US006916809B2

(12) **United States Patent**
Chen et al.

(10) **Patent No.: US 6,916,809 B2**
(45) **Date of Patent: Jul. 12, 2005**

(54) **HETEROCYCLIC ACRIDONE INHIBITORS OF IMPDH ENZYME**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 27 days.

(21) Appl. No.: **10/325,009**

(22) Filed: **Dec. 20, 2002**

(65) **Prior Publication Data**

US 2003/0181497 A1 Sep. 25, 2003

Related U.S. Application Data

(60) Provisional application No. 60/343,234, filed on Dec. 21, 2001.

(51) **Int. Cl.**[7] **C07D 471/14**; C07D 471/04; A61K 31/4375; A61P 19/02; A61P 17/06

(52) **U.S. Cl.** **514/230.5**; 514/255.05; 514/256; 514/293; 544/105; 544/333; 544/405; 544/60; 544/126; 544/361; 544/250; 546/81; 540/575

(58) **Field of Search** 544/105, 333, 544/405, 60, 126, 361; 546/81; 514/230.5, 255.05, 256, 293; 540/575

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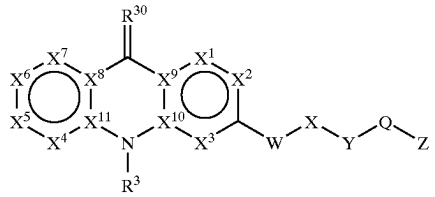
(57) **ABSTRACT**

Compounds having the formula (I),

(I)



wherein R^3 is selected from H, OH and NH_2; R^{30} is selected from =O and =S; W is —C(=O)—, —S(=O)—, or —$S(O)_2$—; or W may be —CH_2— if X is —C(=O)—; X is selected from —CH_2—, —$N(R^4)$—, and —O—, except that when W is —CH_2—, X is —C(=O)—; Y is a bond or —$C(R^{40})(R^{45})$—; Q is a linker; Z is optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl; and X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10} and X^{11} are selected such a tricyclic heteroaryl ring system is formed as further defined in the specification.

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HETEROCYCLIC ACRIDONE INHIBITORS OF IMPDH ENZYME

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/343,234, filed Dec. 21, 2001, incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to compounds which inhibit IMPDH, to methods of making such compounds, and to pharmaceutical compositions containing these compounds. The compounds and pharmaceutical compositions of the invention can be used as therapeutic agents for IMPDH-associated disorders.

BACKGROUND OF THE INVENTION

Inosine monophosphate dehydrogenase (IMPDH) has been shown to be a key enzyme in the regulation of cell proliferation and differentiation. Nucleotides are required for cells to divide and replicate. In mammals, nucleotides may be synthesized through one of two pathways: the de novo synthesis pathway or the salvage pathway. The extent of utilization of each pathway is dependent on the cell type. This selectivity has ramifications with regard to therapeutic utility as described below.

IMPDH is involved in the de novo synthesis of guanosine nucleotides. IMPDH catalyzes the irreversible NAD-dependent oxidation of inosine-5'-monophosphate ("IMP") to xanthosine-5'-monophosphate ("XMP"), Jackson et al., *Nature,* 256:331–333 (1975).

IMPDH is ubiquitous in eukaryotes, bacteria and protozoa. The prokaryotic forms share 30–40% sequence identity with the human enzyme.

Two distinct cDNA's encoding IMPDH have been identified and isolated. These transcripts are labeled type I and type II and are of identical size (514 amino acids). Collart et al., *J. Biol. Chem.,* 263:15769–15772 (1988); Natsumeda et al., *J. Biol. Chem.,* 265:5292–5295 (1990); and U.S. Pat. No. 5,665,583 to Collart et al. These isoforms share 84% sequence identity. IMPDH type I and type II form tetramers in solution, the enzymatically active unit.

B and T-lymphocytes depend on the de novo, rather than salvage pathway, to generate sufficient levels of nucleotides necessary to initiate a proliferative response to mitogen or antigen. Due to the B and T cell's unique reliance on the de novo pathway, IMPDH is an attractive target for selectively inhibiting the immune system without also inhibiting the proliferation of other cells.

