Oversættelse af europæisk patentskift

Patent- og Varemærkesstyrelsen

Int.Cl.: C07C219/08 (2006.01) A61K31/221 (2006.01) C07C229/12 (2006.01)
         C07C229/16 (2006.01) C07C309/18 (2006.01)

Oversættelsen bekendtgjort den: 2018-08-20

Dato for Den Europæiske Patentmyndighedens bekendtgørelse om meddelelse af patentet: 2018-06-06

Europæisk ansøgning nr.: 14767892.4

Europæisk indleveringsdag: 2014-03-14

Den europeiske ansøgningspubliceringsdag: 2016-01-20

International ansøgning nr.: US2014027401

International publikationsnr.: WO2014152494


Designerede stater: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LT LU LV
MC MK MT NL NO PL PT RO RS SE SI SK SM TR

Patenthaver: Alkermes Pharma Ireland Limited, Connaught House, 1 Burlington Road, Dublin 4, Irland

Opfinder: ZEIDAN, Tarek, A., 296 Lexington Street, Watertown, MA 02472, USA
          DUNCAN, Scott, 4 Wayte Road, Bedford, MA 01730, USA
          HENCKEN, Christopher, P., 36 Dwinell Street, Boston, MA 02132, USA
          WYNN, Thomas, Andrew, 94 North Street, Lexington, MA 02420, USA
          SANRAME, Carlos, N., 9 Rumford Road, Lexington, MA 02420, USA

Fuldmaægig i Danmark: Plougmann Vingtoft A/S, Rued Langgaards Vej 8, 2300 København S, Danmark

Benævnelse: PRO-DRUGS AF FUMARATER OG DERES ANVENDELSE I BEHANDLING AF FORSKELLIGE SYGDOMME

Fremdragne publikationer:
WO-A1-2011/085211
WO-A1-2013/119791
WO-A1-2013/181451
WO-A2-2010/022177
DESCRIPTION

RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] The present invention relates to various prodrugs of monomethyl fumarate as defined in the claims. In particular, the present invention relates to derivatives of monomethyl fumarate as defined in the claims which offer improved properties relative to dimethyl fumarate. The invention also relates to the use of said compounds in methods of treating various diseases.

BACKGROUND OF THE INVENTION

and ulcerative colitis; arthritis; and others (Nilsson et al., WO 2006/037342 and Nilsson and Muller, WO 2007/042034).

[0004] Fumaderm®, an enteric coated tablet containing a salt mixture of monoethyl fumarate and dimethyl fumarate (DMF) which is rapidly hydrolyzed to monomethyl fumarate, regarded as the main bioactive metabolite, was approved in Germany in 1994 for the treatment of psoriasis. Fumaderm® is dosed TID with 1-2 grams/day administered for the treatment of psoriasis. Fumaderm® exhibits a high degree of interpatient variability with respect to drug absorption and food strongly reduces bioavailability. Absorption is thought to occur in the small intestine with peak levels achieved 5-6 hours after oral administration. Significant side effects occur in 70-90% of patients (Brewer and Rogers, Clin Expt'l Dermatology 2007, 32, 246-49; and Hoefnagel et al., Br J Dermatology 2003, 149, 363-369). Side effects of current FAE therapy include gastrointestinal upset including nausea, vomiting, diarrhea and/or transient flushing of the skin.

[0005] Multiple sclerosis (MS) is an autoimmune disease with the autoimmune activity directed against central nervous system (CNS) antigens. The disease is characterized by inflammation in parts of the CNS, leading to the loss of the myelin sheathing around neuronal axons (gradual demyelination), axonal loss, and the eventual death of neurons, oligodendrocytes and glial cells.

[0006] Dimethyl fumarate (DMF) is the active component of the experimental therapeutic, BG-12, studied for the treatment of relapsing-remitting MS (RRMS). In a Phase IIb RRMS study, BG-12 significantly reduced gadolinium-enhancing brain lesions. In preclinical studies, DMF administration has been shown to inhibit CNS inflammation in murine and rat EAE. It has also been found that DMF can inhibit astrogliosis and microglial activations associated with EAE. See, e.g., US Published Application No. 2012/0165404.

[0007] There are four major clinical types of MS: 1) relapsing-remitting MS (RRMS), characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression; 2) secondary progressive MS (SPMS), characterized by initial relapsing remitting course followed by progression with or without occasional relapses, minor remissions, and plateaus; 3) primary progressive MS (PPMS), characterized by disease progression from onset with occasional plateaus and temporary minor improvements allowed; and 4) progressive relapsing MS (PRMS), characterized by progressive disease onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression.

[0008] Clinically, the illness most often presents as a relapsing-remitting disease and, to a lesser extent, as steady progression of neurological disability. Relapsing-remitting MS (RRMS) presents in the form of recurrent attacks of focal or multifocal neurologic dysfunction. Attacks may occur, remit, and recur, seemingly randomly over many years. Remission is often incomplete and as one attack follows another, a stepwise downward progression ensues with
increasing permanent neurological deficit. The usual course of RRMS is characterized by repeated relapses associated, for the majority of patients, with the eventual onset of disease progression. The subsequent course of the disease is unpredictable, although most patients with a relapsing-remitting disease will eventually develop secondary progressive disease. In the relapsing-remitting phase, relapses alternate with periods of clinical inactivity and may or may not be marked by sequelae depending on the presence of neurological deficits between episodes. Periods between relapses during the relapsing-remitting phase are clinically stable. On the other hand, patients with progressive MS exhibit a steady increase in deficits, as defined above and either from onset or after a period of episodes, but this designation does not preclude the further occurrence of new relapses.

[0009] Notwithstanding the above, dimethyl fumarate is also associated with significant drawbacks.

[0010] For example, dimethyl fumarate is known to cause side effects upon oral administration, such as flushing and gastrointestinal events including, nausea, diarrhea, and/or upper abdominal pain in subjects. See, e.g., Gold et al., N. Eng. J. Med, 2012, 367(12), 1098-1107. Dimethyl fumarate is dosed BID or TID with a total daily dose of about 480 mg to about 1 gram or more. Further, in the use of a drug for long-term therapy it is desirable that the drug be formulated so that it is suitable for once- or twice-daily administration to aid patient compliance. A dosing frequency of once-daily or less is even more desirable.

[0011] Another problem with long-term therapy is the requirement of determining an optimum dose which can be tolerated by the patient. If such a dose is not determined this can lead to a diminution in the effectiveness of the drug being administered.

[0012] Accordingly, it is an object of the present invention to provide compounds and/or compositions which are suitable for long-term administration.

[0013] It is a further object of the present invention to provide the use of a pharmaceutical active agent in a manner which enables one to achieve a tolerable steady state level for the drug in a subject being treated therewith.

[0014] Because of the disadvantages of dimethyl fumarate described above, there continues to be a need to decrease the dosing frequency, reduce side-effects and/or improve the physicochemical properties associated with DMF. There remains, therefore, a real need in the treatment of neurological diseases, such as MS, for a product which retains the pharmacological advantages of DMF but overcomes its flaws in formulation and/or adverse effects upon administration. The present invention addresses these needs.

BRIEF DESCRIPTION OF THE DRAWINGS
[0015]

Figure 1 depicts the hydrolysis of Compound 16 at pH 7.9, 25°C, showing vinylic region, as observed by NMR over 90 minutes.

Figure 2 depicts the hydrolysis of Compound 16 at pH 7.9, 25°C, showing vinylic region, as observed by NMR over 19 hours.

Figure 3 depicts the hydrolysis of Compound 16 at pH 7.9, 25°C, showing aliphatic region, as observed by NMR over 19 hours.

Figure 4 depicts the hydrolysis of Reference Compound A at pH 7.9, 37°C, showing vinylic region, as observed by NMR over 15 hours.

Figure 5 depicts the hydrolysis of Reference Compound A at pH 7.9, 37°C, showing aliphatic region, as observed by NMR over 15 hours.

Figure 6 depicts a plot of weight loss vs time for Compound 14 and DMF.

Figure 7 depicts the unit cell for crystalline Compound 14.

SUMMARY OF THE INVENTION

[0016] This invention is directed to the surprising and unexpected discovery of novel prodrugs and related methods useful in the treatment of neurological diseases. The methods and compositions described herein comprise one or more prodrugs (e.g., aminoalkyl prodrugs) of monomethyl fumarate (MMF). The methods and compositions provide for a therapeutically effective amount of an active moiety in a subject for a time period of at least about 8 hours to at least about 24 hours.

