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Bosutinib

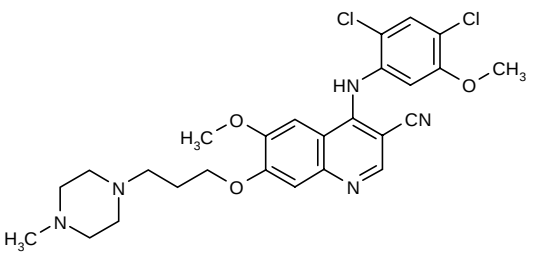
Rec INN; USAN

Dual Src and Abl Kinase Inhibitor
Treatment of Solid Tumors
Treatment of CML and Ph⁺ ALL

SKI-606

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile

InChI=1/C26H29Cl2N5O3/c1-32-6-8-33(9-7-32)5-4-10-36-25-13-21-18(11-24(25)35-3)26(17(15-29)16-30-21)31-22-14-23(34-2)20(28)12-19(22)27/h11-14,16H,4-10H2,1-3H3,(H,30,31)



$C_{26}H_{29}Cl_2N_5O_3$
Mol wt: 530.50

CAS: 380843-75-4

EN: 301966

Abstract

Bosutinib (SKI-606) is a potent inhibitor of Src kinase activity, having IC_{50} values of 1-3 nM in isolated Src enzyme assays. Bosutinib inhibits Src autophosphorylation and the phosphorylation of several known Src substrate proteins in multiple human cancer lines. Bosutinib is orally effective in nude mouse xenograft models, including HT-29, COLO 205, HCT 116 and DLD-1 colorectal tumors and MDA-MB-231 breast tumors, as well as in several *in vivo* models of metastasis. Like many other Src inhibitors, bosutinib is also a potent inhibitor of Abl kinase activity, having an IC_{50} of 1 nM in an enzyme assay. It is a potent antiproliferative agent in chronic myelogenous leukemia (CML) cell lines and inhibits the phosphorylation of Abl substrate proteins in these cells. A 5-day oral regimen of bosutinib caused tumor regression and some cures in a CML xenograft model. Bosutinib was also orally active in models of imatinib-resistant CML. Bosutinib is currently in clinical trials for the treatment of both solid tumors and CML.

Synthesis

Several synthetic routes have been reported for the preparation of bosutinib.

In the first approach, methyl vanillate was alkylated with 3-chloropropyl *p*-toluenesulfonate to give (I) (1). Nitration, followed by reduction of the nitro group, provided aniline (II). Treatment of (II) with dimethylformamide dimethylacetal and subsequent reaction with the anion of acetonitrile led to the 3-quinolinecarbonitrile (III). Phosphorus oxychloride was then used to convert (III) to the 4-chloro analogue (IV). Reaction of (IV) with 2,4-dichloro-5-methoxyaniline resulted in displacement of the 4-chloro group to give (V), with subsequent reaction with 1-methylpiperazine resulting in displacement of the alkyl chloro group to give bosutinib. Scheme 1.

The second route started with 3-fluoro-*p*-anisidine (2). Reaction of this aniline with ethyl (ethoxymethylene)-cyanoacetate, followed by thermal cyclization, provided the 3-quinolinecarbonitrile (VI). Chlorination of (VI) with phosphorus oxychloride and reaction of the resulting (VII) with 2,4-dichloro-5-methoxyaniline gave the key 7-fluoro intermediate (VIII). The fluoro group of (VIII) was readily displaced by alcohols and reaction of (VIII) with 1-(3-hydroxypropyl)-4-methylpiperazine resulted in the formation of bosutinib. This pathway provided bosutinib in only five steps and was also suited to analogue synthesis. Scheme 2.

Another route to intermediate (VIII) is depicted in Scheme 3. The first step is the conversion of 2,4-dichloro-5-methoxyaniline to 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide (IX) via reaction with cyanoacetic acid and diisopropylcarbodiimide (3). Reaction of (IX) with 3-fluoro-*p*-anisidine and triethyl orthoformate led to the

