in phase II clinical trials [103]. SKI-1 is apotent, selective Src kinase inhibitor (IC_{50} values = 44 nM). It is ATP-competitive. Interacts with both ATP and peptide-binding sites. Additionally, its inhibits VEGFR2 (IC_{50}= 0.32 μM), Induces apoptosis [105].



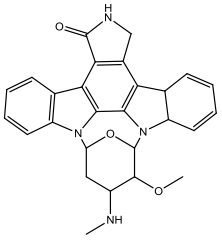


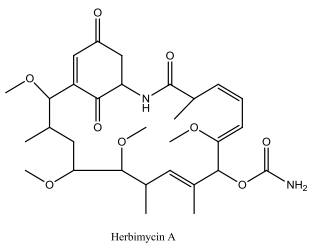


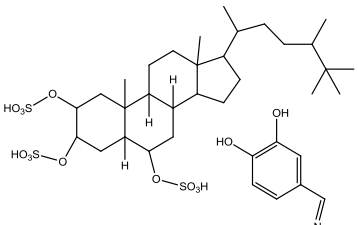
Other template-based inhibitors

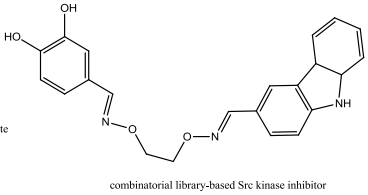
The are other examples of small molecules that are Src kinase inhibitors [36, 106–110], such as phenylaminopyrimidines which bind to the inactive conformation of Src kinase but this compounds are suffered from low activity (IC_{50} =∼ 1 μM). Natural products inhibitors of Src kinase, staurosporine, herbimycin A and halistanol trisulfate provide a novel template relative to chemical diversity of Src inhibitors, despite of their potencies are relatively low compared to many ATP-mimetics, which generally have Src kinase activity (IC_{50} range from 1-10 nM range). It is worth to mention that, Herbimycin A has been found to act as anti-resorptive activities in rodent osteoclast and bone resorption models in both in vivo and invitro studies. The combinatorial library-based Src kinase inhibitor is a potent (IC_{50} = 64 nM), and 75-fold selective for Src kinase over both Fyn and Lyn kinases, and > 1000-fold selective over Lack kinase). Finally, the peptide substrate based inhibitors illustrates the use of combinatorial chemistry combined with drug design focused on the incorporation of both conformational and topographical constraints to attain relative potency with IC_{50}∼ 100 nM range and moderate SFK-selective Src kinase inhibitors.

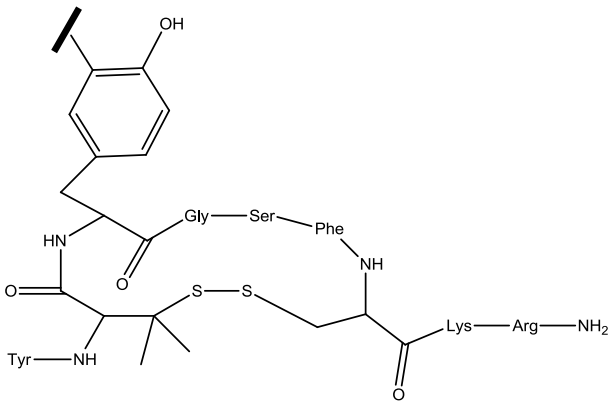
KX-01 is the first clinical Src inhibitor of the novel peptidomimetic class that targets the peptide substrate site of Src providing more specificity toward Src kinase. Combinational index analysis revealed that combinations of KX-01 with Tamoxifen [TAM] resulted in synergistic growth inhibition of breast cancer cell lines. KX-01 combined with TAM resulted in decreased ERα phosphorylation at Src-regulated phosphorylation sites serines 118 and 167 that were associated with reduced ERα transcriptional activity. Orally administered KX-01 resulted in a dose dependent growth inhibition of MCF-7 tumor xenografts, and in combination with TAM exhibited synergistic growth inhibition [112].











Peptide substrate based inhibitors

Conclusion

Following the discovery of Src kinase from 40 years ago, there had been an especial progress in advancing biochemical, cellular, biochemical and in vivo studies of Src kinase toward understanding its roles in both pathophysiology and physiology states, including cancer and bone disease .Src kinase has been approved to be involved in cellular propagation, survival , and migration. Such activities provide an opportunity to gives approaches for drug development, especially for cancer therapy. Noteworthy, there are many Src kinase inhibitors in clinical trails such as BMS-354825 (Dasatinib, Sprycel™) approved by FDA, AZD-0530, and SKI-606. From a chemistry perspective, the opportunity for structure-based drug design to further create novel small-molecule inhibitors of Src kinase has been enabled by recent X-ray crystal structures of many novel ligands. Hopefully, the good works of so many scientists from both past and recent efforts will continue to advance Src kinase inhibitors as part of a molecular armamentarium of chemical and biological medicines for the war against disease.