[0017] More specifically, the compounds of the invention can be converted in vivo, upon oral administration, to monomethyl fumarate. Upon conversion, the active moiety (i.e., monomethyl fumarate) is effective in treating subjects suffering from a neurological disease.

[0018] The present invention refers to the use of the compounds as defined in the claims in methods of treating a neurological disease by administering to a subject in need thereof, a therapeutically effective amount of said compound, such that the disease is treated.

[0019] The present invention also refers to the use of the compounds as defined in the claims in methods of treating multiple sclerosis by administering to a subject in need thereof, a therapeutically effective amount of said compound, such that the multiple sclerosis is treated.

[0020] The present invention also refers to the use of the compounds as defined in the claims
in methods of treating relapsing-remitting multiple sclerosis (RRMS) by administering to a subject in need thereof, a therapeutically effective amount of said compound of the formula described herein, or a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof, such that the multiple sclerosis is treated.

[0021] The present invention also provides the compounds as defined in the claims for use in methods of treating secondary progressive multiple sclerosis (SPMS) by administering to a subject in need thereof, a therapeutically effective amount of a compound of the formula described herein, or a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof, such that the multiple sclerosis is treated.

[0022] The present invention also provides methods of treating primary progressive multiple sclerosis (PPMS) by administering to a subject in need thereof, a therapeutically effective amount of a compound of the formula described herein, or a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof, such that the multiple sclerosis is treated. The present invention also provides methods of treating progressive relapsing multiple sclerosis (PRMS) by administering to a subject in need thereof, a therapeutically effective amount of a compound of the formula described herein, or a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof, such that the multiple sclerosis is treated.

[0023] The present invention also provides methods of treating Alzheimer’s disease by administering to a subject in need thereof, a therapeutically effective amount of a compound of the formula described herein, or a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof, such that the Alzheimer’s disease is treated.

[0024] The present invention also provides methods of treating cerebral palsy by administering to a subject in need thereof, a therapeutically effective amount of a compound of the formula described herein, or a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof, such that the cerebral palsy is treated.

[0025] The present invention also provides compounds and compositions that enable improved oral, controlled- or sustained-release formulations. Specifically, dimethyl fumarate is administered twice or three times daily for the treatment of relapsing-remitting multiple sclerosis. In contrast, the compounds and compositions of the present invention may enable formulations with a modified duration of therapeutic efficacy for reducing relapse rates in subjects with multiple sclerosis. For example, the present compounds and compositions provide therapeutically effective amounts of monomethyl fumarate in subjects for at least about 8 hours, at least about 12 hours, at least about 16 hours, at least about 20 hours or at least about 24 hours.

[0026] The present invention also provides compounds, compositions and methods which may result in decreased side effects upon administration to a subject relative to dimethyl fumarate. For example, gastric irritation and flushing are known side effects of oral administration of dimethyl fumarate in some subjects. The compounds, compositions and
methods of the present invention can be utilized in subjects that have experienced or are at risk of developing such side effects.

[0027] The present invention also provides for compounds and compositions which exhibit improved physical stability relative to dimethyl fumarate. Specifically, dimethyl fumarate is known in the art to undergo sublimation at ambient and elevated temperature conditions. The compounds of the invention possess greater physical stability than dimethyl fumarate under controlled conditions of temperature and relative humidity. Specifically, in one embodiment, the compounds of the formula described herein exhibit decreased sublimation relative to dimethyl fumarate.

[0028] Further, dimethyl fumarate is also known to be a contact irritant. See e.g., Material Safety Data Sheet for DMF. In one embodiment, the compounds of the present invention exhibit reduced contact irritation relative to dimethyl fumarate. For example, the compounds of the formula described herein exhibit reduced contact irritation relative to dimethyl fumarate.

[0029] The present invention also provides for compounds and compositions which exhibit decreased food effect relative to dimethyl fumarate. The bioavailability of dimethyl fumarate is known in the art to be reduced when administered with food. Specifically, in one embodiment, the compounds of the formula described herein exhibit decreased food effect relative to dimethyl fumarate.

[0030] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting.

[0031] Other features and advantages of the invention will be apparent from the following detailed description and claims.

**DETAILED DESCRIPTION OF THE INVENTION**

[0032] The present invention provides novel compounds and methods of treating a neurological disease by administering a compound of Formula (III), and pharmaceutical compositions containing a compound of Formula (III).

[0033] The present invention also refers to the use of the compounds as defined in the claims in methods for the treatment of psoriasis by administering to a subject in need thereof, a
therapeutically effective amount of a said compound, or a pharmaceutically acceptable salt thereof.

[0034] The neurological disease can be multiple sclerosis. The present invention further provides the use of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for the treatment of a neurological disease.

[0035] According to the present invention, a neurological disease is a disorder of the brain, spinal cord or nerves in a subject. In one embodiment, the neurological disease is characterized by demyelination, or degeneration of the myelin sheath, of the central nervous system. The myelin sheath facilitates the transmission of nerve impulses through a nerve fiber or axon. In another embodiment, the neurological disease is selected from the group consisting of multiple sclerosis, Alzheimer's disease, cerebral palsy, spinal cord injury, Amyotrophic lateral sclerosis (ALS), stroke, Huntington's disease, Parkinson's disease, optic neuritis, Devic disease, transverse myelitis, acute disseminated encephalomyelitis, adrenoleukodystrophy and adrenomyeloneuropathy, acute inflammatory demyelinating polynuropathy (AIDP), chronic inflammatory demyelinating polyneuropathy (CIDP), acute transverse myelitis, progressive multifocal leucoencephalopathy (PML), acute disseminated encephalomyelitis (ADEM), and other hereditary disorders, such as leukodystrophies, Leber's optic atrophy, and Charcot-Marie-Tooth disease. In some embodiments, the neurological disorder is an auto-immune disease. In one embodiment, the neurological disease is multiple sclerosis. In another embodiment, the neurological disease is stroke. In another embodiment, the neurological disease is Alzheimer's disease. In another embodiment, the neurological disease is cerebral palsy. In another embodiment, the neurological disease is spinal cord injury. In another embodiment, the neurological disease is Huntington's disease. See, e.g., US Patent No. 8,007,826, WO2005/099701 and WO2004/082684.

[0036] In a further embodiment, the present invention provides the use of the compounds as defined in the claims in methods for the treatment of a disease or a symptom of a disease described herein by administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt thereof. The present invention further provides the use of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for the treatment of a disease or a symptom of a disease described herein.

[0037] The present invention provides a compound of Formula (III), or a pharmaceutically acceptable salt thereof, and the use of said compound in a method for the treatment of a neurological disease by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt thereof:

![Chemical Structure](image-url)
wherein:

\[ R_1 \text{ is unsubstituted C}_1\text{-C}_6 \text{ alkyl;} \]

\[ R_8 \text{ is H or substituted or unsubstituted C}_1\text{-C}_6 \text{ alkyl;} \]

\[ R_6, R_7, R_8 \text{ and } R_9 \text{ are each, independently, H, substituted or unsubstituted C}_1\text{-C}_6 \text{ alkyl, substituted or unsubstituted C}_2\text{-C}_6 \text{ alkenyl, substituted or unsubstituted C}_2\text{-C}_6 \text{ alkynyl or C(O)OR}_6; \text{ and} \]

\[ m \text{ is 0, 1, 2, or 3;} \]

\[ t \text{ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;} \]

or, alternatively, two \( R_{10} \)'s attached to different atoms, together with the atoms to which they are attached, form a substituted or unsubstituted C$_3$-C$_{10}$ carbocycle, substituted or unsubstituted heterocycle comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S, or substituted or unsubstituted heteroaryl comprising one or two 5- or 6-member rings and 1-4 heteroatoms selected from N, O and S.

\[ [0038] \text{ For example, the neurological disease is multiple sclerosis.} \]
[0039] For example, the neurological disease is relapsing-remitting multiple sclerosis (RRMS).

[0040] For example, in the compound of Formula (III), R₁ is methyl.

[0041] For example, in the compound of Formula (III), R₁ is ethyl.

[0042] In the compound of Formula (III),

[0043] For example, in the compound of Formula (III), R₆ is substituted or unsubstituted C₁-C₆ alkyl and R₇, R₈ and R₉ are each H.

[0044] For example, in the compound of Formula (III), R₆ is unsubstituted C₁-C₆ alkyl and R₇, R₈ and R₉ are each H.