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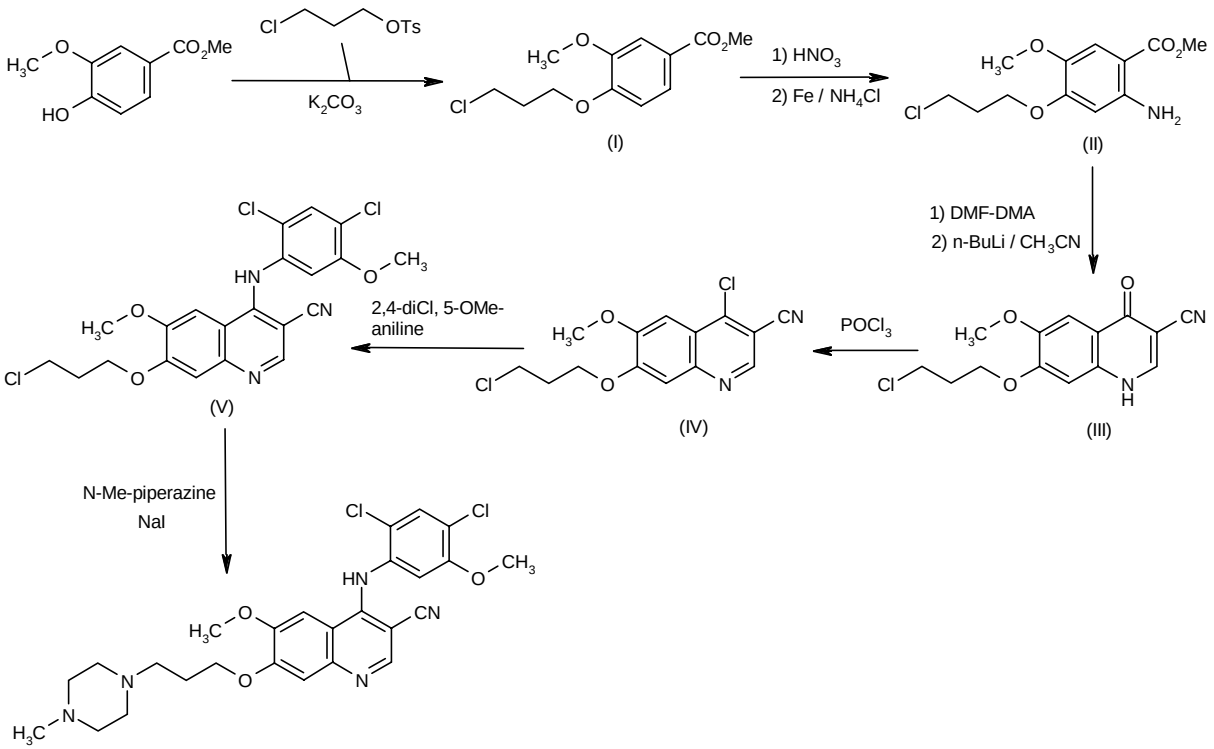
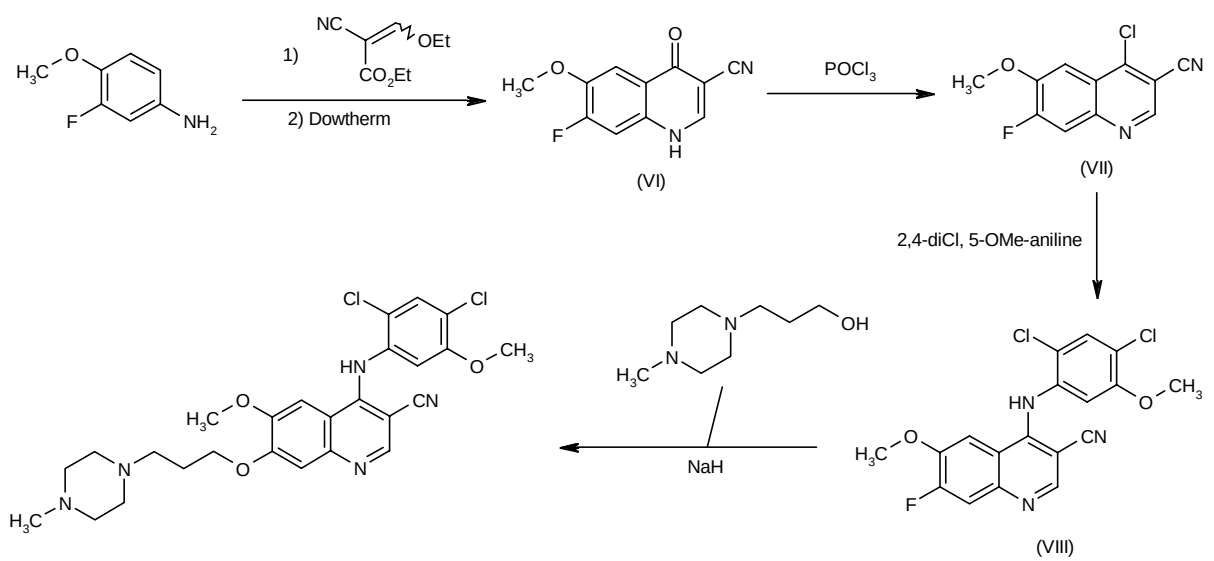
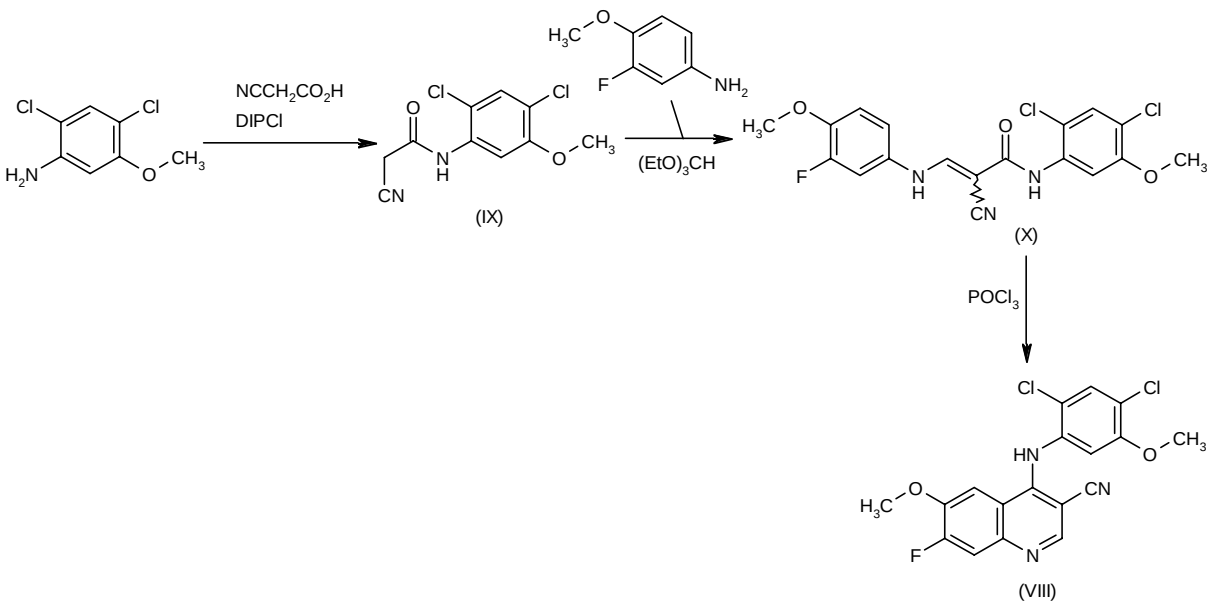
Scheme 1: Synthesis of Bosutinib



