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(54) Title: SALTS AND PRODRUGS OF 1-METHYL-D-TRYPTOPHAN

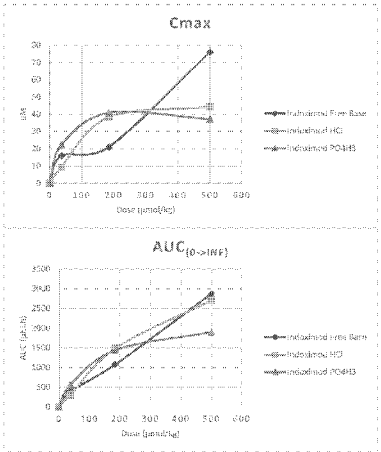

Figure 6: Dose dependency of Cmax and AUC for indoximod and its salts rats after oral dosing in capsule form

(57) Abstract: Presently provided are indoximod prodrug and salt compounds and pharmaceutical compositions comprising salts and prodrugs of indoximod, that produce enhanced plasma concentration and exposure to indoximod compared to direct administration of indoximod, in patients in need of treatment of immunosuppression mediated by the indoleamine-2,3-dioxygenase pathway, such as patients with cancer or chronic infectious diseases.

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SALTS AND PRODRUGS OF 1-METHYL-D-TRYPTOPHAN

Cross-Reference to Related Applications

[0001] This application claims priority to U.S Provisional Application Serial No 62/196,671 filed on July 24, 2015 and U.S Provisional Application Serial No 62/305,748 filed on March 9, 2016, the entire contents of which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present disclosure is related to compounds for inhibition of indoleamine-2,3-dioxygenase pathway, in particular salts and prodrugs of indoximod with enhanced pharmacokinetic properties relative to indoximod

Summary of Related Art

[0003] Tryptophan degradation into kynurenine is mediated by indoleamine-2,3-dioxygenase (IDO1) expressed by plasmacytoid dendritic cells, placental, epithelial and tumor cells and by tryptophan-2,3-dioxygenase (TDO2) expressed mainly by the liver and tumor cells.

[0004] IDO1 plays an important role in the regulation of immune responses by triggering anergy on reactive effector T cells and by modulating differentiation and activation of regulatory T cells (Tregs). From a more general viewpoint, the IDO enzyme is involved in pathway that comprises all proteins that directly or indirectly contribute to modulate the immunosuppressive functions dependent on IDO activity, including proteins that mediate induction of IDO expression, activation of enzymatic activity by reductases, post-translational modifications that regulate activity, protein degradation, and the interpretation and transmission of the signals elicited by low concentrations of Trp and the presence of Trp catabolites [collectively known as kynurenines (Kyns)] including catabolic stress sensors integrated into the General Control

Nonrepressed-2 (GCN2) pathway, the Aryl Hydrocarbon Receptor (AhR) pathway, and the mammalian Target Of Rapamycin (mTOR) pathways. This concept of integrated downstream regulatory pathways with IDO at the center has emerged from studies on multiple model systems by many research groups and this notion may be critically important for understanding how the IDO pathway is induced, how IDO exerts downstream effects, and the mechanism of action of IDO pathway inhibitors that target IDO directly or target other components of the IDO pathway [1, 2].

[0005] Therefore, direct pharmacological inhibition of IDO1 enzymatic activity or inhibition of the upstream factors that activate IDO1 enzyme or inhibition of the downstream effects of IDO1 enzymatic activity should stimulate an immune response by multiple mechanisms that may involve preventing anergy of effector T cells, reactivating anergic effector T cells, preventing the activation of regulatory T cells, promoting phenotypic conversion of Tregs to pro-inflamatory TH17 cells and promoting phenotypic reprogramming of immunosuppressive dendritic cells into immunostimulatory dendritic cells.

[0006] For these reasons, numerous enzymatic inhibitors of IDO have been described and are being developed to treat or prevent IDO related diseases such as cancer and infectious diseases. Numerous molecules that inhibit IDO enzymatic activity either as competitive or non-competitive inhibitors have been described in the literature, for example in patent applications WO2012142237, WO2014159248, WO2011056652, WO2009132238, WO2009073620, WO2008115804, WO 2014150646, WO 2014150677, WO 2015002918, WO 2015006520, WO 2014141110, WO 2014/186035, WO 2014/081689, US 7714139, US 8476454, US 7705022, US 8993605, US 8846726, US 8951536, US7598287.

[0007] One of the first IDO pathway inhibitors studied in preclinical models has been 1-methyl-DL-tryptophan (1mT), a racemic mixture of enantiomers, which was shown to mediate immune dependent rejection of allogeneic fetuses in mice [3] and immune dependent enhancement of antitumor activity of chemotherapy and radiotherapy [4]. Each one of these enantiomers shows different biological properties. 1-methyl-L-tryptophan (L1mT) has been shown to inhibit IDO1 enzymatic activity (Ki=34 μM, [5]) in cell-free assays using purified

recombinant IDO1 enzyme, and in tumor cells treated with INFγ or in tumor cell lines transfected with expression vectors that encode IDO1 under the control of an heterologous promoter, while the D isomer (indoximod) does not inhibit enzymatic activity in these type of assays [6]. Nonetheless, both isomers are capable of restoring T cell proliferation in an MLR assay with IDO+ dendritic cells as the stimulator cells, or in syngeneic antigen-dependent T cell proliferation assays using IDO+ DCs isolated from tumor draining lymph nodes [6]. In this type of assay, where IDO+ DCs are present, T cells do not proliferate. However, inhibition of the IDO pathway by these inhibitors restores the proliferative capacity of T cells. Interestingly, both isomers show different potency in this assay, with indoximod being more potent (EC50=30 μM) than L1mT (EC50= 80-100 μM) or the racemic mixture (80-100 μM) [6]. Moreover, despite the fact that indoximod does not show inhibition of enzymatic activity in other types of assays, it shows inhibition of enzymatic activity in this co-culture assay, as seen by reduced Trp degradation and Kyn synthesis.

[0008] A somewhat puzzling issue has been the fact that indoximod does not show inhibition of IDO1 enzymatic activity in vitro, but somehow mimics the biological consequences of IDO1 inhibition in vivo or in cell based assays. Experimental evidence from a number of research laboratories points to the conclusion that indoximod is participating in the inhibition of the IDO1 pathway. Several possible mechanisms by which this could be taking place are: 1) inhibition of isoforms of IDO1, 2) inhibition of IDO2, 3) alternative formation of indoximod –derived metabolites, 4) racemization of indoximod into L1mT, 5) inhibition of Trp transport, 6) inhibition of the GCN2 pathway by formation of indoximod-tRNA complexes, 7) inhibition of enzymes involved in Trp sensing such as WARS1 or WARS2, 8) alteration of autophagy under conditions of amino acid deprivation induced stress or 9) bypassing mechanisms that inactivate mTOR under conditions of amino acid deficiency [7]. These mechanisms are not necessarily mutually exclusive, and so far are compatible with the current experimental data. Further investigations are needed to elucidate which of these biochemical mechanisms is responsible for the biological activity of indoximod.

[0009] The biological activity of indoximod to relieve immunosuppression in vivo and in vitro is supported by studies performed in several laboratories in murine preclinical models. Indoximod has demonstrated activity in the following biological assays:

1. In combination with chemotherapy, indoximod demonstrates antitumor effects in animal models of ectopic melanoma, colon and lung tumors, and in orthotopic and autochtonous breast tumor models. The antitumor effect of indoximod is lost in nude and IDO1-KO mice [6].
2. indoximod can prevent the process of activation of mature Tregs in vivo, and facilitates the in vitro and in vivo trans-differentiation of Tregs into pro-inflamatory TH17-like T cells [8, 9].
3. In tumor vaccination protocols, the combination of two different antitumor vaccines with indoximod was effective in converting a higher proportion of Treg cells into TH17-like T cells, with concomitant antitumor effect [9].
4. In melanoma models, combination of anti-CTLA4 (ipilimumab) and indoximod, results in synergistic antitumor effect [10].
5. In vivo, indoximod was more efficacious as an anticancer agent in chemo-immunotherapy regimens using cyclophosphamide, paclitaxel, or gemcitabine, when tested in mouse models of transplantable melanoma and transplantable (4T1) and autochthonous (mmTV-neu) breast cancer [6].
6. IDO1 has also been implicated in the differentiation of naïve CD4 T cells into Tregs, by the combined effect of Trp deprivation and the presence of Trp catabolites, through a mechanism that depends on GCN2 [11, 12]. This conversion is interrupted in vivo in the presence of indoximod.
7. Similarly, IDO+ pDCs have also been implicated in the activation of mature Tregs in vivo, which also required an intact GCN2 pathway in the Treg population. This phenomenom could be prevented by excess Trp or by indoximod [8].
8. In addition to preventing the activation of mature Treg cells, indoximod can mediate the conversion of suppressive FoxP3$^+$ Tregs into pro-inflamatory TH17 cells in vitro and in vivo. This conversion of Tregs into TH17 cells required the presence of antigen or

engagement of B7 in the pDCs, and the presence of functional IDO1 and GCN2 genes in the pDCs. Indoximod was able to mimic the phenotypic consequences of IDO1 or GCN2 gene ablation [9], therefore supporting its role in inhibition of the IDO pathway.

9. Antitumor and immunologic studies using IDO1-KO mice or pDCs derived from IDO1-KO mice demonstrated that the beneficial effects of indoximod are lost in the context of a genetic background lacking a functional IDO1 [6]. In particular, it was observed that IDO1-KO mice develop tumors, which are not sensitive to treatment with indoximod in combination with chemotherapy. Additionally, pDCs derived from tumor draining lymph nodes of IDO1-KO mice are able to stimulate the proliferation of T cells in culture, to the same extent as IDO(-) APCs. These observations were interpreted as a genetic validation of IDO1 as the pharmacologic target of indoximod. However, this could also be interpreted as indoximod blocking some other point of action within the IDO pathway.
10. The antitumor and immunologic observations made by administration of indoximod were also reproduced by administration of other well documented IDO1 inhibitors (i.e. molecules that inhibit the enzymatic activity of IDO1 in vitro and in cell based assays) such as 5-Br-brassinin, menadione, methyl-thiohydantoin-tryptophan, and analogs of phenylimidazole (unpublished), thereby validating the IDO1 pathway as the pharmacologic target [4, 13, 14].
11. In preclinical animal models, the in vivo pharmacodynamic effects of indoximod are seen mainly in tumor draining lymph nodes, where the effect is seen as activation and proliferation of CD8α+ cells, reduction in the number of FoxP3 + Tregs, reprogramming of Tregs ($CD40L^-$) to immunostimulatory T cells ($CD40L^+$) and reprogramming of IDO^+ antigen presenting cells from $CD11c^+/CD80/86^-$ to $CD80/86^+$ phenotype.

[0010] For these reasons, indoximod is being investigated in human clinical trials for cancer indications. Indoximod is being studied in several cancer indications in combination with different chemotherapeutic and biological immunotherapeutic agents, such as docetaxel, paclitaxel, gemcitabine, Nab-paclitaxel, temozolomide, ipilimumab, sipuleucel-T, or vaccines.

[0011] Indoximod is orally bioavailable with a favorable pharmacokinetic (PK) profile (Tmax: ~ 3h; half-life: ~10 h) and an excellent safety profile. Pharmacokinetic studies in patients have

demonstrated that indoximod shows a linear PK profile at doses of up to 800 mg/dose, with maximum plasma concentration (Cmax) of 15 μM and drug exposure ($AUC_{(0\text{-}last)}$) levels of ~100 μM.h. However, increasing doses above 800 mg/dose up to 2000 mg/dose, does not result in a linear or proportional increase in Cmax or drug exposure, thus potentially limiting the therapeutic activity of this investigational drug.

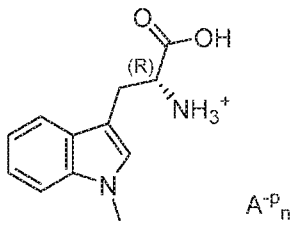
[0012] Mixed-lymphocyte response (MLR) T cell proliferation assay show that T cells that are in an IDO^{+} environment restore ~50% of their proliferative capacity at concentrations of indoximod higher than 30 μM. Murine antitumor experiments show that biological effects of indoximod are observed when mice are dosed with indoximod in the drinking water at 3 mg/mL (~500 mg/kg/day), or dosed orally at 200 mg/kg bid, which results in Cmax higher than 20 μM and exposures greater than 300 μM.h. For these reasons, it is desirable to increase the Cmax and exposure to indoximod in human clinical trials so they may reach the levels necessary for therapeutic activity. However, the non-linear pharmacokinetic profile of this drug makes it unlikely that this could be solved by increasing the dose given to patients.

[0013] For the above mentioned reasons we investigated whether different formulation of indoximod such as spray dry dispersions or salts or indoximod prodrugs in different salt forms would increase solubility and absorption rate or reduce blood clearance to levels that increase the maximum concentration and exposure to indoximod. Moreover, we looked for prodrugs and its salts that could result in increases parameters of exposure when dosed orally and in pill (capsule or tablet) dosage formulation.

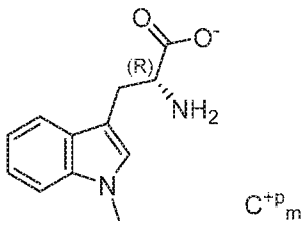
[0014] The results of these investigations showed that a few selected prodrugs resulted in increases in parameters of exposure; and that increases in in vitro solubility and in vivo exposure could be achieved by a few salts of indoximod upon oral administration.

SUMMARY OF THE INVENTION

[0015] In one aspect the invention describes compounds and pharmaceutical compositions comprising compounds according to Formula 1a and 1b



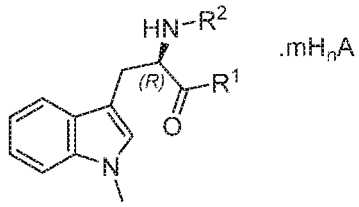
Formula 1a



Formula 1b

Wherein $A^{-p}{}_n$ is an inorganic or organic anion and $C^{+p}{}_m$ is an inorganic cation as defined herein.

[0016] In another aspect, the invention comprises compounds and pharmaceutical compositions comprising compounds according to formula (2)



Formula 2

Where R^1, R^2 and mH_nA are defined herein

[0017] In another aspect, the present disclosure provides

a) pharmaceutical compositions comprising compounds of formula 1a, 1b or formula 2, that result in elevated exposure and maximum concentration to 1-methyl-D-tryptophan (indoximod) after oral administration to a subject, compared to administration of an equivalent molar dose of indoximod formulated as a free base.

b) methods of use of compositions comprising compounds of formulas 1a, 1b or 2, to modulate the activity of indoleamine-2,3-dioxygenase pathway in a subject in need thereof, comprising the oral administration of sufficient amounts such compositions to such subject in an appropriate pharmaceutical form or vehicle.

c) methods of use of compositions comprising compounds of formulas 1a, 1b or 2, for the treatment of cancer in a subject in need thereof, comprising the oral administration of sufficient amounts of such compositions to such subject in an appropriate pharmaceutical form or vehicle.

d) methods of use of compositions comprising compounds of formulas 1a, 1b or 2, to treat tumor-specific immunosuppression associated with cancer, in a subject in need thereof, comprising the oral administration of sufficient amounts such compositions to such subject in an appropriate pharmaceutical form or vehicle.

e) methods of use of compositions comprising compounds of formulas 1a, 1b or 2, to treat immunosuppression associated with infectious diseases (e.g HIV-1 infection, influenza), in a subject in need thereof, comprising the oral administration of sufficient amounts such compositions to such subject in an appropriate pharmaceutical form or vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] **Figure 1** shows the XRPD spectrum of indoximod in free base and in its hydrochloride salt form.

[0019] **Figure 2** shows the thermos gravimetric (TGA) and differential scanning calorimetry (DSC) analysis of indoximod hydrochloride salt.

[0020] **Figure 3** shows the XRPD spectrum of indoximod in free base and in its phosphate salt form.

[0021] **Figure 4** shows the thermos gravimetric (TGA) and differential scanning calorimetry (DSC) analysis of indoximod phosphate salt.

[0022] **Figure 5** shows the measured solubility profile vs. pH of indoximod and its salts in various solvent solutions and simulated biological fluids.

[0023] **Figure 6** shows the maximum plasma concentration (Cmax) and exposure ($AUC_{0\text{-}inf}$) of indoximod vs the molar dose of indoximod, indoximod hydrochloride or indoximod phosphate given to rats in oral capsule form.

DETAILED DESCRIPTION OF THE INVENTION

[0024] Indoximod (1-methyl-D-tryptophan, D1mT) is an investigational inhibitor of the indoleamine-2,3-dioxygenase (IDO) pathway that is being tested in several human clinical trials for multiple cancer indications, in combination with standard and experimental chemotherapeutic and immunomodulatory agents and active immunotherapies.

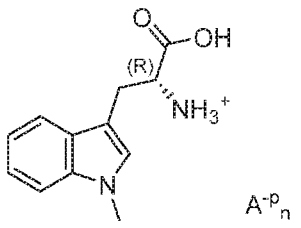
[0025] In the presence of IDO^+ dendritic cells, $CD8^+$ effector T cells become anergic and unable to proliferate. Moreover, regulatory T cells ($CD4^+$ $CD25^+$ $FoxP3^+$) are activated in the presence of IDO^+ DCs and become able to mediate systemic immunosuppression to tumor or viral antigens. Indoximod is capable to revert these processes, allowing effector T cells to proliferate and directing reprogramming of Tregs to a TH17 helper-like phenotype. In *in vitro* assays, these effects are mediated by indoximod with an EC50 of ~ 30 μM [6]. In preclinical murine tumor models, antitumor effects, stimulation of effector T cells and reprogramming of Tregs in the draining lymph nodes requires daily doses of ~ 500 mg/kg, with exposures > 300 μM.h.

[0026] Human pharmacokinetic experiments at oral doses that range between 200 mg to 2000 mg/dose have shown that the pharmacokinetic parameters C_{max} and exposure ($AUC_{0\text{-}inf}$) increase linearly with dose, up to a range of ~ 800 mg/dose. At these doses, C_{max} in plasma reaches an average of ~15 μM and $AUC_{0\text{-}inf}$ reaches ~ 100 μM.h. The C_{max} and AUC parameters do not significantly increase above those values at higher doses of up to 2000 mg/dose. Therefore, in order to achieve indoximod concentration and exposure levels that are comparable to those that produce immunomodulatory and antitumor therapeutic effects in murine models it would be useful to increase the C_{max} and exposure levels of indoximod.

[0027] The present invention describes compounds of formula 1a, 1b and formula 2 that produce a higher exposure and maximum serum concentration of indoximod upon oral administration, compared to oral administration of equivalent molar doses of indoximod.

Salts of Indoximod

[0028] In one embodiment, a salt of indoximod is disclosed. In one embodiment, the salt has a structure according to Formula 1a:



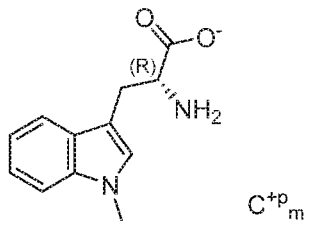
Formula 1a

wherein A^{-p}_n is an inorganic or organic anion in an ionization state $-p$. In one embodiment, the anion is present at a stoichiometric ratio n that ensures molecular charge neutrality.

[0029] In one embodiment, the anion A^{-p}_n is selected from the group consisting of chloride, phosphate, sulfate, mesylate, besylate, acetate, ascorbate, aspartate, glutamate, glutarate, lactate, maleate, malonate, oxalate, succinate, fumarate, tartrate and citrate. In one embodiment, the anion is presented at a stoichiometric ratio n such that the resulting salt is charge neutral. Accordingly, in one embodiment, the anion has an ionization state p of -1, -2 or -3 and is presented at a stoichiometric ratio n of 1, 1/2 or 1/3, respectively, such that the stoichiometric conditions of charge neutrality are satisfied. In one embodiment, the phosphate is HPO_4^{-2}, and the HPO_4^{-2} is present at a stoichiometric ratio n of 0.5. In one embodiment, the phosphate is HPO_4^{-}, and the HPO_4^{-} is present at a stoichiometric ratio n of 1. In one embodiment, the sulfate is SO_4^{-2}, and the SO_4^{-2} is present at a stoichiometric ratio n of 0.5. In one embodiment, the mesylate is $CH_3SO_3^{-}$, and the $CH_3SO_3^{-}$ present at a stoichiometric ratio n of 0.5.

[0030] In another embodiment the anion A^{-p}_n is Cl^- at a stoichiometric ratio n of 1. In another preferred embodiment the anion A^{-p}_n is Cl^- at a stoichiometric ratio n of 1 and the crystalline form is an anhydrous isoform of Form 1.

[0031] In one embodiment, the salt has a structure according to Formula 1b:

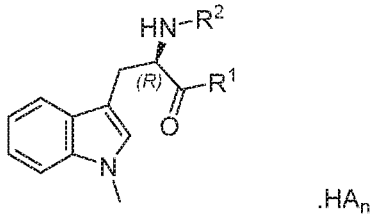


Formula 1b

wherein C^{+p}_m is a cation in an ionization state $+p$. In one embodiment, the cation is present at a stoichiometric ratio m that ensures molecular charge neutrality. In one embodiment, the C^{+p}_m is selected from the group consisting of Li^+, Na^+, K^+, Mg^{+2} and Ca^{+2}. In one embodiment, when p is +1, m is 1, and when p is +2, m is ½.

Indoximod Prodrugs

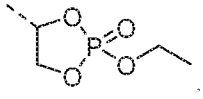
[0032] In one embodiment, a prodrug of indoximod is disclosed. In one embodiment, the structure of the prodrug, in free base or salt form, is provided in Formula 2:



Formula 2

[0033] In one embodiment, R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, $-OC_{1-3}$alkyl-R^3, $-NHC^{(S)}HR^4(COOH)$, $-NHC^{(R)}HR^4(COOH)$, $-OC_{1-6}$alkylR^6, $-OC_{1-2}$alkyl-$C^{(S)}H(NH_2)(COOH)$, or $-OC_{1-2}$alkyl-$C^{(R)}H(NH2)(COOH)$. In one embodiment, R^1 is $-NHC^{(S)}HR^4(COOCH_3)$ or $-NHC^{(R)}HR^4(COOCH_3)$.

[0034] In one embodiment, R^2 is -H, $-C(O)C^{(S)}H(NH_2)R^4$, $-C(O)C^{(R)}H(NH_2)R^4$, $-C(O)CH_2C^{(S)}H(NH_2)$-$C(O)OCH_3$, $-C(O)OR^5$, or $-C(O)NHR^5$.

[0035] In one embodiment, R^3 is tetrahydropyran or  .

[0036] In one embodiment, R^4 is -H, -C_{1-5}alkyl, -$(CH_2)_{1-2}$SH, -C_{1-5}alkylSC_{1-5}alkyl, -C_{1-5}alkylOC_{1-5}alkyl, -CH_2-R^6, -CH_2OH, -CH(OH)CH_3, -$(CH_2)_{1-2}$C(O)NH_2,-$(CH_2)_{1-3}$C(O)OH, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}$NC(=NH_2)NH_2.

[0037] In one embodiment, when R^4 is not -H, $C^{(S)}$ and $C^{(R)}$ are carbons with the *S* or *R* stereochemistry, respectively.

[0038] In one embodiment, R^5 is -H, C_{1-6}alkylR^6, or R^6. In one embodiment, R^6 is selected from the group consisting of -H, aryl, alkylaryl, heteroaryl, cycloalkyl, and heterocycloalkyl, wherein the aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups.

[0039] In one embodiment, each R^7 is independently halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2$R, -$S(O)_2$OR, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$, wherein R is H or C_{1-4}alkyl.

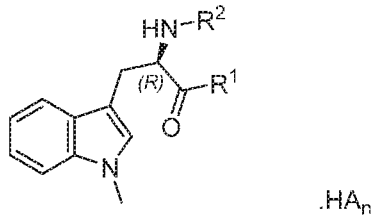
[0040] In some embodiments of the prodrug of Formula 2, R^1 cannot be –OH when R^2 is H.

[0041] Furthermore, in all embodiments, the prodrug cannot be N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan, ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate, or benzyl N^{α}- (*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate.

[0042] In one embodiment, HA_n is an acid. In one embodiment, the acid HA_n is selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid.

[0043] In one embodiment, the acid HA_n is present at a stoichiometric ratio *n* such that the resulting prodrug is charge neutral. Accordingly, in one embodiment, the stoichiometric ratio *n* of the acid HA_n is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

[0044] The invention also provides prodrugs of indoximod, in their free base or salt form. In one embodiment, the prodrugs of indoximod are represented by compounds of Formula 2,

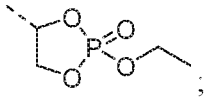


Formula 2

wherein

R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, -OC_{1-3}alkyl-R^3, -$NHC^{(S)}HR^4(COOH)$, -$NHC^{(R)}HR^4(COOH)$, -OC_{1-6}alkylR^6, -OC_{1-2}alkyl, -$C^{(S)}H(NH_2)(COOH)$, or -OC_{1-2}alkyl-$C^{(R)}H(NH2)(COOH)$;

R^2 is -H, -$C(O)C^{(S)}H(NH_2)R^4$, -$C(O)C^{(R)}H(NH_2)R^4$, -$C(O)CH_2C^{(S)}H(NH_2)$-$C(O)OCH_3$, -$C(O)OR^5$, or -$C(O)NHR^5$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is H, -C_{1-5}alkyl, -$(CH_2)_{1-2}SH$, , C_{1-5}alkylSC_{1-5}alkyl, -C_{1-5}alkylOC_{1-5}alkyl, -CH_2-R^6, -CH_2OH, -$CH(OH)CH_3$, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_{1-3}C(O)OH$, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}NC(=NH_2)NH_2$;

wherein $C^{(S)}$ and $C^{(R)}$ represents a carbon with the *S* or *R* stereochemistry, respectively, when R^4 is not -H; wherein R^5 is -H, C_{1-6}alkylR^6; or R^6

wherein R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein such aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

wherein each R^7 is independently selected from halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2R$, -$S(O)_2OR$, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

wherein R is -H or C_{1-4}alkyl;

with the proviso that R^1 cannot be -OH when R^2 is -H, and the compound cannot be

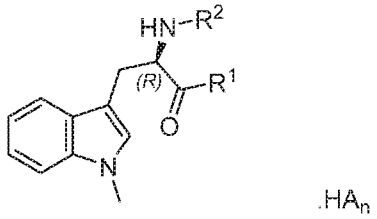
N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan

ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate

benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid; and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

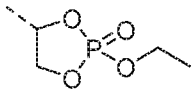
[0045] In a another embodiment, the invention provides prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,



Formula 2

wherein R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3, -

R^2 is H, or $-C(O)C^{(S)}H(NH_2)R^4$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is H, $-C_{1-5}$alkyl, $-(CH_2)_{1-2}SH$, $-(CH_2)_{1-3}SCH_3$, $-(CH_2)_{1-3}OCH_3$, $-CH_2-R^6$, $-CH_2OH$, $-CH(OH)CH_3$, $-(CH_2)_{1-2}C(O)NH_2$, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-4}NH_2$, or $-(CH_2)_{1-3}NC(=NH_2)NH_2$;

wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry, when R^4 is not H;

wherein R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, heterocycloalkyl, wherein such aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

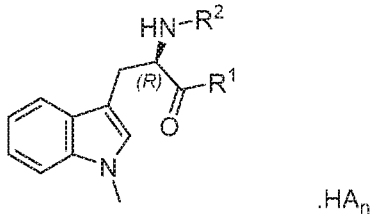
wherein each R^7 is independently halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl,C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2$R, -$S(O)_2$OR, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

wherein R is H or C_{1-4}alkyl;

with the proviso that R^1 cannot be -OH when R^2 is H;

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid; and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0046] In a preferred embodiment, the invention provides prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,

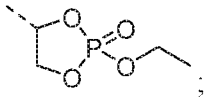


Formula 2

wherein

R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, or -OC_{1-3}alkyl-R^3,

R^2 is H, or -$C(O)C^{(S)}H(NH_2)R^4$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is H, -C_{1-5}alkyl, -CH_2-R^6, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_2SCH_3$, -$(CH_2)_{1-3}C(O)OH$, or -$(CH_2)_{1-4}NH_2$

wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry, when R^4 is not -H;

wherein R^6 is -H, aryl, alkylaryl, or heteroaryl, wherein such aryl, alkylaryl or heteroaryl is optionally substituted with one R^7 group;

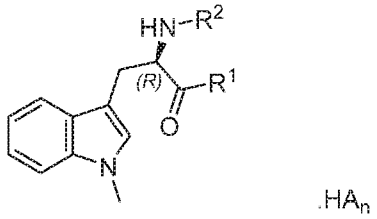
wherein R^7 is selected from halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2$R, -$S(O)_2$OR, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -N(R)C(O)$N(R)_2$;

wherein R is -H or C_{1-4}alkyl;

with the proviso that R^1 cannot be -OH when R^2 is H;

HA_n is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), or $C_6H_5SO_3H$ (benzyl sulfonic acid); and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0047] In another preferred embodiment, the invention provides prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,

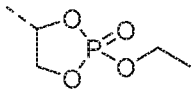


Formula 2

wherein

R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, or -OC_{1-3}alkyl-R^3,

R^2 is H, or -$C(O)C^{(S)}H(NH_2)R^4$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is -$CH_2CH(CH_3)_2$, -$C^{(S)}H(CH)_3CH_2CH_3$, -$(CH_2)_2SCH_3$, -CH_2-R^6, -$(CH_2)_2C(O)NH_2$, -$(CH_2)_3C(O)OH$, or -$(CH_2)_4NH_2$;

wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry;

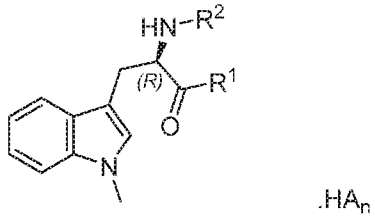
wherein R^6 is phenyl;

with the proviso that R^1 cannot be -OH when R^2 is H;

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid) HSO_3CH_3 (methyl sulfonic acid), and $C_6H_5SO_3H$ (benzyl

sulfonic acid), and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0048] In a most preferred embodiment, the invention provides prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,



Formula 2

wherein

R^1 is $-OC_{2-3}$alkyl, or $-OCH_2CH(OH)CH_2OH$,

R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$,

wherein R^4 is $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, or $-(CH_2)_2C(O)NH_2$;

wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry

with the proviso that R^1 cannot be –OH when R^2 is H,

HA is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid) HSO_3CH_3 (methyl sulfonic acid) or $C_6H_5SO_3H$ (benzyl sulfonic acid); and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

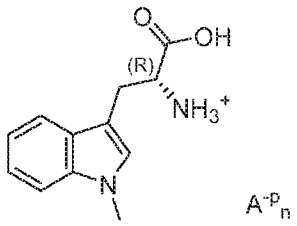
[0049] In a preferred embodiment, the invention provides prodrugs of indoximod, in their free base or as a pharmaceutically appropriate salt form, as represented by compounds of Formula 2 represented in Table 1.

[0050] In one embodiment, the prodrug substantially includes at least one of the following compounds: (i) ethyl N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophanate; (ii) 2,3-dihydroxypropyl 1-methyl-*D*-tryptophanate; (iii) N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophan; (iv) ethyl N^{α}-(*L*-isoleucyl)-1-methyl-*D*-tryptophanate; (v) N^{α}-(*L*-glycyl)-1-methyl-*D*-tryptophan; (vi) (*S*)-5-amino-6-(((*R*)-1-carboxy-2-(1-methyl-1*H*-indol-3-yl)ethyl)amino)-6-oxohexanoic acid; (vii) N^{α}-(*L*-lysyl)-1-methyl-*D*-tryptophan; (viii) N^{α}-(*L*-phenylalanyl)-1-methyl-*D*-tryptophan; (ix) ethyl N^{α}-(*L*-glutaminyl)-1-

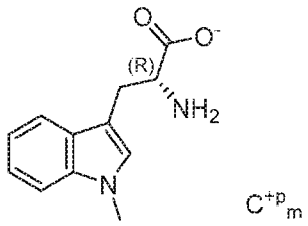
methyl-*D*-tryptophanate; (x) 2-(dimethylamino)ethyl 1-methyl-*D*-tryptophanate; (xi) (2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate; (xii) 2-(tetrahydro-2*H*-pyran-4-yl)ethyl 1-methyl-*D*-tryptophanate; (xiii) ethyl 1-methyl-*D*-tryptophanate; (xiv) isopropyl 1-methyl-*D*-tryptophanate; (xv) N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophan; or (xvi) ethyl N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophanate.

Pharmaceutical Compositions of Indoximod Salts and Prodrugs

[0051] In one aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1a and 1b,



Formula 1a



Formula 1b

wherein A^{-}_{n} is an inorganic or organic anion and C^{+p}_{m} is an inorganic cation in an ionization state and at a stoichiometric ratio that ensures molecular charge neutrality.

[0052] In a second embodiment of the first aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1a, wherein A^{-p}_{n} is an anion selected from the group consisting of chloride, phosphate, sulfate, mesylate, besylate, acetate, ascorbate, aspartate, glutamate, glutarate, lactate, maleate, malonate, oxalate, succinate, fumarate, tartrate and citrate, wherein negative charge *p* is -1, -2 or -3 at stoichiometric ratio *n* of 1, ½ or 1/3, respectively, so that it satisfies stoichiometric conditions of charge neutrality.

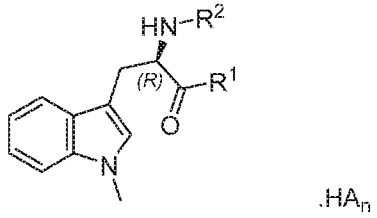
[0053] In a third embodiment of the first aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1b, wherein C^{+p}_{m} is an cation selected from the group of Li^{+}, Na^{+}, K^{+}, Mg^{+2} or Ca^{+2}, wherein positive

charge p is +1 or +2 at stoichiometric ratio m of 1 or ½, respectively, so that it satisfies stoichiometric conditions of charge neutrality.

[0054] In a fourth embodiment of the first aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1a, wherein $A^{-p}{}_n$ is an anion selected from the group consisting of HPO_4^{-2} (phosphate), SO_4^{-2} (sulfate), $H_2PO_4^-$ (phosphate), Cl^-, and $CH_3SO_3^-$ (mesylate), at stoichiometric ratio n of 0.5, 0.5, 1 or 1, respectively.

[0055] In a preferred fifth embodiment of the first aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1a, wherein $A^{-p}{}_n$ is Cl^- at a stoichiometric ratio n of 1.

[0056] In a most preferred fifth embodiment of the first aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1a, wherein $A^{-p}{}_n$ is Cl^- at a stoichiometric ratio n of 1 and the crystalline form is an anhydrous isoform of Form 1.In a second aspect, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or salt form. In one embodiment, the prodrugs of indoximod are represented by compounds of Formula 2,

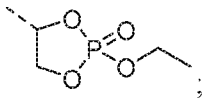


Formula 2

wherein

R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, $-OC_{1-3}$alkyl-R^3, $-NHC^{(S)}HR^4(COOH)$, $-NHC^{(R)}HR^4(COOH)$, $-OC_{1-6}$alkylR^6, $-OC_{1-2}$alkyl, $-C^{(S)}H(NH_2)(COOH)$, or $-OC_{1-2}$alkyl-$C^{(R)}H(NH2)(COOH)$;

R^2 is -H, $-C(O)C^{(S)}H(NH_2)R^4$, $-C(O)C^{(R)}H(NH_2)R^4$, $-C(O)CH_2C^{(S)}H(NH_2)$-$C(O)OCH_3$, $-C(O)OR^5$, or $-C(O)NHR^5$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is H, -C_{1-5}alkyl, -$(CH_2)_{1-2}SH$, , C_{1-5}alkylSC_{1-5}alkyl, -C_{1-5}alkylOC_{1-5}alkyl, -CH_2-R^6, -CH_2OH, -$CH(OH)CH_3$, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_{1-3}C(O)OH$, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}NC(=NH_2)NH_2$;

wherein $C^{(S)}$ and $C^{(R)}$ represents a carbon with the *S* or *R* stereochemistry, respectively, when R^4 is not -H; wherein R^5 is -H, C_{1-6}alkylR^6; or R^6

wherein R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein such aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

wherein each R^7 is independently selected from halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2$R, -$S(O)_2$OR, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

wherein R is -H or C_{1-4}alkyl;

with the proviso that R^1 cannot be -OH when R^2 is -H, and the compound cannot be

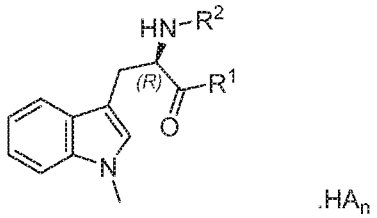
N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan

ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate

benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid; and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

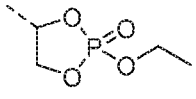
[0057] In a another embodiment of the second aspect, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,



Formula 2

wherein R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, or -OC_{1-3}alkyl-R^3, -

R^2 is H, or -$C(O)C^{(S)}H(NH_2)R^4$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is H, -C_{1-5}alkyl, -$(CH_2)_{1-2}SH$, -$(CH_2)_{1-3}SCH_3$, -$(CH_2)_{1-3}OCH_3$, -CH_2-R^6, -CH_2OH, -$CH(OH)CH_3$, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_{1-3}C(O)OH$, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}NC(=NH_2)NH_2$;

wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry, when R^4 is not H;

wherein R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, heterocycloalkyl, wherein such aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

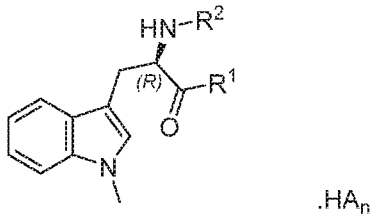
wherein each R^7 is independently halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl,C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2R$, -$S(O)_2OR$, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

wherein R is H or C_{1-4}alkyl;

with the proviso that R^1 cannot be -OH when R^2 is H;

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid; and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0058] In a preferred embodiment of the second aspect, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,

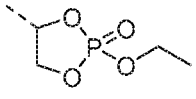


Formula 2

wherein

R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, or -OC_{1-3}alkyl-R^3,

R^2 is H, or -$C(O)C^{(S)}H(NH_2)R^4$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is H, -C_{1-5}alkyl, -CH_2-R^6, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_2SCH_3$, -$(CH_2)_{1-3}C(O)OH$, or -$(CH_2)_{1-4}NH_2$

wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry, when R^4 is not -H;

wherein R^6 is -H, aryl, alkylaryl, or heteroaryl, wherein such aryl, alkylaryl or heteroaryl is optionally substituted with one R^7 group;

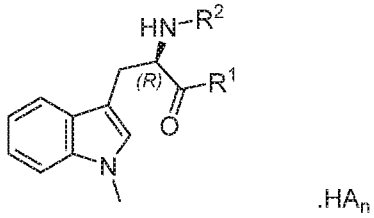
wherein R^7 is selected from halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2R$, -$S(O)_2OR$, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

wherein R is -H or C_{1-4}alkyl;

with the proviso that R^1 cannot be -OH when R^2 is H;

HA_n is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), or $C_6H_5SO_3H$ (benzyl sulfonic acid); and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0059] In a most preferred embodiment of the second aspect, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,

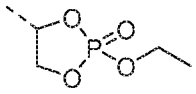


Formula 2

wherein

R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3,

R^2 is H, or $-C(O)C^{(S)}H(NH_2)R^4$,

R^3 is tetrahydropyran, or  ;

wherein R^4 is $-CH_2CH(CH_3)_2$, $-C^{(S)}H(CH)_3CH_2CH_3$, $-(CH_2)_2SCH_3$, $-CH_2-R^6$, $-(CH_2)_2C(O)NH_2$, $-(CH_2)_3C(O)OH$, or $-(CH_2)_4NH_2$;

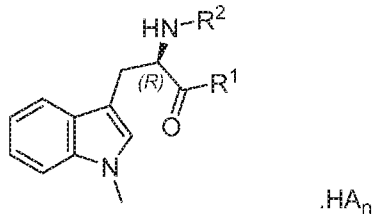
wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry;

wherein R^6 is phenyl;

with the proviso that R^1 cannot be -OH when R^2 is H;

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid) HSO_3CH_3 (methyl sulfonic acid), and $C_6H_5SO_3H$ (benzyl sulfonic acid), and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0060] In a most preferred embodiment of the second aspect, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,



Formula 2

wherein

R^1 is $-OC_{2-3}$alkyl, or $-OCH_2CH(OH)CH_2OH$,

R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$,

wherein R^4 is $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, or $-(CH_2)_2C(O)NH_2$;

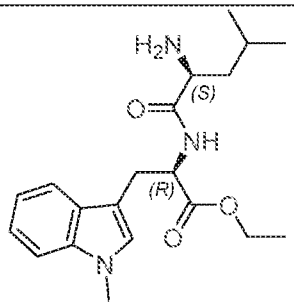
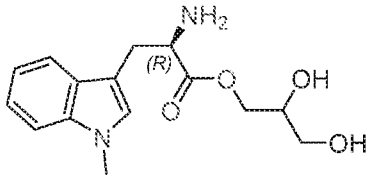
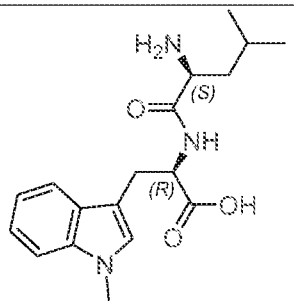
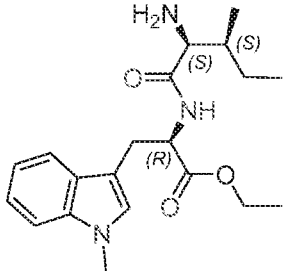
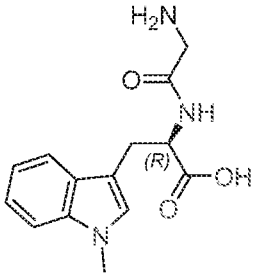
wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry

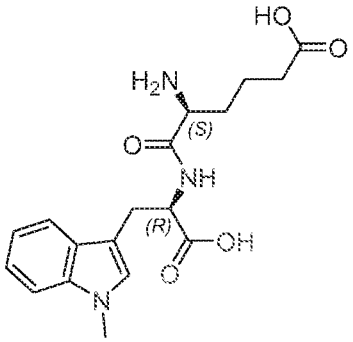
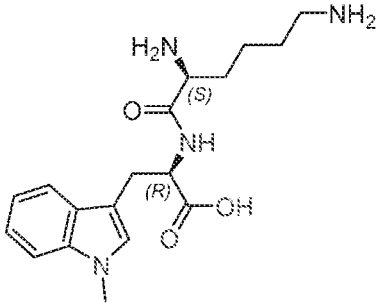
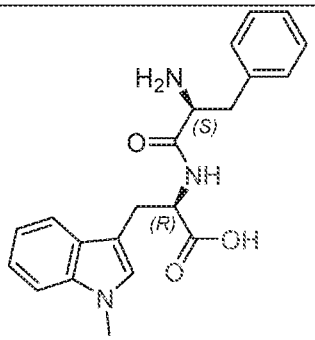
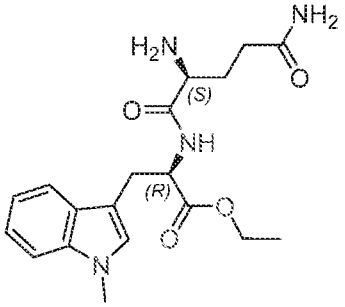
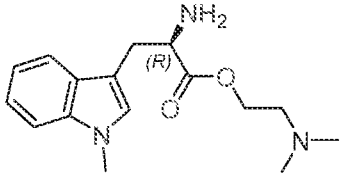
with the proviso that R^1 cannot be –OH when R^2 is H,

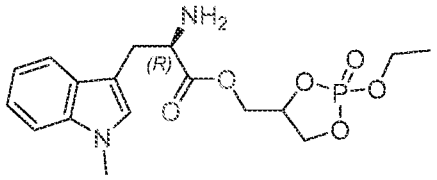
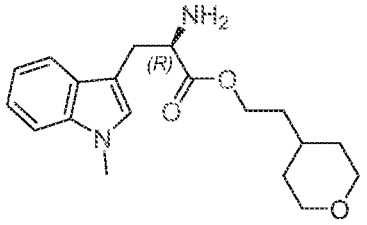
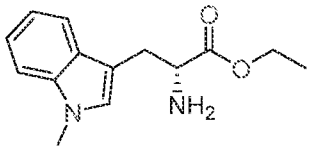
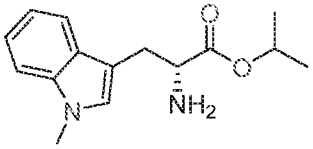
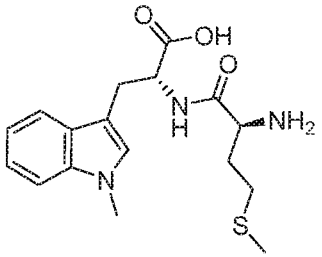
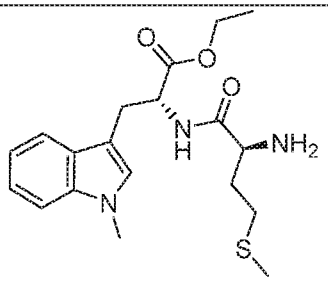
HA is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid) HSO_3CH_3 (methyl sulfonic acid) or $C_6H_5SO_3H$ (benzyl sulfonic acid); and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[0061] In a preferred embodiment, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or as a pharmaceutically appropriate salt form, as represented by compounds of Formula 2 represented in Table 1.

