Drugs of the Future 2008, 33(8): 649-654

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.08.1237313

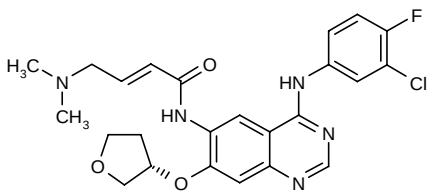
BIBW-2992

Dual EGFR/HER2 Inhibitor
Oncolytic

Tovok™

N-[4-(3-Chloro-4-fluorophenylamino)-7-[tetrahydrofuran-3(*S*)-yloxy]quinazolin-6-yl]-4-(dimethylamino)-2-butenamide

InChI=1/C24H25ClFN5O3/c1-31(2)8-3-4-23(32)30-21-11-17-20(12-22(21)34-16-7-9-33-13-16)27-14-28-24(17)29-15-5-6-19(26)18(25)10-15/h3-6,10-12,14,16H,7-9,13H2,1-2H3,(H,30,32)(H,27,28,29)/b4-3+/t16-/m0/s1



$C_{24}H_{25}ClFN_5O_3$
Mol wt: 485.9383

CAS: 439081-18-2

EN: 323397

Abstract

BIBW-2992 is a potent, irreversible, orally active inhibitor of the epidermal growth factor receptor EGFR and HER2 tyrosine kinases. In preclinical studies, BIBW-2992 showed selectivity over other receptor classes and produced potent and long-lasting growth suppression and in some cases tumor regression in human tumor xenograft models, including squamous cell carcinoma A-431, breast MDA-MB-453, gastric NCI-N87 and ovarian SK-OV-3 carcinomas. It has shown *in vitro* and *in vivo* efficacy in preclinical models of non-small cell lung cancer (NSCLC) with activating mutations that confer resistance to gefitinib and erlotinib. BIBW-2992 is currently in phase II/III clinical trials for the treatment of solid tumors, including breast, prostate and head and neck carcinomas, although its most promising effects have been seen in NSCLC patients. In 2008, fast track designation was assigned by the FDA to BIBW-2992 for the treatment of late-stage NSCLC.

Synthesis

Acylation of 6-amino-4-(3-chloro-4-fluorophenylamino)-7-[tetrahydrofuran-3(*S*)-yloxy]quinazoline (I) with the acid chloride generated from bromocrotonic acid (II) and oxalyl chloride leads to the bromocrotonamide (III), which is finally submitted to bromide displacement with dimethylamine (1). Scheme1.

In an alternative method, aminoquinazoline (I) is acylated with diethylphosphonoacetic acid (IV) by means of carbonyldiimidazole in THF to give the phosphonoacetamide (V), which is finally condensed with (dimethylamino)acetaldehyde diethyl acetal (VI) under basic conditions (2). Scheme 1.

The aminoquinazoline precursor (I) is prepared by condensation of 4-(3-chloro-4-fluorophenylamino)-7-fluoro-6-nitroquinazoline (VII) with 3(*R*)-hydroxytetrahydrofuran (VIII) by means of potassium *tert*-butoxide in DMF to yield the tetrahydrofuranyloxyquinazoline (IX), which is then reduced at the nitro group by catalytic hydrogenation over PtO_2 (1). Scheme 2.

Background

The epidermal growth factor (EGF) family of receptors is formed by EGFR/ErbB-1, HER2/neu, HER3 and HER4. These four members are tyrosine kinase receptors with an extracellular ligand-binding domain and an intracellular kinase domain. Upon ligand binding, the receptors homodimerize or heterodimerize with each other, resulting in activation of the kinase domain and phosphorylation of specific tyrosine residues within the cytoplasmic part of the protein. Other cellular proteins anchor on these phosphorylated residues, leading to the activation of a variety of cellular signaling pathways that promote cell growth, proliferation, differentiation and migration. Interactions between EGFRs allow HER2, which has no identified ligand, and HER3, which has no kinase activity, to participate in effective signaling. HER2 is the preferred partner for all other EGFRs (3).

