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Obatoclax Mesilate

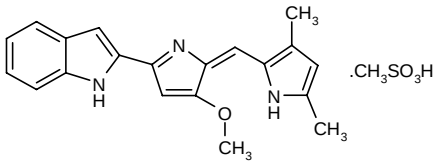
Rec INNM

Bcl-2 Inhibitor
Apoptosis Inducer
Oncolytic

Obatoclax Mesylate (USAN)
GX-015-070
GX15-070
GX15-070MS

2-[2-(3,5-Dimethyl-1*H*-pyrrol-2-ylmethylene)-3-methoxy-2*H*-pyrrol-5-yl]-1*H*-indole methanesulfonate

InChI=1/C20H19N3O.CH4O3S/c1-12-8-13(2)21-16(12)10-19-20(24-3)11-18(23-19)17-9-14-6-4-5-7-15(14)22-17;1-5(2,3)4/h4-11,21-22H,1-3H3;1H3,(H,2,3,4)/b19-10+;



$C_{21}H_{23}N_3O_4S$
Mol wt: 413.4911

CAS: 803712-79-0

CAS: 803712-67-6 (free base)

EN: 390240

Abstract

Obatoclax mesilate (GX15-070, GX15-070MS) is a small molecule specifically designed to inhibit all relevant members of the Bcl-2 protein family, which play critical roles in regulating apoptosis. Preclinical studies demonstrated that obatoclax alone or in combination with other drugs induces apoptosis in many human cancer cell lines. Obatoclax has entered clinical development for the treatment of a variety of cancers, and early results have confirmed potential antitumor activity. Obatoclax is currently in phase II clinical development for the treatment of Hodgkin's lymphoma, myelodysplastic/myeloproliferative disorders and follicular lymphoma, as well as earlier clinical development for several other cancers.

Synthesis

Vilsmeier reaction of 4-methoxy-3-pyrrolin-2-one (I) with phosphoryl bromide and *N,N*-dimethylformamide, followed by basic hydrolysis, provides 5-bromo-3-methoxypyrrole-2-carbaldehyde (II), which is then subjected to Suzuki coupling with 1-Boc-2-indoleboronic acid (III) to afford the indolyl pyrrolealdehyde (IV). In a related method, intermediate (IV) is prepared by reaction of pyrrolinone (I) with phosphoryl bromide and diethylformamide, followed by Suzuki coupling of the resulting bromopyrrole (V) with the indoleboronic acid (III) and basic enamine hydrolysis. The title compound is then obtained by simultaneous condensation and deprotection of pyrrole aldehyde (IV) with 2,4-dimethylpyrrole (VI) in methanolic hydrogen chloride (1). Scheme 1.

Background

Apoptosis, also known as programmed cell death, plays an important role in tissue homeostasis, and defective apoptosis is associated with a variety of diseases, including cancer. The apoptosis-blocking proteins thus provide potential targets for anticancer drug development. B-cell lymphoma-2 (Bcl-2) family proteins, key regulators of apoptosis, are the most prominent intrinsic pathway targets. Overexpression of several of the antiapoptotic Bcl-2 family proteins has been found in various hematological malignancies, including non-Hodgkin's lymphoma (NHL), diffuse large cell lymphoma (DLCL) and chronic lymphocytic leukemia (CLL) (2-6). Several strategies, including directly attacking the proteins with small-molecule drugs, have been proposed to overcome the cytoprotective effects of antiapoptotic proteins in cancer (2).

Small-molecule inhibitors directly targeting Bcl-2 or related antiapoptotic proteins have entered clinical trials for the treatment of cancer. In addition to gossypol, a natural product found in cottonseed, several other synthetic inhibitors, including apogossypol, HA-14-1, BH-3I-1 and BH-3I-2, ABT-737, the epigallocatechin (–)-EGCG, and obatoclax (GX15-070) (Fig. 1), have been studied (2, 7-15).

