

A Novel 1,2,3,4-Tetrahydroquinoline Derivative Useful for the Treatment of Diabetes

Diabetes is a serious health care problem facing the developing world. It would be desirable to provide a safe and effective oral treatment for diabetes. Some successful commercially available oral treatments for type two diabetes (T2D) are believed to act through modulation of the peroxisome proliferator-activated receptor (PPAR) gamma receptor. Administration of these medicines has been associated with undesired adverse effects that sometimes include hypoglycemia, liver damage, gastrointestinal disease, weight gain, or other undesired effects that may be associated with the PPAR gamma activity. New treatment options offering a more desirable safety profile for managing T2D are desired to effectively treat or prevent diabetes in more patients. In particular, novel mechanism-based treatment methods that may minimize or avoid effects that have been associated with PPAR gamma activation are especially desired.

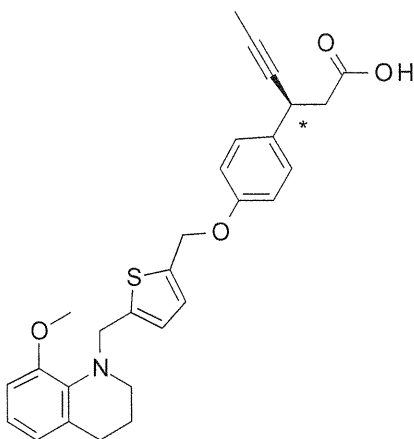
The G protein-coupled receptor 40 (GPR-40), also known as Free Fatty Acid Receptor 1 (FFA1 or FFAR1), is reported as predominately expressed at high levels in rodent pancreatic beta cells, insulinoma cell lines, and human islets. This receptor is activated by medium and long-chain fatty acids. The glucose dependency of insulin secretion is an important feature of activating GPR-40, making this receptor an excellent target for developing efficacious therapies with a desired safety profile for use in the treatment of T2D. Compounds that offer efficacy and a more desirable safety profile compared to existing therapies such as insulin and sulfonylureas can be especially desirable.

Two recently published patent applications, US20110092531 and WO2011066183 disclose compounds possessing a spiro-bicyclic group which exhibit GPR-40 activity.

This ~~invention~~disclosure provides a compound for the treatment of diabetes particularly T2D. The compound for this ~~invention~~disclosure is a potent activator of GPR-40. This ~~invention~~disclosure provides a desired novel treatment option acting through a pharmacological mechanism that is unique compared to commercially available treatments and further provides a compound that selectively activates GPR-40 as compared to PPAR gamma.

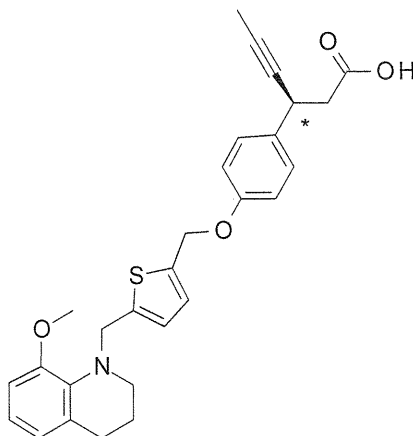
The pharmacological profile of the compound of this ~~invention~~disclosure, as a selective GPR-40 activator, can be particularly desirable for use in the treatment of T2D. Additionally, the selective GPR-40 modulation may provide a particularly desirable safety profile for use in the treatment of T2D by avoiding effects associated with PPAR gamma modulation.

In a first aspect, there is provided a compound which is:



or a pharmaceutically acceptable salt thereof.

The present ~~invention~~disclosure provides a compound of the Formula I below:



I

or a pharmaceutically acceptable salt thereof.

The compound of the present ~~invention~~disclosure can have a chiral carbon identified in the structure above with an asterisk (*). The preferred compound has the configuration shown above, which by convention is known as the S configuration.

In a second aspect, there is provided a pharmaceutical composition comprising a compound as defined above or a pharmaceutically acceptable salt thereof and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

The present ~~invention~~disclosure also provides a pharmaceutical composition comprising a compound of Formula I as described above or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers, diluents or excipients.

The present ~~invention~~disclosure also provides a pharmaceutical composition comprising a compound of Formula I as described above or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers, diluents or excipients, and optionally one or more therapeutic agents.

The present ~~invention~~disclosure also provides a method for treating diabetes in a mammal. The method comprises administering to the mammal in need of treatment a compound as described above for Formula I, or a pharmaceutically acceptable salt thereof. More preferably the present ~~invention~~disclosure provides a method of treating type two diabetes in a mammal in need of treatment by administering to the mammal a compound as described

above for Formula I or a pharmaceutically acceptable salt thereof. Preferably the mammal is a human.

The present ~~invention~~disclosure also provides a method for treating diabetes in a mammal by administering to the mammal in need of treatment a pharmaceutical composition comprising a compound as described above for Formula I, or a pharmaceutically acceptable salt thereof. More preferably the present ~~invention~~disclosure provides a method of treating type two diabetes in a mammal in need of treatment by administering to the mammal a pharmaceutical composition comprising a compound as described above for Formula I, or a pharmaceutically acceptable salt thereof. Preferably the mammal is a human.