Inhibitors of IMPDH have also been described in the art. WO 97/40028 and U.S. Pat. No. 5,807,876 describe a class of urea derivatives that possess a common urea backbone. WO 98/40381 describes a series of heterocyclic substituted anilines as inhibitors of IMPDH.

Tiazofurin, ribavirin and mizoribine also inhibit IMPDH. These nucleoside analogs are competitive inhibitors of IMPDH; however, these agents inhibit other NAD dependent enzymes. This low level of selectivity for IMPDH limits the therapeutic application of tiazofurin, ribavirin and mizoribine. Thus, new agents which have improved selectivity for IMPDH would represent a significant improvement over the nucleoside analogs.

U.S. Pat. Nos. 5,380,879 and 5,444,072 and PCT publi-

phenolic acid ("MPA") and some of its derivatives as potent, uncompetitive, reversible inhibitors of human IMPDH type I and type II. MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen. Immunosuppressants, such as MPA and derivatives of MPA, are useful drugs in the treatment of transplant rejection and autoimmune disorders, psoriasis, inflammatory diseases, including rheumatoid arthritis, tumors and for the treatment of allograft rejection. These are described in U.S. Pat. Nos. 4,686,234, 4,725,622, 4,727,069, 4,753,935, 4,786,637, 4,808,592, 4,861,776, 4,868,153, 4,948,793, 4,952,579, 4,959,387, 4,992,467, and 5,247,083.

Mycophenolate mofetil, sold under the trade name CELLCEPT, is a prodrug which liberates MPA in vivo. It is approved for use in preventing acute renal allograft rejection following kidney transplantation. The side effect profile limits the therapeutic potential of this drug. MPA is rapidly metabolized to the inactive glucuronide in vivo. In humans, the blood levels of glucuronide exceed that of MPA. The glucuronide undergoes enterohepatic recycling causing accumulation of MPA in the bile and subsequently in the gastrointestinal tract. This together with the production of the inactive glucuronide effectively lowers the drug's in vivo potency, while increasing its undesirable gastrointestinal side effects.

The combination of agents for prevention and/or treatment of IMPDH-associated disorders, especially allograft rejection, has been investigated. In one study, it was observed that cyclic AMP agonists, such as the Type 4 Phosphodiesterase (PDE4) inhibitor Rolipram [4-[3-(cyclopentyloxy)-4-methoxy-phenyl]-2-pyrrolidinone] (Schering AG), synergized with IMPDH inhibitor MPA by a cAMP- and IMPDH-dependent mechanism. (P. A. Canelos et al., *J. Allergy and Clinical Immunology,* 107:593 (2001)). The investigators found that cyclic AMP agonists, such as the PDE4 inhibitor Rolipram (Rol), markedly downregulated antigen-specific T lymphocyte responses through their effects on a variety of signaling pathways. The study defined the potential to use a low concentration of Rol (10^{-7} M, approximate IC_{10}) to synergize with a variety of immunosuppressive agents for the prevention and/or treatment of allograft rejection. While little or no synergistic effect on inhibition of antigen-induced proliferation (assessed by ^{3}H Thymidine incorporation) could be demonstrated with calcineurin antagonists (cyclosporine and tacrolimus), sirolimus, or corticosteroids, a marked synergistic effect was demonstrated with MPA, the active metabolite of mycophenolate mofetil (CellCept, Roche). This effect was statistically significant over 4 orders of magnitude (10^{-6} to 10^{-9} M). This synergism was recapitulated with dibuteryl-cAMP (2×10^{-6} M, approximate IC_{10}) and inhibited with the use of H-9, suggesting a mechanism involving both cAMP and protein kinase A.

Since MPA is a selective, uncompetitive, and reversible inhibitor of IMPDH, a key enzyme in the purine salvage pathway, the potential for cAMP-mediated cross-talk at this locus was further investigated. It was found that gene expression for IMPDH types I and II (assessed by RT-PCR) remained unaffected by the administration of rolipram, MPA, or both at low and high concentrations. However, functional reversal of the synergistic effect was demonstrated with the use of deoxyguanosine, a specific antagonist of MPA on IMPDH (% inhibition of proliferation 81±16 vs. 35±12, $p<0.05$). Finally, despite a marked synergistic effect on inhibition of proliferation, no significant downregulation

the administration of Rol 10^{-7} M, MPA 10^{-8} M, or the combination. It was concluded that Rol demonstrates marked synergy with MPA by a cAMP- and IMPDH-dependent mechanism. The utility of this combination of agents for the induction of T cell tolerance was suggested by the specificity of the observed effect for proliferation, without the abrogation of cytokine generation and early signaling processes.

