PROCESS FOR PREPARING BIPHENYL IMIDAZOLE COMPOUNDS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to processes and intermediates for preparing biphenyl imidazole compounds that are useful in preparing compounds having angiotensin II type 1 receptor antagonist activity and neprilysin-inhibition activity.

STATE OF THE ART

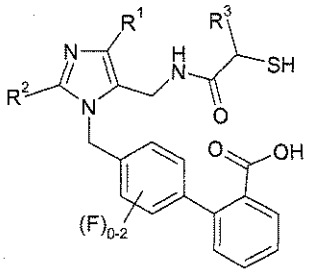
Commonly-assigned U.S. Publication Nos. 2008/0269305 and 2009/0023228, both to Allegretti et al. filed on April 23, 2008, disclose novel compounds that possess AT_1 receptor antagonist activity and neprilysin (NEP) enzyme inhibition activity, the disclosures of which are incorporated herein by reference. In one embodiment, these applications disclose novel compounds such as 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

When preparing compounds for long term storage and when preparing pharmaceutical compositions and formulations, it is often desirable to have a crystalline form of the therapeutic agent that is neither hygroscopic nor deliquescent. It is also advantageous to have a crystalline form that has a relatively high melting point, which allows the material to be processed without significant decomposition. A crystalline freebase form of 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid is disclosed in commonly-assigned U.S. Publication No. 2010/0081697, to Chao et al. filed on September 29, 2009, the disclosure of which is incorporated herein by reference.

The compounds disclosed in these publications and applications are prepared by techniques that typically require that one or more biphenyl imidazole intermediates are purified by chromatography. There are several advantages to developing processes where such purification steps are not necessary. This invention addresses that need.

SUMMARY ~~OF THE INVENTION~~

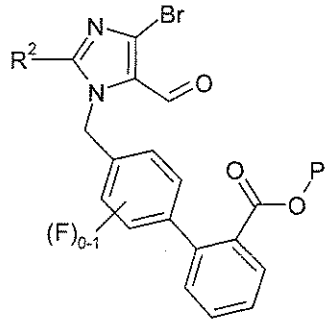
The present ~~invention~~disclosure relates to novel intermediates and improved processes for preparing intermediates useful for preparing compounds of formula IV:



(IV)

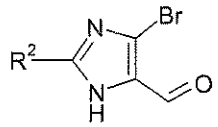
or a salt thereof, where R^1 is -C_{1-6}alkyl; R^2 is -O-C_{1-5}alkyl; and R^3 is -C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, or -C_{0-3}alkylene-C_{3-7}cycloalkyl. In one particular embodiment, the ~~invention~~ present disclosure relates to processes for preparing intermediates useful for preparing 4'-{2-ethoxy-4-ethyl-5-[(*(S)*-2-mercapto-4-methylpentanoylamino)methyl] imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

One ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a process for preparing a compound of formula I:



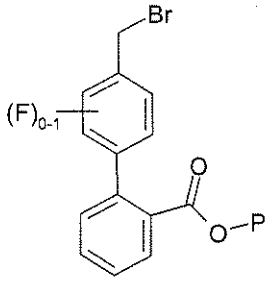
(I)

where R^2 is -O-C_{1-5}alkyl; and P is a carboxylic acid protecting group; the process comprising the step of reacting a compound of formula 1:



(1)

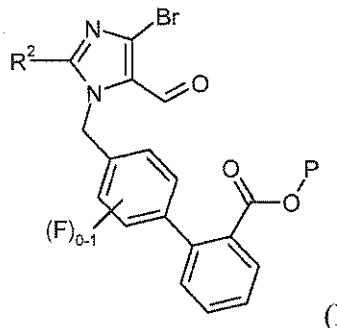
with a compound of formula 2:



(2)

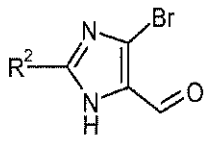
in an organic diluent and a basic aqueous diluent in the presence of a phase transfer catalyst, where the diluents are substantially immiscible, to form a compound of formula I.