In a third aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described above for use in therapy.

In a fourth aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described above for use in the treatment of diabetes in a mammal.

The present ~~invention~~disclosure provides a compound according to Formula I or a pharmaceutically acceptable salt thereof as described above for use in therapy.

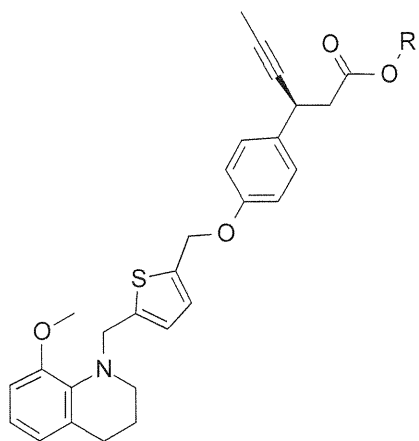
In yet another form, the present ~~invention~~disclosure provides a compound as described above according to Formula I, a pharmaceutically acceptable salt thereof, or pharmaceutical composition for use in the treatment of diabetes in a mammal in need thereof. Preferably the use is for the treatment of type two diabetes and the mammal is a human.

In a fifth aspect, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof, as described above in the manufacture of a medicament to treat diabetes.

The present ~~invention~~disclosure provides use of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of diabetes. Preferably the medicament is for the treatment of type two diabetes and for treating mammal particularly humans.

In yet another form, the present ~~invention~~disclosure provides an intermediate compound of the Formula II

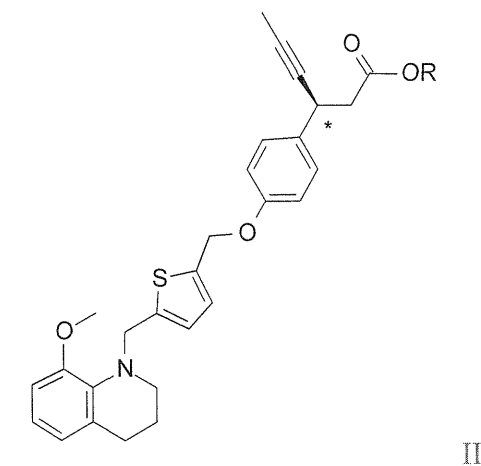
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II.

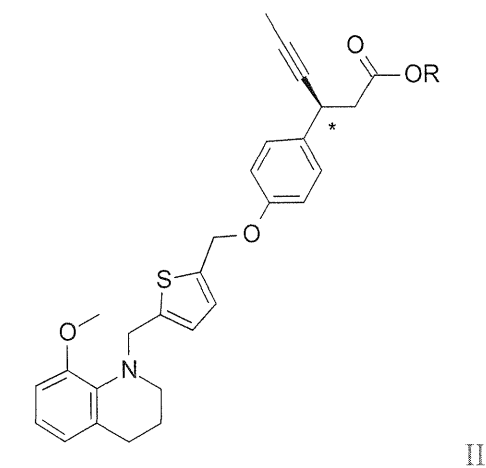
wherein R is selected from a C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₄ alkyl-C₃₋₆ cycloalkyl, phenyl, and C₁₋₅ alkylphenyl to provide a compound of Formula I, or a pharmaceutically acceptable salt thereof. Preferred R groups include C₁₋₂ alkyl, C₁₋₂ haloalkyl, phenyl, and C₁₋₂ alkylphenyl. Particularly preferred R groups include methyl, ethyl, phenyl, and benzyl.

In a sixth aspect, there is provided a compound according to formula II

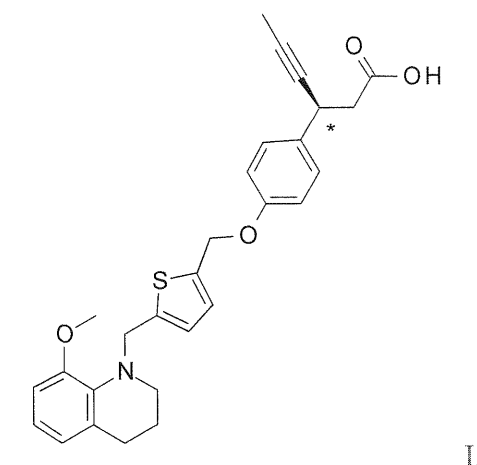


wherein R is selected from: C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₄ alkyl-C₃₋₆ cycloalkyl, phenyl, and C₁₋₅ alkylphenyl.