References

1. Vieth M, Higgs RE, Robertson DH, Shapiro M, Gragg EA, Hemmerle H. Kinomics-structural biology and chemogenomics of kinase inhibitors and targets. Biochim Biophys Acta 2004; 1697:243–257.
2. Cherry M, Williams DH. Recent kinase and kinase inhibitor X-ray structures: mechanisms of inhibition and selectivity insights. Curr Med Chem 2004; 11:663–673.
3. Muegge I, Enyedy IJ. Virtual screening for kinase targets. Curr Med Chem 2004; 11:693–707.
4. Dancey J, Sausville EA. Issues and progress with protein kinase inhibitors for cancer treatment. Nat Rev Drug Discov 2003; 2:296–313.
5. Drevs J, Medinger M, Schmidt–Gersbach C, Weber R, Unger C. Receptor tyrosine kinases: the main targets for new anticancer therapy. Curr Drug Targets 2003; 4:113–121.
6. Diller DJ, Li R. Kinases, homology models, and high throughput docking. J Med Chem 2003; 46:4638–4647.
7. Sawyer TK, Shakespeare WC, Wang Y, Sundaramoorthi R, Huang WS, Metcalf CA, Thomas M, Lawrence BM, Rozamus L, Noehre J, Zhu X, Narula S, Bohacek RS, Weigele M, Dalgarno DC. Protein phosphorylation and signal transduction modulation: chemistry perspectives for small-molecule drug discovery. Med Chem 2005; 1:293–319.
8. Laird AD, Cherrington JM. Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents. Exp Opin Inv Drug 2003; 12:51–64.
9. Nam N-H, Paranga K, Current targets for anticancer drug discovery .Curr Drug Targets 2003; 4:159–179.
10. Blume-Jensen P, Hunter T. Oncogenic kinase signalling. Nature 2002; 411:355–365.
11. Cohen P. Protein kinases--the major drug targets of the twenty-first century?. Nat Rev Drug Disc 2002; 1:309–315.
12. FabbroD, Ruetz S, Buchdunger E, Cowan-Jacob SW, FendrichG, Liebetanz J, MestanJ, O'ReillyT, TraxlerP, Chaudhuri B, FretzH, ZimmermannJ, MeyerT, CaravattiG, Furet P, Manley PW Protein kinases as targets for anticancer agents: from inhibitors to useful drugs. Pharmacol Ther 2002; 93:79–98.
13. Brunelleschi S, Penego L, Santoro MM, Gaudino. G Receptor tyrosine kinases as target for anti-cancer therapy. Curr Pharm Des 2002; 8:1959–1972.
14. Scapin G. Structural biology in drug design: selective protein kinase inhibitors. Drug Disc Today 2002; 11:601–611.
15. Huse M, Kuriyan J. The conformational plasticity of protein kinases. Cell 2002; 109:275–282.
16. Naumann T, Matter H. Structural classification of protein kinases using 3D molecular interaction field analysis of their ligand binding sites: target family landscapes. J Med Chem 2002; 45:2366–2378.
17. Woolfrey JR, Weston GS. The use of computational methods in the discovery and design of kinase inhibitors. Curr Pharm Des 2002; 8:1527–1545.
18. Bridges AJ. Chemical inhibitors of protein kinases. Chem Rev 2001; 101:2541–2572.
19. Dumas J. Protein kinase inhibitors: emerging pharmacophores 1997 – 2000. Exp Opin Ther Pat 2005; 11:405–429.
20. Tsatsanis C, Spandidos DA. The role of oncogenic kinases in human cancer (Review). Int J Mol Med 2000; 5:583–590.
21. De Jong MJ, Verweij J. Multiple targeted tyrosine kinase inhibition in the clinic: all for one or one for all?. Eur J Cancer 2006; 42:1351–1356.
22. Mikalsen T, Gerits N, Moens U. Inhibitors of signal transduction protein kinases as targets for cancer therapy. Biotechnol Annu Rev 2006; 12:153–223.
23. Ventura JJ, Nebreda AR. Protein kinases and phosphatases as therapeutic targets in cancer. Clin Transl Oncol 2006; 8:153–160.
24. Sawyer TK. Novel oncogenic protein kinase inhibitors for cancer therapy. Curr Med Chem Anticancer Agents 2004; 4:449–455.
