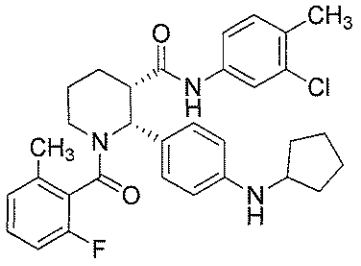
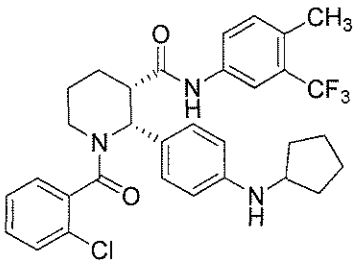


IA



IB



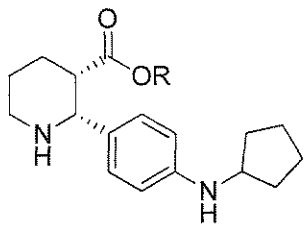
IC

The preparation of compound IA has been provided as shown in Fig. 4, and involves a lengthy synthesis including a classical resolution of isomers (see, for example, the conversion of **6** to **7**).

[0012] There exists a need in the art for more efficient methods of preparation of compounds IA, IB and IC. The present disclosure provides such methods, as well as intermediates in the synthetic pathways.

BRIEF SUMMARY

[0013] Provided herein is a compound useful in the preparation of several C5aR antagonists, having the formula (i-3):

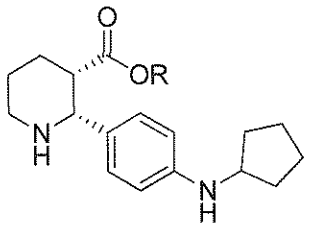


(i-3)

(2R,3S)

wherein R is selected from H, C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, or a salt thereof, which is substantially free of enantiomeric or diastereomeric impurities (the (2R,3R), (2S,3R) and (2S,3S) isomers).

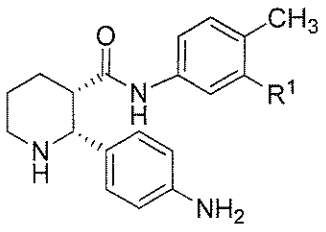
[0013a] In one aspect of the present disclosure, there is provided a compound having the formula (i-3):



(i-3)

wherein R is selected from the group consisting of H, C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.

[0014] There is also provided herein is a compound useful in the preparation of several C5aR antagonists, the compound having the formula (ii-4):

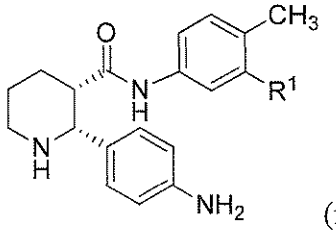


(ii-4)

(2R,3S)

or a salt thereof, wherein R^1 is Cl or CF_3, and wherein the compound is substantially free of enantiomeric or diastereomeric impurities (the corresponding (2R,3R), (2S,3R) and (2S,3S) isomers).

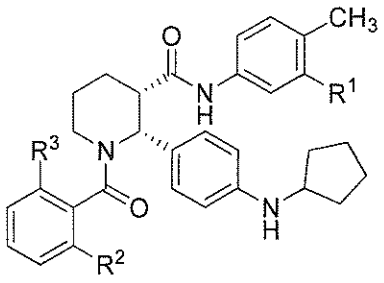
[0014a] In another aspect of the present disclosure, there is provided a compound having the formula (ii-4):



(ii-4)

wherein R^1 is Cl or CF_3, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.

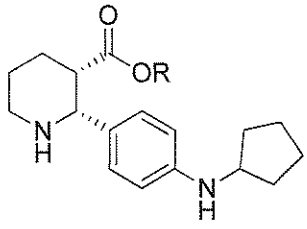
[0015] There is further provided herein is a method of preparing a compound having formula (I):



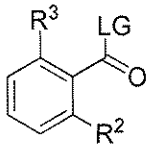
(I)

or a salt thereof, wherein R^1 is Cl or CF_3; R^2 is F or Cl; and R^3 is H or CH_3; and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, the method comprising:

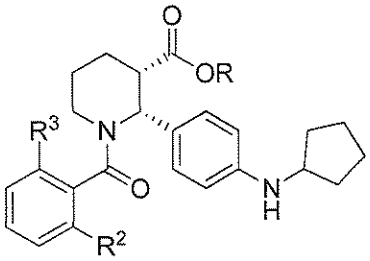
(a) contacting a compound having the formula (i-3):