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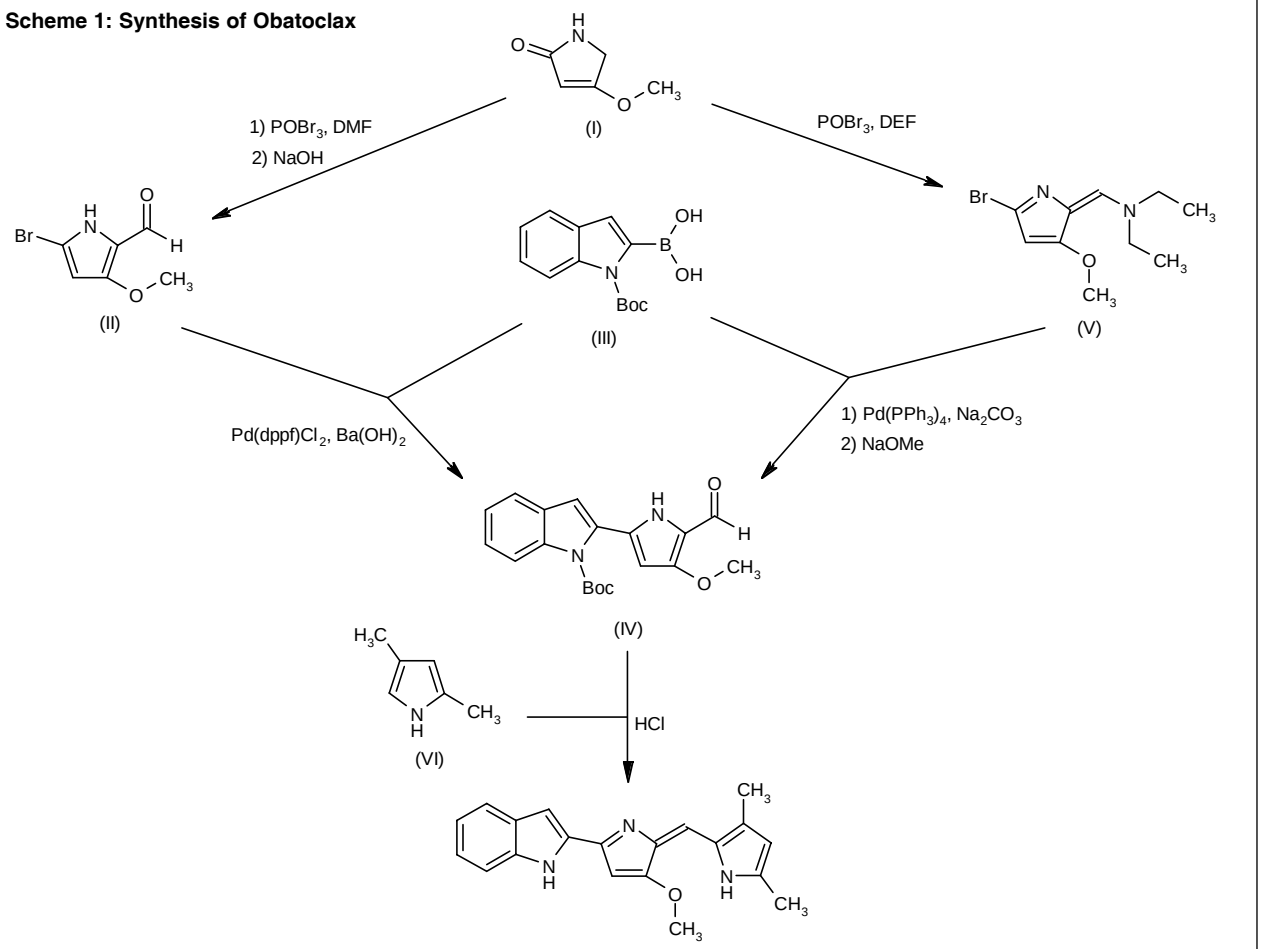
Scheme 1: Synthesis of Obatoclax



Developed at Gemin X Biotechnologies, obatoclax is a small molecule specifically designed to act as an antagonist at the BH3-binding groove of antiapoptotic members of the Bcl-2 protein family. It thereby activates apoptosis and has shown antitumor activity in many human cancer cell lines. Obatoclax is currently in phase II clinical development for the treatment of Hodgkin's lymphoma, myelodysplastic/myeloproliferative disorders and follicular lymphoma, and early clinical studies for the treatment of relapsed or refractory non-small cell lung cancer (NSCLC) and mantle cell lymphoma (MCL) are ongoing.

Preclinical Pharmacology

The antitumor activity of obatoclax alone or in combination with other anticancer drugs has been extensively evaluated. Preclinical studies demonstrated that obatoclax inhibited the viability of a panel of human myeloma cell lines with a mean IC_{50} of 215 nM. Sensitivity to obatoclax was not related to the level of expression of the antiapoptotic proteins Bcl-2, Mcl-1 or Bcl-X_L. The addition of potent multiple myeloma growth factors, including IL-6 and insulin-like growth factor-1 (IGF-1), did not confer resistance to obatoclax. Combination of bortezomib and obatoclax did not show a synergistic interaction (16).

