PROCESS TO MAKE GLP1 RA AND INTERMEDIATES THEREFOR

TECHNICAL FIELD

Disclosed herein is a process for the synthesis of a GLP-1 receptor agonist, 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a salt thereof (herein, GLP1RA), or a hydrate of the salt.

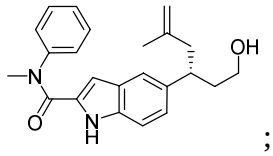
BACKGROUND

GLP1RA was described and claimed in US 10,858,356.

US 10,858,356 describes a synthetic process for preparing GLP1RA. Nevertheless, there is a need for an alternative process for preparing the compound. The process described herein provides one or more benefits over the known process as it goes through different intermediates. In one embodiment, the instant process is more robust and efficient. In one embodiment, the instant process is more scalable. In one embodiment, the instant process provides a higher yield.

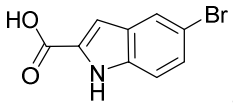
SUMMARY

In an aspect, there is provided a process for making compound 6 of the following structure:



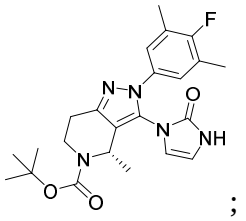
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comprising multi-step chemical reactions starting from compound 1 of the following structure:



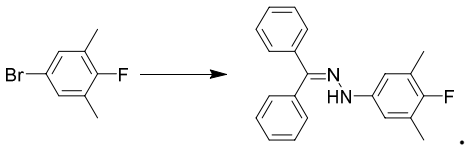
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In another aspect, there is provided a multi-step process for making compound 24 of the following structure:



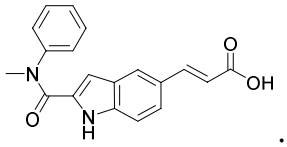
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comprising a chemical reaction from compound 19 to compound 20 as shown below:



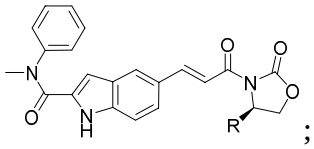
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In another aspect, there is provided a compound of the following structure:



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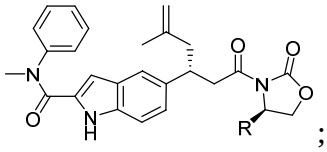
In another aspect, there is provided a compound of the following structure:



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wherein R aryl, heteroaryl, alkyl, cycloalkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, arylalkynyl, or heteroarylalkynyl.

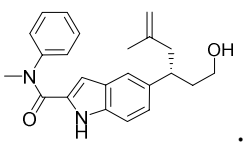
In another aspect, there is provided a compound of the following structure:



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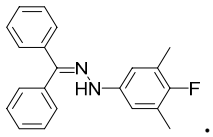
wherein R is aryl, heteroaryl, alkyl, cycloalkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, arylalkynyl, or heteroarylalkynyl.

In another aspect, there is provided a compound of the following structure:

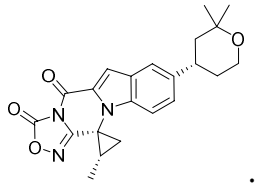


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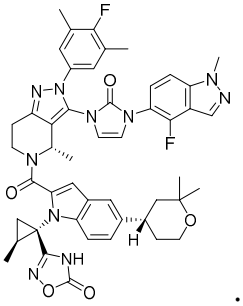
In another aspect, there is provided a compound of the following structure:



In another aspect, there is provided a compound of the following structure:



In another aspect, there is provided the process or compounds as described herein, wherein the process or compound is used in the manufacture of compound 35 having the following structure:



DESCRIPTION

GLP1RA may be prepared as a pharmaceutically acceptable salt. One salt of GLP1RA is a hemi-calcium salt of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one (herein "GLP1RA ½ Ca^{2+}") with the structure as shown below.