Several alterations have been described for EGF proteins in human cancers, such as gene amplification,

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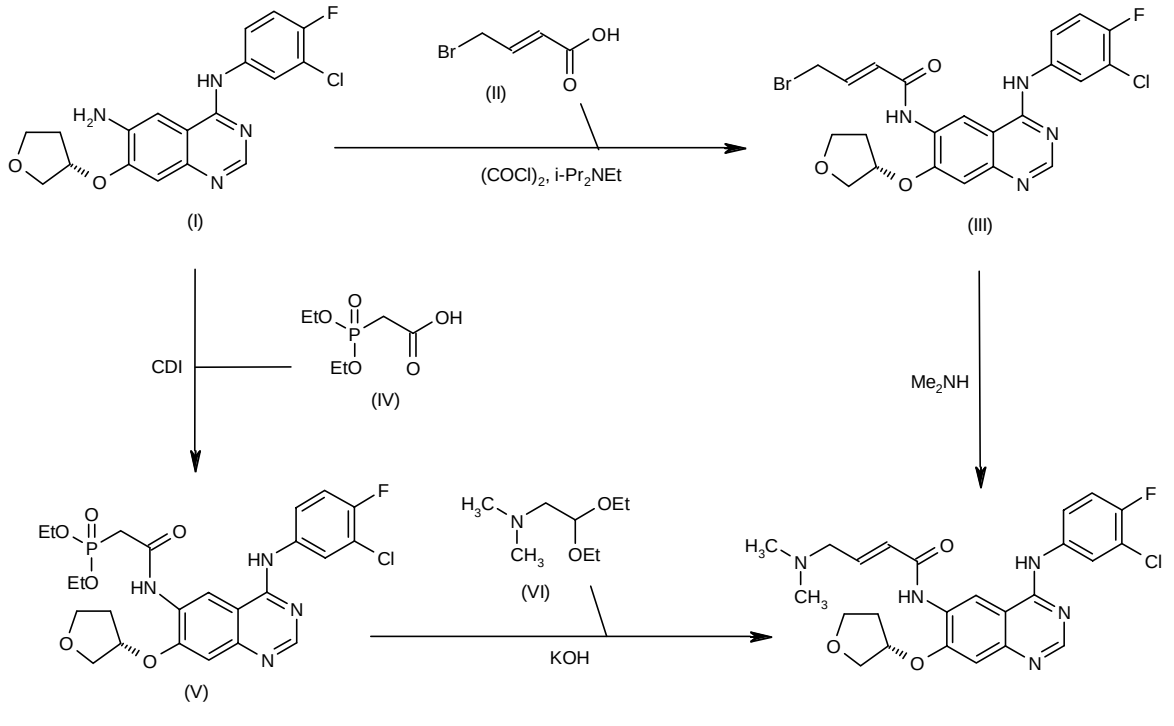
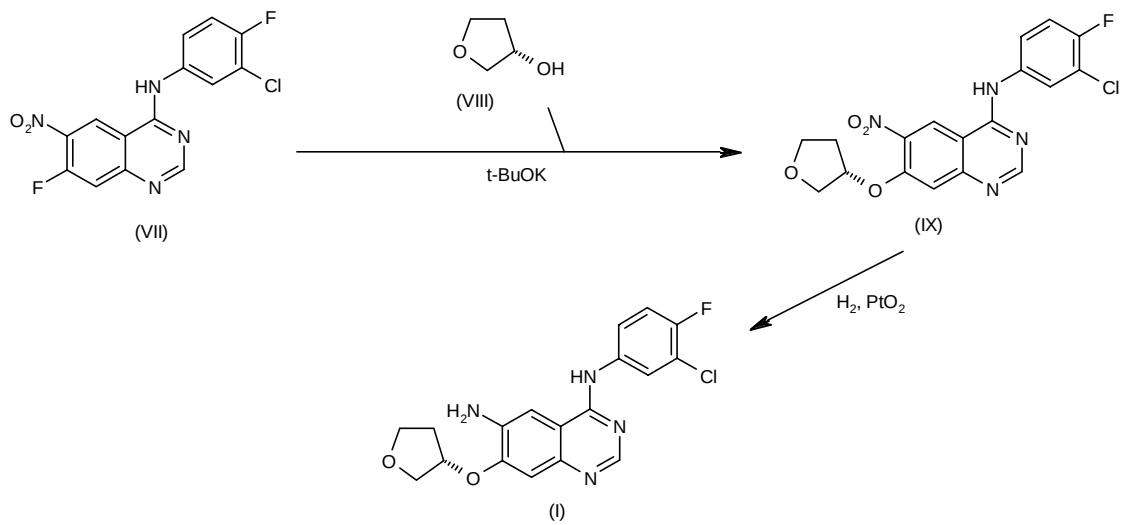
Scheme 1: Synthesis of BIBW-2992



