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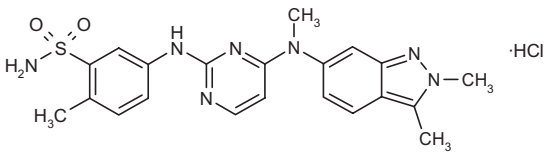
Pazopanib Hydrochloride

Prop INNM; USAN

Oncolytic
Angiogenesis Inhibitor
VEGFR-2 Tyrosine Kinase Inhibitor

786034
GW-786034

5-[4-[*N*-(2,3-Dimethyl-2*H*-indazol-6-yl)-*N*-methylamino]pyrimidin-2-ylamino]-2-methylbenzenesulfonamide hydrochloride



$C_{21}H_{24}ClN_7O_2S$
Mol wt: 473.9799

CAS: 635702-64-6

CAS: 444731-52-6 (as free base)

EN: 334209

Abstract

Tumor progression requires angiogenesis and targeting this process is a particularly attractive anticancer strategy. Vascular endothelial growth factor (VEGF) is a key mediator of neovascularization and research has intensely focused on interfering with the VEGF/VEGF receptor (VEGFR) signaling system in order to modulate angiogenesis. The development of small-molecule tyrosine kinase inhibitors targeting VEGFRs as potential antiangiogenic agents has progressed in recent years, with more than 30 VEGFR inhibitors under active development for the treatment of cancer. The indazolylpyrimidine pazopanib hydrochloride (786034, GW-786034) is one such pan-VEGFR inhibitor that has shown potent preclinical and clinical antitumor activity. It is undergoing phase II development as an antiangiogenic antitumor agent.

Synthesis

Pazopanib is synthesized as follows:

Methylation of 3-methyl-6-nitroindazole (I) to produce the 2,3-dimethylindazole analogue (II) is carried out in the presence of a variety of alkylating reagents, including trimethyloxonium tetrafluoroborate, trimethyl orthoformate/boron trifluoride etherate and dimethyl sulfate/sulfuric acid. Subsequent reduction of 2,3-dimethyl-6-nitroindazole (II) employing $SnCl_2$ and HCl affords the aminoindazole derivative (III), which is condensed with 2,4-dichloropyrimidine (IV) to yield the pyrimidinylaminoindazole (V). After methylation of amine (V) with iodomethane and Cs_2CO_3, the resulting chloropyrimidine (VI) is condensed with 5-amino-2-methylbenzenesulfonamide (VII) to afford pazopanib hydrochloride (1-3). Scheme 1.

Background

Angiogenesis is a complex process defined as the formation of new blood vessels from pre-existing vessels. It is essential for the progression of solid tumor growth to more than 2-3 mm^3. Mediators of this process include the angiogenic cytokines such as vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs), which stimulate endothelial cells to secrete proteases and plasminogen activators. These in turn cause degradation of the vessel basement membrane, allowing cells to invade the surrounding matrix. Cells will then migrate, proliferate and eventually differentiate to form a new lumen-containing vessel. The endothelial cells subsequently deposit a new basement membrane and also secrete growth factors (*e.g.*, platelet-derived growth factor, or PDGF) that attract supporting cells, which, together with angiopoietins and ephrins, ensure and regulate stability of the new vessel (4, 5).

Tumor progression requires angiogenesis and blood vessel density has been shown to correlate with patient survival. Cancers are believed to lie dormant *in situ* until the fine balance between the production of angiogenesis-stimulatory (*e.g.*, VEGF, FGF, PDGF) and -inhibitory (*e.g.*, thrombospondins) factors has been disrupted, causing an angiogenic switch. Tumor cell lines secrete VEGF *in vitro* and VEGF mRNA is increased in most human tumors, while mRNA for VEGF receptors (VEGFRs) is upregulated in endothelial cells associated with tumors. Moreover, elevated serum levels of VEGF and basic FGF (bFGF or FGF-2) have been detected in