25. Becker J. Signal transduction inhibitors--a work in progress. Nat Biotechnol 2004; 22:15–18.
26. Thomas SM, Brugge JS. Cellular functions regulated by Src family kinases. Annu Rev Cell Dev Biol 1997; 13:513–609.
27. Manning G, Whyte DB, Marrtinez R, Hunter T, Sudarasanam S. The protein kinase complement of the human genome. Science 2002; 298:1912–1934.
28. Xu W, Harrison SC, Eck MJ. Three-dimensional structure of the tyrosine kinase c-Src. Nature 1997; 285:595–602.
29. Williams JC, Weijland A, Gonfloni S, Thomson A, Courtneidge SA, Superti-FurgaG, Wierenga RK. The 2.35 A crystal structure of the inactivated form of chicken Src: a dynamic molecule with multiple regulatory interactions. J Mol Biol 1997; 274:757–775.
30. Xu W, Doshi A, Lei M, Eck M, Harrison SC. Crystal structures of c-Src reveal features of its autoinhibitory mechanism. Mol Cell 1999; 3:629–636.
31. Dalgarno D, Stehle T, Narula S, Schelling P, van Schravendijk MR, Adams S, Andrade L, Keats J, Ram M, Jin L, Grossman T, MacNeil I, Metcalf C, ShakespeareW, Wang Y, Keenan T, Sundaramoorthi R, Bohacek R, Weigele M, Sawyer T. Structural basis of Src tyrosine kinase inhibition with a new class of potent and selective trisubstituted purine-based compounds. Chem Biol Drug Des 2006; 67:46–57.
32. Breitenlechner CB, Kairies NA, Honold K, Scheiblich S, Koll H, Greiter E, Koch S, Schafer W, Huber R, Engh RA. Crystal structures of active SRC kinase domain complexes. J Mol Biol 2005; 353:222–231.
33. WarmuthM, Damoiseaux R, Liu Y, Fabbro D, Gray N. SRC family kinases: potential targets for the treatment of human cancer and leukemia. Curr Pharm Des 2004; 9:2043–2059.
34. Sawyer T, Boyce B, Dalgarno D, Iuliucci J. Src inhibitors: genomics to therapeutics. Exp Opin Inv Drug 2001; 10:1327–1344.
35. Susa M, Missbach M, Green J. Src inhibitors: drugs for the treatment of osteoporosis, cancer or both?. Trends Pharmacol Sci 2000; 21:489–495.
36. Cowan-Jacob SW, Fendrich G, Manley PW, Jahnke W, Fabbro D, Liebetanz J, Meyer T. The crystal structure of a c-Src complex in an

active conformation suggests possible steps in c-Src activation. Structure 2005; 13:861–871.
37. Sawyer TK, Wang Y, Shakespeare WC, Metcalf CA, Sundaramoorthi R, Narula S, Dalgarno DC. In: Waksman G (ed) Proteomics and protein–protein interactions: biology chemistry bioinformatics and drug design series: protein reviews. Springer, Berlin Heidelberg New York, 2005; 3:219–253.
38. Metcalf CA III, van Schravendijk MR, Dalgarno DC, Sawyer TK.Targeting protein kinases for bone disease: discovery and development of Src inhibitors. Curr Pharm Design 2002; 8:2049–2075.
39. Shakespeare WC, Metcalf CA III, Wang Y, Sundaramoorthi R, Keenan T, Weigele M, Bohacek RS, Dalgarno DC, Sawyer TK. Novel bone-targeted Src tyrosine kinase inhibitor drug discovery. Curr Opin Drug Disc Dev 2003; 6:729–741.
40. Trevino JG, Summy JM, Gallick GE. SRC inhibitors as potential therapeutic agents for human cancers. Mini Rev Med Chem 2006; 6:681–687.
41. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004; 305:399–401.
42. LombardoLJ, LeeFY, ChenP, NorrisD, BarrishJC, BehniaK, CastanedaS, Cornelius LAM, Das J, Doweyko AM, Fairchild C, Hunt JT, Inigo I, Johnston K, Kamath A, Kan D, Klei H, Marathe P, Pang S, Peterson R, Pitt S, Schieven GL, Schmidt RJ, Tokarski J, Wen M-L, Wityak J, Borzilleri RM. Discovery of N-(2-chloro-6-methyl- phenyl)-2-(6-(4-(2-hydroxyethyl)- piperazin-1-yl)-2-methylpyrimidin-4- ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. J Med Chem 2004; 47:6658–6661.
43. Burgess MR, Skaggs BJ, Shah NP, Lee FY, Sawyers CL. Comparative analysis of two clinically active BCR-ABL kinase inhibitors reveals the role of conformation-specific binding in resistance. Proc Natl Acad Sci USA 2005; 102:3395–3400.
