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MONOGRAPH

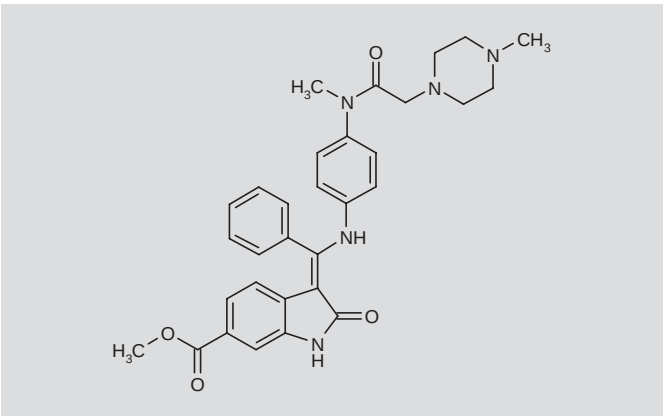
BIBF 1120

Angiogenesis Inhibitor
Oncolytic

Vargatef™

3(*Z*)-[1-[4-[*N*-Methyl-*N*-[2-(4-methylpiperazin-1-yl)acetyl]amino]phenylamino]-1-phenylmethylene]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylic acid methyl ester

InChI: 1S/C31H33N5O4/c1-34-15-17-36(18-16-34)20-27(37)35(2)24-12-10-23(11-13-24)32-29(21-7-5-4-6-8-21)28-25-14-9-22(31(39)40-3)19-26(25)33-30(28)38/h4-14,19,32H,15-18,20H2,1-3H3,(H,33,38)/b29-28-



$C_{31}H_{33}N_5O_4$
Mol wt: 539.6248
CAS: 656247-17-5
CAS: 928326-83-4
EN: 379939

SUMMARY

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a fundamental process for tumor growth and metastasis. BIBF 1120 (planned brand name Vargatef™) is a novel, oral, potent angiokinase inhibitor that simultaneously acts on three key receptor families involved in angiogenesis: vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs) and fibroblast growth factor receptors (FGFRs). In vitro, BIBF 1120 inhibits growth factor-induced intracellular signaling in endothelial and smooth muscle cells, as well as pericytes, resulting in inhibition of cell proliferation and induction of apoptosis. BIBF 1120 is effective in a broad range of preclinical models tested to date, including mice with established human head and neck squamous cell carcinoma FaDu tumor xenografts, as demonstrated by rapid effects on tumor perfusion and permeability and significant inhibition of tumor growth. Based on encouraging results from phase I/II trials, BIBF 1120 has entered phase III clinical development.

