EUROPEAN PATENT SPECIFICATION

INHIBITORS OF IMPDH ENZYME

INHIBITOREN DES IMPDH ENZYMES

INHIBITEURS DE L’ENZYME IMPDH

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References cited:
WO-A1-97/40028
Description

[0001] The present invention relates to compounds which inhibit IMPDH. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for use in inhibiting IMPDH enzyme activity and consequently, may be advantageously used as therapeutic agents for IMPDH-mediated processes. This invention also relates to the compounds of this invention and related compounds for use in inhibiting the activity of IMPDH.

BACKGROUND OF THE INVENTION

[0002] The synthesis of nucleotides in organisms is required for the cells in those organisms to divide and replicate. Nucleotide synthesis in mammals may be achieved through one of two pathways: the de novo synthesis pathway or the salvage pathway. Different cell types use these pathways to a different extent.


[0004] The de novo synthesis of guanosine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells 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 [A. C. Allison et. al., Immunochemical Reviews, 136, pp. 88-93 (1993)]. The prokaryotic forms share 30-40% sequence identity with the human enzyme. Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced [F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et. al., J. Biol. Chem., 265, pp. 5292-5295, (1990)]. Each is 514 amino acids, and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa [Y. Yamada et. al., Biochemistry, 27, pp. 2737-2745 (1988)].

[0005] The de novo synthesis of guanosine nucleotides, and thus the activity of IMPDH, is particularly important in B and T-lymphocytes. These cells 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 [A. C. Allison et. al., Immunochemical Reviews, 136, pp. 88-93 (1993)]. The prokaryotic forms share 30-40% sequence identity with the human enzyme. Two isoforms of human IMPDH, designated type I and type II, have been identified and sequenced [F.R. Collart and E. Huberman, J. Biol. Chem., 263, pp. 15769-15772, (1988); Y. Natsumeda et. al., J. Biol. Chem., 265, pp. 5292-5295, (1990)]. Each is 514 amino acids, and they share 84% sequence identity. Both IMPDH type I and type II form active tetramers in solution, with subunit molecular weights of 56 kDa [Y. Yamada et. al., Biochemistry, 27, pp. 2737-2745 (1988)].

[0006] Immunosuppression has been achieved by inhibiting a variety of enzymes including for example, the phosphatase calcineurin (inhibited by cyclosporin and FK-506); dihydroorotate dehydrogenase, an enzyme involved in the biosynthesis of pyrimidines (inhibited by leflunomide and brequinar); the kinase FRAP (inhibited by rapamycin); and the heat shock protein hsp70 (inhibited by deoxyspergualin). [See B. D. Kahan, Immunological Reviews, 136, pp. 29-49 (1993); R. E. Morris, The Journal of Heart and Lung Transplantation, 12 (6), pp. S275-S286 (1993)].

[0007] Inhibitors of IMPDH are also known. United States patents 5,380,879 and 5,444,072 and PCT publications WO 94/01105 and WO 94/12184 describe mycophenolic acid (MPA) and some of its derivatives as potent, uncompetitive, reversible inhibitors of human IMPDH type I (Ki=33 nM) and type II (Ki=9 nM). MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen [A. C. Allison et. al., Ann. N. Y. Acad. Sci., 696, 63, (1993).]

[0008] Immunosuppressants, such as MPA, are useful drugs in the treatment of transplant rejection and autoimmune diseases, [R. E. Morris, Kidney Intl., 49, Suppl. 53, S-26, (1996)]. However, MPA is characterized by undesirable pharmacological properties, such as gastrointestinal toxicity. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)].

[0009] Nucleoside analogs such as tiazofurin, ribavirin and mizoribine also inhibit IMPDH [L. Hedstrom, et. al. Biochemistry, 29, pp. 849-854 (1990)]. These compounds, however, suffer from lack of specificity to IMPDH.

[0010] Mycophenolate mofetil, a prodrug which quickly liberates free MPA in vivo, was recently approved to prevent acute renal allograft rejection following kidney transplantation. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995); H. W. Sollinger, Transplantation, 60, pp. 225-232 (1995)]. Several clinical observations, however, limit the therapeutic potential of this drug. [L. M. Shaw, et. al., Therapeutic Drug Monitoring, 17, pp. 690-699, (1995)]. MPA is rapidly metabolized to the inactive glucuronide in vivo. [A.C. Allison and E.M. Eugui, Immunological Reviews, 136, pp. 5-28 (1993)]. The glucuronide then undergoes enterohepatic recycling causing accumulation of MPA in the gastrointestinal tract where it cannot exert its IMPDH inhibitory activity on the immune system. This effectively lowers the drug’s in vivo potency, while increasing its undesirable gastrointestinal side effects.

[0011] More recently, IMPDH inhibitors of different classes have been described in PCT publications WO 97/40028 and WO 98/40381.

[0012] It is also known that IMPDH plays a role in other metabolic events. Increased IMPDH activity has been observed in rapidly proliferating human leukemic cell lines and other tumor cell lines, indicating IMPDH as a target for anti-cancer as well as immunosuppressive chemotherapy [M. Nagai et. al., Cancer Res., 51, pp. 3886-3890, (1991)]. IMPDH has also been shown to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH, such as MPA or rapamycin, may be useful in preventing restenosis or other hyperproliferative vascular diseases [C. R. Gregory et al., Transplantation, 59, pp. 655-61 (1995); PCT publication WO 94/12184; and PCT publication WO 94/01105].
Additionally, IMPDH has been shown to play a role in viral replication in some virus-infected cell lines. [S.F. Carr, J. Biol. Chem., 268, pp. 27286-27290 (1993)]. Analogous to lymphocytes and lymphocytic and tumor cell lines, the implication is that the de novo, rather than the salvage, pathway is critical in the process of viral replication.

Thus, there remains a need for potent IMPDH inhibitors with improved pharmacological properties. 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.

SUMMARY OF THE INVENTION

The present invention provides compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of IMPDH. The compounds of this invention can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, anti-inflammatory agents, antibiotics, and immunosuppressants for the treatment or prophylaxis of transplant rejection and autoimmune disease.

Additionally, these compounds are useful, alone or in combination with other agents, as therapeutic and prophylactic agents for antiviral, anti-tumor, anti-cancer, anti-inflammatory agents, antifungal agents, antipsoriatic immunosuppressive chemotherapy and restenosis therapy regimens.

The invention also provides pharmaceutical compositions comprising the compounds of this invention, as well as multi-component compositions comprising additional IMPDH compounds together with an immunosuppressant. The invention also provides the compounds of this invention, for use in the inhibition of IMPDH.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

Designation Reagent or Fragment

<table>
<thead>
<tr>
<th>Designation</th>
<th>Reagent or Fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>CDI</td>
<td>carbonyldiimidazole</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DIEA</td>
<td>disopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DPPA</td>
<td>diphenyl phosphoryl acid EDC 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>IPA</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>t-bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>BOC</td>
<td>butyloxy carbonyl</td>
</tr>
</tbody>
</table>

The following terms are employed herein:

- The terms "halo" or "halogen" refer to a radical of fluorine, chlorine, bromine or iodine.
- The term "immunosuppressant" refers to a compound or drug which possesses immune response inhibitory activity. Examples of such agents include cyclosporin A, FK506, rapamycin, leflunomide, deoxyspergualin, prednisone, azathioprine, mycophenolate mofetil, OKT3, ATAG, interferon and mizoribine.
- The term "interferon" refers to all forms of interferons, such as alpha, beta and gamma forms.
- IMPDH-mediated disease refers to any disease state in which the IMPDH enzyme plays a regulatory role in the metabolic pathway of that disease. Examples of IMPDH-mediated disease include transplant rejection and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, and inflammatory bowel disease, as well as inflammatory diseases, cancer, viral replication diseases and vascular diseases.
For example, the compounds, compositions and methods of using them of this invention may be used in the treatment of transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allografts and heart valve xenografts), rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn’s disease, ulcerative colitis), lupus, diabetes mellitus, myasthenia gravis, psoriasis, dermatitis, eczema, seborrhea, pulmonary inflammation, eye uveitis, hepatitis, Grave’s disease, Hashimoto’s thyroiditis, Behcet’s or Sjögren’s syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic adrenal insufficiency, polyclonal autoimmune syndrome, and glomerulonephritis, scleroderma, lichen planus, vitiligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis, inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma and adult respiratory distress syndrome, as well as in the treatment of cancer and tumors, such as solid tumors, lymphomas and leukemia, vascular diseases, such as restenosis, stenosis and atherosclerosis, and DNA and RNA viral replication diseases, such as retroviral diseases, and herpes.