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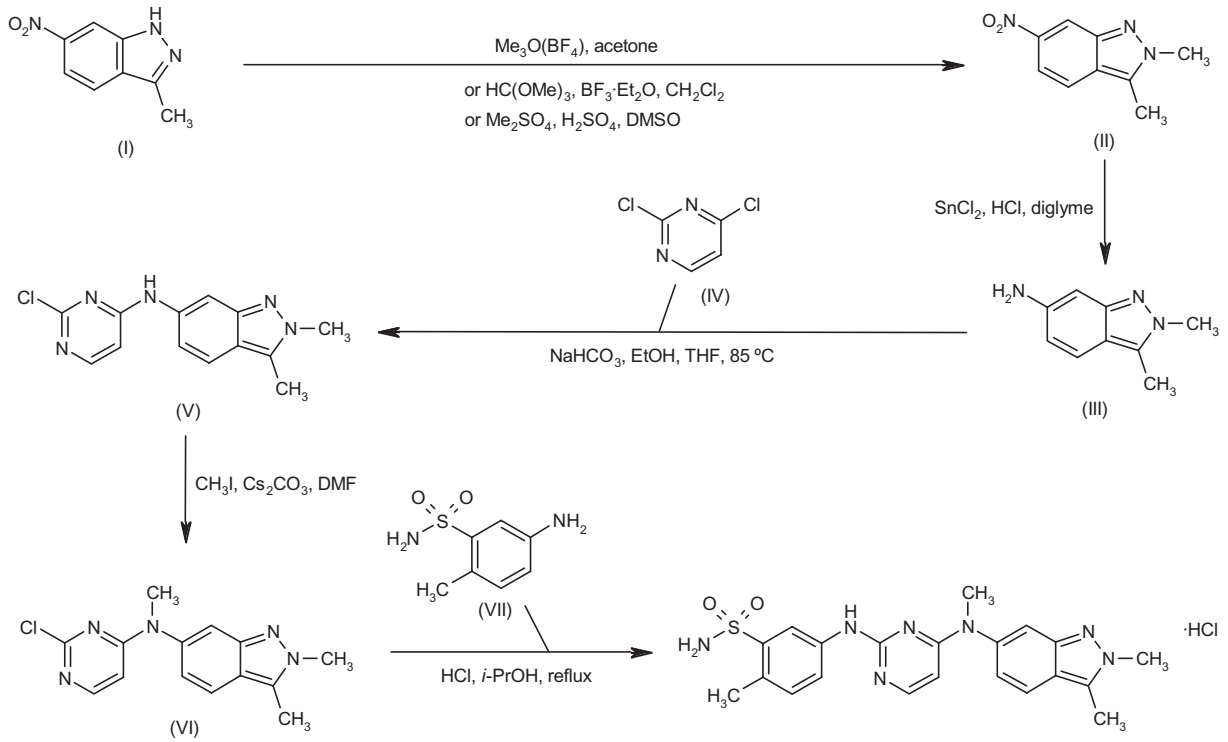
Scheme 1: Synthesis of Pazopanib Hydrochloride



individuals with several tumor types. Thus, interference with VEGF activity represents an attractive target for inhibition of angiogenesis in cancer (6-10).

Targeting angiogenesis and VEGF in particular was validated with the 2004 approval of the first angiogenic agent, bevacizumab (Avastin™; Genentech, Roche), an anti-VEGF monoclonal antibody approved for the treatment of metastatic colon cancer (11). Other antiangiogenic strategies for the treatment of malignancies have emerged and are under active investigation. These include blocking matrix degradation (*i.e.*, matrix metalloproteinase [MMP] inhibitors), blocking VEGF, FGF and PDGF receptor signaling, inhibiting normal endothelial cells and antagonizing integrin. Because VEGF is a key mediator of neovascularization, research has intensely focused on interfering with the VEGF/VEGFR system in order to modulate angiogenesis. The activity of VEGFs is mediated through binding to specific cell-surface receptors: VEGFR-1 (Flt-1), VEGFR-2 (KDR or Flt-2) and VEGFR-3 (Flt-4). VEGFR-1 and VEGFR-2 are expressed predominantly on vascular endothelial cells, while VEGFR-3 is expressed on lymphatic endothelium and is not as important for tumorigenesis. VEGF binding to its receptors induces homo- or heterodimerization of the ligand, which subsequently triggers intracellular autophosphorylation in their kinase domain. A cascade of signal transmission eventually leads to the growth message in the cell nucleus (Fig. 1) (12-14).