Table 1. Prodrugs of indoximod

Cpd Number	Structure	Name
01		ethyl N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophanate
02		2,3-dihydroxypropyl 1-methyl-*D*-tryptophanate
03		N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophan
04		ethyl N^{α}-(*L*-isoleucyl)-1-methyl-*D*-tryptophanate
05		N^{α}-(*L*-glycyl)-1-methyl-*D*-tryptophan

06		(*S*)-5-amino-6-(((*R*)-1-carboxy-2-(1-methyl-1*H*-indol-3-yl)ethyl)amino)-6-oxohexanoic acid
07		N^{α}-(*L*-lysyl)-1-methyl-*D*-tryptophan
08		N^{α}-(*L*-phenylalanyl)-1-methyl-*D*-tryptophan
09		ethyl N^{α}-(*L*-glutaminyl)-1-methyl-*D*-tryptophanate
10		2-(dimethylamino)ethyl 1-methyl-*D*-tryptophanate

11		(2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate
12		2-(tetrahydro-2*H*-pyran-4-yl)ethyl 1-methyl-*D*-tryptophanate
13		ethyl 1-methyl-*D*-tryptophanate
14		isopropyl 1-methyl-*D*-tryptophanate
15		N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophan
16		ethyl N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophanate

[0062] In another aspect, the invention provides methods of use of compositions of formulas 1 and 2, to modulate the activity of indoleamine-2,3-dioxygenase pathway in a subject in need

thereof, comprising the oral administration of therapeutically effective amounts such compositions to such subject in an appropriate pharmaceutical form or vehicle.

[0063] In another aspect, the invention provides methods of use of compositions of formulas 1a, 1b and 2, for the treatment of cancer in a subject in need thereof, comprising the oral administration of therapeutically effective amounts of such compositions to such subject in an appropriate pharmaceutical form or vehicle.

[0064] In another aspect, the invention provides methods of use of compositions of formulas 1a, 1b and 2, for the treatment of tumor-specific immunosuppression associated with cancer, in a subject in need thereof, comprising the oral administration of sufficient amounts such compositions to such subject in an appropriate pharmaceutical form or vehicle.

[0065] In another aspect, the invention provides methods of use of compositions of formulas 1a, 1b and 2, to treat immunosuppression associated with infectious diseases (e.g HIV-1 infection, influenza), in a subject in need thereof, comprising the oral administration of sufficient amounts such compositions to such subject in an appropriate pharmaceutical form or vehicle.

[0066] In one embodiment, a salt and/or a prodrug of indoximod is included in a pharmaceutical composition, and the composition is included in a solid capsule, gelatin capsule, tablet or pill. In one embodiment, the salt and/or the prodrug is included in a dissolvable capsule.

[0067] In specific embodiments, the compositions of the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the oligonucleotide(s) of the formulation.

[0068] In certain embodiments, pharmaceutical compositions of the present invention comprise one or more excipients. In certain such embodiments, excipients are selected from

water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, lactose monohydrate, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, microcrystalline cellulose and polyvinylpyrrolidone.

[0069] In certain embodiments, a pharmaceutical composition of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0070] Additional embodiments relate to the pharmaceutical formulations wherein the formulation is selected from the group consisting of a solid, powder, liquid and a gel. In certain embodiments, a pharmaceutical composition of the present invention is a liquid (e.g., a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical composition is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

[0071] In certain embodiments, a pharmaceutical composition of the present invention is a solid (e.g., a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical composition comprising one or more ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0072] In certain embodiments, a pharmaceutical composition of the present invention comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0073] In certain embodiments, a pharmaceutical composition of the present invention comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant

Polysorbate 80 and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0074] In certain embodiments, a pharmaceutical composition of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release pharmaceutical agents over a period of hours, days, weeks or months.

[0075] In certain embodiments, a pharmaceutical composition of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical composition is formulated by combining one or more agents and pharmaceutically acceptable carriers. Certain of such carriers enable pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, lactose monohydrate, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, microcrystalline cellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical compositions are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (e.g., cross-linked carboxymethyl cellulose, such as croscarmellose sodium, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

[0076] In certain embodiments, dragee cores are provided with coatings. In certain such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide,

lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

[0077] In certain embodiments, pharmaceutical compositions for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more pharmaceutical agents of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical compositions for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more pharmaceutical agents of the present invention are be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[0078] In certain embodiments, pharmaceutical compositions are prepared for buccal administration. Certain of such pharmaceutical compositions are tablets or lozenges formulated in conventional manner.

[0079] In certain embodiments, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity

of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the pharmaceutical agents to allow for the preparation of highly concentrated solutions.

[0080] In certain embodiments, a pharmaceutical composition of the present invention may be an effervescent tablet or granulate. Effervescent tablets most commonly consist of a soluble acid source and a carbonate source to produce carbon dioxide gas, the latter serving as disintegrant. The acidity needed for the effervescent reaction can be derived from food acids, acid anhydrides and acid salts. The food acid can for example be citric acid, tartaric acid, malic acid, fumaric acid, adipic acid or succinic acid. The acid anhydride may be succinic anhydride or citric anhydride or the like. The acid salts may be e.g. sodium dihydrogen phosphate (monosodium phosphate), disodium dihydrogen pyrophosphate (sodium acid pyrophosphate), acid citric salts (sodium dihydrogen citrate and disodium hydrogen citrate), sodium acid sulfite (sodium bisulfite). Suitable carbonate sources are for example sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, sodium sesquicarbonate (mixture of equal molar amounts of sodium carbonate and sodium bicarbonate), glycine carbonate, L-lysine carbonate, arginine carbonate, calcium carbonate.

[0081] Effervescence may also be induced by the formation of other gases such as oxygen, e.g. released from sodium perborate or from a combination of e.g. a peroxygen compound that yields active oxygen on mixture with water (e.g. sodium perborate monohydrate or sodium percarbonate) and a chlorine compound that liberates hypochlorite on contact with water (e.g. sodium dichloroisocyanurate or calcium hypochlorite).

[0082] The pharmaceutical composition of the present invention can be manufactured according to standard methods known in the art. Granulates and effervescent tablets according to the invention can be obtained by dry compaction or wet granulation. These granulates can subsequently be mixed with e.g. suitable disintegrating agents, glidants and lubricants and be compressed into tablets or filled into e.g. sachets of suitable size. Effervescent tablets can also be obtained by direct compression of a suitable powder mixture, i.e. without any preceding granulation of the excipients.

[0083] Suitable powder or granulate mixtures according to the invention are also obtainable by spray drying (e.g., by hot process spray drying or by basic spray drying) , lyophilization, melt extrusion, pellet layering, coating of the active pharmaceutical ingredient or any other suitable method. Preferably, the conditions are chosen such as to prevent amorphization of the active pharmaceutical ingredient. The so obtained powders or granulates can be mixed with one or more suitable ingredients and the resulting mixtures can either be compressed to form effervescent tablets or filled into sachets.

[0084] All publications, patents and patent applications, including any drawings and appendices therein are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent or patent application, drawing, or appendix was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

DEFINITIONS

[0085] Terms used herein may be preceded and/or followed by a single dash, "- ", or a double dash, "=", to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond or a pair of single bonds in the case of a spiro-substituent. In the absence of a single or double dash it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read "left to right" unless a dash indicates otherwise. For example, $C_{1\text{-}6}$alkoxycarbonyloxy and -OC(O)$C_{1\text{-}6}$alkyl indicate the same functionality; similarly arylalkyl, arylalkyl-, and –alkylaryl indicate the same functionality.

[0086] Further, certain terms herein may be used as both monovalent and divalent linking radicals as would be familiar to those skilled in the art, and by their presentation linking between two other moieties. For example, an alkyl group can be both a monovalent radical or divalent radical; in the latter case, it would be apparent to one skilled in the art that an additional hydrogen atom is removed from a monovalent alkyl radical to provide a suitable divalent moiety.

[0087] The term "alkenyl" as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, unless otherwise specified, and containing at least one carbon carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl, and 3,7-dimethylocta 2,6-dienyl.

[0088] The term "alkoxy" as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert butoxy, pentyloxy, and hexyloxy.

[0089] The term "alkyl" as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms, unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl. When an "alkyl" group is a linking group between two other moieties, then it may also be a straight or branched chain; examples include, but are not limited to $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CHC(CH_3)-$, $-CH_2CH(CH_2CH_3)CH_2-$.

[0090] The term C_{1-5}alkyl refers to a linear or branched alkyl of 1 to 5 carbon atoms.

[0091] The term C_{1-6}alkyl refers to a linear or branched alkyl of 1 to 6 carbon atoms.

[0092] The term "aryl," as used herein, means a phenyl (i.e., monocyclic aryl), or a bicyclic ring system containing at least one phenyl ring or an aromatic bicyclic ring containing only carbon atoms in the aromatic bicyclic ring system. The bicyclic aryl can be azulenyl, naphthyl, or a phenyl fused to a monocyclic cycloalkyl, a monocyclic cycloalkenyl, or a monocyclic heterocyclyl. The bicyclic aryl is attached to the parent molecular moiety through any carbon atom contained within the phenyl portion of the bicyclic system, or any carbon atom with the napthyl or azulenyl ring. The fused monocyclic cycloalkyl or monocyclic heterocyclyl portions of the bicyclic aryl are optionally substituted with one or two oxo and/or thia groups. Representative examples of the bicyclic aryls include, but are not limited to, azulenyl, naphthyl, dihydroinden-1-yl, dihydroinden-2-yl, dihydroinden-3-yl, dihydroinden-4-yl, 2,3-dihydroindol-4-yl, 2,3-dihydroindol-5-yl, 2,3-dihydroindol-6-yl, 2,3-dihydroindol-7-yl, inden-1-yl, inden-2-yl, inden-3-

yl, inden-4-yl, dihydronaphthalen-2-yl, dihydronaphthalen-3-yl, dihydronaphthalen-4-yl, dihydronaphthalen-1-yl, 5,6,7,8-tetrahydronaphthalen-1-yl, 5,6,7,8-tetrahydronaphthalen-2-yl, 2,3-dihydrobenzofuran-4-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzofuran-7-yl, benzo[d][1,3]dioxol-4-yl, benzo[d][1,3]dioxol-5-yl, 2H-chromen-2-on-5-yl, 2H-chromen-2-on-6-yl, 2H-chromen-2-on-7-yl, 2H-chromen-2-on-8-yl, isoindoline-1,3-dion-4-yl, isoindoline-1,3-dion-5-yl, inden-1-on-4-yl, inden-1-on-5-yl, inden-1-on-6-yl, inden-1-on-7-yl, 2,3-dihydrobenzo[b][1,4]dioxin-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 2H-benzo[b][1,4]oxazin3(4H)-on-5-yl, 2Hbenzo[b][1,4]oxazin3(4H)-on-6-yl, 2H benzo[b][1,4]oxazin3(4H)-on-7-yl, 2Hbenzo[b][1,4]oxazin3(4H)-on-8-yl, benzo[d]oxazin-2(3H)-on-5-yl, benzo[d]oxazin-2(3H)-on-6-yl, benzo[d]oxazin-2(3H)-on-7-yl, benzo[d]oxazin-2(3H)-on-8-yl, quinazolin-4(3H)-on-5-yl, quinazolin-4(3H)-on-6-yl, quinazolin-4(3H)-on-7-yl, quinazolin-4(3H)-on-8-yl, quinoxalin-2(1H)-on-5-yl, quinoxalin-2(1H)-on-6-yl, quinoxalin-2(1H)-on-7-yl, quinoxalin-2(1H)-on-8-yl, benzo[d]thiazol-2(3H)-on-4-yl, benzo[d]thiazol-2(3H)-on-5-yl, benzo[d]thiazol-2(3H)-on-6-yl, and, benzo[d]thiazol-2(3H)-on-7-yl. In certain embodiments, the bicyclic aryl is (i) naphthyl or (ii) a phenyl ring fused to either a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, or a 5 or 6 membered monocyclic heterocyclyl, wherein the fused cycloalkyl, cycloalkenyl, and heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia.

[0093] The term "arylalkyl," " alkylaryl," and "arylalkyl-" as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphth-2-ylethyl.

[0094] The terms "cyano" and "nitrile" as used herein, mean a -CN group.

[0095] The term "cycloalkyl" as used herein, means a monocyclic or a bicyclic cycloalkyl ring system. Monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups can be saturated or unsaturated, but not aromatic. In certain embodiments, cycloalkyl groups are fully saturated. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic

rings. Bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (*i.e.*, a bridging group of the form $-(CH_2)_w-$, where *w* is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. Fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. Cycloalkyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted by one or two groups which are independently oxo or thia.

[0096] "Cycloalkenyl" as used herein refers to a monocyclic or a bicyclic cycloalkenyl ring system. Monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups are unsaturated (i.e., containing at least one annular carbon carbon double bond), but not aromatic. Examples of monocyclic ring systems include cyclopentenyl and cyclohexenyl. Bicyclic cycloalkenyl rings are bridged monocyclic rings or a fused bicyclic rings. Bridged monocyclic rings contain a monocyclic cycloalkenyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $-(CH_2)_w-$, where w is 1, 2, or 3). Representative examples of bicyclic cycloalkenyls include, but are not limited to, norbornenyl and bicyclo[2.2.2]oct-2-enyl. Fused bicyclic cycloalkenyl ring systems contain a monocyclic cycloalkenyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The bridged or fused bicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the

monocyclic cycloalkenyl ring. Cycloalkenyl groups are optionally substituted with one or two groups which are independently oxo or thia.

[0097] The term "halo" or "halogen" as used herein, means Cl, Br, I or F.

[0098] The term "haloalkyl" as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

[0099] The term "heteroaryl," as used herein, means a monocyclic heteroaryl or a bicyclic ring system containing at least one heteroaromatic ring. The monocyclic heteroaryl can be a 5 or 6 membered ring. The 5 membered ring consists of two double bonds and one, two, three or four nitrogen atoms and optionally one oxygen or sulfur atom. The 6 membered ring consists of three double bonds and one, two, three or four nitrogen atoms. The 5 or 6 membered heteroaryl is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heteroaryl. Representative examples of monocyclic heteroaryl include, but are not limited to, furyl, imidazolyl, indolyl, 1-methyl-indolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The fused cycloalkyl or heterocyclyl portion of the bicyclic heteroaryl group is optionally substituted with one or two groups which are independently oxo or thia. When the bicyclic heteroaryl contains a fused cycloalkyl, cycloalkenyl, or heterocyclyl ring, then the bicyclic heteroaryl group is connected to the parent molecular moiety through any carbon or nitrogen atom contained within the monocyclic heteroaryl portion of the bicyclic ring system. When the bicyclic heteroaryl is a monocyclic heteroaryl fused to a phenyl ring or a monocyclic heteroaryl, then the bicyclic heteroaryl group is connected to the parent molecular moiety through any carbon atom or nitrogen atom within the bicyclic ring system. Representative examples of bicyclic heteroaryl include, but are not limited to, benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzoxathiadiazolyl, benzothiazolyl, cinnolinyl, 5,6-dihydroquinolin-2-yl, 5,6-

dihydroisoquinolin-1-yl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, quinolinyl, purinyl, 5,6,7,8-tetrahydroquinolin-2-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 5,6,7,8-tetrahydroquinolin-4-yl, 5,6,7,8-tetrahydroisoquinolin-1-yl, thienopyridinyl, 4,5,6,7-tetrahydrobenzo[c][1,2,5]oxadiazolyl, and 6,7-dihydrobenzo[c][1,2,5]oxadiazol-4(5H)-onyl. In certain embodiments, the fused bicyclic heteroaryl is a 5 or 6 membered monocyclic heteroaryl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused cycloalkyl, cycloalkenyl, and heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia.

[00100] The term "heteroarylalkyl" and " alkylheteroaryl" as used herein, means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heteroarylalkyl include, but are not limited to, fur-3-ylmethyl, 1H-imidazol-2-ylmethyl, 1H-imidazol-4-ylmethyl, 1-(pyridine-4-yl)ethyl, pyridine-3-ylmethyl, pyridine-4-ylmethyl, pyrimidin-5-ylmethyl, 2-(pyrimidin-2-yl)propyl, thien-2-ylmethyl, and thien-3-ylmethyl.

[00101] The terms "heterocyclyl" or "heterocycloalkyl" as used herein, means a monocyclic heterocycle or a bicyclic heterocycle. The monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle. Representative examples of monocyclic heterocycle include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl,

pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin-3-yl, 2,3-dihydrobenzothien-2-yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro-1H-indolyl, and octahydrobenzofuranyl. Heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the bicyclic heterocyclyl is optionally substituted by one or two groups which are independently oxo or thia.

[00102] The term "hydroxy" as used herein, means an -OH group.

[00103] The term "nitro" as used herein, means a $-NO_2$ group.

[00104] The term "oxo" as used herein means a =O group.

[00105] The term "thia" as used herein means a –S– group.

[00106] The term "saturated" as used herein means the referenced chemical structure does not contain any multiple carbon-carbon bonds. For example, a saturated cycloalkyl group as defined herein includes cyclohexyl, cyclopropyl, and the like.

[00107] The term "unsaturated" as used herein means the referenced chemical structure contains at least one multiple carbon carbon bond, but is not aromatic. For example, a unsaturated cycloalkyl group as defined herein includes cyclohexenyl, cyclopentenyl, cyclohexadienyl, and the like.

[00108] As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[00109] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[00110] In certain embodiments, a therapeutically effective amount can be an amount suitable for

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; or

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

[00111] As used here, the terms "treatment" and "treating" means (i) ameliorating the referenced disease state, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease; or (ii) eliciting the referenced biological effect (e.g., IDO modulation or tryptophan degradation inhibition).

[00112] Manifestation of amelioration of a disease condition with underlying IDO-mediated immunosuppression may require the concomitant or sequential administration of additional

therapeutic agents, such as antineoplastic agents in the case of cancer, or antiretroviral agents in the case of viral diseases. For example, administration of IDO inhibitors for the treatment of cancer does not always produce a direct antitumor effect when used as a single agent. However, when combined with chemotherapeutic drugs (antineoplastic) the antitumor effect observed is higher than the sum of effects of each agent alone.

[00113] As used herein, the terms "catalytic pocket", "catalytic site", "active site" collectively and indistinctly refer to a region of the enzyme that contains amino acid residues responsible for the substrate binding (charge, hydrophobicity, steric hindrance) and catalytic amino acid residues which act as proton donors or acceptors or are responsible for binding a cofactor and participate in the catalysis of a chemical reaction.

[00114] As used herein, the phrase "pharmaceutically acceptable salt" refers to both pharmaceutically acceptable acid and base addition salts and solvates. Such pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH_2)n-COOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

[00115] As used herein, the term "indoximod" refers to 1-methyl-D-tryptophan, also referred to as D-1MT or D1mT.

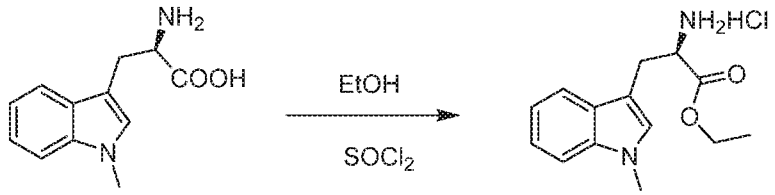
[00116] As used herein, the term "prodrug of indoximod" refers to any substance that after in vivo administration is metabolized to produce indoximod as one of the main metabolites.

EXAMPLES

Example 1: Reagents and Methods of Synthesis

[00117] All reagents and solvents were purchased from commercial sources. All commercial reagents and solvents were used as received without further purification. The reactions were monitored using analytical thin layer chromatography (TLC) with 0.25 mm EM Science silica gel plates (60F-254). The developed TLC plates were visualized by short wave UV light (254 nm) or immersion in potassium permanganate solution followed by heating on a hot plate. Flash chromatography was performed with Selecto Scientific silica gel, 32-63 μm particle sizes. All reactions were performed in flame or oven-dried glassware under a nitrogen atmosphere. All reactions were stirred magnetically at ambient temperature unless otherwise indicated. ^{1}H NMR spectra were obtained with a Bruker DRX400, Varian VXR400 or VXR300. ^{1}H NMR spectra were reported in parts per million (δ) relative to TMS (0.0), DMSO-d_6 (2.50) or CD_3OD (4.80) as an internal reference. All ^{1}H NMR spectra were taken in $CDCl_3$ unless otherwise indicated.

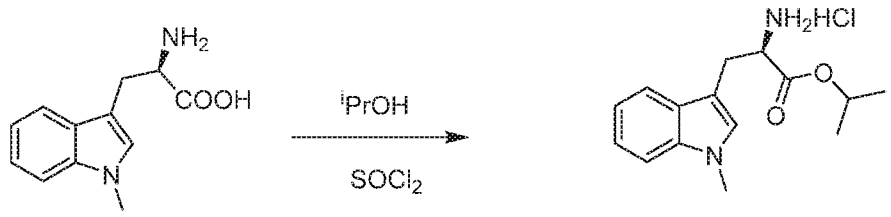
Synthesis of ethyl 1-methyl-D-tryptophanate hydrochloride (NLG-1283)



D-1MT NLG-1283

[00118] To a suspension of D-1MT (4.00 g, 18.3 mmol) in ethanol (50 mL) at 0 °C was added $SOCl_2$ (1.34 mL, 18.3 mmol) and the mixture was stirred at 80 °C overnight. After cooling to rt, the solvent was distilled-off and the crude was diluted with diethyl ether (100 mL), the white solid was filtered-off and washed with dry ether to afford the desired product (5.1 g, 98 %).

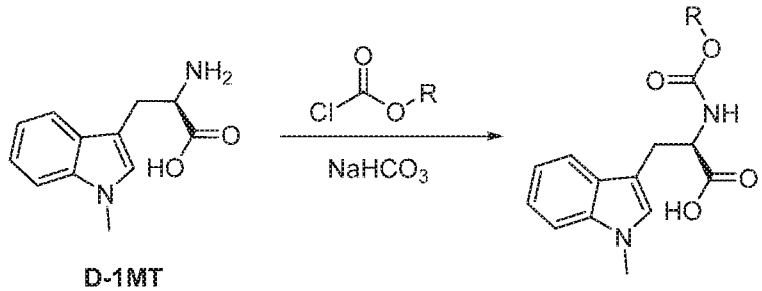
Synthesis of isopropyl 1-methyl-D-tryptophanate hydrochloride (NLG-1284)



D-1MT NLG-1284

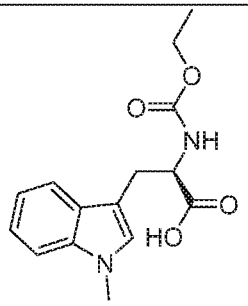
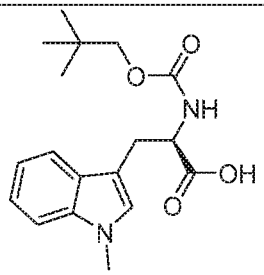
[00119] To a suspension of D-1MT (0.500 g, 2.29 mmol) in isopropanol (15 mL) at 0 °C rt, was added $SOCl_2$ (0.167 mL, 2.29 mmol) and the mixture was stirred at 80 °C overnight. After cooling to rt, the solvent was distilled-off and the crude was basified with 25 % aq $NaHCO_3$ (20 mL), the product was extracted with CH_2Cl_2, the combined organic extract was dried over Na_2SO_4 and the solvent was distilled-off under reduced pressure. The free base was converted to its HCl salt by adding dry HCl in dioxane, the solvent was removed under reduced pressure to afford the desired product as white solid (0.252 g, 37%).

General method for the synthesis of carbamate esters

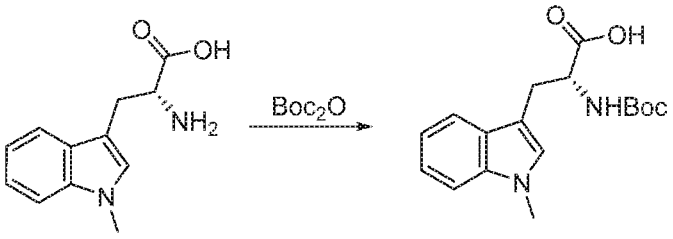


D-1MT

[00120] To a stirred solution of D-1MT (0.150 g, 0.687 mmol) in 1:1 THF/1M $NaHCO_3$ (2.75 mL, 2.75 mmol) was added the appropriate chloroformate dropwise. The mixture was allowed to stir for 30 min. and the solution was diluted with water and extracted with ether 2x. The aqueous layer was cooled to 0 oC and conc HCl solution was added to adjust the pH to ~1. The cold aqueous layer was immediately extracted with ethyl acetate and the combined organic layers were washed with water, brine and dried. The solvent was removed under reduced pressure to afford crude the carbamate. The crude was purified by column chromatography and treated with activated charcoal to afford the pure carbamate.

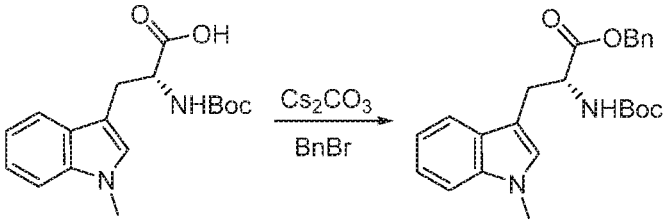
#	Compound	Name	Yield (%)
NLG-1277		N^{α}-(ethoxycarbonyl)-1-methyl-D-tryptophan	81
	1.23 (t, 3H, J = 6.8 Hz), 3.63-3.71 (m, 1H), 3.74 (s, 3H), 4.07-4.12 (m, 2H), 4.69 (dd, 1H, J = 6.7, 11.6 Hz), 5.20 (dd, 1H, J = 6.9, 11.5 Hz), 6.9 (s, 1H), 7.07 (t, 1H, 6.9 Hz), 7.21-7.48 (m, 2H), 7.57 (d, 1H, J = 7.1 Hz), 9.07 (br s, 1H)		
NLG-1278		1-methyl-N^{α}-((neopentyloxy)carbonyl)-D-tryptophan	72
	0.90 (s, 9H), 3.34 (s, 2H), 3.64 (s, 3H), 3.73 (t, 1H, J = 6.8 Hz), 4.75 (d, 1H, J = 7.8 Hz), 5.23 (d, 1H, J = 7.9 Hz), 6.89 (s, 1H), 7.07 (t, 1H, J = 8.2 Hz), 7.25-7.59 (m overlapped with CHCl3, 2H), 7.58 (d, 1H, 7.8 Hz), 8.4 (br s, 2H)		

Synthesis of N^{α}-(*tert*-butoxycarbonyl)-1-methyl-D-tryptophan



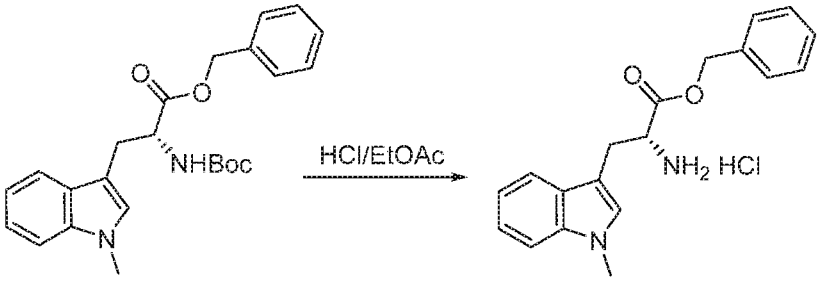
[00121] To a mixture of D-1MT (3.0 g, 13.75 mmol) in dioxane (70 mL) at 0 °C was added NaOH (550 mg dissolved in 30 mL DI water), followed by the addition of Boc_2O. The reaction was stirred at 0 °C for 4 h and stirred overnight at rt. The solution was concentrated under reduced pressure to approx. one third the original volume. The reaction was acidified with 1N HCl at 0 °C and the product was extracted with EtOAc. The organic extract was washed with brine and dried over Na_2SO_4, the solvent was evaporated under reduced pressure to afford the product that was used directly in the next step without further purification (4.3 g, 98%).

Synthesis of benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-D-tryptophanate



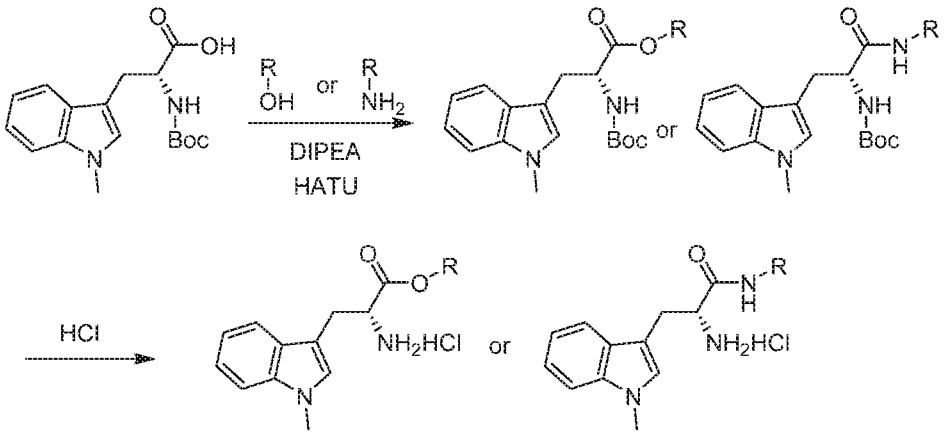
[00122] In 60 ml of DMF was dissolved N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophan (3.00 g, 9.42 mmol) to which Cs_2CO_3 (1.78 g, 5.47 mmol) and benzyl bromide (1.61 mL, 9.42 mmol) was added. The resulting suspension was allowed to stir at room temperature for 2 hours. After the end of reaction (TLC), the DMF was removed under reduced pressure followed by suspending the residue in toluene/ethyl acetate before washing with distilled water (3 x 50 mL) and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica gel (3.5 g, 91%).

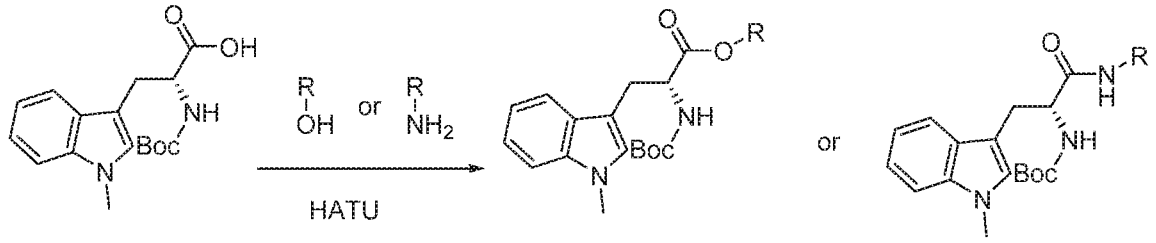
Synthesis of benzyl 1-methyl-D-tryptophanate hydrochloride (NLG-1338)



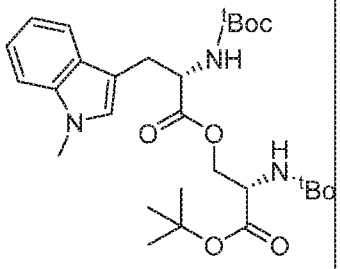
[00123] Ethyl acetate (26.9 mL) and MeOH (8.9 mL) in a RB flask equipped with a septum and a needle vent were cooled in an ice bath with stirring. Acetyl chloride (14.22 mL) was added slowly. The resulting solution was stirred at 0 °C for 20 minutes and MeOH (0.5 mL) was added. A flask containing benzyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate (3.5g, 8.6 mmol) was placed in an ice bath and the cold, freshly prepared HCl (4M in EtOAc) was poured into the flask containing benzyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate slowly. The solution was stirred vigorously at 0 °C for 15 min where the formation of a white suspension was observed and the flask was removed from the ice bath. The suspension was allowed to stir vigorously for 2.5 h. The solution was cooled in an ice bath diluted with ether (50 mL) and the suspension was filtered and the solid cake washed with cold ether. The solid was allowed to dry under high vacuum and the desired product was isolated as a colorless solid (6.45 g, 88%). 1H NMR (d_6-dmdso); 3.28 (dd, 2H, J = 5.6, 15.2 Hz), 3.70 (s, 3H), 4.26-4.29 (m, 1H), 5.08 (d, 1H, J = 12.4 Hz), 5.13 (d, 1H, J = 12.4 Hz), 7.04 (t, 1H, J = 7.6 Hz), 7.06 (s, 1H), 7.10-7.18 (m, 3H), 7.30-7.35 (m, 3H), 7.42 (d, 1H, J = 8 Hz), 7.53 (d, 1H, J = 8 Hz).

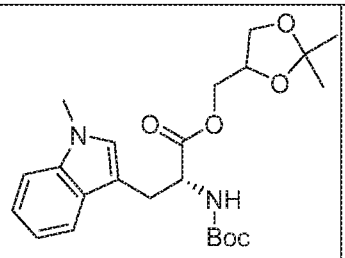
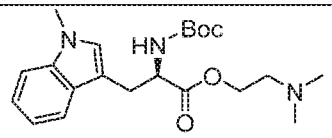
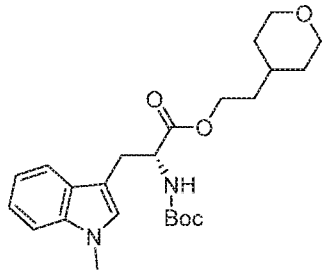
General scheme for the derivatization of –COOH group of D-1MT

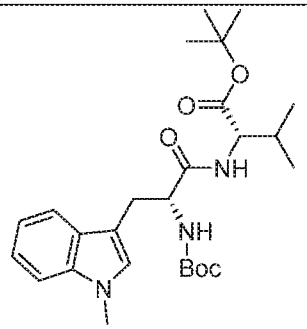
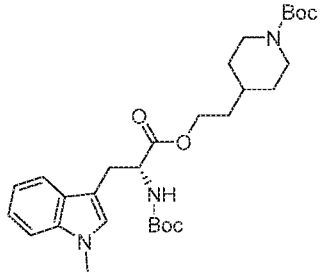
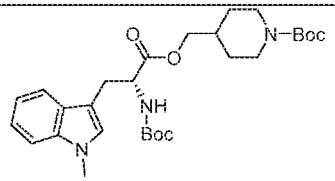


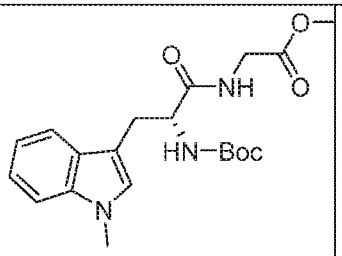


[00124] To a solution of N-(tert-butoxycarbonyl)-1-methyl-D-tryptophan (3.14 mmol), appropriate alcohol or amine (3.14 mmol) and HATU (3.14 mmol) in acetonitrile (30 mL) at 0 °C was added DIPEA (9.42 mmol) and the solution was allowed to warm to rt. After stirring overnight (17 h), the reaction was diluted with water (50 mL) and the product was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extract was washed with water (25 mLx1), brine (25mlx1) dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude. Chromatographic purification afforded the desired product.

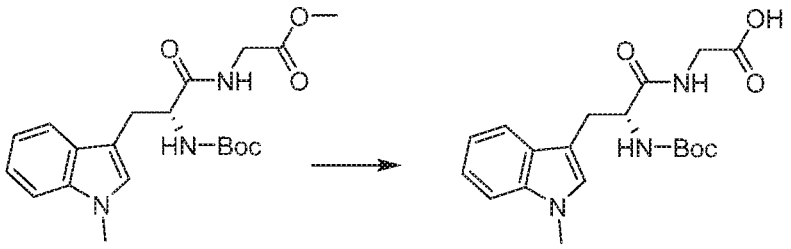
#	Compound	Name	Yield (%)
NLG-1551-B.1-E15		(S)-3-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl Na-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate	40
	1.41 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H), 3.16 (dd, 1H, J = 15.3, 4.8 Hz), 3.29 (dd, 1H, J = 15.3, 4.8 Hz), 3.75 (s, 3H), 4.35-4.52 (m, 3H), 4.61 (d, 1H, J = 6.3 Hz), 4.99 (d, 1H, J = 8.6 Hz), 5.28 (d, 1H, J = 8.7 Hz), 6.87 (s, 1H), 7.11 (t, 1H , J = 7.3 Hz), 7.22 (t, 1H , J = 7.3 Hz), 7.29 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 7.8 Hz).		