Scheme 2: Synthesis of Intermediate (I)



receptor overexpression, activating mutations, overexpression of receptor ligands and loss of negative regulators. Patients whose tumors have alterations in EGFRs show more aggressive disease and poorer outcome (4). Amplification of the *HER2/NEU* gene is found in 25-30% of breast cancers and is associated with poor prognosis and resistance to treatment (5). Activating mutations in the kinase domain of EGFR in non-small cell lung cancer (NSCLC) and gene amplification and overexpression of wild-type EGFR in head and neck cancers demonstrate the important role of EGFR in the development of human cancers (4).

A number of agents targeting individual EGFRs are currently being used in the therapy of human cancer. There are two main groups of agents available: humanized monoclonal antibodies directed against the extracellular domain of the receptors (*e.g.,* trastuzumab [Herceptin™], which targets HER2) and small-molecule tyrosine kinase inhibitors (*e.g.,* gefitinib [Iressa™]). The clinical efficacy of these compounds is not as high as predicted in preclinical studies, with the exception of rare tumors driven by single molecular abnormalities (3). This is not surprising if we consider the complex molecular biology of cancer pathogenesis, where signaling pathways are adaptable and redundant (6).

Approximately 10-15% of patients with NSCLC have tumors that depend on activation of EGFR, as evidenced by mutations in the *EGFR* gene. In these patients, there is often a dramatic response to treatment with the first-generation EGFR tyrosine kinase inhibitors gefitinib and erlotinib. A small number of patients with EGFR mutations have primary resistance to erlotinib and gefitinib, and most patients who initially respond to treatment develop resistance to these first-generation EGFR inhibitors (7).

Cancers that co-overexpress EGFR and HER2 have a worse outcome than do those overexpressing either receptor alone (8). Targeting EGFR and HER2 is a proven strategy to treat cancer, and trials of approved anti-EGFR and anti-HER2 agents in combination are under way. Moreover, there are several dual-targeting agents in development, and as for single agents, monoclonal antibodies and small-molecule kinase inhibitors are available. Novel dual-targeting agents include lapatinib, canertinib (CI-1033), neratinib (HKI-272) and pertuzumab. Pertuzumab and lapatinib are in an advanced stage of development. Lapatinib (Tykerb®, Tyverb®), is a potent, reversible and selective dual inhibitor of EGFR and HER2 kinases. Pertuzumab (2C4, Omnitarg™) is a recombinant humanized monoclonal antibody that binds to the HER2 receptor, blocking its interaction with EGFR. Irreversible binding to the receptors is an attractive feature of novel dual-targeting agents, since irreversible inhibition should provide benefits in terms of target suppression and pharmacodynamics, and allow maximal antitumor activity (3).