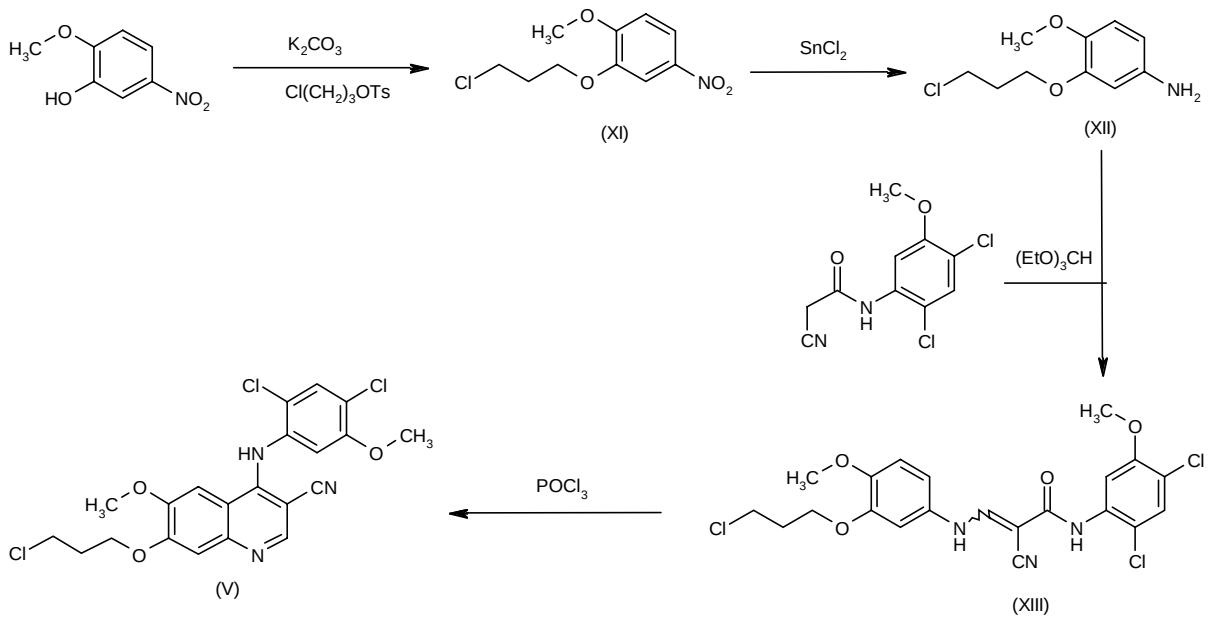
Scheme 2: Synthesis of Bosutinib



Scheme 3: Synthesis of Intermediate (VIII)



