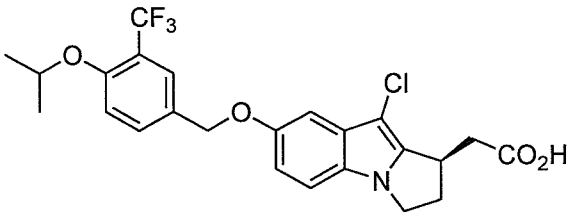
(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**):



(Ia)

has emerged as an important new compound, see PCT patent application, Serial No. PCT/US2009/004851 hereby incorporated by reference in its entirety. Accordingly, new and efficient routes leading to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid, salts, intermediates, and crystalline forms related thereto are needed. The processes and compounds described herein help meet these and other needs.

SUMMARY

The present dislcosure provides, *inter alia*, salts, crystalline forms, and processes for the preparation (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**).

The processes and intermediates of the present disclosure are useful in preparing (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid. The compound (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid is useful in the treatment of S1P1 receptor-associated disorders, such as, psoriasis and multiple sclerosis.

One embodiment of the present disclosure is directed to salts and crystalline forms thereof selected from the group consisting of:

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl) acetic acid sodium salt hydrate;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid ethylenediamine salt hydrate;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid 2-amino-2-hydroxymethyl-propane-1,3-diol (TRIS) salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-arginine salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid zinc salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid calcium salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid *N*-methylglucamine salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid potassium salt; and

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid magnesium salt.

In one aspect, there is provided a salt selected from:

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt hydrate;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid ethylenediamine salt hydrate;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid 2-amino-2-hydroxymethyl-propane-1,3-diol salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-arginine salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid zinc salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid calcium salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid *N*-methylglucamine salt;

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid potassium salt; and

(*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid magnesium salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt hydrate.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid ethylenediamine salt hydrate.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid 2-amino-2-hydroxymethyl-propane-1,3-diol (TRIS) salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-arginine salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid zinc salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid calcium salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid *N*-methylglucamine salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid potassium salt.

One embodiment of the present disclosure is directed to (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid magnesium salt.

One embodiment of the present disclosure is directed a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

In one aspect, there is provided a crystalline form of the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.9 ° and about 11.4 °.

In one aspect, there is provided a crystalline form of the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.7 °, about 21.7 °, and about 22.9 °.

In one aspect, there is provided a crystalline form of the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.6 °, about 13.7 °, about 19.8 °, about 20.6 °, about 21.7 °, about 22.1 °, and about 22.9 °.

In one aspect, there is provided a crystalline form of the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt having an X-ray powder diffraction pattern substantially as shown in Figure 4.

In one aspect, there is provided a crystalline form of the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt having:

1) an X-ray diffraction pattern comprising peaks, expressed in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.7 °, about 21.7 °, and about 22.9 °;
2) a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 213 °C and about 217 °C; and/or
3) a thermogravimetric analysis profile showing less than about 0.1% weight loss up to about 110 °C.

In one aspect, there is provided a crystalline form of the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt having:

1) an X-ray diffraction pattern comprising peaks, expressed in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.6 °, about 13.7 °, about 19.8 °, about 20.6 °, about 21.7 °, about 22.1 °, and about 22.9 °;

2) a differential scanning calorimetry thermogram comprising an endotherm with a first extrapolated onset temperature between about 213 °C and about 217 °C; and a second extrapolated onset temperature between about 220 °C and about 224 °C; and/or

3) a thermogravimetric analysis profile showing less than about 0.1% weight loss up to about 110 °C.

One aspect of the present invention is directed to compositions comprising a salt or a crystalline form, each as described herein.

One aspect of the present invention is directed to pharmaceutical compositions comprising a salt or a crystalline form, each as described herein, and a pharmaceutically acceptable carrier.

One embodiment of the present disclosure is directed to methods for treating an S1P1 receptor-associated disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating a disease or disorder mediated by lymphocytes in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating an autoimmune disease or disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating an inflammatory disease or disorder in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating a microbial infection or disease in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating a viral infection or disease in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating cancer in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein.