[0045] For example, in the compound of Formula (III), R₈ is substituted or unsubstituted C₁-C₆ alkyl and R₆, R₇ and R₉ are each H.

[0046] For example, in the compound of Formula (III), R₈ is unsubstituted C₁-C₆ alkyl and R₆, R₇ and R₉ are each H.

[0047] For example, in the compound of Formula (III), R₆ and R₈ are each, independently, substituted or unsubstituted C₁-C₆ alkyl and R₇ and R₉ are each H.

[0048] For example, in the compound of Formula (III), R₆ and R₈ are each, independently, unsubstituted C₁-C₆ alkyl and R₇ and R₉ are each H.

[0049] For example, in the compound of Formula (III), R₆ and R₇ are each, independently, substituted or unsubstituted C₁-C₆ alkyl and R₈ and R₉ are each H.

[0050] For example, in the compound of Formula (III), R₆ and R₇ are each, independently, unsubstituted C₁-C₆ alkyl and R₈ and R₉ are each H.

[0051] For example, in the compound of Formula (III), R₈ and R₉ are each, independently, substituted or unsubstituted C₁-C₆ alkyl, and R₆ and R₇ are each H.

[0052] For example, in the compound of Formula (III), R₈ and R₉ are each, independently,
unsubstituted C₁-C₆ alkyl, and R₆ and R₇ are each H.

[0053] In one embodiment of Formula (III):

R₁ is unsubstituted C₁-C₆ alkyl;

m is 0, 1, 2, or 3;

t is 2, 4, or 6;

R₆, R₇, R₈ and R₉ are each, independently, H, unsubstituted C₁-C₆ alkyl, or C(O)OR₉, wherein R₉ is H or unsubstituted C₁-C₆ alkyl; and

two R₁₀'s attached to the same carbon atom, together with the carbon atom to which they are attached, form a carbonyl.

[0054] For example, the compound is a compound listed in Table 1 herein.

[0055] Representative compounds of the present invention include compounds listed in Table 1 and in Table 2.

Table 1.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>14</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>15</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>17</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>Molecular Structure</td>
</tr>
<tr>
<td>---</td>
<td>---------------------</td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Molecule 18" /></td>
</tr>
<tr>
<td>21</td>
<td><img src="image" alt="Molecule 21" /></td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Molecule 22" /></td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Molecule 23" /></td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Molecule 24" /></td>
</tr>
<tr>
<td>36</td>
<td><img src="image" alt="Molecule 36" /></td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Molecule 37" /></td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Molecule 38" /></td>
</tr>
<tr>
<td>53</td>
<td><img src="image" alt="Molecule 53" /></td>
</tr>
<tr>
<td>54</td>
<td><img src="image" alt="Molecule 54" /></td>
</tr>
</tbody>
</table>
A⁻ is a pharmaceutically acceptable anion.

[0056] The present invention also provides pharmaceutical compositions comprising one or more compounds of Formula (III) and one or more pharmaceutically acceptable carriers.

[0057] In one embodiment, the pharmaceutical composition is a controlled release composition comprising a compound of Formula (III) and one or more pharmaceutically acceptable carriers, wherein the controlled release composition provides a therapeutically effective amount of monomethyl fumarate to a subject. In another embodiment, the pharmaceutical composition is a controlled release composition comprising a compound of Formula (III) and one or more pharmaceutically acceptable carriers, wherein the controlled release composition provides a therapeutically effective amount of monomethyl fumarate to a subject for at least about 8 hours to at least about 24 hours. In another embodiment, the pharmaceutical composition is a controlled release composition comprising a compound of Formula (III) and one or more pharmaceutically acceptable carriers, wherein the controlled release composition provides a therapeutically effective amount of monomethyl fumarate to a subject for at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 13 hours, at least about 14 hours, at least about 15 hours, at least about 16 hours, at least about 17 hours, at least about 18 hours, at least about 19 hours, at least about 20 hours, at least about 21 hours, at least about 22 hours, at least about 23 hours or at least about 24 hours or longer. For example, at least about 18 hours. For example, at least about 12 hours. For example, greater than 12 hours. For example, at least about 16 hours. For example, at least about 20 hours. For example, at least about 24 hours.

[0058] In another embodiment, a compound of Formula (III) is efficiently converted to the active species, i.e., monomethyl fumarate, upon oral administration. For example, about 50 mole percent, about 55 mole percent, about 60 mole percent, about 65 mole percent, about 70 mole percent, about 75 mole percent, about 80 mole percent, about 85 mole percent, about 90 mole percent, or greater than 90 mole percent of the total dose of a compound of Formula (III)
administered is converted to monomethyl fumarate upon oral administration. In another embodiment, a compound of Formula (III) is converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration more efficiently than dimethyl fumarate. In another embodiment, a compound of Formula (III) is converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration more efficiently than one or more of the compounds described in US 8,148,414. For example, a compound of Formula (III) is essentially completely converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration.

\textbf{[0059]} In another embodiment, any one of the above exemplified compounds according to the invention is efficiently converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration. For example, about 50 percent, about 55 percent, about 60 percent, about 65 percent, about 70 percent, about 75 percent, about 80 percent, about 85 percent, about 90 percent, or greater than 90 percent of the total dose of any one of the above exemplified compounds according to the invention administered is converted to monomethyl fumarate upon oral administration. In another embodiment, any one of the above exemplified compounds according to the invention is converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration more efficiently than dimethyl fumarate. In another embodiment, any one of the above exemplified compounds according to the invention is converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration more efficiently than one or more of the compounds described in US 8,148,414. For example, any one of the above exemplified compounds according to the invention is completely converted to the active species, \textit{i.e.}, monomethyl fumarate, upon oral administration.

\textbf{[0060]} For a drug to achieve its therapeutic effect, it is necessary to maintain the required level of blood or plasma concentration. Many drugs, including dimethyl fumarate, must be administered multiple times a day to maintain the required concentration. Furthermore, even with multiple administrations of such a drug per day, the blood or plasma concentrations of the active ingredient may still vary with time, \textit{i.e.}, at certain time points between administrations there are higher concentrations of the active ingredient than at other times. Thus, at certain time points of a 24-hour period, a patient may receive therapeutically effective amounts of the active ingredient, while at other time points the concentration of the active ingredient in the blood may fall below therapeutic levels. Additional problems with such drugs include that multiple dosing a day often adversely affects patient compliance with the treatment. Therefore, it is desirable to have a drug dosage form wherein the active ingredient is delivered in such a controlled manner that a constant or substantially constant level of blood or plasma concentration of the active ingredient can be achieved by one or at most two dosing per day. Accordingly, the present invention provides controlled-release formulations as described below. In general, such formulations are known to those skilled in the art or are available using conventional methods.

\textbf{[0061]} As used herein, "controlled-release" means a dosage form in which the release of the active agent is controlled or modified over a period of time. Controlled can mean, for example, sustained, delayed or pulsed-release at a particular time. For example, controlled-release can mean that the release of the active ingredient is extended for longer than it would be in an
immediate-release dosage form, i.e., at least over several hours.

[0062] As used herein, "immediate-release" means a dosage form in which greater than or equal to about 75% of the active ingredient is released within two hours, or, more specifically, within one hour, of administration. Immediate-release or controlled-release may also be characterized by their dissolution profiles.

[0063] Formulations may also be characterized by their pharmacokinetic parameters. As used herein, "pharmacokinetic parameters" describe the in vivo characteristics of the active ingredient over time, including for example plasma concentration of the active ingredient. As used herein, "C_{max}" means the measured concentration of the active ingredient in the plasma at the point of maximum concentration. "T_{max}" refers to the time at which the concentration of the active ingredient in the plasma is the highest. "AUC" is the area under the curve of a graph of the concentration of the active ingredient (typically plasma concentration) vs. time, measured from one time to another.

[0064] The controlled-release formulations provided herein provide desirable properties and advantages. For example, the formulations can be administered once daily, which is particularly desirable for the subjects described herein. The formulation can provide many therapeutic benefits that are not achieved with corresponding shorter acting, or immediate-release preparations. For example, the formulation can maintain lower, more steady plasma peak values, for example, C_{max}, so as to reduce the incidence and severity of possible side effects.