Additionally, IMPDH enzymes are also known to be present in bacteria and thus may regulate bacterial growth. As such, the IMPDH-inhibitor compounds, compositions and methods described herein may be useful in treatment or prevention of bacterial infection, alone or in combination with other antibiotic agents.

The term “treating” as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. As used herein, the term “patient” refers to a mammal, including a human.

The terms “HBV”, “HCV” and “HGV” refer to hepatitis-B virus, hepatitis-C virus and hepatitis-G virus, respectively.

The compounds of the present invention are compounds of formula 1A

\[
\begin{align*}
\text{R}_1 & \quad \text{N} \quad \text{O} \\
\text{R}_2 & \quad \text{O} \\
\text{R}_9 & \quad \text{H} \\
\text{R}_{10} & \quad \text{H} \\
\text{R}_{11} & \quad \text{H}
\end{align*}
\] (1A)

wherein according to embodiment 1:

one of R₁ or R₂ is selected from hydrogen, ethyl or phenyl; and the other of R₁ or R₂ is selected from -CH₂OH, -CH₂CN, -CH₂CH₂CN or -CH₂N(CH₂CH₃)₂; or R₁ and R₂ are taken together to form a 3-tetrahydrofuranyl ring; R₉ is selected from (S)-methyl, (S)-ethyl, or (S)-hydroxymethyl; R₁₀ is selected from -C=N or 5-oxazolyl; and R₁₁ is selected from halo, -O-(C₁-C₃) straight alkyl, or -O-(C₂-C₃) straight alkenyl or alkynyl.

2. The compound according to 1, wherein R₉ is (S)-methyl.

3. The compound according to 1, wherein R₁₁ is selected from O-methyl, O-ethyl or O-isopropyl.

4. The compound according to 1, wherein said compound is selected from:
5. The compound according to 4, wherein said compound is compound 169.

6. A compound of formula 181:

![Chemical Structure](image)

[0029] Applicants have discovered that the presence of an (S) oriented moiety at R₉ imparts surprising and unexpectedly increased IMPDH inhibitory activity.

[0030] According to a preferred embodiment, the compound of formula IA is selected from any of those set forth in Table 1, below.

<table>
<thead>
<tr>
<th></th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td><img src="image" alt="Chemical Structure" /> Chiral</td>
</tr>
<tr>
<td>163</td>
<td><img src="image" alt="Chemical Structure" /></td>
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<td>164</td>
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<tr>
<td>166</td>
<td><img src="image" alt="Chemical Structure" /> Chiral</td>
</tr>
<tr>
<td>167</td>
<td><img src="image" alt="Chemical Structure" /> Chiral</td>
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<td>Page</td>
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<td>------</td>
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</tr>
<tr>
<td>168</td>
<td><img src="image1" alt="Structure 168" /></td>
</tr>
<tr>
<td>169</td>
<td><img src="image2" alt="Structure 169" /></td>
</tr>
<tr>
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<tr>
<td>182</td>
<td><img src="image7" alt="Structure 182" /></td>
</tr>
<tr>
<td>183</td>
<td><img src="image8" alt="Structure 183" /></td>
</tr>
</tbody>
</table>
In the above table, certain compounds are shown as salts. It should be understood that the scope of the compounds set forth in any given entry in the table covers all forms of the depicted compound, not just the salt shown.

When stereochemistry is not specifically indicated, the compounds of this invention may contain one or more asymmetric carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention, unless otherwise indicated. Each stereogenic carbon may be of the R or S configuration.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds that possess stability sufficient to allow manufacture and maintenance of the integrity for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

As used herein, the compounds of this invention, are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention. Particularly favored derivatives are those which increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzene sulfonate, bisulfate, butyrate, citrate, camphorate, camphor sulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picro, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine or lysine.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such
as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl or phenethyl bromides. Water or oil-soluble or dispersible products are thereby obtained.

[0037] The compounds of this invention may be synthesized using conventional techniques. Advantageously, these compounds are conveniently synthesized from readily available starting materials. More specifically, the compounds of this invention may be synthesized by the schemes set forth in Examples 1 and 2.

[0038] The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

[0039] The novel compounds of the present invention are excellent ligands for IMPDH. Accordingly, these compounds are capable of targeting and inhibiting IMPDH enzyme. Inhibition can be measured by various methods, including, for example, IMP dehydrogenase HPLC assays (measuring enzymatic production of XMP and NADH from IMP and NAD) and IMP dehydrogenase spectrophotometric assays (measuring enzymatic production of NADH from NAD). [See C. Montero et al., Clinica Chimica Acta, 238, pp. 169-178 (1995)].

[0040] Compositions of this invention comprise a compound of this invention or a salt thereof; an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound; and any pharmaceutically acceptable carrier, adjuvant or vehicle. Alternate compositions of this invention comprise a compound of this invention or a salt thereof; and a pharmaceutically acceptable carrier, adjuvant or vehicle. Such composition may optionally comprise an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, anti-inflammatory agent, antifungal agent, antibiotic, or an anti-vascular hyperproliferation compound. Preferably, the compositions of this invention are pharmaceutical compositions.

[0041] The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[0042] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include for instance ion exchangers, alumina, aluminum stearate, lecinthin, self-emulsifying drug delivery systems (SEDDS) such as α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial gliyde mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of this invention.

[0043] The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intraarterial, intrasynovial, intraperitoneal, intralethal, intrallesional and intracranial injection or infusion techniques.

[0044] The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents.
The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including such as capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase and combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include cocoa butter, beeswax or polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include for instance mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include for instance mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldecanoil, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 75 mg/kg body weight per day of the IMPDH inhibitory compounds described herein are useful in a monotherapy and/or in combination therapy for the prevention and treatment of IMPDH-mediated disease. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

When the compositions of this invention comprise a combination of an IMPDH inhibitor of this invention and one or more additional therapeutic or prophylactic agents, both the IMPDH inhibitor and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 to 80% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

According to one embodiment, the pharmaceutical compositions of this invention comprise an additional immunosuppression agent. Examples of additional immunosuppression agents include for instance cyclosporin A, FK506, rapamycin, lefunomide, deoxypergualin, prednisone, azathioprine, mycophenolate motefil, OKT3, ATAG, interferon and mizoribine.

According to an alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an anti-cancer agent. Examples of anti-cancer agents include for instance cisplatin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, teniposide, taxol, colchicine, cyclosporin A, phenothiazines, interferon and thioanoxethers.

According to an alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an anti-viral agent. Examples of anti-viral agents include for instance Cytovene, Ganciclovir, trisodium phosphonofomate, Ribavirin, d4T, ddl, AZT, and acyclovir.

According to another alternate embodiment, the pharmaceutical compositions of this invention may additionally comprise an anti-vascular hyperproliferative agent. Examples of anti-vascular hyperproliferative agents include for instance HMG Co-A reductase inhibitors such as lovastatin, thromboxane A2 synthetase inhibitors, eicosapentanoic acid, ciprostene, trapidil, ACE inhibitors, low molecular weight heparin, mycophenolic acid, rapamycin and 5-(3’-pyridi-nylmethyl)benzofuran-2-carboxylate.

Upon improvement of a patient’s condition, a maintenance dose of a compound, composition or combination
of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[0056] As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, the patient’s disposition to the disease and the judgment of the treating physician.

[0057] In an alternate embodiment, this invention provides the pharmaceutical compositions and combinations described above for use in treating or preventing IMPDH-mediated disease in a mammal. If the pharmaceutical composition only comprises the IMPDH inhibitor of this invention as the active component, an agent selected from an anti-inflammatory agent, immunosuppressant, an anti-cancer agent, an anti-viral agent or an anti-vascular hyperproliferation compound may be additionally administered. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the IMPDH inhibitor composition.

[0058] In a preferred embodiment, these compositions are useful in suppressing an immune response in a mammal. Such compositions are useful in treating or preventing diseases, including, transplant rejection (e.g., kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, small bowel and skin allografts and heart valve xenografts), graft versus host disease, and autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease (Crohn’s disease, ulcerative colitis), lupus, diabetes, mellitus myasthenia gravis, psoriasis, dermatitis, eczema, seborrhea, pulmonary inflammation, eye uveitis, Grave’s disease, Hashimoto’s thyroiditis, Behcet’s or Sjorgen’s syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, idiopathic adrenal insufficiency, polyglandular autoimmune syndrome, glomerulonephritis, scleroderma, lichen planus, viteligo (depigmentation of the skin), autoimmune thyroiditis, and alveolitis.

[0059] These compositions comprise a compound of this invention and a pharmaceutically acceptable adjuvant which is to be administered to the mammal. Such compositions may be additionally administered. Such additional agent may be administered to the mammal prior to, concurrently with, or following the administration of the IMPDH inhibitor composition.