One embodiment of the present disclosure is directed to methods for treating a disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a salt, a crystalline form, or a pharmaceutical composition, each as described herein, wherein said disorder is selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

One aspect of the present invention pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of an S1P1 receptor-associated disorder.

One aspect of the present invention pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, or biliary cirrhosis.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of a disease or disorder mediated by lymphocytes.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of an autoimmune disease or disorder.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of an inflammatory disease or disorder.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of a microbial infection or disease.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of a viral infection or disease.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of cancer.

One embodiment of the present disclosure pertains to the use of a salt or a crystalline form, each as described herein, in the manufacture of a medicament for the treatment of an S1P1 receptor-associated disorder selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive

nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

One aspect of the present invention pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of the human or animal body by therapy.

One aspect of the present invention pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of an S1P1 receptor-associated disorder.

One aspect of the present invention pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, or biliary cirrhosis.

One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of a disease or disorder mediated by lymphocytes.

One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of an autoimmune disease or disorder.

One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of an inflammatory disease or disorder.

One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of a microbial infection or disease.

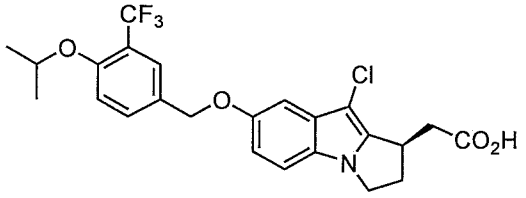
One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of a viral infection or disease.

One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of cancer.

One embodiment of the present disclosure pertains to a salt, a crystalline form, or pharmaceutical composition, each as described herein, for use in a method for the treatment of an S1P1 receptor-associated disorder selected from the group consisting of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, and biliary cirrhosis.

One aspect of the present invention pertains to processes for preparing compositions comprising admixing a salt or a crystalline form, each as described herein, and a pharmaceutically acceptable carrier.

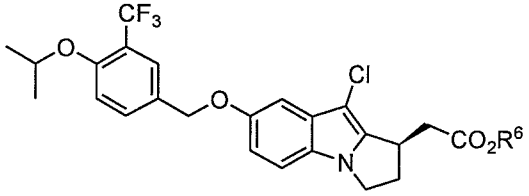
In one aspect, there is provided a process for preparing an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**):



(**Ia**),

comprising the steps of:

a) hydrolyzing said compound of Formula (**IIn**):



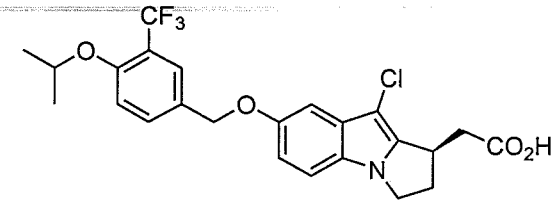
(**IIn**),

wherein R^6 is C_1-C_4 alkyl;

in the presence of a hydrolyzing-step base and a hydrolyzing-step solvent to form said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid; and

b) contacting said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid with L-lysine or a salt thereof, in the presence of a contacting-step solvent and H_2O to form said L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

In one aspect, there is provided a process for preparing an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**):

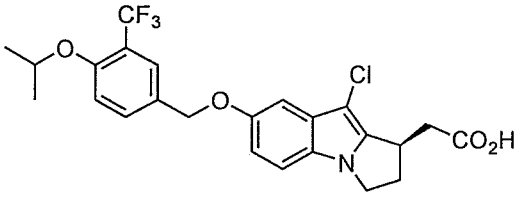


(**Ia**),

comprising the step of:

contacting the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid with L-lysine or a salt thereof, in the presence of a contacting-step solvent and H_2O to form said L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

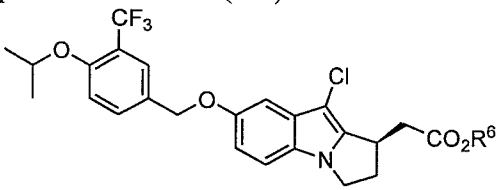
In one aspect, there is provided a process for preparing (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**):