(i-3)

wherein R is selected from C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, which is substantially free of enantiomeric or diastereomeric impurities, or a salt thereof, with a compound having the formula:



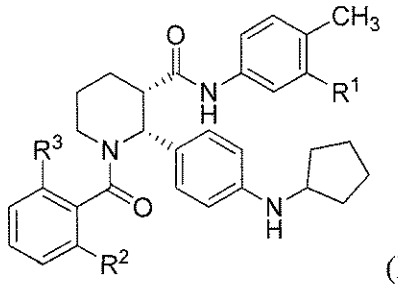
wherein LG is a leaving group; under conditions sufficient to form a compound of formula (i-4):



(i-4); and

(b) converting the compound of formula (i-4) to said compound of formula (I) wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities.

[0015a] In a further aspect of the present disclosure, there is provided a method of preparing a compound having formula (I):



(I)

or a salt thereof, wherein

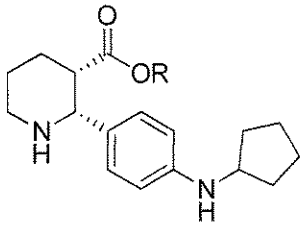
R^1 is Cl or CF_3;

R^2 is F or Cl; and

R^3 is H or CH_3;

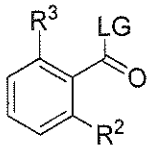
and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, said method comprising:

(a) contacting a compound having the formula (i-3):

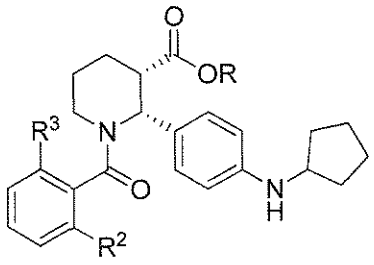


(i-3)

wherein R is selected from the group consisting of H, C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, which is substantially free of enantiomeric or diastereomeric impurities, or a salt thereof, with a compound having the formula:



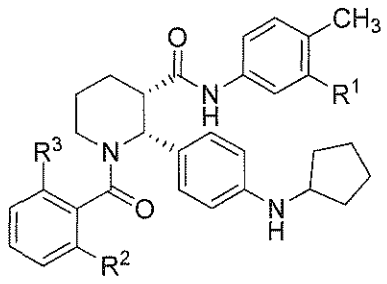
wherein LG is a leaving group; R^2 is F or Cl; and R^3 is H or CH_3; under conditions sufficient to form a compound of formula (i-4):



(i-4); and

(b) converting said compound of formula (i-4) to said compound of formula (I) wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities.

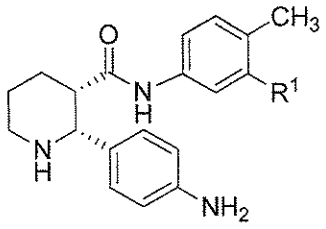
[0016] There is also provided herein is another method of preparing a compound having formula (I):



(I)

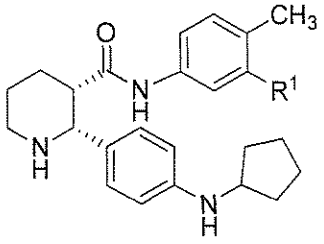
or a salt thereof, wherein R^1 is Cl or CF_3; R^2 is F or Cl; and R^3 is H or CH_3; and wherein the compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, the method comprising:

(a) contacting a compound having the formula (ii-4):



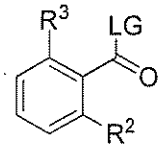
(ii-4)

or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities, with cyclopentanone and a reducing agent under conditions sufficient to form a compound having the formula (ii-5):



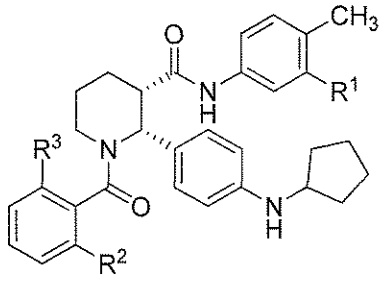
(ii-5) ; and

(b) contacting said compound of formula (ii-5) with a compound having the formula:



wherein LG is a leaving group; under conditions sufficient to form a compound of formula (I) which is substantially free of enantiomeric or diastereomeric impurities.