Unlike type I, type II mRNA is preferentially upregulated in human leukemic cell lines K562 and HL-60. Weber, *J. Biol. Chem.,* 266: 506–509 (1991). In addition, cells from human ovarian tumors and leukemic cells from patients with chronic granulocytic, lymphocytic and acute myeloid leukemias also display an up regulation type II mRNA. This disproportionate increase in IMPDH activity in malignant cells may be addressed through the use of an appropriate IMPDH inhibitor. IMPDH has also been shown to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH may be useful in preventing restenosis or other hyperproliferative vascular diseases.

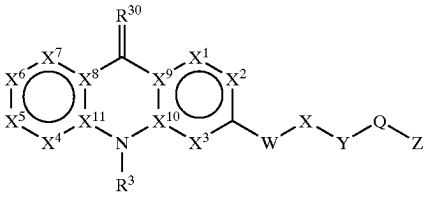
IMPDH has been shown to play a role in viral replication in some viral cell lines. Carr, *J. Biol. Chem.,* 268:27286–27290 (1993). The IMPDH inhibitor VX-497, is currently being evaluated for the treatment of hepatitis C virus in humans. Ribavirin has also been used in the treatment of hepatitis C and B viruses and when used in combination with interferon an enhancement in activity was observed. The IMPDH inhibitor ribavirin is limited by its lack of a sustained response in monotherapy and broad cellular toxicity.

There remains a need for potent selective inhibitors of IMPDH with improved pharmacological properties, physical properties and fewer side effects. Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-vascular hyperproliferative agents, anti-inflammatory agents, antifungal agents, antipsoriatic and anti-viral agents. The compounds of the present invention are effective inhibitors of IMPDH. Inhibitors of IMPDH enzyme are also described in U.S. patent application Ser. No. 10/324,306, titled "Acridone Inhibitors of IMPDH Enzyme," having the same assignee as the present invention and filed concomitantly herewith, the entire contents of which is incorporated herein by reference. Said application also claims priority to U.S. patent application Ser. No. 60/343,234, filed Dec. 21, 2001.

SUMMARY OF THE INVENTION

The present invention provides compounds of the following formula (I), their enantiomers, diastereomers, tautomers and pharmaceutically acceptable salts and solvates thereof, for use as IMPDH inhibitors:

(I)



wherein:

X^1 is selected from a bond, CR^1 and N;

X^2 is selected from CR^{25}, N, NR^2, O and S;

X^4 is selected from CR^1, N, NR^2, O and S;

X^5 is CR^1 or N;

X^6 is selected from CR^{25}, N, NR^2, O, and S;

X^7 is selected from a bond, CR^1 and N;

X^8, X^9, X^{10} and X^{11} are independently selected from C and N;

Provided, however, that at least one of X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10} and X^{11} is N, NR^2, O or S; and provided further that X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^9, X^{10} and X^{11} are selected such that a tricyclic heteroaryl ring system is formed;

W is —C(=O)—, —S(=O)—, or —$S(O)_2$—; or W may be —CH_2— if X is —C(=O)—, —S(=O)—, or —$S(O)_2$—;

X is selected from —CH_2—, —$N(R^4)$—, and —O—, except that when W is —CH_2—, X is selected from —C(=O)—, —S(=O)—, or —$S(O)_2$—;

Y is a bond or —$C(R^{40})(R^{45})$—;

Q is selected from a bond, —$C(R^{26})(R^{46})$—, —C(=O)—, —CH_2—O—, —CH_2—O—CH_2—, —CH_2—CO_2—NR^4—, —CH_2—CO_2—, —C(=O)NR^4—, and —CH=$C(R^{26})$—;

Z is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl, and when Y is —$C(R^{40})(R^{45})$— and Q is a bond or —$C(R^{26})(R^{46})$—, Z may be CO_2H or CO_2alkyl;

R^1 is the same or different and is selected from hydrogen, halogen, cyano, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O—R^7, —(C=O)R^7, —(C=O)—O—R^7, NR^8R^9, —(C=O)NR^8R^9, —SR^{20}, —S(=O)R^{20}, —SO_2R^{20} and —C≡C—$Si(OH_3)_3$;