(**Ia**),

comprising the step of:

hydrolyzing a compound of Formula (**IIn**):



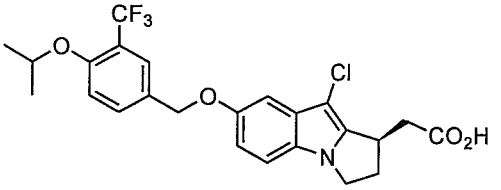
(**IIn**)

,

wherein R^6 is C_1-C_4 alkyl;

in the presence of a hydrolyzing-step base and a hydrolyzing-step solvent to form said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

The present disclosure further provides, *inter alia*, processes for preparing an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**):

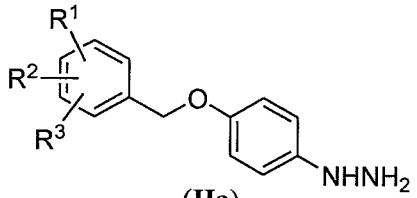


(**Ia**)

,

comprising the following steps:

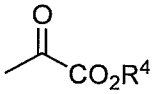
a) reacting a compound of Formula (**IIa**) or a salt thereof:



(**IIa**)

,

wherein R^1, R^2, and R^3 are each selected independently from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, and nitro; with a compound of:

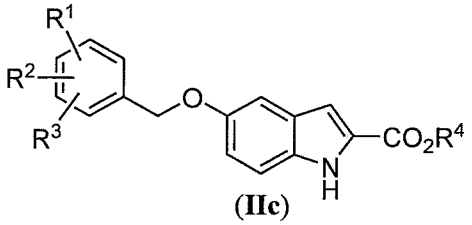


(**IIb**)

,

wherein R^4 is C_1-C_4 alkyl;

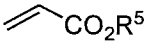
in the presence of an indole-forming-step acid and an indole-forming-step solvent to form a compound of Formula (**IIc**):



(**IIc**)

,

b) cyclizing the compound of Formula (**IIc**) with a compound of Formula (**IId**):



(**IId**)

,

wherein R^5 is C_1-C_4 alkyl;

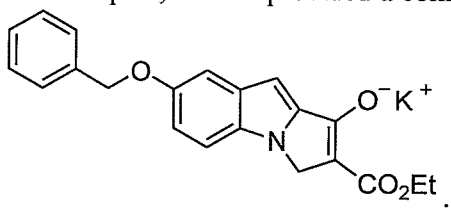
in the presence of an alkali metal C_1-C_4 alkoxide base and a cyclizing-step solvent to form a compound of Formula (**IIe**), or a keto tautomer thereof:

j) contacting the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid with L-lysine or a salt thereof, in the presence of a contacting-step solvent and H_2O to form the L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

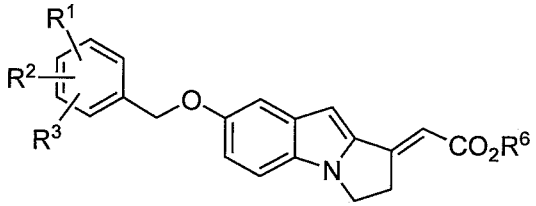
One embodiment of the present disclosure pertains to one or more of the processes as described above in Steps a) through j), either provided separately or together, that are useful in the preparation of an intermediate for use directly or indirectly in the preparation of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (**Ia**), salts, and/or crystalline forms thereof.

In one aspect, there is provided a salt prepared by a process as disclosed herein, wherein said salt is an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

In one aspect, there is provided a compound of the following formula:



In one aspect, there is provided a compound of Formula (**IIh**)-*E*, or a salt thereof:



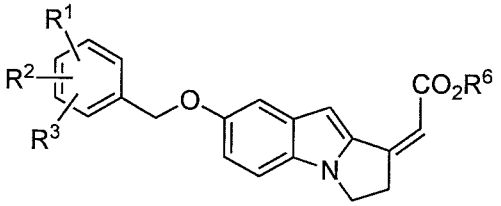
(**IIh**)-*E*

wherein:

R^1, R^2, and R^3 are each selected independently from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, and nitro; and

R^6 is C_1-C_4 alkyl.

