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Review article

Drug design of Src Kinase inhibitor: An overview

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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].

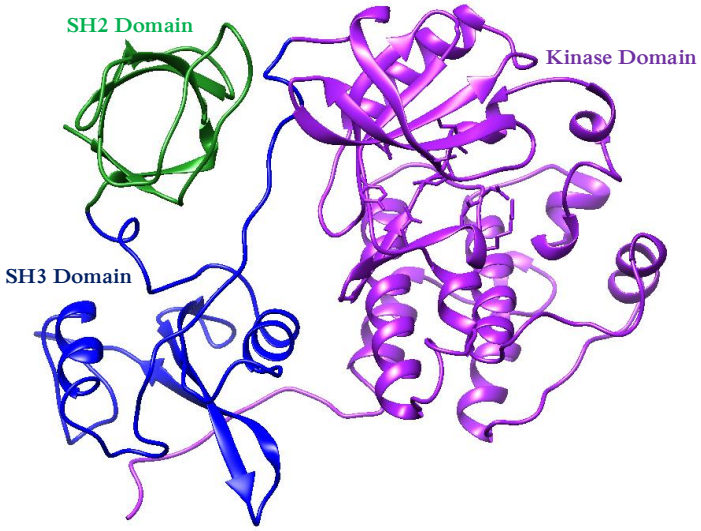


Figure 1. X-ray structure of Src SH3-SH2-tyrosine kinase pdb: 2SRC [111].

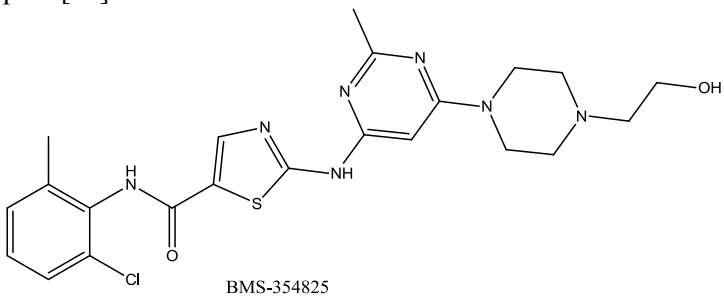
Finally, several studies had been performed to exploit protein engineering to mutate the ATP- binding pockets of protein kinase and enhance the selectivity for synthetic ATP inhibitors [66-68] using Src tyrosine kinase as prototype model . In summary, mutation of the conserved amino acid in the ATP binding 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].

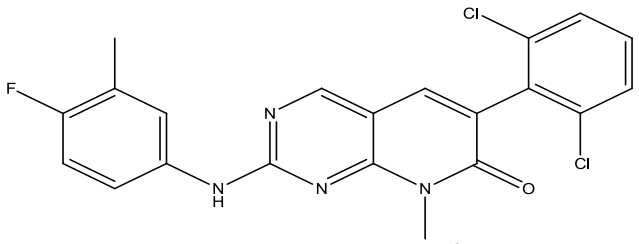


BMS-354825

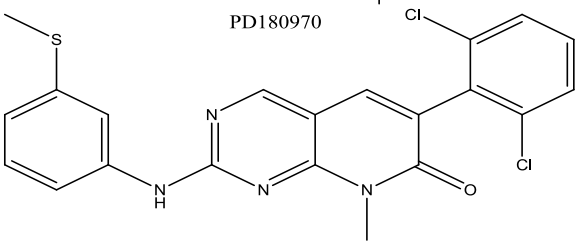
Pyridopyrimidinone template-based inhibitors (PD180970, PD173955 and PD166326)

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

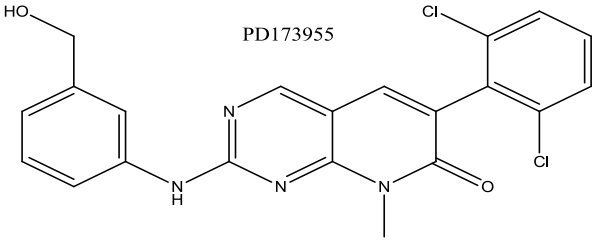
crisis and cells expressing the Imatinib-resistant T315I BCR/ABL mutant. The response to JNJ-26854165 is associated with the down regulation of BCR/ABL dependently of proteosome activation. Moreover, combining JNJ-26854165 and tyrosine kinase inhibitor (TKI) Imatinib or PD180970 leads to a synergistic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