Small-molecule tyrosine kinase inhibitors which target VEGFRs are a particularly promising antiangiogenic approach and there are more than 30 VEGFR inhibitors under active development for the treatment of cancer. The indazolylpyrimidine pazopanib hydrochloride (786034, GW-786034) is one such pan-VEGFR inhibitor that has shown particular promise as an antineoplastic agent and was chosen for further development as an antiangiogenic antitumor agent (15, 16).

Preclinical Pharmacology

In vitro study results demonstrated that pazopanib inhibited VEGFR-1, VEGFR-2 and VEGFR-3 with IC_{50} values of 10, 30 and 47 nM, respectively. The agent inhibited VEGF-induced proliferation of human umbilical vein endothelial cells (HUVEC) more potently than bFGF-stimulated proliferation (IC_{50} = 21 nM *vs.* 721 nM) and concentration-dependently inhibited VEGF-induced VEGFR-2 phosphorylation (IC_{50} = 7 nM) in these cells. Pazopanib showed over 1,400- and 48-fold selectivity for VEGF-induced HUVEC proliferation compared to several tumor cell lines and fibroblasts, respectively. It also potently inhibited angiogenesis in Matrigel plug and corneal micropocket assays (15, 16).

Pazopanib displayed potent antineoplastic activity against multiple myeloma (MM) cells both *in vitro* and *in vivo*. It inhibited the migration, growth and survival of MM