44. Trevino JG, Summy JM, Lesslie DP, Parikh NU, Hong DS, Lee FY, Donato NJ, Abbruzzese JL, Baker CH, Gallick GE. Inhibition of SRC expression and activity inhibits tumor progression and metastasis of human pancreatic adenocarcinoma cells in an orthotopic nude mouse model. Am J Pathol 2006; 168:962–972.
45. Johnson FM, Saigal B, Talpaz M, Donato NJ. Dasatinib (BMS-354825) tyrosine kinase inhibitor suppresses invasion and induces cell cycle arrest and apoptosis of head and neck squamous cell carcinoma and non-small cell lung cancer cells. Clin Cancer Res 2005; 11:6924–6932.
46. NamS, KimD, Cheng JQ, Zhang S, Lee JH, Buettner R, Mirosevich J, Lee FY, JoveR. Action of the Src family kinase inhibitor, dasatinib (BMS-354825), on human prostate cancer cells. Cancer Res 2005; 65:9185–9189.
47. Appel CK , Gallego-Pedersen S, Andersen L, Blancheflor Kristensen S, Ding M, Falk S, Sayilekshmy M, Gabel-Jensen C, Heegaard AM. The Src family kinase inhibitor dasatinib delays pain-related behaviour and conserves bone in a rat model of cancer-induced bone pain. Sci Rep 2017; 1:4792.
48. Wang YD, Miller K, Boschelli DH, Ye F, Wu B, Floyd MB, Powell DW, Wissner A, Weber JM, Boschelli F. Inhibitors of src tyrosine kinase: the preparation and structure-activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. Bioorg Med Chem Lett 2000; 10:2477–2480.
49. Dorsey JF, Jove R, Kraker AJ, Wu J. The pyrido[2,3-d]pyrimidine derivative PD180970 inhibits p210Bcr-Abl tyrosine kinase and induces apoptosis of K562 leukemic cells. Cancer Res 2000; 60:3127–3131.
50. Huang M, Dorsey JF, Epling-Burnette PK, Nimmanapalli R, Landowski TH, Mora LB, NiuG, SinibaldiD, BaiF, KrakerA, YuH, Moscinski L, Wei S, DjeuJ, DaltonWS, Bhalla K, Loughran TP, Wu J, Jove R . Inhibition of Bcr-Abl kinase activity by PD180970 blocks constitutive activation of Stat5 and growth of CML cells. Oncogene 2002; 21:8804–8816.
51. La Rosee P, Corbin AS, Stoffregen EP, Deininger MW, Druker BJ. Activity of the Bcr-Abl kinase inhibitor PD180970 against clinically relevant Bcr-Abl isoforms that cause resistance to imatinib mesylate (Gleevec, STI571). Cancer Res 2002; 62:7149–7173.
52. Hamby JM, Connolly CJ, Schroeder MC, Winters RT, Showalter HD, Panek RL, Major TC, OlsewskiB, RyanMJ, Dahring T, LuGH, Keiser J, AmarA, Shen C, KrakerAJ, Slintak V, Nelson JM, Fry DW, Bradford L, Hallak H, Doherty AM.Structure-activity relationships for a novel series of pyrido[2,3-d]pyrimidine tyrosine kinase inhibitors. J Med Chem 1997; 40:2296–2303.
53. KlutchkoSR, HambyJM, BoschelliDH, WuZ, KrakerAJ, AmarAM, HartlBG, Shen C, KlohsWD, Steinkampf RW, Driscoll DL, Nelson JM, ElliottWL, Roberts BJ, StonerCL, Vincent PW, DykesDJ, PanekRL, LuGH, MajorTC, DahringTK, HallakH, Bradford LA, Showalter HD, Doherty AM. 2-Substituted Aminopyrido[2,3-d]pyrimidin-7(8H)-ones. Structure−Activity Relationships against Selected Tyrosine Kinases and in Vitro and in Vivo Anticancer Activity. J Med Chem 1998; 41:3276–3292.
54. Kraker AJ, Hartl BG, Amar AM, Barvian MR, Showalter HD, Moore CW. Biochemical and cellular effects of c-Src kinase-selective pyrido[2, 3-d]pyrimidine tyrosine kinase inhibitors. Biochem Pharmacol 2000; 60:885–898.
55. Wisniewski D, Lambek CL, Liu C, Strife A, Veach DR, Nagar B, Young MA, Schindler T, Bornmann WG, Bertino JR, Kuriyan J, Clarkson B. Characterization of potent inhibitors of the Bcr-Abl and the c-kit receptor tyrosine kinases. Cancer Res 2002; 62:4244– 4255.
56. Nimmanapalli R, O'Bryan E, Huang M, Bali P, Burnette PK, Loughran T, TepperbergJ, Jove R, Bhalla K. Molecular characterization and sensitivity of STI-571 (imatinib mesylate, Gleevec)-resistant, Bcr-Abl-positive, human acute leukemia cells to SRC kinase inhibitor PD180970 and 17-allylamino-17-demethoxygeldanamycin. Cancer Res 2002; 62:5761–5769.