In an aspect, there is provided a process for preparing a compound of formula I



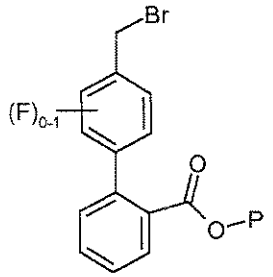
(I)

where R^2 is -0-C_{1-5}alkyl and P is a carboxylic acid protecting group being selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; the process comprising the step of reacting a compound of formula 1 :



(1)

with a compound of formula 2:

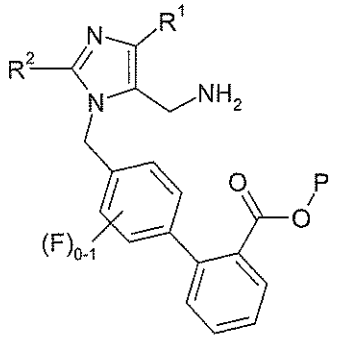


(2)

in an organic diluent and a basic aqueous diluent in the presence of a phase transfer catalyst, where the diluents do not mix to form a solution, to form a compound of formula I.

In one embodiment, this process further comprises the step of preparing a crystalline form of the compound of formula I. One ~~aspect~~embodiment of the ~~invention~~present disclosure relates to crystalline 4'-(4-bromo-2-ethoxy-5-formylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid tert-butyl ester.

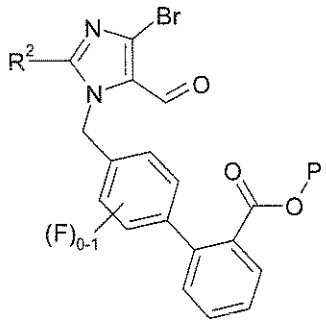
Another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a process for preparing a compound of formula II:



(II)

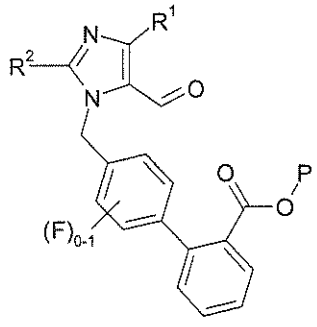
or a salt thereof; where R^1 is -C_{1-6} alkyl; R^2 is -O-C_{1-5}alkyl; and P is a carboxylic acid protecting group; the process comprising the steps of:

(a) reacting a compound of formula I:



(I)

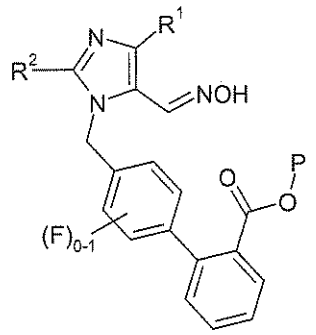
with a potassium-C_{1-6}alkyl-trifluoroborate reagent in the presence of a palladium-phosphine catalyst to form a compound of formula 3:



(3)

;

(b) reacting the compound of formula 3 with hydroxylamine or a salt thereof to form a compound of formula 4:



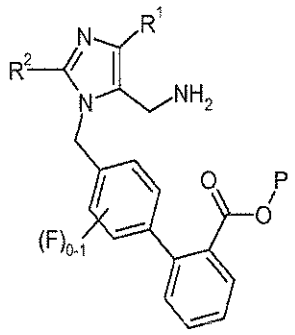
(4)

;

and

(c) reacting the compound of formula 4 with a reducing agent to form a compound of formula II or a salt thereof.

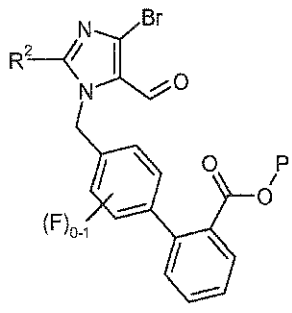
In another aspect, there is provided a process for preparing a compound of formula II:



(II)

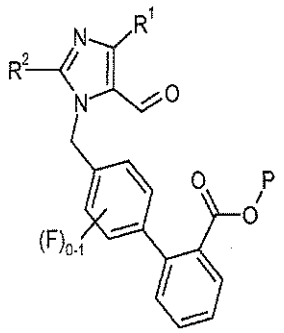
or a salt thereof; where R^1 is -C_{1-6} alkyl; R^2 is -O-C_{1-5}alkyl; and P is a carboxylic acid protecting group being selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; the process comprising the steps of:

(a) reacting a compound of formula I prepared according to the process as defined above:



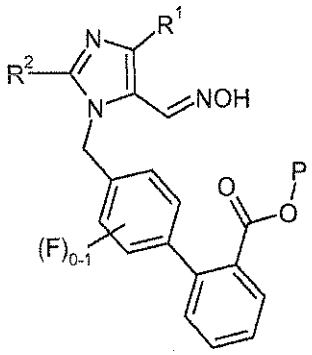
(I)

with a potassium-C_{1-6}alkyl-trifluoroborate reagent in the presence of a palladium-phosphine catalyst to form a compound of formula 3:


(3)

;

(b) reacting the compound of formula 3 with hydroxylamine or a salt thereof to form a compound of formula 4:

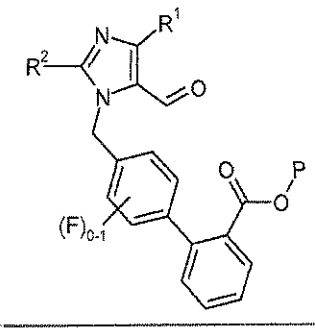

(4)

and

(c) reacting the compound of formula 4 with a reducing agent to form a compound of formula II or a salt thereof.

In one embodiment, this process further comprises the step of preparing a crystalline form of the compound of formula II. One ~~aspect~~embodiment of the ~~invention~~present disclosure relates to crystalline 4'-(5-aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester.

In an aspect, there is provided a compound of formula 3:


(3)

where R^1 is -C_{1-6}alkyl; R^2 is -O-C_{1-5}alkyl; and P is a carboxylic acid protecting group being selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl.

In another aspect, there is provided crystalline 4'-(5 -aminomethyl-2-ethoxy-4-ethylimidazol- 1 -ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 5.24±0.2, 10.43±0.2, 15.65±0.2, 20.63±0.2, and 31.91±0.2.

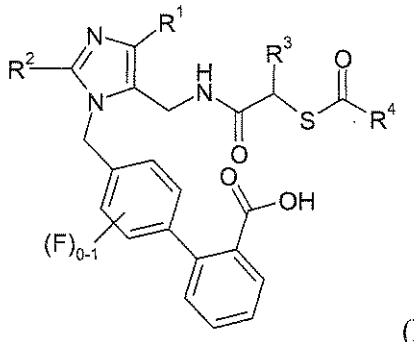
In yet another aspect, there is provided a process for preparing the crystalline compound as defined above, comprising:

a) treating 4'-(5 -aminomethyl-2-ethoxy-4-ethylimidazol- 1 -ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester with heptanes to complete dissolution;

b) cooling to effect crystallization; and

c) isolating the resulting solids to yield the crystalline compound as defined above.

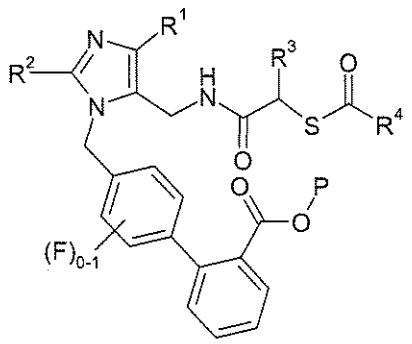
Yet another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a process for preparing a compound of formula III:



(III)

or a salt thereof; where R^1 is -C_{1-6}alkyl; R^2 is -O-C_{1-5}alkyl; R^3 is -C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, or -C_{0-3}alkylene-C_{3-7}cycloalkyl; and R^4 is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl, -C_{0-6}alkylenearyl, or -C_{0-6}alkylenemorpholine; the process comprising the steps of:

(a) reacting a compound of formula I:

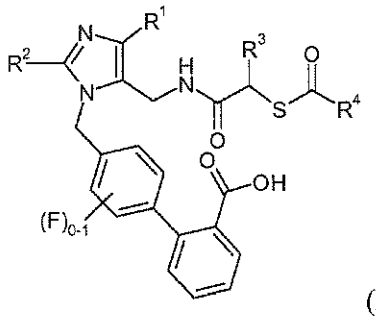


(6)

or a salt thereof; and

(e) removing the carboxylic acid protecting group, P, from the compound of formula 5 or a salt thereof, to form a compound of formula III or a salt thereof.