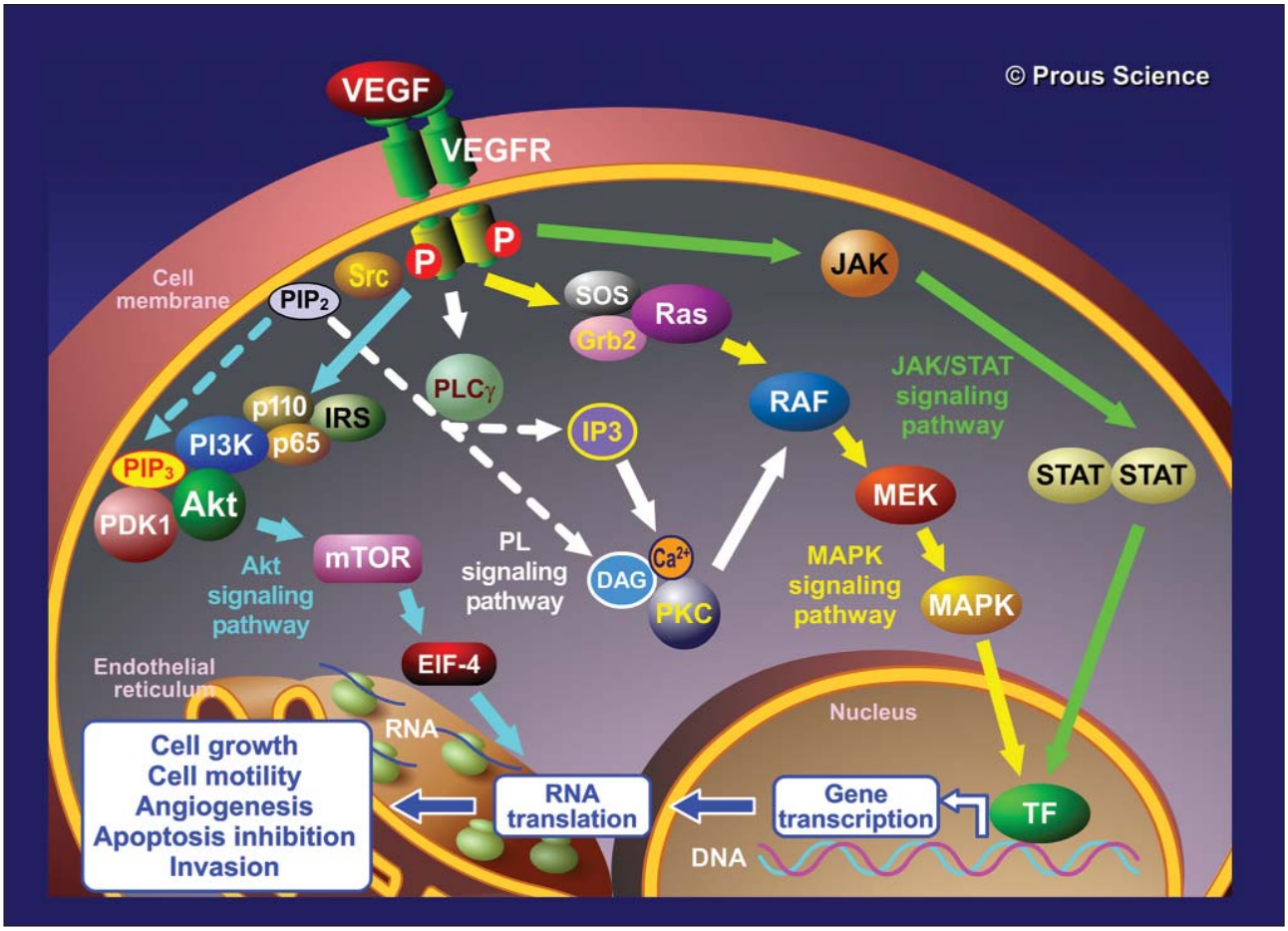


Fig. 1. VEGFR signaling pathways.

cells *in vitro*. Treatment of cells suppressed VEGF-induced VEGFR phosphorylation, blocked the activation of downstream Src kinase and triggered caspase-8 (but not caspase-9) and PARP (poly[ADP-ribose]polymerase, NAD^+ ADP-ribosyltransferase) cleavage. In addition, pazopanib-treated cells exhibited downregulation of several transcriptional signaling pathways, particularly c-Myc, and downregulation of the proapoptotic molecules survivin, c-IAP1, c-IAP2 and Mcl-1. VEGF-induced upregulation of adhesion proteins (ICAM-1 and VCAM-1) was inhibited by the agent in both MM and endothelial cells, resulting in attenuation of HUVEC-MM cell adhesion and tumor cell proliferation. Additional results indicated that pazopanib sensitized tumor cells bound to endothelial cells to DNA-damaging agents such as melphalan. Moreover, pazopanib exerted antiangiogenic and antitumor effects *in vivo* in a mouse multiple myeloma xenograft model (17, 18).

Pharmacokinetics and Metabolism

Pazopanib exhibited good oral absorption in mice and dogs, with an oral bioavailability of 49% in the latter species. Further experiments in dogs revealed a low clearance of 1.4 ml/min/kg and a low steady-state volume of distribution of 0.3 l/kg (15).

A study in mice examining the pharmacokinetics of pazopanib administered as either an oral bolus or a continuous infusion (via osmotic minipumps) demonstrated that the antitumor and antiangiogenic activity of the agent requires a threshold steady-state plasma concentration that is similar to the concentration required for inhibition of VEGF-induced VEGFR-2 phosphorylation in mouse lung *in vivo* (19, 20).

A dose-escalating phase I study in 28 patients with solid tumors showed that administration of daily oral doses of pazopanib (50, 100, 200 and 400 mg) resulted in plasma concentrations comparable to effective antitumor and antiangiogenic doses required in preclinical models (21).

The safety, tolerability and pharmacokinetics of escalating doses of pazopanib (50 mg 3 times weekly to 2000 mg once daily) were examined in a phase I trial conducted in 43 patients with solid tumors. The mean half-life of the agent was approximately 35 h; an accumulation of 1.5-3-fold and a C_{max}/C_{min} ratio of about 2 were observed at steady state. Doses of 800 mg once daily or more resulted in maximum exposure to the agent (*i.e.*, trough concentrations > 18 μg/ml) (22).

