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TIVOZANIB

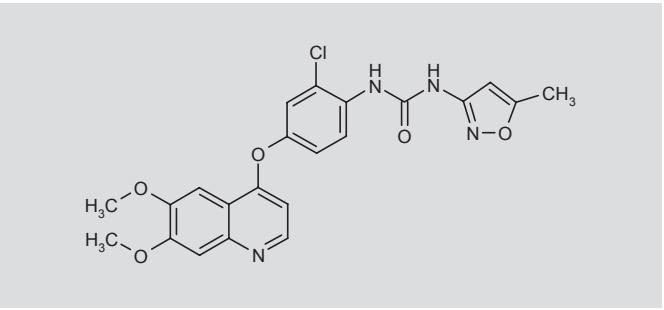
USAN

VEGFR Tyrosine Kinase Inhibitor
Angiogenesis Inhibitor
Oncolytic

AV-951
KRN-951

N-[2-Chloro-4-(6,7-dimethoxyquinolin-4-yloxy)phenyl]-*N*'-(5-methylisoxazol-3-yl)urea

InChI: 1S/C22H19ClN4O5/c1-12-8-21(27-32-12)26-22(28)25-16-5-4-13(9-15(16)23)31-18-6-7-24-17-11-20(30-3)19(29-2)10-14(17)18/h4-11H,1-3H3,(H2,25,26,27,28)



$C_{22}H_{19}ClN_4O_5$
Mol wt: 454.863
CAS: 475108-18-0
EN: 330073

ABSTRACT

Tivozanib is a novel oral quinoline urea derivative with potent and selective activity against vascular endothelial growth factor (VEGFR) tyrosine kinase. Preclinical data indicate that tivozanib blocks the proliferation and migration of endothelial cells in vitro, and suppresses angiogenesis and growth of human tumor xenografts in vivo. Tivozanib has been shown to be safe and orally bioavailable when given to cancer patients. Early clinical trials demonstrated inhibition of angiogenesis and tumor progression in several types of advanced solid tumors. The compound is under early clinical investigation for the treatment of renal cell carcinoma and non-small cell lung carcinoma, as well as in combination with other chemotherapies in breast, colorectal, and other gastrointestinal cancer patients.

SYNTHESIS

Treatment of 3',4'-dimethoxyacetophenone (I) with cold concentrated nitric acid in the presence of a trace amount of $NaNO_2$ gives the 2'-nitro-acetophenone derivative (II), which is then reduced to the corresponding *ortho*-amino-acetophenone (III) by catalytic hydrogenation over Pd/C in AcOH/MeOH. Condensation of 2'-amino-acetophenone (III) with ethyl formate using sodium methoxide in THF leads to 6,7-dimethoxyquinolin-4-one (IV), which is converted to the chloroquinoline (V) by treatment with $POCl_3$ in refluxing toluene (1). Subsequent coupling of 4-chloro-6,7-dimethoxyquinoline (V) with 4-amino-3-chlorophenol (VI) by means of either sodium hydride in DMSO (2, 3) or potassium *tert*-butoxide in dimethylacetamide (1) gives the phenoxyquinoline adduct (VII). Finally, tivozanib is obtained by reaction of 3-amino-5-methylisoxazole (VIII) with phenyl chloroformate in pyridine/dimethylacetamide followed by coupling of the acylating intermediate with the aniline derivative (VII) (1), or alternatively, by activation of aniline (VII) with triphosgene and triethylamine followed by addition of 3-amino-5-methylisoxazole (VIII) (2, 3). Scheme 1.