In one aspect, there is provided a compound of Formula (**IIh**)-*Z*, or a salt thereof:



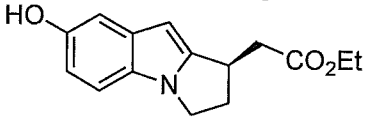
(**IIh**)-*Z*

wherein:

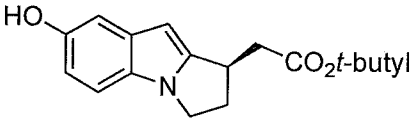
R^1, R^2, and R^3 are each selected independently from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, and nitro; and

R^6 is C_1-C_4 alkyl.

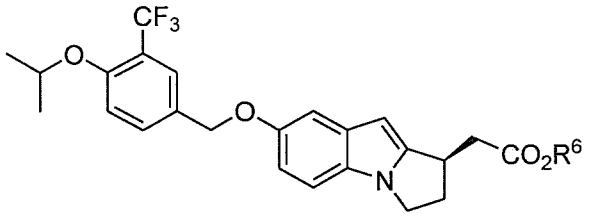
In one aspect, there is provided a compound of the following formula; or a salt thereof:



In one aspect, there is provided a compound of the following formula; or a salt thereof:



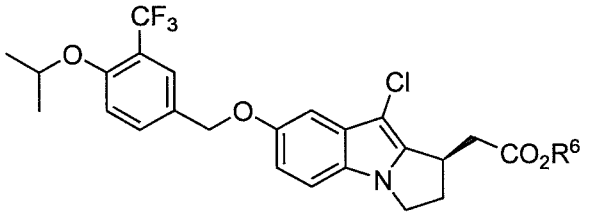
In one aspect, there is provided a compound of Formula (**IIm**), or a salt thereof:



(IIm) ,

wherein R^6 is C_1-C_4 alkyl.

In one aspect, there is provided a compound of Formula (**IIn**), or a salt thereof:



(IIn) ,

wherein R^6 is C_1-C_4 alkyl.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a powder X-ray diffraction pattern (PXRD) for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid (PANalytical X'Pert Plus Powder X-Ray Diffractometer; 5.0 to 40.0 °2θ).

Figure 2 shows a differential scanning calorimetry (DSC) thermogram for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid (TA Instruments DSC Q2000; 10 °C/min). **Figure 2** also depicts a thermogravimetric analysis (TGA) thermogram for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid (TA Instruments TGA Q50000 in open cell; 10 °C/min).

Figure 3 shows a dynamic moisture sorption profile for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

Figure 4 shows a powder X-ray diffraction pattern (PXRD) for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt (PANalytical X'Pert Plus Powder X-Ray Diffractometer; 5.0 to 40.0 °2θ).

Figure 5 shows a differential scanning calorimetry (DSC) thermogram for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt (TA Instruments DSC Q2000; 10 °C/min). **Figure 5** also depicts a thermogravimetric analysis (TGA) thermogram for a sample containing a crystalline form of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-

Claims

1. A salt selected from:

   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1 H pyrrolo[1,2-a]indol-1-yl)acetic acid sodium salt hydrate;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid ethylenediamine salt hydrate;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid 2-amino-2-hydroxymethyl-propane-1,3-diol salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-arginine salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid zinc salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid calcium salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid *N*-methylglucamine salt;
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid potassium salt; and
   (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid magnesium salt.

2. The salt according to claim 1 that is (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid L-lysine salt.

3. A crystalline form of the salt according to claim 2 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.9 ° and about 11.4 °.

4. A crystalline form of the salt according to claim 2 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.7 °, about 21.7 °, and about 22.9 °.

5. A crystalline form of the salt according to claim 2 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.6 °, about 13.7 °, about 19.8 °, about 20.6 °, about 21.7 °, about 22.1 °, and about 22.9 °.

6. A crystalline form of the salt according to claim 2 having an X-ray powder diffraction pattern substantially as shown in Figure 4.

7. A crystalline form of the salt according to any one of claims 2 to 6 having a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 213 °C and about 217 °C.