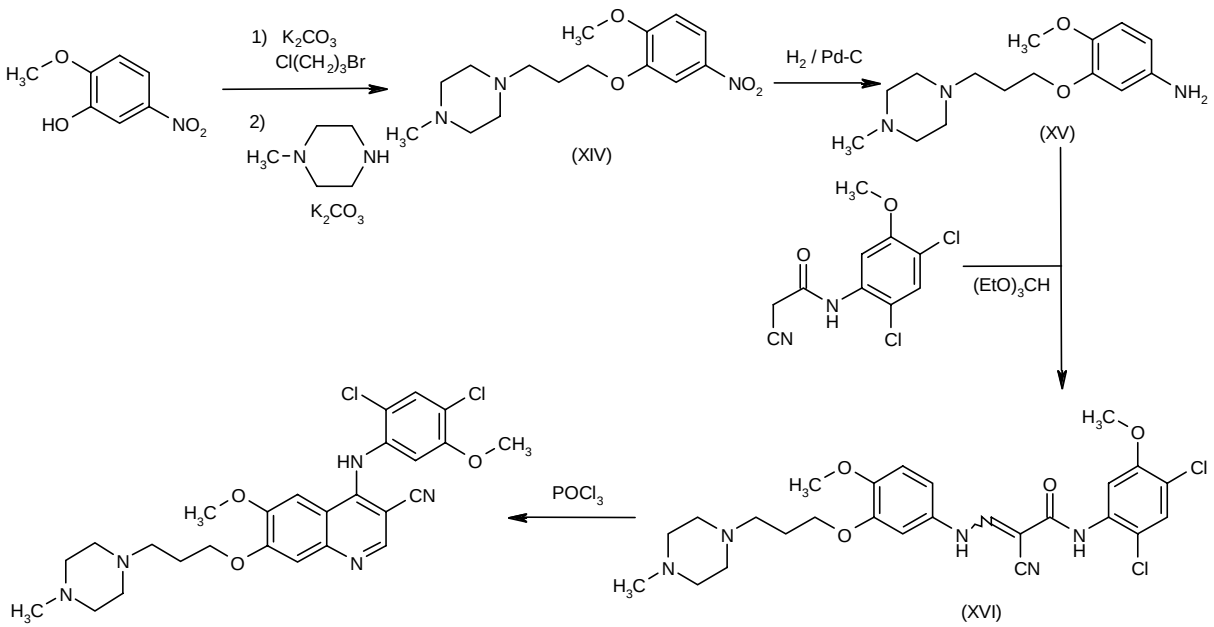
Scheme 4: Synthesis of Intermediate (V)



cyanopropenamide intermediate (X) as a mixture of *cis*- and *trans*-isomers. Upon treatment of (X) with phosphorus oxychloride at elevated temperature, the key 3-quinolinecarbonitrile intermediate (VIII), previously prepared via Scheme 2, was obtained.

Further application of the reaction sequence depicted in Scheme 3 led to an alternate route to key intermediate (V) (3). Alkylation of 2-methoxy-5-nitrophenol with 3-chloropropyl *p*-toluenesulfonate to obtain (XI), followed by tin(II)chloride reduction, provided (XII). Reaction of

Scheme 5: Synthesis of Bosutinib



(XII) with 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide and triethyl orthoformate gave the cyanopropenamide (XIII), with subsequent cyclization with phosphorus oxychloride resulting in (V), the penultimate precursor to bosutinib via the route shown in Scheme 1. One advantage of this route is the lower cost of the starting 2-methoxy-5-nitrophenol compared to that of 3-fluoro-*p*-anisidine. Scheme 4.

In the final reported route to bosutinib, reaction of 2-methoxy-5-nitrophenol with 1-bromo-3-chloropropane followed by 1-methylpiperazine resulted in intermediate (XIV) (3). Catalytic hydrogenation of (XIV) provided the aniline (XV), which upon reaction with 2-cyano-*N*-(2,4-dichloro-5-methoxyphenyl)acetamide and triethyl orthoformate gave the cyanopropenamide (XVI). Finally, cyclization of (XVI) with phosphorus oxychloride led directly to bosutinib. Scheme 5.

Several crystalline forms of bosutinib were evaluated for stability, with the most stable form being the monohydrate (4).

Background

The nonreceptor tyrosine kinase Src is a member of the highly conserved Src family of kinases, the SFKs, which includes Lyn, Lck, Hck, Fyn and others (5-7). Src is the prototype member of this family and is overexpressed in several human cancers, including breast, lung, melanoma, pancreas, head and neck, ovarian and colon cancers (7-15). In the case of colorectal cancer, increases in Src activity correlate with tumor progression (8).

The effect of Src on tumor growth and metastasis may arise from its ability to weaken interactions between the tumor cell and the surrounding stroma by phosphorylating proteins that control these interactions. For instance, Src phosphorylation of focal adhesion kinase (FAK) results in an increase in cell motility (16). Src-mediated phosphorylation of β-catenin causes it to dissociate from E-cadherin, resulting in the breakdown of adhesive junctions, opening gaps in the endothelium, and altered transcription of β-catenin/T-cell factor (TCF)-dependent genes (17-19). In addition, tumor metastasis is typified by increased vascular endothelial growth factor (VEGF)-mediated vascular permeability, which is dependent on Src kinase activity (20). Src knockout mice had a reduction in metastasis of VEGF-expressing tumors compared to wild-type animals (21). These properties make the inhibition of Src kinase activity an attractive target for new anticancer drugs.

