PHARMACEUTICAL FORMULATIONS OF A BRUTON'S TYROSINE KINASE INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. patent application Ser. No. 15/862,995, filed Jan. 5, 2018, which is a continuation of U.S. patent application Ser. No. 15/467,414, filed Mar. 23, 2017, now abandoned, which is a continuation of U.S. patent application Ser. No. 15/060,010, filed Mar. 3, 2016, now U.S. Pat. No. 9,655,857, issued May 23, 2017, which claims the benefit of U.S. Provisional Application No. 62/127,717, filed Mar. 3, 2015, and U.S. Provisional Application No. 62/193,518, filed Jul. 16, 2015, which are each incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

Described herein is the Bruton's tyrosine kinase (Btk) inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including pharmaceutical compositions, solvates and pharmaceutically acceptable salts thereof, as well as pharmaceutical formulations that include the Btk inhibitor and methods of using the Btk inhibitor compositions or formulations in the treatment of diseases or conditions that would benefit from inhibition of Btk activity.

BACKGROUND OF THE INVENTION

Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

Btk is a key regulator of B-cell development, activation, signaling, and survival. In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one or 2-Propen-1-one, 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein.

SUMMARY OF THE INVENTION

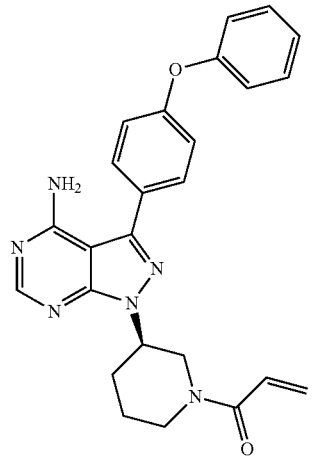
Described herein is the Btk inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including pharmaceutically acceptable compositions, formulations, and methods of uses thereof. Also described are pharmaceutically acceptable compositions and formulations of the Btk inhibitor, 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, used in the manufacture of medicaments for the treatment of diseases or

conditions that are associated with Btk activity. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is an irreversible Btk inhibitor. Further described are pharmaceutical compositions and formulations of the Btk inhibitor, 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, and methods of using the Btk inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of Btk provides therapeutic benefit to a mammal having the disease or condition).

Also described herein is a process for preparing a pharmaceutical composition of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one by a wet granulation method. Further described are pharmaceutical formulations that include a pharmaceutical composition of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one prepared by a wet granulation method.

In one aspect is a pharmaceutical composition comprising ibrutinib, wherein ibrutinib is a compound with the structure of Compound 1,

Compound 1



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and wherein the pharmaceutical composition comprises at least 50% w/w of ibrutinib.

In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 50% w/w to about 90% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 50% w/w to about 80% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 60% w/w to about 80% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 60% w/w to about 75% w/w of ibrutinib. In another embodiment is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, wherein the pharmaceutical composition comprises intragranular and extragranular ingredients. In another embodiment is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, wherein the pharmaceutical composition is prepared using a wet granulation method. In another embodiment is a pharmaceutical composition comprising at least