BIBW-2992 is one of the most promising dual EGFR/HER2 inhibitors in development. This potent, highly selective, irreversible and orally active dual inhibitor of EGFR and HER2 tyrosine kinases has demonstrated antitumor activity both *in vitro* and *in vivo*. It is currently in phase II/III clinical trials for the treatment of solid tumors, with very good results in NSCLC bearing activating mutations in EGFR.

Preclinical Pharmacology

In receptor binding studies, BIBW-2992 revealed high inhibitory potency against EGFR and HER2 kinases, with IC_{50} values of 0.5 and 14 nM, respectively. BIBW-2992 was highly selective for these kinases and no inhibition of other receptor classes or signaling pathways was observed. The compound blocked EGF-stimulated EGFR phosphorylation in squamous cell carcinoma A-431 cells (IC_{50} = 13 nM). Similarly, at nanomolar concentrations, BIBW-2992 caused dephosphorylation of constitutively active HER2 in gastric cancer NCI-N87 and breast cancer BT-474 cells, and inhibited cell proliferation *in vitro* (IC_{50} = 4-12 nM) (9).

The presence of gain-of-function mutations within the tyrosine kinase domain of EGFR in a subgroup of NSCLC has been associated with increased sensitivity to treatment with the first-generation small-molecule EGFR inhibitors gefitinib and erlotinib, which are reversible inhibitors of EGFR. However, other mutations, such as T790M, are associated with acquired resistance to gefitinib and erlotinib. In an *in vitro* study, BIBW-2992 potently inhibited EGFR phosphorylation in and proliferation of human lung cancer NCI-H1666 cells that express wild-type EGFR, NCI-H3255 cells harboring the activating mutation L858R (IC_{50} = 0.7 nM) and NCI-H1975 cells with T790M mutations (IC_{50} = 99 nM) resistant to gefitinib and erlotinib (10, 11). BIBW-2992 potently inhibited EGFR phosphorylation in all three cell lines (11). Recently, a mutation causing acquired resistance to erlotinib and gefitinib has been described (T854A). Surrogate kinase assays using cells transiently expressing the T854A mutation showed that BIBW-2992 overcame such resistance (12).

Moreover, BIBW-2992 showed marked efficacy in an NCI-H1975 xenograft model, while lapatinib or erlotinib showed no effect. The efficacy of BIBW-2992 against double EGFR mutants was confirmed in a transgenic mouse lung cancer model (C7-04) based on the tetracycline-inducible expression of EGFR-L858R/T790M in pneumocytes (13).

Potent, long-lasting growth suppression or even tumor regressions were observed in human cancer xenograft models of A-431 squamous cell carcinoma, breast MDA-MB-453, gastric NCI-N87 and ovarian SK-OV-3 carcinomas (9). Preclinical effects of BIBW-2992 in head and neck squamous cell carcinomas (HNSCC) have been studied using Ba/F3 and FaDu cells. BIBW-2992 inhibited the proliferation of transfected Ba/F3 cells expressing the wild-type EGFR with an EC_{50} of 0.8 nM. The compound showed similar potency in Ba/F3 cells expressing the EGFRvIII mutant receptor (EC_{50} = 0.5 nM), which lacks the extracellular domain (14). BIBW-2992 showed clear antiproliferative effects in the FaDu HNSCC cell line *in vitro* and dose-dependent antitumor activity against FaDu tumor xenografts *in vivo* (14, 15). The combination of BIBW-2992 and radiation was associated with only marginal radiosensitizing effects *in vitro* and *in vivo* (15).

Combination of BIBW-2992 with cytotoxic agents such as docetaxel, doxorubicin or 5-fluorouracil induced supraadditive inhibitory effects in SK-OV-3 ovarian carcinoma cells. *In vivo* experiments in nude mice bearing s.c. SK-OV-3 xenografts using docetaxel and doxorubicin combined with BIBW-2992 confirmed the *in vitro* observations (16).