[0060] Alternatively, a composition comprises a compound of this invention; an additional immunosuppressive agent and a pharmaceutically acceptable adjuvant which is to be administered to the mammal.

[0061] In an alternate preferred embodiment, these compositions are useful for inhibiting viral replication in a mammal. Such compositions may be additionally administered. Such additional agent comprises an additional anti-inflammatory agent and a pharmaceutically acceptable adjuvant which is to be administered to the mammal.

[0062] A composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant is to be administered to the mammal. In a preferred embodiment, additionally a composition comprising an additional anti-viral agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

[0063] Alternatively, a composition comprising a compound of this invention; an additional anti-viral agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

[0064] In another alternate preferred embodiment, these compositions are useful for inhibiting vascular cellular hyperproliferation in a mammal. Such compositions may be additionally administered. Such additional agent comprises an additional anti-vascular hyperproliferative agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

[0065] A composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant is to be administered to the mammal. In a preferred embodiment, additionally a composition comprising an additional anti-vascular hyperproliferative agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

[0066] Alternatively, a composition comprising a compound of this invention; an additional anti-vascular hyperproliferative agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

[0067] In another alternate preferred embodiment, these compositions are useful for inhibiting tumors and cancer in a mammal. Such compositions may be additionally administered. Such additional agent comprises an additional anti-vascular hyperproliferative agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.
A composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant is to be administered to the mammal. In a preferred embodiment, additionally a composition comprising an additional anti-tumor or anti-cancer agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

Alternatively, a composition comprising a compound of this invention; an additional anti-tumor or anti-cancer agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

In another alternate preferred embodiment, these compositions are useful for inhibiting inflammation and inflammatory diseases in a mammal. Such compositions are useful in treating or preventing diseases, including, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma and adult respiratory distress syndrome.

A composition comprising a compound of this invention, and a pharmaceutically acceptable adjuvant is to be administered to the mammal. In a preferred embodiment, additionally a composition comprising an anti-inflammatory agent and a pharmaceutically acceptable adjuvant is to be administered to the mammal.

In order that this invention be more fully understood, the following examples are set forth.

Reference

EXAMPLE 1

Synthesis of Compound 41

A. Synthesis of C4

To a solution of glacial acetic acid (46mL), acetic anhydride (46mL, 485mmole) and 2-methyl-5-nitroanisole (10.0g, 60mmole) at 0°C was added conc. H₂SO₄ (6.9mL) in a dropwise fashion. Upon complete addition, CrO₃ (8.08g, 80.8mmole) was added portion-wise over 60 mins. Following an additional 15 mins of stirring at 0 °C, the reaction mixture was poured over ice and the resulting precipitate was isolated by filtration, rinsing with cold H₂O. Purification by flash chromatography, eluting with a gradient of 15-50% EtOAc in hexanes, provided 8.14g (24%, 51% based on recovered starting material) C1 as a white solid. The ¹H NMR was consistent with that of the desired structure.

A stirred suspension of C1 (81.94g, 307mmole) in dioxane (100mL) was treated with concentrated HCl (20mL) and heated at reflux overnight. Upon cooling to ambient temperature, the product C2 precipitated as a light yellow crystalline solid in a yield of 40.65g (73.1%). The filtrate was concentrated to a volume of ca. 80mL and a second crop of product crystals was driven from solution by the addition of hexanes, yielding 8.91g (16.0%). Both batches were identical by ¹H NMR and TLC analysis and were consistent with that of the desired material. The total yield of C2 was 49.56g (89.1%).
A solution of C2 (456mg, 2.51mmole), tosylmethyl isocyanide (490mg, 2.51mmole) and K₂CO₃ (347mg, 2.51mmole) were dissolved in methanol and heated to reflux for 1.5 hours. The product mixture was then concentrated \textit{in vacuo}, redissolved in CH₂Cl₂, washed with water and brine, dried over Na₂SO₄ and again concentrated \textit{in vacuo}. Purified product C3 was obtained through recrystallization (Et₂O/hexanes) to yield 375mg (68%). The \(^1\)H NMR was consistent with that of the desired structure.

A solution of C3 (4.214g, 19.1mmole) in EtOAc (150mL) was treated with 10%Pd/C (1.05g, 25 wt.% of C3) and subjected to 40psi H₂(g) (Parr Hydrogenation Apparatus) overnight. The reaction mixture was filtered and concentrated \textit{in vacuo}. Pure product C4 was obtained through flash chromatography, eluting with a gradient of 30-40% EtOAc/hexanes, in a yield of 3.4g (93%). The \(^1\)H NMR was consistent with that of the desired structure.

B. Synthesis of Compound I113

A solution of 3-aminobenzylamine (826mg, 6.87mmole) and triethylamine (2.39mL, 17.18mmole) was treated with di-t-butyldicarbonate (1.50g, 6.87mmole) and the mixture was stirred at ambient temperature for 2 hours. The reaction was then diluted with CH₂Cl₂, washed with NaHCO₃(aq), water and brine, dried (Na₂SO₄) and concentrated \textit{in vacuo}. Pure E1 was obtained by flash chromatography, eluting with 25% EtOAc in hexanes in a yield of 200mg (46%). The \(^1\)H NMR was consistent with that of the desired structure.
A solution of C4 (150mg, 0.789mmole) and 1,1-dicarbonylimidazole (160mg, 0.986mole) were combined in THF (5mL) and stirred for 6 hours at ambient temperature. The precipitation of imidazole was noted. To this was then added E1 (351mg, 1.58mmole) and N,N-dimethylaminopyridine (97mg, 0.789mmole) and the mixture was refluxed overnight, resulting in a homogenous solution. Upon cooling to ambient temperature, the reaction was diluted with EtOAc (20mL), washed with KH2SO4(aq), water, and brine, dried (MgSO4) and concentrated. Pure I113 was obtained through flash chromatography, eluting with a gradient of 20-30-35% acetone in hexanes in a yield of 164mg (47%). 1H NMR (500MHz, d6-DMSO) δ 8.90 (s), 8.75 (s), 8.38 (s), 7.60 (d), 7.51 (s), 7.3-7.46 (m), 7.21-7.27 (t), 7.05 (dd), 6.87 (d), 4.12 (d), 3.93 (s), 1.44 (s). Rf 0.21 (5% MeOH/CH2Cl2).

C. Synthesis of Compound I168

A suspension of I113 (250mg, 5.76mmol) in CH2Cl2 (1mL) was treated in a dropwise fashion at ambient temperature with several equivalents of trifluoroacetic acid and stirred for 90min. The resulting solution was stripped in vacuo and titrated with CH2Cl2 and methanol. Pure product I168 was isolated by filtration in a yield of 258mg (99%). The 1H NMR was consistent with that of the desired product.

D. Synthesis of Compound 41

To a room temperature solution of 1-methoxy-2-propanol (75 mg, 832 μmole) in THF (1.0 mL) was added solid 1,1'-carbonyl diimidazole (121 mg, 749 μmole) in one portion. The resulting mixture was stirred at room temperature overnight, then treated sequentially with TEA (174 μL, 1.25 mmole), solid compound I168 (376 mg, 832 μmole), and DMF (1.0 mL). The resulting solution was stirred at room temperature for one day, then diluted with ethyl acetate, washed sequentially with water and brine, dried over MgSO4, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography (silica gel, 97.5/1.5 CH2Cl2). The chromatographed product was then triturated with a 9/1 mixture of ethyl ether/ethyl acetate to give compound 41 (65 mg, 56% yield) as a white, powdery solid. 1H NMR (500 MHz, acetone-d6): 8.34 (s, 1H); 8.21 (s, 1H); 8.12 (s, 1H); 7.67 (s, 1H); 7.65 (d, 1H); 7.50 (d, 1H); 7.47 (d, 1H); 7.43 (s, 1H); 7.25 (dd, 1H); 7.10 (dd, 1H); 6.97 (d, 1H); 6.68 (m, 1H); 4.92 (m, 1H); 4.32 (d, 2H); 4.01 (s, 3H); 3.43 (dd, 1H); 3.33 (dd, 1H); 3.31 (s, 3H); 1.18 (d, 3H).

Other compounds of this invention may be prepared in a similar manner substituting the appropriate alcohol for 1-methoxy-2-propanol [i.e., HO-CH(R1) (R2)] in step C.