NLG-1558-A-E23		(2,2-dimethyl-1,3-dioxolan-4-yl)methyl N-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate	78
	1.27 (s, 3H), 1.33 (s, 3H), 1.35 (s, 9 H), 3.21 (d, 2H, J = 5.6 Hz),3.44-3.50 (m, 1H), 3.67 (s, 3H), 3.80-3.86 (m, 1H), 3.99-4.03 (m, 2H), 4.07-4.12 (m, 1H), 4.58 (q, 1H, J = 6.5 Hz), 4.99 (d, 1H, J = 8.2 Hz), 6.82 (s, 1H), 7.03 (t, 1H, J = 7.4 Hz), 7.14 (t, 1H, J = 7.4 Hz), 7.21 (d, 1H, J = 8.1 Hz), 7.47 (d, 1H, J = 8.0 Hz).		
NLG-1557-B-E14		2-(dimethylamino)ethyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate	38
	1.33 (s, 1H), 1.43 (s, 8H), 2.23 (s, 5H), 2.29 (s, 1H), 2.43 – 2.60 (m, 4H), 3.27 (d, *J* = 5.6 Hz, 2H), 3.74 (s, 3H), 4.1 – 4.23 (m, 2H), 4.63 (m, 1H), 5.10 (m, 1H), 6.91 (s, 1H), 7.10 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.21 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.28 (d, *J* = 8.0, 1H), 7.54 (d, *J* = 8.0 Hz, 1H).		
NLG-1572-A-E39		2-(tetrahydro-2H-pyran-4-yl)ethyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate	60
	1.29 – 1.35 (m, 2H), 1.42 (s, 9H), 1.60-1.67 (m, 5H), 3.17 – 3.35 (m, 4H), 3.74 (s, 3H), 3.84 – 3.93 (m, 2H), 4.10 (dq, 2H, *J* = 10.4, 6.4 Hz), 4.55 – 4.65 (m, 1H), 5.06 (d, 1H, *J* = 8.2 Hz), 6.86 (s, 1H), 7.09 (ddd, 1H, *J* = 8.0, 7.0, 1.1 Hz), 7.21 (ddd, 1H, *J* = 8.2, 6.9, 1.1 Hz), 7.28 (d, 1H, *J* = 7.4 Hz), 7.48 – 7.59 (m, 1H)		

NLG-1556-A-E22		tert-butyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophyl-L-valinate	91
	0.69 (d, 3H, J = 6.8 Hz), 0.75 (d, 3H, J = 6.8 Hz), 1.42 (s, 18H), 1.98-2.03 (m, 1H), 3.18 (dd, 1H, J = 14.4, 7.2 Hz), 3.27-3.35 (m, 1H), 3.73 (s, 3H), 4.35-4.39 (m, 1H), 4.50 (br s, 1H), 5.07 (br s, 1H), 6.31 (d, 1H, J = 8.8 Hz), 6.92 (s, 1H), 7.12 (t, 1H, J = 7.2 Hz), 7.22 (t, 1H, J = 7.2 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz)		
NLG-1561-A-E29		tert-butyl 4-(2-((N$^{\alpha}$-(tert-butoxycarbonyl)-1-methyl-D-tryptophyl)oxy)ethyl)piperidine-1-carboxylate	92
	0.95-1.05 (m, 2H), 1.47 (s, 18H), 1.32-1.40 (m, 3H), 1.55 (d, 2H, J = 2.4 Hz), 2.59 (dt, 2H, J = 2.7, 12.8 Hz), 3.25 (d, 2H, J = 5.6 Hz), 3.74 (s, 3H), 3.99-4.05 (m, 2H), 4.94-5.00 (m, 2H), 5.08 (d, 1H, J = 8.0 Hz), 6.52 (br s, 1H), 6.86 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz).		
NLG-1563-A-E30		tert-butyl 4-(((N$^{\alpha}$-(tert-butoxycarbonyl)-1-methyl-D-tryptophyl)oxy)methyl)piperidine-1-carboxylate	83
	0.93-1.10 (m, 2H), 1.29-1.32 (m, 1H), 1.45 (s, 18H), 1.63-1.69 (m, 2H), 2.59 (tt, 2H, J = 2.4, 13.2 Hz), 3.25 (t, 2H, J = 5.4 Hz), 3.75 (s, 3H), 3.84-3.92 (m, 2H), 4.01-4.06 (m, 2H), 5.06 (d, 1H, J = 8.0 Hz), 6.35 (br s, 1H), 6.86 (s, 1H), 7.10 (dt, 1H, J = 1.2, 6.8 Hz), 7.24 (dt, 1H, J = 1.2, 6.8 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 8.0 Hz)		

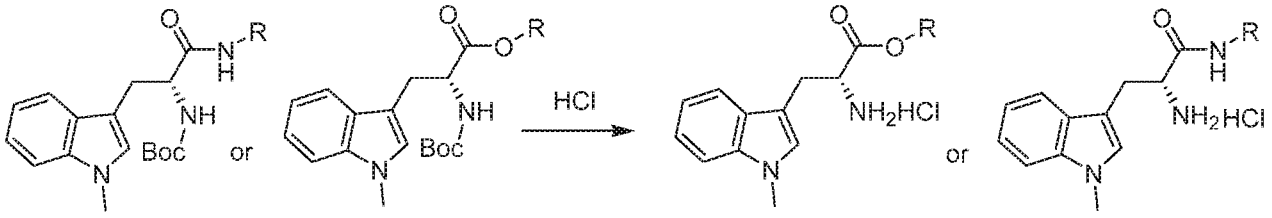
NLG-1578-A-E43		methyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophylglycinate	91
	1.25 (s, 9H), 3.15-3.25 (m, 2H), 3.67 and 3.69 (two s, 3H), 3.70 and 3.71 (two s, 3H), 3.90-3.92 (m, 2H), 5.21 and 4.48 (s, 1H), 6.54-6.52 (m, 1H), 6.93 (s, 1H), 7.13 – 7.03 (m, 1H), 7.14 – 7.30 (m, 2H), 7.59 (d, 1H, J = 8.0 Hz).		

Synthesis of N^{α}-(*tert*-butoxycarbonyl)-1-methyl-D-tryptophylglycine (NLG-1579-A-E44)



NLG-1578-A-E43 **NLG-1579-A-E44**

[00125] To a solution of **NLG-1578-A-E43** (300 mg, 0.770 mmol) in THF (10 mL) was added water (2 mL) and lithium monohydrate (49 mg, 1.16 mmol) and the mixture stirred under ambient temperature for 2.0 h. The mixture was neutralized with 1M HCl (at 0 °C) and poured into ice cold water (20 mL). The aqueous layer was extracted with EtOAc (3 x 35 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography to afford the desired product as white solid (260 mg, 90 %). ^{1}H NMR: 1.25 and 1.39 (two s, 9H). 3.18-3.24 (m, 2H), 3.70 (s, 3H), 3.81-4.05 (m, 2H), 4.55 (s, 1H), 5.20 – 5.33 (m, 1H), 6.63 (s, 1H), 6.92 (s, 1H), 7.10 (t, 1H, J = 7.2 Hz), 7.15 – 7.25 (m, 2H), 7.59 (dt, 1H, J = 7.9 Hz)

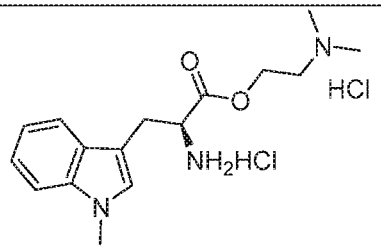


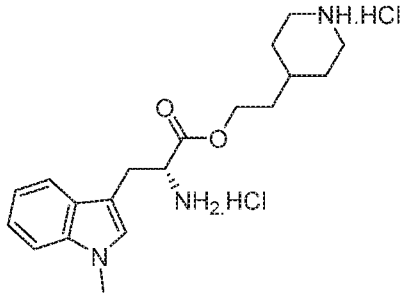
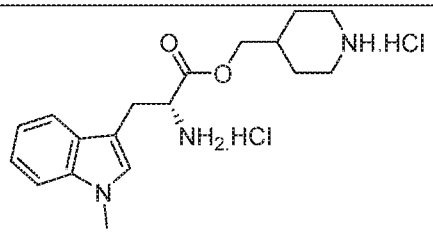
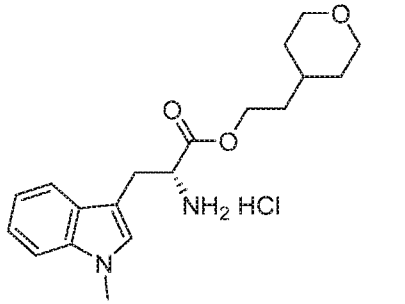
R = H, alkyl, alkylaryl

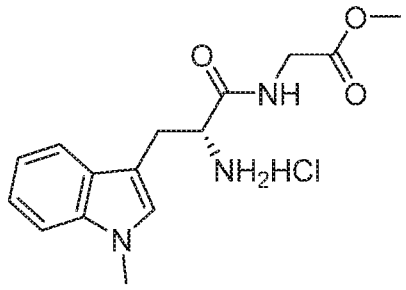
R = H, alkyl, alkylaryl

[00126] To a mixture of tBoc protected amine (1.57 mmol) in dioxane (15 mL) at rt was added HCl (4 mL, 4.0 M solution in dioxane). After stirring for 2.5 h, the solvent was distilled-off under reduced pressure. The residue was stirred with methyl *tert*-butyl ether (10 mL), the solid was filtered and dried under reduced pressure to afford the desired product.

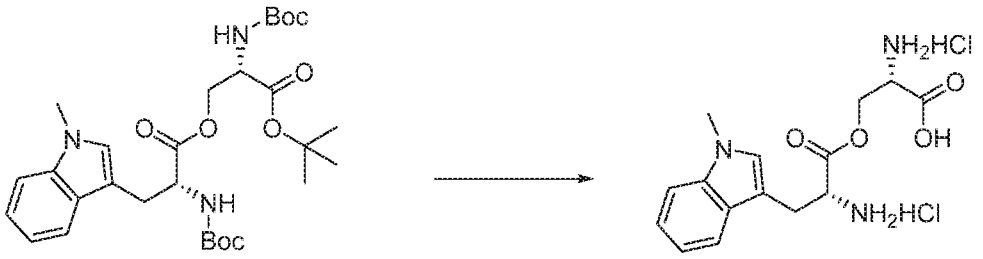
[00127] The following compounds were synthesized following procedures described in the above sections.

#	Compound	Name	Yield (%)
NLG-1557		2-(dimethylamino)ethyl 1-methyl-D-tryptophanate dihydrochloride	42
	^{1}H NMR (400 MHz, Methanol-d_4): 2.69 (s, 3H), 2.77 (s, 3H), 3.46 (dd, J = 6.7, 2.1 Hz, 2H), 3.81 (s, 3H), 4.35 (m, 1H), 4.46 (t, J = 6.6 Hz, 1H), 4.54 (m, Hz, 1H), 7.11 (dd, J = 8.0 1.2 Hz, 1H), 7.18 – 7.25 (m, 2H), 7.40 (d, J = 8.0), 7.58 (d, J = 8.0, 1H).		

NLG-1561		2-(piperidin-4-yl)ethyl 1-methyl-D-tryptophanate dihydrochloride	64
	(DMSO-d6) 1.24-1.45 (m, 5H), 1.60 (d, 2H, J = 13.2 Hz), 2.64-2.72 (m, 2H), 3.11-3.14 (m, 2H), 3.25 (dd, 1H, J = 14.4, 7.6 Hz), 3.33-3.83 (m, 1H, merged with H_2O from DMSO), 3.75 (s, 3H), 3.99-4.08 (m, 2H), 4.15 (t, 1H, J = 6.6 Hz), 7.04 (t, 1H, J = 7.4 Hz), 7.16 (t, 1H, J = 7.6 Hz), 7.24 (s, 1H), 7.42 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 8.75 (br s, 3H), 8.95 (br s, 1H), 9.16 (br s, 1H)		
NLG-1563		piperidin-4-ylmethyl 1-methyl-D-tryptophanate dihydrochloride	50
	(DMSO-d6) 1.16-1.34 (m, 2H), 1.41 (d, 1H, J = 13.6 Hz), 1.53 (d, 1H, J = 13.6 Hz), 1.61-1.66 (m, 1H), 2.66-2.70 (m, 2H), 3.08-3.16 (m, 2H), 3.22-3.28 (m, 1H), 3.36-3.44 (m, 1H), 3.74 (s, 3H), 3.78-3.88 (m, 2H), 4.12-4.17 (m, 1H), 7.05 (t, 1H, J = 7.4 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.24 (s, 1H), 7.40 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 7.6 Hz), 8.83 (br s 3H), 9.06 (br s, 1H), 9.34 (br s, 1H)		
NLG-1572		2-(tetrahydro-2H-pyran-4-yl)ethyl 1-methyl-D-tryptophanate hydrochloride	94
	^{1}H NMR(DMSO-d_6, 400 MHz): δ = 0.93 – 1.11 (m, 2H), 1.18 (d, 1H, J = 6.2 Hz), 1.26 – 1.43 (m, 4H), 3.14 (d, 2H, J = 11.2 Hz), 3.23 (dd, 1H, J = 14.7, 7.7 Hz), 3.29 – 3.39 (m, 2H), 3.69-3.78 (m, 4H), 4.04 (d, 2H, J = 6.2 Hz), 4.17 (t, 1H, J = 6.6 Hz), 7.04 (ddd, 1H, J = 8.0, 7.1, 1.0 Hz), 7.16		

	(ddd, 1H, *J* = 8.3, 7.0,1.2 Hz), 7.23 (s, 1H), 7.42 (d, 1H, *J* = 8.2 Hz), 7.53 (dd, 1H, *J* = 8.1, 1.4 Hz), 8.69 (br s, 3H).		
NLG-1578		methyl 1-methyl-D-tryptophylglycinate hydrochloride	93
	3.12 (dd, 1H, *J* = 14.7, 7.8 Hz,), 3.25 (dd, 1H, *J* = 14.7, 5.7 Hz), 3.64 (s, 3H), 3.72 (s, 3H), 3.93 (t, 2H, *J* = 6.0 Hz), 3.97-4.06 (m, 1H), 7.03 (t, 1H, *J* = 7.5 Hz), 7.14 (t, 1H, *J* = 7.20 Hz), 7.19 (s, 1H), 7.39 (d, 1H, *J* = 8.2 Hz), 7.71 (d, 1H, *J* = 8.0 Hz), 8.21 (s, 2H), 9.15 (m, 1H).		

Synthesis of O-(1-methyl-D-tryptophyl)-L-serine dihydrochloride (NL-G1551)

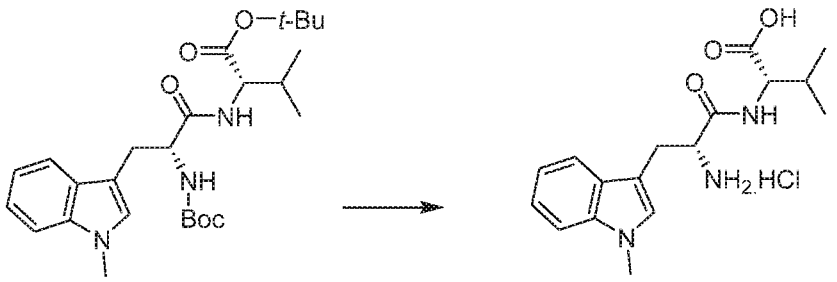


NLG-1551-B.1-E15 NLG-1551

[00128] To a solution of **NLG-1551-B.1-E15** (0.450 g, 824.66 mmol) in CH_2Cl_2 (10 mL) was added HCl (2 mL, 4 M solution in dioxane) at 0 °C and the solution was allowed to warm to rt. After stirring for 5 h, the solvent was evaporated and the reaction was diluted with trifluoroacetic acid (8 mL) and the solution was stirred for 7 h at rt. After evaporating trifluoroacetic acid the reaction was diluted with dry HCl solution (1 mL, 4 M solution in dioxane) and the mixture was stirred for 10 min. The solvent was evaporated under reduced pressure, the product was triturated with ethanol:ether (10:90, 15 mL) and the product was filtered and washed with dry ether (10 mL).The product was dried under reduced pressure (0.190 g, 61%). ^{1}H NMR (400 MHz, CD_3OD): 3.22-3.28 (m, 1H), 3.43 (dd, 1H, J = 15.4, 4.7 Hz), 3.70 (s, 3H), 4.23 (t, 1H, J = 3.9 Hz),

4.35 (dd, 1H, J = 8.0, 4.9 Hz), 4.60 (d, 2H, J = 3.8 Hz), 6.99-7.04 (m, 1H), 7.05 (s, 1H), 7.09-7.16 (m, 1H), 7.29 (d, 1H, J = 8.3 Hz), 7.50 (d, 1H, J = 7.9 Hz).

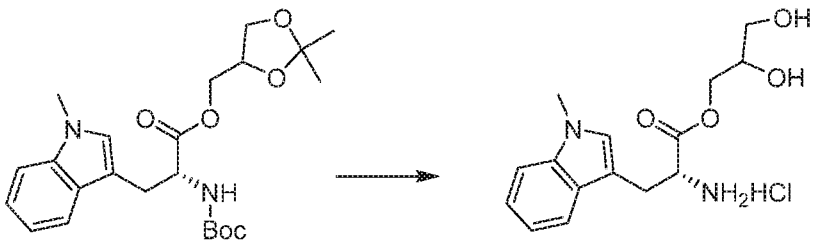
Synthesis of 1-methyl-D-tryptophyl-L-valine hydrochloride (NLG-1556)



NLG-1556-A-E22 NLG-1556

[00129] Dioxane (7 mL) and MeOH (1.20 mL, 28.6 mmol) in a RB flask equipped with a septum and a needle vent were cooled in an ice bath with stirring. Acetyl chloride (2.00 mL, 28.6 mmol) was added slowly. The resulting solution was stirred at 0 °C for 20 minutes and MeOH (0.1 mL) was added. A flask containing **NLG-1556-A-E22** (678 mg, 1.43 mmol) was placed in an ice bath and the cold, freshly prepared HCl (4M in dioxane) was poured into the flask containing **NLG-1556-A-E22** slowly. The solution was allowed to warm to RT and stirred vigorously for 18 h. The solvent was removed using rotary evaporator to afford pure white solid (205 mg, 40%).(DMSO-d6) 0.71-0.77 (m, 6H), 1.91-2.00 (m, 1H), 3.08 (dd, 1H, J = 14.4, 8.4 Hz), 3.23 (dd, 1H, J = 14.4, 8.4 Hz), 3.73 (s, 3H), 4.12-4.17 (m, 2H), 7.06 (t, 1H, J = 7.4 Hz), 7.17 (t, 1H, J = 7.8 Hz), 7.20 (s, 1H), 7.40 (d, 1H, J = 8.4 Hz), 7.74 (d, 1H, J = 8.0 Hz), 8.2 (br s, 3H), 8.74 (d, 1H, J = 8.4 Hz)

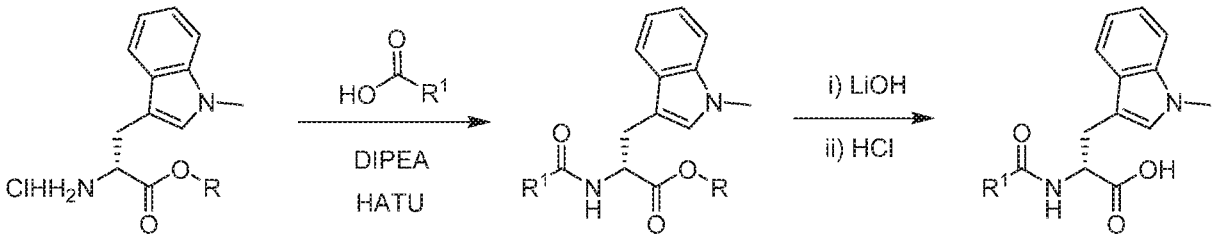
Synthesis of 2,3-dihydroxypropyl 1-methyl-D-tryptophanate hydrochloride (NLG-1558)

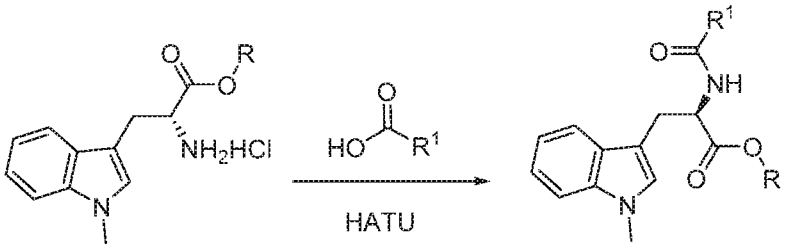


NLG1558-A-E23 **NLG-1558**

[00130] A solution of **NLG1558-A-E23** (11.5 g, 26.59 mmol) in THF (100 mL) at 0 °C was added TFA (16.3 mL, 212.7 mmol) and water (0.958 g, 53.18 mmol) and the cooling bath was removed, the mixture was stirred at rt for 2 h. HCl (13.3 mL, 53.18 mmol; 4.0 M solution in dioxane) was added and continued stirring for 1 h. The reaction was stirred at 40 °C for 45 minutes. The precipitated white solid was filtered and washed with MTBE to afford the hydrochloride salt (4.5 g, 51%). ^{1}H NMR (400 MHz, DMSO-d_6): 3.32-3.40 (m, 1H), 3.44-3.52 (m, 3H), 3.76-3.86 (m, 4H), 4.16-4.37 (m, 3H), 7.10 (t, 1H, J = 7.4 Hz), 7.14 (s, 1H), 7.19 (t, 1H, J = 7.6 Hz), 7.38 (d, 1H, J = 8.2 Hz), 7.58 (d, 1H, J = 7.9 Hz).

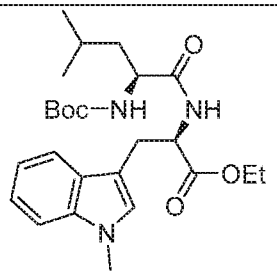
General scheme for the derivatization of the –NH_2 and –COOH group of D-1MT

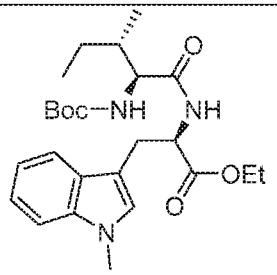
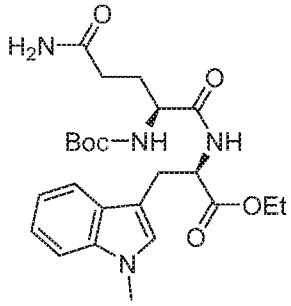
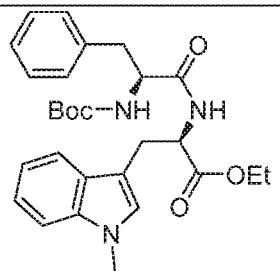


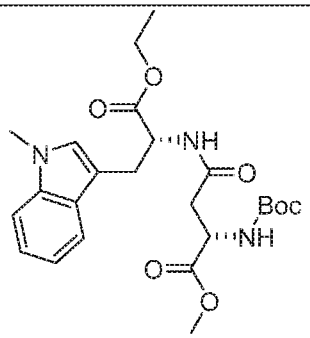
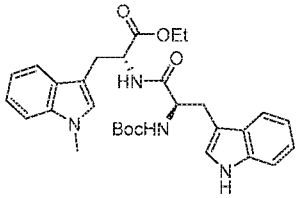
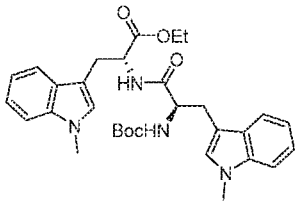


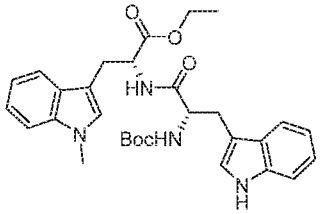
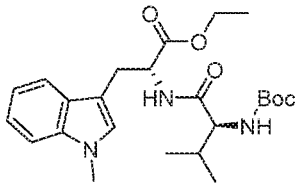
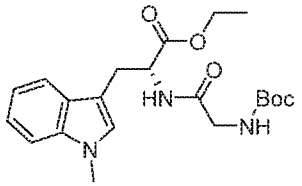
R = Et, Bn

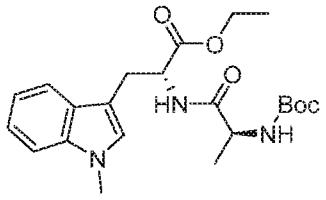
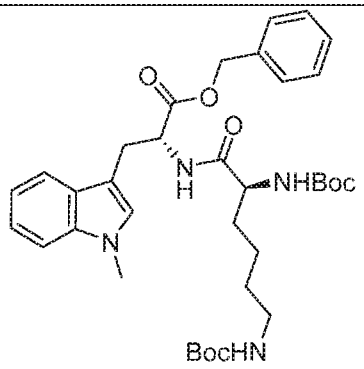
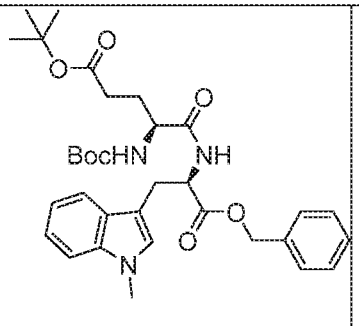
[00131] Appropriate D-tryptophanate hydrochloride ester (1.0 g, 3.54 mmol) and appropriate acid (3.54 mmol) were stirred in acetonitrile (50 mL) at 0 °C. HATU (1.48 g, 3.89 mmol) and iPr_2NEt (2.46 mL, 14.15 mmol) were added and the reaction stirred overnight at room temperature. The solvent was removed under reduced pressure and the crude was diluted with water (50 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to afford the desired product.

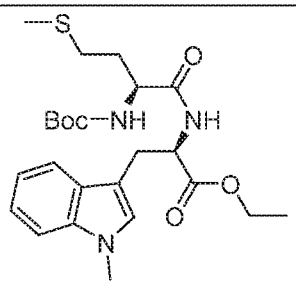
#	Compound	Name	Yield (%)
NLG-1564-B-E31		ethyl N^{α}-((tert-butoxycarbonyl)-L-leucyl)-1-methyl-D-tryptophanate	92
	0.86 (dd, 6H, J = 6.2, 2.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.39 (s, 9H), 1.55-1.58 (m, 2H), 3.29 (d, 2H, J = 5.7 Hz), 3.74 (s, 3H), 4.03-4.18 (m, 3H), 4.79-4.86 (m, 2H), 6.60 (d, 1H, J = 7.8 Hz), 6.87 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.26 (s, 1H), 7.52 (d, 1H, J = 7.9 Hz)		

NLG-1565-A-E32		ethyl N^{α}-((tert-butoxycarbonyl)-L-isoleucyl)-1-methyl-D-tryptophanate	93
	0.80-0.84 (m, 6H), 1.02 – 0.91 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz), 1.40 (s, 9 H), 1.87 (m, 1H), 3.28 (t, 2H, *J* = 5.4 Hz), 3.72 (s, 3H), 4.00 – 4.04 (m, 1H), 4.05- 4.16 (m, 2H), 4.85 (q, 1H, *J* = 6.4 Hz), 4.95 (d, 1H, *J* = 9.0 Hz), 6.46 (d, 1H, *J* = 7.7 Hz), 6.87 (s, 1H), 7.10 (ddd, 1H, *J* = 8.0, 6.8, 1.1 Hz), 7.20 (ddd, 1H, *J* = 8.2, 6.9, 1.2 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.53 (dt, 1H, *J* = 7.9, 1.0 Hz).		
NLG-1566-A-E37		ethyl N^{α}-((tert-butoxycarbonyl)-L-glutaminyl)-1-methyl-D-tryptophanate	90
	1.16 (t, 3H, *J* = 7.1 H), 1.33 (s, 9H), 1.79 – 1.99 (m, 2H), 2.05 (ddd, 1H, *J* = 15.2, 6.9, 5.7 Hz), 2.18 (ddd, 1H, *J* = 14.8, 8.6, 5.9 Hz), 3.21 (d, 2H, *J* = 5.9 Hz), 3.68 (s, 3H), 4.00 – 4.14 (m, 3H), 4.75 (dt, 1H, *J* = 7.7, 5.9 Hz), 5.22 (s, 1H), 5.55 (d, 1H, *J* = 7.0 Hz), 5.90 (s, 1H), 6.85 (s, 1H), 6.87 – 6.93 (m, 1H), 7.04 (ddd, 1H, *J* = 8.0, 6.9, 1.1 Hz), 7.14 (ddd, 1H, *J* = 8.2, 6.9, 1.1 Hz), 7.17 – 7.21 (m, 1H), 7.45 (d, 1H, *J* = 7.9 Hz).		
NLG-1574-A-E40		ethyl N^{α}-((tert-butoxycarbonyl)-L-phenylalanyl)-1-methyl-D-tryptophanate	80
	1.14 (t, 3H, *J* = 7.1 H), 1.29 (s, 9H), 2.82 (s, 2H), 2.91-3.02 (m, 1H), 3.03-3.10 (m, 2H), 3.25		

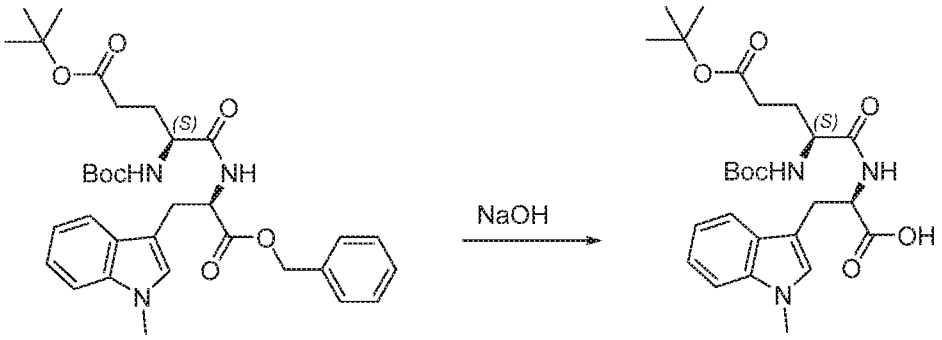
	(dd, 1H, *J* = 14.78, 5.2 Hz), 3.67 (s, 3H), 3.99 - 4.07 (m, 2H), 4.33 (br s, 1H), 4.79 (q, 1H, *J* = 6.2 Hz), 6.37 (d, 1H , *J* = 7.8 Hz), 6.57 (s, 1H), 7.06 (ddd, 1H , *J* = 8.0, 6.8, 1.2 Hz), 7.14 – 7.25 (m, 6H), 7.41 (d, 1H, *J* = 7.9 Hz).		
NLG-1585-A-E45		methyl N^2-(tert-butoxycarbonyl)-N^4-((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)-L-asparaginate	71
	1.18 (t, 3H, *J* = 7.2 Hz), 1.39 (s, 9H), 2.63 (dd, 1H, *J* = 17.1, 6.1 Hz), 2.95 (dd, 1H, J = 17.2, 4.4 Hz), 3.29 (d, 2H, *J* = 5.8 Hz), 3.62 (s, 3H), 3.74 (s, 3H), 4.03-4.13 (m, 2H), 4.53 (br s, 1H), 4.79-4.83 (m, 1H), 5.61 (d, 1H, *J* = 9.0 Hz), 6.88 (s, 1H), 7.01-7.10 (m, 2H), 7.19 (ddd, 1H, *J* = 8.2, 6.9, 1.2 Hz), 7.24-7.27 (m, 1H), 7.51 (m, 1H).		
NLG-1546-B-E20		ethyl Nα-((tert-butoxycarbonyl)-D-tryptophyl)-1-methyl-D-tryptophanate	97
	1.18 (t, 3H, *J* = 7.1 Hz), 1.38 (s, 9H), 1.73 (br s, 1H), 3.13 (dd, 2H, *J* = 5.4, 2.5 Hz), 3.32 (s, 1H), 3.57 (s, 3H), 4.05 (dd, 2H, *J* = 17.2, 7.2 Hz), 4.43 (s, 1H), 4.72 – 4.80 (m, 1H), 5.07 (s, 1H), 6.22 (s, 1H), 6.42 (s, 1H), 6.90 (s, 1H), 6.97 (s, 1H), 7.04 – 7.25 (m, 5H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.87 (s, 1H)		
NLG-1549-A-E26		ethyl Nα-(Nα-(tert-butoxycarbonyl)-1-methyl-D-tryptophyl)-1-methyl-D-tryptophanate	95
	1.16 (t, 3H, *J* = 7.1 Hz), 1.37 (s, 9H), 3.02 – 3.20 (m, 3H), 3.35 (d, 1H, *J* = 15.0 Hz), 3.57 (s, 3H), 3.68 (s, 3H), 3.94 – 4.10 (m, 2H), 4.42 (br s, 1H), 4.75 (d, 1H, *J* = 6.8 Hz), 5.04 (s, 1H), 6.24 (br s, 1H), 6.37 (s, 1H), 6.84 (br s, 1H), 6.94 (s, 1H), 7.08-7.18 (m, 3H), 7.17 – 7.25 (m, 2H), 7.27 – 7.33 (m, 1H), 7.65 (d, 1H, *J* = 7.9 Hz)		

NLG-1560-B-E28		ethyl Nα-((tert-butoxycarbonyl)-L-tryptophyl)-1-methyl-D-tryptophanate	97
	1.12 (t, 3H, *J* = 7.1 Hz), 1.39 (s, 9H), 2.90 (d, 1H, *J* = 15.2 Hz), 3.05 – 3.32 (m, 3H), 3.56 (s, 3H), 3.91 – 4.10 (m, 2H), 4.44 (br s, 1H), 4.75 (br s, 1H), 5.15 (br s, 1H), 6.18 (d, 1H, *J* = 7.8 Hz), 6.27 (s, 1H), 6.86 (d, 1H, *J* = 2.3 Hz), 7.04 (ddd, 1H, *J* = 8.0, 6.8, 1.2 Hz), 7.14 (ddd, 1H, *J* = 8.0, 7.1, 1.2 Hz), 7.16 – 7.27 (m, 3H), 7.30 (dt, 1H, *J* = 8.1, 1.0 Hz), 7.37 (d, 1H, *J* = 8.2 Hz), 7.68 (d, 1H, *J* = 7.7 Hz), 7.80 (s, 1H)		
NLG-1553-B-E21		ethyl N^{α}-((tert-butoxycarbonyl)-L-valyl)-1-methyl-D-tryptophanate	95
	0.80 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.8 Hz), 1.19 (t, 3H, J = 7.2 Hz), 1.40 (s, 9H), 2.09-2.17 (m, 1H), 3.25-3.32 (m, 2H), 3.74 (s, 3H), 3.94-3.97 (m, 1H), 4.09-4.15 (m, 2H), 4.84-4.89 (m, 1H), 4.93-4.95 (m, 1H), 6.45 (d, 1H, J = 7.6 Hz), 6.87 (s, 1H), 7.10 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 7.6 Hz), 7.53 (dd, 1H, J = 8.0, 1.2 Hz)		
NLG-1554-A-E25		ethyl N^{α}-((tert-butoxycarbonyl)glycyl)-1-methyl-D-tryptophanate	94
	1.22 (t, 3H, J = 7.2 Hz), 1.42 (s, 9H), 3.31 (d, 2H, J = 5.2 Hz), 3.72-3.77 (m, 2H), 3.74 (s, 3H), 4.07-4.17 (m, 2H), 4.86-4.91 (m, 1H), 5.04 (br s, 1H), 6.50 (d, 1H, J = 7.6 Hz), 6.86 (s, 1H), 7.10 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.4 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 7.6 Hz)		

NLG-1555-A-E27		ethyl N^{α}-((tert-butoxycarbonyl)-L-alanyl)-1-methyl-D-tryptophanate	95
	1.20 (t, 3H, J = 7.0 Hz), 1.29 (d, 3H, J = 7.2 Hz), 1.40 (s, 9H), 3.30 (d, 1H, J = 5.6 Hz), 3.75 (s, 3H), 4.09-4.16 (m, 3H), 4.81-4.86 (m, 1H), 4.93 (br s, 1H), 6.61 (br s, 1H), 6.87 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 8.4 Hz, merged with chloroform), 7.52 (d, 1H, J = 8.0 Hz)		
NLG-1548-A-E18		benzyl N^{α}-(N^{2},N^{6}-bis(tert-butoxycarbonyl)-L-lysyl)-1-methyl-D-tryptophanate	91
	^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.25 (q, *J* = 7.7 Hz, 2H), 1.39 (s, 9H), 1.44 (s, 9H), 1.47 – 1.55 (m, 1H), 1.67 – 1.80 (m, 2H), 3.02 (t, *J* = 6.7 Hz, 2H), 3.29 (d, *J* = 5.5 Hz, 2H), 3.66 (s, 3H), 4.04 (s, 1H), 4.53 (s, 1H), 4.90 (q, *J* = 6.1 Hz, 1H), 4.97 (s, 1H), 5.09 (q, *J* = 12.2 Hz, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.64 (s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.23 – 7.29 (m, 4H overlapped with $CHCl_3$), 7.30 – 7.39 (m, 3H), 7.49 (d, *J* = 7.9 Hz, 1H).		
NLG-1547-D-E17		tert-butyl (S)-5-(((R)-1-(benzyloxy)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate	93
	δ 1.38 (s, 9H), 1.43 (s, 9H), 1.76 – 1.91 (m, 1H), 1.94 – 2.09 (m, 1H), 2.20 (dt, *J* = 16.6, 7.0 Hz, 1H), 2.31 (dt, *J* = 16.6, 7.3 Hz, 1H), 3.19 – 3.36 (m, 2H), 3.67 (s, 3H), 4.90 (dt, *J* = 8.1, 5.6 Hz, 1H), 5.00 – 5.14 (m, 2H), 5.19 (s, 1H), 6.70 (s overlapping m, 2H), 7.08 (ddd, *J* = 8.0, 6.9, 1.2		

	Hz, 1H), 7.18 – 7.28 (m, 4H), 7.29 – 7.37 (m, 2H), 7.50 (dt, *J* = 8.0, 1.0 Hz, 1H).		
DD-00508-B-E078		ethyl N^{α}-((tert-butoxycarbonyl)-L-methionyl)-1-methyl-D-tryptophanate	84
	δ 1.21 (t, *J*=7.2 Hz, 3H), 1.40 (s, 9H), 1.79 – 1.89 (m, 1H), 1.94 – 2.00 (m, 1H), 2.01 (s, 3H), 2.31-2.36 (m, 1H), 2.36-2.46 (m, 1H), 3.30 (dd, *J*=5.7, 3.6 Hz, 2H), 3.75 (s, 3H), 4.12 (q, *J*=7.2 Hz, 2H), 4.26 (d, *J*=7.5 Hz, 1H), 4.84 (q, *J*=6.4 Hz, 1H), 5.17 (d, *J*=8.3 Hz, 1H), 6.67 (d, *J*=7.2 Hz, 1H), 6.89 (s, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 7.21 (t, *J*=7.2 Hz, 1H), 7.28 (d, *J*=7.5 Hz, 1H), 7.53 (d, *J*=7.9 Hz, 1H).		

Synthesis of N^{α}-((S)-5-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)-5-oxopentanoyl)-1-methyl-D-tryptophan (NLG-1547-E.2-E17)

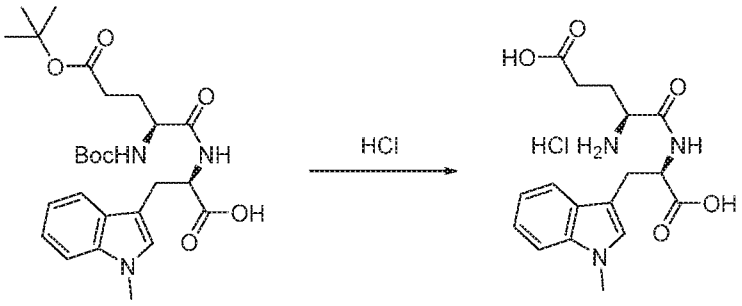


NLG-1547-D-E17 **NLG-1547-E.2-E17**

[00132] tert-Butyl(S)-5-(((R)-1-(benzyloxy)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-4-((tert-butoxycarbonyl)amino)-5-oxopentanoate (800 mg, 1.38 mmol) was suspended in MeOH (8 mL) and THF (8 mL). After cooling to 0 °C, NaOH sol'n (2.4 mL, 2M) was added and the reaction stirred for 1 h. The solution was acidified with 1M HCl to pH = 4 and the solvents were concentrated under reduced pressure (40 °C). The solution was partitioned between

water and DCM in a separatory funnel and the organic layer was collected. The aqueous layer was extracted with DCM (2 x 15 mL) and the combined organic layer was washed with water and brine. Chromatographic purification afforded the desired product (0.502 g, 72%). ^{1}H NMR(Chloroform-*d*, 400 MHz): δ = 1.38 (s, 9H), 1.44 (s, 9H), 1.68 – 1.81 (m, 1H), 1.84 – 1.99 (m, 1H), 2.12 – 2.33 (m, 3H), 3.23 – 3.42 (m, 2H), 4.23 (s, 3H), 4.86 (d, 1H, *J* = 6.9 Hz), 5.41 (d, 1H, *J* = 8.6 Hz), 6.83 (d, 1H, *J* = 7.5 Hz), 6.93 (s, 1H), 7.09 (dt, 1H, *J* = 8.0, 1.2 Hz), 7.18 (t, 1H, *J* = 7.8 Hz), 7.23 (apparent d overlapped with $CDCl_3$, 1H,), 7.60 (d, 1H, *J* = 7.9 Hz).

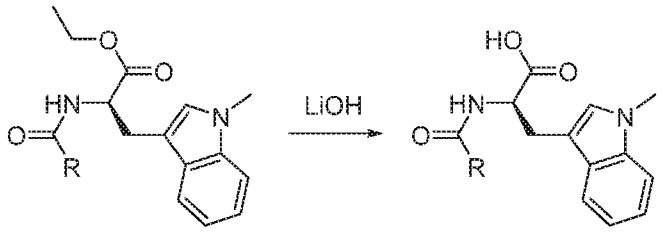
Synthesis of (S)-4-amino-5-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-5-oxopentanoic acid hydrochloride (NLG-1547)



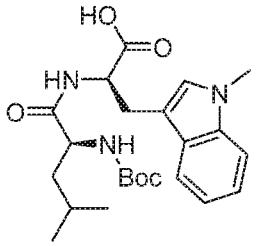
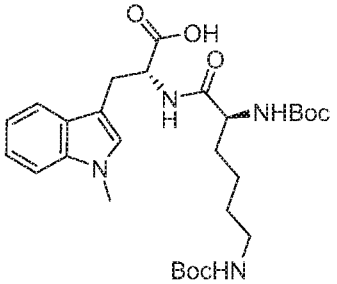
(NLG-1547-E.2-E17) (NLG-1547)

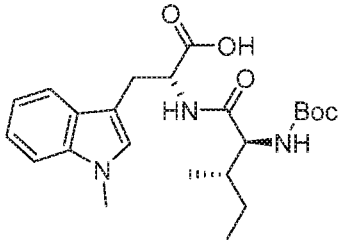
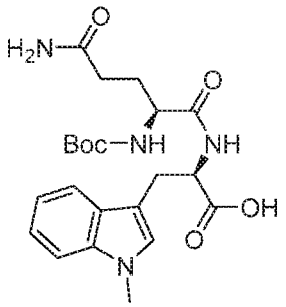
[00133] To N^{α}-((S)-5-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)-5-oxopentanoyl)-1-methyl-D-tryptophan (470 mg, 0.93 mmol) was added HCl (4M in dioxane) (4.7 mL). The resulting solution was allowed to stir at room temperature for 5 hours. The solution was concentrated and the solid was dissolved in MeOH and treated with activated charcoal and heated to 60 °C for 1h. The solution was filtered through celite and the filtrate concentrated to afford the desired product as a beige solid (0.304, 85 %). ^{1}H NMR (DMSO-d_6, 400 MHz): (mixture of rotamers) 1.73 – 2.21 (m, 4H), 2.93 – 3.12 (m, 1H), 3.14 – 3.27 (m, 1H), 3.70 (s, 3H), 3.83 (q, 1H, *J* = 5.8 Hz), 4.53 – 4.72 (m, 1H), 7.01 (tt, 1H, *J* = 7.3, 3.7 Hz), 7.07 – 7.19 (m, 2H), 7.35 (dt, 1H, *J* = 7.5, 3.5 Hz), 7.44 – 7.61 (m, 1H), 8.42 (br s, 3H), 8.83 – 9.10 (m, 1H).