R^2 is selected from hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

R^3 is selected from H, OH and NH_2;

R^4 is selected from H, OH and C_{1-4} alkyl;

R^7 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, substituted cycloalkyl, C(=O)alkyl, C(=O)substituted alkyl, C(=O)cycloalkyl, C(=O)substituted cycloalkyl, C(=O)aryl, C(=O)substituted aryl, C(=O)O-alkyl, C(=O)O-substituted alkyl, C(=O)heterocyclo, —C(=O)—NR^8R^9, C(=O)heteroaryl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, heteroaryl and substituted heteroaryl;

R^8 and R^9 are independently selected from hydrogen, OR^7, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, C(=O)alkyl, C(=O)substituted alkyl, C(=O)cycloalkyl, C(=O)substituted cycloalkyl, C(=O)aryl, C(=O)substituted aryl, C(=O)O-alkyl, C(=O)O-substituted alkyl, C(=O)heterocyclo, C(=O)heteroaryl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl and substituted heteroaryl, or R^8 and R^9 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic ring of 3 to 8 atoms, or substituted or unsubstituted heteroaryl ring of 5 atoms;

R^{20} is selected from alkyl and substituted alkyl;

R^{25} is the same or different and is selected from hydrogen, halogen, nitro, cyano, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, O—R^7, NR^8R^9, SR^7, S(O)R^7, SO_2R^7, SO_3R^7, $SO_2NR^8R^9$, —C(=O)R^7, CO_2R^7, C(=O)NR^8R^9, and —C=C—Si(

R^{26} and R^{46} are independently selected from hydrogen, C_{1-4}alkyl, hydroxy, halogen, hydroxyC_{1-4}alkyl, haloC_{1-4} alkyl, and heterocycloC_{1-4}alkyl, or taken together form a C_{3-7}cycloalkyl ring; and

R^{40} and R^{45} are independently selected from hydrogen, cyano, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, heteroaryl and substituted heteroaryl, or R^{40} and R^{45} are taken together to form a substituted or unsubstituted cycloalkyl ring of 3 to 8 atoms or a substituted or unsubstituted heterocyclo ring of 3 to 8 atoms.

The present invention also relates to pharmaceutical compositions containing compounds of formula (I), and methods for treating IMPDH-associated disorders using the compounds of formula (I), alone or in combination with PDE4 inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

The following are definitions of the terms as used throughout this specification and claims. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbons atoms, preferably 1 to 8 carbon atoms, and most preferably 1 to 4 carbon atoms. The term "lower alkyl" refers to an alkyl group of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group as defined above, having one, two, or three substituents selected from the group consisting of halo, cyano, O—R^5, S—R^5, NR^6R^{6a}, nitro, oxo, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, heteroaryl, substituted heteroaryl, CO_2R^5, S(O)R^5, SO_2R^5, SO_3R^5, $SO_2NR^6R^{6a}$, C(=O) NR^6R^{6a}, $NR^6CO_2R^{6a}$, $C_2NR^6NR^{6a}$ and C(=O)R^5.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and one, two or three double bonds, preferably 2 to 6 carbon atoms and one double bond.

The term "substituted alkenyl" refers to an alkenyl group as defined above having one, two, or three substituents selected from the group consisting of halo, cyano, O—R^5, S—R^5, NR^6R^{6a}, nitro, oxo, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, heteroaryl, substituted heteroaryl, CO_2R^5, S(O)R^5, SO_2R^5, SO_3R^5, $SO_2NR^6R^{6a}$, C(=O)NR^6R^{6a}, $NR^6CO_2R^{6a}$, $CO_2NR^6R^{6a}$ and C(=O)R^5.