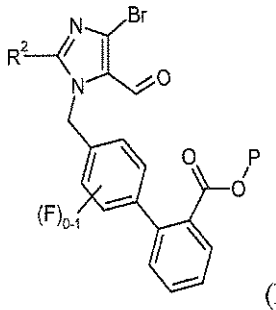
In yet another aspect, there is provided a process for preparing a compound of formula III:



(III)

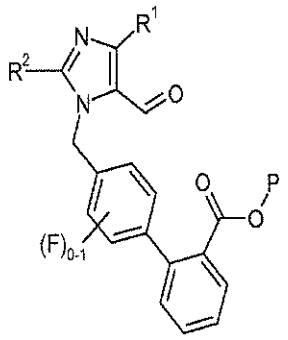
or a salt thereof; where R^1 is -C_{1-6}alkyl; R^2 is -O-C_{1-5}alkyl; R^3 is -C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, or -C_{0-3}alkylene-C_{3-7}cycloalkyl; and R^4 is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl, -C_{0-6}alkylenearyl, or -C_{0-6}alkylenemorpholine; the process comprising the steps of:

(a) reacting a compound of formula I prepared according to the process as defined above:



(I)

with a potassium-C_{1-6}alkyl-trifluoroborate reagent in the presence of a palladium-phosphine catalyst to form a compound of formula 3:

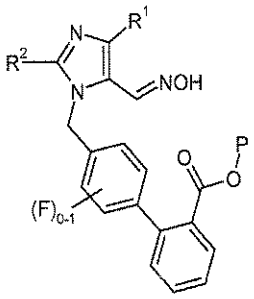


(3)

,

where P is a carboxylic acid protecting group being selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl;

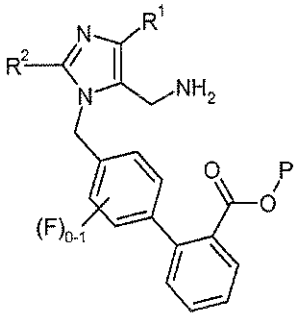
(b) reacting the compound of formula 3 with hydroxylamine or a salt thereof to form a compound of formula 4:



(4)

;

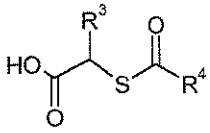
(c) reacting the compound of formula 4 with a reducing agent to form a compound of formula II:



(II)

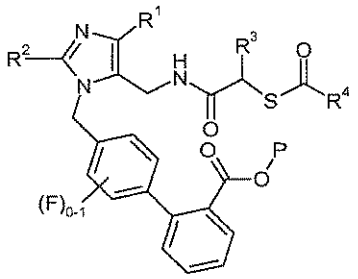
or a salt thereof;

(d) reacting the compound of formula II or a salt thereof with a compound of formula 5 :



(5)

or a salt thereof, in the presence of an amine-carboxylic acid coupling reagent to form a compound of formula 6:



(6)

or a salt thereof; and

(e) removing the carboxylic acid protecting group, P, from the compound of formula 6 or a salt thereof, to form a compound of formula III or a salt thereof.

In one embodiment, this process further comprises the step of preparing a crystalline form of the compound of formula III. One ~~aspect~~embodiment of the ~~invention~~present disclosure relates to crystalline 4'-{5-[(*(S)*-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

In an aspect, there is provided crystalline 4'- {5-[(*(S)*-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid, characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 5.24±0.2, 7.16±0.2, 13.68±0.2, and 15.98±0.2.

In another aspect, there is provided a process for preparing the crystalline compound as defined above, comprising:

a) treating 4'- {5-[(*(S)*-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid with isopropyl acetate to complete dissolution;

b) cooling to effect crystallization; and

c) isolating the resulting solids to yield the crystalline compound as defined above.

Another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a novel intermediates used in the processes of the ~~invention~~present disclosure. In one such ~~aspect of the invention~~embodiment novel intermediates have formula 3 or 4.

BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the present invention are illustrated by reference to the accompanying drawings.

FIG. 1 shows a powder x-ray diffraction (PXRD) pattern of the crystalline form of 4'-(5-aminomethyl-2-ethoxy-4-ethylimidazol-1-ylmethyl)-3'-fluorobiphenyl-2-carboxylic acid *t*-butyl ester (formula IIa). FIG. 2 shows a differential scanning calorimetry (DSC) thermograph and a thermal gravimetric analysis (TGA) for this crystalline compound.

FIG. 3 shows a powder x-ray diffraction (PXRD) pattern of the crystalline form of 4'-{5-[(*(S)*-2-acetylsulfanyl-4-methylpentanoylamino)methyl]-2-ethoxy-4-ethylimidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid (formula IIIa). FIG. 4 shows a DSC thermograph and a TGA for this crystalline compound.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to novel processes for preparing compounds of formula I: