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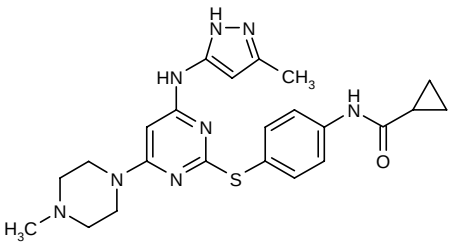
VX-680/MK-0457

Aurora Kinase Inhibitor
Oncolytic

N-[4-[4-(4-Methylpiperazin-1-yl)-6-(3-methyl-1*H*-pyrazol-5-ylamino)pyrimidin-2-ylsulfanyl]phenyl]cyclopropanecarboxamide

InChI=1/C23H28N8OS/c1-15-13-20(29-28-15)25-19-14-21(31-11-9-30(2)10-12-31)27-23(26-19)33-18-7-5-17(6-8-18)24-22(32)16-3-4-16/h5-8,13-14,16H,3-4,9-12H2,1-2H3,(H,24,32)(H2,25,26,27,28,29)



$C_{23}H_{28}N_8OS$
Mol wt: 464.5877

CAS: 639089-54-6

EN: 330736

Abstract

VX-680/MK-0457 is a small-molecule Aurora kinase inhibitor with inhibition constants (K_i) of 0.6, 18 and 4.6 nM for Aurora kinase A, B and C, respectively; it also inhibits Flt-3 and Abl kinases, particularly mutant forms. The compound displays potent antitumor activity in a broad range of cancer cell lines and is well tolerated in preclinical studies. A phase I clinical trial of VX-680/MK-0457 was carried out in patients with chronic myeloid leukemia (CML) or acute lymphocytic leukemia (ALL) with the T315I Bcr-Abl resistance mutation and patients with refractory JAK2-positive myeloproliferative disease. VX-680/MK-0457 demonstrated encouraging antitumor activity and a good overall safety profile.

Synthesis

VX-680/MK-0457 can be synthesized as follows:

The oxidation of 4,6-dichloro-2-(methylsulfanyl)pyrimidine (I) with MCPBA in dichloromethane gives 4,6-dichloro-2-(methylsulfonyl)pyrimidine (II), which is condensed with *N*-(4-sulfanylphenyl)cyclopropanecarboxamide (III) in hot butanol to yield the diaryl thioether (IV). The reaction of (IV) with 3-methyl-1*H*-pyrazol-5-amine (V) by means of DIEA in hot DMF affords the secondary amine (VI), which is finally condensed with 1-methylpiperazine (VII) by heating at 110 ºC to provide the target compound (1). Scheme 1.

Background

Aurora kinases (Aurora kinase A, B and C) play an important role in regulating mitosis and are often overexpressed in a wide range of human tumors, including breast, colon, pancreatic, ovarian and gastric tumors. Aurora kinases are therefore considered potential targets for anticancer drug development. A number of compounds have been shown to be active against Aurora kinases, several of which are now being evaluated in clinical trials (see Table I). Among these, VX-680/MK-0457, a 4,6-diaminopyrimidine, is one of the few compounds proven to target all three Aurora kinases (2). Although it displays significant selectivity over most other kinases tested, VX-680/MK-0457 has also been found to potently inhibit Flt-3 and Abl kinases, particularly the multidrug-resistant mutant T315I form of the latter (3-7). Based on the encouraging results of preclinical and early clinical studies, VX-680/MK-0457 was advanced to phase II clinical evaluation.

Preclinical Pharmacology

VX-680/MK-0457 inhibits Aurora kinase A, B and C *in vitro* with inhibition constants (K_i) of 0.6, 18 and 4.6 nM, respectively; it also inhibits Flt-3 (K_i = 30 nM). *In vitro* experiments showed that VX-680/MK-0457 inhibited the proliferation of a broad range of human tumor cell lines (IC_{50} = 15-113 nM) and induced cell death via apoptosis. Of the cell lines tested, VX-680/MK-0457 was particularly effective against leukemia, lymphoma and colorectal cancer cells. The compound also exhibited potent activity against primary acute myeloid leukemia (AML) cells from patients who failed to respond to standard treatments (IC_{50} = 35-100 nM). In contrast, it had no effect on normal human peripheral blood mononuclear cells (PBMCs).

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Scheme 1: Synthesis of VX-680/MK-0457

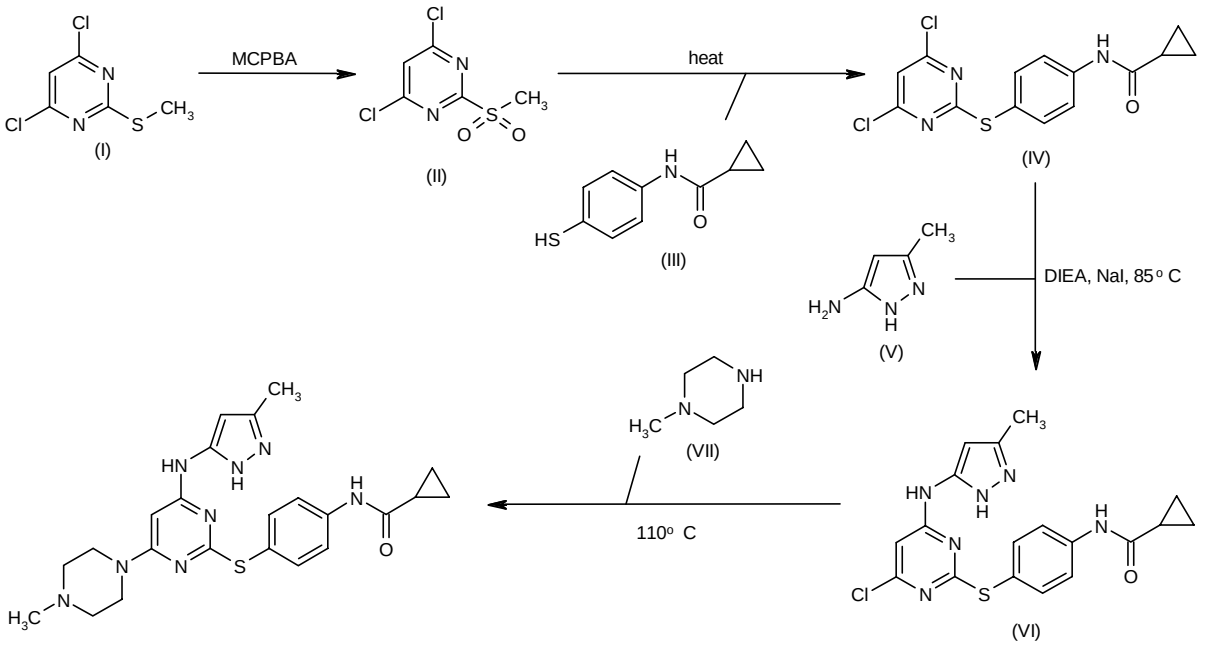
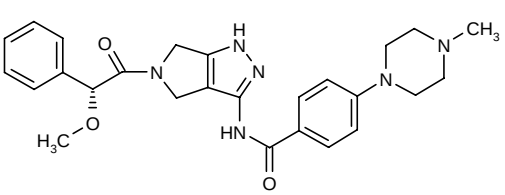


Table I: Aurora kinase inhibitors under active clinical development (Prous Science Integrity®)

Drug	Source	Phase
1. PHA-739358	Nerviano Medical Sciences	II
2. VX-680/MK-0457	Vertex/Merck & Co.	II
3. AT-9283*	Astex Therapeutics	I/II
4. AZD-1152	AstraZeneca	I
5. MK-6592*	Merck & Co./Vertex	I
6. MLN-8054	Millennium Pharmaceutical	I
7. R-763/AS-703569*	Merck Serono/Rigel	I
8. CYC-116*	Cyclacel	IND Filed



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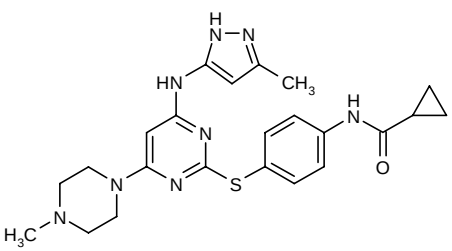

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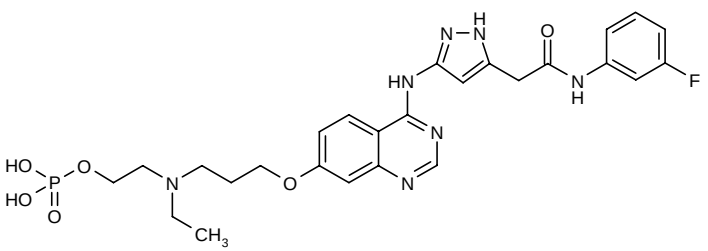

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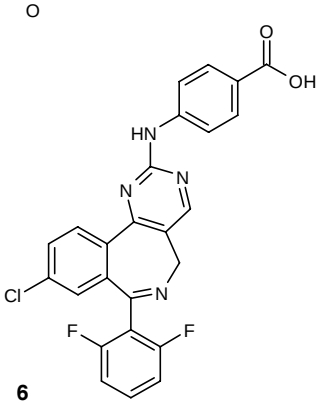

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*Structure not available

Suppression of histone H3 phosphorylation was observed in human cells, confirming that it acts by inhibiting Aurora kinase. *In vivo,* VX-680/MK-0457 caused marked inhibition of tumor growth in a variety of xenograft models, leading to regression of leukemia, colon and pancreatic tumors. In nude mice bearing human HL-60 leukemia, VX-680/MK-0457 75 mg/kg i.p. b.i.d. for 13 days reduced mean tumor volume by 98% and was well tolerated. The compound also induced regression of 7 of 10 human pancreatic MIA PaCa-2 tumors at a dose (50 mg/kg i.p. b.i.d.) that was well tolerated. Also, a dose of 1 mg/kg by i.v. infusion for 3 days/week induced tumor regression in 4 of 7 rats bearing human colon tumor HCT 116 xenografts. In addition, VX-680/MK-0457 markedly increased median survival time and induced sustained remission in a murine leukemia model. Inhibition of tumor growth was associated with a reduction in phosphorylation of histone H3 and a significant increase in apoptosis within the tumor tissue (4-7).