[0065] Sustained-release dosage forms release their active ingredient into the gastrointestinal tract of a patient over a sustained period of time following administration of the dosage form to the patient. Particular dosage forms include: (a) those in which the active ingredient is embedded in a matrix from which it is released by diffusion or erosion; (b) those in which the active ingredient is present in a core which is coated with a release rate-controlling membrane; (c) those in which the active ingredient is present in a core provided with an outer coating impermeable to the active ingredient, the outer coating having an aperture (which may be drilled) for release of the active ingredient; (d) those in which the active ingredient is released through a semi-permeable membrane, allowing the drug to diffuse across the membrane or through liquid filled pores within the membrane; and (e) those in which the active ingredient is present as an ion exchange complex.

[0066] It will be apparent to those skilled in the art that some of the above means of achieving sustained-release may be combined, for example a matrix containing the active compound may be formed into a multiparticulate and/or coated with an impermeable coating provided with an aperture.

[0067] Pulsed-release formulations release the active compound after a sustained period of time following administration of the dosage form to the patient. The release may then be in the form of immediate- or sustained-release. This delay may be achieved by releasing the drug at
particular points in the gastro-intestinal tract or by releasing drug after a pre-determined time. Pulsed-release formulations may be in the form of tablets or multiparticulates or a combination of both. Particular dosage forms include: (a) osmotic potential triggered release (see U.S. Pat. No. 3,952,741); (b) compression coated two layer tablets (see U.S. Pat. No. 5,464,633); (c) capsules containing an erodible plug (see U.S. Pat. No. 5,474,784); sigmoidal releasing pellets (referred to in U.S. Pat. No. 5,112,621); and (d) formulations coated with or containing pH-dependent polymers including shellac, phthalate derivatives, polyacrylic acid derivatives and crotonic acid copolymers.

[0068] Dual release formulations can combine the active ingredient in immediate release form with additional active ingredient in controlled-release form. For example, a bilayer tablet can be formed with one layer containing immediate release active ingredient and the other layer containing the active ingredient embedded in a matrix from which it is released by diffusion or erosion. Alternatively, one or more immediate release beads can be combined with one or more beads which are coated with a release rate-controlling membrane in a capsule to give a dual release formulation. Sustained release formulations in which the active ingredient is present in a core provided with an outer coating impermeable to the active ingredient, the outer coating having an aperture (which may be drilled) for release of the active ingredient, can be coated with drug in immediate release form to give a dual release formulation. Dual release formulations can also combine drug in immediate release form with additional drug in pulsed release form. For example, a capsule containing an erodible plug could liberate drug initially and, after a predetermined period of time, release additional drug in immediate- or sustained-release form.

[0069] In some embodiments, the dosage forms to be used can be provided as controlled-release with respect to one or more active ingredients therein using, for example, hydroxypropylocellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the pharmaceutical compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, and caplets that are adapted for controlled-release are encompassed by the present invention.

[0070] Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradually and continually release of additional amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

[0071] Controlled-release of an active ingredient can be stimulated by various inducers, for example pH, temperature, enzymes, concentration, or other physiological conditions or compounds.
[0072] Powdered and granular formulations of a pharmaceutical preparation of the invention may be prepared using known methods. Such formulations may be administered directly to a subject, used, for example, to form tablets, to fill capsules, or to prepare an aqueous or oily suspension or solution by addition of an aqueous or oily vehicle thereto. Each of these formulations may further comprise one or more of a dispersing agent, wetting agent, suspending agent, and a preservative. Additional excipients, such as fillers, sweeteners, flavoring, or coloring agents, may also be included in these formulations.

[0073] A formulation of a pharmaceutical composition of the invention suitable for oral administration may be prepared or packaged in the form of a discrete solid dose unit including, but not limited to, a tablet, a hard or soft capsule, a cachet, a troche, or a lozenge, each containing a predetermined amount of the active ingredient. In one embodiment, a formulation of a pharmaceutical composition of the invention suitable for oral administration is coated with an enteric coat.

[0074] A tablet comprising the active ingredient may, for example, be made by compressing or molding the active ingredient, optionally with one or more additional ingredients. Compressed tablets may be prepared by compressing, in a suitable device, the active ingredient in a free flowing form such as a powder or granular preparation, optionally mixed with one or more of a binder, a lubricant, an excipient, a surface-active agent, and a dispersing agent. Molded tablets may be made by molding, in a suitable device, a mixture of the active ingredient, a pharmaceutically acceptable carrier, and at least sufficient liquid to moisten the mixture. Pharmaceutically acceptable excipients used in the manufacture of tablets include, but are not limited to, inert diluents, granulating and disintegrating agents, binding agents, and lubricating agents. Known dispersing agents include, but are not limited to, potato starch and sodium starch glycolate. Known surface-active agents include, but are not limited to, sodium lauryl sulphate and poloxamers. Known diluents include, but are not limited to, calcium carbonate, sodium carbonate, lactose, microcrystalline cellulose, calcium phosphate, calcium hydrogen phosphate, and sodium phosphate. Known granulating and disintegrating agents include, but are not limited to, corn starch and alginic acid. Known binding agents include, but are not limited to, gelatin, acacia, pre-gelatinized maize starch, polyvinylpyrrolidone, and hydroxypropyl methylcellulose. Known lubricating agents include, but are not limited to, magnesium stearate, stearic acid, silica, and talc.

[0075] Tablets may be non-coated or they may be coated using known methods to achieve delayed disintegration in the gastrointestinal tract of a subject, thereby providing sustained release and absorption of the active ingredient. By way of example, a material such as glyceryl monostearate or glyceryl distearate may be used to coat tablets. Further by way of example, tablets may be coated using methods described in U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotically-controlled release tablets, optionally, with laser drilling. Tablets may further comprise a sweetener, a flavoring agent, a coloring agent, a preservative, or some combination of these in order to provide for pharmaceutically elegant and palatable formulations.
[0076] Hard capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin or HPMC. Such hard capsules comprise the active ingredient, and may further comprise additional ingredients including, for example, an inert solid diluent such as calcium carbonate, calcium phosphate, or kaolin.

[0077] Soft gelatin capsules comprising the active ingredient may be made using a physiologically degradable composition, such as gelatin. Such soft capsules comprise the active ingredient, which may be mixed with water or an oil medium such as peanut oil, liquid paraffin, or olive oil.

[0078] As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intended to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, or n-hexyl.

[0079] In certain embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0080] As used herein, "alkyl linker" is intended to include C_1, C_2, C_3, C_4, C_5, or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5, or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl linker is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl linker groups. Examples of alkyl linker include, moieties having from one to six carbon atoms, such as, but not limited to, methyl (-CH_2-), ethyl (-CH_2CH_2-), n-propyl (-CH_2CH_2CH_2-), i-propyl (-CH(CH_3)CH_2-), n-butyl (-CH_2CH_2CH_2CH_2-), s-butyl (-CH(CH_3)CH_2CH_2-), i-butyl (-CH(CH_3)CH(CH_3)CH_2-), n-pentyl (-CH_2CH_2CH_2CH_2CH_2-), s-pentyl (-CH(CH_3)CH_2CH_2CH_2CH_2-), or n-hexyl (-CH_2CH_2CH_2CH_2CH_2CH_2-). The term "substituted alkyl linker" refers to alkyl linkers having substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents do not alter the sp3-hybridization of the carbon atom to which they are attached and include those listed below for "substituted alkyl."

[0081] "Heteroalkyl" groups are alkyl groups, as defined above, that have an oxygen, nitrogen, sulfur or phosphorous atom replacing one or more hydrocarbon backbone carbon atoms.

[0082] As used herein, the term "cycloalkyl", "C_3, C_4, C_5, C_6, C_7 or C_8 cycloalkyl" or "C_3-C_8 cycloalkyl" is intended to include hydrocarbon rings having from three to eight carbon atoms in their ring structure. In one embodiment, a cycloalkyl group has five or six carbons in the ring structure.
The term "substituted alkyl" refers to alkyl moieties having substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonate, phosphinito, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkythio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "alkylaryl" or an "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl(benzyl)).

Unless the number of carbons is otherwise specified, "lower alkyl" includes an alkyl group, as defined above, having from one to six, or in another embodiment from one to four, carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, two to six or of two to four carbon atoms.

"Aryl" includes groups with aromaticity, including "conjugated", or multicyclic, systems with at least one aromatic ring. Examples include phenyl, benzyl, naphthyl, etc. "Heteroaryl" groups are aryl groups, as defined above, having from one to four heteroatoms in the ring structure, and may also be referred to as "aryl heterocycles" or "heteroaromatics". As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and S(O)ₚ where p=1 or 2). It is to be noted that total number of S and O atoms in the heteroaryl is not more than 1.

Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

As used herein, "Ph" refers to phenyl, and "Py" refers to pyridinyl.

Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxypyphenyl, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine.

In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic
(e.g., 2,3-dihydroindole), although all of the rings may be aromatic (e.g., quinoline). The second ring can also be fused or bridged.

[0090] The aryl or heteroaryl aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, alkyl, alkenyl, aminyl, halogen, hydroxyl, alkoxy, alkylcarboxyloxy, arylicarbonyloxy, alkoxyacarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarboxyl, alkyaminocarbonyl, alkylaminocarboxyl, aralkylaminocarbonyl, alkylaminocarboxyl, alkylcarboxyl, aralkylcarboxyl, alkenylcarboxyl, alkoxycarbonyl,aminocarboxyl, alklythiocarboxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarboxylamino, alkenylcarboxylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarbamoyl, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (e.g., tetratin, methylenedioxyphenyl).

[0091] As used herein, "carbocycle" or "carbocyclic ring" is intended to include any stable monocyclic, bicyclic or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. For example, a C₃-C₁₄ carbocycle is intended to include a monocyclic, bicyclic or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopropyl, cyclopentyl, cyclcopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicycleoctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane and [2.2.2]bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In one embodiment, bridge rings are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (e.g., naphthyl, tetrahydronaphthyl) and spiro rings are also included.

[0092] As used herein, "heterocycle" includes any ring structure (saturated or partially unsaturated) which contains at least one ring heteroatom (e.g., N, O or S). Examples of heterocycles include, but are not limited to, morpholine, pyrrolidine, tetrahydrothiophene, piperidine, pipеразине, and tetrahydrofuran.

[0093] Examples of heterocyclic groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoazolyl, benzoazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanly, chromenyl, cinnolnly, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isocinolyl, isocinazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl,
octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolS(4H)-one, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperdinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyrazolyl, pyridazinyl, pyridoxazole, pyridoimidazole, pyridothiazole, pyrindinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolyl, quinolinyl, 4H-quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0094] The term "substituted", as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0095] The term "acyl", as used herein, includes moieties that contain the acyl radical (--C(O)-) or a carbonyl group. "Substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by, for example, alkyl groups, alkenyl groups, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxyacarbonyloxy, aryloxycarbonyloxy, carbamate, alkylcarbonyl, arylcarbonyl, alkoxyacarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkyloxyacarbonyl, alkoxycarbonyl, alkylamino, phosphatocarbonyl, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylocarbonylamino, arylocarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarbonylate, sulfates, alkylsulfinitol, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0096] The description of the disclosure herein should be construed in congruity with the laws and principals of chemical bonding. For example, it may be necessary to remove a hydrogen atom in order accommodate a substituent at any given location. Furthermore, it is to be understood that definitions of the variables (i.e., "R groups"), as well as the bond locations of the generic formula of the invention, will be consistent with the laws of chemical bonding known in the art. It is also to be understood that all of the compounds of the invention described above will further include bonds between adjacent atoms and/or hydrogens as required to satisfy the valence of each atom. That is, bonds and/or hydrogen atoms are added to provide the following number of total bonds to each of the following types of atoms: carbon: four bonds; nitrogen: three bonds; oxygen: two bonds; and sulfur: two-six bonds.
[0097] As used herein, a "subject in need thereof" is a subject having a neurological disease. In one embodiment, a subject in need thereof has multiple sclerosis. A "subject" includes a mammal. The mammal can be e.g., any mammal, e.g., a human, primate, bird, mouse, rat, fowl, dog, cat, cow, horse, goat, camel, sheep or a pig. In one embodiment, the mammal is a human.

[0098] The present invention provides methods for the synthesis of the compounds of the formula described herein. The present invention also provides detailed methods for the synthesis of various disclosed compounds of the present invention according to the following schemes and as shown in the Examples.

[0099] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0100] The synthetic processes of the invention can tolerate a wide variety of functional groups; therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt, polymorph, hydrate, solvate or co-crystal thereof.

[0101] Compounds of the present invention can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., March's Advanced Organic Chemistry Reactions, Mechanisms, and Structure, 5th edition, John Wiley & Sons: New York, 2001; and Greene, T. W., Wuts, P. G. M., Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons: New York, 1999, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present invention.

[0102] Compounds of the present invention can be conveniently prepared by a variety of methods familiar to those skilled in the art. The compounds of this invention of the formula described herein may be prepared according to the following procedures from commercially
available starting materials or starting materials which can be prepared using literature procedures. These procedures show the preparation of representative compounds of this invention.

EXPERIMENTAL

General Procedure 1

[0103] To a mixture of monomethyl fumarate (MMF) (1.0 equivalent) and HBTU (1.5 equivalents) in DMF (25 ml per g of MMF) was added Hünig’s base (2.0 equivalents). The dark brown solution was stirred for 10 minutes, where turned into a brown suspension, before addition of the alcohol (1.0 - 1.5 equivalents). The reaction was stirred for 18 hours at room temperature. Water was added and the product extracted into ethyl acetate three times. The combined organic layers were washed with water three times, dried with magnesium sulphate, filtered and concentrated in vacuo at 45 °C to give the crude product. The crude product was purified by silica chromatography and in some cases further purified by trituration with diethyl ether to give the clean desired ester product. All alcohols were either commercially available or made following known literature procedures.

[0104] As an alternative to HBTU (N,N,N’,N’-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate), any one of the following coupling reagents can be used: EDCI/HOBt (N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride/hydroxybenzotriazole hydrate); COMU ((1-cyano-2-ethoxy-2-oxoethyldenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate); TBTU ((O-benzotriazol-1-yl)-N,N,N’,N’-tetramethyluronium tetrafluoroborate); TATU (O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate); Oxyc (ethyl (hydroxyimino)cyanoacetate); PyBOP ((benzotriazol-1-ylxylo)tritylpyrroldinophosphonium hexafluorophosphate); HOTT (S-(1-oxido-2-pyridyl)-N,N,N’,N’-tetramethylthiuronium hexafluorophosphate); FDPP (pentafluorophenyl diphenylphosphinate); T3P (propylphosphonic anhydride); DMTMM (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate); PyOxim ([ethyl cyano(hydroxyimino)acetato-O^2]tri-1-pyrrolidinylphosphonium hexafluorophosphate); TSTU (N,N,N’,N’-tetramethyl-O-(N-succinimidyl)uronium tetrafluoroborate); TDBTU (O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-N,N,N’,N’-tetramethyluronium tetrafluoroborate); TPTU (O-(2-oxo-1(2H)pyridyl)-N,N,N’,N’-tetramethyluronium tetrafluoroborate); TOTU (O-[(ethoxy carbonyl)cyanomethylenamino]-N,N,N’,N’-tetramethyluronium tetrafluoroborate); IIDQ (isobutyl 1,2-dihydro-2-isobutoxy-1-quinolinecarboxylate); or PyC1U (chlorodipyrrrolidinocarbenium hexafluorophosphate).

[0105] As an alternative to Hünig’s base (diisopropylethylamine), any one of the following amine bases can be used: triethylamine; tributylamine; triphenylamine; pyridine; lutidine (2,6-dimethylpyridine); collidine (2,4,6-trimethylpyridine); imidazole; DMAP (4-(dimethylamo)pyridine); DABCO (1,4-diazabicyclo[2.2.2]octane); DBU (1,8-diazabicyclo[5.4.0]
undec-7-ene); DBN (1,5-diazabicyclo[4.3.0]non-5-ene); or proton sponge® (N,N,N',N'-tetramethyl-1,8-naphthalenediamine).

**General Procedure 2- Conversion of the Ester Product into the Hydrochloride Salt**

[0106] To a mixture of the ester product in diethyl ether (25 ml per g) was added 2M HCl in diethyl ether (1.5 equivalents). The mixture was stirred at room temperature for two hours. The solvent was decanted, more diethyl ether added and the solvent decanted again. The remaining mixture was then concentrated in vacuo at 45 °C and further dried in a vacuum oven at 55 °C for 18 hours to give the solid HCl salt.