8. A crystalline form of the salt according to any one of claims 2 to 6 having a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 220 °C and about 224 °C.

9. A crystalline form of the salt according to any one of claims 2 to 6 having a differential scanning calorimetry thermogram comprising an endotherm with a first extrapolated onset temperature between about 213 °C and about 217 °C; and a second extrapolated onset temperature between about 220 °C and about 224 °C.

10. A crystalline form of the salt according to any one of claims 2 to 6 having a differential scanning calorimetry thermogram substantially as shown in Figure 5.

11. A crystalline form of the salt according to any one of claims 2 to 10 having a thermogravimetric analysis profile showing less than about 0.1% weight loss up to about 110 °C.

12. A crystalline form of the salt according to any one of claims 2 to 10 having a thermogravimetric analysis profile substantially as shown in Figure 5.

13. A crystalline form of the salt according to claim 2 having:

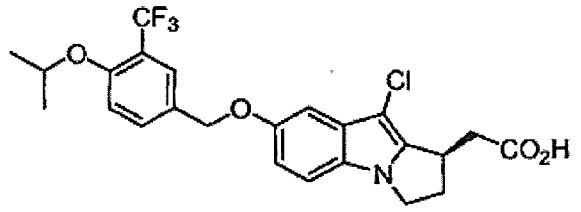
1) an X-ray diffraction pattern comprising peaks, expressed in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.7 °, about 21.7°, and about 22.9 °;
2) a differential scanning calorimetry thermogram comprising an endotherm with an extrapolated onset temperature between about 213 °C and about 217 °C; and/or
3) a thermogravimetric analysis profile showing less than about 0.1% weight loss up to about 110 °C.

14. A crystalline form of the salt according to claim 2 having:

1) an X-ray diffraction pattern comprising peaks, expressed in terms of 2θ, at about 6.9 °, about 11.4 °, about 13.6 °, about 13.7 °, about 19.8 °, about 20.6 °, about 21.7 °, about 22.1 °, and about 22.9 °;
2) a differential scanning calorimetry thermogram comprising an endotherm with a first extrapolated onset temperature between about 213 °C and about 217 °C; and a second extrapolated onset temperature between about 220 °C and about 224 °C; and/or
3) a thermogravimetric analysis profile showing less than about 0.1 % weight loss up to about 110 °C.

15. The salt according to claim 1 that is (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid 2-amino-2-hydroxymethyl-propane-1,3-diol salt.

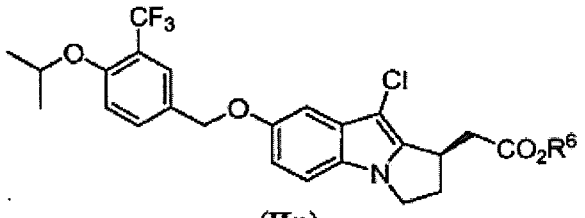
16. A process for preparing an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula **(Ia)**:



(Ia)

comprising the steps of:

a) hydrolyzing said compound of Formula **(IIn)**:

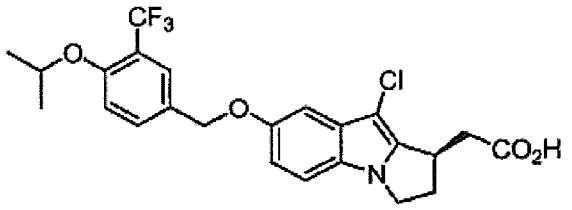


(IIn)

wherein R^6 is C_1-C_4 alkyl; in the presence of a hydrolyzing-step base and a hydrolyzing-step solvent to form said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid; and

b) contacting said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid with L-lysine or a salt thereof, in the presence of a contacting-step solvent and H_2O to form said L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

17. A process for preparing an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (Ia):



(Ia)

comprising the step of:

contacting the (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid with L-lysine or a salt thereof, in the presence of a contacting-step solvent and H_2O to form said L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

18. The process according to claim 17, wherein said contacting-step solvent comprises acetonitrile, tetrahydrofuran, acetone, or ethyl acetate.