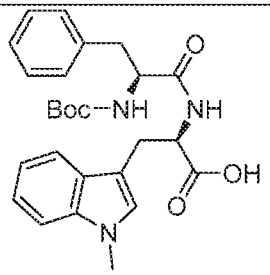
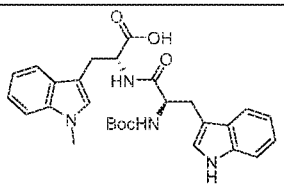
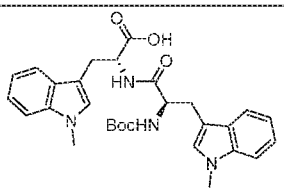
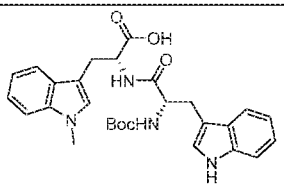
General method for the hydrolysis of substituted D-1MT ethyl esters

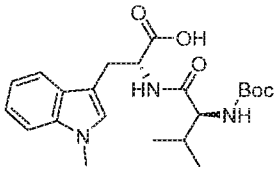
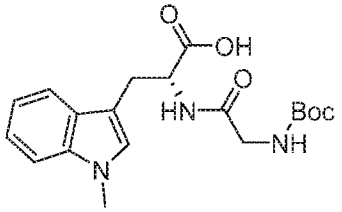
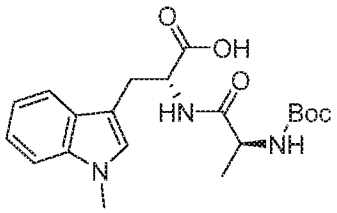


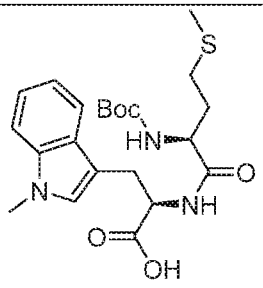
[00134] To a solution of appropriate amide (0.991 mmol) in THF (10 mL) was added water (3 mL) and lithium monohydrate (67 mg, 1.59 mmol) and the mixture stirred under ambient temperature for 2 h. The mixture was neutralized with 1M HCl (at 0 °C) and poured into ice cold water (20 mL). The aqueous layer was extracted with EtOAc (3 x 35 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography to afford the desired product.

#	Compound	Name	Yield (%)
NLG-1570-A-E33		N^{α}-((tert-butoxycarbonyl)-L-leucyl)-1-methyl-D-tryptophan	87
	0.76 – 0.96 (m, 6H), 1.39 (s, 9H), 1.40-1.54 (m, 3H), 3.29 (dd, 1H, *J* = 15.1, 5.3 Hz), 3.40 (dd,1H, *J* = 14.9, 5.7 Hz), 3.70 (s, 3H), 4.41 (td, 1H , *J* = 9.3, 5.4 Hz), 4.86 (q, 1H, *J* = 6.7, 5.8 Hz), 5.26 (d, 1H, *J* = 9.1 Hz), 6.88 (br s, 1H), 7.05 – 7.11 (m, 1H), 7.14 – 7.28 (m, 3H), 7.59 (d, 1H, *J* = 7.9 Hz)		
NLG-1548-B-E18		N^{α}-(N^{2},N^{6}-bis(tert-butoxycarbonyl)-L-lysyl)-1-methyl-D-tryptophan	91

	1.05 – 1.20 (m, 2H), 1.37 (s, 9H), 1.44 (s, 9H), 1.65 – 1.80 (m, 2H), 2.98 (br d, 2H), 3.15 – 3.51 (m, 2H), 3.69 (s, 3H), 3.84 – 4.04 (m, 1H), 4.15 (d, 1H, *J* = 7.6 Hz), 4.69 (s, 1H), 4.85 (d, 1H, *J* = 6.6 Hz), 5.43 (s, 1H), 5.73 – 6.18 (m, 2H), 6.91 (s, 1H), 7.06 (t, 1H, *J*=7.4 Hz), 7.18 (t, 1H, *J* = 7.5 Hz), 7.24 (d, 1H, *J* = 8.3 Hz), 7.60 (d, 1H, *J* = 7.9 Hz).		
NLG1571-A-E34		N^{α} -((tert-butoxycarbonyl)-L-isoleucyl)-1-methyl-D-tryptophan	88
	0.75-0.88 (m, 8 H), 1.37 (s, 9H), 1.62-1.70 (m, 1H), 3.13-3.17 and 3.30-3.32 (two m, 2H), 3.65 and 3.70 (two s, 3H), 4.89-4.92 (m, 1H), 5.33 (d, 1H, *J* = 9.2 Hz), 6.79 (t, 1H, *J* = 7.1 Hz), 6.92 (s, 1H), 7.08 (t, 1H, *J* = 7.4 H), 7.19 (t, 1H, *J* = 7.7 Hz), 7.25 (d, 1H, *J* = 6.8 Hz), 7.56 and 7.62 (two d, 1H, *J* = 8.0 Hz).		
NLG1569-A-E38		N^{α}-((tert-butoxycarbonyl)-L-glutaminyl)-1-methyl-D-tryptophan	83
	1.34 (s, 9H), 1.59 (dd, 1H, *J* = 14.1, 7.9 Hz), 1.73-1.77 (m, 1H), 1.94-2.04 (m, 2H), 3.02 (dd, 1H , *J* = 14.6, 7.9 Hz), 3.13 (dd, 1H, *J* = 14.5, 5.2 Hz,), 3.69 (s, 3H), 3.90-3.96 (m, 1H), 4.40-4.45 (m, 1H), 6.72 (s, 1H), 6.80 (d, 1H, *J* = 8.3 Hz), 6.96-7.02 (m, 1H), 7.05 (s, 1H), 7.10 (ddd, 1H, *J* = 8.2, 7.0, 1.1 Hz), 7.18 (s, 1H), 7.34 (d, 1H, *J* = 8.2 Hz), 7.51 (d, 1H, *J* = 7.9 Hz), 7.98 (d, 1H, *J* = 7.9 Hz), 12.70 (br s, 1H).		

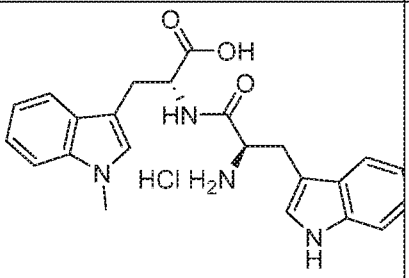
NLG1575-A-E41		N^{α}-((tert-butoxycarbonyl)-L-phenylalanyl)-1-methyl-D-tryptophan	75
	1.30 (s, 9H), 2.81-2.88 (m, 1H), 2.94-3.00 (m, 1H), 3.08 (dd, 1H, *J* = 14.8, 5.8 Hz), 3.21-3.25 (m, 1H), 3.66 (s, 3H), 4.41 (d, 1H, *J* = 6.7 Hz), 4.79-4.86 (m, 1H), 5.13 (d, 1H, *J* = 8.3 Hz), 6.56 (d, 1H, *J* = 6.5 Hz), 6.63 (s, 1H), 6.95-7.25 (m, 8H), 7.46 (d, 1H, *J* = 7.9 Hz).		
NLG-1546-C-E20		N^{α}-((tert-butoxycarbonyl)-D-tryptophyl)-1-methyl-D-tryptophan	84
	1.31 (s, 9H), 3.05-3.13 (m, 3H), 3.29 (s, 1H), 3.55 (s, 3H), 4.44 (s, 1H), 4.75 (q, *J* = 6.1 Hz, 1H), 5.10 (s, 1H), 6.26 (s, 1H), 6.58 (s, 1H), 6.89 (s, 2H), 7.07 – 7.24 (m, 5H), 7.31 (d, 1H, *J* = 8.0 Hz), 7.64 (d, 1H, *J* = 6.6 Hz), 8.09 – 8.35 (m, 1H)		
NLG-1549-B-E26		N^{α}-(N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophyl)-1-methyl-D-tryptophan	40
	1.27 (s, 9H), 2.99 (dd, 1H, *J* = 14.7, 5.4 Hz), 3.09 (dd, 1H, *J* = 14.3, 6.7 Hz), 3.16 (dd, 1H, *J* = 14.8, 5.2 Hz), 3.25 – 3.44 (m, 1H), 3.57 (s, 3H), 3.69 (s, 3H), 4.39 (br s, 1H), 4.76 (dt, 1H, *J* = 8.1, 5.5 Hz), 5.01 (br s, 1H), 6.29 (br s, 1H), 6.53 (s, 1H), 6.79 (br s, 1H), 6.91 (s, 1H), 6.97 (br s, 2H), 7.07 – 7.18 (m, 2H), 7.20 (d, 1H, *J* = 8.2 Hz), 7.21 – 7.34 (m overlapped with $CDCl_3$, 2H), 7.62 (d, 1H, *J* = 7.9 Hz)		
NLG-1560-C.1-E28		N^{α}-((tert-butoxycarbonyl)-L-tryptophyl)-1-methyl-D-tryptophan	91
	1.35 (s, 9H), 3.08 (2.79 – 3.25, 4H), 3.50 (s, 3H), 3.71 – 3.79 (m, 1H), 4.31 – 4.55 (m, 1H), 4.62 – 4.96 (m, 1H), 6.45 (s, 1H), 6.70 – 6.91 (m, 1H), 6.98 – 7.06 (m, 1H), 7.08 (t, 1H, *J* =		

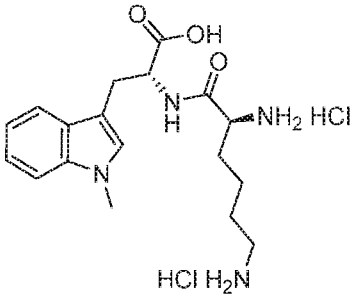
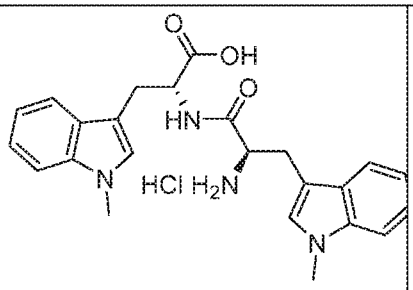
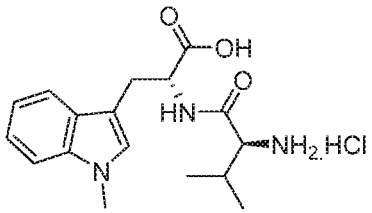
	7.5 Hz), 7.12 – 7.25 (m, 4H), 7.44 (q, 2H, *J* = 8.8 Hz), 7.56 (d, 1H, *J* = 7.9 Hz), 8.02 (br s, 1H).		
NLG-1553-C-E21		N^{α}-((tert-butoxycarbonyl)-L-valyl)-1-methyl-D-tryptophan	100
	0.77 (d, 3H, J = 6.8 Hz), 0.81 (d, 3H, J = 6.4 Hz), 1.38 (s, 9H), 1.84-1.92 (m, 1H), 3.30-3.32 (m, 1H), 3.66-3.77 (m, 4H), 4.08-4.12 (m, 1H), 4.88-4.92 (m, 1H), 5.23 (d, 1H, J = 9.2 Hz), 6.66 (d, 1H, J = 7.2 Hz), 6.92 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.26 (d, 1H, J = 8.4 Hz, merged with chloroform), 7.62 (d, 1H, J = 8.0 Hz)		
NLG-1554-B-E25		N^{α}-((tert-butoxycarbonyl)glycyl)-1-methyl-D-tryptophan	83
	1.39 (s, 9H), 3.25-3.35 (m, 2H), 3.2-3.74 (m, 5H), 4.85-4.90 (m, 1H), 5.21 (br s, 1H), 6.63 (br s, 1H), 6.90 (s, 1H), 7.08 (t, 1H, J = 7.4 Hz), 7.17-7.27 (m, 2H, merged with chloroform), 7.55 (d, 1H, J = 7.6 Hz)		
NLG-1555-B-E27		N^{α}-((tert-butoxycarbonyl)-L-alanyl)-1-methyl-D-tryptophan	86
	1.21 (d, 3H, J = 7.2 Hz), 1.38 (s, 9H), 3.19-3.38 (m, 3H), 3.73 (s, 3H), 4.22-4.27 (m, 1H), 4.84 (br s, 1H), 6.77 (br s, 1H), 6.87 (s, 1H), 7.08 (t, 1H, J = 7.4 Hz), 7.19 (t, 1H, J = 7.4 Hz), 7.24 (d, 1H, J = 8.8 Hz, merged with chloroform), 7.57 (d, 1H, J = 7.6 Hz)		

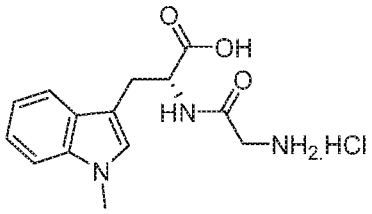
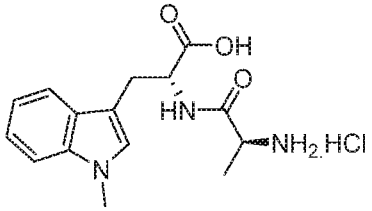
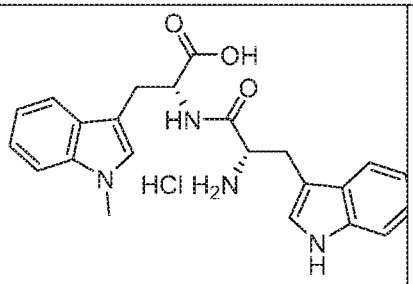
DD00510-A-E079		N^{α}-((tert-butoxycarbonyl)-L-methionyl)-1-methyl-D-tryptophan	92
	1.36 (s, 9H), 1.68 – 1.87 (m, 2H), 1.94 and 2.01 (s, 3H), 2.25-2.43 (two m, 2H), 3.23 (dd, *J*=14.9, 6.5 Hz, 1H), 3.36 (dd, *J*=14.6, 4.8 Hz, 1H), 3.71 (s, 3H), 4.23-4.34 (two m, 1H), 4.82-4.94 (two m, 1H), 5.52 (d, *J*=6.7 Hz, 1H), 6.79 – 6.99 (m, 2H), 7.09 (t, *J*=7.4 Hz, 1H), 7.19 (t, *J*=7.4 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.58 (d, *J*=8.0 Hz 1H)		

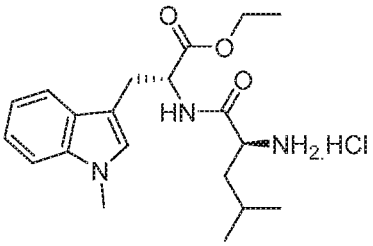
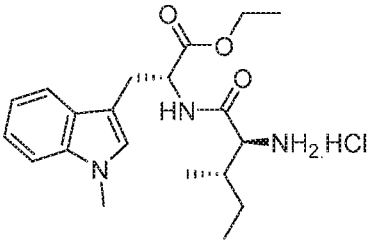
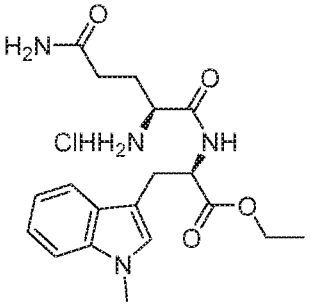
General method for ^{t}Boc deprotection.

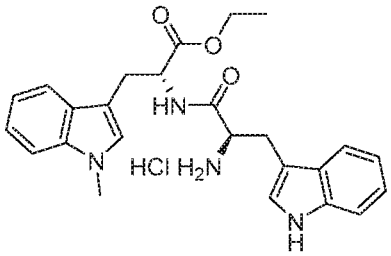
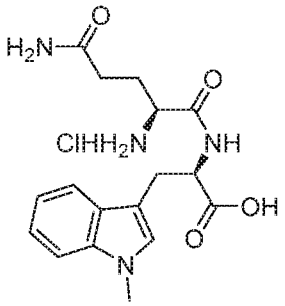
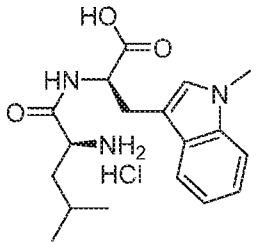
[00135] To a solution of appropriate ^{t}Boc protected amine (0.707 mmol) in dioxane (2 mL) was added HCl solution (1.77 mL, 4.0 M solution in dioxane) at 0 °C. The solution was allowed to warm to rt and stirred vigorously for 2.5-18 h. The solvent was removed using rotary evaporator. The solid was diluted with dry ether (15 mL) and the product was filtered to afford the crude product. The crude was dried under high vacuum to afford the desired product.

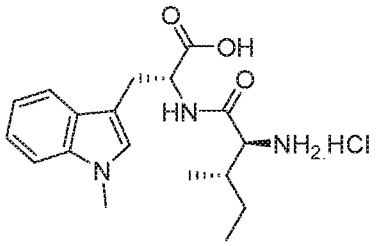
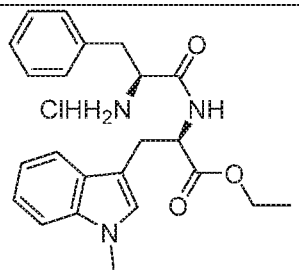
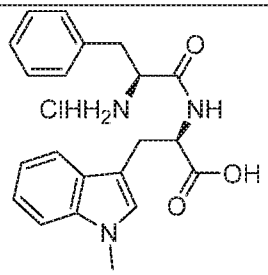
#	Compound	Name	Yield (%)
NLG-1546		N^{α}-(D-tryptophyl)-1-methyl-D-tryptophan hydrochloride	95
	^{1}H NMR (400 MHz, Methanol-d_4) δ 3.15 (d, *J* = 8.5 Hz, 1H), 3.19 (d, *J* = 8.5 Hz, 1H), 3.36 (d, 1H, *J* = 4.9 Hz), 3.37 – 3.41 (m, 1H), 3.71 (s, 3H), 4.06 (t, 1H, *J* = 3.6 Hz), 4.74 (s, 1H), 6.93 (s, 1H), 7.02 (t, 1H, *J* = 6.2 Hz), 7.04 – 7.07 (m, 1H), 7.14 (td, 2H, *J* = 7.9, 1.7 Hz), 7.20 (s, 1H), 7.22		

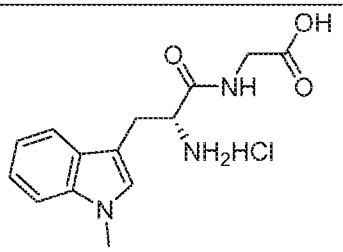
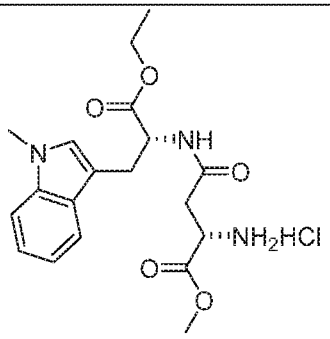
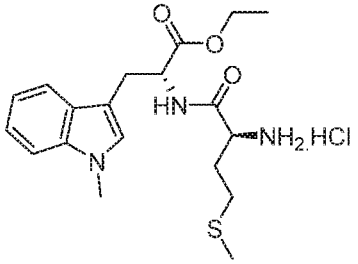
	(d, J = 8.1 Hz, 1H), 7.30 (d, 1H, J = 8.2 Hz), 7.38 (d, 1H, J = 8.1 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.65 (d, 1H, J = 7.9 Hz), 7.70 (d, 1H, J = 8.2 Hz)		
NLG-1548		N^{α}-(L-lysyl)-1-methyl-D-tryptophan dihydrochloride	87
	^{1}H NMR (400 MHz, DMSO-d_6): 0.88 – 1.13 (m, 2H), 1.33 – 1.56 (m, 4H), 2.54 (t, 2H, J = 7.1 Hz), 2.95 – 3.10 (m, 1H), 3.15 – 3.24 (m, 1H), 3.42 (apparent q overlapping with H_2O, 1H, J = 7.0 Hz), 3.73 (s, 3H), 4.50 – 4.67 (m, 1H), 7.01 (t, 1H, J = 7.5 Hz), 7.06 – 7.18 (m, 2H), 7.38 (d, 1H, J = 8.3 Hz), 7.55 (d, 1H, J = 7.9 Hz), 8.02 (br s, 3H), 8.20 (br s, 3H), 8.83 (d, 1H, J = 8.1 Hz), 12.93 (br s, 1H)		
NLG-1549		1-methyl-N^{α}-(1-methyl-D-tryptophyl)-D-tryptophan hydrochloride	92
	^{1}H NMR (400 MHz, DMSO-d_6): 3.10 (td, 2H, J = 15.5, 7.9 Hz), 3.24 (ddd, 2H, J = 17.5, 15.1, 5.9 Hz), 3.72 (s, 2H), 3.73 (s, 4H), 4.02 (dd, 1H, J = 8.3, 5.1 Hz), 4.58 (q, 1H, J = 7.0 Hz), 7.04 (td, 2H, J = 7.4, 4.2 Hz), 7.09 – 7.23 (m, 4H), 7.40 (t, 2H, J = 8.1 Hz), 7.58 (d, 1H, J = 7.9 Hz), 7.74 (d, 1H, J = 7.9 Hz), 8.11 (s, 1H), 8.97 (d, 1H, J = 7.7 Hz), 12.82 (br s, 1H)		
NLG-1553		N^{α}-(L-valyl)-1-methyl-D-tryptophan hydrochloride	92
	^{1}H NMR (400 MHz, DMSO-d_6): 0.54 (d, 3H, J = 7.2 Hz), 0.72 (d, 3H, J = 6.8 Hz),1.89-1.94 (m, 1H), 3.01 (dd, 1H, J = 14.8, 9.6 Hz), 3.22 (dd, 1H, J = 14.6, 5.0 Hz), 3.56-3.65 (m, 1H), 3.70 (s, 3H), 4.61-4.66 (m, 1H), 7.01 (t, 1H, J = 7.6 Hz), 7.12 (s, 1H), 7.12 (t, 1H, J = 7.6 Hz), 7.36 (t, 1H,		

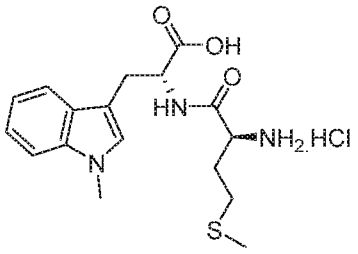
	J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 8.09 (br s, 3H), 8.78 (d, 1H, J = 8.4 Hz), 12.8 (br s, 1H)		
NLG-1554		N^{α}-glycyl-1-methyl-D-tryptophan hydrochloride	87
	^{1}H NMR (400 MHz, DMSO-d_6): 3.02-3.08 (m, 1H), 3.17-3.22 (m, 1H), 3.48-3.60 (m, 2H), 3.74 (s, 3H), 4.55-4.58 (m, 1H), 7.03 (t, 1H, J = 7.8 Hz), 7.12-7.18 (m, 2H), 7.38 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 8.13 (br s, 3H), 8.76 (d, 1H, J = 8.0 Hz), 12.87 (br s, 1H)		
NLG-1555		N^{α}-(L-alanyl)-1-methyl-D-tryptophan hydrochloride	44
	^{1}H NMR (400 MHz, DMSO-d_6): 1.18 (d, 3H), 3.02-3.06 (m, 1H), 3.17-3.23 (m, 1H), 3.72 (s, 3H), 4.05-4.09 (m, 1H), 4.57-4.62 (m, 1H), 7.02 (t, 1H, J = 7.6 Hz), 7.12-7.15 (m, 2H), 7.38 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 7.6 Hz), 8.16 (br s, 3H), 8.88-8.92 (m, 1H)		
NLG-1560		N^{α}-(L-tryptophyl)-1-methyl-D-tryptophan hydrochloride	90
	^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.88 (dd, 1H, J = 14.7, 8.2 Hz), 2.98 (dd, 1H, J = 14.5, 7.9 Hz), 3.08 (dt, 2H, J = 14.7, 5.0 Hz), 3.63 (s, 3H), 4.06 (br s, 1H), 4.55 (q, 1H, J = 7.9), 6.87 (dd, 1H, J = 8.0, 7.0 Hz), 6.97 (s, 1H), 7.01 (t, 1H, J = 7.4 Hz), 7.06 (t, 1H, J = 7.4 Hz), 7.08 – 7.15 (m, 2H), 7.34 (d, 2H, J = 8.2 Hz), 7.56 (dd, 2H, J = 8.0, 5.1 Hz), 8.09 (s, 3H), 8.95 (d, 1H, J = 8.1 Hz), 11.02 (s, 1H)		

NLG-1564		ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate hydrochloride	93
	^{1}H NMR (400 MHz, DMSO-d_6): 0.70 (t, 6H, J = 5.7 Hz). 1.13 (t, 3H, J = 7.1 Hz), 1.38 – 1.23 (m, 3H), 3.01 (dd, 1H , J = 14.5, 9.4 Hz), 3.18 (dd, 1H , J = 14.5, 5.2 Hz), 3.70 (s, 3H), 4.08 (q, 2H , J = 7.1 Hz), 4.62 – 4.53 (m, 1H), 7.00 (ddd, 1H, J = 7.8, 7.0, 1.0 Hz), 7.09-7.13 (m, 2H), 7.36 (d, 1H , J = 8.2 Hz), 7.50 (dd, 1H, J = 7.6, 1.1 Hz), 8.18 (br s, 3H), 8.99 (d, 1H, J = 8.1 Hz).		
NLG-1565		ethyl N^{α}-(L-isoleucyl)-1-methyl-D-tryptophanate hydrochloride	93
	^{1}H NMR (400 MHz, DMSO-d_6): 0.60 – 0.66 (m, 6H), 0.75 – 0.82 (m, 2H), 1.12 (t, 3H, J = 7.1 Hz, 4H), 1.63 (br s, 1H), 3.02 (dd, 1H, J = 14.6, 9.4 Hz), 3.17 (dd, 1H, J = 14.6, 5.2 Hz), 3.61 (br s, 1H), 3.69 (s, 3H), 4.07 (q, 2H, J = 7.1 Hz), 4.62 (br s, 1H), 7.01 (t, 1H, J = 7.5 Hz), 7.10 – 7.14 (m, 2H), 7.36 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.9 Hz), 8.00 (br s, 2H), 8.85 (br s, 1H).		
NLG-1566		ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate hydrochloride	59
	^{1}H NMR (400 MHz, DMSO-d_6): 1.08 (t, 3H, J = 7.1 Hz),1.81-1.97 (m, 2H), 2.01-2.12 (m, 2H), 3.07 (dd, 1H, J = 14.4, 8.4 Hz), 3.16 (dd, 1H, J = 14.4, 6.0 Hz), 3.70 (s, 3H), 3.82 (t, 1H, J = 6.0 Hz), 4.03 (q, 2H, J = 7.1 Hz), 4.53 (q, 1H, J = 7.0 Hz), 6.93 (s, 1H), 7.02 (ddd, 1H, J = 7.9, 7.0, 1.0 Hz), 7.09-7.14 (m, 2H), 7.35 (d, 1H, J = 8.2 Hz), 7.40 (s, 1H), 8.24 (br s, 3H), 9.01 (d, 1H, J = 7.2 Hz).		

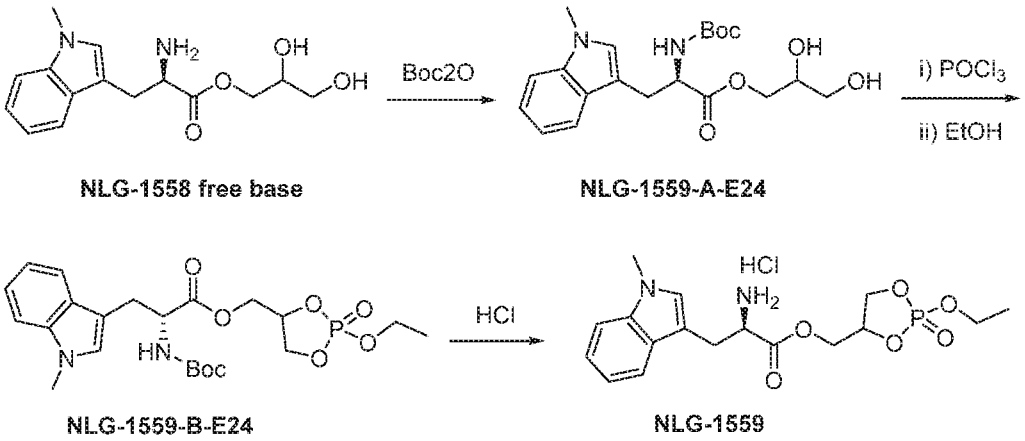
NLG-1567		ethyl N^{α}-(D-tryptophyl)-1-methyl-D-tryptophanate hydrochloride	97
	^{1}H NMR (400 MHz, DMSO-d_6): 1.19 (t, 3H, J = 7.1 Hz), 1.91 (br s, 2H), 2.87 (m, 1H), 3.25 (d, 2H, J = 5.6 Hz), 3.33 (dd, 1H, J = 14.5, 4.4 Hz), 3.66 (s, 3H), 3.70 (dd, 1H, J = 9.0, 4.7 Hz), 4.10 (m, 1H), 4.87 (dt, 1H, J = 8.5, 5.5 Hz), 6.71 (d, 1H, J = 8.5 Hz), 6.95 (d, 1H, J = 2.6 Hz), 7.00 – 7.10 (m, 2H), 7.12 – 7.22 (m, 2H), 7.24 (d, 2H, J = 6.1 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.51 (d, 1H, J = 7.7 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.66 (d, 1H, J = 8.3 Hz), 8.15 (s, 1H).		
NLG-1569		N^{α}-(L-glutaminyl)-1-methyl-D-tryptophan hydrochloride	97
	^{1}H NMR (400 MHz, DMSO-d_6): 1.79-1.84 (m, 2H), 1.95-2.06 (m, 2H), 3.04 (dd, 1H, J = 14.6, 8.5 Hz), 3.19 (dd, 1H, J = 14.6, 5.2 Hz), 3.49 – 3.35 (m, 2H), 3.70 (s, 3H), 3.78 – 3.88 (m, 1H), 4.53 (td, 1H, J = 8.3, 5.2 Hz), 6.93 (s, 1H), 7.00 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz), 7.16 – 7.07 (m, 2H), 7.35 (dt, 1H, J = 8.3, 0.9 Hz), 7.38 (s, 1H), 7.54 (dt, 1H, J = 7.9, 1.0 Hz), 8.28 (d, 2H, J = 4.2 Hz), 8.87 (d, 1H, J = 8.1 Hz)		
NLG-1570		N^{α}-(L-leucyl)-1-methyl-D-tryptophan hydrochloride	95
	^{1}H NMR (400 MHz, DMSO-d_6): 0.68 (t, 6H, J = 5.5 Hz). 1.34 – 1.17 (m, 3H), 2.99 (dd, 1H , J = 14.5, 9.6 Hz), 3.20 (dd, 1H, J = 14.6, 4.7 Hz), 3.34 – 3.40 (m, 3H), 3.68 (s, 3H), 4.52 – 4.62 (m, 1H), 6.99 (t, 1H, J = 7.4 Hz), 7.16 – 7.08 (m, 2H), 7.35 (d, 1H, J = 8.2 Hz), 7.54 (d, 1H, J = 7.9		

	Hz), 8.17 (br s, 2H), 8.85 (d, 1H, J = 8.3 Hz)		
NLG-1571		N^{α}-(L-isoleucyl)-1-methyl-D-tryptophan hydrochloride	94
	^{1}H NMR (400 MHz, DMSO-d_6): 0.55-0.65 (m, 6 H), 0.71 – 0.75 (m, 1H), 1.03-1.12 (m, 1H), 1.57 – 1.63 (m, 1H), 2.99 (dd, 1H, J = 14.6, 9.8 Hz), 3.19 (dd, 1H, J = 14.6, 4.7 Hz), 3.61-3.63 (m, 1H), 3.69 (s, 3H), 4.58-4.64 (m, 1H), 7.0 (t, 1H, J = 7.6 Hz), 7.08 – 7.13 (m, 2H), 7.35 (d, 1H, J = 8.2 Hz), 7.53 (d, 1H, J = 7.9 Hz), 8.10 (br s, 3H), 8.72 (d, 1H, J = 8.1 Hz).		
NLG-1574		ethyl N^{α}-(L-phenylalanyl)-1-methyl-D-tryptophanate hydrochloride	60
	^{1}H NMR (400 MHz, DMSO-d_6): 1.15 (t, 3H, J = 7.1 Hz), 2.52 (dd, 1H, J = 13.7, 9.9 Hz), 3.17 – 3.23 (m, 3H), 3.46 (dd, 1H, J = 9.9, 4.1 Hz), 3.64 (s, 3H), 4.03-4.11 (m, 2H), 4.83 (dt,1H, J = 8.4, 5.6 Hz), 6.72 (s, 1H), 6.99 (ddd, 1H, J = 8.0, 6.9, 1.1 Hz), 7.31 – 7.05 (m, 7H), 7.45 (d, 1H, J = 7.9 Hz), 7.61 (d, 1H, J = 8.4 Hz)		
NLG-1575		N^{α}-(L-phenylalanyl)-1-methyl-D-tryptophan hydrochloride	91
	^{1}H NMR (400 MHz, DMSO-d_6): 2.78 (dd, 1H, J = 13.9, 7.1 Hz), 2.89-2.97 (m, 2H), 3.10 (dd, 1H, J = 14.5, 5.3 Hz), 3.35 (br s, 3H), 3.47 (s, 3H), 4.05 (dd, 1H, J = 7.1, 5.6 Hz), 4.51 (td, 1H, J = 8.2, 5.3 Hz), 6.92 – 6.94 (m, 2H), 6.99 – 7.18 (m, 6H), 7.36 (dt, J = 8.3, 0.9 Hz, 1H), 7.56 (dt, J = 8.0, 0.9 Hz, 1H), 8.89 (d, J = 8.1 Hz, 1H).		

NLG-1579		1-Methyl-D-tryptophylglycine hydrochloride	90
	^{1}H NMR (400 MHz, Methanol-d_4): 3.25 (dd, 2H , J = 14.8, 7.9 Hz), 3.43 (dd, 1H, J = 14.8, 6.1 Hz), 3.77 (s, 3H), 3.92 (d, 2H, J = 5.5 Hz), 4.14-4.19(m, 1H), 7.09 (t, 1H, J = 7.5 Hz), 7.16- 7.24 (m, 2H), 7.36 (d, 1H , J = 8.1 Hz), 7.67 (d, 1H, J = 7.9 Hz).		
NLG-1585		methyl N^4-((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)-L-asparaginate hydrochloride	92
	^{1}H NMR (400 MHz, DMSO-d_6): 1.12 (t, 3H, J = 7.1 Hz), 2.64-2.76 (m, 2H), 3.06 (dd, 1H, J = 14.5, 8.2 Hz), 3.17 (dd, 1H, J = 14.6, 5.9 Hz), 3.58 (s, 3H), 3.73 (s, 3H), 4.04-4.13 (m, 3H), 4.57 (td, 1H, J = 8.0, 5.9 Hz), 7.02 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz), 7.12-7.16 (m, 2H), 7.39 (dt, 1H, J = 8.3, 0.9 Hz), 7.51 (dt, 1H, J = 8.0, 1.0 Hz), 8.27 (s, 3H), 9.00 (d, 1H, J = 7.8 Hz)		
NLG-3272-01		ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate hydrochloride	90
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.69 (t, J=7.1 Hz, 3H), 2.44 (s, 3H), 2.61 – 2.82 (m, 2H), 3.59 (dd, J=14.5, 9.5 Hz, 1H), 3.74 (dd, J=14.6, 5.0 Hz, 1H), 4.27 (s, 3H), 4.37 (s, 1H), 4.63 (q, J=7.1 Hz, 2H), 5.05 – 5.22 (m, 1H), 7.56 (t, J=7.4 Hz, 1H), 7.62 – 7.75 (m, 2H), 7.91 (d, J=8.2 Hz, 1H), 8.05 (d, J=7.8 Hz, 1H), 8.86 (s, 2H), 9.60 (d, J=7.8 Hz, 1H).		

NLG-3380-01		N^{α}-(L-methionyl)-1-methyl-D-tryptophan hydrochloride	76
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.73-1.77 (m, 2H), 1.88 (s, 3H), 2.11-2.17 (m, 2H), 3.03 (dd, *J*=14.6, 9.3 Hz, 1H), 3.24 (dd, *J*=14.6, 4.7 Hz, 1H), 3.73 (s, 3H), 3.78 (t, *J*=5.7 Hz, 1H), 4.51 – 4.67 (m, 1H), 7.02 (t, *J*=7.4 Hz, 1H), 7.11-7.15 (m, 2H), 7.37 (d, *J*=8.1 Hz, 1H), 7.56 (d, *J*=8.1 Hz, 1H), 8.78 (br s, 1H)		

Synthesis of (2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-D-tryptophanate hydrochloride (NLG-1559)



2,3-dihydroxypropyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate (NLG-1559-A-E24)

[00136] To a solution **NLG-1558** free base (0.750 mg, 2.57 mmol) in acetonitrile (10 mL) at 0 °C was added Boc_2O (560 mg, 2.57 mmol) and the reaction was allowed to warm to RT and stirred for 4 h. The solvent was removed under reduced pressure and the crude was purified by column chromatography to afford the desired product (760 mg, 75%). ^{1}H NMR: 1.34 (s, 9H),

3.13-3.23 (m, 2H, 3.35-3.38 (m, 1H), 3.42-3.45 (m, 1H), 3.67-3.72 (m, 4H), 4.01-4.08 (m, 2H), 5.01-5.04 (m, 1H), 6.83 (s, 1H), 7.05 (t, 1H, J = 7.4 Hz), 7.16 (t, 1H, J = 7.3 Hz), 7.23 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.9 Hz).

(2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl Na-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate (NLG-1559-B-E24)

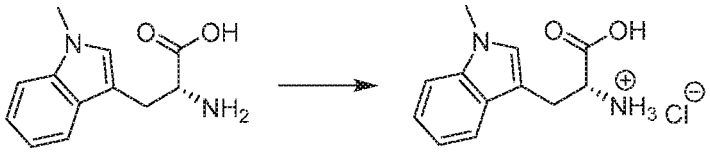
[00137] To a solution of **NLG-1559-A-E24** (650 mg, 1.66 mmol) in dry pyridine (2 mL) at 0 °C was added $POCl_3$ and the solution was allowed to warm to rt. After stirring overnight (18 h), ethanol (1.5 mL) was added and the reaction continued for 4 h. The solvent was removed under reduced pressure and the crude was purified by column chromatography (460 mg, 57%). ^1H NMR: 1.13 (t, 3H, J = 7.0 Hz), 1.30 (s, 9H), 3.10-3.20 (m, 2H), 3.47-3.55 (m, 1H), 3.60 (s, 3H), 41.9-4.44 (m, 3H), 4.55-4.57 (m, 1H), 5.23-5.27 (m, 1H), 6.79 and 6.83 (two s, 1H), 7.01 (t, 1H, J = 7.4 Hz), 7.12 (t, 1H, J = 7.2 Hz), 7.18 (d, 1H, J = 9.2 Hz), 7.46 (d, 1H, J = 7.7 Hz).

(2-Ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-D-tryptophanate hydrochloride (NLG-1559)

[00138] To a solution **NLG-1559-B-E24** (550 mg, 1.14 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added anhydrous HCl (1.4 mL, 4 M solution in dioxane) and the mixture was allowed to warm to rt. After stirring for 2 h, the solvent was removed under reduced pressure and the crude was washed with dry ether (3 x 15 mL). The white solid was filtered and the product was dried under reduced pressure (0.241 g, 61 %). (CD3OD-d_4) 1.20 (td, 3H, J = 7.1, 4.3 Hz), 3.26-3.42 (m, 2H), 3.44 (dd, 1H, J = 5.1, 3.0 Hz), 3.48-3.56 (m, 1H), 3.71 (s, 3H), 3.95 (h, 2H, J = 7.1 Hz), 4.21-4.36 (m, 3H), 4.37-4.53 (m, 1H), 7.02 (t, 1H, J = 7.4 Hz), 7.07 (d, 1H, J = 4.0 Hz), 7.10-7.17 (m, 1H), 7.30 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.4 Hz).

Pharmaceutically acceptable salt composition(s)

Synthesis of (R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethan-1-aminium chloride (NLG-1607)

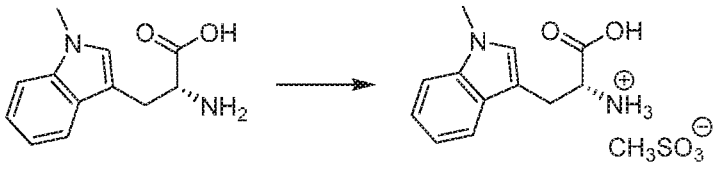


D-1MT NLG-1607

[00139] To an ice cold aqueous HCl (15.5 mL, 30.9 mmol; 2M) solution was added D1MT (4.5 g, 20.6 mmol). After stirring for 30 minutes, the clear solution was evaporated under reduced pressure and the crude was evaporated thrice with Ethanol (40 mL). The crude was stirred in Ethanol and *tert*-butylmethylether and filtered to afford the desired product (4.25 g, 81%).