Over the last several years, several small-molecule kinase inhibitors have been approved by the FDA for the treatment of cancer, the first of which was imatinib, initially known as STI-571, an inhibitor of Bcr-Abl kinase (22, 23). Marketed by Novartis as Gleevec®/Glivec®, imatinib was granted approval in 2001 for the treatment of chronic myelogenous leukemia (CML). The hallmark of CML is the expression of Bcr-Abl, a constitutively active form of the tyrosine kinase Abl, which results in the uncontrolled growth of white blood cells (24, 25). Expression of Bcr-Abl is the result of a genetic abnormality known as the Philadelphia chromosome. Although first observed in CML, there is a form of acute lymphoblastic leukemia (ALL) that also expresses Bcr-Abl, known as Ph^+ ALL

(26). Both CML and Ph^+ ALL are driven by a single oncogene, making them optimal diseases for a targeted therapeutic.

While imatinib is highly effective in treating newly diagnosed CML patients, over time many patients develop resistance (27). Mechanisms of resistance include the amplification of the *BCR-ABL* gene and upregulation of alternate cell pathways, including SFKs, with the principal route to imatinib resistance being the acquisition of mutations in the kinase domain of Bcr-Abl (28, 29). Crystallographic analysis showed that these mutated residues were those amino acids either in direct contact with the inhibitor, or those that were key to retaining the conformation of the kinase in the inactive form (30, 31). While imatinib only binds the inactive form of Abl, other Abl inhibitors can bind the active form of this kinase. Since the active conformation of Abl is similar to that of Src, many of these Abl inhibitors also inhibit Src kinase activity. Dasatinib, marketed by Bristol-Myers Squibb under the trade name of Sprycel®, is a dual inhibitor of Abl and Src that was approved by the FDA in 2006 for the treatment of imatinib-resistant CML (32). While dasatinib is effective in inhibiting the activity of most imatinib-resistant Abl mutants, it is not active against the T315I mutant, one of the most common mutations observed in the clinic (33). Like imatinib, dasatinib makes a key hydrogen bonding interaction with Thr315. Replacement of this amino acid with the larger isoleucine residue disrupts dasatinib binding to the kinase (34).

An assay using a yeast strain with a galactose-inducible chimeric *v-Src* gene with the catalytic domain of human c-Src was used to screen compounds for Src-inhibitory activity (35). To determine if compounds identified in the screen were direct inhibitors of Src kinase activity, the hits from the yeast assay were examined in an ELISA format Src kinase assay. One hit, 4-[(2,4-dichlorophenyl)amino]-6,7-dimethoxy-3-quinolinecarbonitrile, had an IC_{50} of 30 nM for inhibition of Src kinase activity. Optimization of the 4-anilino group and the substituent at C-7 of the 3-quinolinecarbonitrile core led to the identification of bosutinib (SKI-606), which had an IC_{50} of 1.2 nM in the ELISA format Src kinase assay (1), and was later found to have an IC_{50} of 3.8 nM in a subsequently developed Lance format Src kinase assay (2).

Preclinical Pharmacology

Bosutinib was profiled against a number of other kinases in either isolated enzyme or cell-based assays, and was found to be a weak inhibitor of HER2, with greatly reduced activity against platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and insulin-like growth factor receptor-1 (IGFR-1) (1). Activity was observed against other SFK members. An additional *in vitro* characterization study with a panel of over 50 kinases indicated that bosutinib had IC_{50} values of 0.17 and 0.85 nM for inhibition of Fgr and Lyn, with lesser activity against Csk, Syk, Alk and Pim-2 and no appreciable inhibition of other kinases (36).

When tested in standard tumor cell proliferation assays, low micromolar activity was observed against many human tumor lines. In an assay where HT-29 colon cells were grown in a monolayer on plastic, IC_{50} values of 1.5-5 μM were observed depending on the conditions of the assay, including the plating density of the cells (1, 36). Under assay conditions where bosutinib gave an IC_{50} of 1.5 μM for inhibition of the proliferation of HT-29 cells, an IC_{50} of 2.5 μM was obtained against COLO 205 cells, a colon tumor line that expresses about one-half the level of Src as HT-29 cells (37). In an HT-29 colony formation assay in soft agar, bosutinib had an IC_{50} of 400 nM. In a spheroid growth assay with COLO 205 cells, it had an IC_{50} of 2.5 μM. Under reduced-serum conditions in more prolonged growth assays, the proliferation of MDA-MB-231 breast tumor cells was inhibited by submicromolar concentrations of bosutinib (38).