**General Procedure 3**

[0107] To a 100 mL, one-necked, round-bottomed flask, fitted with a magnetic stirrer and nitrogen inlet/outlet, were added 11 mL of an MTBE solution containing freshly prepared monomethyl fumaryl chloride (4.9 g, 33 mmol) and 50 mL of additional MTBE at 20 °C. The resulting yellow solution was cooled to <20 °C with an ice water bath. Then, the alcohol, (33 mmol, 1 eq) was added dropwise, via syringe, over approximately 10 minutes. The reaction mixture was allowed to stir at <20 °C for 10 minutes after which time the cooling bath was removed and the reaction was allowed to warm to 20 °C and stir at 20 °C temperature for 16 hours. The reaction was deemed complete by TLC after 16 hours at RT. The reaction mixture was filtered through a medium glass fritted funnel to collect the off-white solids. The solids were dried in a vacuum oven at 25 °C overnight to afford the final product as an HCl salt. All alcohols were either commercially available or made following known literature procedures.

**General Procedure 4- Alkylation with an Appropriate Alkyl Mesylate**

[0108] A mixture of monomethyl fumarate (MMF) (1.3 equivalent), the alkyl mesylate (1 equivalent), and potassium carbonate (1.5 equivalent) in acetonitrile (50 ml per g of MMF) was heated at reflux overnight. The mixture was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate, and the organic phase dried (MgSO₄). Filtration and removal of the solvent under reduced pressure gave the crude product which was purified in each case by silica chromatography.

**General Procedure 5- Alkylation with an Appropriate Alkyl Chloride**

[0109] A mixture of monomethyl fumarate (MMF) (1.3 equivalent), the alkyl chloride (1 equivalent), and potassium carbonate (1.5 equivalent) in acetonitrile or dimethylformamide (50 ml per g of MMF) was heated at 20 to 65 °C overnight. The mixture was partitioned between
ethyl acetate and saturated aqueous sodium hydrogen carbonate, and the organic phase dried (MgSO₄). Filtration and removal of the solvent under reduced pressure gave the crude product which was further purified by silica chromatography.

**Chemical Analysis/Procedures**

[0110] The NMR spectra described herein were obtained with a Varian 400 MHz NMR spectrometer using standard techniques known in the art.

**Examples**

**2-(4,4-difluoropiperidin-1-yl)ethyl methyl fumarate hydrochloride (5)**

[0111]

[0112] 2-(4,4-difluoropiperidin-1-yl)ethyl methyl fumarate 5 was synthesized following general procedure 1 and was converted to the HCl salt: 2-(4,4-difluoropiperidin-1-yl)ethyl methyl fumarate hydrochloride (procedure 2) (780 mg, 87 %).

1H NMR (300 MHz, DMSO): δ 11.25 (1H, bs); 6.84 (2H, dd, J = 16.1 Hz); 4.50 (2H, bs); 3.35-4.00 (8H, m); 3.05-3.30 (2H, m); 2.20-2.45 (3H, s). [M+H]+ = 278.16.

**2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (14)**

[0113]

[0114] 2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate 14 was synthesized following general procedure 1 (1.03 g, 35 %).

1H NMR (400 MHz, DMSO): δ 6.81 (2H, dd, J = 15.8 Hz); 4.36 (2H, t, J = 5.3 Hz); 3.84 (2H, t, J = 5.1 Hz); 3.80 (3H, s); 2.73 (4H, s). [M+H]+ = 256.07.

**Methyl (2-(piperidin-1-yl)ethyl) fumarate hydrochloride (15)**
Methyl (2-(piperidin-1-yl)ethyl) fumarate hydrochloride 15 was synthesized following general procedure 3.

$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 10.76 (s, 1H), 6.94 - 6.77 (m, 2H), 4.58 - 4.51 (m, 2H), 3.76 (s, 3H), 3.48 - 3.36 (m, 4H), 2.94 (dddd, $J = 15.9, 12.1, 9.2, 4.4$ Hz, 2H), 1.91 - 1.64 (m, 5H), 1.37 (dtt, $J = 16.4, 11.3, 4.9$ Hz, 1H). [M+H]$^+$ = 241.93.

2-(1,4-dioxo-8-azaspiro[4,5]decan-8-yl)ethyl methyl fumarate hydrochloride (17)

Methyl (2-(pyrrolidin-1-yl)ethyl) fumarate hydrochloride 18 was synthesized following general procedure 3.

$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 11.26 (s, 1H), 6.91 (d, $J = 15.9$ Hz, 1H), 6.82 (d, $J = 15.9$ Hz, 1H), 4.58 - 4.51 (m, 2H), 3.93 (s, 4H), 3.76 (s, 3H), 3.57 - 3.43 (m, 4H), 3.22 - 3.03 (m, 2H), 2.20 - 2.02 (m, 2H), 1.89 - 1.79 (m, 2H). [M+H]$^+$ = 300.00.

Methyl (2-(pyrrolidin-1-yl)ethyl) fumarate hydrochloride (18)

Methyl (2-(pyrrolidin-1-yl)ethyl) fumarate hydrochloride 18 was synthesized following general procedure 3.

$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 11.12 (s, 1H), 6.94 (d, $J = 15.8$ Hz, 1H), 6.82 (d, $J = 15.8$ Hz, 1H), 4.53 - 4.46 (m, 2H), 3.76 (s, 3H), 3.61 - 3.45 (m, 4H), 3.11 - 2.94 (m, 2H), 2.06 - 1.79 (m, 4H). [M+H]$^+$ = 228.46.
2-(3,3-difluoropyrrolidin-1-yl)ethyl methyl fumarate hydrochloride (21)

[0121]

[0122] 2-(3,3-Difluoropyrrolidin-1-yl)ethyl methyl fumarate 21 was synthesised from 2-(3,3-difluoropyrrolidin-1-yl)ethanol following general procedure 1.

[0123] 2-(3,3-difluoropyrrolidin-1-yl)ethyl methyl fumarate was converted to 2-(3,3-difluoropyrrolidin-1-yl)ethyl methyl fumarate hydrochloride following general procedure 2 (0.55 g, 69%).

$^1$H NMR (300 MHz, DMSO): $\delta$ 6.79 (2H, d); 4.20-4.39 (2H, m), 3.81 (2H, t), 3.66 (3H, s), 3.53-3.65 (4H, m), 2.54 (2H, sep). $m/z$ [M+H]$^+$ = 264.14.

2-(2,4-Dioxo-3-azabicyclo[3.1.0]hexan-3-yl)ethyl methyl fumarate (22)

[0124]

[0125] 3-oxabicyclo[3.1.0]hexane-2,4-dione (1.0 g, 8.9 mmol) and ethanolamine (545 mg, 8.9 mmol) were heated neat at 200 °C for 2 hours. The crude reaction mixture was purified by silica chromatography (EtOAc) giving 3-(2-Hydroxyethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (1.06 g, 77%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.71 (2H, t), 3.56 (2H, t), 2.51 (2H, dd), 1.95 (1H, br s), 1.59-1.43 (2H, m).

[0126] 2-(2,4-dioxo-3-azabicyclo[3.1.0]hexan-3-yl)ethyl methyl fumarate 22 was synthesised from 3-(2-Hydroxyethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione following general procedure 1 (452 mg, 53%).
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.81 (2H, d), 4.28 (2H, t), 3.80 (3H, s), 3.69 (2H, t), 2.48 (2H, dd), 1.59-1.49 (1H, m), 1.44-1.38 (1H, m). \(m/z\) [M+H]\(^+\) = 268.11.

[0127] 2-(2,2-Dimethyl-5-oxoppyrrolidin-1-yl)ethyl methyl fumarate 24 was synthesised from 1-(2-chloroethyl)-5,5-dimethylpyrrolidin-2-one following general procedure 5 (1.02 g, 41%).
\(^1\)H NMR (300 MHz, CDCl\(_3\)): 6.85 (2H, d), 4.33 (2H, t), 3.80 (3H, s), 3.41 (2H, t), 2.39 (2H, t), 1.88 (2H, t), 1.23 (6H, s). \(m/z\) [M+H]\(^+\) = 270.17.