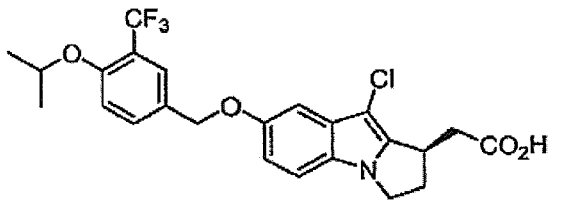
19. The process according to claim 17, wherein said contacting-step solvent comprises ethanol or isopropanol.

20. The process according to any one of claims 17 to 19, wherein the molar ratio between said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid and L-lysine is about 1.0 : 1.0 to about 1.0 : 1.2.

21. The process according to any one of claims 17 to 20, said process further comprising the step of isolating said L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

22. The process according to claim 21, wherein after said isolating, said L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid has a purity of about 97% or greater, and an enantiomeric excess of about 97% or greater.

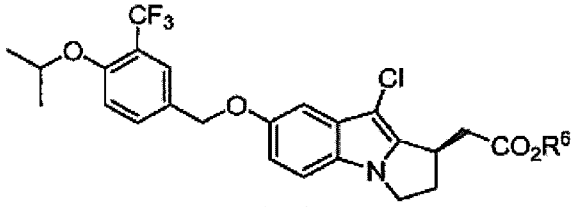
23. A process for preparing (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid of Formula (Ia):



(Ia)

comprising the step of:

hydrolyzing a compound of Formula (IIn):



(IIn)

wherein R^6 is C_1-C_4 alkyl;
in the presence of a hydrolyzing-step base and a hydrolyzing-step solvent to form said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetic acid.

24. The process according to claim 23, wherein R^6 is CH_2CH_3.

25. The process according to claim 23 or 24, wherein said hydrolyzing-step base comprises sodium hydroxide.

26. The process according to any one of claims 23 to 25, wherein said hydrolyzing-step solvent comprises dioxane, methanol, and water.

27. The process according to any one of claims 23 to 26, wherein said hydrolyzing further comprises the step of isolating said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

28. The process according to claim 27, wherein after said isolating, said (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid has an enantiomeric excess of about 97% or greater.

29. A salt prepared by a process according to any one of claims 16 to 22, wherein said salt is an L-lysine salt of (*R*)-2-(9-chloro-7-(4-isopropoxy-3-(trifluoromethyl)benzyloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-a]indol-1-yl)acetic acid.

30. A composition comprising said salt according to claim 1, 2, or 15, or said crystalline form according to any one of claims 3 to 14.

31. The composition according to claim 30, wherein said salt or said crystalline form comprises about 97% or greater by weight of said composition.

32. A pharmaceutical composition comprising said salt according to claim 1, 2, 15, or 29, or said crystalline form according to any one of claims 3 to 14, and a pharmaceutically acceptable carrier.

33. A process for preparing a composition comprising admixing a salt according to claim 1, 2, 15, or 29, or said crystalline form according to any one of claims 3 to 14, and a pharmaceutically acceptable carrier.

34. A salt according to claim 1, 2, 15, or 29, or a crystalline form according to any one of claims 3 to 14, or a pharmaceutical composition according to claim 32, for use in a method for the treatment of the human or animal body by therapy.

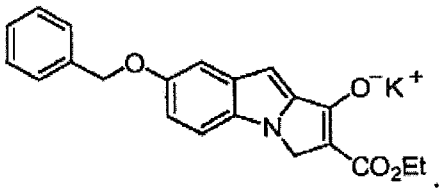
35. A salt according to claim 1, 2, 15, or 29, or a crystalline form according to any one of claims 3 to 14, or a pharmaceutical composition according to claim 32, for use in a method for the treatment of an S1P1 receptor-associated disorder.

36. A salt according to claim 1, 2, 15, or 29, or a crystalline form according to any one of claims 3 to 14, or a pharmaceutical composition according to claim 32, for use in a method for the treatment of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, or biliary cirrhosis.