To determine if bosutinib was directly inhibiting Src activity in cells, rat fibroblasts were prepared that expressed v-Src fusions with the catalytic domain of human c-Src (35). These cells exhibited a transformed morphology that returned to normal in the presence of bosutinib. In a proliferation assay where these Src-transformed rat fibroblasts were grown in suspension, bosutinib had an IC_{50} of 100 nM (1). In these cells, a concentration of 500 nM of bosutinib completely blocked the Src-mediated phosphorylation of the Src substrate cortactin Y421, with an IC_{50} of < 100 nM (39). Inhibition of the phosphorylation of additional Src substrates was also observed, including FAK Y925, caveolin Y14 and Src autophosphorylation of Y418 (40, 41).

Bosutinib inhibited Src autophosphorylation on Y418 in HT-29 cells with an IC_{50} of 250 nM, and similar activity was seen in COLO 205 cells (37). Bosutinib also inhibited the phosphorylation of FAK in both these tumor lines. In addition, bosutinib induced apoptosis in two epidermal growth factor receptor (EGFR)-dependent non-small cell lung cancer (NSCLC) lines, HCC827 and H3255, which have increased levels of Src phosphorylation (42). It is worth noting that, for most tumor lines, the antiproliferative activity of bosutinib does not correlate with inhibition of Src.

Small interfering RNA (siRNA)-mediated knockdown of Src reduced tyrosine phosphorylation of β-catenin in DLD-1 colorectal tumor cells (19). Treatment of DLD-1 cells with 1.5 μM of bosutinib also reduced the tyrosine phosphorylation of β-catenin. Bosutinib did not affect the levels of β-catenin, but caused its relocalization to the plasma membrane and increased its association with E-cadherin. In addition to strengthening cell-cell junctions, bosutinib also inhibited β-catenin translocation to the nucleus and its transcriptional activity. In an *in vitro* wound-healing assay in DLD-1 cells, exposure to 1.5 μM of bosutinib for 4 days provided an 80% decrease in cell migration, consistent with its ability to strengthen cell-cell associations. Similarly, COLO 205 cells treated with bosutinib aggregated as dense clumps, with relocalization of both β-catenin and E-cadherin to regions of cell-cell contact (43). In contrast to DLD-1 cells, no phospho-

rylation of β-catenin was observed in these cells, although some bosutinib-sensitive tyrosine phosphorylation of p120 catenin occurred. The migration of both MDA-MB-231 and MDA-MB-435 breast tumor cells was severely restricted by 1 μM bosutinib in a wound-healing assay, with an associated decrease in phosphorylation of Src, Pyk2, FAK and $p130^{cas}$ (38, 44). In MDA-MB-231 cells, 0.1 μM bosutinib also retarded cell migration (38). As was the case with colorectal tumor cells, treatment of MDA-MB-231, MDA-MB-435 and MCF7 breast tumor cells with 1 μM bosutinib caused increased β-catenin localization to the plasma membrane (44).

Further testing of bosutinib against a panel of tumor cell lines resulted in the discovery of potent inhibition of K562 and KU812 cell proliferation, with IC_{50} values of 20 and 5 nM, respectively (45). Both of these cell lines are CML lines and therefore contain an activated form of Abl kinase, Bcr-Abl. When tested under identical assay conditions, imatinib had IC_{50} values of 88 and 210 nM, respectively, for inhibition of the proliferation of the KU812 and the K562 lines. In an isolated Abl kinase assay and in a proliferation assay with v-Abl-transformed rat fibroblasts, bosutinib had IC_{50} values of 1 and 90 nM, respectively.

When bosutinib was tested in proliferation assays with two additional CML lines, LAMA-84 and KCL22, IC_{50} values of 1 and 3 nM, respectively, were observed (36). In this study, IC_{50} values of 20 and 3 nM, respectively, were obtained for inhibition of the K562 and KU812 lines, in accordance with initially reported results. Bosutinib also inhibited the proliferation of the PEER human T-cell acute lymphoblastic leukemia (T-ALL) line that expresses another activated form of Abl kinase, NUP214-ABL1 (46).

Bosutinib reduced the phosphorylation of Bcr-Abl in both K562 and KU812 lines and phosphorylation of the SFKs Lyn and Hck in these lines was also reduced (45). Inhibition of STAT5 (signal transducer and activator of transcription 5) phosphorylation in these lines corresponded with antiproliferative activity, with IC_{50} values of 10 and 25 nM in the KU812 and K562 lines, respectively. In an imatinib-resistant K562R line that expresses high levels of Lyn, bosutinib blocked the phosphorylation of both Bcr-Abl and Lyn and also the proliferation of these cells (47). Treatment of Bcr-Abl-expressing 32D murine myeloid cells with bosutinib resulted in G1 growth arrest associated with a sustained inactivation of the cyclin-dependent kinase CDK2 (48). Interestingly, bosutinib also inhibited Bcr-Abl-mediated phosphorylation of β-catenin in CML cells, much as was observed in tumor cells of epithelial origin (49).