Safety

In the above studies, treatment was generally well tolerated. In the first study, adverse events related to treatment included hypertension (grade 1, n=1; grade 3, n=1), gastrointestinal hemorrhage (grade 1, n=1; grade 4, n=1), emesis (grade 1, n=2), diarrhea (grade 1, n=2), myoclonus (grade 3, n=1), ecchymoses (grade 1, n=1) and grade 1 increased alkaline phosphatase (n=1), serum SGOT (n=1), serum SGPT (n=1) and bilirubin (n=1) (21). In the second study, the maximum tolerated dose (MTD) was not reached. One of 3 patients treated with 2000 mg once daily developed dose-limiting toxicity (DLT) of grade 3 fatigue. The most common adverse events were nausea (grade 1/2, n=15; grade 3, n=1), diarrhea (grade 1/2, n=15), fatigue (grade 1/2, n=12; grade 3, n=1), hypertension (grade 1/2, n=6; grade 3, n=6), anorexia (grade 1/2, n=12) and vomiting (grade 1/2, n=9; grade 3, n=1); of the 14 patients receiving doses of 800 mg or more, 6 developed hair depigmentation. The 800-mg dose was associated with the greatest alterations in blood pressure, which correlated with trough concentrations of > 20 μg/ml; hypertension responded to treatment and could be reversed upon drug discontinuation. Hypertension and hair depigmentation are effects associated with modulation of VEGFR and c-Kit (22).

A case of hair depigmentation associated with pazopanib treatment was reported in a 69-year-old women with metastatic renal cell cancer participating in a phase I study. It was suggested that pazopanib also targets other receptor tyrosine kinases in addition to VEGFR, such as the class III tyrosine kinase c-Kit (23).

Clinical Studies

Preliminary antitumor activity was detected in the second study described above. Three patients with renal cell cancer and 1 patient with Hurthel cell tumor showed a minimal response of tumor shrinkage at doses of 800 mg or more. Stable disease lasting for at least 6 months was obtained in 1 patient with melanoma, 3 patients with sarcoma, 1 patient with lung cancer and 1 patient with neuroendocrine tumors (22).

An open-label, dose-escalating phase I study in 33 patients with solid tumors examined the safety and pharmacokinetics of concurrent once-daily administration of lapatinib and pazopanib (lapatinib/pazopanib: 750/250 or 500 mg; 1000/250, 400 or 500 mg; 1250/250 or 400 mg; 1500/200 mg). Preliminary analysis revealed mean plasma pazopanib concentrations on day 22 at 24 h postdosing of approximately 19 and 23 μg/ml, respectively, at doses of 250 and 500 mg. These levels were comparable to those achieved following dosing with 800 mg pazopanib alone (23.1 μg/ml), as reported in other studies. Plasma levels of lapatinib following administration of 750-1500 mg were similar to levels obtained with monotherapy. Analysis is ongoing, although it was suggested that lapatinib may influence the pharmacokinetics of pazopanib. Co-administration of the two agents was generally well tolerated. The most common adverse events were generally mild to moderate diarrhea (n=15), fatigue (n=12; grade 4, n=1), nausea (n=11), anorexia (n=11), vomiting (n=9), hair depigmentation (n=7), rash (n=7) and abdominal cramps (n=6). A total of 10 patients with renal cell cancer, colorectal cancer, gastrointestinal stromal tumor, mesothelioma, adenocarcinoma or aggressive fibromatosis had prolonged disease stabilization for more than 16 weeks. Two patients with renal cell cancer and 1 patient with giant cell tumor of the bone had stable disease (24, 25).

Several phase I and II studies are evaluating pazopanib in cancer patients, including a phase I study in patients with advanced solid tumors to determine the MTD of oral pazopanib administered twice daily (26), and a multicenter, randomized phase II study with a discontinuation design examining the safety and efficacy of pazopanib (800 mg once daily for 12 weeks) in up to 230 patients with metastatic or locally recurrent renal cell carcinoma of clear cell histology. The study includes a screening period, lead-in phase, randomized phase, follow-up continuation phase and post-treatment follow-up (27, 28). Other phase II trials are recruiting patients to investigate the safety, efficacy and pharmacokinetics of oral pazopanib in patients with ovarian cancer, relapsed or refractory multiple myeloma and relapsed or refractory soft tissue sarcoma (29-31). In addition, a randomized, double-blind, placebo-controlled, parallel-assignment phase III trial is recruiting patients with metastatic renal cell carcinoma who progressed following cytokine-based first-line treatment, to examine the efficacy and safety of pazopanib (32).

Source

GlaxoSmithKline (US).

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