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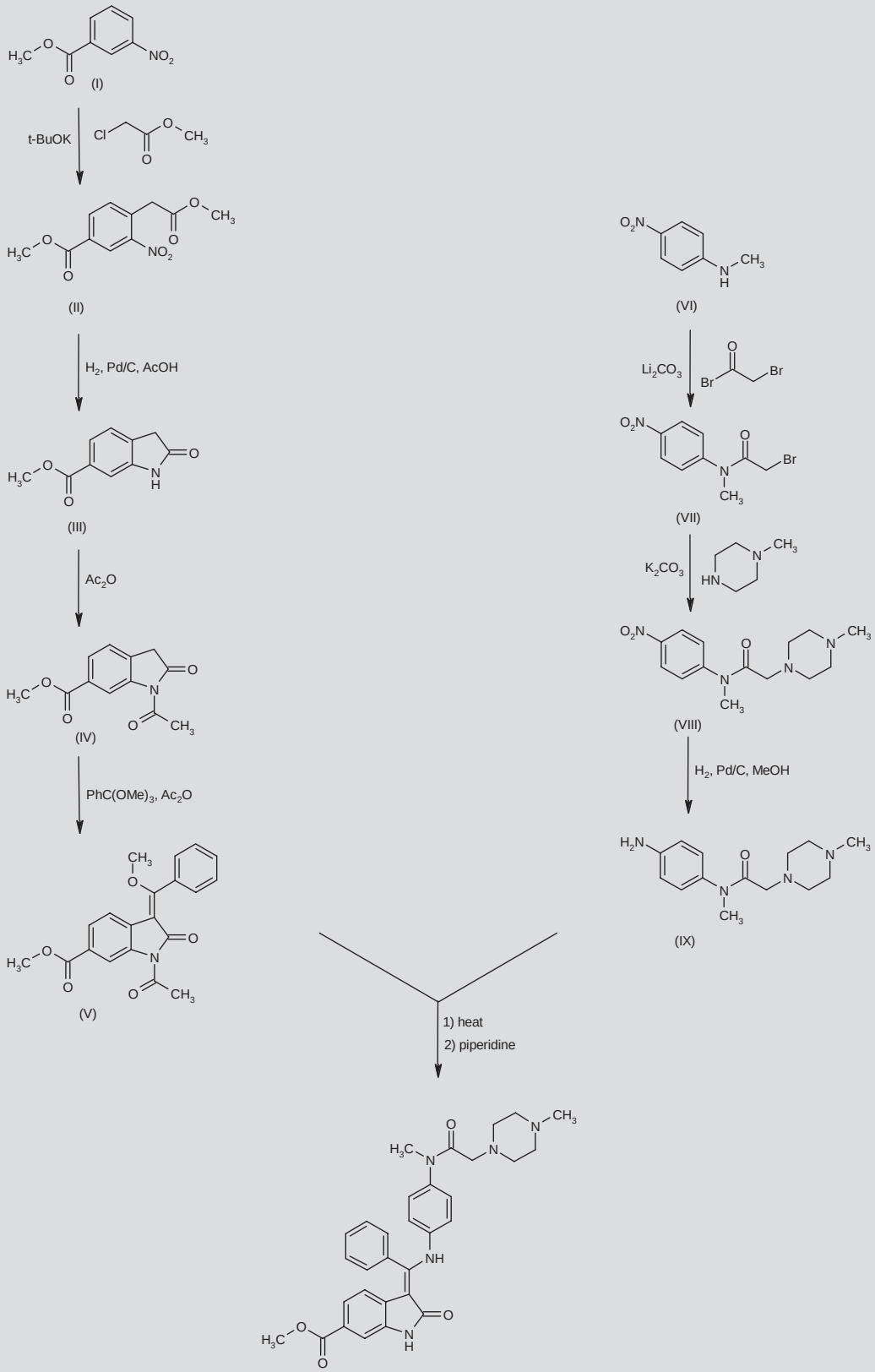
SYNTHESIS

BIBF 1120 can be prepared by a straightforward sequence comprising five linear steps (eight steps in total) starting from commercially available materials. The synthesis follows a convergent route, with 1-acetyl-6-(methoxycarbonyl)indolin-2-one (IV) and *N*-(4-aminophenyl)-*N*-methyl-2-(4-methylpiperazin-1-yl)acetamide (IX) as central intermediates (Scheme 1).

Since indolinones substituted in position 6 have rarely been described in the literature, several routes of synthesis were developed for (IV) by adapting known procedures (1). Intermediate (IV), in particular, can be obtained in good yield by introducing the acetic acid moiety via vicarious nucleophilic substitution with methyl chloroacetate using 3-nitrobenzoic acid methyl ester (I) as starting material. The product of this reaction (II) undergoes spontaneous ring closure upon hydrogenation of the nitro group in acidic media to give indolinone (III). Refluxing compound (III) in acetic anhydride furnishes the *N*-acetylated indolinone (IV), activating position 3 for further derivatization. On the other hand, the aromatic amine (IX) is prepared by well-established chemical transformations (1). Methyl(4-nitrophenyl)amine (VI) is *N*-acylated using bromoacetyl bromide. The resulting compound (VII) is reacted with *N*-methylpiperazine to give adduct (VIII). Reduction of the nitro group by hydrogenation in methanol completes the synthesis of building block (IX). Further derivatization of indolinone (IV) is achieved by refluxing the intermediate in a mixture of *ortho*-benzoic acid trimethyl ester and acetic anhydride. This step initiates the introduction of the side-chain functionality in position 3. The resulting compound (V) displays a methoxy moiety which serves as a leaving group in the final step. Reaction with aromatic amine (IX) in an addition–elimination sequence, followed by in situ acetyl cleavage by addition of piperidine, concludes the synthesis of BIBF 1120. The double bond geometry in the final compound is locked in a *Z*-conformation due to an intramolecular hydrogen bond between the NH group of the aromatic amine and the indolinone carbonyl.

Scheme 1. Synthesis of BIBF 1120



BACKGROUND

Cancer represents a major worldwide public health concern. In recent years, advances in molecular biology have led to a better understanding of the mechanisms underlying cancer, resulting in the development of new therapeutic agents designed to specifically target these pathways. These advances, alongside the idea of personalized therapy based on predefined genetic subpopulations, have resulted in significant improvements in cancer treatment and survival.