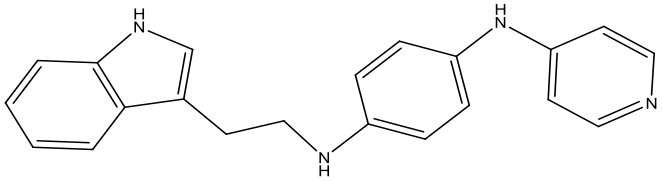
PD180970



PD173955



PD166326

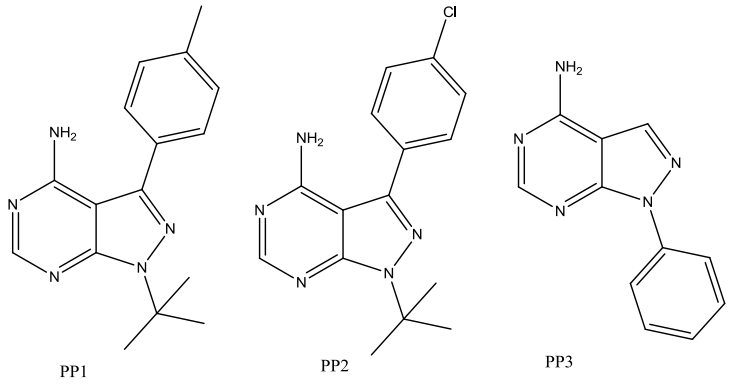


JNJ-26854165

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].

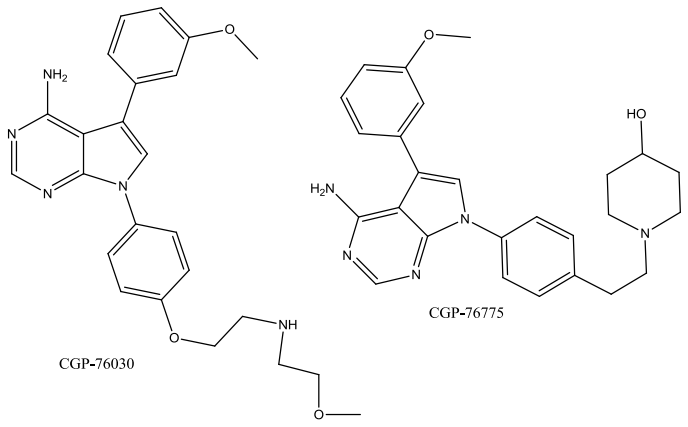


PP1 PP2 PP3

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.

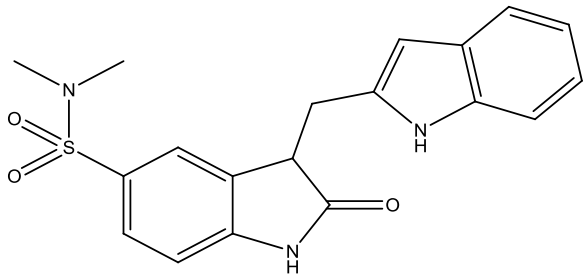


CGP-76030 CGP-76775

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].