In a seventh aspect, there is also provided a method of preparing (3S)-3-[4-[[5-[(8-Methoxy-3,4-dihydro-2H-quinolin-1-yl)methyl]-2-thienyl]methoxy]phenyl]hex-4-ynoic acid or a pharmaceutically acceptable salt thereof, said method comprising de-esterifying a compound of formula II;



Where R is selected from: C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₄ alkyl-C₃₋₆ cycloalkyl, phenyl, and C₁₋₅ alkylphenyl to provide a compound of formula I, or a pharmaceutically acceptable salt thereof



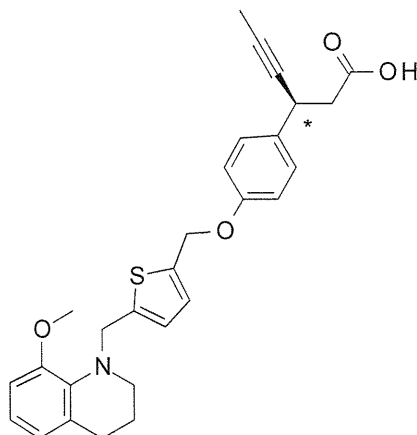
The present ~~invention~~disclosure also provides a process of preparing (3S)-3-[4-[[5-[(8-Methoxy-3,4-dihydro-2H-quinolin-1-yl)methyl]-2-thienyl]methoxy]phenyl]hex-4-ynoic acid described above for Formula I. The method comprises deprotecting or de-esterifying the intermediate compound according to Formula II to prepare the compound of Formula 1 or a pharmaceutically acceptable salt thereof.

One skilled in the art would readily understand and be able to implement deprotecting reactions without undue experimentation. It will be recognized by those skilled in the art that in addition to the carboxylic acid and protected carboxylic acid, other functional groups that can be readily converted to a carboxylic acid can be used in place the carboxylic acid or protected acid. Such functional groups, preparations, and transformations of these groups to carboxylic acids can be found in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" by Larock. R.C, Wiley VCH, 1999 and in "March's Advanced Organic Chemistry, Reactions, Mechanisms and Structure" Smith, M.B., and March, J., Wiley-Interscience, 6th Ed. 2007.

The compound of the present ~~invention~~disclosure, (3S)-3-[4-[[5-[(8-Methoxy-3,4-dihydro-2H-quinolin-1-yl)methyl]-2-thienyl]methoxy]phenyl]hex-4-ynoic acid, can be provided as a pharmaceutically acceptable salt. "Pharmaceutically-acceptable salt" refers to salts of the compound of the ~~invention~~disclosure considered to be acceptable for clinical and/or veterinary use. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. See, e.g., P. Stahl, *et al.*, Handbook of Pharmaceutical Salts: Properties, Selection and Use, (VCHA/Wiley-VCH, 2002); S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977.

What is claimed is:

1. A compound which is:



or a pharmaceutically acceptable salt thereof.

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2. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

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~~3. A pharmaceutical composition according to claim 2 further comprising one or more additional therapeutic agents.~~

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~~4. A method of treating diabetes in a mammal in need thereof, comprising administering to the mammal a compound, or a pharmaceutically acceptable salt thereof according to claim 1.~~

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~~5. A method of treating diabetes in a mammal in need thereof, comprising administering to the mammal a pharmaceutical composition according to claim 2 or 3.~~

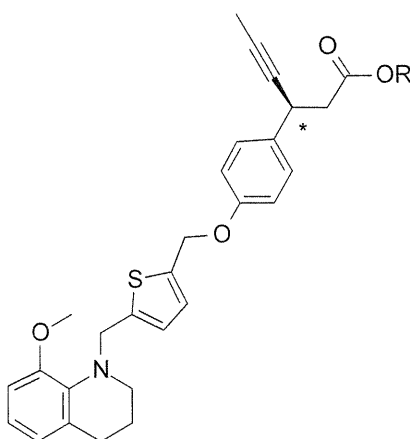
~~6. A method according to claim 4 or 5 wherein treating diabetes comprises treating a mammal for type two diabetes.~~

~~73.~~ A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 for use in therapy.

84. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 for use in the treatment of diabetes in a mammal.

95. Use of a compound, or a pharmaceutically acceptable salt thereof, according to claim 1 in the manufacture of a medicament to treat diabetes.

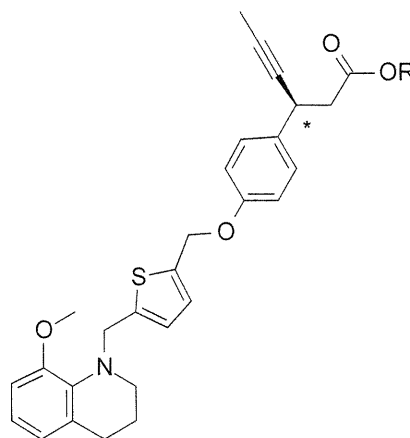
106. A compound according to formula II



II

wherein R is selected from: C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, C₁₋₄ alkyl-C₃₋₆ cycloalkyl, phenyl, and C₁₋₅ alkylphenyl.

117. A method of preparing (3S)-3-[4-[[5-[(8-Methoxy-3,4-dihydro-2H-quinolin-1-yl)methyl]-2-thienyl]methoxy]phenyl]hex-4-ynoic acid or a pharmaceutically acceptable salt thereof, said method comprising de-esterifying a compound of formula II;



II