2-(1,3-Dioxoisooindolin-2-yl)ethyl methyl fumarate (36)

[0128]

[0129] 2-(1,3-Dioxoisooindolin-2-yl)ethyl methyl fumarate 36 was synthesised from 2-(2-hydroxyethyl)isoindoline-1,3-dione following general procedure 1 (0.63 g, 79%).
\(^1\)H NMR (300 MHz, MeOD): 7.87-7.77 (4H, m), 6.74-6.73 (2H, m), 4.45-4.40 (2H, m), 4.01-3.96 (2H, m), 3.76 (3H, s). \(m/z\) [M+H]\(^+\) = 304.1

2-(3,3-Dimethyl-2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (36)

[0130]

[0131] 2-(3,3-Dimethyl-2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate 36 was synthesised from 1-(2-hydroxyethyl)-3,3-dimethylpyrrolidine-2,5-dione following general procedure 1 (0.72 g, 74%).
\(^1\)H NMR (300 MHz, CDCl\(_3\)): 6.83 (1H, d), 6.77 (1H, d), 4.38 (2H, t), 3.82 (1H, t), 3.80 (3H, s), 2.55 (2H, s), 1.31 (6H, s). \(m/z\) [M+H]\(^+\) = 284.1
Methyl (2-(2-oxopyrrolidin-1-yl)ethyl) fumarate (38)

[0132]

[0133] Methyl (2-(2-oxopyrrolidin-1-yl)ethyl) fumarate 38 was synthesised from 1-(2-hydroxyethyl)pyrrolidin-2-one following general procedure 1 (0.68 g, 73%).

$^1$H NMR (300 MHz, MeOD): 6.85 (2H, s), 4.33 (2H, t), 3.80 (3H, s), 3.59 (2H, t), 3.46 (2H, t), 2.37 (2H, t), 2.03 (2H, dt). [M+H]$^+$ = 242.1

2-((3R,4S)-3,4-Dimethyl-2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate (23)

[0134]

[0135] Racemic 2-((3R,4S)-3,4-dimethyl-2,5-dioxopyrrolidin-1-yl)ethyl methyl fumarate 23 was synthesised from racemic (3R,4S)-1-(2-hydroxyethyl)-3,4-dimethylpyrrolidine-2,5-dione following general procedure 1 (0.54 g, 44%).

$^1$H NMR (300 MHz, CDCl$_3$): 6.81-6.80 (2H, m), 4.37 (2H, t), 3.82 (2H, t), 3.80 (3H, s), 3.00-2.88 (2H, m), 1.25-1.18 (6H, m). m/z [M+H]$^+$ = 284.2

Reference Compound A

2-(diethylamino)-2-oxoethyl methyl fumarate

[0136]

[0137] 2-(diethylamino)-2-oxoethyl methyl fumarate was synthesized following general
procedure 3 and conformed to reported data in US Patent No. 8,148,414.

**Example 2: Aqueous Chemical Stability of Several Compounds**

[0138] Stock solutions of the compounds in acetonitrile or acetonitrile/methanol were prepared at 20 mg/mL and 20 μL, spiked into 3mL of buffer phosphate (100mM) and incubated at 37 °C. Aliquots (50 μL) were sampled at different time points and diluted 20 fold with ammonium formate (pH 3.5)/acetonitrile. The diluted samples were analyzed by HPLC. The peak areas corresponding to the compounds were plotted against time and the data were fitted to a first-order mono-exponential decay where the rate constant and the half-life were determined (Table 3). In some cases, in which the half life is too long (>360min), an estimated value of the half life is reported using the initial slope at low conversion (<10%).

Table 3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>pH 8 (t ½, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>144</td>
</tr>
<tr>
<td>15</td>
<td>3.0</td>
</tr>
<tr>
<td>17</td>
<td>11.0</td>
</tr>
<tr>
<td>18</td>
<td>5.0</td>
</tr>
<tr>
<td>Reference Compound A</td>
<td>120</td>
</tr>
</tbody>
</table>

[0139] Stock solutions of the compounds in acetonitrile or acetonitrile/MeOH were prepared at 0.05M. A 0.010 mL aliquot of the stock was spiked into 1 mL of 50 mM buffer phosphate pH 8 and incubated at 37 °C. Typically, aliquots (0.010 mL) were sampled at different time points and immediately injected in the HPLC with UV detection (211nm). The peak areas corresponding to the compounds were plotted against time and the data were fitted to a first-order mono-exponential decay where the rate constant and the half-life were determined from the slope (Table 4).

Table 4.

<table>
<thead>
<tr>
<th>Compound</th>
<th>pH 8 (t ½, min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>22</td>
<td>144</td>
</tr>
<tr>
<td>23</td>
<td>186</td>
</tr>
<tr>
<td>37</td>
<td>182</td>
</tr>
<tr>
<td>38</td>
<td>201</td>
</tr>
</tbody>
</table>

**Example 3: Evaluation of Aqueous Chemical Stability with NMR**
The chemical hydrolysis was followed by dissolving the ester in phosphate buffered D$_2$O (pH 7.9) in an NMR tube, heating the NMR tube to 37° C and periodically recording the spectra. These various species produced by hydrolysis of the diesters were followed over time. See Figures 1-5.

**Example 4- Delivery of MMF in Rats Upon Oral Administration of Prodrugs**

Rats were obtained commercially and were pre-cannulated in the jugular vein. Animals were conscious at the time of the experiment. All animals were fasted overnight and until 4 hours post-dosing of a prodrug in the disclosure.

Blood samples (0.25 mL/sample) were collected from all animals at different time-points up to 24 hours post-dose into tubes containing sodium fluoride/sodium EDTA. Samples were centrifuged to obtain plasma. Plasma samples were transferred to plain tubes and stored at or below -70° C prior to analysis.

To prepare analysis standards, 20 uL of rat plasma standard was quenched with 60 uL of internal standard. The sample tubes were vortexed for at least 1 min and then centrifuged at 3000 rpm for 10 min. 50 uL of supernatant was then transferred to 96-well plates containing 100 µL water for analysis by LC-MS-MS.

LC-MS/MS analysis was performed using an API 4000 equipped with HPLC and autosampler. The following HPLC column conditions were used: HPLC column: Waters Atlantis T3; flow rate 0.5 mL/min; run time 5 min; mobile phase A: 0.1% formic acid in water; mobile phase B: 0.1% formic acid in acetonitrile (ACN); gradient: 98% A/2% B at 0.0 min; 98% A/2% B at 1 min; 5% A/95% B at 3 min; 5% A/95% B at 3.75 min; 97% A/3% B at 4 min; and 98% A/2% B at 5.0 min. MMF was monitored in positive ion mode.

MMF, DMF or MMF prodrug was administered by oral gavage to groups of two to six adult male Sprague-Dawley rats (about 250 g). Animals were conscious at the time of the experiment. MMF, DMF or MMF prodrug was orally administered in an aqueous solution of 0.5% hydroxypropyl methyl cellulose (HPMC), 0.02% polysorbate 80, and 20 mM citrate buffer (pH 5), at a dose of 10 mg-equivalents MMF per kg body weight.

The percent absolute bioavailability (F%) of MMF was determined by comparing the area under the MMF concentration vs time curve (AUC) following oral administration of MMF, DMF or MMF prodrug with the AUC of the MMF concentration vs time curve following intravenous administration of MMF on a dose normalized basis.

The MMF prodrugs, when administered orally to rats at a dose of 10 mg/kg MMF-equivalents in the aqueous vehicle, exhibited an absolute oral bioavailability (relative to IV)
ranging from about 3% to about 96% (See Tables 5 and 6). Tables 5 and 6 show data from two independent studies.

Table 5.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Percent Absolute Bioavailability (F%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF</td>
<td>43%</td>
</tr>
<tr>
<td>DMF</td>
<td>53%</td>
</tr>
<tr>
<td>14</td>
<td>96%</td>
</tr>
</tbody>
</table>

Table 6.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Percent Absolute Bioavailability (F%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF</td>
<td>69.6</td>
</tr>
<tr>
<td>DMF</td>
<td>69.6</td>
</tr>
<tr>
<td>5</td>
<td>81.1</td>
</tr>
</tbody>
</table>

Example 5- Delivery of MMF in Dogs Upon Oral Administration of Prodrugs

[0148] Male Beagle dogs were obtained from the test facility's colony of non-native animals. All animals were fasted overnight prior to dose administration.

[0149] Oral doses were administered via oral gavage. The gavage tube was flushed with 10 mL of water prior to removal.

[0150] All animals were observed at dosing and at each scheduled collection. All abnormalities were recorded.

[0151] Blood samples were collected in Sodium Fluoride/Na₂EDTA tubes and stored on wet ice until processed to plasma by centrifugation (300 rpm at 5°C) within 30 minutes of collection. All plasma samples were transferred into separate 96-well plates (matrix tubes) and stored at - 80 °C until concentration analysis was performed via LC/MS/MS using an RGA 3 assay.

**Extraction Procedure:**

[0152] Note: Thawed test samples at 4°C. (Kept in ice while on bench).

1. 1. Aliquoted 20uL of study sample, standard, and QC samples into labeled 96-well plate.
2. 2. Added 120uL of appropriate internal standard solution (125ng/mL mouse embryo fibroblasts (MEF)) to each tube, except for the double blank to which 120uL of appropriate acetonitrile:FA (100:1) was added.
3. Sealed and vortexed for one minute.
4. Centrifuged at 3000 rpm for 10 minutes.
5. Transferred 100uL of supernatant to a clean 96-well plate containing 100uL water.
6. Sealed and vortexed gently for 2 minutes.

[0153] The percent absolute bioavailability (F%) of MMF was determined by comparing the area under the MMF concentration vs time curve (AUC) following oral administration of MMF prodrug with the AUC of the MMF concentration vs time curve following intravenous administration of MMF on a dose normalized basis.

[0154] The MMF prodrugs, when administered orally to dogs at a dose of 10 mg/kg MMF-equivalents in the aqueous vehicle, exhibited an absolute oral bioavailability (relative to IV) ranging from about 31% to about 78% (See Table 7).

Table 7

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Percent Absolute Bioavailability (F%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>78%</td>
</tr>
</tbody>
</table>

Example 6- Physical Stability of the Instant Prodrugs and DMF in Crystalline Form

[0155] The physical stability of compounds of the present invention and DMF were measured via thermogravimetric analysis (TGA). Figure 6 shows a plot of weight loss at 60 °C vs time for Compound 14 (12.15 mg), no change, and DMF (18.40 mg). ~100 % weight loss in less than 4 hours. These data indicate that DMF undergoes sublimation while Compound 14 is physically stable under similar conditions.

Example 7- Single Crystal X-ray Data for Compound 14

[0156] Compound 14 produced by the method described in Example 1 was analyzed. Figure 7 depicts the unit cell. The single crystal x-ray data are included below:

Single crystal data:

Empirical formula: C11 H13 N O6

Formula weight: 255.22

Temperature: 173(2) K

Wavelength: 1.54178 Å

Space group: P-1
Unit cell dimensions:

1. \( a = 6.07750(10) \, \text{Å} \) \( \alpha = 84.9390(10)^\circ \).
2. \( b = 7.96290(10) \, \text{Å} \) \( \beta = 80.0440(10)^\circ \).
3. \( c = 12.7850(2) \, \text{Å} \) \( \gamma = 71.9690(10)^\circ \).

Volume: 579.080(15) Å\(^3\)

\( Z \): 2

Density (calculated): 1.464 Mg/m\(^3\)

Absorption coefficient: 1.034 mm\(^{-1}\)

\( F(000) \): 268

Crystal size: 0.37 x 0.15 x 0.15 mm\(^3\)

Reflections collected: 8446

Independent reflections: 2229 [R(int) = 0.0249]

Refinement method: Full-matrix least-squares on \( F^2 \)

Goodness-of-fit on \( F^2 \): 1.049

Final \( R \) indices [\( I > 2\sigma(I) \)]: \( R_1 = 0.0317, \, wR_2 = 0.0850 \)

\( R \) indices (all data): \( R_1 = 0.0334, \, wR_2 = 0.0864 \)

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader’s convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US61782445A
- US61934365A
Non-patent literature cited in the description


• **GREENE, T. W. WUTS, P. G. M.** Protective Groups in Organic Synthesis John Wiley & Sons 1999 00000 [0101]
Patentkrav

1. Forbindelse af formel (III), eller et farmaceutisk acceptabelt salt deraf:

![Chemical Structure](image)

hvor:

![Chemical Structure](image)

$R_1$ er usubstitueret C$_{1}$-C$_{6}$ alkyl;

$R_6$, $R_7$, $R_8$ og $R_9$ er hver, uafhængigt, H, substitueret eller usubstitueret C$_{1}$-C$_{6}$ alkyl, substitueret eller usubstitueret C$_{2}$-C$_{6}$ alkenyl, substitueret eller usubstitueret C$_{2}$-C$_{6}$ alkynyl eller C(O)OR$_a$;

$R_a$ er H eller substitueret eller usubstitueret C$_{1}$-C$_{6}$ alkyl;

m er 0, 1, 2, eller 3;

t er 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 eller 10; og

hver $R_{10}$ er, uafhængigt, H, halogen, substitueret eller usubstitueret C$_{1}$-C$_{6}$ alkyl, substitueret eller usubstitueret C$_{2}$-C$_{6}$ alkenyl, substitueret eller usubstitueret C$_{2}$-C$_{6}$ alkynyl, substitueret eller usubstitueret C$_{3}$-C$_{10}$ carbocykel, substitueret eller usubstitueret heterocykel omfattende en eller to 5- eller 6-leddet ringe og 1-4 heteroatomer valgt fra N, O og S, eller substitueret eller usubstitueret heteroaryl omfattende en eller to 5- eller 6-leddet ringe og 1-4 heteroatomer valgt fra N, O og S;
eller, alternativt, to \( R_{10} \) er fastgjort til det samme kulstofatom, sammen med kulstofatomet til hvilket de er fastgjort, danner et carbonyl, substitueret eller usubstitueret \( C_3-C_{10} \) carbocykel, substitueret eller usubstitueret heterocykel omfattende en eller to 5- eller 6-ledet ringe og 1-4 heteroatomer valgt fra N, O og S; eller substitueret eller usubstitueret heteroaryl omfattende en eller to 5- eller 6-ledet ringe og 1-4 heteroatomer valgt fra N, O og S;

eller, alternativt, to \( R_{10} \) er fastgjort til forskellige atomer, sammen med atomerne til hvilke de er fastgjort, danner et substitueret eller usubstitueret \( C_3-C_{10} \) carbocykel, substitueret eller usubstitueret heterocykel omfattende en eller to 5- eller 6-ledet ringe og 1-4 heteroatomer valgt fra N, O og S; eller substitueret eller usubstitueret heteroaryl omfattende en eller to 5- eller 6-ledet ringe og 1-4 heteroatomer valgt fra N, O og S.

2. Forbindelsen ifølge krav 1, hvor \( R_1 \) er methyl.

3. Forbindelsen ifølge krav 1 eller 2, hvor \( R_6, R_7, R_8 \) og \( R_9 \) er hver H.

4. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor \( m \) er 2 eller 3.

5. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor \( t \) er 0, 1, 2, 3, eller 4.

6. Forbindelsen ifølge et hvilket som helst af de foregående krav, hvor to \( R_{10} \) er fastgjort til det samme kulstofatom, sammen med kulstofatomet til hvilket de er fastgjort, danner et carbonyl.
7. Forbindelsen ifølge krav 1, hvor forbindelsen er:

```
\begin{align*}
&\text{\smaller F} \\
&\text{\smaller F} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.

5 8. Forbindelsen ifølge krav 1, hvor forbindelsen er:

```
\begin{align*}
&\text{\smaller O} \\
&\text{\smaller O} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.

9. Forbindelsen ifølge krav 1, hvor forbindelsen er:

```
\begin{align*}
&\text{\smaller O} \\
&\text{\smaller O} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.

10. Forbindelsen ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående af:

```
\begin{align*}
&\text{\smaller F} \\
&\text{\smaller F} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.

```
\begin{align*}
&\text{\smaller O} \\
&\text{\smaller O} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.

```
\begin{align*}
&\text{\smaller O} \\
&\text{\smaller O} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.

```
\begin{align*}
&\text{\smaller O} \\
&\text{\smaller O} \\
\end{align*}
```

eller et farmaceutisk acceptabelt salt deraf.
og

5 eller et farmaceutisk acceptabelt salt deraf.

11. Forbindelsen ifølge krav 1, hvor forbindelsen er valgt fra gruppen bestående af:

10

15
eller et farmaceutisk acceptabelt salt deraf.

12. Farmaceutisk sammensætning omfattende:
   (i) forbindelse af formel (III), eller et farmaceutisk acceptabelt salt deraf, 
   ifølge et hvilket som helst af kravene 1-11; og 
   (ii) en farmaceutisk acceptabel bærer.
13. Forbindelse af formel (III), et pharmaceutisk acceptabelt salt deraf, ifølge et hvilket som helst af kraven 1-11, eller en sammensætning ifølge krav 12, til anvendelse i behandling af en neurologisk sygdom.


15. Forbindelsen eller sammensætning til anvendelse ifølge krav 13, hvor den neurologiske sygdom er valgt fra relapserende-remitterende multipel sklerose, sekundær progressiv multipel sklerose, primær progressiv multipel sklerose, eller progressiv-relapserende multipel sklerose.