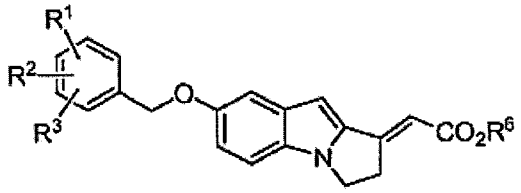
37. Use of a salt according to claim 1, 2, 15, or 29, or a crystalline form according to any one of claims 3 to 14, in the manufacture of a medicament for the treatment of an S1P1 receptor-associated disorder.

38. Use of a salt according to claim 1, 2, 15, or 29, or a crystalline form according to any one of claims 3 to 14, in the manufacture of a medicament for the treatment of psoriasis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, type I diabetes, acne, myocardial ischemia-reperfusion injury, hypertensive nephropathy, glomerulosclerosis, gastritis, polymyositis, thyroiditis, vitiligo, hepatitis, or biliary cirrhosis.

39. A compound of the following formula:



40. A compound of Formula **(IIh)-*E***, or a salt thereof:

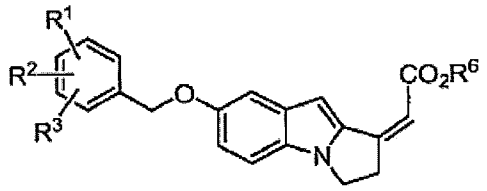


(IIh)-*E*

wherein:

R^1, R^2, and R^3 are each selected independently from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, and nitro; and
R^6 is C_1-C_4 alkyl.

41. A compound of Formula **(IIh)-Z**, or a salt thereof:



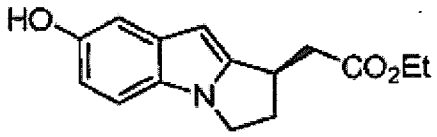
(IIh)-*Z*

wherein:

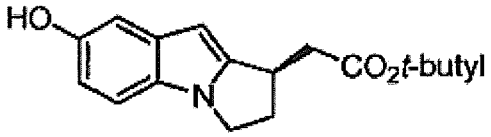
R^1, R^2, and R^3 are each selected independently from H, C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, and nitro; and
R^6 is C_1-C_4 alkyl.

42. The compound according to claim 40 or 41, wherein R^1, R^2, and R^3 are each H, and R^6 is CH_2CH_3 or *t*-butyl.

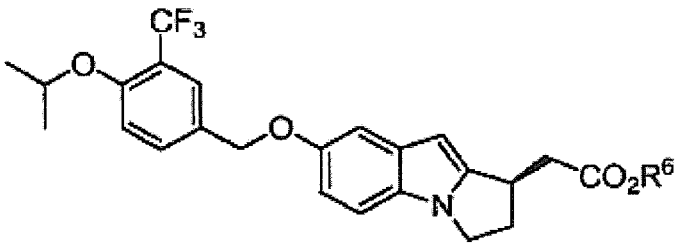
43. A compound of the following formula; or a salt thereof:



44. A compound of the following formula; or a salt thereof:



45. A compound of Formula (**IIm**), or a salt thereof:



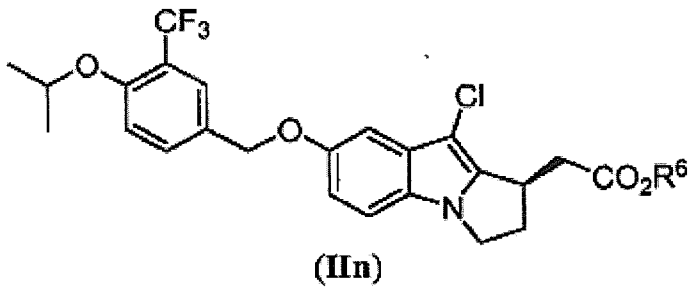
(IIm)

wherein R^6 is C_1-C_4 alkyl.

46. The compound according to claim 45, wherein R^6 is CH_2CH_3 or *t*-butyl.

47. The compound according to claim 45, wherein R^6 is CH_2CH_3.

48. A compound of Formula (**IIn**), or a salt thereof:



(IIn)

wherein R^6 is C_1-C_4 alkyl.

49. The compound according to claim 48, wherein R^6 is CH_2CH_3 or *t*-butyl.

50. The compound according to claim 48, wherein R^6 is CH_2CH_3.