[00140] An alternative method was developed where ~ 10 g of D-1MT was suspended in 250 mL glass bottle with 100 mL of acetonitrile. 10 mL HCl solution pre-dissolved in acetonitrile (511.2 mg/mL) was added into the D-1MT free form solution according to 1:1 molar ratio to free base:acid, and then kept shaking at room temperature overnight to form salt. The filtered solid was dried under vacuum at 30°C overnight. A white powder (11.1 g) was obtained by the above process, and characterized by XRPD, DSC and TGA (Figures 1-2). The purity was 99.7% area based on the HPLC analysis, and the stoichiometry was analyzed by ELSD, the calculated molar ratio (API:HCl acid) were 1:1.0. The powder was crystalline as assessed by polarized light microscopy (PLM) and by X-ray powder dispersion spectrometry (XRPD, Figure 1). The salt was anhydrous as assessed by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) (Figure 2).

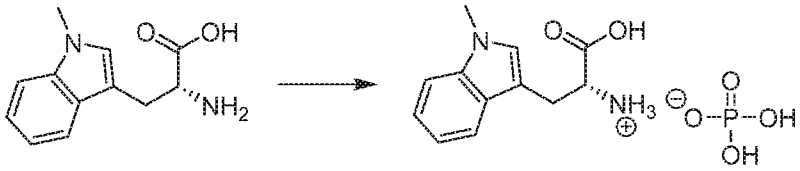
Synthesis of (R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethan-1-aminium methanesulfonate (NLG-1619)



D-1MT NLG-1619

[00141] To a stirred solution methane sulfonic acid (1.50 mL, 22.9 mmol) in DI water (50 mL) was added D-1MT (1.0g, 4.48 mmol) in 100 mg portions. The solution was stirred vigorously for 3h at 75 °C until the solution was homogeneous. The solution was concentrated under reduced pressure and the solid collected (1.38 g, 96%). ^{1}H NMR(Methanol-d_4, 400 MHz): δ = 2.69 (s, 3H), 3.32 – 3.39 (m, 1H), 3.49 (dd, 1H, J = 15.3, 4.9 Hz), 3.80 (s, 3H), 4.25 (dd, 1H, J = 7.8, 4.9 Hz), 7.10 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz), 7.14 (s, 1H), 7.21 (ddd, 1H, J = 8.2, 7.0, 1.1 Hz), 7.38 (dd, 1H, J=8.3, 1.1 Hz), 7.62 (dt, 1H, J = 8.0, 0.9 Hz)

Synthesis of (R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethan-1-aminium dihydrogen phosphate (NLG-1660)



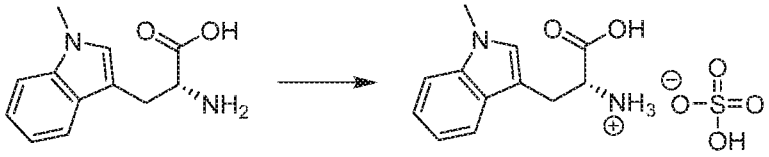
D-1MT NLG-1660

[00142] To the solution of phosphoric acid (0.673g, 6.87mmol) in deionized water (30 mL) at 50 °C, was added D-1MT (0.5g, 2.29) portion wise and the mixture was stirred at 50 °C overnight. Solution was then concentrated to half of its original volume and allowed to stand at room temperature overnight. Resulting precipitate was filtered, washed with cold ethanol, and dried to yield **NLG-1660** as white solid (0.250, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.95 (dd,

1H, J = 15.1, 8.6 Hz), 3.22 – 3.29 (m, 1H), 3.46 (dd, 1H, J = 8.6, 4.2 Hz), 3.71 (s, 3H), 7.00 (ddd, 1H, J = 8.0, 7.1, 1.0 Hz), 7.09 – 7.15 (m, 2H), 7.37 (d, 1H, J = 8.4 Hz), 7.55 (d, 1H, J = 7.9 Hz).

[00143] An alternative method was developed where ~ 10 g of D-1MT was suspended in 500 mL glass bottle with 100 mL of THF. 20 mL of H_3PO_4 solution pre-dissolved in THF (792.3 mg/mL) was added into the D-1MT free form solution according to 1:3 molar ratio to free base:acid, and then kept shaking at room temperature overnight to form salt. The filtered solid was dried under vacuum at 30°C overnight, checked by XRPD, DSC, TGA and ELSD. A white powder (11.1 g) was obtained, which showed to be crystalline by PLM and XRPD pattern (Figure 3). The salt was anhydrous based on DSC and TGA data (Figure 4). The purity was 99.8%, and the stoichiometry was analyzed by ELSD, the calculated molar ratio (free base:phosphoric acid) were 1:0.57.

Synthesis of (R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethan-1-aminium hydrogen sulfate (NLG-1667)



D-1MT NLG-1667

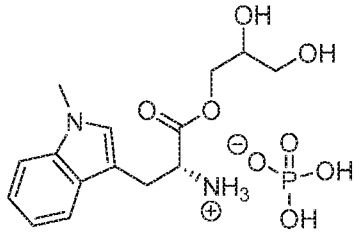
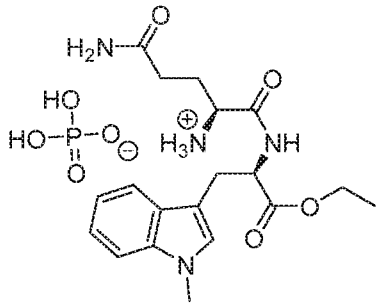
[00144] To a suspension of D-1MT (1.00 g, 4.58 mmol) in water/THF (4:1, 100 mL) at rt, was added 0.5M H_2SO_4 (9.16 mL, 4.58 mmol) and the mixture was stirred at rt overnight. The white solid was filtered-off and washed with cold THF to afford the sulfate salt of D-1MT (0.429 g, 34%). (DMSO-d_6) 3.17 (dd, 1H, J = 15.1, 7.2 Hz), 3.27 (dd, 1H, J = 15.0, 5.3 Hz), 3.74 (s, 3H), 3.96 (t, 1H, J = 6.2 Hz), 7.04 (t, 1H, J = 7.4 Hz), 7.12-7.21 (m, 2H), 7.41 (d, 1H, J = 8.2 Hz), 7.58 (d, 1H, J = 8.0 Hz), 8.52 (br s, 4H).

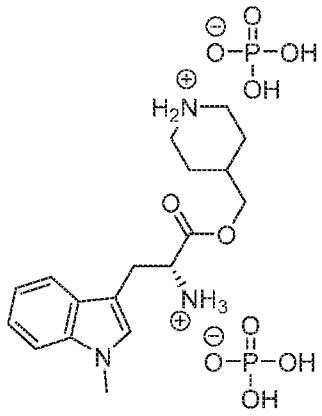
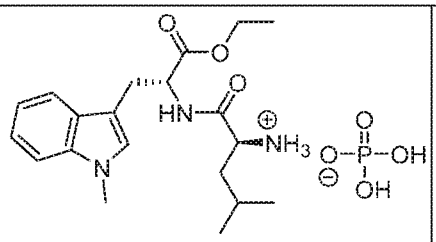
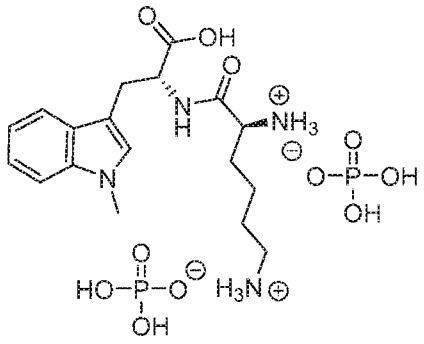
General method for the generation of mono and di phosphate salts of indoximod prodrugs.

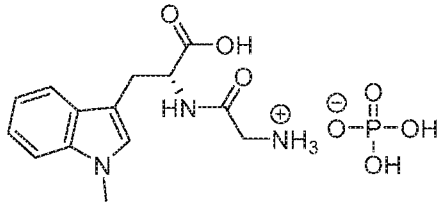
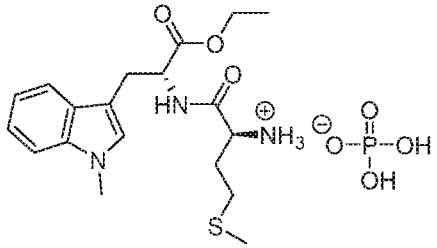
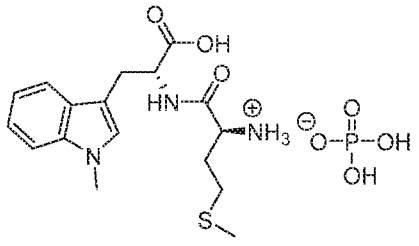
To a solution of free base (0.747 mmol) in EtOH (5ml) at 0 °C was added phosphoric acid (0.747 mmol; a solution in EtOH 1 mL) or (1.494 mmol in case of diamine) and the mixture was allowed

to warm to RT and stirred for 5-18 h. The solvent was removed under reduced pressure and the residue was diluted with methyl *tert*-butylether (10 mL), after stirring for 1-5 h the solid was filtered and dried under reduced pressure to afford the desired product. For **NLG-03380-02**, the free base was generated from **NLG-03380-01** using ion-exchange resin.

[00145]

#	Compound	Name	Yield (%)
NLG-1626		(2R)-1-(2,3-dihydroxypropoxy)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-aminium dihydrogen phosphate	44
	^{1}H NMR (DMSO-d_6, 400 MHz): 3.07-3.15 (m, 2H), 3.27-3.38 and 3.43-3.50 (m, 2H), ^{1}H NMR (400 MHz, DMSO-d_6): 3.60-3.68 (m, 1H), 3.73 (s, 3H), 3.84 (br s, 1H), 3.90-3.96 (m, 1H), 4.02-4.12 (m, 1H), 6.95 (br s, 3H), 7.02 (ddd, 1H, J = 8.0. 70. 1.0 Hz), 7.11-7.19 (m, 2H), 7.38 (dt, 1H, J = 8.3, 0.9 Hz), 7.49-7.56 (m, 1H).		
NLG-1629		(S)-5-amino-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-aminium dihydrogen phosphate	59
	^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (t, 3H, J =7.0 Hz), 1.64-1.70 (m, 1H), 1.75-1.85 (m, 1H), 2.06 (t, 2H, J = 7.9 Hz), 3.06-3.18 (m, 2H), 3.44 (br s 1H), 3.72 (s, 3H), 4.04 (q, 2H , J = 7.1 Hz), 4.52 (q, 1H , J = 7.1 Hz), 6.80 (s, 1H), 7.02 (t, 1H , J = 7.5 Hz), 7.11– 7.16 (m, 2H), 7.32-7.38 (m, 2H), 7.50 (d, 1H , J = 7.9 Hz), 7.82 (br s, 3H), 8.57 (s, 1H).		

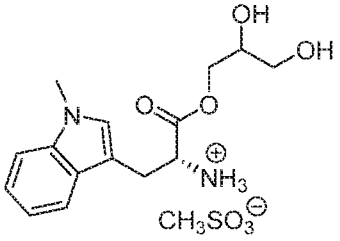
NLG-1664		(R)-4-(((2-ammonio-3-(1-methyl-1H-indol-3-yl)propanoyl)oxy)methyl)piperidin-1-ium dihydrogen phosphate	31
	(DMSO-d_6) 1.35-1.56 (m, 4H), 1.63-1.68 (m, 1H), 2.61-2.73 (m, 2H), 3.09-3.26 (m, 4H), 3.73 (s, 3H), 3.81 (dd, 1H, J = 5.1, 10.9 Hz), 3.88 (dd, 1H, J = 5.1, 11.1 Hz), 3.95 (t, 1H, J = 6.7 Hz), 7.02 (t, 1H, J = 7.4 Hz), 7.09-7.17 (m, 1H), 7.21 (s, 1H), 7.38 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.9 Hz), 8.44 (br s, 10H)		
NLG-1665		(S)-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-4-methyl-1-oxopentan-2-aminium dihydrogen phosphate	59
	^{1}H NMR (400 MHz, DMSO-d_6): 0.77 (dd, 6H, J = 6.5, 6H, 2.2 Hz), 1.1 (t, 3H, J = 7.1, 7.1 Hz), 1.18-1.32 (m, 1H), 1.39-1.50 (m, 1H), 1.39 - 1.49 (m, 1H), 3.06 (dd, 1H, J = 14.5, 8.4 Hz), 3.17 (dd, 1H, J = 14.4, 5.4 Hz), 3.40 (dd, 1H, J = 8.6, 5.7 Hz), 3.72 (s, 3H), 4.06 (q, 2H, J = 7.1, 7.1, 7.1 Hz), 4.55 (td, 1H, J = 8.1, 8.1, 5.5 Hz), 5.52 (bs, 8H), 7.02 (t, 1H, J = 7.2 Hz), 7.10 – 7.15 (m, 2H), 7.38 (d, 1H, J = 8.3 Hz), 7.51 (d, 1H, J = 7.9 Hz), 8.62 (d, 1H, J = 7.9 Hz).		
NLG-1670		(S)-6-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-6-oxohexane-1,5-diaminium dihydrogen phosphate	81

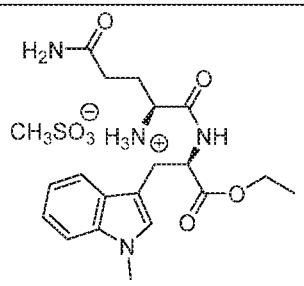
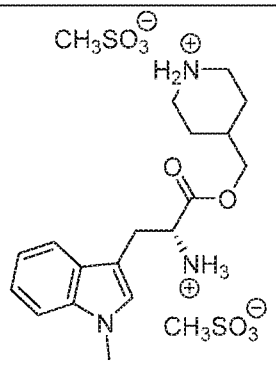
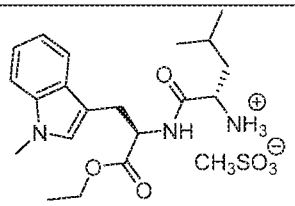
	^{1}H NMR(Deuterium Oxide, 400 MHz): δ = 0.39 – 0.78 (m, 2H), 1.21 (ddd, 2H, *J* = 9.1, 6.8, 2.6 Hz), 1.28 – 1.49 (m, 2H), 2.39 (td, 2H, *J* = 7.4, 3.8 Hz), 3.08 (dd, 1H, *J* = 15.0, 10.9 Hz), 3.45 (ddd, 1H, *J* = 15.1, 4.5, 1.0 Hz), 3.74 (s, 3H), 3.79 (t, 1H, *J* = 6.7 Hz), 4.68 – 4.77 (m, 1H), 7.14 (d, 1H, *J* = 0.8 Hz), 7.14 – 7.20 (m, 1H), 7.28 (ddd, 1H, *J* = 8.3, 7.1, 1.1 Hz), 7.41 – 7.47 (m, 1H), 7.70 (dd, 1H, *J* = 7.9, 0.9 Hz) ppm		
NLG-1677		(R)-2-((1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-2-oxoethan-1-aminium dihydrogen phosphate	80
	(DMSO-d6) 3.01-3.05 (m, 1H), 3.18-3.22 (m, 1H), 3.42-3.56 (m, 2H), 3.72 (s, 3H), 4.42-4.50 (m, 1H), 7.01-7.14 (m, 3H), 7.33-7.37 (m, 1H), 7.51-7.55 (m, 1H), 8.44 (br s, 9H), 8.65 (s, 1H)		
NLG-03272-02		(S)-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-4-(methylthio)-1-oxobutan-2-aminium dihydrogen phosphate	75
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.13 (t, *J*=7.1 Hz, 3H), 1.64-1.72 (m, 1H), 1.73 – 1.84 (m, 1H), 1.93 (s, 3H), 2.28 (t, *J*=7.9 Hz, 2H), 3.08 (dd, *J*=14.6, 8.5 Hz, 1H), 3.18 (dd, *J*=14.5, 5.2 Hz, 1H), 3.54 (t, *J*=6.0 Hz, 1H), 3.73 (s, 3H), 4.07 (q, *J*=7.1 Hz, 2H), 4.56 (q, *J*=6.8, 6.1 Hz, 1H), 7.02 (t, *J*=7.4 Hz, 1H), 7.07 – 7.23 (m, 2H), 7.38 (d, *J*=8.2 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 1H), 7.98 (br s, 5H), 8.68 (d, *J*=7.7 Hz, 1H)		
NLG-03380-02		(S)-1-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-4-(methylthio)-1-oxobutan-2-aminium dihydrogen phosphate	78
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.63 – 1.79 (m, 2H), 1.85 (s, 3H), 2.13 (t, *J*=8.1		

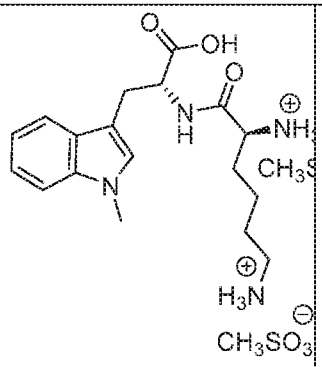
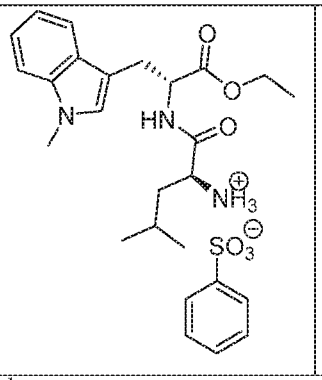
	Hz, 2H), 3.01 (dd, *J*=14.6, 9.0 Hz, 1H), 3.23 (dd, *J*=14.7, 4.6 Hz, 1H), 3.72 (s, 4H), 4.51 (s, 1H), 7.00 (t, *J*=7.5 Hz, 1H), 7.06 – 7.20 (m, 2H), 7.36 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=7.9 Hz, 1H), 8.63 (s, 6H)

General method for the generation of mono and di methanesulfonate and benzenesulfonate salts of indoximod prodrugs.

[00146] To a solution of free base (0.25g, 0.723mmol) in ethanol (10 mL) at rt, was added methanesulfonic or benzenesulfonic acid (0.723 mmol or 1.446 mmol in case of diamines) and the mixture was stirred at rt overnight. Ethanol was evaporated and the crude product was stirred in methyl *tert*-butyl ether for 1-5 h. The precipitate was filtered and dried to yield the corresponding methanesulfonate or benzenesulfonate salt.

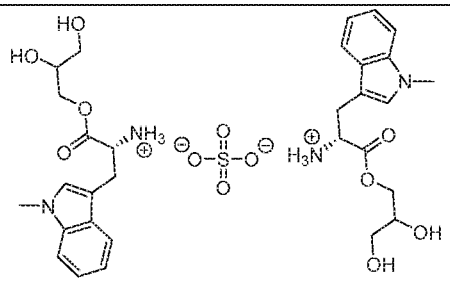
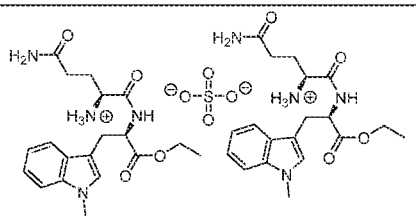
#	Compound	Name	Yield (%)
NLG-1627		(2R)-1-(2,3-dihydroxypropoxy)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-aminium methanesulfonate	41
	^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (s, 3H), 3.24- 3.29 (m, 2H), 3.29 -3.41 (m, 2H), 3.65-3.68 (m, 1H), 3.75 (s, 3H), 4.04 (dd, 1H, *J* = 11.1, 6.3 Hz), 4.16 (dd, 1H, *J* = 11.0, 4.0 Hz), 4.28 (br s, 1H), 7.06 (ddd, 1H , *J* = 8.0, 7.1, 1.0 Hz), 7.17 (ddd, 1H , *J* = 8.2, 7.1, 1.1 Hz), 7.21 (s, 1H), 7.39-7.46 (m, 1H), 7.54 (dt, 1H, *J* = 8.1, 0.9 Hz), 8.29 (br s, 3H).		

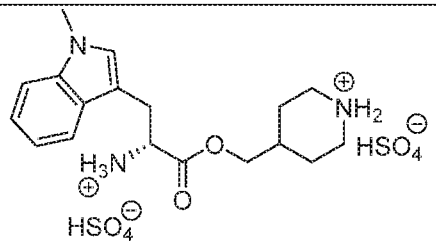
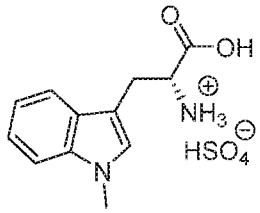
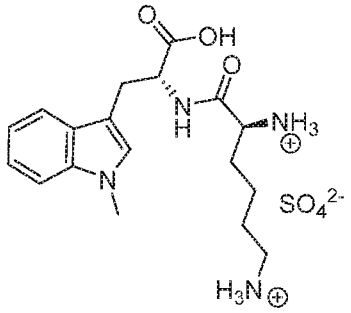
NLG-1631		((S)-5-amino-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-aminium methanesulfonate	78
	^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (t, 3H, J = 7.1 Hz), 1.80-1.86 (m, 2H), 1.97- 2.13 (m, 2H), 2.31 (s, 3H), 3.08 (dd, 1H , J = 14.5, 8.2 Hz), 3.18 (dd, 1H , J = 14.5, 6.0 Hz), 3.72 (s, 3H), 3.85 (q, 1H , J = 5.6 Hz), 4.06 (q, 2H , J = 7.1 Hz), 4.59 (td, 1H , J = 8.0, 6.0 Hz), 6.98 (s, 1H), 7.03 (ddd, 1H, J = 8.0, 6.9, 1.0 Hz), 7.09-7.18 (m, 2H), 7.34-7.42 (m, 2H), 7.52 (dt, 1H , J = 7.9, 1.0 Hz), 8.12 (d, 3H, J = 5.6 Hz), 8.93 (d, 1H, J = 7.9 Hz).		
NLG-1662		(R)-4-(((2-ammonio-3-(1-methyl-1H-indol-3-yl)propanoyl)oxy)methyl)piperidin-1-ium methanesulfonate	32
	(DMSO-d$_6$) 1.25 (dt, 2H, J = 8.3, 34.3 Hz), 1.49 (ddd, 3H, J = 8.0, 12.1, 23.2 Hz), 2.50 (s, 6H), 2.54-2.69 (m, 2H), 3.01-3.15 (m, 2H), 3.58 (s, 3H), 3.70 (dd, 1H, J = 4.2, 11.0 Hz), 3.79 (dd, 1H, J = 4.1, 11.0 Hz), 3.96-4.07 (m ,1H), 6.88 (t, 1H, J = 7.5 Hz), 6.95-7.03 (m, 2H), 7.12 (d, 1H, J = 8.1 Hz), 7.31 (d, 1H, J = 7.9 Hz), 8.13-8.33 (m, 3H), 8.59 (t, 1H, J = 10.5 Hz)		
NLG-1666		(S)-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-4-methyl-1-oxopentan-2-aminium methanesulfonate	69
	^{1}H NMR (400 MHz, DMSO-d_6): 0.73 (dd, 6H, J = 8.2, 6.3 Hz, 6H), 1.16 (t, 3H, J = 7.1, 7.1 Hz, 3H), 1.24 (t, 2H, J = 7.1, 7.1 Hz, 2H), 1.32 (dt, 1H, J = 13.0, 6.7, 6.7 Hz, 1H), 2.29 (s, 3H), 3.03 (dd, 1H, J = 14.5, 9.3 Hz, 1H), 3.20 (dd,1H, J = 14.5, 5.3 Hz), 3.72 (s, 3H), 4.11 (q, 2H, J = 7.1,		

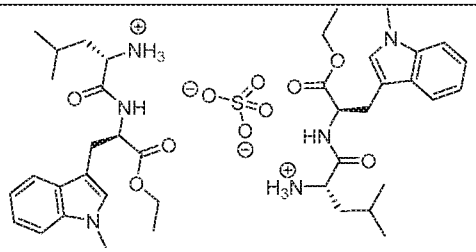
	7.1, 7.1 Hz), 4.64 (td, 1H, *J* = 8.8, 8.8, 5.5 Hz), 7.02 (t, 1H, *J* = 7.5, 7.5 Hz), 7.13 (d, 2H, *J* = 9.8 Hz), 7.38 (d, 1H, *J* = 8.2 Hz), 7.52 (d, 1H, *J* = 7.9 Hz), 8.01 (s, 3H), 8.92 (d, 1H, *J* = 8.2 Hz, 1H).		
NLG-1668		(S)-6-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-6-oxohexane-1,5-diaminium methanesulfonate	79
	^{1}H NMR(Methanol-d_4, 400 MHz): δ = 0.82 – 0.98 (m, 2H), 1.26 – 1.40 (m, 2H), 1.42 – 1.56 (m, 2H), 1.73 (dt, 1H, *J* = 15.3, 7.5 Hz), 1.96 (dddd, 1H, *J* = 26.4, 16.4, 12.9, 6.1 Hz), 2.53 (ddd, 2H, *J* = 13.0, 6.6, 4.6 Hz), 2.71 (s, 6H), 3.14 (dd, 1H, *J* = 14.9, 10.0 Hz), 3.44 (ddd, 1H, *J* = 14.9, 4.6, 1.0 Hz), 3.78 (s, 3H), 3.81 (t, 1H, *J* = 6.5 Hz), 7.03 – 7.11 (m, 2H), 7.19 (ddd, 1H, *J* = 8.3, 7.1, 1.2 Hz), 7.36 (dt, 1H, *J* = 8.3, 0.9 Hz), 7.60 (dt, 1H, *J* = 8.0, 1.0 Hz) ppm		
NLG-1671		ethyl N$^{\alpha}$-((S)-2-(λ^4-azanyl)-4-methylpentanoyl)-1-methyl-D-tryptophanate besylate	68
	^{1}H NMR (400 MHz, DMSO-d_6): 0.73 (dd, 6H, *J* = 8.2, 6.3 Hz), 1.16 (t, 3H, *J* = 7.1, 7.1 Hz), 1.24 (t, 2H, *J* = 7.3, 7.3 Hz), 1.32 (dt, 1H, *J* = 13.0, 6.5, 6.5 Hz), 2.98 – 3.09 (m, 1H), 3.20 (dd, 1H, *J* = 14.5, 5.2 Hz), 3.72 (s, 3H), 4.11 (q, 2H, *J* = 7.1, 7.1, 7.1 Hz), 4.64 (td, 1H, *J* = 8.9, 8.9, 5.4 Hz), 6.99 – 7.05 (m, 1H), 7.09 – 7.17 (m, 2H), 7.26 – 7.35 (m, 3H), 7.38 (d, 1H, *J* = 8.2 Hz), 7.52 (d, 1H, *J* = 8.0 Hz), 7.59 (dd, 2H, *J* = 7.7, 1.9 Hz), 8.00 (s, 3H), 8.92 (d, 1H, *J* = 8.2 Hz).		

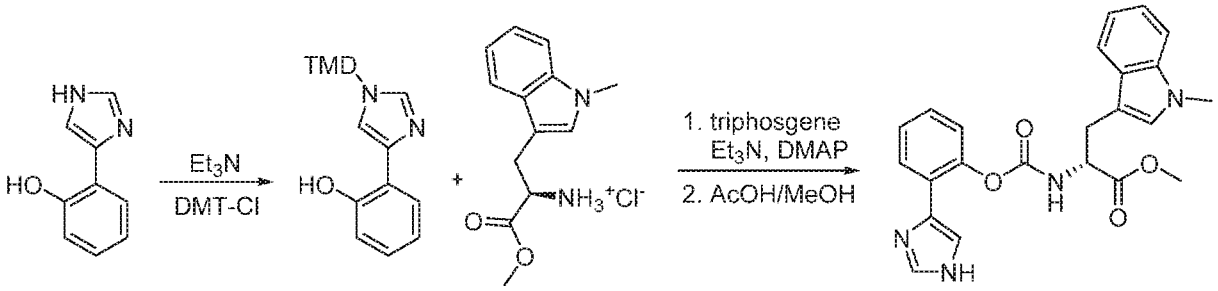
General method for the generation of mono, disulfate and hydrogen sulfate salts of indoximod and indoximod prodrugs.

[00147] To a solution of free base (1.22 mmol) in dry THF (10 mL) at 0 °C was added sulfuric acid (0.611 mmol or 1.22 mmol) as a solution in THF (2 mL) and the solution was allowed to warm to rt. After stirring for 2-6 h, the solvent was distilled-off and the crude was stirred with methyl *tert*-butyl ether, the solid was filtered and dried under vacuum to yield the desired product.

#	Compound	Name	Yield (%)
NLG-1628		(2R)-1-(2,3-dihydroxypropoxy)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-aminium sulfate	43
	^{1}H NMR (400 MHz, DMSO-d_6): 3.05-3.19 (m, 2H), 3.29 - 3.40 and 3.44-3.55 (two m, 2H), 3.62-3.69 (m, 1H), 3.74 (s, 3H), 3.89-3.99 (m, 2H), 4.07 – 4.12 (m, 1H), 6.25 (br s, 2H), 7.03 (t, 1H, J = 7.7 Hz), 7.11-7.21 (m, 2H), 7.40 (d, 1H, J = 8.1 Hz), 7.51-7.57 (m, 1H).		
NLG-1630		(S)-5-amino-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-aminium sulfate	83
	^{1}H NMR (400 MHz, DMSO-d_6) : 1.10 (t, 3H , J = 7.1 Hz), 1.63-1.74 (m, 1H), 1.75-1.86 (m, 1H), 2.02-2.07 (m, 2H), 3.13 (qd, 2H , J = 14.5, 6.8 Hz), 3.52 (dd, 1H , J = 7.4, 5.0 Hz), 3.72 (s, 3H), 4.04 (q, 2H, J = 7.1 Hz), 4.55 (q, 1H, J = 1.6 Hz), 6.47 (br s, 2H), 6.85 (s, 1H), 7.03 (t, 1H, J = 7.5 Hz), 7.10 -7.19 (m, 2H), 7.29 (s, 1H), 7.38 (d,1H, J = 8.2 Hz), 7.51 (d, 1H, J = 7.9 Hz), 8.59 (d, 1H, J = 7.9 Hz).		

NLG-1663		(R)-4-(((2-ammonio-3-(1-methyl-1H-indol-3-yl)propanoyl)oxy)methyl)piperidin-1-ium hydrogen sulfate	25
	(DMSO-d_6) 1.08-1.30 (m, 2H), 1.42-1.59 (m, 2H), 1.64-.178 (m, 1H), 2.64-2.84 (m, 2H), 3.11-3.35 (m, 4H), 3.75 (s, 3H), 3.81-3.90 (m, 2H), 4.22-4.27 (m, 1H), 5.79 (br s, 7H), 7.06 (t, 1H, J = 7.4 Hz), 7.11-7.24 (m, 2H), 7.43 (d, 1H, J = 8.1 Hz), 7.51 (d, 1H, J = 7.7 Hz), 8.17 (s, 1H), 8.39 (s, 2H), 8.51 (s, 1H)		
NLG-1667		(R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethan-1-aminium hydrogen sulfate	30
	(DMSO-d_6) 3.17 (dd, 1H, J = 15.1, 7.2 Hz), 3.27 (dd, 1H, J = 15.0, 5.3 Hz), 3.74 (s, 3H), 3.96 (t, 1H, J = 6.2 Hz), 7.04 (t, 1H, J = 7.4 Hz), 7.12-7.21 (m, 2H), 7.41 (d, 1H, J = 8.2 Hz), 7.58 (d, 1H, J = 8.0 Hz), 8.52 (br s, 4H)		
NLG-1669		(S)-6-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-6-oxohexane-1,5-diaminium sulfate	82
	^{1}H NMR(DMSO-d_6, 400 MHz): δ = 1.08 – 1.58 (m, 7H), 2.55 – 2.71 (m, 2H), 3.03 (dd, 1H, *J* = 14.6, 8.8 Hz), 3.21 (dd, 1H, *J* = 14.6, 4.9 Hz), 3.63 (s, 1H), 3.72 (s, 3H), 4.53 (d, 1H, *J* = 7.9 Hz), 7.02 (t, 1H, *J* = 7.4 Hz), 7.09 – 7.18 (m, 2H), 7.37 (d, 1H, *J* = 8.2 Hz), 7.56 (d, 1H, *J* = 7.9 Hz), 8.25 (br s, 6H) ppm		

NLG-1691		ethyl N^{α}-((S)-2-(λ^4-azanyl)-4-methylpentanoyl)-1-methyl-D-tryptophanate sulfate	29
	^{1}H NMR (400 MHz, DMSO-d_6): 0.72 – 0.78 (m, 6H), 1.11 (t, 3H, J = 7.2, 7.2 Hz), 1.14 – 1.18 (m, 1H), 1.22 – 1.30 (m, 1H), 1.45 (dt, 1H, J = 13.5, 6.8, 6.8 Hz), 3.00 – 3.08 (m, 1H), 3.15 (dd, 1H, J = 14.5, 5.6 Hz), 3.70 (s, 3H), 4.05 (q, 2H, J = 7.1, 7.1, 7.1 Hz), 4.54 (q, 1H, J = 7.5, 7.5, 7.4 Hz), 7.00 (t, 1H, J = 7.5, 7.5 Hz), 7.11 (m, 2H), 7.36 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.9 Hz), 8.48 (d, 1H, J = 7.9 Hz).		



Synthesis of (*R*)-methyl 2-(((2-(1*H*-imidazol-4-yl)phenoxy)carbonyl)amino)-3-(1-methyl-1*H*-indol-3-yl)propanoate (NLG-1264)

[00148] To a solution of 2-(1H-imidazol-4-yl)phenol (1.0 mmol) (prepared according to J. Med. Chem., 2008, 51 (16), pp 4968--4977) in DMF (3 mL) was added triethylamine (1.1 mmol). After stirred for 10 min, a solution of 4,4'-Dimethoxytrityl chloride (1.0 mmol) in DMF (2 mL) was added dropwise. After stirred overnight under a nitrogen atmosphere, the reaction mixture was poured into ice water (10 mL). The solid was filtered off, washed with cold water and dissolved in

ethyl acetate. The organic layer was dried over Na2SO4 and concentrated the crude product was taken into next step without further purification. To a suspension of (R)-methyl 2-amino-3-(1-methyl-1H-indol-3-yl)propanoate (0.5 mmol) (prepared as described by Paul Cox, Donald Craig, Stephanos Ioannidis, Volker S. Rahn, Tetrahedron Letters 2005, 46, 4687) in DCM (3 mL) was added triphosgene (0.5 mmol) and Et3N (2.0 mmol) at 0 oC. The solution was allowed to stir for 1h and was concentrated to dryness. The crude residue was used immediately in the next step without purification. The crude residue was dissolved in DCM (5 mL), the phenyl imidazole derivative (0.5 mmol) and DMAP (1.5 mmol) were added. The resulting solution was allowed to stir at rt overnight. The solvent was removed under reduced pressure and the crude residue was filtered through a plug of silica gel and concentrated. To the residue was added MeOH (3 mL) and AcOH (2 mL) and the solution was stirred at rt for 30 min. The solution was diluted with water and made basic with solid K2CO3 (pH ~ 8-9). The aqueous was extracted with EtOAc and the combined organic layers were washed with water, brine and dried (Na2SO4). The crude residue was purified by column chromatography on silica gel afforded the compound (21% yield).1H NMR: 3.20-3.48 (m, 2H), 3.66 (s,3H), 3.70 (s,3H), 4.61-4.75 (m, 1H), 6.57 (d, 1H, J = 7.2 Hz), 6.90-7.30 (m, 7 H), 7.50-7.58 (m, 1H), 7.10-7.76 (m, 2H).

Example 2: Characterization of solid form of indoximod free base

[00149] D-1MT (HPLC purity 99.6%) free base is a white powder and it displays birefringence, needle shape and crystalline appearance under the polarized light microscope (PLM) and by X-ray powder dispersion spectroscopy (XRPD) (Figure 1). It only shows single melt endothermic peak with onset at 293.8°C by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and ~0.01% weight loss from 30-200°C, indicating that is an anhydrate form. This crystalline form is non-hygroscopic (0.09% weight gain from 0-80 %RH), and does not show changes after dynamic vapor sorption method (DVS). Furthermore, stability studies of the solid powder form indicate that D-1MT is chemically stable at the tested conditions (25°C/60%RH, 40°C, 40°C/75%RH, 60°C and 70°C) for 4 weeks. Additionally, it is also stable in solution in 0.1 N HCl, and 50 mM phosphate buffers pH 2-8 at 25°C for 24 hours, while it shows

minor degradation (0.45%-3.3%) in pH 2 and pH 8 buffers with 0.3% H_2O_2 (the most impurity was RRT=0.58).

Example 3: Characterization of indoximod free base solubility

[00150] The solubility of indoximod as free base in buffered or un-buffered solutions, as well as in simulated biological fluids (SGF, FaSSIF or FeSSIF) is shown in Figure 5 (open symbols). Solubility of indoximod in aqueous solutions of pH 2-8 is 1.8-2.0 mg/mL, with higher solubility at pH <1.5 or >10. This low solubility at neutral pH range is likely due to the high molecular packing energy of indoximod in the crystal, which is reflected by the very high melting point of 293.8°C. This low solubility of indoximod in the pH range corresponding to intestinal pH may in part explain the limiting dose absorption at doses higher than 800 mg in humans. Therefore, we studied whether salts or sprayed dry dispersions of indoximod could increase solubility and exposure after oral dosing.

Example 4: Characterization of indoximod salts and their solubility

[00151] Several salts of indoximod were manufactured and their physicochemical properties were evaluated (Table 2). The hydrochloride, sulfate, phosphate, hemi-phosphate, mesylate and hemi-mesylate salts were solid white powders that showed crystalline properties by PLM and XRPD and were anhydrous by TGA. These salts showed lower melting point than the free base, suggesting increased solubility in water in the range of pH between >1.5 and <10. Most of these salts showed increases of solubility to ~4.7-8.6 mg/mL in water and 5.5-10.6 mg/mL in SGF, with the hydrochloride salt showing a very significant increase to >200 mg/mL in water or SGF.

[00152] Another indoximod salt tested was the maleic acid salt, which showed low melting point of 194°C and poor crystallinity by PLM and XRPD. This salt has the appearance of a sticky white powder of hydrate or solvate form (4.5% weight loss by TGA).

[00153] The tosylate salt shows the appearance of a brown oil, which may be advantageous as that could increase the intestinal absorption of the active ingredient.

[00154] Other salts had less favorable physico-chemical properties. For example, lactate and N-methyl glucamine did not form a salt with indoximod, and the crystal showed a mixture of indoximod free base crystals and N-methyl glucamine or lactate crystals.

[00155] The sodium salt did not show crystalline morphology, it was a hydrate or solvate with very low melting and multiple decomposition peaks by TGA or DSC and thus it was not further characterized.

Table 2: Physico-chemical properties of indoximod and its salts

Salt	Appearance	DSC (Melting or decomposition point)	TGA (Weight loss)	Stoichiom. (API:acid)	Purity	Cristalinity		Hygroscopicity (0-80% RH)	Solubility (25°C, mg/mL)	
						PLM	XRPD		Water (pH)	SGF (pH)
Free base	Anhydrate white powder	293.80°C	~ 0.01% (30 - 200°C)	-	99.6	Yes	Yes (Free Base)	0.09	1.8 (6.03)	3.6 (2.32)
HCl Salt	Anhydrate white powder	230.59°C	~ 0.13% (30 - 120°C)	1 : 1.05	99.7	Yes	HCl Salt Form 1	0.017	> 200 (1.06)	> 200 (1.03)
Sulfate	Anhydrate white powder	225.86°C	~ 1.89% (26 - 120°C)	1 : 0.51	99.6	Yes	Sulfate Form 1	3.4	4.7 (2.03)	5.5 (1.68)
Hemi-Phosphate	Anhydrate white powder	216.1°C	~ 0.6% (30 - 150°C)	1 : 0.60	99.0	Yes	Phosphate Form 1	-	8.6 (2.42)	10.6 (2.05)
Phosphate	Anhydrate white powder	225.09°C	~ 0.15% (30 - 150°C)	1 : 1.01	98.9	Yes	Phosphate Form 1	1.7	8.32 (NA)	9.83 (NA)
Hemi-Mesylate	Anhydrate white powder	266.2°C	~ 0.3% (30 - 150°C)	1 : 0.56	99.7	Yes	Poor crystaline	-	5.5 (2.34)	6.0 (1.84)
Mesylate	Anhydrate white powder	209.71°C	~ 0.18% (30 - 150°C)	1 : 0.98	99.5	Yes	Mesylate + Free Base	0.12*	5.1 (1.84)	6.0 (1.43)
Maleate	Hydrate or solvate	102.6°C 194.3°C	~ 4.5% (25 - 150°C)	1 : 0.50	99.3	Yes	Maleate Form 1	-	-	-
Tosylate	Brown oil	-	-	-	97.3	No	NA	-	-	-
Lactate	White suspension			1:01			Lactic Acid + Free Base			
N-methyl glucamine	White suspension			1:01			Glucamine + Free Base			
Sodium Salt	Hydrate or solvate	63.82°C	~ 16.9% (30 - 100°C)	1 : 1.03	98.8	No	Na salt Form 1	-	-	-

Example 4: Sprayed dry dispersions of indoximod

[00156] A list of indoximod sprayed dry dispersion (SDD) formulations were made in order to assess whether any SDD formulation was able to increase the molecular absorption by generating and maintaining a supersaturated state of indoximod in gastrointestinal fluid so that its absorption could be enhanced. In this study, SDD formulations were made by two methods: hot process spray dry – formulation solution heated up to 110°C before spraying dry, and basic spray dry – formulation pH raised up to ~ 11.5 (room temperature) before spraying dry. The performance of each SDD formulation was investigated by in-vitro dissolution test in simulated gastric buffer (GB) and simulated intestinal fluid (SIF). As shown in Table 3, C_{maxGB} represented the maximum concentration of indoximod in solution when enough of the SDD formulation was dissolved in GB for 30 min; C_{max90} represents the maximum indoximod concentration when the SDD was dissolved in SIF for 90 min; $UltraC_{90}$ represents the concentration in SIF after 90 min of dissolution followed by ultracentrifugation to remove any particulates and $UltraC_{1200}$ represents the concentration in SIF after 1200 min of dissolution followed by ultracentrifugation to remove any particulates. It was expected that the enhanced concentrations of indoximod in GB and SIF increased the absorption of indoximod when the SDD formulation was dosed in animals as well as human beings. Another criterion to evaluate these SDD formulations was physical and chemical stability of indoximod in these formulations. It was found that SDD formulations made by hot process spray drug method were in general more stable than those made by basic process spray dry. In addition, higher drug load in the powder was preferred since it could decrease the dose amount of the final formulation. Based on all these criteria, two SDD formulations were selected for further in vivo PK studies in monkeys. The first one was 50% indoximod/ 50% PVPVA-64, which showed a 1.8-fold increased predicted intestinal concentration than indoximod ($UltraC_{90}$ 3293 ng/mL vs 1849 ng/mL); and the second was 50% indoximod/ 50% Affinisol 126, which showed a 2.3-fold higher predicted intestinal concentration than indoximod ($UltraC_{90}$ 4340 ng/mL vs 1849 ng/mL). These SDDs were prepared by the hot process dry spray which showed better stability properties.