BACKGROUND

The sustained growth and dissemination of solid tumors are dependent on the process of new vessel formation, or angiogenesis (4, 5). Angiogenesis is a key step during embryonic development but is also involved in several pathological conditions, such as cancer (4). To grow, tumors trigger the development of their own blood supply by disrupting the balance of factors that promote and inhibit angiogenesis. Vascular endothelial growth factor (VEGF) is a key mediator of normal and tumor-induced angiogenesis and activates VEGF receptors (VEGFR) to promote the proliferation and survival of endothelial cells and increase vascular permeability. The VEGF family currently includes five members and several splicing isoforms for its prototype VEGF, with different affinities for the three VEGFR: VEGFR-1, -2 and -3. Both VEGFR-1 and -2 are expressed in vascular endothelial cells and hematopoietic stem cells. VEGFR-3 regulates lymphadenogenesis and its expression is restricted to lymphatic endothelial cells. The phosphorylation and activation of VEGFRs

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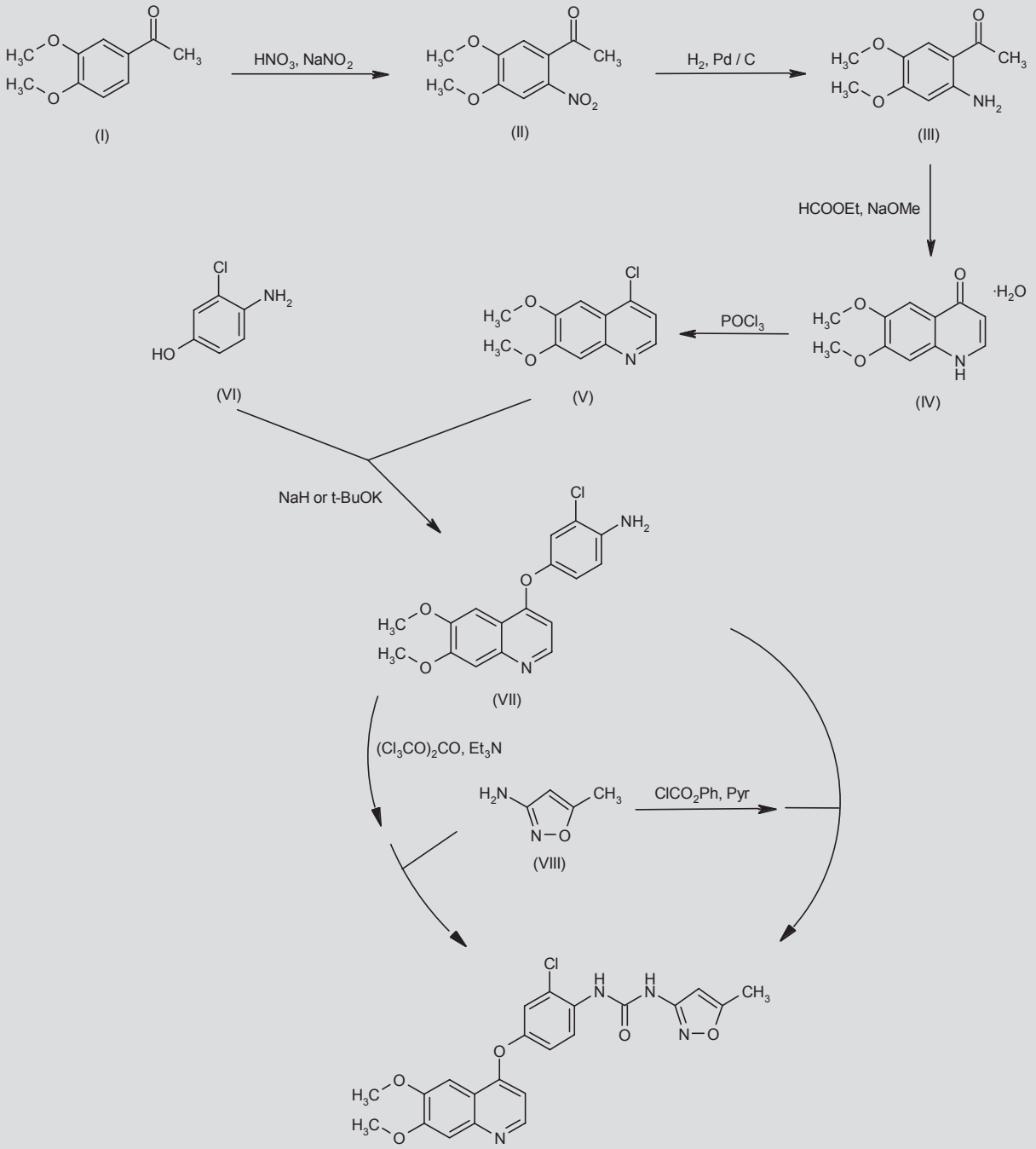
Scheme 1. Synthesis of Tivozanib