EXAMPLE 2

Preparation of Compound 169

A. Preparation of the left hand side coupling intermediate (R10 = cyano):

[0085]
Copper(I)cyanide (7.2 g, 80.8 mmole) was combined with 2-bromo-5-nitroanisole (I) (15 g, 64.6 mmole) in NMP (70 mL) and heated to 150°C overnight under an N₂ atmosphere. The mixture was treated with Celite, cooled to room temperature, then diluted with EtOAc and 1.0 N NaOH and allowed to stir for 15 minutes. The heterogeneous mixture was filtered through a pad of Celite with EtOAc, the phases were separated, and the aqueous phase was washed 3 times with EtOAc. The combined organics were washed sequentially with 1.0 N NaOH, water, and brine, then dried over Na₂SO₄, filtered and concentrated in vacuo.

The crude product was dissolved in CH₂Cl₂, filtered through a short pad of silica gel to remove solids and most colored impurities, then concentrated in vacuo to give II (10.41 g, 90%) as a brownish-orange solid.

1H NMR (500 MHz, CDCl₃): 7.90 (d, 1H); 7.84 (s, 1H); 7.77 (d, 1H); 4.07 (s, 3H).

To a room temperature solution of II (7.2 g, 40.4 mmoles) in EtOAc-EtOH (220-15 mL) was added 10% Pd/C (1.8 g) resulting in a heterogeneous black mixture. The reaction was placed under 1 atmosphere (balloon) of H₂, warmed to 50°C, and stirred overnight. Reaction was cooled to room temperature, the catalyst was removed via filtration, and the filtrate was concentrated in vacuo to give III (5.56 g, 93%) as a crystalline solid. 1H NMR (500 MHz, CDCl₃): 7.29 (d, 1H); 6.22 (d, 1H); 6.17 (s, 1H); 4.20 (broad s, 2H); 3.85 (s, 3H).

To a room temperature, biphasic mixture of phenyl chloroformate (1.6 mL, 12.82 mmoles) in EtOAc (20 mL) and sat. NaHCO₃ (~1M, 16 mL) was added III (950 mg, 6.41 mmoles) as a solution in EtOAc (10 mL) over a 10 minute period. The resulting heterogeneous mixture was stirred at room temperature for 30 minutes and then the phases were separated. The organic phase was washed with brine, dried over Na₂SO₄, filtered through a pad of silica gel with EtOAc, and concentrated in vacuo to give a thick oil. This resulting oil was diluted in toluene (30 mL) and treated with hexanes (30 mL) resulting in a thick precipitate. This mixture was stirred for 30 minutes, filtered, solids washed with 1:1 toluene:hexanes, then hexanes alone, and dried to constant weight under high vacuum to give IV (1.65 g, 96%) as a white powder. 1H NMR (500 MHz, dmso-d6); 10.76 (s, 1H); 7.69 (d, 1H); 7.44 (d, 1H); 7.40 (d, 1H); 7.26 (m, 3H); 7.15 (d, 1H); 3.85 (s, 3H).

B. Preparation of the right hand side coupling intermediate (R9 = S-methyl):

To a room temperature solution of V (200 g, 1.21 moles) in EtOH (2 L) was added NaBH₄ (50.3 g, 1.33 moles) portionwise over 30 minutes, not allowing the internal temperature to rise over 40°C. The reaction was allowed to stir at room temperature for 4 hours. It was then quenched with water (~100 mL), concentrated in vacuo, diluted with EtOAc,
washed twice with water, once with sat. NaHCO₃, dried over MgSO₄, filtered, and concentrated in vacuo to give VI (191.7 g, 95%) as a yellowish power.

1H NMR (500 MHz, CDCl₃): 8.21 (s, 1H); 8.09 (d, 1H); 7.70 (d, 1H); 7.49 (dd, 1H); 5.01 (dd, 1H); 2.45 (s, 1H); 1.52 (d, 3H).

To a room temperature solution of VI (181 g, 1.08 moles) was added DPPA (250 mL, 1.16 moles) at a rate slow enough to keep the reaction temperature under 45°C. Once the addition of DPPA was complete, the mixture was treated with DBU (177 mL, 1.18 moles) at a rate slow enough to keep the reaction temperature under 45°C. Upon complete addition, the reaction was warmed to 60°C and maintained at that temperature overnight. The resulting biphasic mixture was cooled to room temperature, washed sequentially with water, then 0.5 M HCl. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a yellow-green oil that was not purified further.

1H NMR (500 MHz, CDCl₃): 8.21 (s, 1H); 8.18 (d, 1H); 7.68 (d, 1H); 7.56 (q, 1H) ; 4.76 (dd, 1H); 1.59 (d, 3H).

To a room temperature solution of VII (8.17 g, 42.51 mmoles) in THF-water (80 mL-10 mL) was added Ph₃P (12.3 g, 46.76 mmoles) as a solution in THF (20 mL) over a 10 minute period. Nitrogen evolution was immediate and constant throughout the addition. The reaction was then heated to 65°C overnight, then cooled to room temperature. The crude mixture was concentrated in vacuo, diluted with EtOAc, washed with brine, dried over Na₂SO₄, and filtered. The resulting filtrate was treated with 1 N HCl/Et₂O at room temperature over a 10 minute period resulting in precipitate formation. The mixture was stirred at room temperature for 15 minutes, then filtered. The solids were washed with Et₂O to give a yellow powder. The crude amine hydrochloride salt was suspended in brine/EtOAc, and treated with 10 N NaOH (5 mL, 50 mmoles) at room temperature. The resulting mixture was stirred at room temperature until all solids were dissolved. The phases were separated, the aqueous phase was washed with EtOAc twice, the combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude amine was diluted in MeOH (50 mL) and added to a refluxing solution of L-()-tartaric acid (5.33 g, 35.33 mmoles) in MeOH (450 mL). A precipitate formed immediately and was then dissolved in the MeOH mixture upon refluxing for 15 minutes. The internal temperature was lowered to 50°C and maintained there overnight. The internal temperature was then lowered to 30°C and maintained for another 24 hours followed by another 24 hours at room temperature. The resulting crystals (spikes) were filtered, washed with MeOH and Et₂O, and the mother liquor discarded. The resulting crystals were dissolved in 200 mL of refluxing MeOH, cooled slowly as described above, filtered, and washed with MeOH, then Et₂O to give the first crop of VIII (2.21 g, 20%) as a white solid. The mother liquor was concentrated in vacuo, solids dissolved in 50 mL of refluxing MeOH, cooled as above, filtered, and washed with MeOH and Et₂O to give a second crop of VIII (1.50 g, 13%) as a white solid. The optical purity was determined on the corresponding phenyl carbamate of each crop to be >97% ee.

Enantiomeric excesses were determined using a Chiralcel OD column (0.46cmx25cm) made by Daicel Chemical Industries and purchased from Chiral Technologies. The mobile phase employed was a 70:30 hexane:IPA mixture in an isocratic run out to 65 minutes at 0.8 ml/min flow rate using a 3-4 µl injection of a 1-2 mg/ml solution of the phenyl carbamate dissolved in above mentioned hexane:IPA mixture. The desired S-methyl enantiomer elutes first at -47.2 minutes while the undesired R-methyl enantiomer comes off at -51.7 minutes while monitoring at 214, 254, 280nm wavelength.

C. Preparation of Compound 169

To a heterogeneous suspension of VIII (1.11 g, 3.51 mmoles) in EtOAc (20 mL) and brine (20 mL) was added 10 N NaOH (0.77 mL, 7.72 mmoles) at room temperature. The resulting mixture was stirred at room temperature until all salts had dissolved. The phases were then separated, and the aqueous phase washed with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude nitrobenzylamine was diluted in 7M NH₃-MeOH (20 mL), 20% Pd(OH)₂-C added, and placed under 45 psi of H₂ for 5 hours. The resulting mixture was filtered to remove the catalyst, concentrated in vacuo, azeotroped once with CH₂Cl₂, then placed under high vacuum to give IX (455mg, 95%) as a waxy white solid.

1H NMR (500 MHz, dmso-d₆): 6.91 (dd, 1H); 6.56 (s, 1H); 6.50 (d, 1H); 6.38 (d, 1H); 4.90 (broad s, 2H); 3.82 (q, 1H); 3.31 (broad s, 2H); 1.18 (d, 3H).

C. Preparation of Compound 169

All samples were run on a Hewlett Packard Series 1050 HPLC with a diode array detector.