Table 3: Dissolution tests for sprayed dry dispersion formulations of indoximod

Composition	Process Method	C_{maxGB} (µg/mL)	C_{max90} (µg/mL)	$UltraC_{90}$ (µg/mL)	$UltraC_{1200}$ (µg/mL)
Indoximod API (control)	NA	5,154	2,213	1,849	1,854
10% Indoximod/ 90% Affinisol 126	hot process spray dry	6,253	3,027	2,982	3,392
25% Indoximod/ 75% Affinisol 126	basic spray dry	7,466	4,064	3,023	3,096
25% Indoximod/ 75% HPMC-E3	basic spray dry	17,281	7,313	3,943	3,171
25% Indoximod/ 75% PVPVA-64	basic spray dry	20,116	9,349	2,531	2,908
25% Indoximod/ 75% Affinisol 126	hot process spray dry	6,831	3,932	3,892	3,976
25% Indoximod/ 75% Eudragit L100	hot process spray dry	4,015	2,487	2,494	2,598
25% Indoximod/ 75% PVPVA-64	hot process spray dry	8,488	3,623	3,372	2,840
50% Indoximod/ 50% PVPVA-64	basic spray dry	10,442	4,745	4,828	2635
50% Indoximod/ 50% HPMC E3	basic spray dry	9,967	4,630	4,802	3,067
50% Indoximod/ 50% Affinisol 126	hot process spray dry	6,078	3,455	3,690	3,471
50% Indoximod/ 50% Affinisol 912	hot process spray dry	5,931	3,352	3,599	3,228
50% Indoximod/ 50% PVPVA-64	hot process spray dry	8,481	3,695	3,293	3,018
50% Indoximod/ 50% Affinisol 126	hot process spray dry	8,995	4,187	4,340	4,194

Example 5: Pharmacokinetic comparison of indoximod free base, indoximod salts and indoximod SDD in cynomolgus monkeys

[00157] In order to determine whether salts or SDDs that show increase in solubility compared to indoximod free base result in an increase in the maximum concentration (Cmax) and total exposure ($AUC_{0->\infty}$) of indoximod, we carried out a comparative crossover pharmacokinetic study in cynomolgus monkeys, which is a common species used to predict human oral bioavailability. Two groups of 4 monkeys each (all males) were orally dosed at 275 µmol/kg (Group 1) or 825 µmol/kg (Group 2) with: 1) indoximod free base capsules; 2) indoximod hydrochloride capsules; 3) indoximod hemi phosphate capsules; 4) SDD1 suspension (indoximod 50%/50%PVPVA-64, (w/w)) and 5) SDD2 suspension (indoximod 50%/Affinisol 126 50% (w/w)). Each monkey was dosed with each of the 5 dose formulations once every 7 days, and blood samples were obtained at 0, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h and 48 h. Concentration of indoximod was determined from plasma by a validated LC-MS/MS analytical method. C_{max} and $AUC_{(0\text{-}48h)}$ was calculated by non-compartmental analysis using WinNonLin software (Certara). For indoximod in capsule formulation, animals in Group 1 were orally dosed with 3 capsules A and animals in Group 2 were dosed with 4 capsules B. Compositions of capsules A and B are shown in Table 4. For indoximod in SDD formulation, animals in Group 1 were dosed with 4 mL/kg of a 15 mg indoximod/mL suspension and animals in Group 2 were dosed with 4 mL/kg of a 45 mg indoximod/mL suspension. The SDD suspension formulations were prepared in 0.5% methylcellulose (Methocel).

Table 4: Composition of capsules containing indoximod in its free base or salt forms for oral dosing to cynomolgus monkeys

	Indoximod Free Base		Indoximod HCl		Indoximod 0.5 PO_4H_3	
MW (g/mol)	218.26		254.76		267.3	
Ingredients (mg)	Cap A	Cap B	Cap A	Cap B	Cap A	Cap B
Active Ingredient (mg)	100	225	116.7	262.5	122.4	275.5
Avicel PH101 (mg)	17.9	40.2	20.8	46.9	21.9	49.2
Mannitol (mg)	17.9	40.2	20.8	46.9	21.9	49.2

Croscarmellose Sodium (mg)	7.1	16.1	8.3	18.8	8.7	19.7
Total	142.9	321.4	166.7	375	174.9	393.6

[00158] The average Cmax and $AUC_{(0\text{-}48h)}$ parameter values observed in each group obtained after dosing with each formulation of indoximod are shown in Table 5. The percentage of increase in these values as well as the P value obtained for the comparison of each formulation against that of indoximod free base is shown in Table 5. Dosing of indoximod HCl capsules results in a significant increase in Cmax (31-65%) and exposure (37-53%) at both dose levels tested compared to dosing of indoximod free base capsules. Similarly, indoximod hemi phosphate capsules produced a significant increase in Cmax (7-44%) and exposure (27-34%). On the contrary, indoximod in SDD1 or SDD2 formulation produced a significant increase in Cmax (15-94%) but failed to increase the overall exposure with respect to indoximod free base capsules. For these reasons, indoximod salts in their hydrocholoride, hemi-phosphate or phosphate salts are preferred over indoximod in its free base form, either in capsules or in spray dry dispersions.

Table 5: Comparison of Cmax and total exposure (AUC0->∞) between indoximod free base vs its salts or sprayed dry dispersions in monkeys

	indoximod Free Base	indoximod HCl	indoximod $0.5.H_3PO_4$	indoximod PVPVA-64	indoximod Affinisol 126
Dose			275 µmol/kg		
Number of Animals	4	4	4	4	4
Cmax, average (µM)	12.9±3.3	21.3±8.9	18.5±4.8	25±5	21.3±5
% Increase over indoximod FB	NA	65	44	94	65
P value	NA	0.047	0.033	0.010	0.017
AUC(0->48h) (µM.h)	66±17	101±18	89±15	72.5±18	83±25
% Increase over indoximod FB	NA	53	34	9	26
P value	NA	0.043	0.065	0.36	0.2
Dose			825 µmol/kg		
Number of Animals	4	4	4	4	4

Cmax, average (μM)	25.6±12.8	33.4±12	23.4±12.7	29.4±10	33.7±8.4
% Increase over indoximod FB	NA	31	7	15	32
P value	NA	0.010	0.042	0.041	0.025
AUC(0->48h) (μM.h)	127±73	173±75	161±81	141±61	136±57
% Increase over indoximod FB	NA	37	27	11	7
P value	NA	0.012	0.015	0.18	0.29

[00159] This study shows that the hydrochloride and phosphate salts of indoximod can produce an increase in Cmax and AUC pharmacokinetic parameters with respect to the free base, in the range of doses between 275-825 μmol/kg.

Example 6: Pharmacokinetic testing of indoximod salts in capsule formulation in rats

[00160] In order to determine whether salt formation increased the maximum concentration (Cmax) and total exposure ($AUC_{0->\infty}$) of indoximod in rats, we tested the hydrochloride, phosphate, sulfate and mesylate salts of indoximod, and formulated these into capsules by mixing them with appropriate excipients. Three dose levels were investigated: 37, 185 or 500 μmol/kg .

[00161] Gelatin capsules (Torpac, 20 mg capacity) were prepared containing 11.4, 28.6 or 50 μmol/capsule of indoximod or its salts, with or without excipients consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate, in proportions shown in Table 6.1-6.3. Capsules were manually filled and the composition uniformity of a representative sample of capsules from each batch was verified by weight and by LC-MS/MS to determine the average indoximod content.

Table 6.1: Composition of capsules A containing indoximod in its free base or salt forms for oral dosing of rats at 37 μmol/kg

	indoximod Free Base		indoximod HCl		indoximod H_3PO_4		indoximod H_2SO_4		indoximod CH_3SO_3H	
MW (g/mol)	218.26		254.76		316.25		316.33		314.36	
	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)

Active Ingredient	2.50	12.50	2.92	14.59	3.62	18.11	3.62	18.11	3.60	18.00
Microcrystalline Cellulose	7.45	37.25	7.3	36.50	7.1	35.50	7.1	35.49	7.1	35.50
Lactose Monohydrate	7.45	37.25	7.3	36.50	7.1	35.50	7.1	35.49	7.1	35.50
Croscarmellose Sodium	2.4	12.00	2.28	11.40	1.98	9.90	1.98	9.90	2	10.00
Magnesium Stearate	0.2	1.00	0.2	1.00	0.2	1.00	0.2	1.00	0.2	1.00
Total	20.00	100	20.00	100	20.00	100	20.00	100	20.00	100
µmol/capsule	11.4		11.4		11.4		11.4		11.4	
Capsules/animal	1		1		1		1		1	
µmol/kg	37		37		37		37		37	
mg free base/kg	8		8		8		8		8	

Table 6.2: Composition of capsules B containing indoximod in its free base or salt forms for oral dosing of rats at 185 µmol/kg

MW (g/mol)	indoximod Free Base 218.26		indoximod HCl 254.76		D1mT 0.5.H_3PO_4 267.3	
	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)
Active Ingredient	6.25	31%	7.3	37%	7.65	38%
Microcrystalline Cellulose	5.55	28%	5.1	26%	5.05	25%
Lactose Monohydrate	5.55	28%	5.1	26%	5.05	25%
Croscarmellose Sodium	2.45	12%	2.3	12%	2.05	10%
Magnesium Stearate	0.2	1%	0.2	1%	0.2	1%
Total	20.00	100	20.00	100	20.00	100
µmol/capsule	28.6		28.6		28.6	
Capsules/animal	2		2		2	
µmol/kg	185		185		185	
mg free base/kg	40		40		40	

Table 6.3: Composition of capsules C containing indoximod in its free base or salt forms for oral dosing of rats at 500 µmol/kg

MW (g/mol)	indoximod Free Base 218.26		indoximod HCl 254.76		D1mT $0.5.H_3PO_4$ 267.3	
	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)
Active Ingredient	10.83	100%	12.6	100%	13.27	100%
Total	10.83	100	12.6	100	13.27	100
µmol/capsule	50		50		50	
Capsules/animal	3		3		3	
µmol/kg	500		500		500	
mg free base/kg	110		110		110	

[00162] To test the pharmacokinetic profile achieved by dosing indoximod in its free base or salt forms, rats were dosed by intra-stomach delivery with 1 capsule A, 2 capsules B or 3 capsules C to achieve dose levels of 37, 185 and 500 µmol/kg (equivalent to 8, 40 and 110 mg/kg of indoximod, respectively). Rats were fasted 16h prior to dosing to eliminate any confounding food effects, and food was returned 2h after dosing. Blood samples were obtained from each rat at 0, 15 min, 30 min, 1h, 2h, 4h, 6h, 10h, 24h, 48h and 72h after dosing. The concentration of indoximod in plasma was determined by LC-MS/MS, and pharmacokinetic parameters were calculated using the software WinNonLin (Certara).

[00163] The most relevant pharmacokinetic parameters that were evaluated were the maximum concentration of indoximod (Cmax) and total exposure ($AUC_{0->\infty}$). Tables 7.1-7.3 and Figure 6 show a summary of the experimental results.

[00164] Indoximod hydrochloride salt form results in non-statistically significant decrease in Cmax at low dose level, a statistically significant increase at the intermediate dose and a statistically significant decrease at high level. The drug exposure (AUC) for the hydrochloride salt did not show a significant change at the low and high dose level but showed a significant increase at the intermediate level. The different behavior of indoximod hydrochloride in rodents compared to primates is unexpected based on the solubility and dissolution profile of this salt, and it does

not follow a dose dependent trend, which highlights the importance of conducting species-specific and dose-dependent tests for the prediction of pharmacokinetic profiles in humans.

[00165] Indoximod phosphate and hemiphosphate showed a significant increase in Cmax and AUC at the low and intermediate dose levels but a significant decrease in Cmax and a non-statistically significant decrease in exposure at the highest dose level.

[00166] The dose-dependent correlation for Cmax and AUC for the free base, HCl and PO_4H_3 forms of indoximod is shown in Figure 6. This figure shows an increase in Cmax for the HCl and PO_4H_3 salts with respect to the free base at the low and intermediate dose levels but a saturation in the Cmax dose-response curve at the highest dose level, which is not seen for the free base. The dose-response curve for AUC shows a more linear increase of AUC with dose, except for the PO_4H_3 salt which seems to increase less than dose proportional at the highest dose level tested.

[00167] Similarly, other salt forms of indoximod such as sulfate or mesylate increase the Cmax and AUC ~30-40% when tested at 37 µmol/kg.

[00168] These tests indicate that the hydrochloride and phosphate salts of indoximod have increased solubility with respect to the free base form and display increased Cmax and AUC parameter values.

Table 7.1: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs its salt forms in rats dosed at 37 µmol/kg

Dose: 37 µmol/kg	indoximod Free Base	indoximod HCl	indoximod H_3PO_4	indoximod H_2SO_4	indoximod CH_3SO_3H
Number of Animals	11	4	10	4	4
Cmax, average (µM)	15.9±8	9.5±2	22.3±9	22.6±7	20.3±2
% Increase over indoximod Free Base	NA	-40	40	42	28
P value	NA	0.069	0.044	0.077	0.18
AUC(0->∞) (µM.h)	390±166	299±77	558±185	553±196	537±194
% Increase over indoximod Free Base	NA	-23	43	42	38
P value	NA	0.159	0.018	0.065	0.2

Table 7.2: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs its salt forms in rats dosed at 185 µmol/kg

Dose: 185 µmol/kg	indoximod Free Base	indoximod HCl	indoximod H_3PO_4
Number of Animals	8	6	6
Cmax, average (µM)	20.8±4	38.4±10	40.9±5
% Increase over indoximod Free Base	NA	84	96
P value	NA	<0.0001	<0.0001
AUC(0->∞) (µM.h)	1080±478	1493±728	1446±645
% Increase over indoximod Free Base	NA	38	34
P value	NA	<0.0001	<0.0001

Table 7.3: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs its salt forms in rats dosed at 500 µmol/kg

Dose: 500 µmol/kg	indoximod Free Base	indoximod HCl	indoximod H_3PO_4
Number of Animals	6	5	6
Cmax, average (µM)	76.2±25	44.4±8	37.2±10
% Increase over indoximod Free Base	NA	-42	-51
P value	NA	0.012	0.0027
AUC(0->∞) (µM.h)	2871±1379	2706±847	1902±1288
% Increase over indoximod Free Base	NA	-6	-34
P value	NA	0.41	0.12

Example 7: Pharmacokinetic testing of indoximod prodrugs in liquid formulation

[00169] The pharmacokinetic profile of indoximod obtained after oral administration of several indoximod prodrugs was tested in such a way that reflected only differences in intestinal permeability and conversion of prodrug to indoximod in vivo without reflecting differences in solid state form such as differences in polymorphic crystals or amorphous solids which may impact solubility or solubilization rate for the different prodrugs. Therefore, indoximod and each of its prodrugs was solubilized in appropriate vehicle which was either saline solution, Cremaphor®:ethanol:saline (10:10:80), or Chremaphor:EtOH:saline:HCl (10:10:80:0.1N). Indoximod or its prodrugs were dissolved at a concentration of 1 mg/mL and dosed to rats by oral gavage at 10 mL/kg to achieve a final dose of 10 mg/kg; or dissolved at 25 mg/mL and dosed to rats by oral gavage at 2 mL/kg to achieve a final dose of 50 mg/kg; or dissolved at a concentration of 10 mg/mL and dosed orally to mice by oral gavage at 5 mL/kg to achieve a final dose of 50 mg/kg. Blood samples (0.1-0.2 mL) were collected from the femoral artery port from rats or by retro-orbital bleeding from mice and plasma was immediately collected by centrifugation and stored on dry ice to avoid prodrug hydrolysis after plasma collection. Blood samples were collected at 0, 15 min, 30 min, 1h, 2h, 4h, 6h, 10h, 24h, 48h and 72h after dosing from rats or at 0, 30 min, 1h, 2h, 4h, 6h, 16h and 24h after dosing from mice. The concentration of indoximod and of each prodrug in plasma was determined by LC-MS/MS, and pharmacokinetic parameters were calculated for indoximod and its prodrugs. The pharmacokinetic parameters reflect the average of individual parameter values obtained from each individual rat (n) or one common parameter from a single pharmacokinetic curve derived from blood samples obtained from a group of mice (n).

[00170] Tables 8.1 and 8.2 show the indoximod Cmax and $AUC_{(0->\infty)}$ obtained after dosing either indoximod or each one of the test prodrugs. Since all rats were orally dosed at the same dose of 10 mg/kg, but each prodrug has different molecular weight, in order to compare the values of Cmax and $AUC_{(0->\infty)}$ obtained after dosing each prodrug vs. dosing indoximod as a free base, the measured Cmax and $AUC_{(0->\infty)}$ and were normalized by multiplying them by the ratio of $MW_{Prodrug}/MWi_{indoximod}$, thus assuming linear pharmacokinetics within a ~2-fold dose range.

[00171] Table 8.1 shows that some prodrugs result in an effective increase in either Cmax, AUC or both pharmacokinetic parameters. Since the prodrugs were administered in completely soluble form, this suggests that those prodrugs that show enhanced Cmax and/or AUC of

indoximod in plasma do so by a mechanism that involves a combination of factors including enhanced permeability of the prodrug through the intestinal cell wall, reduced clearance of the prodrug with respect to indoximod and good rate of conversion of the prodrug to indoximod in vivo. Not every prodrug form of indoximod resulted in enhanced maximum concentration and exposure of indoximod compared to administration of indoximod. In particular, exposure (AUC) to indoximod seems to be enhanced when dosing NLG-1563, NLG-1564, NLG-1566, NLG-1548, NLG-1572, NLG-1557, NLG-1559, NLG-1570, NLG-1565, NLG-1554, NLG-1558, NLG-1551, and NLG-1547, while indoximod Cmax seems to be enhanced when dosing NLG-1557, NLG-1558, NLG-1554, NLG-1566, NLG-1570, NLG-1283 and NLG-1263.

[00172] Table 8.2 shows prodrugs that did not result in an effective increase in indoximod Cmax nor indoximod exposure when dosed orally to rats at 10 mg/kg, indicating that some of these chemical substitutions may either decrease permeability, or the rate of conversion to indoximod or increase the rate of prodrug clearance by routes that do not result in conversion to indoximod, or a combination of those effects.

[00173] Table 8.3 shows prodrugs that were tested by oral dosing to rats at 50 mg/kg. NLG-1283 causes an increase in Cmax and AUC when dosed to rats at 50 mg/kg. However, this prodrug results in a decrease in Cmax and AUC when dosed to mice at 50 mg/kg. Conversely, the highly similar molecule NLG-1284 does not produce a significant increase in Cmax or AUC when dosed at 50 mg/kg to rats, but it does produce a significant increase in Cmax and AUC in mice, suggesting that different species have different rates of absorption, elimination and metabolization of these prodrugs and that minimal changes in molecular structure can affect the outcome in different species. A dose dependent PK was carried out in mice, which were dosed at 10, 50 and 100 mg/kg of indoximod, or at similar doses for prodrug NLG-1626 or NLG-1665. A caveat of the comparison between dosing prodrugs vs indoximod as a free base was that prodrugs were fully soluble in the dosing formulation, while indoximod was insoluble at doses of 50 and 100 mg/kg. This may result in a time-dependent controlled release effect for indoximod which could result in lower Cmax but higher AUCs than when dosed in fully soluble form. NLG-1626 and NLG-1665 resulted in a significant increase in indoximod Cmax compared to what is observed when dosing indoximod in suspension, at all doses tested. However, NLG-1626 showed

a dose dependent increase AUC for indoximod, where the percentage of increase in AUC decreases at higher doses. Table 8.3 also indicates that formation of carbamates on the amino group of indoximod result in prodrugs with marked reduction in pharmacokinetic parameters for indoximod.

Example 8: Pharmacokinetic testing of indoximod prodrug salts in solid capsule formulation in rats

[00174] To test which prodrugs have the best combined set of pharmacological properties (solubilization rate, solubility, intestinal permeability, clearance rate and rate of metabolization to indoximod) needed to achieve greater plasma concentrations of indoximod and increased exposure to indoximod after oral dosing in a capsule formulation, the prodrugs that showed enhanced indoximod Cmax or exposure when dosed in solution were prepared in several salt forms and mixed with excipients to form a powder blend. These blends were formulated so that each capsule contained the same molar dose of each prodrug. Gelatin capsules (Torpac, 20 mg capacity) were prepared containing 11 µmol/capsule A, 28 µmol/capsule B or 50 µmol/capsule C of indoximod free base (2.5, 6.3 or 11.4 mg/capsule, respectively) or its prodrugs in diverse salt forms, in an excipient blend consisting of microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate, in proportions shown in Tables 9.1a and 9.1b. The composition and uniformity of a representative sample of capsules from each batch was verified by weight and by LC-MS/MS to determine the average indoximod or prodrug content.

[00175] To test the pharmacokinetic profile achieved by dosing indoximod prodrugs in different salt forms, 1 capsule A (11 µmol/capsule) or 2 capsules B (28 µmol/capsule) or 3 capsules C (50 µmol/capsule) were dosed to rats by intra-stomach delivery. The dose levels tested were equivalent to 8 mg/kg (37 µmol/kg) of indoximod equivalent when dosing 1 capsule A of 11 µmol/capsule, 40 mg/kg (185 µmol/kg) of indoximod equivalent when dosing 2 capsules B of 28 µmol/capsule and 110 mg/kg (500 µmol/kg) of indoximod equivalent when dosing 3 capsules C of 50 µmol/capsule. Rats were fasted 16h prior to dosing to eliminate any confounding food effects, and food was returned 2h after dosing. Blood samples were obtained from each rat at 0, 15 min, 30 min, 1h, 2h, 4h, 6h, 10h, 24h, 48h and 72h after dosing. The concentration of

indoximod in plasma was determined by LC-MS/MS, and pharmacokinetic parameters were calculated using the software WinNonLin (Certara).

[00176] The most relevant evaluated pharmacokinetic parameters were the maximum concentration of indoximod (Cmax) and total indoximod exposure ($AUC_{0->\infty}$). Tables 10.1 and 10.2 show a summary of the experimental results.

[00177] The statistical comparison of pharmacokinetic parameters indicated that ethyl N^{α}-(L-leucyl)-1-methyl-*D*-tryptophanate in its hydrochloride (NLG-1564), phosphate (NLG-1665), mesylate (NLG-1666) or besylate (NLG-1671) salt forms dosed at 37-185 μmol/kg was able to significantly ($p<0.05$) increase exposure of indoximod by 33-127%, while its sulfate salt (NLG-1691) did not result in a significant increase in Cmax or AUC at those doses. Similarly, significant increases in Cmax were observed for NLG-1564, NLG-1665 and NLG-1666. At doses of 500 μmol/kg, NLG-1564 hydrochloride, showed a minor increase in Cmax and AUC compared to indoximod.

[00178] Table 10.2 shows that 2,3-dihydroxypropyl 1-methyl-*D*-tryptophanate in its phosphate (NLG-1626) form resulted in significant increase in Cmax (37-153%) and AUC (46-75%), while its hydrocholoride (NLG-1558), and sulfate (NLG-1628) salts resulted in less significant increases in Cmax and AUC. Interestingly, the mesylate salt of 2,3-dihydroxypropyl 1-methyl-D-tryptophanate (NLG-1627) resulted in a decrease in Cmax and AUC, thought this decrease was not statistically significant.

[00179] Table 10.2 also shows that ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate (HCl, and phosphate salts, NLG-3272) show a statistically significant increase in Cmax and AUC at doses of 37-500 μmol/kg.

[00180] Other prodrugs that were studied included: a) ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate (free base, HCl, phosphate or mesylate salts), b) N^{α}-glycyl-1-methyl-D-tryptophan (HCl or phosphate salt), c) methyl N^{4}-((R)-1-ethoxy-3-(1-methyl-1*H*-indol-3-yl)-1-oxopropan-2-yl)-*L*-asparaginate (HCl form) and d) N^{α}-(L-lysyl)-1-methyl-D-tryptophan (free base, HCl, sulfate or phosphate salts). These prodrugs resulted in minor and non-statistically significant variations in

the Cmax or AUC for indoximod compared to an equivalent molar dose of indoximod (Table 10.3).

[00181] Interestingly, piperidin-4-ylmethyl 1-methyl-D-tryptophanate in its HCl or phosphate salt forms (NLG-1563 and NLG-1664) resulted in a statistically significant decrease in Cmax (69-79%, $p<0.004$) and AUC (54-64%, $p<0.014$) for indoximod. Since this compound showed an increase in Cmax (24%) and AUC (75%) when administered via oral solution, the difference in solubilization rate or final solubility may account for the observed differences when administered in powder form.

Example 9: Pharmacokinetic testing of indoximod prodrug salts in solid capsule formulation in cynomolgous monkeys

[00182] Since the rat shows a non-saturable linear increase in exposure with doses of indoximod of up to 100 mg/kg, while humans show a saturable exposure above doses of 10 mg/kg, we decided to evaluate two of the prodrug in primates, which may constitute a better model to predict human pharmacokinetics than rats. Cynomolgous monkeys (4.5-5 kg) were dosed with indoximod, NLG-1564 HCl or NLG-3272 HCl at doses of 92, 275 or 875 µmol/kg in a crossover study design where each animal received the same molar dose of either indoximod, NLG1564 HCl or NLG-3272 HCl every 7 days. Capsules were prepared according to the formulation described in Table 9.2. Monkeys were orally dosed with 1 or 3 capsules A (458 µmol/capsule) or 4 capsules B (1032 µmol/capsule). Blood samples were collected at 0, 5 min, 15 min, 30 min, 1, 2, 4, 8, 12, 24, 26 and 48 h post-dose, and the concentrations of prodrug and indoximod were analyzed by validated LC-MSMS methods.

[00183] The data in Table 11.1 shows that NLG-1564 HCl increases the Cmax of indoximod from ~ 230-500% and AUC from 195-518% in a statistically significant manner. Similarly, NLG-3272 HCl increases the Cmax of indoximod from ~ 305-411% and AUC from 136-393% in a statistically significant manner. The increase in pharmacodynamics indicators in primates was unexpectedly superior from the results observed in rats, indicating that in primates, prodrugs of indoximod of the present invention can provide a significant improvement in the maximum

concentration and exposure to indoximod and are expected to improve exposure to the drug and therapeutic efficacy in human patients.

Table 8.1: Cmax and AUC for indoximod after orally dosing rats with solutions of indoximod or its prodrugs

Prodrug ID	Name	Salt form	MW (g/mol)	Dose (mg/kg)	n	Cmax (μM)	Norm. Cmax (μM)	% Change in Norm. Cmax	$AUC_{(0->\infty)}$ (μM.h)	Norm. $AUC_{(0->\infty)}$ (μM.h)	% Change in Norm AUC
indoximod	1-methyl-*D*-tryptophan	HCl	218	10	5	17.3	17.3	0	508	508	0
NLG-1563	piperidin-4-ylmethyl 1-methyl-*D*-tryptophanate	HCl	389	10	5	12.1	21.5	24	500	889	75
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-*D*-tryptophanate	HCl	396	10	3	9.3	16.2	-6	490	888	75
NLG-1566	ethyl N^{α}-(L-glutaminyl)-1-methyl-*D*-tryptophanate	HCl	411	10	5	13	24.4	41	428	806	58
NLG-1548	N^{9}-(L-lysyl)-1-methyl-*D*-tryptophan	HCl	419	10	5	8.7	16.7	-3	414	795	56
NLG-1572	2-(tetrahydro-2*H*-pyran-4-yl)ethyl 1-methyl-*D*-tryptophanate	HCl	367	10	3	8.9	15	-14	460	774	52
NLG-1557	2-(dimethylamino)ethyl 1-methyl-*D*-tryptophanate	HCl	362	10	3	23.8	39.5	128	440	731	44
NLG-1559	(2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate	HCl	419	10	3	8.8	16.9	-2	327	628	23
NLG-1570	N^{9}-(*L*-leucyl)-1-methyl-*D*-tryptophan	HCl	368	10	3	14.5	24.4	41	366	617	21
NLG-1565	ethyl N^{α}-(*L*-isoleucyl)-1-methyl-*D*-tryptophanate	HCl	396	10	3	7.1	12.8	-26	334	606	19
NLG-1554	N^{α}-glycyl-1-methyl-*D*-tryptophan hydrochloride	HCl	312	10	3	19.6	28	62	419	599	18
NLG-1558	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	HCl	329	10	5	22.1	33.3	92	395	595	17
NLG-1551	*O*-(1-methyl-*D*-tryptophyl)-*L*-serine	HCl	378	10	3	7.7	13.3	-23	339	588	16
NLG-1547	N^{α}-(*L*-glutamyl)-1-methyl-*D*-tryptophan	HCl	384	10	3	10	17.6	2	326	574	13
NLG-1283	ethyl 1-methyl-*D*-tryptophanate	HCl	283	10	3	17	22	27	350	454	-11

Table 8.2: Cmax and AUC for indoximod after orally dosing rats with solutions of indoximod or its prodrugs

Prodrug ID	Name	Salt form	MW (g/mol)	Dose (mg/kg)	n	Cmax (μM)	Norm. Cmax (μM)	% Change in Norm. Cmax	$AUC_{(0->\infty)}$ (μM.h)	Norm. $AUC_{(0->\infty)}$ (μM.h)	% Change in Norm AUC
indoximod	1-methyl-*D*-tryptophan	HCl	218	10	5	17.3	17.3	0	508	508	0
NLG-1575	N^{α}-(L-phenylalanyl)-1-methyl-*D*-tryptophan	HCl	402	10	3	6.4	11.9	-31	231	425	-16
NLG-1560	N^{α}-(*L*-tryptophyl)-1-methyl-*D*-tryptophan	HCl	368	10	3	7.1	12	-31	246	415	-18
NLG-1569	N^{α}-(L-glutaminyl)-1-methyl-*D*-tryptophan	HCl	383	10	3	4.8	8.5	-51	212	372	-27
NLG-1553	N^{α}-(*L*-valyl)-1-methyl-*D*-tryptophan	HCl	354	10	3	8.8	14.2	-18	209	338	-33
NLG-1574	ethyl N^{α}-(L-phenylalanyl)-1-methyl-*D*-tryptophanate	HCl	430	10	3	4	7.9	-54	167	329	-35
NLG-1571	N^{α}-(*L*-isoleucyl)-1-methyl-*D*-tryptophan	HCl	368	10	3	7.4	12.5	-28	187	316	-38
NLG-1555	N^{α}-(*L*-alanyl)-1-methyl-*D*-tryptophan	HCl	326	10	3	9	13.4	-22	207	310	-39
NLG-1549	1-methyl-N^{α}-(1-methyl-D-tryptophyl)-D-tryptophan	HCl	455	10	3	1.5	3	-83	126	262	-48
NLG-1556	1-methyl-*D*-tryptophyl-L-valine	HCl	354	10	3	1	1.6	-91	125	202	-60
NLG-1546	N^{α}-(*D*-tryptophyl)-1-methyl-*D*-tryptophan	HCl	441	10	3	1.6	3.2	-82	90	182	-64
NLG-1561	2-(piperidin-4-yl)ethyl 1-methyl-*D*-tryptophanate	HCl	402	10	3	1.3	2.4	-86	59.9	110	-78
NLG-1567	ethyl N^{α}-(*D*-tryptophyl)-1-methyl-*D*-tryptophanate	HCl	469	10	3	0	0	-100	0	0	-100

n: number of rats used to determine the average pharmacokinetic parameters.
Cmax (μM): maximum concentration of indoximod observed in plasma. Value is the average of n values.
Norm. Cmax (μM): maximum average concentration of indoximod calculated by multiplying the observed Cmax of indoximod in plasma by the ratio of MW of each prodrug and the MW of indoximod and by the ratio of dose of indoximod and the prodrug (in mg/kg). This normalizes Cmax to the same molar dose (μmol/kg).
% Change in Norm. Cmax: Calculated as [Cmax (indoximod from Prodrug)/Cmax(indoximod from indoximod)-1] x 100
$AUC_{(0->\infty)}$ (μM.h): Area under the curve [indoximod] vs Time observed in plasma. Value is the average of n values.
Norm. $AUC_{(0->\infty)}$ (μM.h): average AUC calculated by multiplying the observed $AUC_{(0->\infty)}$ of indoximod in plasma by the ratio of MW of each prodrug and the MW of indoximod and by the ratio of dose of indoximod and the prodrug (in mg/kg). This normalizes AUC to the same molar dose (μmol/kg).

% Change in $AUC_{(0->\infty)}$: Calculated as [$AUC_{(0->\infty)}$ (indoximod from Prodrug)/ $AUC_{(0->\infty)}$ (indoximod from indoximod)-1] x 100

Table 8.3: Pharmacokinetic parameters for indoximod after orally dosing mice or rats with solutions of indoximod or its prodrugs

Drug/ Prodrug	Name	Salt form	MW (g/mol)	Dose (mg/kg)	Route	Species	n	Tmax (h)	$t_{1/2}$ (h)	Cmax (µM)	Dose Norm. Cmax (µM)	% Change in Norm. Cmax	$AUC_{(0->\infty)}$ (µM.h)	Dose Norm. $AUC_{(0->\infty)}$ (µM.h)	% Increase in Norm AUC
indoximod	1-methyl-*D*-tryptophan	HCl	218	50	PO	Rat	1	8	28	27	27	0%	1323	1323	0%
NLG-1277	N^{α}-(ethoxycarbonyl)-1-methyl-*D*-tryptophan	FB	290	50	PO	Rat	1	4	25	4.5	6.0	-78%	172	229	-83%
NLG-1278	1-methyl-N^{α}-((neopentyloxy)carbonyl)-*D*-tryptophan	FB	333	50	PO	Rat	1	2	27.4	0.10	0.15	-99%	3.6	5.5	-100%
NLG-1280	1-methyl-N^{α}-((neopentyloxy)carbonyl)-*D*-tryptophan	FB	290	50	PO	Rat	1	8	30	5.4	7.2	-73%	281	374	-72%
NLG-1283	ethyl 1-methyl-*D*-tryptophanate	HCl	246	50	PO	Rat	1	6	27	58	66	143%	2645	2988	126%
NLG-1284	isopropyl 1-methyl-*D*-tryptophanate	FB	261	50	PO	Rat	1	6	21	23.4	28	4%	877	1051	-21%
NLG-1338	benzyl 1-methyl-D-tryptophanate	HCl	345	50	PO	Rat	1	8	20	17.8	28	4%	650	1028	-22%
NLG-1546	N^{α}-(*D*-tryptophyl)-1-methyl-*D*-tryptophan	HCl	441	50	PO	Rat	3	10	58	1.6	3.2	-88%	90	182	-86%
indoximod	1-methyl-*D*-tryptophan	FB	218	10	PO	Mouse	10	0.5	1.8	9	9	0%	34	34	0%
indoximod	1-methyl-*D*-tryptophan	FB	218	50	PO	Mouse	10	1	2.7	30	30	0%	137	137	0%
indoximod	1-methyl-*D*-tryptophan	HCl	218	50	PO	Mouse	7	1	2.2	16	16	-47%	61	61	-55%
indoximod	1-methyl-*D*-tryptophan	FB	218	100	PO	Mouse	10	1	3.5	43	43	0%	325	325	0%
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	390	13.3	PO	Mouse	10	0.5	4.6	13.3	18	99%	44	59	74%
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	390	66.5	PO	Mouse	10	0.75	4.4	49.1	66	120%	162	218	59%
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	390	133	PO	Mouse	10	0.75	3.7	71	96	122%	242	326	0%
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	457	14	PO	Mouse	10	0.5	1.5	6.5	10	8%	19	28	-18%
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	457	70	PO	Mouse	10	0.75	2.3	33.3	50	66%	98	147	7%
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	457	140	PO	Mouse	10	0.5	2.7	77.6	116	170%	168	252	-23%
NLG-1277	N^{α}-(ethoxycarbonyl)-1-methyl-*D*-tryptophan	FB	290	50	PO	Mouse	7	0.5	1.1	0.13	0.17	-99%	0.29	0.39	-100%
NLG-1280	1-methyl-N^{α}-((neopentyloxy)carbonyl)-*D*-tryptophan	FB	290	50	PO	Mouse	7	NA	NA	BLQ	BLQ	-100%	0	0.0	-100%
NLG-1283	ethyl 1-methyl-*D*-tryptophanate	HCl	246	50	PO	Mouse	7	0.25	3.9	24	27.1	-10%	27	30.5	-78%
NLG-1284	isopropyl 1-methyl-*D*-tryptophanate	FB	261	50	PO	Mouse	7	0.5	4.4	70	84	180%	218	261	91%

Table 9.1a: Capsule Compositions – Rat Oral Dosing

Active Ingredient	Name	Salt form	Dose (μmol/capsule)	n of capsules/rat	% w/w				
					Active Ingredient	Microcrystalline Cellulose	Lactose monohydrate	Croscarmelose	Magnesium Stearate
indoximod	1-methyl-D-tryptophan	free base	11	1	12.5	37.3	37.3	12.0	1.0
indoximod	1-methyl-D-tryptophan	free base	28	2	31.3	27.8	27.8	12.3	1.0
indoximod	1-methyl-D-tryptophan	free base	50	3	100	0	0	0	0
NLG-1676	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	free base	11	1	19.8	33.0	33.0	13.2	1.0
NLG-1548	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	HCl	11	1	24.0	32.5	32.5	10.0	1.0
NLG-1669	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	H_2SO_4	11	1	25.5	31.5	31.5	10.5	1.0
NLG-1670	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	H_3PO_4	11	1	31.1	29.0	29.0	9.9	1.0
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	11	1	22.7	32.0	32.0	12.3	1.0
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	28	2	57.6	16.2	16.2	10.0	1.0
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	50	3	100	0	0	0	0
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	11	1	26.0	30.8	30.8	11.5	1.0
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	28	2	53.1	17.7	17.7	10.5	1.0
NLG-1666	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	CH_3SO_3H	11	1	25.3	31.3	31.3	11.2	1.0
NLG-1671	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	Besylate	11	1	29.6	30.0	30.0	9.4	1.0
NLG-1691	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_2SO_4	11	1	23.4	31.5	31.5	12.6	1.0
NLG-1558	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	HCl	11	1	18.8	33.5	33.5	13.2	1.0
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	11	1	22.4	32.5	32.5	11.6	1.0
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	28	2	55.9	16.7	16.7	9.6	1.0
NLG-1627	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	CH_3SO_3H	11	1	22.2	32.3	32.3	12.3	1.0
NLG-1628	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_2SO_4	11	1	19.6	33.5	33.5	12.4	1.0
NLG-1672	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	free base	11	1	21.4	32.5	32.5	12.5	1.0
NLG-1566	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	HCl	11	1	23.5	31.3	31.3	13.0	1.0
NLG-1629	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	H_3PO_4	11	1	27.1	30.5	30.5	10.9	1.0
NLG-1630	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	H_2SO_4	11	1	24.3	31.2	31.2	12.2	1.0
NLG-1631	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	CH_3SO_3H	11	1	26.9	30.0	30.0	12.1	1.0

Table 9.1b: Capsule Compositions – Rat Oral Dosing

Active Ingredient	Name	Salt form	Dose (μmol/capsule)	n of capsules/rat	% w/w				
					Active Ingredient	Microcrystalline Cellulose	Lactose monohydrate	Croscarmelose	Magnesium Stearate
NLG-1563	piperidin-4-ylmethyl 1-methyl-D-tryptophanate	HCl	11	1	22.2	32.0	32.0	12.8	1.0
NLG-1664	piperidin-4-ylmethyl 1-methyl-D-tryptophanate	H_3PO_4	11	1	29.3	28.8	28.8	12.2	1.0
NLG-1663	piperidin-4-ylmethyl 1-methyl-D-tryptophanate	H_2SO_4	11	1	27.6	29.5	29.5	12.5	0.9
NLG-1585	methyl N^4-((R)-1-ethoxy-3-(1-methyl-1*H*-indol-3-yl)-1-oxopropan-2-yl)-*L*-asparaginate	HCl	11	1	23.6	31.5	31.5	12.4	1.0
NLG-1554	N^{α}-glycyl-1-methyl-D-tryptophan hydrochloride	HCl	11	1	17.9	33.5	33.5	14.1	1.0
NLG-1677	N^{α}-glycyl-1-methyl-D-tryptophan hydrochloride	H_3PO_4	11	1	22.2	31.7	31.7	13.4	0.9
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	H_3PO_4	11	1	27.2	30.4	30.4	11.0	1.0
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	H_3PO_4	28	2	48.3	21.6	21.6	7.8	0.7
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	11	1	23.7	31.9	31.9	11.5	1.0
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	28	2	43.7	23.5	23.5	8.5	0.8
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	50	3	100	0	0	0	0
NLG-3380	N^{α}-(L-methionyl)-1-methyl-D-tryptophan	HCl	11	1	23.3	32.0	32.0	11.5	1.0
NLG-3380	N^{α}-(L-methionyl)-1-methyl-D-tryptophan	HCl	28	2	42	24.2	24.2	8.8	0.8
NLG-3380	N^{α}-(L-methionyl)-1-methyl-D-tryptophan	H_3PO_4	28	2	45.6	22.7	22.7	8.2	0.7