57. Wolff NC, Veach DR, Tong WP, BornmannWG, Clarkson B, Ilaria RL Jr.PD166326, a novel tyrosine kinase inhibitor, has greater antileukemic activity than imatinib mesylate in a murine model of chronic myeloid leukemia. Blood 2005; 105:3995–4003.
58. Moasser MM, Srethapakdi M, Sachar KS, Kraker AJ, Rosen N. Inhibition of Src kinases by a selective tyrosine kinase inhibitor causes mitotic arrest. Cancer Res 1999; 59:6145–6152.
59. You L, Liu H, Huang J, Xie W, Wei J, Ye X, Qian W. The novel anticancer agent JNJ-26854165 is active in chronic myeloid leukemic cells with unmutated BCR/ABL and T315I mutant BCR/ABL through promoting proteosomal degradation of BCR/ABL proteins. Oncotarget 2017; 5:7777-7790.
60. Hanke JH, Gardner JP, Dow RL, Changelian PS, Brissette WH, Weringer EJ, Pollok BA, Connelly PA . Discovery of a novel, potent, and Src family-selective tyrosine kinase inhibitor. Study of Lck- and FynT-dependent T cell activation. J Biol Chem 1996; 271:695–701.
61. Eliceiri BP, Paul R, Schwartzbert PI, Hood JD, Leng J, Cheresch DA. Selective requirement for Src kinases during VEGF-induced angiogenesis and vascular permeability. J Mol Cell 1999; 4:915–924.
62. Paul R, Zhang ZG, Eliceiri BP, Jiang Q, Boccia AD, Zhang RL, Chopp M, Cheresh DA. Src deficiency or blockade of Src activity in mice provides cerebral protection following stroke. Nat Med 2001; 7:222–227.
63. Belsches-Jablonski AP, Biscardi JS, Peavy DR, Tice DA, Romney DA, Parsons SJ. Src family kinases and HER2 interactions in human breast cancer cell growth and survival. Oncogene 2000; 20:1464–1475.
64. Menke A, Philipp C, Vogelmann R, Seidel B, LutzMP, Adler G, Wedlich D. Down-regulation of E-cadherin gene expression by collagen type I and type III in pancreatic cancer cell lines. Cancer Res 2001; 61:3508–3517.
65. Tatton L, Morley GM, Chopras R, Khwaja A .The Src-selective Kinase Inhibitor PP1 Also Inhibits Kit and Bcr-Abl Tyrosine Kinases. J Biol Chem 2003; 278:4847–4853.
66. Warmuth M, Simon N, Mitina O, Mathes R, Fabbro D, Manley PW, Buchdunger E,Forster K, Moarefi I, Hallek M .The Src-selective kinase inhibitor PP1 also inhibits Kit and Bcr-Abl tyrosine kinases. Blood 2003; 101:664–672.
67. Wilson MB, Schreiner SJ, Choi H-J, Kamens J, Smithgall TS. Selective pyrrolo-pyrimidine inhibitors reveal a necessary role for Src family kinases in Bcr-Abl signal transduction and oncogenesis. Oncogene 2002; 21:8075–8088.
68. Tatton L, Morley GM, Chopra R, Khwaja A. The Src-selective kinase inhibitor PP1 also inhibits Kit and Bcr-Abl tyrosine kinases. J Biol Chem 2003; 278:4847–4853.
69. Warmuth M, Simon N, Mitina O, Mathes R, Fabbro D, Manley PW, Buchdunger E,Forster K, Moarefi I, Hallek M. Dual-specific Src and Abl kinase inhibitors, PP1 and CGP76030, inhibit growth and survival of cells expressing imatinib mesylate-resistant Bcr-Abl kinases. Blood 2003; 101:664–672.
70. Gilmore ES, Stutts MJ, Milgram SL. SRC family kinases mediate epithelial Na+ channel inhibition by endothelin. J Biol Chem; 2001, 276:42610–42617 15.
71. Klinger M, Kudlacek O, Seidel MG, Freissmuth M, Sexl V. MAP kinase stimulation by cAMP does not require RAP1 but SRC family kinases. J Biol Chem 2002;2 77:32490–32497.
72. Kong L, Deng Z, Shen H, Zhang Y. Src family kinase inhibitor PP2 efficiently inhibits cervical cancer cell proliferation through down-regulating phospho-Src-Y416 and phospho-EGFR-Y1173.Mol Cell Biochem. 2011; 348:11-19.