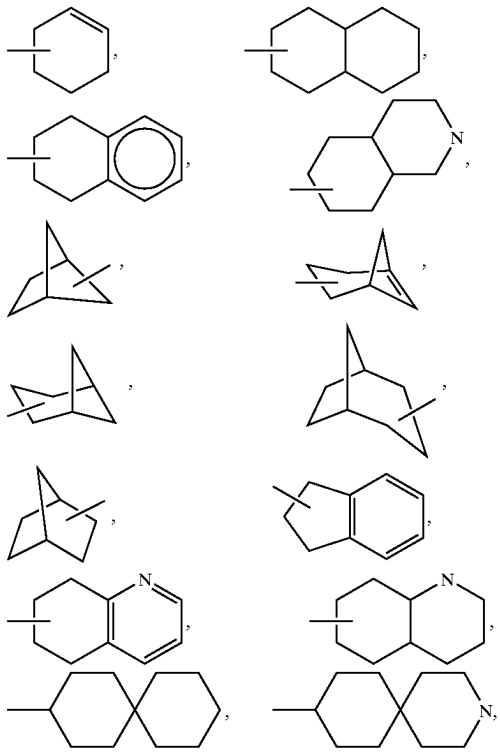
The term "alkynyl" refers to straight or branched chain hydrocarbon group having 2 to 12 carbon atoms and one, two or three triple bonds, preferably 2 to 6 carbon atoms and one triple bond.

The term "substituted alkynyl" refers to an alkynyl group as defined above having one, two or three substituents selected from the group consisting of halo, cyano, O—R^5, S—R^5, NR^6R^{6a}, nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl, heterocyclo, heteroaryl, CO_2R^5, S(O)R^5, SO_2R^5, SO_3R^5, $SO_2NR^6R^{6a}$, C(=O)NR^6R^{6a}, and C(=O)R^5.

The term "halo" refers to chloro, bromo, fluoro, and iodo, with chloro, bromo and fluoro being preferred.

The term "cycloalkyl" refers to fully saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons atoms, preferably 3 to 7 carbon atoms. Also included in this definition are bicyclic rings where the cycloalkyl ring as defined above has a bridge of one, two or three carbon atoms in the bridge, or a second ring attached in a fused or spiro fashion, i.e., a fused aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclo, substituted heterocyclo, heteroaryl or substituted heteroaryl ring, or a spirocycloalkyl or spiroheterocycloalkyl ring, provided that the point of attachment is in the cycloalkyl ring.

Thus, the term "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc., as well as the following ring systems,



and so forth.

The term "substituted cycloalkyl" refers to such cycloalkyl groups as defined above having one, two or three substituents attached to any available carbon atom of a monocyclic ring or any available carbon or nitrogen atom of a bicyclic ring, wherein said substituents are selected from the group consisting of halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, aryl, heterocyclo, heteroaryl, oxo (=O), —OR^5, —CO_2R^5, —C(=O) NR^6R^{6a}, —OC(=O)R^5, —OC(=O)R^5, —OC(=O) OR^6R^{6a}, —$OCH_2CO_2R^5$, —C(=O)R^5, NR^6R^{6a}, —NR^{10}C (=O)R^5, —NR^{10}C(=O)OR^5, —NR^{10}C(=O)C(=O)OR^5, —NR^{10}C(=O)C(=O)NR^6R^{6a}, —NR^{10}C(=O)C(=O) alkyl, —NR^{10}C(NCN)OR^5, NR^{10}C(=O)NR^6R^{6a}, —NR^{10} (NCN)NR^6R^{6a}, —$NR^{10}C(NR^{11})NR^6R^{6a}$, —$NR^{10}SO_2NR^6R^{6a}$, —$NR^{10}SO_2R^5$, —$SR^5$, —S(O)$R^5$, —$SO_2R^5$, —$SO_3R^5$, —$SO_2NR^6R^{6a}$, —$NHOR^5$, —$NR^{10}NR^6R^{6a}$, —N[C(=O)$R^5$][$OR^{10}$], —N($CO_2R^5$) OR^{10}, —C(=O)$NR^{10}(CR^{12}R^{13})_rR^5$, —C(=O)$(CR^{12}R^{13})_p$ $O(CR^{14}R^{15})_qCO_2R^5$, —C(=O)$(CR^{12}R^{13})_rOR^5$, —C(=O) $(CR^{12}R^{13})_pO(CR^{14}R^{15})_qR^5$, —C(=O)$(CR^{12}R^{13})_rNR^6R^{6a}$, —OC(=O)$O(CR^{12}R^{13})_m$ NR^6R^{6a}, —OC(=O)$N(CR^{12}$-$R^{13})_rR^5$, —$O(CR^{12}R^{13})_m$ NR^6R^{6a}, —NR^{10}C(=O)

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