To a heterogeneous suspension of VIII (1.11 g, 3.51 mmoles) in EtOAc (20 mL) and brine (20 mL) was added 10 N NaOH (0.77 mL, 7.72 mmoles) at room temperature. The resulting mixture was stirred at room temperature until all salts had dissolved. The phases were then separated, and the aqueous phase washed with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude nitrobenzylamine was diluted in 7M NH₃-MeOH (20 mL), 20% Pd(OH)₂-C added, and placed under 45 psi of H₂ for 5 hours. The resulting mixture was filtered to remove the catalyst, concentrated in vacuo, azeotroped once with CH₂Cl₂, then placed under high vacuum to give IX (455mg, 95%) as a waxy white solid.
To a room temperature solution of 3-(R)-hydroxy pentanitrile (212 mg, 2.14 mmoles) was added CDI (521 mg, 3.21 mmoles) in one portion. The resulting mixture was stirred at room temperature for 1 hour, then treated with solid silica gel. The heterogeneous mixture was stirred vigorously for 10 minutes, filtered through a short pad of silica gel with 4:1 EtOAc:IPA, concentrated in vacuo, azeotroped twice with MeCN, then combined with IX (350 mg, 2.57 mmoles) in MeCN (2 mL) and stirred at room temperature for 1 day. The resulting mixture was diluted with EtOAc, washed with water and then brine, dried over Na$_2$SO$_4$, filtered, concentrated, and flash chromatographed (silica gel, 1/2?1/3?1/4?0/1 hexanes/EtOAc/IPA) to give X (472 mg, 84%) as a clear, thick oil.

$^1$H NMR (500 MHz, dmso-d$_6$): 7.73 (d, 1H); 6.94 (dd, 1H) ; 6.51 (s, 1H) ; 6.47 (d, 1H); 6.38 (d, 1H); 4.98 (broad s, 2H) ; 4.67 (m, 1H); 4.49 (m, 1H); 2.82 (m, 2H); 1.62 (m, 2H); 1.27 (d, 3H); 0.89 (dd, 3H).

To a room temperature solution of X (470 mg, 1.80 mmoles) in EtOAc (5 mL) was added IV (440 mg, 1.63 mmoles) and TEA (0.23 mL, 1.63 mmoles). The resulting mixture was heated to reflux and stirred at that temperature for 6 hours. The resulting crude mixture was cooled to room temperature, diluted with EtOAc, washed with brine/1N HCl, followed by brine alone, dried over Na$_2$SO$_4$, filtered, concentrated in vacuo, and flash chromatographed (silica gel, 1/1?1/2?1/3?1/4?1 hexanes/EtOAc/IPA) to give 169 (740 mg, 100%) as a white, foamy solid.

$^1$H NMR (500 MHz, dmso-d$_6$): 9.21 (s, 1H); 8.84 (s, 1H); 7.93 (d, 1H); 7.59 (d, 1H); 7.51 (s, 1H); 7.41 (s, 1H); 7.29 (d, 1H); 7.23 (dd, 1H); 7.01 (d, 1H); 6.92 (d, 1H); 4.69 (m, 1H); 4.63 (m, 1H); 3.89 (s, 3H); 2.82 (m, 2H); 2.62 (m, 2H); 1.31 (d, 3H); 0.90 (t, 3H)

**EXAMPLE 3**

IMPDH Activity Inhibition Assay

IMP dehydrogenase activity was assayed following an adaptation of the method first reported by Magasanik. [B. Magasanik et al., J. Biol. Chem., 226, p. 339 (1957), the disclosure of which is herein incorporated by reference]. Enzyme activity was measured spectrophotometrically, by monitoring the increase in absorbance at 340 nm due to the formation of NADH ($^\lambda$340 = 6220 M$^{-1}$ cm$^{-1}$). The reaction mixture contained 0.1 M potassium phosphate 8.0, 0.5 mM EDTA, 2 mM DTT, 200 mM IMP and enzyme (IMPDH human type II) at a concentration of 15 to 50 nM. This solution is incubated at 37°C for 10 minutes. The reaction is started by adding NAD to a final concentration of 200 µM and the initial rate is measured by following the linear increase in absorbance at 340 nm for 10 minutes. For reading in a standard spectrophotometer (path length 1 cm) the final volume in the cuvette is 1.0 ml. The assay has also been adapted to a 96 well microtiter plate format; in this case the concentrations of all the reagents remain the same and the final volume is decreased to 200 µl.

For the analysis of inhibitors, the compound in question is dissolved in DMSO to a final concentration of 20 mM and added to the initial assay mixture for preincubation with the enzyme at a final volume of 2-5% (v/v). The reaction is started by the addition of NAD, and the initial rates measured as above. Ki determinations are made by measuring the initial velocities in the presence of varying amounts of inhibitor and fitting the data using the tight-binding equations of Henderson (Henderson, P. J. F. (1972) Biochem. J. 127, 321).

These results are shown in Table 2. Category "A" indicates a $K_i$ of 10 nM or less, category "B" indicates a $K_i$ of greater than 10 and less than 50 nM, category "C" indicates a $K_i$ of 50 nM or greater, "ND" indicates inhibitory activity was not determined.

**TABLE 2**

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Table 2. IMPDH inhibitory activity.

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[0102] Other compounds of this invention will also have IMPDH inhibitory activity.

EXAMPLE 4

Cellular Assays

A. Isolation of peripheral blood mononuclear cells (PBMCs):

[0103] Human venous blood was drawn from normal healthy volunteers using heparin as an anti-coagulant. PBMCs were isolated from blood by centrifugation over Ficoll-paque gradient or CPT tubes (Becton-Dickinson) using standard conditions. PBMCs were harvested, washed and re-suspended in complete RPMI, counted and diluted to 1x10^6 cells/mL.

B. PBMC and splenocyte proliferation assays:

[0104] 5x10^4 cells (for human PBMC T cells) or 1x10^5 cells (for human PBMC B cells) were added per well of a 96-well plate. For T-cell assays, phyto-hemagglutinin (PHA) was added to a final concentration of 10-20 μg/mL per well for cell. For B-cell assays, Staphylococcal protein A (SPAS) was added to a final concentration of 2 μg/mL per well.

[0105] Serial 4-fold dilutions of inhibitor stocks were made in complete RPMI and added to cells such that the final concentration of compounds ranged from 20 μM to 20 nM, while DMSO was maintained at a final concentration of 0.1%. The cells were then incubated for 3 days. All samples were tested in triplicate. Tritiated thymidine (0.4 μCi/well) was added for the last 24 hours of the assay. The cells were harvested onto Betaplate filters and counted in a scintillation counter. Concentrations of compounds required to inhibit proliferation of cells by 50% (IC50 values) were calculated using the SoftMax Pro™ (Molecular Devices) computer software package.

[0106] The results of these assays are shown in Table 3. Category "A" indicates a IC50 of 100 nM or less, category "B" indicates a IC50 of greater than 100 and less than 1000 nM, category "C" indicates a IC50 of 1000 nM or greater, "ND" indicates inhibitory activity was not determined in the indicated cellular assay.
### Table 3. Cellular Activity

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* *
EXAMPLE 5 Compounds of the invention

Anti-Viral Assays

[0107] The anti-viral efficacy of compounds may be evaluated in various in vitro and in vivo assays. For example, compounds may be tested in in vitro viral replication assays. In vitro assays may employ whole cells or isolated cellular components. In vivo assays include animal models for viral diseases. Examples of such animal models include, but are not limited to, rodent models for HBV or HCV infection, the Woodchuck model for HBV infection, and chimpanzee model for HCV infection.

Claims

1. A compound of formula (IA):
wherein:

one of R₁ or R₂ is selected from hydrogen, ethyl or phenyl; and the other of R₁ or R₂ is selected from -CH₂OH, -CH₂CN, -CH₂CH₂CN or -CH₂N(CH₂CH₃)₂, or R₁ and R₂ are taken together to form a 3-tetrahydrofuranyl ring;

R₉ is selected from (S)-methyl, (S)-ethyl, or (S)-hydroxymethyl;
R₁₀ is selected from -C=N or 5-oxazolyl; and
R₁₁ is selected from halo, -O-(C₁-C₃) straight alkyl, or -O-(C₂-C₃) straight alkenyl or alkynyl.

2. The compound according to claim 1, wherein R₉ is (S)-methyl.
3. The compound according to claim 1, wherein R₁₁ is selected from O-methyl, O-ethyl or O-isopropyl.
4. The compound according to claim 1, wherein said compound is selected from:
5. The compound according to claim 4, wherein said compound is compound 169.

6. A composition comprising a compound according to any of claims 1 to 5 and a pharmaceutically acceptable carrier, adjuvant or vehicle.

7. The composition according to claim 6, further comprising an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, an anti-inflammatory agent, an antifungal agent, an antibiotic, or an anti-vascular hyperproliferation compound.