73. Missbach M, Jeschke M, Feyen J, Muller K, Glatt M, Green J, Susa M. A novel inhibitor of the tyrosine kinase Src suppresses phosphorylation of its major cellular substrates and reduces bone resorption in vitro and in rodent models in vivo. Bone 1999; 24:437–449
74. Recchia I, Rucci N, Funari A, Migliaccio S, Taranta A, Longo M, Kneissel M, Susa M, Fabbro D, Teti A. Reduction of c-Src activity by substituted 5,7-diphenyl-pyrrolo[2,3-d]-pyrimidines induces osteoclast apoptosis in vivo and in vitro. Involvement of ERK1/2 pathway. Bone 2004; 34:65–79.
75. Recchia I, Rucci N, Festuccia C, Bologna M, MacKay AR, Migliaccio S, Longo M, Susa M, Fabbro D, Teti A. Pyrrolopyrimidine c-Src inhibitors reduce growth, adhesion, motility and invasion of prostate cancer cells in vitro. Eur J Cancer 2003; 39:1927–1935.
76. Hu Y, Liu Y, Pelletier S, Buchdunger E, Warmuth M, Fabbro D, Hallek M, Van Etten RA, Li S. Requirement of Src kinases Lyn, Hck and Fgr for BCR-ABL1-induced B-lymphoblastic leukemia but not chronic myeloid leukemia. Nat Genet 2004; 36:453–461.
77. Blake RA, Broome MA, Liu X, Wu J, Gishizky M, Sun L, Courtneidge SA. SU6656, a selective src family kinase inhibitor, used to probe growth factor signaling. J Mol Cell Biol 2000; 20:9018–9027.
78. Servitja JM, Marinissen MJ, Sodhi A, Bustelo XR, Gutkind JS. Rac1 function is required for Src-induced transformation. Evidence of a role for Tiam1 and Vav2 in Rac activation by Src. J Biol Chem 2003; 278:34339–34346.
79. Cuneo KC, Geng L, Tan J, Brousal J, Shinohara ET, Osusky K, Fu A, Shyr Y, Wu H, Hallahan DE. SRC family kinase inhibitor SU6656 enhances antiangiogenic effect of irradiation. Int J Radiat Oncol Biol Phys 2006; 64:1197–1203.
80. Morinaga K, Yamauchi T, Kimura S, Maekawa T, Ueda T. Overcoming imatinib resistance using Src inhibitor CGP76030, Abl inhibitor nilotinib and Abl/Lyn inhibitor INNO-406 in newly established K562 variants with BCR-ABL gene amplification. Int J Cancer. 2008; 11:2621-2627.
81. Brunton VG, Avizienyte E, Fincham VJ, Serrels B, Metcalf CA, Sawyer TK, Frame MC. Identification of Src-specific phosphorylation site on focal adhesion kinase: dissection of the role of Src SH2 and catalytic functions and their consequences for tumor cell behavior. Cancer Res 2005; 65:1335–1342.
82. Boyce BF, Xing L, Shakespeare W, Wang Y, Dalgarno D, Iuliucci J, Sawyer T. Regulation of bone remodeling and emerging breakthrough drugs for osteoporosis and osteolytic bone metastases. Kidney Intern. 2003; 85:52–55.
83. Wang Y, Metcalf CA III, Shakespeare WC, Sundaramoorthi R, Keenan TP, Bohacek RS, van Schravendijk MR, Violette SM, Narula SS, Dalgarno DC, Haraldson C, Keats J, Liou S, Mani U, Pradeepan S, RamM, Adams S, WeigeleM, Sawyer TK. Bone-targeted 2,6,9-trisubstituted purines: novel inhibitors of Src tyrosine kinase for the treatment of bone diseases. Bioorg Med Chem Lett 2003; 13:3067–3070.
84. Boyce BF, Xing L, Yao Z, Yamashita T, Shakespeare WC, Wang Y, Metcalf CA III, Sundaramoorthi R, Dalgarno DC, Iuliucci JD, Sawyer TK. SRC inhibitors in metastatic bone disease. Clin Cancer Res 2006;12:6291s–6295s.
85. El-Hashim AZ, Khajah MA, Renno WM, Babyson RS, Uddin M, Benter IF, Ezeamuzie C, Akhtar S. Src-dependent EGFR transactivation regulates lung inflammation via downstream signaling involving ERK1/2, PI3Kδ /Akt and NFκ B induction in a murine asthma model. Sci Rep 2017; 7: 9919.
86. Han LY, Landen CN, Trevino JG, Halder J, Lin YG, Kamat AA, Kim TJ, MerrittWM, Coleman RL, Gershenson DM, Shakespeare WC, Wang Y, Sundaramoorth R, Metcalf CA , Dalgarno DC, Sawyer TK, Gallick GE, Sood AK. Antiangiogenic and antitumor effects of SRC inhibition in ovarian carcinoma. Cancer Res 2006; 66:8633–8639.