Further *in vitro* experiments demonstrated that VX-680/MK-0457 tightly binds to wild-type Abl and the majority of the drug-resistant variants (K_d = 5-50 nM), but shows no significant binding to Kit variants. It inhibited wild-type Abl and Abl(T315I) enzymes with IC_{50} values of 10 and 30 nM, respectively; for comparison, imatinib inhibited wild-type enzyme with an IC_{50} of 0.4 μM but did not significantly inhibit the mutant at up to 10 μM. In cell-based assays in Ba/F3 cells expressing wild-type and mutant Bcr-Abl(T315I), VX-680/MK-0457 inhibited proliferation with IC_{50} values of 100-200 nM (8).

Aurora kinase A and B are highly expressed in primary human and murine prostate cancer cell lines. Preclinical studies demonstrated that VX-680/MK-0457 reduced cancer cell (PC-3, LNCaP, C1A) survival. When used in combination with the chemotherapeutic drug doxorubicin, VX-680/MK-0457 could further reduce cell viability by > 2-fold (9).

Results from studies in cells expressing wild-type p53 and cells lacking p53 indicated that the response to VX-680/MK-0457 is dependent on the integrity of the p53-$p21^{Waf1/Cip1}$-dependent postmitotic checkpoint and that cells with compromised checkpoint function are most likely to undergo endoreduplication followed by apoptosis (10, 11).

The viability of leukemia MV-4-11, MOLT-4, Molm-13, K-562, LAMA-84, MEG-01 and KU812F cells was potently inhibited by VX-680/MK-0457 (IC_{50} = 20-300 nM), as was that of Ba/F3 cells with wild-type and mutant Bcr-Abl (IC_{50} = 300 nM). Treatment with VX-680/MK-0457 followed by idarubicin or doxorubicin was associated with greater synergistic inhibition than co-administration of the agents, and co-administration of VX-680/MK-0457 and imatinib resulted in synergistic inhibition of human chronic myeloid leukemia (CML)-derived cell lines and Ba/F3 cells expressing wild-type Bcr-Abl (12).

VX-680/MK-0457 was also found to inhibit mutant Bcr-Abl(V299L) kinase activity in Ba/F3 cells at low micromolar concentrations, as well as in primary human PBMCs from a dasatinib-resistant patient with the V299L mutation (13).

In vivo studies were performed in mice bearing Ba/F3 cells expressing an activating human Flt-3 mutation. Following treatment with VX-680/MK-0457 15 mg/kg i.p. b.i.d. for 3 days biweekly, median survival increased from 21-25 days in control mice to 31 days (*vs.* 38 and 34.5 days, respectively, on doxorubicin 3 mg/kg weekly and MLN-518 60 mg/kg b.i.d.), and all mice treated with VX-680/MK-0457 at higher doses of 45 mg/kg on the same schedule or 75 mg/kg i.p. b.i.d. every other day survived to day 42; no minimum residual disease was seen following sacrifice in animals treated at 75 mg/kg. Sustained remission was observed at 38 days after discontinuation in 100% and 33% of animals treated with VX-680/MK-0457 75 and 45 mg/kg, respectively (14).

Clinical Studies

On the basis of the encouraging antitumor activity of VX-680/MK-0457 *in vitro* and *in vivo*, a phase I/II clinical study was carried out in patients with refractory hematological malignancies. The patients received a 5-day continuous i.v. infusion every 2-3 weeks of escalating doses of VX-680/MK-0457 (8, 12, 16, 20, 24, 28 and 32 mg/m^2/h). Dose-related myelosuppression was seen at all dose levels tested, but no significant extramedullary toxicity. Of 14 evaluable patients with CML, 11 achieved an objective response, all of whom had the T315I mutation (1 major and 4 minor hematological responses, and 1 complete, 2 partial and 1 minor cytogenetic responses). The patient with T315I-mutant acute lymphocytic leukemia (ALL) also achieved an objective response, and 6 of the 8 evaluable patients with JAK2-positive refractory myeloproliferative disease had an objective response. The safety and efficacy of VX-680/MK-0457 are being evaluated at a dose of 36 mg/m^2/h (15-19).

Further phase I clinical studies of VX-680/MK-0457 for the treatment of advanced solid tumors, including colorectal cancer (20, 21) and relapsed or refractory AML, ALL, CML or myelodysplastic syndrome (MDS) (22) are currently ongoing, as are phase II clinical trials for the treatment of CML and Philadelphia chromosome-positive (Ph+) ALL with documented T315I mutation (23) and non-small cell lung cancer (24).

Sources

Vertex Pharmaceuticals, Inc. (US); developed in collaboration with Merck & Co. (US).

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