8. A composition according to claim 6 or 7 for use in treating or preventing an IMPDH-mediated disease or condition in a mammal, wherein such disease or condition is selected from: transplant rejection; graft versus host disease; autoimmune diseases; multiple sclerosis; diabetes mellitus; asthma; osteoarthritis; inflammatory bowel disease; inflammatory diseases; cancer; viral diseases; vascular diseases; fungal infections; bacterial infections; kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, and small bowel transplant rejections; skin allografts; heart valve xenografts; rheumatoid arthritis; juvenile diabetes; asthma; Crohn’s disease; ulcerative colitis; lupus; myasthenia gravis; psoriasis; dermatitis; eczema; seborrhea; pulmonary inflammation; eye uveitis; hepatitis; Grave’s disease; Hashimoto’s thyroiditis; Behcet’s or Sjorgen’s syndrome; pernicious or immunohaemolytic anaemia; idiopathic adrenal insufficiency; polyglandular autoimmune syndrome; glomerulonephritis; scleroderma; lichen planus; vitiligo; autoimmune thyroiditis; alveolitis; acute pancreatitis; chronic pancreatitis; adult respiratory distress syndrome; cancerous tumors; solid tumors; lymphomas; leukemia; restenosis; stenosis; atherosclerosis; DNA virus diseases; retroviral diseases; and herpes.

9. Composition according to claim 8, wherein said IMPDH-mediated disease or condition is selected from transplant rejection, graft versus host disease, or an autoimmune disease.

10. Composition according to claim 8, wherein said pharmaceutical composition further comprises an additional immunosuppressant in a separate dosage form or as part of said composition.

11. Composition according to claim 6 or 7 for use in inhibiting viral replication in a mammal.
12. Composition according to claim 11, wherein said mammal is suffering from a viral infection caused by a virus selected from orthomyxovirus, paramyxovirus, herpesvirus, retrovirus, flavivirus, pestivirus, hepatotropic virus, bunyavirus, Hantaan virus, Caraparu virus, human papilloma virus, encephalitis virus, arena virus, reovirus, vesicular stomatitis virus, rhinovirus, enterovirus, Lassa fever virus, togavirus, poxvirus, adenovirus, rubiola, or rubella.

13. Composition according to claim 11, wherein said pharmaceutical composition further comprises an additional antiviral agent in a separate dosage form or as part of said composition.

14. A composition according to claim 6 or 7 for use in inhibiting vascular cellular hyperproliferation in a mammal.

15. Composition according to claim 14, wherein said pharmaceutical composition is useful for treating or preventing restenosis, stenosis, artherosclerosis or other hyperproliferative vascular disease.

16. Composition according to claim 14, wherein said pharmaceutical composition further comprises an additional anti-vascular hyperproliferative agent in a separate dosage form or as part of said composition.

17. A composition according to claim 6 or 7 for use in inhibiting tumors and cancer in a mammal.

18. Composition according to claim 17, wherein said pharmaceutical composition is useful for treating or preventing lymphoma, leukemia and other forms of cancer.

19. Composition according to claim 18, wherein said pharmaceutical composition further comprises an additional antitumor or anti-cancer agent in a separate dosage form or as part of said composition.

20. A composition according to claim 6 or 7 for use in inhibiting inflammation or an inflammatory disease in a mammal.

21. Composition according to claim 20, wherein said pharmaceutical composition is useful for treating or preventing osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma or adult respiratory distress syndrome.

22. Composition according to claim 21, wherein said pharmaceutical composition further comprises an additional anti-inflammatory agent in a separate dosage form or as part of said composition.

23. A compound of formula 181:

\[
\text{181}
\]

24. A composition comprising a compound according to claim 23 for use in an amount effective to inhibit IMPDH and a pharmaceutically acceptable carrier, adjuvant or vehicle.

25. The composition according to claim 24, further comprising an additional agent selected from an immunosuppressant, an anti-cancer agent, an anti-viral agent, an anti-inflammatory agent, an antifungal agent, an antibiotic, or an anti-vascular hyperproliferation compound.

26. A composition according to claim 24 or 25 for use in treating or preventing an IMPDH-mediated disease or condition in a mammal, wherein such disease or condition is selected from: transplant rejection; graft versus host disease; autoimmune diseases; multiple sclerosis; diabetes mellitus; asthma; osteoarthritis; inflammatory bowel disease; inflammatory diseases; cancer; viral diseases; vascular diseases; fungal infections; bacterial infections; kidney, liver, heart, lung, pancreas (islet cells), bone marrow, cornea, and small bowel transplant rejections; skin allografts; heart valve xenografts; rheumatoid arthritis; juvenile diabetes; asthma; Crohn’s disease; ulcerative colitis; lupus; myasthenia gravis; psoriasis; dermatitis; ecze-
27. Composition according to claim 26, wherein said IMPDH-mediated disease or condition is selected from transplant rejection, graft versus host disease, or an autoimmune disease.

28. Composition according to claim 26, wherein said composition further comprises an additional immunosuppressant in a separate dosage form or as part of said composition.

29. A composition according to claim 24 or 25 for use in inhibiting viral replication in a mammal.

30. Composition according to claim 29, wherein said mammal is suffering from a viral infection caused by a virus selected from orthomyxovirus, paramyxovirus, herpesvirus, retrovirus, flavivirus, pestivirus, hepatotropic virus, bunyavirus, Hantaan virus, Caraparu virus, human papilloma virus, encephalitis virus, arena virus, reovirus, vesicular stomatitis virus, rhinovirus, enterovirus, Lassa fever virus, togavirus, poxvirus, adenovirus, rubiola, or rubella.

31. Composition according to claim 29, wherein said pharmaceutical composition further comprises an additional antiviral agent in a separate dosage form or as part of said composition.

32. Composition according to claim 24 or 25 for use in inhibiting vascular cellular hyperproliferation in a mammal.

33. Composition according to claim 32, wherein said pharmaceutical composition is useful for treating restenosis, stenosis, atherosclerosis or other hyperproliferative vascular disease.

34. Composition according to claim 32, wherein said pharmaceutical composition further comprises an additional anti-vascular hyperproliferative agent in a separate dosage form or as part of said composition.

35. A composition according to claim 24 or 25 for use in inhibiting tumors and cancer in a mammal.

36. Composition according to claim 35, wherein said pharmaceutical composition is useful for treating lymphoma, leukemia and other forms of cancer.

37. Composition according to claim 36, wherein said pharmaceutical composition further comprises an additional antitumor or anti-cancer agent in a separate dosage form or as part of said composition.

38. A composition according to claim 24 or 25 for use in inhibiting inflammation or an inflammatory disease in a mammal.

39. Composition according to claim 38, wherein said pharmaceutical composition is useful for treating osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma or adult respiratory distress syndrome.

40. Composition according to claim 39, wherein said pharmaceutical composition further comprises an additional anti-inflammatory agent in a separate dosage form or as part of said composition.

Patentansprüche

1. Verbindung der Formel (IA):
wobei:

einer der Reste $R_1$ oder $R_2$ ausgewählt ist aus Wasserstoff, Ethyl oder Phenyl; und der andere der Reste $R_1$ oder $R_2$ ausgewählt ist aus $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}_2\text{CN}$ oder $-\text{CH}_2\text{N(}\text{CH}_2\text{CH}_3\text{)}_2$, oder $R_1$ und $R_2$ zusammen genommen einen 3-Tetrahydrofuranrylring bilden;

$R_9$ ausgewählt ist aus (S)-Methyl, (S)-Ethyl oder (S)-Hydroxymethyl;

$R_{10}$ ausgewählt ist aus $-\text{C}=\text{N}$ oder 5-Oxazolyl; und

$R_{11}$ ausgewählt ist aus Halogen, geradkettigem $-\text{O-}(\text{C}_1\text{-C}_3)$-Alkyl oder geradkettigem $-\text{O-}(\text{C}_2\text{-C}_3)$-Alkenyl oder -Alkinyl.

2. Verbindung gemäß Anspruch 1, wobei $R_9$ (S)-Methyl ist.

3. Verbindung gemäß Anspruch 1, wobei $R_{11}$ aus O-Methyl, O-Ethyl oder O-Isopropyl ausgewählt ist.

4. Verbindung gemäß Anspruch 1, wobei die Verbindung ausgewählt ist aus:

\[162\]

\[164\]
5. Verbindung gemäß Anspruch 4, wobei die Verbindung Verbindung 169 ist.

6. Zusammensetzung, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 5 und ein(en) pharmazeutisch verträglichen(s) Träger, Adjuvans oder Vehikel.

7. Zusammensetzung gemäß Anspruch 6, weiterhin umfassend ein zusätzliches Mittel, ausgewählt aus einem Im-
munsupressivum, einem Anti-Krebsmittel, einem antiviralen Mittel, einem entzündungshemmenden Mittel, einem Antimykotikum, einem Antibiotikum oder einer Verbindung gegen vaskuläre Hyperproliferation.

8. Zusammensetzung gemäß Anspruch 6 oder 7 zur Verwendung in der Behandlung oder Vorbeugung einer/eines durch IMPDH vermittelten Erkrankung oder Zustandes in einem Säuger, wobei diese Erkrankung oder dieser Zustand ausgewählt ist aus: Transplantatabstoßung; Graft-versus-Host-Reaktion; Autoimmune Erkrankungen; multipler Sklerose; Diabetes mellitus; Asthma: Osteoarthritis; chronisch-entzündlicher Darmerkrankung; entzündlichen Erkrankungen; Krebs; viralen Erkrankungen; vaskulären Erkrankungen; Pilzinfektionen; bakteriellen Infektionen; Nieren-, Leber-, Herz-, Lungen-, (Inselzellen des) Pankreas-, Knochenmarks-, Kornea- und Dünn darmtransplantatabstoßungen; allogenen Hauttransplantaten; Herzklappenerthrotrotransplantaten; rheumatoider Arthritis; juvenilem Diabetes; Asthma; Morbus Crohn; Collitis ulcerosa; Lupus; Myasthenia gravis; Psoriasis; Dermatitis; Ekzem; Seborrhö; entzündlichen Lungeneränderungen; Augenveränderungen; Hepatitis; Morbus Basedow; Hashimoto-Thyroiditis; Behcet- oder Sjögren-Syndrom; pemizöser oder immunohämolytischer Anämie; idipathischer Nebenniereninsuffizienz; polyglandulärem Autoimmunsyndrom; Glomerulonephritis; Sclerodermie; Lichen planus; Vitiligo; Autoimmun-Thyroiditis; Alveolitis; akuter Pankreatitis; chronischer Pankreatitis; respiratorischem Belastungssyndrom bei Erwachsenen; cancerösen Tumoren; soliden Tumoren; Lymphomen; Leukämie; Restenose; Senose; Atherosklerose; DNA-Virus-erkrankungen; retroviralen Erkrankungen; und Herpes.


10. Zusammensetzung gemäß Anspruch 8, wobei die pharmazeutische Zusammensetzung weiterhin ein zusätzliches Immunsuppressivum in einer separaten Darreichungsform oder als Teil der Zusammensetzung umfasst.


22. Zusammensetzung gemäß Anspruch 21, wobei die pharmazeutische Zusammensetzung weiterhin ein zusätzliches entzündungshemmendes Mittel in einer separaten Darreichungsform oder als Teil der Zusammensetzung umfasst.

23. Verbindung der Formel 181:

24. Zusammensetzung, umfassend eine Verbindung gemäß Anspruch 23 zur Verwendung in einer Menge, welche wirksam ist, um IMPDH zu hemmen, und ein(en) pharmazeutisch verträglichem(s) Träger, Adjuvans oder Vehikel.


26. Zusammensetzung gemäß Anspruch 24 oder 25 zur Verwendung in der Behandlung oder Vorbeugung einer/eines durch IMPDH vermittelten Erkrankung oder Zustandes in einem Säuger, wobei diese Erkrankung oder dieser Zustand ausgewählt ist aus: Transplantatabstoßung; Graft-versus-Host-Reaktion; Autoimmunerkrankungen; multipler Sklerose; Diabetes mellitus; Asthma; Osteoarthritis; chronisch-entzündlicher Darmerkrankung; entzündlichen Erkrankungen; Krebs; viralen Erkrankungen; vaskulären Erkrankungen; Pilzinfektionen; bakteriellen Infektionen; Nieren-, Leber-, Herz-, Lungen-, (Inselzellen des) Pankreas-, Knochenmarks-, Koma- und Dünndarmtransplantatabstoßungen; allogenen Hauttransplantaten; Herzklappenheterotransplantaten; rheumatoide Arthritis; juvenillem Diabetes; Asthma; Morbus Crohn; Collitis ulcerosa; Lupus; Myasthenia gravis; Psoriasis; Dermatitis; Ekzem; Seborrhö; entzündlicher Lungenveränderung; Augenuveritis; Hepatitis; Morbus Basedow; Hashimoto-Thyroiditis; Behcet- oder Sjögren-Syndrom; perniziöser oder immunhämatolischer Anämie; idiopathischer Nebenniereninsuffizienz; polyglandulärem Autoimmunsyndrom; Glomerulonephritis; Sclerodermie; Lichen planus; Vögel; Autoimmun-Thyroiditis; Alveolitis; akuter Pankreatitis; chronischer Pankreatitis; respiratorischem Belastungs syndrom bei Erwachsenen; cancerösen Tumoren; soliden Tumoren; Lymphomen; Leukämie; Restenose; Stenose; Atherosklerose; Virus- oder bakteriellen Erkrankungen; und Herpes.

27. Zusammensetzung gemäß Anspruch 26, wobei die durch IMPDH vermittelte Erkrankung oder der Zustand ausgewählt ist aus Transplantatabstoßung, Graft-versus-Host-Reaktion oder einer Autoimmunkrankheit.

28. Zusammensetzung gemäß Anspruch 26, wobei die Zusammensetzung weiterhin ein zusätzliches Immunsuppressivum in einer separaten Darreichungsform oder als Teil der Zusammensetzung umfasst.


34. Zusammensetzung gemäß Anspruch 32, wobei die pharmazeutische Zusammensetzung weiterhin ein zusätzliches Mittel gegen vaskuläre Hyperproliferation in einer separaten Darreichungsform oder als Teil der Zusammensetzung umfasst.


37. Zusammensetzung gemäß Anspruch 36, wobei die pharmazeutische Zusammensetzung weiterhin ein zusätzliches Antitumor- oder Antikrebsmittel in einer separaten Darreichungsform oder als Teil der Zusammensetzung umfasst.


40. Zusammensetzung gemäß Anspruch 39, wobei die pharmazeutische Zusammensetzung weiterhin ein zusätzliches entzündungshemmendes Mittel in einer separaten Darreichungsform oder als Teil der Zusammensetzung umfasst.

Revendications

1. Composé de formule (IA) :

\[ \text{(IA)}; \]

dans laquelle :

- l’un de \( R_1 \) ou \( R_2 \) est choisi parmi un atome d’hydrogène, un groupe éthyle ou phényle ;
- et l’autre de \( R_1 \) ou \( R_2 \) est choisi parmi un groupe \(-\text{CH}_2\text{OH}, \text{-CH}_2\text{CN}, \text{-CH}_2\text{CH}_2\text{CN} \) ou \( \text{-CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2 \), ou \( R_1 \) et \( R_2 \) pris ensemble forment un cycle 3-tétrahydrofuranyle ;
- \( R_9 \) est choisi parmi un groupe (S)-méthyle, (S)-éthyle ou (S)-hydroxyméthyle ;
- \( R_{10} \) est choisi parmi un groupe -C=N ou 5-oxazolyle ; et
- \( R_{11} \) est choisi parmi un atome d’halogène, un groupe -O-alkyle en C\(_1\)-C\(_3\) linéaire ou un groupe -O-alcényle ou alcynyle en C\(_2\)-C\(_3\) linéaire.
2. Composé selon la revendication 1, dans lequel $R_9$ est un groupe (S)-méthyle.

3. Composé selon la revendication 1, dans lequel $R_{11}$ est un groupe O-méthyle, O-éthyle ou O-isopropyly.

4. Composé selon la revendication 1, ledit composé étant choisi parmi :
5. Composé selon la revendication 4, ledit composé étant le composé 169.

6. Composition comprenant un composé selon l’une quelconque des revendications 1 à 5 et un excipient, un adjuvant ou un véhicule pharmaceutiquement acceptable.

7. Composition selon la revendication 6, comprenant en outre un agent supplémentaire choisi parmi un immunosuppresseur, un agent anticancéreux, un agent antiviral, un agent anti-inflammatoire, un agent antifongique, un antibiotique ou un composé antihyperprolifération vasculaire.