induces the migration and proliferation of endothelial cells, resulting in the formation of new tumor vasculature (4, 5).

Several experiments performed in the early 1990's demonstrated that many malignant tumors secrete VEGF and that blockade of VEGF alone can substantially suppress the angiogenesis and growth of many types of solid tumors (4). Therefore, VEGFRs became an attractive therapeutic target for the treatment of cancer and the anti-VEGFR drugs available on the market (bevacizumab, sorafenib, sunitinib) have shown promising results (5-8).

Tivozanib (AV-951, KRN-951) is a novel oral quinoline urea derivative that is a highly potent and selective VEGFR tyrosine kinase inhibitor, with specificity for VEGFR-1, -2 and -3. The compound has demon-

strated antiangiogenic and antitumor activity in vitro and in vivo and is under early clinical trials for the treatment of several solid cancers.

PRECLINICAL PHARMACOLOGY

Tivozanib has been shown to potently inhibit VEGF-stimulated phosphorylation of VEGFR-1, -2 and -3 tyrosine kinase in cellular assays, with IC_{50} values of 0.21, 0.16 and 0.24 nM, respectively. It also inhibited the phosphorylation of c-kit and PDGF-R-β with respective IC_{50} values of 1.63 and 1.72 nM, but showed a weak inhibitory effect on the phosphorylation of FGFR-1, FLT3 and c-Met (HGFR). Tivozanib also showed partial inhibition of EGFR and IGF-I receptor phosphorylation (9).

Moreover, tivozanib blocked VEGF-driven but not VEGF-independent activation of mitogen-activated protein kinases (MAPK) and the proliferation of endothelial cells in vitro. In a co-culture with fibroblasts, tivozanib suppressed capillary tube formation of endothelial cells in a concentration-dependent manner and suppressed VEGF-mediated migration of human umbilical vein endothelial cells (9). The compound did not show direct cytotoxic activity in vitro on various cancer cells at concentrations below 1 μM (10, 11), suggesting that its main activity is suppression of angiogenesis and not a direct effect on cancer cells.

Tivozanib has shown in vivo antiangiogenic and antitumor activity. Once-daily oral administration of tivozanib in athymic mice and rats resulted in significant inhibition of the growth of various types of human tumor xenografts, including breast, colon, liver, lung, ovarian, pancreas, prostate, brain and renal xenografts (9-11). Dynamic contrast-enhanced magnetic resonance imaging (MRI) showed that tivozanib treatment in nude rats bearing tumor xenografts reduced microvessel density and vascular permeability in the tumor tissues in a dose-dependent manner. Tivozanib also attenuated VEGFR-2 phosphorylation in the tumor tissue of the treated animals (9). These effects were more pronounced in the tumor rim than in the tumor center (9, 12).

Tivozanib was also tested in a rat model of disseminated intraperitoneal carcinomatosis induced by peritoneal inoculation of the rat colon cancer cell line RCN-9. Once-daily oral administration of tivozanib (1 and 3 mg/kg) given from the day of inoculation significantly reduced the number of tumor nodules and tumor angiogenesis of the mesenteries, and inhibited the accumulation of malignant ascites. Moreover, tivozanib administration initiated at 14 days after inoculation, when well-established tumor nodules and malignant ascites were observed, produced similar significant antitumor activity, including loss of malignant ascites. Continuous daily administration of tivozanib significantly prolonged the survival of rats bearing both early- and advanced-stage tumors (13).

