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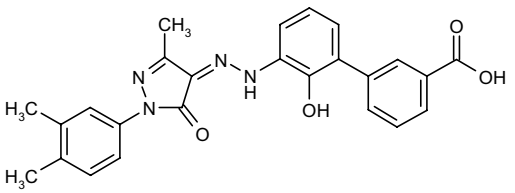
Eltrombopag

Prop INN; USAN

Antithrombocytopenic
Thrombopoietin Receptor Agonist

497115
SB-497115
SB-497115-GR (as olamine)
Promacta

3'-[2(*Z*)-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-ylidene]hydrazino]-2'-hydroxybiphenyl-3-carboxylic acid



$C_{25}H_{22}N_4O_4$
Mol wt: 442.4667

CAS: 496775-61-2

CAS: 376591-99-0 (as undefined isomer)

CAS: 443130-00-5 (as undefined isomer hydrate)

CAS: 496775-62-3 (as olamine)

EN: 313630

Abstract

Eltrombopag is an orally available small-molecule platelet growth factor being developed for the treatment of thrombocytopenia, a condition in which a reduced number of platelets in the bloodstream predisposes the patient to bleeding. Thrombocytopenia complicates a number of diseases, including end-stage liver disease, chronic hepatitis C virus (HCV) infection, certain myelosuppressive therapies (including intensive chemotherapies) and chronic immune thrombocytopenic purpura (ITP). Eltrombopag interacts with the thrombopoietin receptor of bone marrow megakaryocytes to stimulate the production of new platelets. In patients with ITP and patients with HCV-associated thrombocytopenia, eltrombopag significantly increased platelet counts compared to placebo.

Synthesis

The nitration of 2-bromophenol (I) with $NaNO_3$ and H_2SO_4 in water gives 2-bromo-6-nitrophenol (II), which is methylated by means of CH_3I and K_2CO_3 in refluxing acetone to yield 2-bromo-6-nitroanisole (III). The condensation of (III) with 3-carboxyphenylboronic acid (IV) by means of $Pd(PPh_3)_4$ and Na_2CO_3 in refluxing dioxane affords 2'-methoxy-3'-nitrobiphenyl-3-carboxylic acid (V), which is demethylated by means of aqueous 48% HBr in refluxing acetic acid to provide 2'-hydroxy-3'-nitrobiphenyl-3-carboxylic acid (VI). The reduction of the nitro group of (VI) by means of H_2 over Pd/C in ethanol/aqueous NaOH gives the 3'-amino-2'-hydroxybiphenyl-3-carboxylic acid (VII), which is treated with $NaNO_2$ and HCl in water and condensed with 1-(3,4-dimethylphenyl)-3-methyl-2,5-dihydro-1*H*-pyrazol-5-one (VIII) to provide the target pyrazolone derivative. The intermediate (VIII) is obtained by cyclization of 3,4-dimethylphenylhydrazine (IX) with ethyl acetoacetate (X) by means of NaOAc in refluxing acetic acid (1, 2). Scheme 1.

Background

Thrombopoietin (TPO) is a glycoprotein hormone produced primarily by the liver that activates megakaryocytes in the bone marrow, causing them to differentiate and fragment into platelets. Under normal circumstances, the bloodstream platelet counts range from 150,000 to 400,000/μl. However, under conditions that lead to a reduced platelet count, or thrombocytopenia, platelet counts may drop below 50,000/μl. Under these circumstances, patients are predisposed to bleeding, particularly at mucous membranes, and in some cases the bleeding may become severe enough to require treatment (3, 4).

Thrombocytopenia is commonly associated with cancer chemotherapy and a number of other conditions, including AIDS, myelodysplastic syndrome (MDS), idiopathic thrombocytopenic purpura (ITP) and chronic liver

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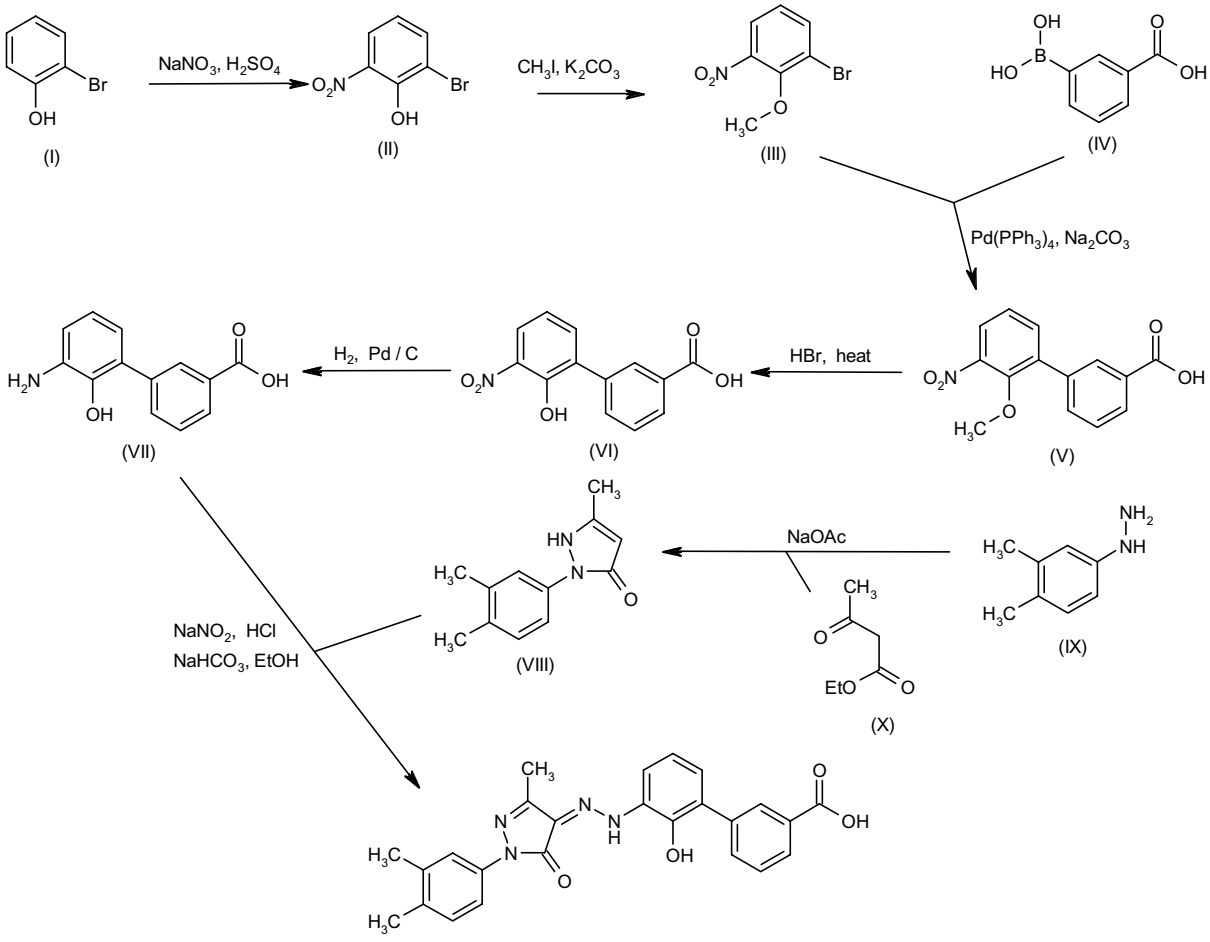
Scheme 1: Synthesis of Eltrombopag



disease. The only treatment currently available for severe thrombocytopenia is platelet transfusion, but the known limitations and risks of this therapy have spurred investigation into novel methods of stimulating platelet production. Several recombinant thrombopoietins (rhTPO, PEG-rHuMGDF) have been evaluated in the clinic but development was subsequently discontinued due to the finding of neutralizing antibodies with the pegylated form (4).

A small-molecule, nonpeptide TPO agonist would be expected to offer several advantages in terms of safety, cost and ease of administration. Eltrombopag (497115, SB-497115, Promacta) is one such orally available small molecule that has been shown to activate the human TPO receptor (perhaps by inducing receptor dimerization), resulting in activation of the JAK/STAT (Janus kinase/signal transducer and activator of transcription) signal transduction pathways to stimulate the proliferation and differentiation of megakaryocytes. Activity has been demonstrated *in vitro* in human bone marrow assays and in clinical trials (5).

Preclinical Pharmacology

Eltrombopag was identified from a compound library using a BAF3 hematopoietic cell line expressing the human TPO receptor. The compound potently stimulated the proliferation of BAF3/TPOR cells (EC_{50} = 30 nM), whereas cells without the human TPO receptor showed no response to eltrombopag. In cultures of human bone marrow cells, eltrombopag induced normal CD34+ progenitor cells to differentiate into CD41+ cells, with an EC_{50} equivalent to that of recombinant human TPO (100 nM) (5-8).

Eltrombopag is specific for human and chimpanzee TPO receptors, with no effect on those of other species, including cynomolgus monkeys. Domain-swapping and point mutation experiments identified His499 in the transmembrane domain of the human TPO receptor as one of the residues responsible for this specificity, suggesting that the compound interacts with His499 to activate the receptor (6-10).

Because of its high specificity, the only suitable animal model to test the efficacy of eltrombopag is the chimpanzee. Following 5 daily oral doses of 10 mg/kg eltrombopag (the highest dose tested), all 3 chimpanzees demonstrated a 1.3-2.4-fold increase in platelets. Eltrombopag was well tolerated at 0.1-10 mg/kg/day p.o. (10, 11).

Platelet stimulation could represent a liability for eltrombopag, and this has been tested in cell-based assays. Whereas recombinant human TPO activated the signal transduction components STAT1, 3 and 5, and Akt in platelets obtained from healthy volunteers, priming the platelets for activation (as measured by enhanced P-selectin expression) and enhancing ADP- and collagen-induced aggregation, eltrombopag activated only STAT1 and 5; there was no enhancement of P-selectin expression and eltrombopag did not enhance ADP- or collagen-induced platelet aggregation. Neither eltrombopag nor recombinant human TPO inhibited platelet aggregation induced by ADP, collagen or thrombin receptor-activating protein (TRAP), indicating that eltrombopag does not interfere with normal platelet function (12-14).

Pharmacokinetics

The oral bioavailability of eltrombopag was determined to be 26%, 83% and 89%, respectively, in rats, dogs and monkeys (5).

Safety

Daily oral doses of 3-40 mg/kg/day in rats, 3-30 mg/kg/day in dogs and 0.1-10 mg/kg/day in chimpanzees for 14 days were well tolerated (11).

In phase I safety studies, 72 healthy male volunteers were administered escalating daily oral doses of eltrombopag of 5-75 mg or placebo for up to 10 days. Eltrombopag was well tolerated, with no serious adverse events and no changes in laboratory or cardiovascular safety parameters. Adverse events were generally mild and there was no relationship between the incidence and severity of adverse events and dose (7, 15-19).

Clinical Studies

In the above phase I studies, eltrombopag dose-dependently increased platelet count at doses of 3 mg and above (7, 15-19).

Eltrombopag was tested in a phase II study in adults with chronic ITP. One hundred and four patients diagnosed at least 6 months prior to screening, having failed at least one prior therapy and with platelet counts of < 30,000/μl were randomized to daily oral doses of eltrombopag 30, 50 or 75 mg or placebo for 6 weeks. The proportion of responders achieving the primary endpoint of > 50,000 platelets/μl was as follows: 16% on placebo (mean platelet count = 16,000/μl), 28% on 30 mg eltrombopag (mean platelet count = 29,000/μl), 67% on 50 mg (mean platelet count = 132,000/μl) and 86% on 75 mg (mean platelet count = 202,000/μl); a subset of 52% of patients in the highest dose group achieved a platelet count of > 200,000/μl. The response was not significantly affected by splenectomy status, concomitant ITP therapy or baseline platelet count. The drug was safe, with no dose-dependent safety concerns identified. The most common adverse event was headache (21% of patients on 75 mg compared to 15% on placebo) (20, 21).

An open-label phase II extension study (EXTEND) (22) and a double-blind, randomized, parallel-group phase III study (23) have been initiated in ITP patients.

Initial results from a phase II study of eltrombopag in HCV-related thrombocytopenia indicated a positive response. HCV hepatitis patients with a platelet count of 70,000/μl or less were randomized to daily oral doses of eltrombopag 30, 50 or 75 mg or placebo for 4 weeks. No serious adverse events were observed in any group and there were no discontinuations due to adverse events. Platelet counts increased dose-dependently, with 9 of 10 patients in the 75-mg group achieving the primary endpoint of > 100,000/μl. In a second part of this study, those achieving the primary endpoint with respect to platelet count will receive an additional 8 weeks of daily eltrombopag or placebo with peginterferon/ribavirin therapy (24, 25).

Eltrombopag is also being tested in phase I and II studies in cancer patients receiving thrombocytopenic chemotherapy (26, 27).

Sources

GlaxoSmithKline (US); developed in collaboration with Ligand Pharmaceuticals, Inc. (US).

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