8. Composition selon la revendication 6 ou 7, pour une utilisation dans le traitement ou la prévention d’une maladie ou d’une pathologie médieée par l’IMPDH chez un mammifère, dans laquelle une telle maladie ou pathologie est choisie parmi : le rejet de greffe ; la maladie du greffon contre l’hôte ; les maladies auto-immunes ; la sclérose en plaques ; le diabète ; l’asthme ; l’arthrose ; la maladie intestinale inflammatoire ; les maladies inflammatoires ; le cancer ; les maladies virales ; les maladies vasculaires ; les infections fongiques ; les infections bactériennes ; les rejets de greffe du foie, du rein, du coeur, du poumon, du pancréas (cellules des îlots pancréatiques), de la moelle osseuse, de la corne et de l’intestin grêle ; les allogreffes de peau ; les xénogreffes de valvule cardiaque ; la polyarthrite rhumatoïde ; le diabète juvénile ; l’asthme ; la maladie de Crohn ; la rectocolite hémorragique ; le lupus ; la myasthénie grave ; le psoriasis ; la dermatite ; l’eczéma ; la séborrhée ; l’inflammation pulmonaire ; l’uvéite oculaire ; l’hépatite ; la maladie de Grave ; la thyroïdite de Hashimoto ; le syndrome de Behcet ou Sjorgen ; l’anémie pernicieuse ou hémolytique auto-immune ; l’insuffisance surnéale idiopathique ; le syndrome polyglandulaire auto-immun ; la glomérulonéphrite ; la sclérodermie ; le lichen plan ; le vitiligo ; la thyréodystrophie ; l’alvéole ; la pancréatite aiguë ; la pancréatite chronique ; le syndrome de détresse respiratoire chez l’adulte ; les tumeurs cancéreuses ; les tumeurs solides ; les lymphomes ; la leucémie ; la resténose ; la sténose ; l’athérosclérose ; les maladies causées par des virus à ADN ; les maladies rétroviraux ; et l’herpès.

9. Composition selon la revendication 8, dans laquelle ladite maladie ou pathologie médieée par l’IMPDH est choisie parmi le rejet de greffe, la maladie du greffon contre l’hôte, ou une maladie auto-immune.

10. Composition selon la revendication 8, ladite composition pharmaceutique comprenant en outre un immunosuppresseur supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

11. Composition selon la revendication 6 ou 7, pour une utilisation pour inhiber une réplication virale chez un mammifère.

12. Composition selon la revendication 11, dans laquelle ledit mammifère souffre d’une infection virale provoquée par un virus choisi parmi l’orthomyxovirus, le paramyxovirus, le virus de l’herpès, le rétrovirus, le flavivirus, le pestivirus, le virus hépatotrophique, le bunyavirus, le virus Hantaan, le virus Caraparu, le papillomavirus humain, le virus encéphalitique, l’arénavirus, le réovirus, le virus vésiculaire stomatique, le rhinovirus, l’entérovirus, le virus de la fièvre de Lassa, le togavirus, le poxvirus, l’adénovirus, la rougeole ou la rubéole.

13. Composition selon la revendication 11, ladite composition pharmaceutique comprenant en outre un agent antiviral supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.
14. Composition selon la revendication 6 ou 7, pour une utilisation pour inhiber l'hyperprolifération cellulaire vasculaire chez un mammifère.

15. Composition selon la revendication 14, ladite composition pharmaceutique étant utile pour le traitement ou la prévention de la resténose, de la sténose, de l'athérosclérose ou d'une autre maladie vasculaire hyperproliférative.

16. Composition selon la revendication 14, ladite composition pharmaceutique comprenant en outre un agent antihyperprolifération vasculaire supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

17. Composition selon la revendication 6 ou 7 pour une utilisation pour inhiber des tumeurs et un cancer chez un mammifère.

18. Composition selon la revendication 17, ladite composition pharmaceutique étant utile pour le traitement ou la prévention d'un lymphome, d'une leucémie ou d'autres formes de cancer.

19. Composition selon la revendication 18, ladite composition pharmaceutique comprenant en outre un agent antitumoral ou anticancéreux supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

20. Composition selon la revendication 6 ou 7 pour une utilisation pour inhiber une inflammation ou une maladie inflammatoire chez un mammifère.

21. Composition selon la revendication 20, ladite composition pharmaceutique étant utile pour le traitement ou la prévention de l'arthrose, de la pancréatite aiguë, de la pancréatite chronique, de l'asthme ou du syndrome de détresse respiratoire chez l'adulte.

22. Composition selon la revendication 21, ladite composition pharmaceutique comprenant en outre un agent anti-inflammatoire supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

23. Composé de formule (181):

24. Composition comprenant un composé selon la revendication 23 pour une utilisation en une quantité efficace pour inhiber l'IMPDH et un excipient, un adjuvant ou un véhicule pharmaceutiquement acceptable.

25. Composition selon la revendication 24, comprenant en outre un agent supplémentaire choisi parmi un immunosuppresseur, un agent anticancéreux, un agent antiviral, un agent anti-inflammatoire, un agent antifongique, un antibiotique ou un composé antihyperprolifération vasculaire.

26. Composition selon la revendication 24 ou 25 pour une utilisation dans le traitement ou la prévention d'une maladie ou d'une pathologie médiee par l'IMPDH chez un mammifère, dans laquelle une telle maladie ou pathologie est choisie parmi : le rejet de greffe ; la maladie du greffon contre l'hôte ; les maladies auto-immunes ; la sclérose en plaques ; le diabète ; l'arthrose ; la maladie intestinale inflammatoire ; les maladies inflammatoires ; le cancer ; les maladies virales ; les maladies vasculaires ; les infections fongiques ; les infections bactériennes ; les rejets de greffe du foie, du rein, du coeur, du poumon, du pancréas (cellules des îlots pancréatiques), de la moelle osseuse, de la cornée et de l'intestin grêle ; les allogreffes de peau ; les xénogreffes de valvule cardiaque ; la polyarthrite rhumatoïde ; le diabète juvénile ; l'asthme ; la maladie de Crohn ; la rectocolite hémorragique ; le lupus ; la myasthénie grave ; le psoriasis ; la dermatite ; l'eczéma ; la séborrhée ; l'inflammation pulmonaire ; l'uvéite oculaire ; l'hépatite ; la maladie de Grave ; la thyroïdite de Hashimoto ; le syndrome de Behcet ou Sjorgen ; l'anémie
pernicieuse ou hémolytique auto-immune ; l'insuffisance surrénale idiopathique ; le syndrome polyglandulaire auto-immun ; la gloméronéphrite ; la sclérodermie ; le lichen plan ; le vitiligo ; la thyroïdite auto-immune ; l'algéoolite ; la pancréatite aiguë ; la pancréatite chronique ; le syndrome de détresse respiratoire chez l'adulte ; les tumeurs cancéreuses ; les tumeurs solides ; les lymphomes ; la leucémie ; la resténose ; la sténose ; l'athérosclérose ; les maladies causées par des virus à ADN ; les maladies rétrovirales ; et l'hérpès.

27. Composition selon la revendication 26, dans laquelle ladite maladie ou pathologie médie par l'IMPDH est choisie parmi le rejet de greffe, la maladie du greffon contre l'hôte, ou une maladie auto-immune.

28. Composition selon la revendication 26, ladite composition pharmaceutique comprenant en outre un immunosuppresseur supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

29. Composition selon la revendication 24 ou 25, pour une utilisation pour inhiber une réplication virale chez un mammifère.

30. Composition selon la revendication 29, dans laquelle le dit mammifère souffre d’une infection virale provoquée par un virus choisi parmi l’orthomyxovirus, le paramyxovirus, le virus de l’herpès, le rétrovirus, le flavivirus, le pestivirus, le virus hépatotrophique, le bunyavirus, le virus Hantaan, le virus Caraparu, le papillomavirus humain, le virus encéphalitique, l’arénavirus, le réovirus, le virus vésiculaire stomatique, le rhinovirus, l’entérovirus, le virus de la fièvre de Lassa, le togavirus, le poxvirus, l’adénovirus, la rougeole ou la rubéole.

31. Composition selon la revendication 29, ladite composition pharmaceutique comprenant en outre un agent antiviral supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

32. Composition selon la revendication 24 ou 25, pour une utilisation pour inhiber l’hyperprolifération cellulaire vasculaire chez un mammifère.

33. Composition selon la revendication 32, ladite composition pharmaceutique étant utile pour le traitement de la resténose, de la sténose, de l’athérosclérose ou d’une autre maladie vasculaire hyperproliférative.

34. Composition selon la revendication 32, ladite composition pharmaceutique comprenant en outre un agent antihyperprolifération vasculaire supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

35. Composition selon la revendication 24 ou 25 pour une utilisation pour inhiber des tumeurs et un cancer chez un mammifère.

36. Composition selon la revendication 35, ladite composition pharmaceutique étant utile pour le traitement d’un lymphome, d’une leucémie ou d’autres formes de cancer.

37. Composition selon la revendication 36, ladite composition pharmaceutique comprenant en outre un agent antitumoral ou anticancéreux supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.

38. Composition selon la revendication 24 ou 25 pour une utilisation pour inhiber une inflammation ou une maladie inflammatoire chez un mammifère.


40. Composition selon la revendication 39, ladite composition pharmaceutique comprenant en outre un agent anti-inflammatoire supplémentaire sous une forme posologique séparée ou faisant partie de ladite composition.
REFERENCES CITED IN THE DESCRIPTION

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