87. Trevino JG, Gray MJ, Nawrocki ST, Summy JM, Lesslie DP, Evans DB, Sawyer TK, ShakespeareWC, Watowich SS, Chiao PJ, McConkey DJ, Gallick GE. Src activation of Stat3 is an independent requirement from NF-kappaB activation for constitutive IL-8 expression in human pancreatic adenocarcinoma cells. Angiogenesis 2006; 9:101–110.
88. Boyce BF, Xing L, Yao Z, Shakespeare WC, Wang Y, Metcalf CA III, Sundaramoorthi R, Dalgarno DC, Iuliucci JD, Sawyer TK . Future anti-catabolic therapeutic targets in bone disease. Ann NY Acad Sci 2006; 1068:447–457.
89. Lesslie DP, Summy JM, Parikh NU, Fan F, Trevino JG, Sawyer TK, Metcalf CA, Shakespeare WC, Hicklin DJ, Ellis LM, Gallick GE. Vascular endothelial growth factor receptor-1 mediates migration of human colorectal carcinoma cells by activation of Src family kinases. Br J Cancer 2006; 94:1710–1717.
90. Carragher NO, Walker SM, Scott Carragher LA, Harris F, Sawyer TK, Brunton VG, Ozanne BW, Frame MC. Calpain 2 and Src dependence distinguishes mesenchymal and amoeboid modes of tumour cell invasion: a link to integrin function. Oncogene 2006; 25:5726–5740.
91. Summy JM, Trevino JG, Lesslie DP, Baker CH, Shakespeare WC, Wang Y, Sundaramoorthi R, Metcalf CA III, Keats JA, Sawyer TK, Gallick GE. AP23846, a novel and highly potent Src family kinase inhibitor, reduces vascular endothelial growth factor and interleukin-8 expression in human solid tumor cell lines and abrogates downstream angiogenic processes. Mol Cancer Ther 2005; 4:1900–1911.
92. Brunton VG, Avizienyte E, Fincham VJ, Serrels B, Metcalf CA, Sawyer TK, Frame MC. Identification of Src-specific phosphorylation site on focal adhesion kinase: dissection of the role of Src SH2 and catalytic functions and their consequences for tumor cell behavior. Cancer Res 2005; 65:1335–1342.
93. O'Hare T, Pollock R, Stoffregen EP, Keats JA, Abdullah OM, Moseson EM, Rivera VM, Tang H, Metcalf CA III, Bohacek RS, Wang Y, Sundaramoorthi R, Shakespeare WC, Dalgarno D, Clackson T, Sawyer TK, Deininger MW, Druker BJ. Inhibition of wild-type and mutant Bcr-Abl by AP23464, a potent ATP-based oncogenic protein kinase inhibitor: implications for CML. Blood 2004;104: 2532–2539
94. Azam M, Nardi V, Shakespeare WC, Metcalf CA III, Bohacek RS, Wang Y, Sundaramoorthi R, Sliz P, Veach DR, BornmannWG, Clarkson B, DalgarnoDC, Sawyer TK, Daley GQ. Activity of dual SRC-ABL inhibitors highlights the role of BCR/ABL kinase dynamics in drug resistance. Proc Natl Acad Sci USA 2006; 103:9244–9249.
95. Corbin AS, Demehri S, Griswold IJ, Wang Y, Metcalf CA, Sundaramoorthi R, Shakespeare WC, Snodgrass J, Wardwell S, Dalgarno D, Iuliucci J, Sawyer TK, Heinrich MC, Druker BJ, Deininger MW. In vitro and in vivo activity of ATP-based kinase inhibitors AP23464 and AP23848 against activation-loop mutants of Kit.Blood 2005; 106:227–234.
96. Vultur A, Buettner R, Kowolik C, Liang W, Smith D, Boschelli F, Jove R. SKI-606 (bosutinib), a novel Src kinase inhibitor, suppresses migration and invasion of human breast cancer cells. Mol Cancer Ther 2008; 5:1185-1194.
97. Summy JM, Trevino JG, Lesslie DP, Baker CH, Shakespeare WC, Wang Y, Sundaramoorthi R, Metcalf CA 3rd, Keats JA, Sawyer TK, Gallick GE. AP23846, a novel and highly potent Src family kinase inhibitor, reduces vascular endothelial growth factor and interleukin-8 expression in human solid tumor cell lines and abrogates downstream angiogenic processes.Mol Cancer Ther 2005; 12:1900-1911.