Pharmacokinetics and Metabolism

A pharmacokinetic (PK) study in healthy volunteers using a single oral dose of [^{14}C]-radiolabeled BIBW-2992 showed that the major route of elimination of BIBW-2992 was via the feces (85.4%), with an overall recovery of radioactivity of 89.5%. Maximum plasma concentrations were reached at approximately 6 h after dosing and the mean terminal half-life was 33.9 h. Radioactivity results suggested the presence of one or more metabolites of BIBW-2992 in plasma and whole blood with longer terminal half-lives than the parent drug (17). Similar results were reported in two phase I dose-escalating studies in patients with advanced solid tumors (18). High interpatient variability has been described for BIBW-2992 in all PK parameters, but was within the normal range expected for an orally administered drug (19, 20).

Safety

A phase I trial of BIBW-2992 given for 21 days followed by a 7-day break defined the recommended dose as 40 mg. Dose-limiting toxicities (DLTs) consisted of diarrhea and skin rash at 65 mg/day (21). A parallel phase I trial demonstrated that BIBW-2992 at 70 mg/day could be administered safely on a 2-weeks-on/2-weeks-off schedule. At 100 mg, DLTs were grade 3 skin rash and diarrhea, at 85 mg there were 2 cases of dose-limiting diarrhea, and at 70 mg 3 of 18 patients had dose-limiting diarrhea (19, 20). When administered on a 3-weeks-on/2-weeks-off schedule, the recommended dose was 55 mg, with dose-dependent toxicity mainly consisting of diarrhea, skin rash, pruritus, mucositis, nausea and vomiting (22). Several phase I trials of BIBW-2992 given once daily on a continuous schedule have defined the recommended dose as 40-50 mg (23-26). In one study, DLT of grade 3 diarrhea was observed at 60 mg daily (23). In another trial, 1 case of dose-limiting dyspnea at 30 mg, 2 cases of grade 3 acneiform rash at 40 and 50 mg, and 2 cases of grade 3 diarrhea at 50 mg were seen (24-26).

In summary, the most common toxicities observed in phase I clinical studies of BIBW-2992 were typical of receptor tyrosine kinase inhibitors, including skin rash, pruritus, mucositis and gastrointestinal disturbances.

Clinical Studies

Evidence of antitumor activity was seen in several of the early trials, including 2 partial responses in patients with lung adenocarcinoma (24) and 3 partial responses in patients with NSCLC (25, 26).

A phase II study of weekly alternating sequential administration of BIBW-2992 and the antiangiogenic agent BIBF-1120 in 46 patients with advanced metastatic colorectal cancer showed an acceptable safety profile but no signs of clinical efficacy (27).

BIBW-2992 is in phase II/III clinical studies in patients with several types of solid tumors, either alone or in combination with other drugs. Three phase II clinical trials are currently ongoing in breast cancer patients with HER2-positive or -negative tumors (28-30). BIBW-2992 is also being studied in phase II trials in head and neck cancer patients (31), and the combination of BIBW-2992 with cisplatin/paclitaxel or cisplatin/5-FU in patients with advanced solid tumors will be evaluated soon in a phase I study (32). A phase II study of BIBW-2992 in combination with an antiangiogenic agent is under way in hormone-refractory prostate cancer (33).

The most promising effects of BIBW-2992 have been seen in lung cancer studies. A phase II study in patients with adenocarcinoma of the lung bearing activating EGFR mutations is being conducted in the U.S. and Taiwan. Six of the first 10 patients who were treated for at least 28 consecutive days had tumor responses. Manageable cutaneous toxicity and diarrhea were the main adverse events (10). Two other phase II studies in NSCLC are currently being performed (34, 35).

In 2008, fast track designation was assigned to BIBW-2992 by the FDA for the treatment of late-stage NSCLC (36), which corroborates the potential of BIBW-2992 to address this unmet clinical need.

Source

Boehringer Ingelheim (DE).

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