The effect of tivozanib combined with the mTOR inhibitor rapamycin resulted in complete tumor growth inhibition in a genetically engineered HER2 (erbB-2)-driven breast adenocarcinoma model. Treatment of these breast tumors with rapamycin and tivozanib resulted in partial regression and histological evidence of both mechanisms. At day 42 of treatment, the emergence of regions with proliferating cells was observed in tumors treated with either rapamycin or tivozanib as single agents, whereas no evidence of emerging drug-resistant tumor regions was seen with the combination of drugs (14).

Experiments using a panel of genetically engineered murine breast tumors designed to characterize variations in response to tivozanib showed that resistance to this drug was observed with two different phenotypes: one class exhibited reduction in vascularity while continuing to proliferate, whereas another class appeared to maintain angiogenic features despite treatment with tivozanib (15).

VEGF and VEGFR-1 are involved in pathological angiogenesis in rheumatoid arthritis and inhibition of signaling though VEGFR-1 showed a decrease in pathological symptoms and immune reactions. In a murine arthritis model treatment with tivozanib reduced disease progression when compared to untreated animals (16).

PHARMACOKINETICS AND METABOLISM

The pharmacokinetic profile of the drug was analyzed in athymic rats after a single oral dose (0.04, 0.2, 1 or 5 mg/kg). In this dose range both AUC and C_{max} increased proportionally to the dose, whereas clearance, apparent volume of distribution and elimination half-life were similar, suggesting that tivozanib has an approximately linear pharmacokinetic profile in athymic rats at this dose range. Pharmacokinetic simulation analysis showed that tivozanib achieved steady state soon after repeated oral administration (9).

Pharmacokinetic analysis in phase I studies conducted in cancer patients revealed dose-dependent drug exposure and peak plasma concentrations after oral administration of 1-2 mg/day tivozanib (17-19).

SAFETY

A phase I study in 20 patients showed that tivozanib could be administered safely at oral doses up to 1.5 mg when given once daily for 28 days followed by 14 days off treatment (17-19). Higher doses induced grade 3 and 4 adverse events such as asymptomatic proteinuria, ataxia and intracranial hemorrhage. At 1.5 mg hypertension occurred in 15 of 19 patients but could be medically controlled, and other frequently occurring mild side effects were hoarseness, anorexia, nausea, diarrhea and fatigue (17, 18).

Interim results of a phase II study in renal cell carcinoma (RCC) patients treated with tivozanib 1.5 mg/day for 3 weeks on/1 week off showed that the most common adverse events were hypertension (42%) and dysphonia (16%). Minimal (all grades) diarrhea, fatigue, stomatitis and hand-foot syndrome were observed. Laboratory abnormalities were notable for minimal neutropenia and elevations of AST and ALT (20, 21).

CLINICAL STUDIES

Results from phase I studies in patients with advanced solid tumors indicated that tivozanib was able to decrease tumor perfusion and induce partial tumor responses, especially in RCC (18, 19).

Tivozanib is currently in phase II clinical trials as monotherapy in patients with RCC (22) and non-small cell lung carcinoma (NSCLC) (23). Interim results of the study in RCC patients show that tivozanib is active against RCC, with an overall response rate of 27.2% and stable disease seen in 60.5% of patients (20, 21).

Tivozanib is also in phase I/II studies in breast cancer in combination with paclitaxel (24), in colorectal and other gastrointestinal tumors

in combination with FOLFOX6 (25), and in RCC in combination with the rapamycin analogue temsirolimus (26). The drug is also undergoing clinical early studies in Japan (27).

SOURCES

AVEO Pharmaceuticals, Inc. (US); licensed from Kyowa Hakko Kirin for all markets outside Asia.

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