The inhibition of Bcl-2 signaling by obatoclax was also examined in acute myelogenous leukemia (AML) cell lines and primary AML samples. Obatoclax inhibited the growth of HL-60, U-937, OCI/AML-3 and KG-1 cell lines with IC_{50} values of 0.1, 0.5, 0.5 and 2.5 μM, respectively, and overexpression of Bcl-2 or Bcl-X_L did not confer resistance to obatoclax. In HL-60 cells, disruption of Mcl-1/Bak heterodimerization with obatoclax was associated with a decrease in mitochondrial inner membrane potential, with 64 ± 4.8% of cells losing membrane potential at 72 h. In 6 of 7 primary AML samples, obatoclax induced apoptosis in $CD34^+$ progenitor cells (IC_{50} = 3.6 ± 1.2 μM at 24 h). The results indicate that obatoclax induces apoptosis in myeloid leukemia cells by disrupting Mcl-1/Bak dimerization and activating the intrinsic apoptotic cascade (17, 18).

Chronic lymphoid leukemia (CLL) is associated with loss of normal cellular apoptotic function. The induction of apoptosis by obatoclax in CLL cells was evaluated *ex vivo*. Obatoclax induced concentration-dependent apoptosis, with an EC_{50} of 1.7 μM for sensitive samples. An

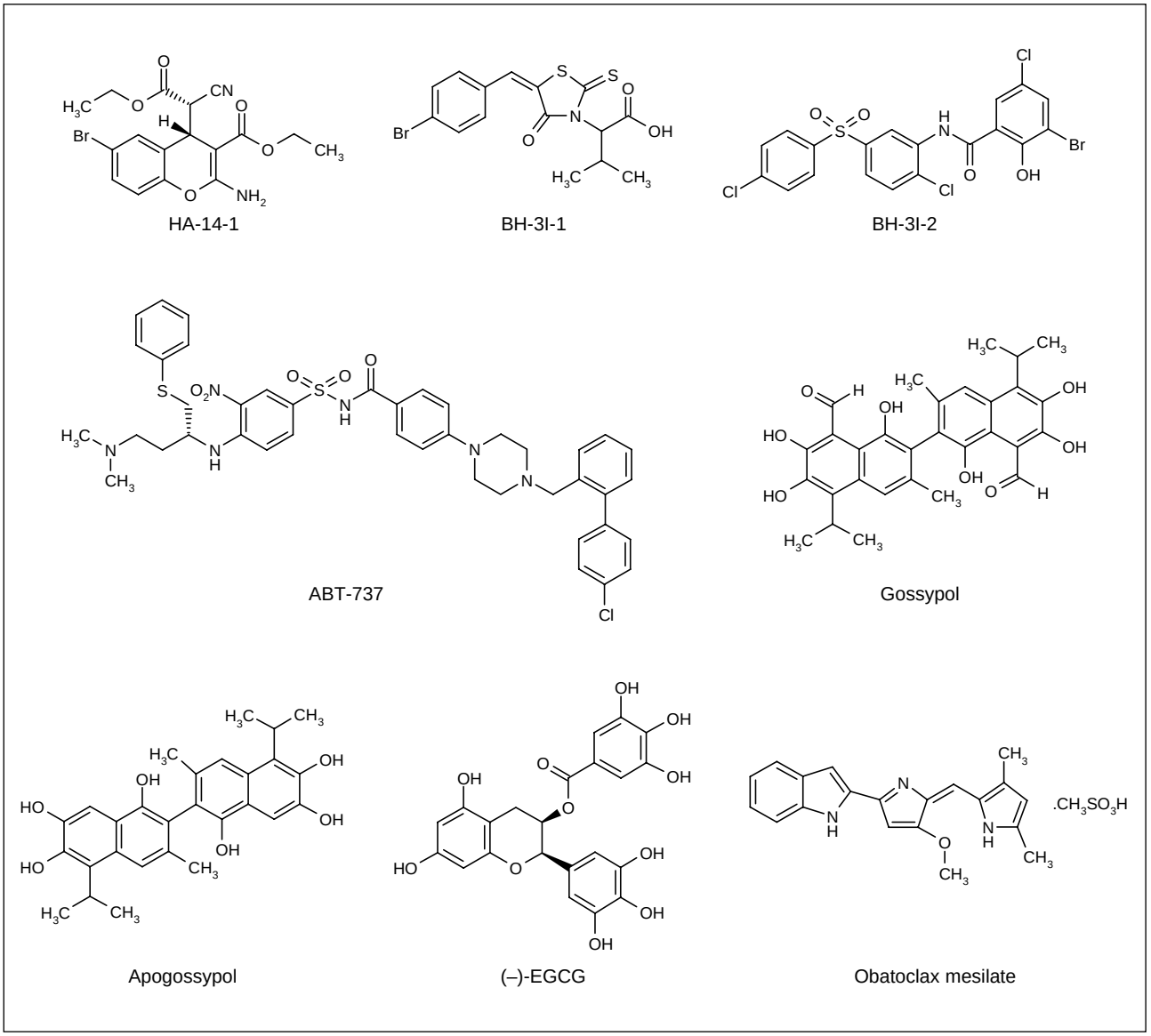


Fig. 1. Structures of nonpeptide antagonists of Bcl-2 family proteins.

additive effect was noted at 500 μM when combined with fludarabine and chlorambucil (19, 20).

The ability of obatoclax to sensitize human cholangiocarcinoma cells to TRAIL (TNF-related apoptosis-inducing ligand)-mediated apoptosis was examined in another study. Compared with TRAIL (1 ng/ml) alone, addition of obatoclax (0.5 μM) increased the apoptosis rates by 3-5-fold in all the cancer cell lines tested, whereas no such effect was seen in normal cells. The effect of obatoclax appeared to be mediated by inhibition of the binding of the antiapoptotic proteins Bak and Bim to Mcl-1 (21).

Apoptosis induction by obatoclax alone or in combination with other drugs was further tested in a panel of human multiple myeloma cell lines. Apoptosis was detected at concentrations of 0.15-5 μM. When combined with other drugs such as melphalan and bortezomib, obatoclax demonstrated an additive apoptotic effect, and synergistic activity was seen in combination with mapatumumab (22).

In primary mantle cell lymphoma (MCL) cells and MCL cell lines, obatoclax (0.5-5 μM) exhibited significant cytotoxicity. Moreover, preincubation with obatoclax (0.1-1.0 μM) followed by bortezomib (1-10 nM) led to a synergistic cytotoxic effect with a reduction in Mcl-1 levels and enhanced accumulation of the proapoptotic protein Noxa. This combination allowed significant bortezomib dose reductions (23, 24). The effect of obatoclax with and without vincristine was also examined in MCL. All 3 MCL cell lines tested showed sensitivity to obatoclax, and the combination of obatoclax and low concentrations of vincristine led to additive growth inhibition in each of the cell lines (25). The activity of obatoclax was further tested in other MCL cell lines. Obatoclax again induced apoptosis in all MCL cell lines in a concentration- and time-dependent

manner, and it enhanced the activity of proteasome inhibitors (NPI-0052 and bortezomib) and doxorubicin (26, 27).

Using leukemia cell lines with *MLL* t(4;11) translocations, obatoclax demonstrated potent cytotoxic activity, with IC_{50} values of 43.5, 123 and 156 nM in RS4:11, MV-4-11 and SEM-K2 cell lines, respectively, which was due to apoptosis. Fixed concentrations of obatoclax proved synergistic in combination with cytarabine, dexamethasone and doxorubicin (28).

The effect of obatoclax on the antitumor activity of rituximab was also studied using the rituximab-sensitive NHL cell lines Raji and RL. *In vitro* exposure of Raji and RL cells to obatoclax caused a concentration-dependent decrease in DNA synthesis and increase in cell death, and preincubation with obatoclax markedly increased rituximab-mediated antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity. The effect of obatoclax on the antitumor activity of other chemotherapeutic agents, including cisplatin, doxorubicin and vincristine, was further studied in a panel of rituximab-sensitive and -resistant NHL cell lines. Obatoclax induced concentration-dependent cell death and a decrease in DNA synthesis in all the cell lines tested. Synergistic cytotoxic and antiproliferative effects were seen when obatoclax was combined with cisplatin and doxorubicin (29, 30).

The activity of obatoclax alone and in combination with the epidermal growth factor receptor (EGFR)/HER-2/neu inhibitor GW-2974 was studied *in vitro*. Concentration-dependent growth inhibition was noted in both control and HER-2/neu-transfected MCF7 breast cancer cell lines treated with obatoclax (50-500 nM), and combination of obatoclax and GW-2974 (0.25-10 μM) led to synergistic growth inhibition (31, 32).

The activity of obatoclax alone and in combination with EGFR tyrosine kinase inhibitors or traditional cytotoxic agents was also evaluated in non-small cell lung cancer (NSCLC) cells. No clear relationship was found between EGFR or Bcl-2 family protein expression and sensitivity to obatoclax. Obatoclax induced apoptosis in a subset of lung cancer cell lines. Obatoclax in combination with gefitinib was synergistic in a cell line dependent on EGFR for survival. Synergistic effects were also noted when obatoclax was combined with cisplatin (33). However, results from other experiments indicated that using obatoclax to target Bcl-2 in NSCLC cell lines was much less effective than in MCL cell lines (33, 34).

Pharmacokinetics and Metabolism

The pharmacokinetics of obatoclax (1.25-7 mg/m^2 by 1-h i.v. infusion) were evaluated in two phase I studies in 7 patients with solid tumors (weekly) or CLL (every 3 weeks). Pharmacokinetic analysis showed rapid initial distribution phases ($t_{1/2\alpha}$ = 0.35 h, $t_{1/2\beta}$ = 1.5 h), followed by a longer elimination phase ($t_{1/2\gamma}$ = 13.4 h). While AUC increased in a dose-proportional manner from 17.97 to 38.4 ng.h/ml over the entire dose range tested, initial results indicated that the C_{max} was not proportional to dose (35).

The pharmacokinetics and pharmacodynamics of obatoclax were also evaluated in a phase I trial in patients with refractory solid tumors or lymphoma. Patients (n=15) received a 3-h i.v. infusion at doses of 5-14 mg/m^2 every week for 4 weeks. Pharmacokinetic analysis demonstrated a rapid initial distribution phase with a half-life of 0.6 h and a long elimination phase with a half-life of 43.8 h. At the highest dose, AUC and C_{max} were 276 ng.h/ml and 98 ng/ml, respectively (36).

Another phase I trial was carried out in 14 patients with myeloid malignancies and CLL who received a 24-h infusion at doses ranging from 7 to 40 mg/m^2 every 2 weeks. C_{max} and AUC values were proportional to dose on this schedule (37).

A phase I study evaluated 15 patients with CLL who received obatoclax 3.5-14 mg/m^2 by 1-h i.v. infusion or 20 mg/m^2 by 3-h i.v. infusion. Pharmacokinetic analysis again showed a triexponential concentration-time profile, with a rapid distribution phase ($t_{1/2\alpha}$ = 0.55 h) and a longer elimination phase ($t_{1/2\gamma}$ = 39.0 h). AUC increased in a dose-proportional manner (38).

Safety

Obatoclax has generally been well tolerated in the clinical trials conducted to date. Adverse events have been mostly mild to moderate, transient and occur during or shortly after infusion. The most common toxicities have included somnolence, ataxia, euphoria, pain and hypotension. Neutropenia, thrombocytopenia and lymphopenia have not been reported (35-38).

Clinical Studies

The antitumor activity of obatoclax was first evaluated in the two phase I clinical trials in patients with solid tumors or CLL mentioned above. At the time of reporting, of the 5 patients with solid tumors, 1 had stable disease at 6 weeks. The patient with CLL showed a significant reduction of bulky lymphadenopathy and a near normalization of peripheral counts after 2 cycles (35).

In another phase I study of obatoclax in patients with myelodysplastic syndrome (MDS), AML or CLL, hematological improvement was noted in 3 of 8 MDS patients and a reduction in bone marrow blasts was seen in another patient. Based on this study, dosing with 28 mg/m^2 over 24 h every 2 weeks was commenced in a phase II study (37).

In previously treated CLL patients, improvements in hematological parameters (reduction in peripheral lymphocyte counts, increase in platelet count or hemoglobin) were observed in a number of patients. An unconfirmed partial response was noted in 1 patient and 7 patients had stable disease for 6 weeks or more (38).

The FDA has granted obatoclax orphan drug designation for the CLL indication (39). Obatoclax is currently in phase II clinical development for the treatment of

Hodgkin's lymphoma, myelodysplastic/myeloproliferative disorders and follicular lymphoma, alone or in combination with rituximab. Early clinical studies are ongoing in the treatment of relapsed or refractory NSCLC in combination with docetaxel and in relapsed or refractory MCL in combination with bortezomib (40-46).

Source

Gemin X Biotechnologies, Inc. (CA).

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