Table 9.2: Capsule Compositions – Monkey Oral Dosing

Active Ingredient	Name	Salt form	Dose (μmol/capsule)	n of capsules dosed	% w/w				
					Active Ingredient	Microcrystalline Cellulose	Mannitol	Croscarmelose	Magnesium Stearate
indoximod	1-methyl-D-tryptophan	free base	458	1, 3	70	12.5	12.5	5.0	0.0
indoximod	1-methyl-D-tryptophan	free base	1032	4	70	12.5	12.5	5.0	0.0
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	458	1, 3	70	12.5	12.5	5.0	0.0
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	1032	4	70	12.5	12.5	5.0	0.0
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	458	1, 3	70	12.5	12.5	5.0	0.0
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	1032	4	70	12.5	12.5	5.0	0.0

Table 10.1: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs. its prodrugs in different salt forms after oral dosing of rats with capsules

Drug/ Prodrug ID	Name	Salt form	Dose (μmol/kg)	n	Cmax (μM)	% Change Cmax	p Value	$AUC_{(0->\infty)}$ (μM.h)	% Change in AUC	pValue
indoximod	1-methyl-D-tryptophan	free base	37	11	15.9±8	0		390±166	0	
indoximod	1-methyl-D-tryptophan	free base	185	8	20.8±4	0		1080±478	0	
indoximod	1-methyl-D-tryptophan	free base	500	6	76.2±25	0		2871±1379	0	
NLG-1676	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	free base	37	4	13.3±2	-17	0.26	340±57	-13	0.28
NLG-1548	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	HCl	37	4	17.2±9	8	0.39	350±83	-10	0.33
NLG-1669	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	H_2SO_4	37	4	15.3±5	-4	0.44	446±101	10	0.27
NLG-1670	N^{α}-(L-lysyl)-1-methyl-D-tryptophan	H_3PO_4	37	4	11.5±4	4	0.15	325±61	-17	0.23
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	37	4	30.4±10	92	0.005	664±134	70	0.006
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	185	8	44.2±10	112	<0.0001	1860±609	87	<0.0001
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	500	6	80.0±22	5	0.39	3300±391	15	0.26
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	37	7	29.2±13	84	0.008	628±145	61	0.003
NLG-1665	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_3PO_4	185	10	35.3±7	69	0.0001	1433±858	33	0.024
NLG-1666	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	CH_3SO_3H	37	4	33.6±3	111	0.0004	886±273	127	0.0004
NLG-1671	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	Besylate	37	4	20.5±2	29	0.14	565±82	45	0.034
NLG-1691	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	H_2SO_4	37	4	12.2±4	-23	0.19	369±145	-5	0.41

Table 10.2: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs. its prodrugs in different salt forms after oral dosing of rats with capsules

Drug/ Prodrug ID	Name	Salt form	Dose (μmol/kg)	n	Cmax (μM)	% Change Cmax	p Value	$AUC_{(0->\infty)}$ (μM.h)	% Change in AUC	pValue
indoximod	1-methyl-D-tryptophan	free base	37	11	15.9±8	0		390±166	0	
indoximod	1-methyl-D-tryptophan	free base	185	8	20.8±4	0		1080±478	0	
indoximod	1-methyl-D-tryptophan	free base	500	6	76.2±25	0		2871±1379	0	
NLG-1558	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	HCl	37	4	20.2±5	28	0.16	472±58	21	0.18
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	37	8	21.7±3	37	0.032	571±95	46	0.0067
NLG-1626	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_3PO_4	185	7	52.8±23	153	0.0002	1896±765	75	0.014
NLG-1627	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	CH_3SO_3H	37	4	11.6±5	-27	0.16	285±39	-27	0.12
NLG-1628	2,3-dihydroxypropyl 1-methyl-D-tryptophanate	H_2SO_4	37	4	17.6±2	2	0.34	472±120	21	0.19
NLG-3380	N^{α}-(L-methionyl)-1-methyl-D-tryptophan	HCl	37	8	18.4±7	16	0.25	485±130	24	0.099
NLG-3380	N^{α}-(L-methionyl)-1-methyl-D-tryptophan	HCl	185	8	92.7±69	345	0.005	3043±2700	181	0.003
NLG-3380	N^{α}-(L-methionyl)-1-methyl-D-tryptophan	H_3PO_4	185	2	45.4±15	118	0.0009	1794±761	66	0.00002
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	H_3PO_4	37	8	21.0±11	32	0.13	400±136	2	0.45
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	H_3PO_4	185	8	31.1±8	49	0.003	1236±498	14	0.27
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	37	8	19.2±6	21	0.16	439±114	13	0.24
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	185	8	52.4±15	152	<0.0001	1898±852	76	0.017
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	500	6	121±46	59	0.031	4269±1255	49	0.048

Table 10.3: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs. its prodrugs in different salt forms after oral dosing of rats with capsules

Drug/ Prodrug ID	Name	Salt form	Dose (μmol/kg)	n	Cmax (μM)	% Change Cmax	p Value	$AUC_{(0->\infty)}$ (μM.h)	% Change in AUC	pValue
indoximod	1-methyl-D-tryptophan	free base	37	11	15.9±8			390±166		
indoximod	1-methyl-D-tryptophan	free base	185	8	20.8±4			1080±478		
indoximod	1-methyl-D-tryptophan	free base	500	6	76.2±25			2871±1379		
NLG-1672	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	free base	37	4	16.7±9	5	0.43	327±12	-16	0.24
NLG-1566	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	HCl	37	4	17.8±4	12	0.33	386±89	-1	0.48
NLG-1629	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	H_3PO_4	37	4	10.9±3	-32	0.12	280±21	-28	0.11
NLG-1630	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	H_2SO_4	37	4	19±8	20	0.25	314±105	-20	0.21
NLG-1631	ethyl N^{α}-(L-glutaminyl)-1-methyl-D-tryptophanate	CH_3SO_3H	37	4	16.5±6	4	0.45	342±97	-12	0.3
NLG-1563	piperidin-4-ylmethyl 1-methyl-D-tryptophanate	HCl	37	4	4.9±0.4	-69	0.008	180±18	-54	0.014
NLG-1664	piperidin-4-ylmethyl 1-methyl-D-tryptophanate	H_3PO_4	37	4	3.3±1	-79	0.004	141±45	-64	0.006
NLG-1585	methyl N^{α}-((R)-1-ethoxy-3-(1-methyl-1*H*-indol-3-yl)-1-oxopropan-2-yl)-*L*-asparaginate	HCl	37	4	19.9±6	25	0.18	409±72	5	0.41
NLG-1554	N^{α}-glycyl-1-methyl-D-tryptophan hydrochloride	HCl	37	4	17.5±2	10	0.35	394±103	1	0.48
NLG-1677	N^{α}-glycyl-1-methyl-D-tryptophan hydrochloride	H_3PO_4	37	4	15.4±5	-3	0.45	403±153	3	0.45

Table 11.1: Comparison of Cmax and total exposure ($AUC_{0->\infty}$) between indoximod free base vs. its prodrugs in different salt forms after oral dosing of cynomolgous monkeys with capsules

Drug/ Prodrug ID	Name	Salt form	Dose (μmol/kg)	n	Cmax (μM)	% Change Cmax	p Value	$AUC_{(0->\infty)}$ (μM.h)	% Change in AUC	pValue
indoximod	1-methyl-D-tryptophan	free base	92	3	8.2±0.4			38.5±4		
indoximod	1-methyl-D-tryptophan	free base	275	3	17.5±3			74.9±5		
indoximod	1-methyl-D-tryptophan	free base	875	3	27.8±8			165±52		
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	92	3	50.6±8	518	0.0004	114±2	195	<0.0001
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	275	3	101±28	476	0.003	463±36	518	<0.0001
NLG-1564	ethyl N^{α}-(L-leucyl)-1-methyl-D-tryptophanate	HCl	875	2	92±17	230	0.005	853±349	416	0.017
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	92	3	33±5	305	0.0005	90.7±11	136	0.0007
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	275	3	88±32	402	0.009	370±113	393	0.005
NLG-3272	ethyl N^{α}-(L-methionyl)-1-methyl-D-tryptophanate	HCl	875	3	142±57	411	0.013	761±516	369	0.059

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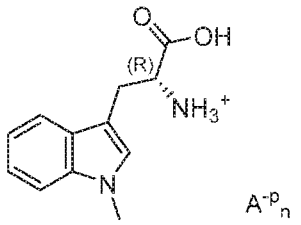
11. Munn, D.H., et al., *GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase.* Immunity, 2005. **22**(5): p. 633-42.
12. Fallarino, F., et al., *The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor zeta-chain and induce a regulatory phenotype in naive T cells.* J Immunol, 2006. **176**(11): p. 6752-61.
13. Kumar, S., et al., *Structure based development of phenylimidazole-derived inhibitors of indoleamine 2,3-dioxygenase.* J Med Chem, 2008. **51**(16): p. 4968-77.
14. Banerjee, T., et al., *A key in vivo antitumor mechanism of action of natural product-based brassinins is inhibition of indoleamine 2,3-dioxygenase.* Oncogene, 2008. **27**(20): p. 2851-7.

CLAIMS

We claim:

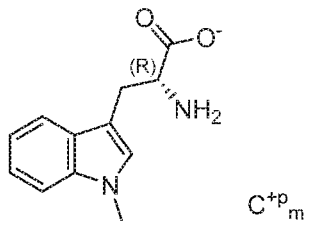
1. A salt of indoximod according to Formula 1a:



Formula 1a

wherein $A^{-p}{}_n$ is an inorganic or organic anion in an ionization state $-p$, the anion present at a stoichiometric ratio n that ensures molecular charge neutrality.

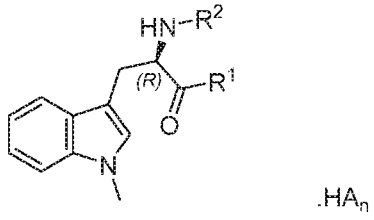
2. The salt of claim 1, wherein $A^{-p}{}_n$ is an anion selected from the group consisting of chloride, phosphate, sulfate, mesylate, besylate, acetate, ascorbate, aspartate, glutamate, glutarate, lactate, maleate, malonate, oxalate, succinate, fumarate, tartrate and citrate, wherein the ionization state $-p$ is -1, -2 or -3 and the stoichiometric ratio n is 1, ½ or 1/3, respectively, so that it satisfies stoichiometric conditions of charge neutrality.
3. The salt of claim 2, wherein the phosphate is HPO_4^{-2}, the HPO_4^{-2} present at a stoichiometric ratio n of 0.5.
4. The salt of claim 2, wherein the phosphate is HPO_4^{-}, the HPO_4^{-} present at a stoichiometric ratio n of 1.
5. The salt of claim 1, wherein the anion A^{-pn} is Cl^{-}, the Cl^{-} present at a stoichiometric ratio n of 1.
6. The salt of claim 2, wherein the mesylate is $CH_3SO_3^{-}$, the $CH_3SO_3^{-}$ present at a stoichiometric ratio n of 1.
7. A salt of indoximod, according to Formula 1b:



Formula 1b

wherein C^{+p}_m is an inorganic cation in an ionization state $+p$, the cation present at a stoichiometric ratio m that ensures molecular charge neutrality of the salt.

8. The salt of claim 7 wherein C^{+p}_m is selected from the group consisting of Li^+, Na^+, K^+, Mg^{+2} and Ca^{+2}, wherein when p is +1, m is 1, and when p is +2, m is ½.
9. A prodrug of indoximod, in free base or salt form, according to Formula 2:

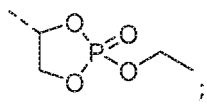


Formula 2

wherein:

(a) R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, -OC_{1-3}alkyl-R^3, -$NHC^{(S)}HR^4(COOH)$, -$NHC^{(R)}HR^4(COOH)$, -OC_{1-6}alkylR^6, -OC_{1-2}alkyl-$C^{(S)}H(NH_2)(COOH)$, or -OC_{1-2}alkyl-$C^{(R)}H(NH_2)(COOH)$;

(b) R^2 is H, -$C(O)C^{(S)}H(NH_2)R^4$, -$C(O)C^{(R)}H(NH_2)R^4$, -$C(O)CH_2C^{(S)}H(NH_2)$, -$C(O)OCH_3$, -$C(O)OR^5$, or -$C(O)NHR^5$;

(c) R^3 is tetrahydropyran or  ;

(d) R^4 is H, -C_{1-5}alkyl, -$(CH_2)_{1-2}SH$, C_{1-5}alkylSC_{1-5}alkyl, C_{1-5}alkylOC_{1-5}alkyl, -CH_2-R^6, -CH_2OH, -$CH(OH)CH_3$, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_{1-3}C(O)OH$, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}NC(=NH_2)NH_2$;

(e) $C^{(S)}$ and $C^{(R)}$ are carbons with the *S* or *R* stereochemistry, respectively, when R^4 is not H;

(f) R^5 is H, C_{1-6}alkylR^6, or R^6

(g) R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one, two or three R^7 groups;

(h) each R^7 is independently halogen, cyano, nitro, -OR, $-N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, $-C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, $-S(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, $-S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, $-OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)C(O)N(R)_2$, wherein R is H or C_{1-4}alkyl;

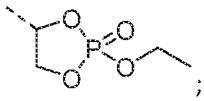
with the proviso that R^1 cannot be –OH when R^2 is H, and the compound cannot be N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan, ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate, or benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate; and

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid, wherein the stoichiometric ratio *n* of the acid is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

10. The prodrug of claim 9, wherein:

(a) R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3;

(b) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$,

(c) R^3 is tetrahydropyran, or  ;

(d) R^4 is H, $-C_{1-5}$alkyl, $-(CH_2)_{1-2}SH$, $-(CH_2)_{1-3}SCH_3$, $-(CH_2)_{1-3}OCH_3$ $-CH_2-R^6$, $-CH_2OH$, $-CH(OH)CH_3$, $-(CH_2)_{1-2}C(O)NH_2$, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-4}NH_2$, or $-(CH_2)_{1-3}NC(=NH_2)NH_2$;

(e) $C^{(S)}$ is a carbon with the *S* stereochemistry, when R^4 is not H;

(f) R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

(g) each R^7 is independently halogen, cyano, nitro, -OR, $-N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, $-C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, $-S(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, $-S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, $-OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)C(O)N(R)_2$, wherein R is H or C_{1-4}alkyl;

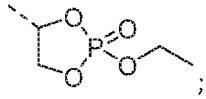
with the proviso that R^1 cannot be –OH when R^2 is H; and

HA_n is an acid selected from the group consisting of of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid, wherein the stoichiometric ratio *n* is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

11. The prodrug of claim 9, wherein:

(a) R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3;

(b) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^3 is tetrahydropyran, or  ;

(d) R^4 is H, $-C_{1-5}$alkyl, $-(CH_2)_2SCH_3$, $-CH_2-R^6$, $-(CH_2)_{1-2}C(O)NH_2$, $-(CH_2)_{1-3}C(O)OH$, or $-(CH_2)_{1-4}NH_2$;

(e) $C^{(S)}$ is a carbon with the *S* stereochemistry, when R^4 is not H;

(f) R^6 is H, aryl, alkylaryl, or heteroaryl, wherein the aryl, alkylaryl or heteroaryl is optionally substituted with one R^7 group;

(g) each R^7 is independently halogen, cyano, nitro, -OR, $-N(R)_2$, -SR, -C(O)OR, $-C_{1-6}$alkyl, C_{1-6}haloalkyl, $-C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, $-S(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, $-S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, $-OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)C(O)N(R)_2$, whereinR is H or C_{1-4}alkyl;

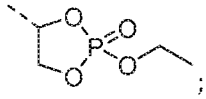
with the proviso that R^1 cannot be –OH when R^2 is H;

HA_n is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), wherein the stoichiometric ratio *n* of the acid is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

12. The prodrug of claim 9, wherein

(a) R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3;

(b) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^3 is tetrahydropyran, or  ;

(d) R^4 is $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, $-C^{(S)}H(CH_3)CH_2CH_3$, $-CH_2-R^6$, $-(CH_2)_2C(O)NH_2$, $-(CH_2)_3C(O)OH$, or $-(CH_2)_4NH_2$;

(e) $C^{(S)}$ is a carbon with the *S* stereochemistry;

(f) R^6 is phenyl;

with the proviso that R^1 cannot be –OH when R^2 is H;

HA_n is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), and wherein the stoichiometric ratio *n* of the acid is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

13. The prodrug of claim 9, wherein:

(a) R^1 is $-OC_{2-3}$alkyl or $-OCH_2CH(OH)CH_2OH$;

(b) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^4 is $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$ or $-(CH_2)_2C(O)NH_2$;

(d) $C^{(S)}$ is a carbon with the *S* stereochemistry;

with the proviso that R^1 cannot be –OH when R^2 is H;

HA_n is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid) or $C_6H_5SO_3H$ (benzyl sulfonic acid); and wherein the stoichiometric ratio *n* of the acid is of 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

14. A prodrug comprising one of the following compounds:

ethyl N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophanate;

ethyl N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophanate;

2,3-dihydroxypropyl 1-methyl-*D*-tryptophanate;

N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophan;

N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophan;

ethyl N^{α}-(*L*-isoleucyl)-1-methyl-*D*-tryptophanate;

N^{α}-(*L*-glycyl)-1-methyl-*D*-tryptophan;

(*S*)-5-amino-6-(((*R*)-1-carboxy-2-(1-methyl-1*H*-indol-3-yl)ethyl)amino)-6-oxohexanoic acid;

N^{α}-(*L*-lysyl)-1-methyl-*D*-tryptophan;

N^{α}-(*L*-phenylalanyl)-1-methyl-*D*-tryptophan;

ethyl N^{α}-(*L*-glutaminyl)-1-methyl-*D*-tryptophanate;

2-(dimethylamino)ethyl 1-methyl-*D*-tryptophanate;

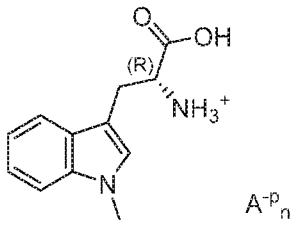
(2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate;

2-(tetrahydro-2*H*-pyran-4-yl)ethyl 1-methyl-*D*-tryptophanate;

ethyl 1-methyl-*D*-tryptophanate; or

isopropyl 1-methyl-*D*-tryptophanate.

15. A pharmaceutical composition of indoximod according to Formula 1a:

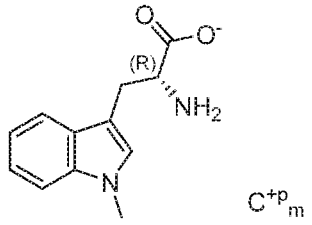


Formula 1a

wherein $A^{-p}{}_n$ is an inorganic or organic anion in an ionization state $-p$, the anion present at a stoichiometric ratio n that ensures molecular charge neutrality.

16. The pharmaceutical composition of claim 15, wherein $A^{-p}{}_n$ is an anion selected from the group consisting of chloride, phosphate, sulfate, mesylate, besylate, acetate, ascorbate, aspartate, glutamate, glutarate, lactate, maleate, malonate, oxalate, succinate, fumarate, tartrate and citrate, wherein the ionization state p is -1, -2 or -3 and the stoichiometric ratio n is 1, ½ or 1/3, respectively, so that it satisfies stoichiometric conditions of charge neutrality.
17. The pharmaceutical composition of claim 16, wherein the phosphate is HPO_4^{-2}, the HPO_4^{-2} present at a stoichiometric ratio n of 0.5.
18. The pharmaceutical composition of claim 16, wherein the phosphate is HPO_4^{-}, the HPO_4^{-} present at a stoichiometric ratio n of 1.

19. The pharmaceutical composition of claim 15, wherein the anion A^{-pn} is Cl^-, the Cl^- present at a stoichiometric ratio n of 1.
20. The pharmaceutical composition of claim 16, wherein the mesylate is $CH_3SO_3^-$, the $CH_3SO_3^-$ present at a stoichiometric ratio *n* of 1.
21. A pharmaceutical composition of indoximod, according to Formula 1b:

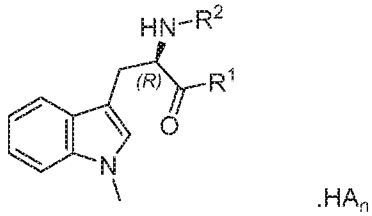


Formula 1b

wherein $C^{+p}{}_m$ is a cation in an ionization state $+p$, the cation present at a stoichiometric ratio *m* that ensures molecular charge neutrality of the salt.

22. The pharmaceutical composition of claim 21 wherein $C^{+p}{}_m$ is selected from the group consisting of Li^+, Na^+, K^+, Mg^{+2} and Ca^{+2}, wherein when *p* is +1, *m* is 1, and when *p* is +2, *m* is ½.

23. A pharmaceutical composition of indoximod, in free base or salt form, according to Formula 2:

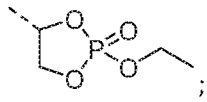


Formula 2

wherein:

(a) R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, $-OC_{1-3}$alkyl-R^3, $-NHC^{(S)}HR^4(COOH)$, $-NHC^{(R)}HR^4(COOH)$, $-OC_{1-6}$alkylR^6, $-OC_{1-2}$alkyl, $-C^{(S)}H(NH_2)(COOH)$, or $-OC_{1-2}$alkyl-$C^{(R)}H(NH_2)(COOH)$;

(b) R^2 is H, $-C(O)C^{(S)}H(NH_2)R^4$, $-C(O)C^{(R)}H(NH_2)R^4$, $-C(O)CH_2C^{(S)}H(NH_2)$, $-C(O)OCH_3$, $-C(O)OR^5$, or $-C(O)NHR^5$;

(c) R^3 is tetrahydropyran or  ;

(d) R^4 is H, -C_{1-5}alkyl, -$(CH_2)_{1-2}SH$, C_{1-5}alkylSC_{1-5}alkyl, C_{1-5}alkylOC_{1-5}alkyl,-CH_2-R^6, -CH_2OH, -$CH(OH)CH_3$, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_{1-3}C(O)OH$, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}NC(=NH_2)NH_2$;

(e) $C^{(S)}$ and $C^{(R)}$ are carbons with the *S* or *R* stereochemistry, respectively, when R^4 is not H;

(f) R^5 is H, C_{1-6}alkylR^6, or R^6

(g) R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

(h) each R^7 is independently halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2$R, -$S(O)_2$OR, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$, wherein R is H or C_{1-4}alkyl;

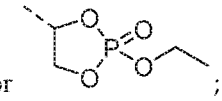
with the proviso that R^1 cannot be –OH when R^2 is H, and the compound cannot be N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan, ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate, or benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate; and

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid, wherein the stoichiometric ratio *n* of the acid is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

24. The pharmaceutical composition of claim 23, wherein:

(a) R^1 is -OH, -OC_{2-3}alkyl, -$OCH_2CH(OH)CH_2OH$, -$O(CH_2)_2N(CH_3)_2$, or -OC_{1-3}alkyl-R^3;

(b) R^2 is H or -$C(O)C^{(S)}H(NH_2)R^4$,

(c) R^3 is tetrahydropyran, or  ;

(d) R^4 is H, -C_{1-5}alkyl, -$(CH_2)_{1-2}SH$, -$(CH_2)_{1-3}SCH_3$, -$(CH_2)_{1-3}OCH_3$, -CH_2-R^6, -CH_2OH, -$CH(OH)CH_3$, -$(CH_2)_{1-2}C(O)NH_2$, -$(CH_2)_{1-3}C(O)OH$, -$(CH_2)_{1-4}NH_2$, or -$(CH_2)_{1-3}NC(=NH_2)NH_2$;

(e) $C^{(S)}$ is a carbon with the *S* stereochemistry, when R^4 is not H;

(f) R^6 is H, aryl, alkylaryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, alkylaryl, heteroaryl, cycloalkyl or heterocycloalkyl is optionally substituted with one two or three R^7 groups;

(g) each R^7 is independently halogen, cyano, nitro, -OR, $-N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, $-C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, $-S(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, $-S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, $-OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)C(O)N(R)_2$, wherein R is H or C_{1-4}alkyl;

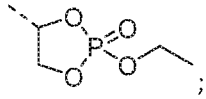
with the proviso that R^1 cannot be –OH when R^2 is H; and

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), $C_6H_5SO_3H$ (benzyl sulfonic acid), acetic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, lactic acid, maleic acid, malonic acid, oxalic acid, succinic acid, fumaric acid, tartaric acid and citric acid, wherein the stoichiometric ratio *n* is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

25. The pharmaceutical composition of claim 23, wherein:

(a) R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3;

(b) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^3 is tetrahydropyran, or  ;

(d) R^4 is H, $-C_{1-5}$alkyl, $-(CH_2)_2SCH_3$, $-CH_2-R^6$, $-(CH_2)_{1-2}C(O)NH_2$, $-(CH_2)_{1-3}C(O)OH$, or $-(CH_2)_{1-4}NH_2$;

(e) $C^{(S)}$ is a carbon with the *S* stereochemistry, when R^4 is not H;

(f) R^6 is H, aryl, alkylaryl, or heteroaryl, wherein the aryl, alkylaryl or heteroaryl is optionally substituted with one R^7 group;

(g) each R^7 is independently halogen, cyano, nitro, -OR, $-N(R)_2$, -SR, -C(O)OR, $-C_{1-6}$alkyl, C_{1-6}haloalkyl, $-C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, $-S(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, $-S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, $-OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, and $-N(R)C(O)N(R)_2$, whereinR is H or C_{1-4}alkyl;

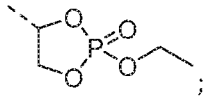
with the proviso that R^1 cannot be –OH when R^2 is H;

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), and $C_6H_5SO_3H$ (benzyl sulfonic acid), wherein the stoichiometric ratio *n* of the acid is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

26. The pharmaceutical composition of claim 23, wherein:

(a) R^1 is -OH, $-OC_{2-3}$alkyl, $-OCH_2CH(OH)CH_2OH$, $-O(CH_2)_2N(CH_3)_2$, or $-OC_{1-3}$alkyl-R^3;

(b) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^3 is tetrahydropyran, or  ;

(d) R^4 is $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, $-C^{(S)}H(CH_3)CH_2CH_3$, $-CH_2-R^6$, $-(CH_2)_2C(O)NH_2$, $-(CH_2)_3C(O)OH$, or $-(CH_2)_4NH_2$;

(e) $C^{(S)}$ is a carbon with the *S* stereochemistry;

(f) R^6 is phenyl;

with the proviso that R^1 cannot be –OH when R^2 is H;

HA_n is an acid selected from the group consisting of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid), and $C_6H_5SO_3H$ (benzyl sulfonic acid), and wherein the stoichiometric ratio *n* of the acid is 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

27. The pharmaceutical composition of claim 23, wherein:

(e) R^1 is $–OC_{2-3}$alkyl or $-OCH_2CH(OH)CH_2OH$;

(f) R^2 is H or $-C(O)C^{(S)}H(NH_2)R^4$;

(g) R^4 is $-CH_2CH(CH_3)_2$, $-(CH_2)_2SCH_3$, or $-(CH_2)_2C(O)NH_2$;

(h) $C^{(S)}$ is a carbon with the *S* stereochemistry;

with the proviso that R^1 cannot be –OH when R^2 is H,

HA_n is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid), HSO_3CH_3 (methyl sulfonic acid) or $C_6H_5SO_3H$ (benzyl sulfonic acid); and wherein the stoichiometric ratio *n* of the acid is of 0, 0.5, 1 or 2 such that the prodrug is charge neutral.

28. A pharmaceutical composition comprising one of the following compounds:

ethyl N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophanate;

ethyl N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophanate;

2,3-dihydroxypropyl 1-methyl-*D*-tryptophanate;

N^{α}-(*L*-leucyl)-1-methyl-*D*-tryptophan;

N^{α}-(*L*-methionyl)-1-methyl-*D*-tryptophan;

ethyl N^{α}-(*L*-isoleucyl)-1-methyl-*D*-tryptophanate;

N^{α}-(*L*-glycyl)-1-methyl-*D*-tryptophan;

(*S*)-5-amino-6-(((*R*)-1-carboxy-2-(1-methyl-1*H*-indol-3-yl)ethyl)amino)-6-oxohexanoic acid;

N^{α}-(*L*-lysyl)-1-methyl-*D*-tryptophan;

N^{α}-(*L*-phenylalanyl)-1-methyl-*D*-tryptophan;

ethyl N^{α}-(*L*-glutaminyl)-1-methyl-*D*-tryptophanate;

2-(dimethylamino)ethyl 1-methyl-*D*-tryptophanate;

(2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate;

2-(tetrahydro-2*H*-pyran-4-yl)ethyl 1-methyl-*D*-tryptophanate;

ethyl 1-methyl-*D*-tryptophanate; or

isopropyl 1-methyl-*D*-tryptophanate.

29. The pharmaceutical composition of any of claims 15-28, wherein the composition is a solid capsule, tablet or pill.

30. The pharmaceutical composition of any of claims 15-28, wherein the composition is a dissolvable capsule.

31. A method of use of the pharmaceutical composition of any of claims 15-30 to modulate the activity of indoleamine-2,3-dioxygenase pathway in a subject in need thereof, comprising orally administering a therapeutically effective amount of the composition to the subject in an appropriate pharmaceutical form or vehicle.

32. A method of use of the pharmaceutical composition of any of claims 15-30 for the treatment of cancer in a subject in need thereof, comprising orally administering a therapeutically effective amount of the composition to the subject in an appropriate pharmaceutical form or vehicle.

33. A method of use of the pharmaceutical composition of any of claims 15-30 for the treatment of tumor-specific immunosuppression associated with cancer in a subject in need thereof, comprising orally administering a sufficient amount of the composition to the subject in an appropriate pharmaceutical form or vehicle.

34. A method of use of the pharmaceutical composition of any of claims 15-30 to treat immunosuppression associated with infectious diseases (e.g HIV-1 infection, influenza), in a subject in need thereof, comprising orally administering a sufficient amount of the composition to the subject in an appropriate pharmaceutical form or vehicle.