[0016a] In another aspect of the present disclosure, there is provided a method of preparing a compound having formula (I):



(I)

or a salt thereof, wherein

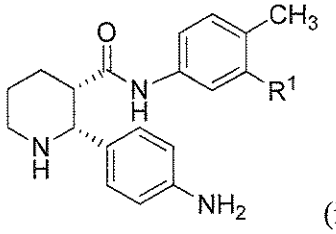
R^1 is Cl or CF_3;

R^2 is F or Cl; and

R^3 is H or CH_3;

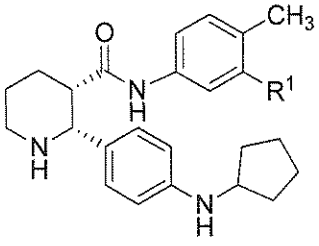
and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, said method comprising:

(a) contacting a compound having the formula (ii-4):



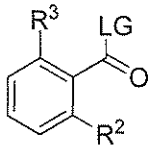
(ii-4)

wherein R^1 is Cl or CF_3; or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities, with cyclopentanone and a reducing agent under conditions sufficient to form a compound having the formula (ii-5):



(ii-5) ; and

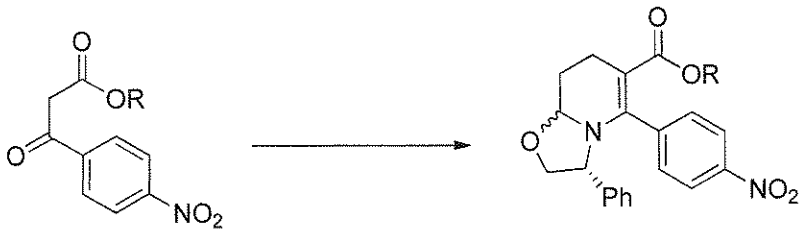
(b) contacting said compound of formula (ii-5) with a compound having the formula:



wherein LG is a leaving group, R^2 is F or Cl; and R^3 is H or CH_3; under conditions sufficient to form a compound of formula (I) which is substantially free of enantiomeric or diastereomeric impurities.

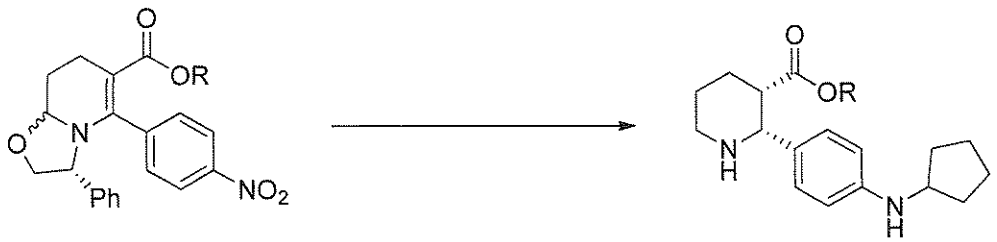
[0016b] In a further aspect of the present disclosure, there is provided a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or rotamer thereof, comprising any two, three or four of the steps (a), (b), (c), and (d), or optionally steps (d1) and (d2), which steps can be contiguous in the synthetic scheme or non-contiguous:

(a) reacting an ester of 3-(4-nitrophenyl)-3-oxo-propanoate (i-1) wherein R is selected from the group consisting of C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, (*R*)-(−)-2-phenylglycinol, and acrolein diethyl acetal or an equivalent thereof, to produce compound (i-2);



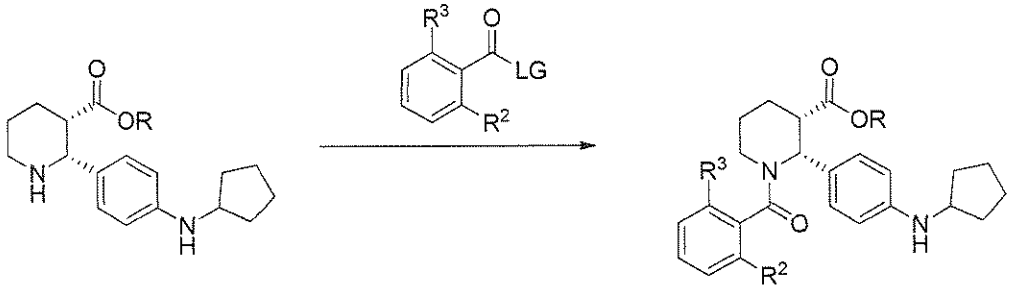
(i-1) (i-2)

(b) hydrogenating or reducing and (i-2) to produce an intermediate amine and converting the intermediate to (i-3) with cyclopentanone and a reducing agent;