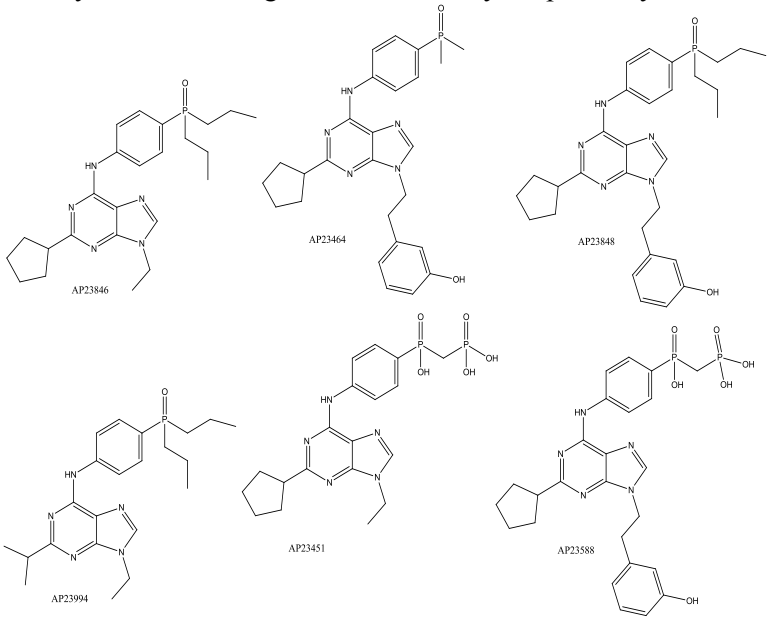


SU-6656

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

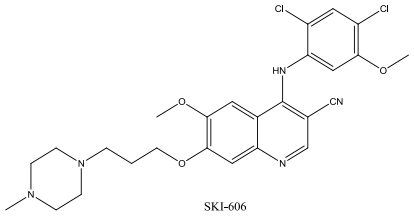
Purine template-based inhibitors (AP23464, AP23848, AP23846, AP23994, AP23451, and AP23588) [7, 24, 34, 37-39, 83–90] are highly potent anticancer activity with IC_{50} range from 1-10 nM. AP23464 has been used to examine the functional relationship of Src and FAK in adhesion turnover combined with the 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.



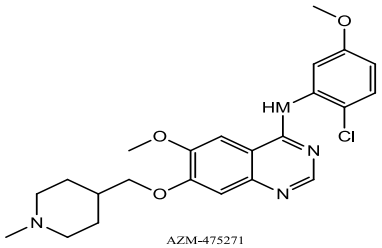
Quinoline template-based inhibitor SKI-606 (Bosutinib)

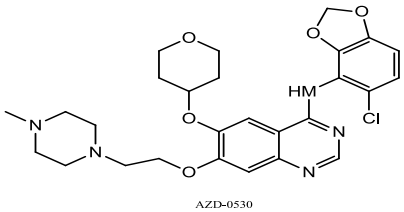
SK-606 [91-95] has been determined to be effective Src kinase inhibitor (IC_{50}= 1.1 nM), and AbI kinase inhibitor (IC_{50}= 1nM). In addition, this compound has selectivity inhibit Src over non-Src family kinase and inhibit Src-dependent cell proliferation (IC_{50} = 100 nM). SKI-606 is an orally active 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].

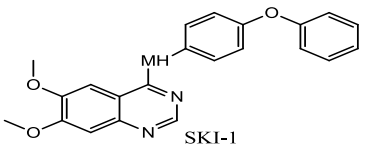


Quinazoline template-based inhibitors AZM475271 (M475271) and AZD0530

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].



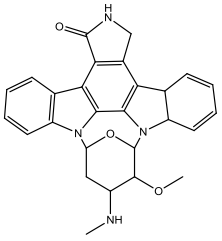


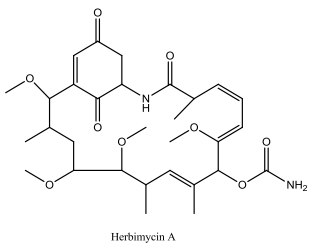


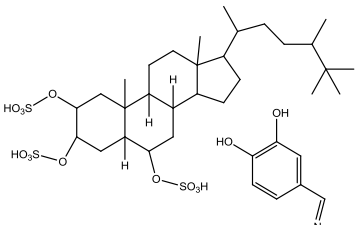
Other template-based inhibitors

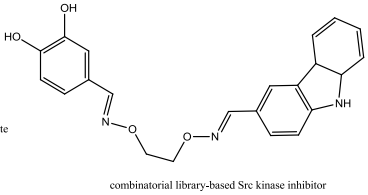
The are other examples of small molecules that are Src kinase inhibitors [36, 106–110], such as phenylaminopyrimidines which bind to the inactive conformation of Src kinase but this compounds are suffered from low activity (IC_{50} =∼ 1 μM). Natural products inhibitors of Src kinase, staurosporine, herbimycin 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.

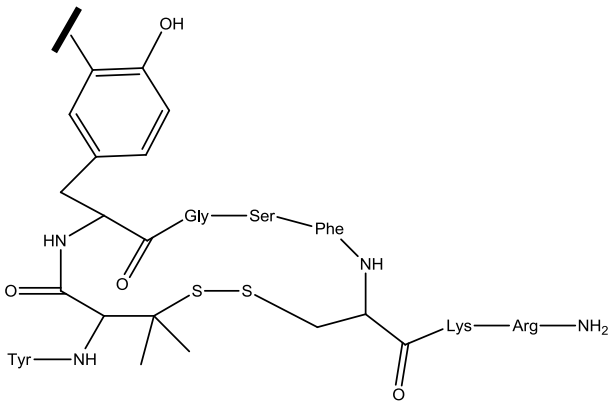
KX-01 is the first clinical Src inhibitor of the novel peptidomimetic class that targets the peptide substrate site of Src providing more specificity toward Src kinase. Combinational index analysis revealed that combinations of KX-01 with Tamoxifen [TAM] resulted in synergistic growth inhibition of breast 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.

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