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a process fundamental to tumor growth and metastasis (2-4). This process is controlled by a complex balance of positive and negative regulators; tumors are able to stimulate the development of their own blood supply by tipping the balance towards proangiogenic factors (5).

Known proangiogenic regulators of physiological and pathological angiogenesis include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) (6). Of these, VEGF is believed to be the most important, and has therefore emerged as a key target for antiangiogenic therapy (7). VEGF actions are mediated through binding to receptor tyrosine kinases on the surface of vascular endothelial cells (2). This promotes angiogenesis, increases vascular permeability and recruits circulating endothelial precursor cells. Ligand binding to PDGF receptors (PDGFRs) and FGF receptors (FGFRs) controls the migration and adherence of pericytes and smooth muscle cells to endothelial cells, providing support and stability to the vessel wall (vessel maturation and stabilization) (3). Furthermore, pathways involving basic FGF (bFGF) and FGFR-2 are currently being discussed as possible escape mechanisms for evasion of VEGF/VEGFR inhibition (8).

Several pharmacological approaches have been developed to inhibit the VEGF signaling pathway. Monoclonal antibodies targeting VEGF, such as bevacizumab, VEGF antagonists, such as VEGF-Trap, and small-molecule inhibitors targeting VEGFR kinases, such as sunitinib and sorafenib, are currently registered or undergoing clinical investigation. Treatment with bevacizumab, a humanized variant of a murine monoclonal antibody to human VEGF-A, resulted in clinically meaningful improvements in survival among patients with metastatic colorectal, breast or lung cancer when used in combination with chemotherapy (9-11). However, clinical trials have identified specific tolerability concerns with bevacizumab treatment, namely the occurrence of life-threatening/fatal hemorrhages predominantly in patients with squamous cell lung cancer or untreated central nervous system metastases, excluding approximately 50% of non-small cell lung cancer (NSCLC) patients from bevacizumab therapy (10, 12).

Although the ultimate target of antiangiogenic drugs is the genetically stable, activated endothelial cell of a growing tumor blood vessel rather than the genetically unstable tumor cell population, it is becoming apparent that resistance can develop over time to angiogenesis inhibitors (13-15). Whilst VEGF is a key driver of angiogenesis, multiple other proangiogenic factors also contribute to the angiogenic process, resulting in extensive redundancy and a decreased dependence on VEGF in certain tumors (16). Following treatment with agents targeting single proangiogenic factors, such as VEGF or VEGFR inhibitors, resistance occurs because redundant pathways remain active and act as salvage mechanisms to overcome hypoxia induced following initial treatment (6).

Multitargeted tyrosine kinase inhibitors are the latest class of agents with the potential to circumvent the problem of resistance to antiangiogenic therapy. A variety of multiple-target antiangiogenic agents have been developed, including sunitinib, an oral inhibitor of VEGFR, PDGFR, c-kit and FLT3, sorafenib, an oral inhibitor of C-Raf, B-Raf, VEGFR, PDGFR-β, c-kit and FLT3, and vandetanib, an oral inhibitor of VEGFR, epidermal growth factor receptor (EGFR) and rearranged during transfection (RET) receptor tyrosine kinase activity.

BIBF 1120 is a novel, oral angiokinase inhibitor that acts simultaneously on three key receptor families involved in the process of angiogenesis: VEGFR, PDGFR and FGFR (17). By inhibiting these receptors expressed on endothelial cells, smooth muscle cells and pericytes, BIBF 1120 potentially prevents both tumor growth and dissemination, while also avoiding resistance. In addition, wild-type and mutated forms of PDGFR and FGFR are also expressed by tumor cells in subsets of human cancers, and thus BIBF 1120 may have an expanded therapeutic potential by targeting tumor cells directly (18, 19).