Although bosutinib is a potent inhibitor of wild-type Abl, in an isolated kinase assay with mutated T315I Abl, an IC_{50} of only 344 nM was observed (50). The ability of bosutinib to inhibit other clinically relevant imatinib-resistant Abl point mutations was examined in proliferation assays with murine Ba/F3 cells stably transformed with either wild-type or mutated Abl (36). Bosutinib had an IC_{50} of 13 nM for inhibition of the growth of the wild-type Abl cells and activity was retained against the D276G and Y253F mutants, with IC_{50} values of 25 and 40 nM, respectively. Reduced activity was seen against the E255K mutant, with an IC_{50} of 394 nM. In correlation with the enzyme assay, reduced activity was observed in a proliferation assay with cells transformed with the T315I mutant (IC_{50} = 1.9 μM). In phosphorylation assays with these cells, bosutinib had a slightly greater effect in inhibiting the phosphorylation of Y253F than wild-type Abl or the D276G and E255K mutants. As expected, bosutinib had a much weaker inhibitory effect on the phosphorylation of the T315I mutant. Molecular modeling of bosutinib with the intermediate conformation of Abl indicated the likelihood of a hydrogen bond between the hydroxyl group of T315 with the C-3 carbonitrile group of bosutinib (36). While neither residue E255 nor Y253 is predicted to make contact with bosutinib, E255 seems to be more important than Y253 in stabilizing the P-loop.

The previously discussed Src-transformed rat fibroblasts grow as tumors in nude mice. In a xenograft study with unstaged tumors, a dose of 30 mg/kg i.p. b.i.d. of bosutinib for 2 weeks resulted in a T/C of 18% (1). In a second xenograft study where the tumors were staged to 100 mg before dosing, a dose of 25 mg/kg i.p. b.i.d. for 10 days resulted in a T/C of 25%. Since the growth of these tumors is completely dependent on Src activity, the ability of bosutinib to effectively block their growth confirmed that the compound was functioning as an Src inhibitor *in vivo*.

Bosutinib was also tested in an HT-29 colon tumor xenograft model where the tumors were staged to 250 mg (37). Once-daily oral doses of 25, 50, 100 and 150 mg/kg for 21 days provided dose-dependent inhibition of tumor growth, with the dose of 50 mg/kg providing reproducible activity. No deaths or weight loss were observed in the animals given the highest dose. In xenograft studies with other colon tumor lines, namely COLO 205, HCT 116 and DLD-1, bosutinib caused inhibition of tumor growth when dosed orally at 75 mg/kg b.i.d. for 21 days. As in the HT-29 study, these tumors were staged to about 200 mg prior to dosing and no toxicity was observed. Src autophosphorylation was inhibited in HT-29 tumors 24 h after oral administration of bosutinib at 150 mg/kg.

When bosutinib was tested in models of lung metastases using both CT26, a murine colon cancer line, and D121, a human Lewis lung line, a dose of 10 mg/kg i.p. b.i.d. for 3 days resulted in a 60% reduction in lung metastatic lesions (51). The dose of 10 mg/kg was chosen based on this being the concentration needed to return levels of vascular permeability to those of the control in a Miles assay.

Bosutinib was orally effective in an *in vivo* model of breast tumor metastases (38). In this study, MDA-MB-231 cells were transfected with a plasmid encoding green fluorescent protein (GFP). These MDA-MB-231-GFP cells were implanted into nude mice and allowed to grow to 30-50 mg. When these mice were treated with an oral dose of 150 mg/kg of bosutinib administered 5 days weekly for 4 weeks, a reduction in tumor growth was observed. The

lungs, spleens and livers were removed from these animals and tissue slices of these organs were analyzed for the presence of fluorescent tumor cells. Animals treated with bosutinib had a significant reduction in the number and the size of metastases. Protein lysates of the primary tumors from this study were analyzed for phosphorylation levels of Src, along with MAPK (mitogen-activated protein kinase) and FAK. As was seen in the *in vitro* study, treatment with bosutinib led to reduced phosphorylation of all three substrates. Increased E-cadherin localization at the plasma membrane also occurred in tumors from treated animals. In addition, reduced neovascularization and proliferation and increased apoptosis were observed in the tumors from treated animals.

Bosutinib was evaluated in a K562 xenograft model where the tumors were suspended in Matrigel and staged to 200-300 mg (45). Treatment with a dose of 75 mg/kg orally twice a day for 10 days resulted in tumor regression, with no regrowth of the tumor for 2 months. When the animals were administered a once-daily oral dose of 100 or 150 mg/kg for 5 days, they remained tumor-free for 6 weeks, with no toxicity observed. Of the animals that received a daily dose of 50 mg/kg orally for 5 days, 50% had tumors reappear after 6 weeks. If after implantation the tumors were allowed to grow to 800-900 mg prior to dosing, 100 mg/kg bosutinib once a day for 5 days resulted in the animals being tumor-free after 40 days.