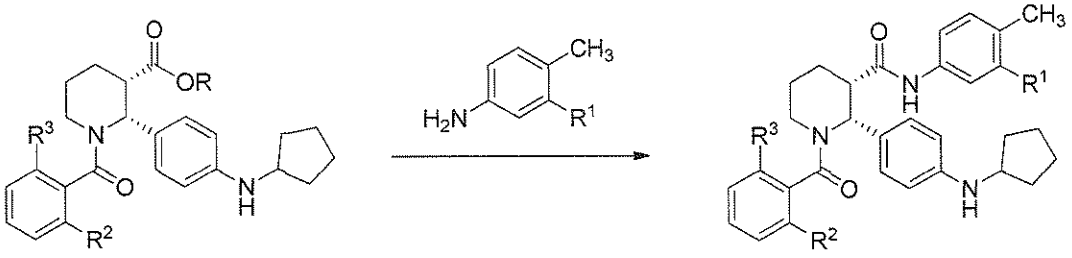
(i-2) (i-3)

(c) combining (i-3) with either 2-fluoro-6-methylbenzoyl chloride or 2-chlorobenzoyl chloride to provide (i-4);



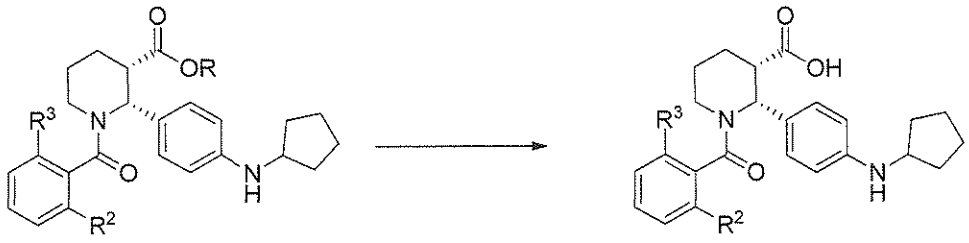
(i-3) (i-4)

(d) combining (i-4) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline under conditions sufficient to provide a compound of formula (I);



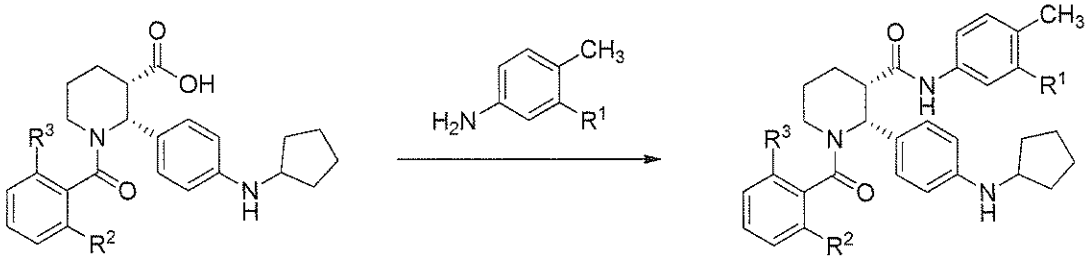
(i-4) (I)

(d)(1) conversion of the ester (i-4) to a carboxylic acid (i-5):



(i-4) (i-5)

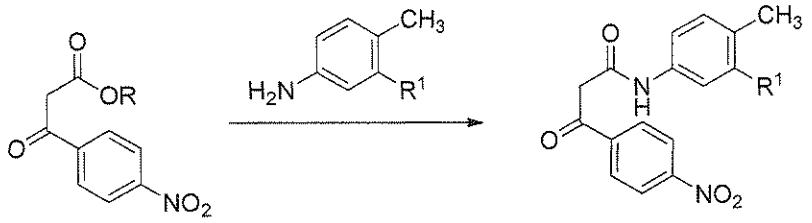
(d)(2) combining (i-5) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline under conditions sufficient to provide a compound of formula (I)



(i-5) (I).

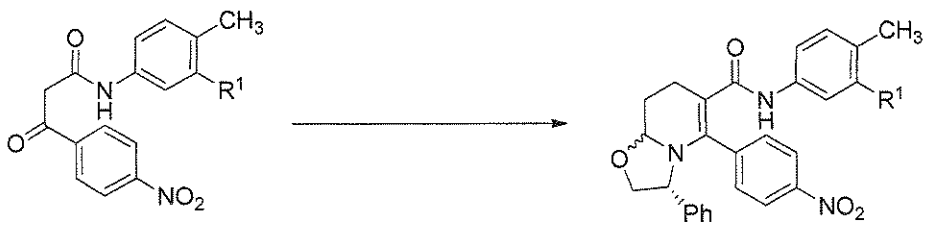
[0016c] In another aspect of the present disclosure, there is provided a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or rotamer thereof, comprising any two, three or four of the steps (a'), (b'), (c'), (d') and (e'), which steps can be contiguous in the overall synthetic pathway, or non-contiguous:

(a') reacting an ester of 3-(4-nitrophenyl)-3-oxo-propanoate (i-1, or ii-1, wherein R is selected from the group consisting of C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline under conditions sufficient to provide a compound of formula (ii-2);



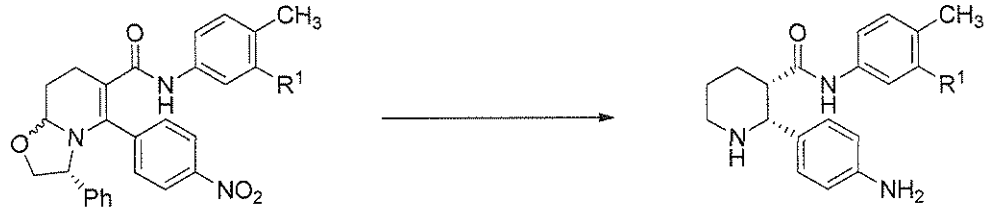
(i-1, ii-1) (ii-2)

(b') reacting (ii-2), (*R*)-(−)-2-phenylglycinol, and acrolein diethyl acetal or an equivalent thereof, to produce compound (ii-3);



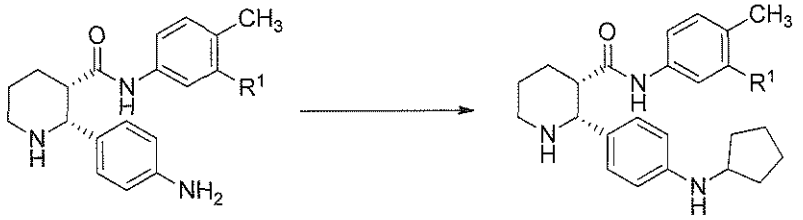
(ii-2) (ii-3)

(c') reducing (ii-3) under conditions sufficient to produce an intermediate diamine (ii-4) that is substantially free of enantiomeric or diastereomeric impurities;



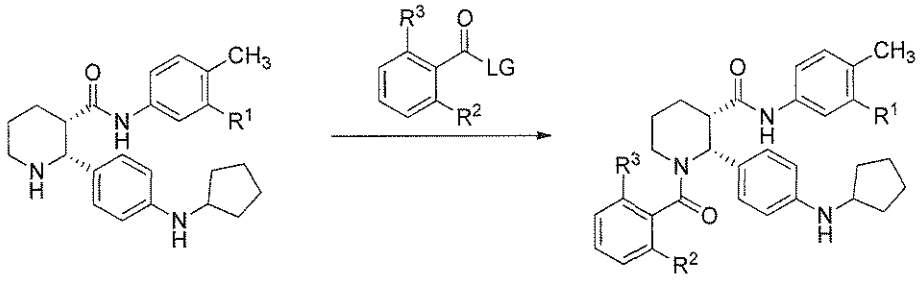
(ii-3) (ii-4)

(d') converting (ii-4) to (ii-5) with cyclopentanone and a reducing agent; and



(ii-4) (ii-5)

(e') combining (ii-5) with either 2-fluoro-6-methylbenzoyl chloride or 2-chlorobenzoyl chloride to provide (I);



(ii-5) (I).

[0017] *Still other processes are provided as described below having two, three, or four or more* synthetic transformations resulting in the preparation of compounds IA, IB and/or IC, or their pharmaceutically acceptable salts.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Fig. 1 provides a scheme generally illustrating the steps useful in preparation compounds IA, IB and IC, utilizing a hydrogenation step to set the (2R,3S) stereochemistry, followed by a reductive amination of cyclopentanone, benzoylation of the piperidine nitrogen, and addition of an aniline to form the C3 amide.

[0019] Fig. 2 provides a scheme in which the C3 amide formation (final step of Scheme 1) is carried out via conversion of a C3 ester to a C3 carboxylic acid – which upon treatment with a suitable aniline can provide compounds such as IA, IB and IC.

[0020] Fig. 3 provides a scheme in which the C3 amide is constructed at an earlier stage of synthesis, followed by steps in which hydrogenation is used to set the (2R,3S) stereochemistry, followed by a reductive amination of cyclopentanone, and concluding with benzoylation of the piperidine nitrogen to provide compounds such as IA, IB and IC.

[0021] Fig. 4 provides a scheme for the preparation of IA as described in U.S. Patent No. 8,445,515 B2, utilizing a classical resolution step to prepare compound **7** having (2R,3S) stereochemistry.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0022] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* $C_{1\text{-}8}$ means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-