PRECLINICAL PHARMACOLOGY

Cocrystalization with recombinant VEGFR-2 and x-ray diffraction confirmed that BIBF 1120 binds to the adenosine-5-triphosphate (ATP) binding site in the cleft between the $-NH_2$ and $-COOH$ terminal lobes of the VEGFR-2 kinase domain. Biochemical assays show that BIBF 1120 inhibits a narrow range of kinases at pharmacologically relevant concentrations. BIBF 1120 inhibits VEGFR types 1, 2 and 3 (IC_{50} = 34, 21 and 13 nmol/L, respectively), PDGFR-α and PDGFR-β (IC_{50} = 59 and 65 nmol/L, respectively), FGFR types 1, 2 and 3 (IC_{50} = 69, 37 and 108 nmol/L, respectively), FLT3 and members of the Src family (Src, Lyn and LCK). At concentrations below 1000 nmol/L, BIBF 1120 does not inhibit other receptor tyrosine kinases, including EGFR, receptor tyrosine-protein kinase erbB-2 (HER2), insulin-like growth factor 1 receptor (IGF-I receptor) or the cell cycle kinases CDK1, CDK2 and CDK4 (17).

The effect of BIBF 1120 on growth and survival has been investigated in cellular cultures. In vitro treatment of VEGF-stimulated human umbilical vein endothelial cells (HUVEC) and human skin microvascular endothelial cells (HSMEC) resulted in inhibition of cell proliferation (EC_{50} = 9 and 7 nM, respectively). Furthermore, BIBF 1120 showed inhibition of intracellular signaling pathways and phosphorylation of mitogen-activated protein kinase (MAPK) and Akt in endothelial cells, pericytes and smooth muscle cells stimulated with VEGF and bFGF (endothelial cells) and PDGF and bFGF (pericytes and smooth muscle cells). BIBF 1120 was also shown to inhibit the proliferation of PDGF-stimulated pericytes and smooth muscle cells with EC_{50} values of 79 and 69 nmol/L, respectively) (17).

BIBF 1120 differs from other angiogenesis inhibitors with regard to its cellular duration of action and pharmacokinetics. A pulse-chase experiment with VEGFR-2-transfected NIH/3T3 cells was conducted to determine the duration of VEGFR-2 inhibition. Cells were exposed to BIBF 1120 for 1 h, washed off and cell proliferation or

VEGFR-2 activation/phosphorylation was analyzed after various periods of time. Following treatment with 50 nmol/L BIBF 1120 for 1 h, inhibition of receptor phosphorylation was sustained for at least 32 h, indicating the potential for a long-lasting antiangiogenic effect (17).

In vivo experiments show that BIBF 1120 induces rapid effects on tumor perfusion and permeability in human FaDu head and neck squamous cell carcinoma xenografts, as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Xenografts growing in nude mice were analyzed before and 72 h after initiation of daily oral treatment with BIBF 1120 at 100 mg/kg. The effects of BIBF 1120 treatment were readily visible on the DCE-MRI scan following 3 days of treatment, indicating a rapid response (17).

To confirm that BIBF 1120 affects the tumor vasculature, mice with established FaDu tumor xenografts were treated orally for 4 consecutive days with either BIBF 1120 100 mg/kg or vehicle control. After the last application, tumors were dissected and analyzed by immunohistochemistry. Compared to the control tumors, treatment with BIBF 1120 reduced tumor vessel density and the number of PDGFR-β-expressing perivascular cells (17).

In preclinical in vivo experiments designed to investigate the effect of BIBF 1120 on tumor growth, continuous once-daily treatment of mice with established FaDu tumor xenografts with BIBF 1120 (50 or 100 mg/kg p.o.) resulted in a highly significant inhibition of tumor growth. BIBF 1120 was also well tolerated across all dose levels, with no weight loss during the treatment period. Of note, inhibition of tumor growth was demonstrated in all preclinical xenograft models investigated to date across a range of histotypes, including human renal cell carcinoma (Caki-1), colorectal carcinoma (HT-29), ovarian carcinoma (SK-OV-3), non-small cell lung carcinoma (NSCLC; Calu-6), prostate carcinoma (PAC-120) and a syngeneic rat glioblastoma model (cell line GS-9L) (17).

PHARMACOKINETICS AND METABOLISM

In human liver microsomes, [^{14}C]-BIBF 1120 cleavage by esterase-catalyzed hydrolysis was the prevalent metabolic reaction, of which only 5% was cytochrome P450 (CYP)-dependent metabolism. In addition, BIBF 1120 did not show any relevant inhibition or induction of the major drug-metabolizing CYP enzymes such as CYP3A4 or the genetically polymorphic enzymes, e.g., CYP2D6. Therefore, metabolic drug–drug interactions based on inhibition or induction of CYP by BIBF 1120 with other drugs that are substrates for CYP enzymes are unlikely to occur.

Pharmacokinetic studies following oral BIBF 1120 treatment (50 mg/kg) in mice revealed a peak plasma concentration of about 1000 nmol/L 2 h after administration. Trough plasma levels were determined to be below 8 nmol/L at 24 h after administration (17). In humans, BIBF 1120 was absorbed moderately fast (t_{max} = 1-4 h) and it showed a terminal half-life of 7-19 h. Maximum plasma concentrations and exposure increased dose-proportionally after single doses and reached steady state following once- and twice-daily dosing. There was no decrease in exposure over time. [^{14}C]-Radiolabeled BIBF 1120 was mainly eliminated via the liver, with a fecal excretion rate of 93.4% within 120 h after dosing (20).

CLINICAL STUDIES

Thus far, BIBF 1120 has been investigated in various clinical trials in patients suffering from different advanced solid tumors. Several phase I dose-escalation studies have investigated the maximum tolerated dose (MTD), safety and pharmacokinetics of BIBF 1120 monotherapy in Caucasian and Japanese patients (21-23). From these studies, the MTD was defined as 250 mg for once- and twice-daily continuous dosing. Thus, splitting the cumulative daily dose into two daily administrations allowed an increase in the tolerable total daily dose, thereby permitting an increased exposure to BIBF 1120. The most common side effects were mild to moderate nausea, vomiting, diarrhea and abdominal pain.

Phase I dose-escalation trials investigating BIBF 1120 with various other anticancer compounds have also been performed and are ongoing (24-27). Results from these studies demonstrate that BIBF 1120 can be administered at a recommended dose of 200 mg twice daily with standard doses of carboplatin/paclitaxel in patients with advanced gynecological malignancies or NSCLC, with standard-dose pemetrexed in previously treated patients with NSCLC, or with standard-dose docetaxel in patients with hormone-refractory prostate cancer. The adverse event profiles observed in these studies are consistent with those seen for BIBF 1120 monotherapy and the respective chemotherapeutic agent. In addition, encouraging efficacy signals have been observed, especially in patients suffering from NSCLC, ovarian or renal cancer.

Several phase II trials in various indications have been performed and are also still ongoing. A double-blind, two-arm, randomized study assessed the clinical efficacy and safety of continuous treatment with two doses of BIBF 1120 in patients with advanced-stage NSCLC (28). A total of 73 patients with an ECOG score of 0-2 with locally advanced or metastatic (stage IIIB/IV) relapsed NSCLC after failure of first- or second-line chemotherapy were randomly assigned to BIBF 1120 250 mg b.i.d. or 150 mg b.i.d. Patients with an ECOG score of 0-1 (n = 57) had a median progression-free survival (PFS) of 11.6 weeks, a median overall survival of 38 weeks and a stable disease rate of 59%. Tumor shrinkage was seen as a best response in 20 patients, with tumor shrinkage close to partial response (PR) in 5 patients and a confirmed PR in 1 patient. The overall safety was shown to be consistent with the data from the phase I monotherapy trials. The most frequent adverse events included mild to moderate nausea, diarrhea, vomiting, anorexia and fatigue. No hand–foot syndrome, hematological side effects or severe hypertension have been observed.

BIBF 1120 has also been investigated as maintenance monotherapy in a two-arm, double-blind, placebo-controlled trial in patients suffering from ovarian cancer who had shown a response to prior chemotherapy for a first, second or third relapse of the disease (29, 30). Of 84 patients randomized, 5 patients receiving BIBF 1120 completed 9 months of treatment compared to no patient receiving placebo. At 36 weeks, PFS rates were 14.3% for BIBF 1120 (95% confidence interval [CI]: 3.8-27.3) and 2.9% for placebo (95% CI: 0.0-8.4), and the PFS hazard ratio (HR) was 0.68 (95% CI: 0.42-1.09). In addition, the median PFS according to radiological examinations was 4.8 months versus 2.8 months, with a PFS HR of 0.68 (95% CI: 0.42-1.09). Expected gastrointestinal toxicities occurred slightly

more frequently in the BIBF 1120 arm (16% compared to 10% for placebo), as did elevated liver enzymes.

Based on these promising phase I and II efficacy and tolerability data, BIBF 1120 has entered phase III clinical development for the treatment of patients suffering from NSCLC and ovarian cancer.

SOURCE

Boehringer Ingelheim GmbH (DE).

DISCLOSURES

The authors are employees of Boehringer Ingelheim GmbH & Co. KG.

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