In a xenograft model with KU812 cells, tumors were staged to 400 mg before oral dosing of bosutinib at 75 mg/kg twice a day for 11 days (36). In a second model, the tumors were smaller (289 mg) and bosutinib was administered at doses of 75 mg/kg twice a day and also at 150 mg/kg once a day. In all models the animals remained tumor-free for 210 days, although some weight loss was observed. This weight loss was reduced when the 150 mg/kg dose was given for 11 days on a 5 days on/2 days off schedule. Bosutinib was also tested in xenograft models with Ba/F3 cells expressing Abl and three of the most common imatinib-induced Abl point mutations. In these experiments, bosutinib was dosed at 150 mg once a day for 11 days using the intermediate dosing schedule associated with less weight loss in the KU812 xenograft model. The greatest inhibition of tumor growth was observed against the wild-type Abl cells, followed by the D276G mutant. Moderate inhibition of tumor growth was seen in the xenograft with the Y253F mutant and no effect was observed with the T315I mutant.

Several years ago, it was shown that the major phenotype of Src knockout mice was the development of osteopetrosis, due to the loss of Src-dependent osteoclast-mediated bone resorption (52). This finding led to the hypothesis that Src inhibition could be therapeutically effective in treating osteolytic metastastic bone disease (11). When tested in an orthotopic intratibial model of bone metastasis, oral administration of bosutinib at 150 mg/kg 5 days a week for 9 weeks inhibited MDA-MB-435 tumor growth in the bone (53).

Studies with Src knockout mice also showed that these animals had reduced brain injury in a model of ischemic stroke due to their resistance to VEGF-mediated vascular permeability (54). In this study, PP1, a low-molecular-weight Src inhibitor, was shown to be effective. In a rat model of transient focal ischemia, bosutinib provided a reduction in both brain infarct size and neurological deficits (55, 56), and reduced blood-brain barrier permeability following ischemic injury (57). Bosutinib was also active in models of permanent focal ischemia (58), hemorrhagic stroke (59) and myocardial infarction (60).

Studies with bosutinib in primitive progenitor CML cells from patients indicated that it inhibits the proliferation of these cells, whereas it does not appreciably affect the proliferation of normal primitive progenitors (61). In studies with cells from blast-phase CML patients, bosutinib inhibited the phosphorylation of Bcr-Abl, Lyn and Hck (62). Treatment of cells from patients with the E255V, E255K, F359V and Y253H imatinib-resistant Abl mutations with bosutinib caused a G1 phase arrest and increased apoptosis. In a transcriptional profiling study, K562 cells were treated with 10 nM bosutinib, resulting in modification of the expression of 121 genes, including those involved in signal transduction and transcriptional and cell cycle regulation (63).

Pharmacokinetics and Metabolism

Administration of a single oral dose of 50 mg/kg of bosutinib in a vehicle of 0.5% methylcellulose and 0.4% polysorbate 80 (Tween 80) to nude mice resulted in a peak plasma concentration of 2.74 μM and a trough level of 90 nM (37). Increasing the dose to 150 mg/kg gave an increase in the peak concentration to 3.3 μM and a larger increase in the trough level to 350 nM. Bosutinib had an oral bioavailability of 18%, a half-life of 8.6 h and a large volume of distribution (18.6 l/kg).

Clinical Studies

Preliminary results of a phase I/II study of bosutinib in CML patients have been reported (64). The 18 patients enrolled in the phase I portion were in chronic phase with imatinib-intolerant, relapsed or refractory disease and a median age of 62 years. Three patients received a daily dose of 400 mg, another 3 a daily dose of 500 mg, and the remaining 12 a daily dose of 600 mg. The adverse effects observed were mainly diarrhea (87%) and nausea (33%), and in some patients rash, in 1 case severe. These effects were observed at the 600-mg dose, resulting in 500 mg being selected as the phase II dose. In contrast to imatinib and dasatinib, pleural effusion and pulmonary edema were not observed in patients treated with bosutinib, which may be a result of its lack of significant activity against PDGFR and c-Kit. Of 7 patients treated with bosutinib for at least 12 weeks, 3 had a complete cytogenetic response and 1 patient had a partial response. Complete hematological responses were seen in all 7 patients in hematological relapse before receiving bosutinib for at least 1 month. Six of these patients had pre-existing imatinib-resistant mutations. This clinical trial

has been expanded to include patients in all phases of CML and also those with Ph^+ ALL.

Conclusions

The utility of Abl kinase inhibition in clinical settings is well established. Src inhibition, on the other hand, remains a promising but unproven clinical modality. The clinical development of bosutinib and other Src inhibitors will prove an interesting study of the ability of pharmaceutical companies and clinicians to provide innovative leadership in developing drugs based on the physiological activities of the therapeutic target in a complex and interactive tumor-host setting.

Source

Wyeth Pharmaceuticals (US).

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