98. Boschelli DH, Ye F, Wang YD, Dutia M, Johnson SL, Wu B, Miller K, Powell DW, YaczkoD, YoungM, TischlerM, ArndtK, DiscafaniC, Etienne C, Gibbons J, Grod J, Lucas J, Weber JM, Boschelli F. Optimization of 4-phenylamino-3-quinolinecarbonitriles as potent inhibitors of Src kinase activity. J Med Chem 2001; 44:3965–3977.
99. Golas JM, Lucas J, Etienne C, Golas J, DiscafaniC, Sridharan L, Boghaert E, Arndt K, Ye F, Boschelli DH, Li F, Titsch C, Huselton C, Chaudhary I, Boschelli F. SKI-606, a Src/Abl inhibitor with in vivo activity in colon tumor xenograft models. Cancer Res 2005; 65:5358–5364.
100. Boschelli DH, Wang YD, Johnson S, Wu B, Ye F, Barrios Sosa AC, Golas JM, Boschelli F. 7-Alkoxy-4-phenylamino-3-quinolinecarbonitriles as dual inhibitors of Src and Abl kinases. J Med Chem 2004; 47:599–601.
101. Boschelli DH, Wang YD, Ye F, Wu B, Zhang N, Dutia M, Powell DW, Wissner A, Arndt K, Weber JM, Boschelli F. Synthesis and Src kinase inhibitory activity of a series of 4-phenylamino-3-quinolinecarbonitriles. J Med Chem 2001; 44:822–833.
102. Wang YD, Miller K, Boschelli DH, Ye F, Wu B, Floyd MB, Powell DW, Wissner A, Weber JM, Boschelli F. Inhibitors of src tyrosine kinase: the preparation and structure-activity relationship of 4-anilino-3-cyanoquinolines and 4-anilinoquinazolines. Bioorg Med Chem Lett 2000; 10:2477–2480.
103. Green TP, Fennell M, Whittaker R, Curwen J, Jacobs V, Allen J, Logie A, Hargreaves J, Hickinson DM, Wilkinson RW, Elvin P, Boyer B, Carragher N, Plé PA, Bermingham A, Holdgate GA, Ward WH, Hennequin LF, Davies BR, Costello GF. Preclinical anticancer activity of the potent, oral Src inhibitor AZD0530. Mol Oncol. 2009; 3:248-261.
104. Zimmerman J, Buchdunger E, Mett H, Meyer T, Lydon NB. Potent and selective inhibitors of the ABL-kinase: phenylaminopyrimidine (PAP) derivatives. Bioorg Med Chem Lett 1997; 7:187–192.
105. Mrad M, Imbert C, Garcia V, Rambow F, Therville N , Carpentier S, Ségui B, Levade T , Azar R, Marine JC, Diab-Assaf M, Colacios C, Andrieu-Abadie N. Downregulation of sphingosine kinase-1 induces protective tumor immunity by promoting M1 macrophage response in melanoma. Oncotarget 2016; 7:1873-71886.
106. Nakano H, Kobayashi E, Takahashi I, Tamaoki T, Kuzuu Y, Iba H. Staurosporine inhibits tyrosine-specific protein kinase activity of Rous

sarcoma virus transforming protein p60. J Antibiot (Tokyo) 1987; 40:706–708.
107. Yoneda T, Lowe C, Lee C-H, Gutierrez G, Niewolna M, Williams PJ, Izbicka E, Uehara Y, Mundy GR, Herbimycin A. a pp60c-src tyrosine kinase inhibitor, inhibits osteoclastic bone resorption in vitro and hypercalcemia in vivo. J Clin Invest 1993; 91:2791–2795.
108. Slate DL, Lee RH, Rodriguez J, Crews P. The marine natural product, halistanol trisulfate, inhibits pp60v-src protein tyrosine kinase activity. Biochem Biophys Res Comm 1994; 203:260– 264.
109. Maly DJ, Choong IC, Ellman JA. Combinatorial target-guided ligand assembly: identification of potent subtype-selective c-Src inhibitors. Proc Natl Acad Sci USA 2000; 97:2419–2424.
110. Kumar A1, Ye G, Wang Y, Lin X, Sun G, Parang K. Synthesis and structure-activity relationships of linear and conformationally constrained peptide analogues of CIYKYY as Src tyrosine kinase inhibitors. J Med Chem 2006; 49:3395-401.
111. Xu W, Doshi A, Lei M, Eck MJ, Harrison SC. Crystal structures of c-Src reveal features of its autoinhibitory mechanism. Mol Cell 1999; 5:629-38.
112. Anbalagan M, Carrier L, Glodowski S, Hangauer D, Shan B, Rowan BG. KX-01, a novel Src kinase inhibitor directed toward the peptide substrate site, synergizes with tamoxifen in estrogen receptor α positive breast cancer. Breast Cancer Res Treat 2012; 2:391-409.