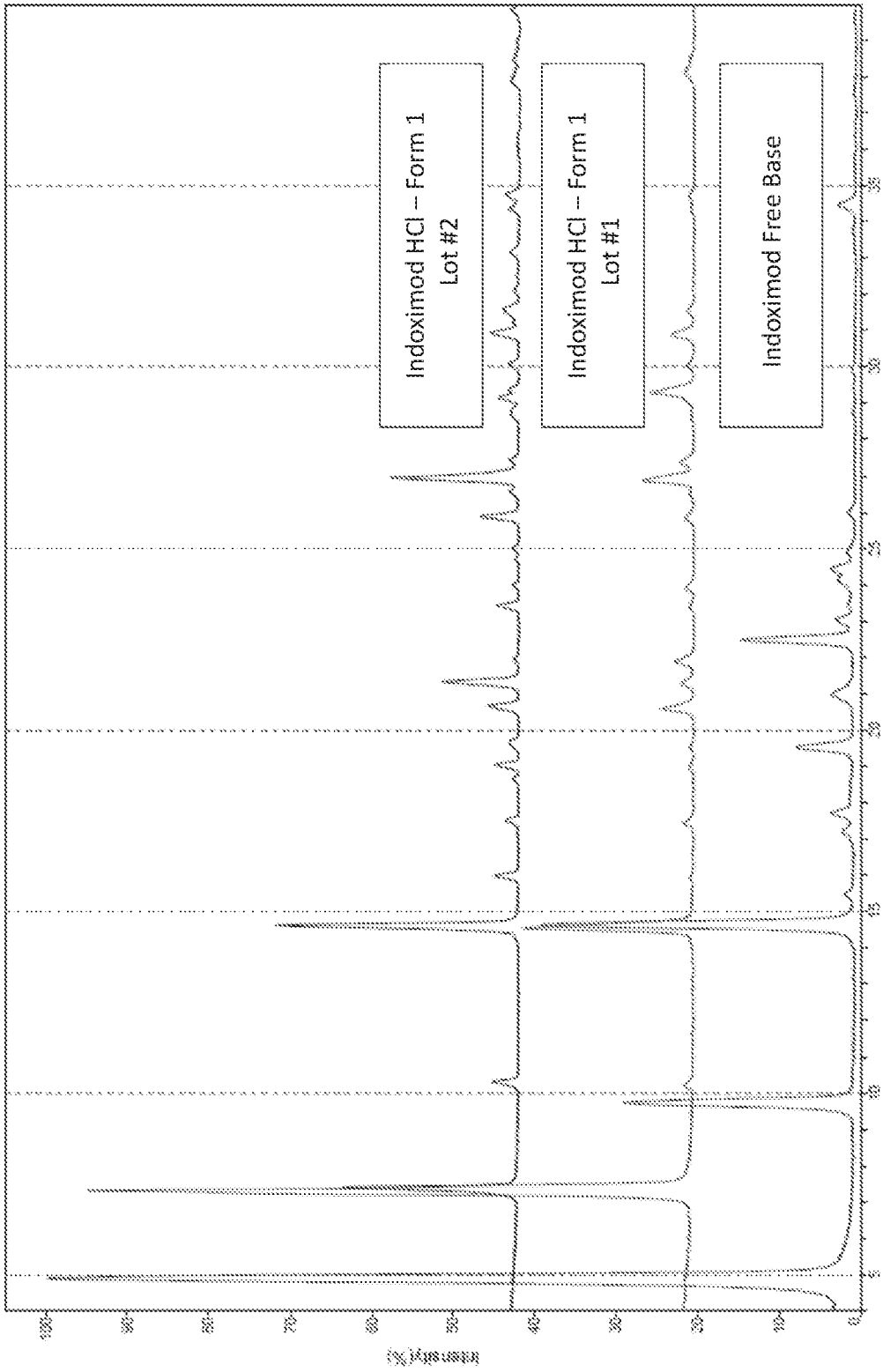


Figure 1: XRPD of indoximod and indoximod HCl

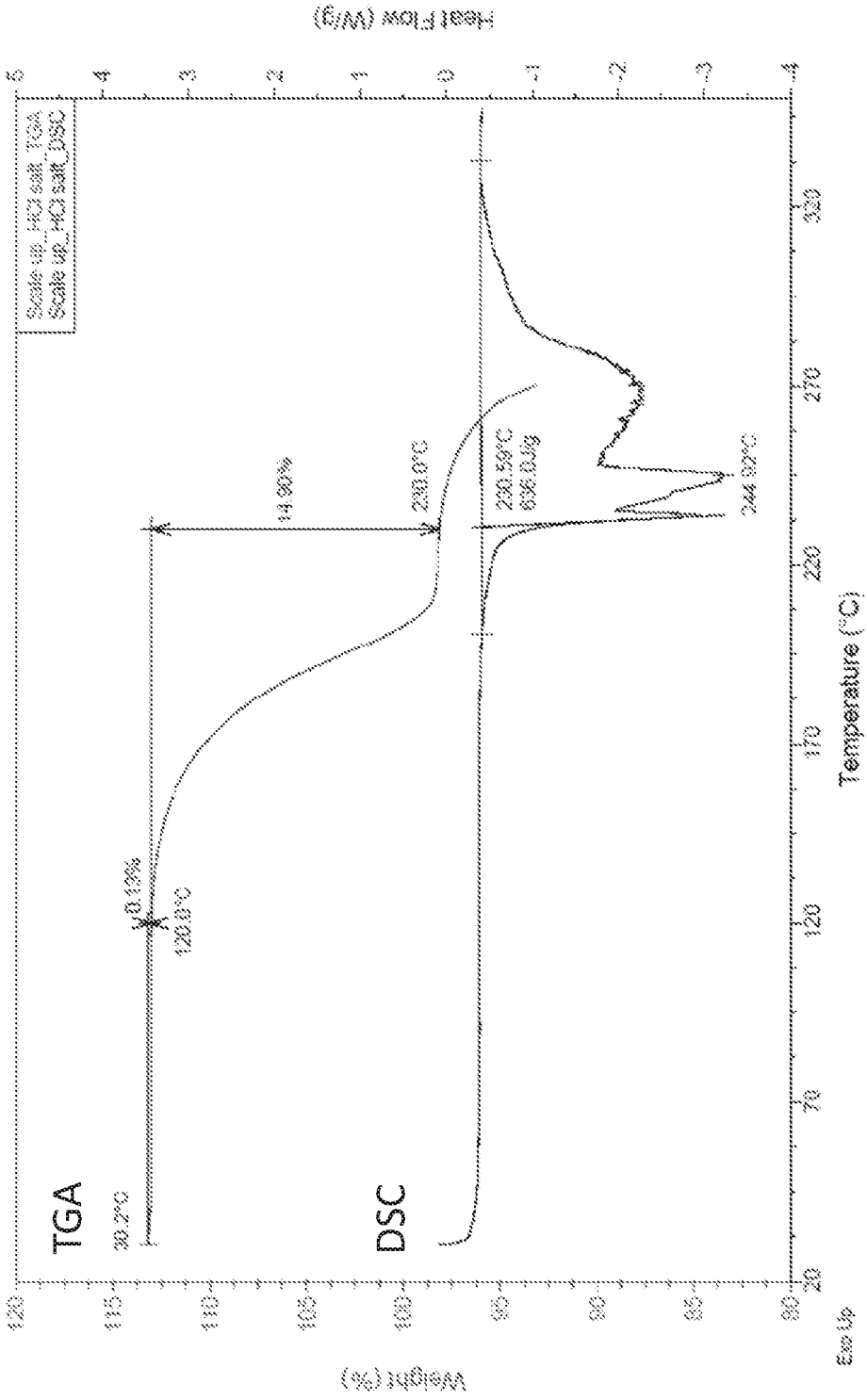


Figure 2: TGA and DSC analysis of indoximod HCl

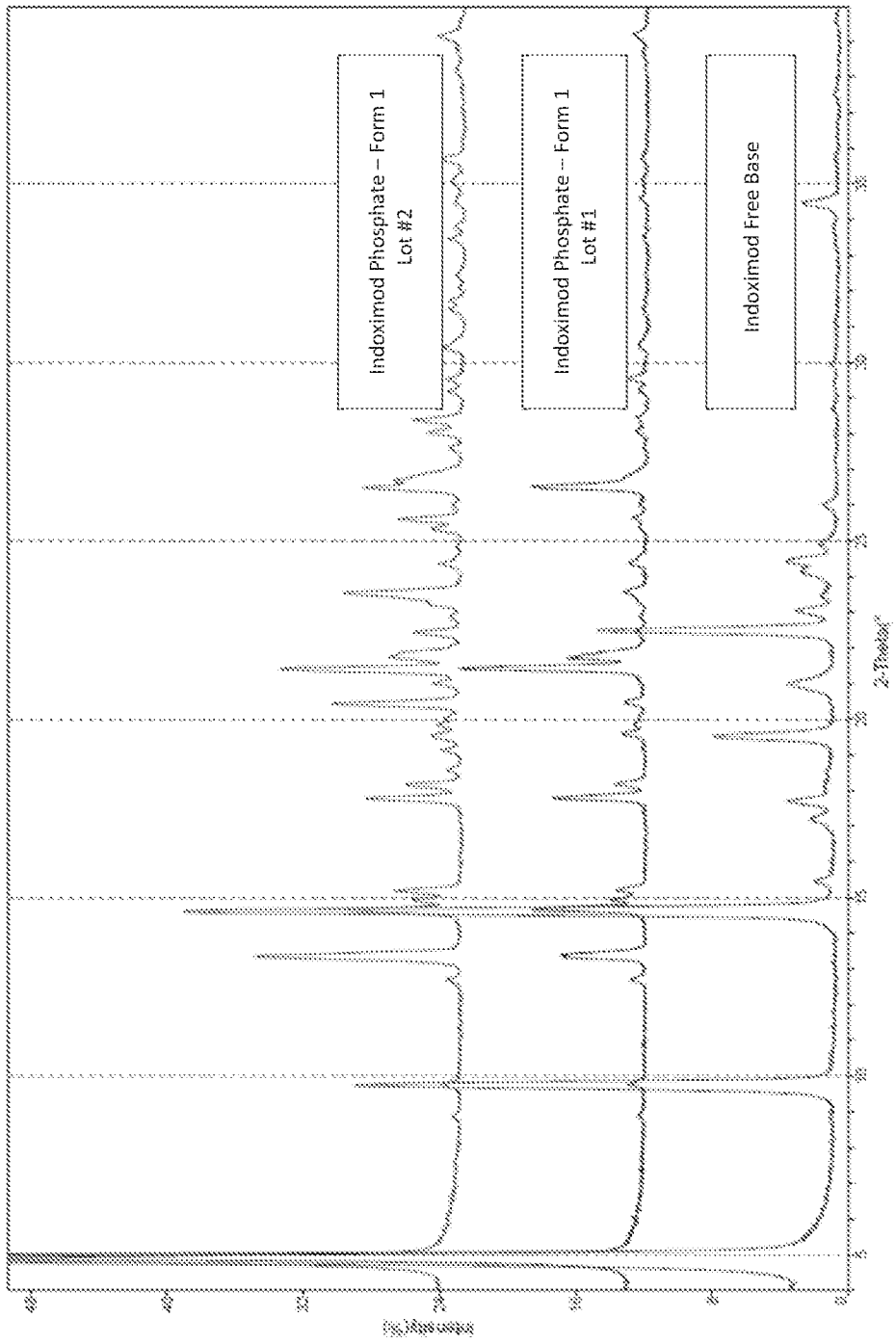


Figure 3: XRPD of indoximod and indoximod phosphate

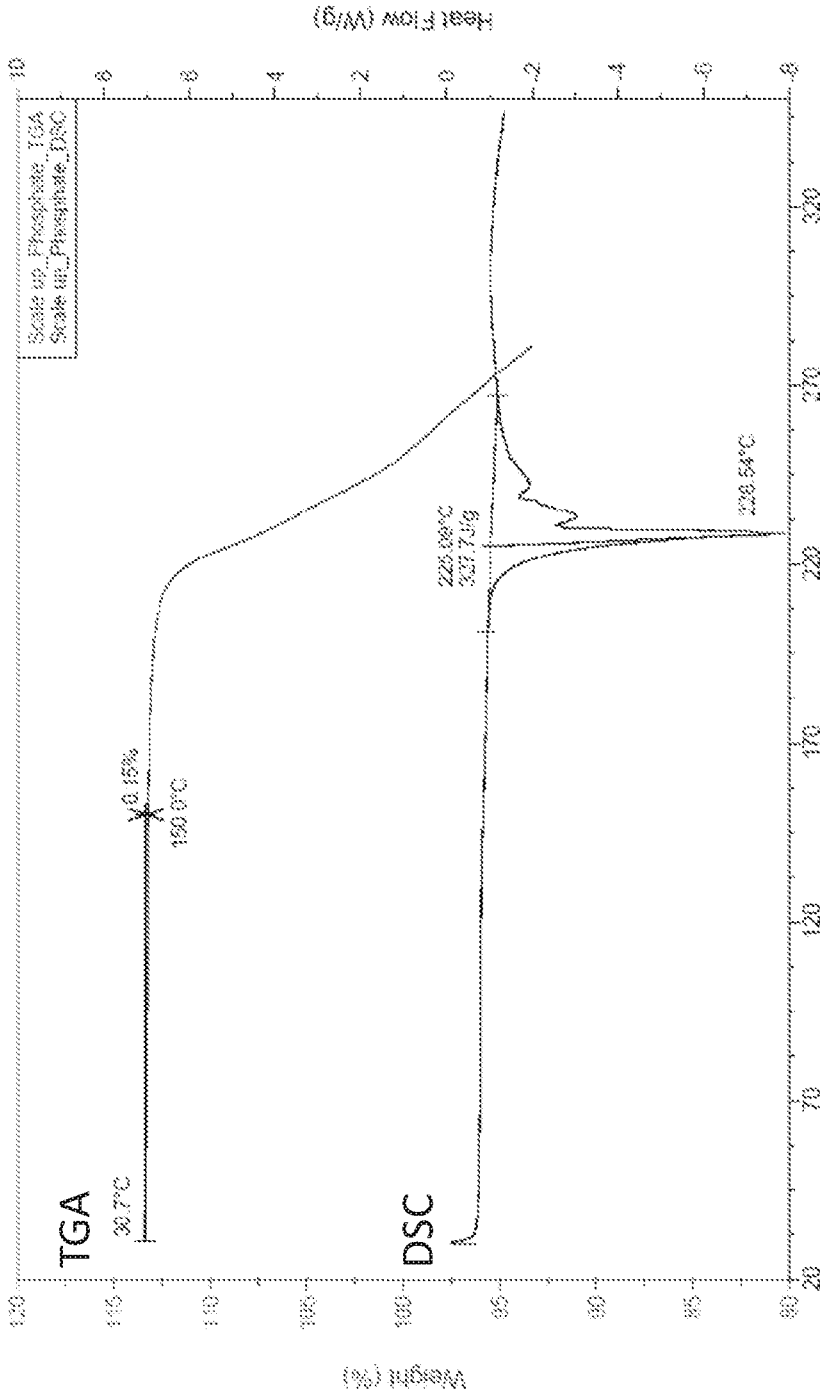
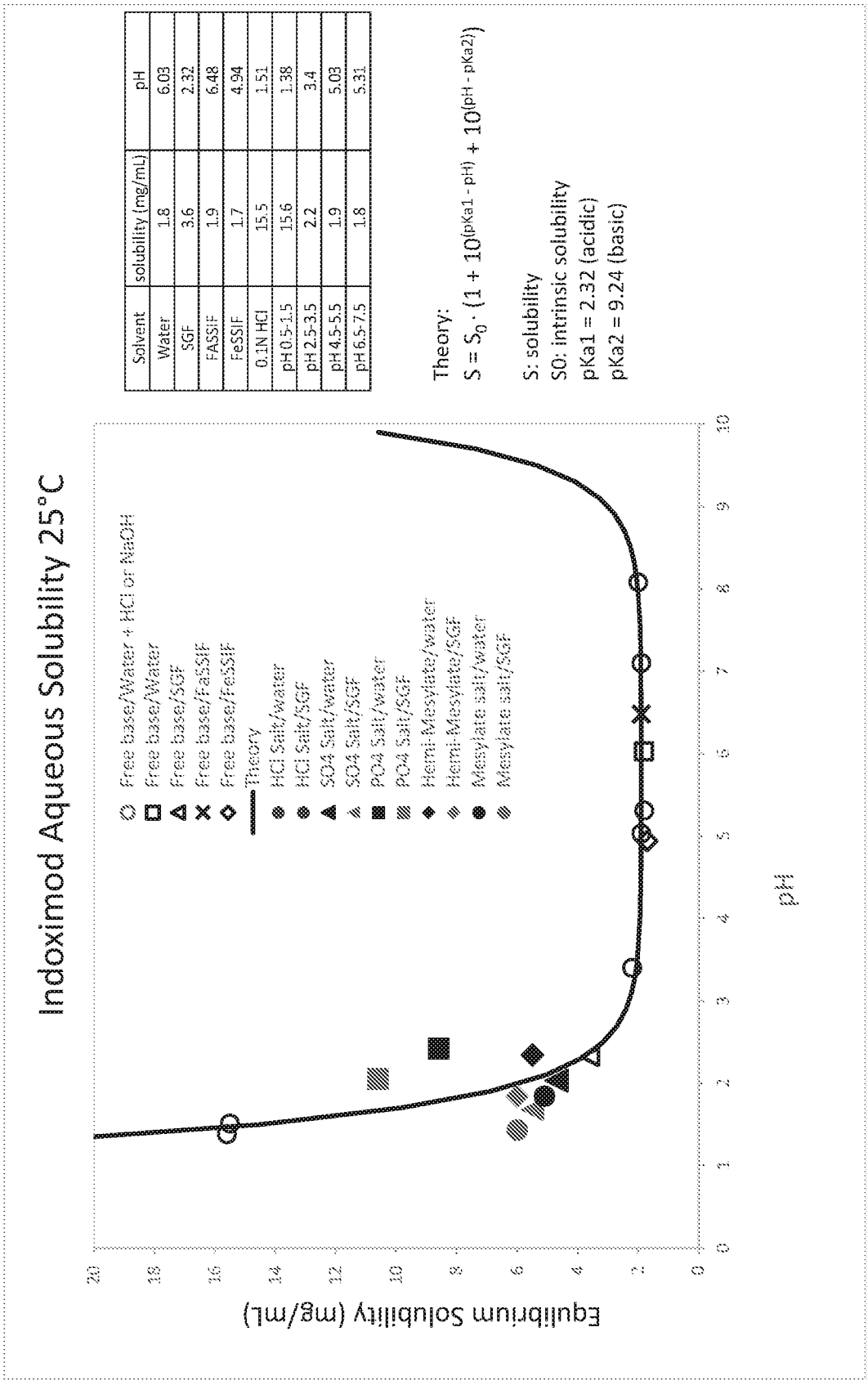


Figure 4: TGA and DSC analysis of indoximod phosphate



Solvent	solubility (mg/mL)	pH
Water	1.8	6.03
SGF	3.6	2.32
FASSIF	1.9	6.48
FeSSIF	1.7	4.94
0.1N HCl	15.5	1.51
pH 0.5-1.5	15.6	1.38
pH 2.5-3.5	2.2	3.4
pH 4.5-5.5	1.9	5.03
pH 6.5-7.5	1.8	5.31

Figure 5: Solubility of indoximod and its salts in different solvents

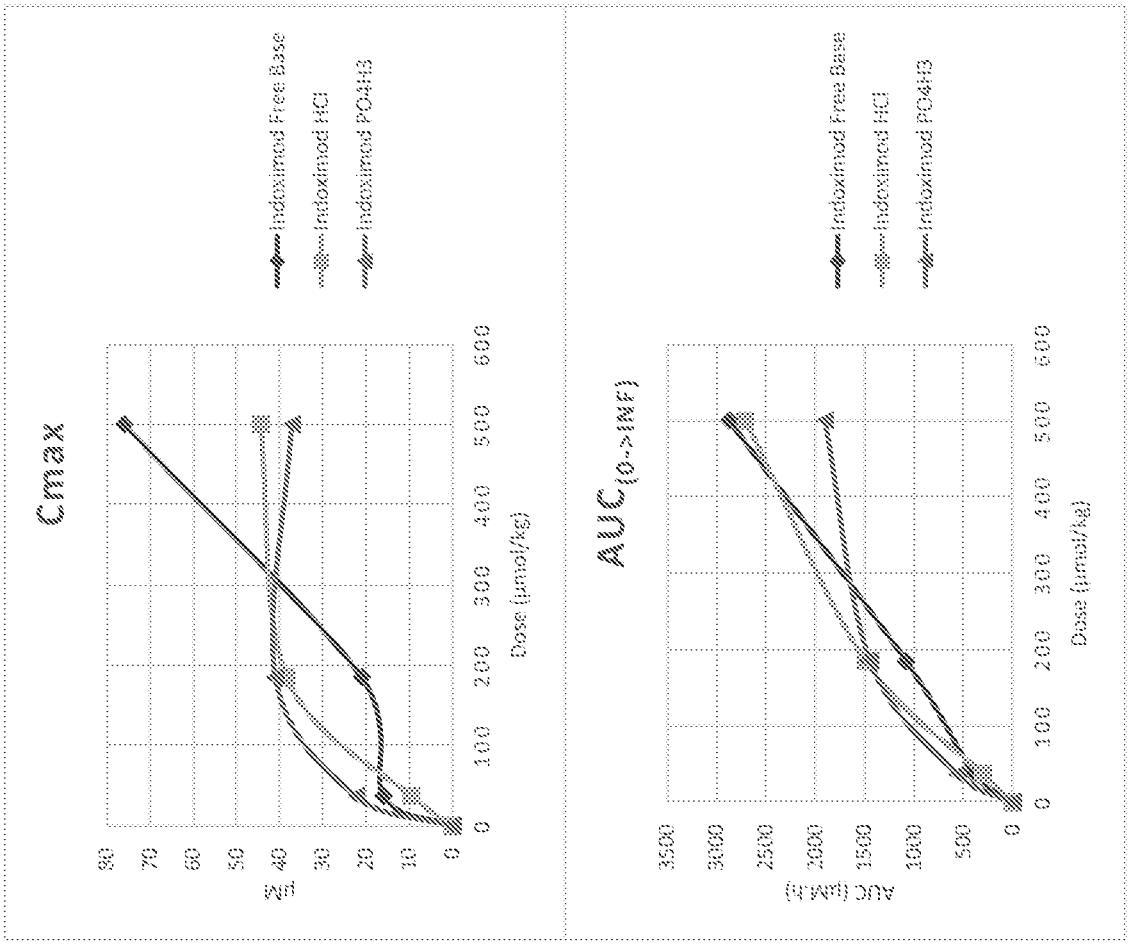


Figure 6: Dose dependency of Cmax and AUC for indoximod and its salts rats after oral dosing in capsule form

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/35391

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/405; A61K 31/198; A61K 31/661 (2016.01)
CPC - A61K31/405; A61K31/661; A61K31/198
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/405; A61K 31/198; A61K 31/661 (2016.01)
CPC: A61K31/405; A61K31/661; A61K31/198

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/419

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, PubWEST
indoximod, 1-methyl-D-tryptophan, salt, hydrochloride, mesylate/methanesulfonate, phosphate, hydrogen phosphate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0377307 A1 (MUNN et al.) 25 December 2014 (25.12.2014) para [0008], [0053], [0062]	1-6, 15-20 and 29-30
Y	US 3,825,559 A (TAZUKE et al.) 23 July 1974 (23.07.1974) col 3, ln 25-40; col 5, ln 10 to col 6, ln 2	1-6, 15-20 and 29-30
Y	US 5,185,157 A (CASTON) 09 February 1993 (09.02.1993) col 10, ln 33-44	3-4, 17-18, (29-30)/(17-18)
Y	US 4,072,691 A (CHIBATA et al.) 07 February 1978 (07.02.1978) col 4, ln 35-47	6, 20, (29-30)/20
A	US 2013/0060048 A1 (TAM et al.) 07 March 2013 (07.03.2013) para [0055]	1-6, 15-20 and 29-30
A	US 2005/0032804 A1 (CYPES et al.) 10 February 2005 (10.02.2005) Entire Document	1-6, 15-20 and 29-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2016 (17.10.2016)	16 NOV 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/35391

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 31-34
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
--Please see attached sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6, 15 20 and (20 30) (in part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/35391

Attachment to Box.No.III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: Claims 1-6, 15-20 and (29-30) (in part) directed to a salt of indoximod according to Formula Ia and a pharmaceutical composition comprising the same.

Group II: Claims 7-8, 21-22 and (29-30) (in part) directed to a salt of indoximod according to Formula Ib and a pharmaceutical composition comprising the same.

Group III: Claims 9-14, 23-28 and (29-30) (in part) directed to a prodrug of indoximod according to Formula 2, and a pharmaceutical composition containing the same.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I includes the technical feature of a salt of Formula Ia, not required by Groups II-III.

Group II includes the technical feature of a salt of Formula Ib, not required by Groups I and III.

Group III includes the technical feature of a prodrug of Formula 2, not required by Groups I-II.

Common technical features:

Groups I-III share the technical feature of indoximod and a pharmaceutical composition comprising the same.

This shared technical feature, however, does not provide a contribution over the prior art as being anticipated by US 8,232,313 B2 to Munn et al. published on 31 July 2012 (hereinafter 'Munn') which discloses a pharmaceutical composition comprising 1-methyl-D-tryptophan also known as indoximod (abstract; col 11, ln 5-7; col 12, ln 9-24).

Groups I and II further share the technical feature of a salt of indoximod.

This shared technical feature, however, does not provide a contribution over the prior art as being obvious over Munn in view of US 3,825,559 A to Tazuke et al. published on 23 July 1974 (hereinafter 'Tazuke').

Munn discloses indoximod (col 11, ln 5-7, 1-methyl-D-tryptophan) but does not disclose a salt of indoximod. However, Tazuke teaches an acid addition salt of D-tryptophan isolated by resolution of DL-tryptophan hydrochloride formed by treating tryptophan with hydrochloric acid (col 3, ln 25-40; col 5, ln 10 to col 6, ln 2, D-tryptophan-1-hydrochloride). It would have been obvious to one of ordinary skill in the art to produce the hydrochloride salt of indoximod for therapeutic use, by applying the method of Tazuke to indoximod disclosed in Munn, because both Munn and Tazuke teach tryptophan compounds.

As said compound and salt were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I-III. Groups I-III thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 31-34 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are, therefore, not included in the above analysis.

(19)中华人民共和国国家知识产权局

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A61K 31/198(2006.01)
A61K 31/661(2006.01)

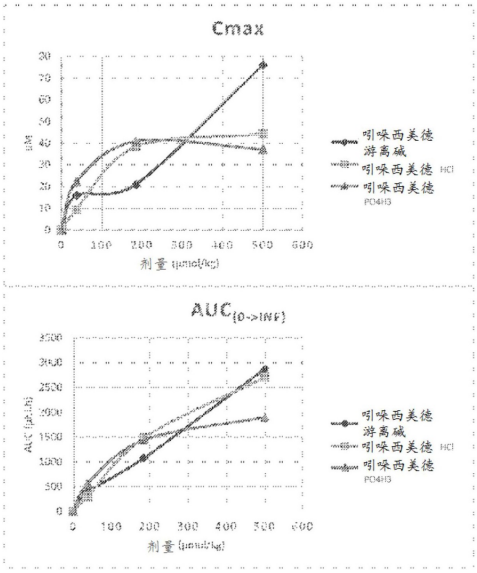
权利要求书8页 说明书78页 附图6页

(54)发明名称

1-甲基-D-色氨酸的盐和前药

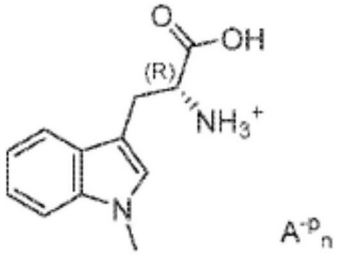
(57)摘要

本发明提供了吲哚西美德前药和盐化合物及包含吲哚西美德盐和前药的药物组合物，其在需要由吲哚胺-2,3-双加氧酶途径介导的免疫抑制治疗的患者，诸如患有癌症或慢性传染病的患者中，相较于直接施用吲哚西美德产生了提高的血浆浓度和吲哚西美德暴露。



CN 107847486 A

1.一种根据式1a的吲哚西美德的盐：



式 1a

其中$A^{-p}{}_n$是呈电离态-p的无机或有机阴离子，所述阴离子以确保分子电中性的化学计量比n存在。

2.如权利要求1所述的盐，其中$A^{-p}{}_n$是选自由以下组成的组的阴离子：氯离子、磷酸根、硫酸根、甲磺酸根、苯磺酸根、乙酸根、抗坏血酸根、天冬氨酸根、谷氨酸根、戊二酸根、乳酸根、马来酸根、丙二酸根、草酸根、丁二酸根、富马酸根、酒石酸根和柠檬酸根，其中所述电离态-p分别是-1、-2或-3且所述化学计量比n分别是1、1/2或1/3，使得其满足电中性的化学计量条件。

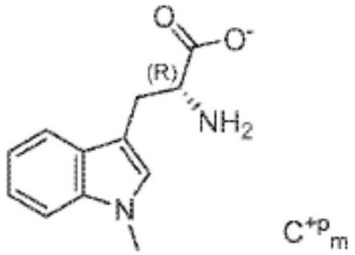
3.如权利要求2所述的盐，其中所述磷酸根是HPO_4^{-2}，所述HPO_4^{-2}以0.5的化学计量比n存在。

4.如权利要求2所述的盐，其中所述磷酸根是HPO_4^{-}，所述HPO_4^{-}以1的化学计量比n存在。

5.如权利要求1所述的盐，其中所述阴离子A^{-pn}是Cl^{-}，所述Cl^{-}以1的化学计量比n存在。

6.如权利要求2所述的盐，其中所述甲磺酸根是$CH_3SO_3^{-}$，所述$CH_3SO_3^{-}$以1的化学计量比n存在。

7.一种根据式1b的吲哚西美德的盐：

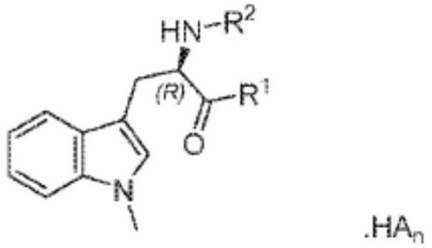


式 1b

其中$C^{+p}{}_m$是呈电离态+p的无机阳离子，所述阳离子以确保所述盐的分子电中性的化学计量比m存在。

8.如权利要求7所述的盐，其中$C^{+p}{}_m$选自由以下组成的组：Li^{+}、Na^{+}、K^{+}、Mg^{+2}和Ca^{+2}，其中当p是+1时m是1，并且当p是+2时m是1/2。

9.一种根据式2的呈游离碱或盐形式的吲哚西美德的前药：

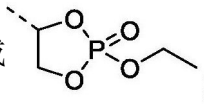


式 2

其中：

(a) R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$、$-OC_{1-3}$烷基$-R^3$、$-NHC^{(S)}HR^4(COOH)$、$-NHC^{(R)}HR^4(COOH)$、$-OC_{1-6}$烷基R^6、$-OC_{1-2}$烷基$-C^{(S)}H(NH_2)(COOH)$或$-OC_{1-2}$烷基$-C^{(R)}H(NH_2)(COOH)$；

(b) R^2是H、$-C(O)C^{(S)}H(NH_2)R^4$、$-C(O)C^{(R)}H(NH_2)R^4$、$-C(O)CH_2C^{(S)}H(NH_2)$、$-C(O)OCH_3$、$-C(O)OR^5$或$-C(O)NHR^5$；

(c) R^3是四氢吡喃或  ；

(d) R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、C_{1-5}烷基SC_{1-5}烷基、C_{1-5}烷基OC_{1-5}烷基、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

(e) 当R^4不是H时$C^{(S)}$和$C^{(R)}$分别是具有S或R立体化学的碳；

(f) R^5是H、C_{1-6}烷基R^6或R^6

(g) R^6是H、芳基、烷基芳基、杂芳基、环烷基或杂环烷基，其中所述芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

(h) 每个R^7独立地是卤素、氰基、硝基、-OR、$-N(R)_2$、-SR、-C(O)OR、C_{1-6}烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、-C(O)R、-S(O)R、-S(O)OR、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、-OC(O)R、-OC(O)OR、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$，其中R是H或C_{1-4}烷基；

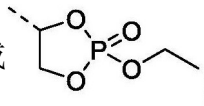
前提是当R^2是H时R^1不能是-OH，并且所述化合物不能是N^{α}-叔丁氧基羰基-1-甲基-D-色氨酸、N^{α}-苄基-1-甲基-D-色氨酸乙酯或N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯；且

HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸，其中所述酸的化学计量比n是0、0.5、1或2，使得所述前药是电中性的。

10.如权利要求9所述的前药，其中：

(a) R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$；

(b) R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

(c) R^3是四氢吡喃或  ；

(d) R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、$-(CH_2)_{1-3}SCH_3$、$-(CH_2)_{1-3}OCH_3-CH_2-R^6$、$-CH_2OH$、-CH(OH)

CH_3、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

(e)当R^4不是H时，$C^{(S)}$是具有S立体化学的碳；

(f)R^6是H、芳基、烷基芳基、杂芳基、环烷基或杂环烷基，其中所述芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

(g)每个R^7独立地是卤素、氰基、硝基、$-OR$、$-N(R)_2$、$-SR$、$-C(O)OR$、C_{1-6}烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$，其中R是H或C_{1-4}烷基；

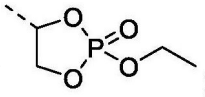
前提是当R^2是H时R^1不能是-OH；且

HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸，其中所述化学计量比n是0、0.5、1或2，使得所述前药是电中性的。

11.如权利要求9所述的前药，其中：

(a)R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$；

(b)R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$；

(c)R^3是四氢吡喃或  ；

(d)R^4是H、$-C_{1-5}$烷基、$-(CH_2)_2SCH_3$、$-CH_2-R^6$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$或$-(CH_2)_{1-4}NH_2$；

(e)当R^4不是H时，$C^{(S)}$是具有S立体化学的碳；

(f)R^6是H、芳基、烷基芳基或杂芳基，其中所述芳基、烷基芳基或杂芳基被一个R^7基团任选地取代；

(g)每个R^7独立地是卤素、氰基、硝基、$-OR$、$-N(R)_2$、$-SR$、$-C(O)OR$、$-C_{1-6}$烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$，其中R是H或C_{1-4}烷基；

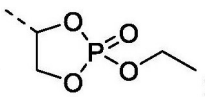
前提是当R^2是H时R^1不能是-OH；

HA_n是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)，其中所述酸的化学计量比n是0、0.5、1或2，使得所述前药是电中性的。

12.如权利要求9所述的前药，其中

(a)R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$；

(b)R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$；

(c)R^3是四氢吡喃或  ；

(d)R^4是$-CH_2CH(CH_3)_2$、$-(CH_2)_2SCH_3$、$-C^{(S)}H(CH_3)CH_2CH_3$、$-CH_2-R^6$、$-(CH_2)_2C(O)NH_2$、$-(CH_2)_3C(O)OH$或$-(CH_2)_4NH_2$；

(e)$C^{(S)}$是具有S立体化学的碳；

(f)R^6是苯基；

前提是当R^2是H时R^1不能是-OH；

HA_n是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)，并且其中所述酸的化学计量比n是0、0.5、1或2，使得所述前药是电中性的.

13.如权利要求9所述的前药，其中：

(a)R^1是-OC_{2-3}烷基或-$OCH_2CH(OH)CH_2OH$；

(b)R^2是H或-$C(O)C^{(S)}H(NH_2)R^4$；

(c)R^4是-$CH_2CH(CH_3)_2$、-$(CH_2)_2SCH_3$或-$(CH_2)_2C(O)NH_2$；

(d)$C^{(S)}$是具有S立体化学的碳；

前提是当R^2是H时R^1不能是-OH；

HA_n是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)或$C_6H_5SO_3H$(苄基磺酸)；并且其中所述酸的化学计量比n是0、0.5、1或2，使得所述前药是电中性的。

14.一种包含以下化合物中一种的前药：

N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯；

N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯；

1-甲基-D-色氨酸2,3-二羟丙酯；

N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-异亮氨酰)-1-甲基-D-色氨酸乙酯；

N^{α}-(L-甘氨酰)-1-甲基-D-色氨酸；

(S)-5-氨基-6-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-6-氧代己酸；

N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-苯基丙氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯；

1-甲基-D-色氨酸2-(二甲基氨基)乙酯；

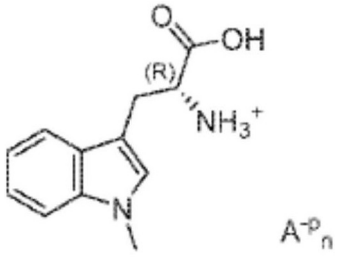
1-甲基-D-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯；

1-甲基-D-色氨酸2-(四氢-2H-吡喃-4-基)乙酯；

1-甲基-D-色氨酸乙酯；或

1-甲基-D-色氨酸异丙酯。

15.一种根据式1a的吲哚西美德的药物组合物：



式 1a

其中$A^{-p}{}_n$是呈电离态-p的无机或有机阴离子，所述阴离子以确保分子电中性的化学计量比n存在。

16.如权利要求15所述的药物组合物，其中$A^{-p}{}_n$是选自由以下组成的组的阴离子：氯离子、磷酸根、硫酸根、甲磺酸根、苯磺酸根、乙酸根、抗坏血酸根、天冬氨酸根、谷氨酸根、戊二酸根、乳酸根、马来酸根、丙二酸根、草酸根、丁二酸根、富马酸根、酒石酸根和柠檬酸根，其中所述电离态p分别是-1、-2或-3且所述化学计量比n分别是1、1/2或1/3，使得其满足电中性的化学计量条件。

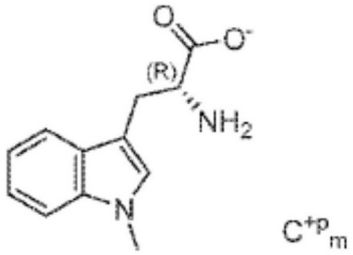
17.如权利要求16所述的药物组合物，其中所述磷酸根是HPO_4^{-2}，所述HPO_4^{-2}以0.5的化学计量比n存在。

18.如权利要求16所述的药物组合物，其中所述磷酸根是HPO4-，所述HPO_4^{-}以1的化学计量比n存在。

19.如权利要求15所述的药物组合物，其中所述阴离子A^{-pn}是Cl^-，所述Cl^-以1的化学计量比n存在。

20.如权利要求16所述的药物组合物，其中所述甲磺酸根是$CH_3SO_3^-$，所述$CH_3SO_3^-$以1的化学计量比n存在。

21.一种根据式1b的吲哚西美德的药物组合物：

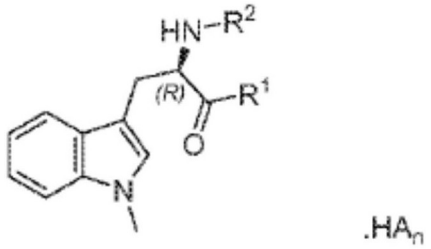


式1b

其中$C^{+p}{}_m$是呈电离态+p的阳离子，所述阳离子以确保所述盐的分子电中性的化学计量比m存在。

22.如权利要求21所述的药物组合物，其中$C^{+p}{}_m$选自由以下组成的组：Li^+、Na^+、K^+、Mg^{+2}和Ca^{+2}，其中当p是+1时m是1且当p是+2时m是1/2。

23.一种根据式2的呈游离碱或盐形式的吲哚西美德的药物组合物：



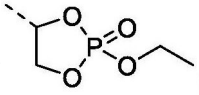
式 2

其中：

(a) R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$、$-OC_{1-3}$烷基$-R^3$、$-NHC^{(S)}HR^4(COOH)$、$-NHC^{(R)}HR^4(COOH)$、$-OC_{1-6}$烷基R^6、$-OC_{1-2}$烷基、$-C^{(S)}H(NH_2)(COOH)$或$-OC_{1-2}$烷基$-C^{(R)}H$

$(NH_2)(COOH)$；

(b) R^2是H、$-C(O)C^{(S)}H(NH_2)R^4$、$-C(O)C^{(R)}H(NH_2)R^4$、$-C(O)CH_2C^{(S)}H(NH_2)$、$-C(O)OCH_3$、$-C(O)OR^5$或$-C(O)NHR^5$；

(c) R^3是四氢吡喃或  ；

(d) R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、C_{1-5}烷基SC_{1-5}烷基、C_{1-5}烷基OC_{1-5}烷基、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

(e) 当R^4不是H时，$C^{(S)}$和$C^{(R)}$分别是具有S或R立体化学的碳；

(f) R^5是H、C_{1-6}烷基R^6或R^6

(g) R^6是H、芳基、烷基芳基、杂芳基、环烷基或杂环烷基，其中所述芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

(h) 每个R^7独立地是卤素、氰基、硝基、$-OR$、$-N(R)_2$、$-SR$、$-C(O)OR$、C_{1-6}烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$，其中R是H或C_{1-4}烷基；

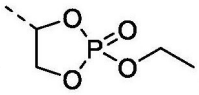
前提是当R^2是H时R^1不能是-OH，并且所述化合物不能是N^{α}-叔丁氧基羰基-1-甲基-D-色氨酸、N^{α}-苄基-1-甲基-D-色氨酸乙酯或N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯；且

HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸，其中所述酸的化学计量比n是0、0.5、1或2，使得所述前药是电中性的。

24.如权利要求23所述的药物组合物，其中：

(a) R^1是$-OH$、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$；

(b) R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

(c) R^3是四氢吡喃或  ；

(d) R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、$-(CH_2)_{1-3}SCH_3$、$-(CH_2)_{1-3}OCH_3$、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

(e) 当R^4不是H时$C^{(S)}$是具有S立体化学的碳；

(f) R^6是H、芳基、烷基芳基、杂芳基、环烷基或杂环烷基，其中所述芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

(g) 每个R^7独立地是卤素、氰基、硝基、$-OR$、$-N(R)_2$、$-SR$、$-C(O)OR$、C_{1-6}烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$，其中R是H或C_{1-4}烷基；

前提是当R^2是H时R^1不能是-OH；且

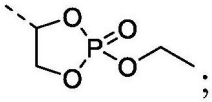
HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺

酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸,其中所述化学计量比n是0、0.5、1或2,使得所述前药是电中性的。

25.如权利要求23所述的药物组合物,其中:

(a) R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$;

(b) R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^3是四氢吡喃或  ;

(d) R^4是H、$-C_{1-5}$烷基、$-(CH_2)_2SCH_3$、$-CH_2-R^6$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$或$-(CH_2)_{1-4}NH_2$;

(e) 当R^4不是H时,$C^{(S)}$是具有S立体化学的碳;

(f) R^6是H、芳基、烷基芳基或杂芳基,其中所述芳基、烷基芳基或杂芳基被一个R^7基团任选地取代;

(g) 每个R^7独立地是卤素、氰基、硝基、-OR、$-N(R)_2$、-SR、-C(O)OR、$-C_{1-6}$烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、-OC(O)R、-OC(O)OR、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$和$-N(R)C(O)N(R)_2$,其中R是H或C_{1-4}烷基;

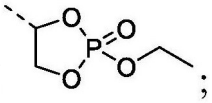
前提是当R^2是H时R^1不能是-OH;

HA_n是选自由以下组成的组的酸:PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)和$C_6H_5SO_3H$(苄基磺酸),其中所述酸的化学计量比n是0、0.5、1或2,使得所述前药是电中性的。

26.如权利要求23所述的药物组合物,其中:

(a) R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$;

(b) R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$;

(c) R^3是四氢吡喃或  ;

(d) R^4是$-CH_2CH(CH_3)_2$、$-(CH_2)_2SCH_3$、$-C^{(S)}H(CH_3)CH_2CH_3$、$-CH_2-R^6$、$-(CH_2)_2C(O)NH_2$、$-(CH_2)_3C(O)OH$或$-(CH_2)_4NH_2$;

(e) $C^{(S)}$是具有S立体化学的碳;

(f) R^6是苯基;

前提是当R^2是H时R^1不能是-OH;

HA_n是选自由以下组成的组的酸:PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)和$C_6H_5SO_3H$(苄基磺酸),并且其中所述酸的化学计量比n是0、0.5、1或2,使得所述前药是电中性的。

27.如权利要求23所述的药物组合物,其中:

(e) R^1是$-OC_{2-3}$烷基或$-OCH_2CH(OH)CH_2OH$;

(f) R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$;

(g) R^4是$-CH_2CH(CH_3)_2$、$-(CH_2)_2SCH_3$或$-(CH_2)_2C(O)NH_2$;

(h)$C^{(S)}$是具有S立体化学的碳；

前提是当R^2是H时R^1不能是-OH，

HA_n是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)或$C_6H_5SO_3H$(苄基磺酸)；并且其中所述酸的化学计量比n是0、0.5、1或2，使得所述前药是电中性的。

28.一种包含以下化合物中一种的药物组合物：

N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯；

N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯；

1-甲基-D-色氨酸2,3-二羟丙酯；

N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-异亮氨酰)-1-甲基-D-色氨酸乙酯；

N^{α}-(L-甘氨酰)-1-甲基-D-色氨酸；

(S)-5-氨基-6-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-6-氧代己酸；

N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-苯基丙氨酰)-1-甲基-D-色氨酸；

N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯；

1-甲基-D-色氨酸2-(二甲基氨基)乙酯；

1-甲基-D-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯；

1-甲基-D-色氨酸2-(四氢-2H-吡喃-4-基)乙酯；

1-甲基-D-色氨酸乙酯；或

1-甲基-D-色氨酸异丙酯。

29.如权利要求15-28中任一项所述的药物组合物，其中所述组合物是固体胶囊剂、片剂或丸剂。

30.如权利要求15-28中任一项所述的药物组合物，其中所述组合物是可溶性胶囊剂。

31.一种在有需要的受试者中使用如权利要求15-30中任一项所述的药物组合物调节吲哚胺-2,3-双加氧酶途径活性的方法，所述方法包括向所述受试者经口施用在适当的药物形式或媒介物中的治疗有效量的所述组合物。

32.一种在有需要的受试者中使用如权利要求15-30中任一项所述的药物组合物治疗癌症的方法，所述方法包括向所述受试者经口施用在适当的药物形式或媒介物中的治疗有效量的所述组合物。

33.一种在有需要的受试者中使用如权利要求15-30中任一项所述的药物组合物治疗与癌症相关的肿瘤-特异性免疫抑制的方法，所述方法包括向所述受试者经口施用在适当的药物形式或媒介物中的足够量的所述组合物。

34.一种在有需要的受试者中使用如权利要求15-30中任一项所述的药物组合物治疗与传染病(如HIV-1感染、流感)相关的免疫抑制的方法，所述方法包括向所述受试者经口施用在适当的药物形式或媒介物中的足够量的所述组合物。

1-甲基-D-色氨酸的盐和前药

[0001] 相关申请的交叉引用

[0002] 本申请要求2015年7月24日提交的美国临时申请序列号62/196,671和2016年3月9日提交的美国临时申请序列号62/305,748的优先权,其全部内容通过引用在此整体并入。

[0003] 发明背景

发明领域

[0004] 本公开涉及用于抑制吲哚胺-2,3-双加氧酶途径的化合物,特别是具有相对于吲哚西美德(indoximod)具有增强的药代动力学特性的吲哚西美德的盐和前药

[0005] 相关技术的概述

[0006] 色氨酸降解成犬尿氨酸通过由类浆细胞树突细胞、胎盘细胞、上皮细胞和肿瘤细胞表达的吲哚胺-2,3-双加氧酶(IDO1)介导,并通过主要由肝脏和肿瘤细胞表达的色氨酸-2,3-双加氧酶(TDO2)介导。

[0007] IDO1通过在反应性效应T细胞上引发无反应性并通过调节调节性T细胞(Treg)的分化和活化来在调节免疫应答中起重要作用。从更一般的观点来看,IDO酶参与包括所有直接或间接有助于调节依赖于IDO活性的免疫抑制功能的蛋白质(包括介导IDO表达诱导、由还原酶激活酶促活性、调节活性的翻译后修饰、蛋白质降解以及由低浓度Trp和存在Trp分解代谢物[统称为犬尿氨酸(Kyns)]引发的信号的解译和传播)的途径,包括整合到通用控制非阻抑-2(GCN2)途径、芳基烃受体(AhR)途径和哺乳动物雷帕霉素靶标(mTOR)途径的分解代谢应激传感器。这个在中心处具有IDO的整合下游调控途径的概念已经出现在由多个研究组进行的多个模型系统的研究中,并且这个注释对于对于了解IDO途径如何被诱导、IDO如何发挥下游效应以及直接靶向IDO或靶向IDO途径的其它组件的IDO途径抑制剂的作用机制可能是非常关键的[1,2]。

[0008] 因此,直接药理学抑制IDO1酶促活性或抑制激活IDO1酶的上游因子或抑制IDO1酶促活性的下游效应应通过多个机制刺激免疫应答,所述机制可能涉及阻止效应T细胞的无反应性、重新激活无反应性效应T细胞、预防调节性T细胞的激活、促进Treg至促炎症TH17细胞的表型转化,并促进免疫抑制树突细胞至免疫刺激树突细胞的表型重编程。

[0009] 由于这些原因,许多IDO的酶促抑制剂已经被描述,并正在开发用于治疗或预防IDO相关疾病,诸如癌症和传染性疾病。文献中已经描述了作为竞争性或非竞争性抑制剂来抑制IDO酶促活性的许多分子,例如在专利申请WO2012142237、WO2014159248、WO2011056652、WO2009132238、WO2009073620、WO2008115804、WO2014150646、WO2014150677、WO2015002918、WO2015006520、WO2014141110、WO2014/186035、WO2014/081689、US7714139、US8476454、US7705022、US 8993605、US 8846726、US 8951536、US7598287中。

[0010] 临床前模型中研究的第一IDO途径抑制剂之一是1-甲基-DL-色氨酸(1mT),一种对映异构体的外消旋混合物,其显示可介导小鼠中同种异体胎儿的免疫依赖性排斥[3]和化疗和放疗的抗肿瘤活性的免疫依赖性增强[4]。这些对映异构体的每一种显示了不同的生

物特性。已经证明1-甲基-L-色氨酸(L1mT)在使用纯化的重组IDO1酶的无细胞测定中和在用INFγ处理的肿瘤细胞中或在异源启动子控制下编码IDO1的表达载体转染的肿瘤细胞系中抑制IDO1酶促活性(Ki＝34μM,[5]),而D异构体(吲哚西美德)在这些类型的测定中不抑制酶促活性[6]。尽管如此,两种异构体都能够在使用IDO+树突细胞作为刺激细胞的MLR测定中或者使用从肿瘤引流淋巴结分离的IDO+DC进行的同基因抗原依赖性T细胞增殖测定恢复T细胞增殖[6]。在存在IDO+DC的这种类型的测定中,T细胞不增殖。然而,这些抑制剂对IDO途径的抑制恢复了T细胞的增殖能力。有趣的是,两种异构体在该测定中显示不同的效力,其中吲哚西美德比L1mT(EC50＝80-100μM)或外消旋混合物(80-100μM)更有效(EC 50＝＝30μM)[6]。此外,尽管事实上吲哚西美德在其它类型的测定中不显示出酶促活性的抑制,但是其显示出在这种共培养测定中抑制酶促活性,如通过降低的Trp降解和Kyn合成所见。

[0011] 一个有点令人困惑的问题是,吲哚西美德在体外不显示IDO1酶促活性的抑制,但是以某种方式模拟在体内或在基于细胞的测定中的IDO1抑制的生物学后果。许多研究实验室的实验证据指出,吲哚西美德参与了IDO1途径的抑制。这可能发生的几种可能的机制是:1)抑制IDO1的同种型,2)抑制IDO2,3)可替代形成吲哚西美德-衍生的代谢物,4)吲哚西美德外消旋化为L1mT,5)抑制Trp转运,6)通过形成吲哚西美德-tRNA复合物抑制GCN2途径,7)抑制参与Trp感应的酶诸如WARS1或WARS2,8)在氨基酸耗竭诱导的应激条件下自噬的改变或9)在氨基酸缺乏条件下失活mTOR的旁路机制[7]。这些机制未必是相互排斥的,并且到目前为止与当前的实验数据是相容的。需要进一步的研究来阐明这些生物化学机制中的哪一种负责吲哚西美德的生物活性。

[0012] 吲哚西美德在体内和体外解除免疫抑制的生物学活性得到了在许多实验室中在小鼠临床前模型中进行的研究的支持。吲哚西美德已经在以下生物学测定中证明了活性:

[0013] 1.联合化疗,吲哚西美德在异位黑素瘤、结肠肿瘤和肺肿瘤的动物模型中以及原位和内生乳腺肿瘤模型中表现出抗肿瘤作用。吲哚西美德的抗肿瘤作用在裸小鼠和IDO1-KO小鼠中丧失[6]。

[0014] 2.吲哚西美德可以预防体内成熟Treg的活化过程,并促进Treg的体外和体内反式分化为促炎性TH17样T细胞[8,9]。

[0015] 3.在肿瘤疫苗接种方案中,两种不同抗肿瘤疫苗与吲哚西美德的组合可有效将较高比例的Treg细胞转化成TH17样T细胞,同时具有抗肿瘤作用[9]。

[0016] 4.在黑素瘤模型中,抗CTLA4(伊匹单抗)和吲哚西美德的组合导致协同抗肿瘤作用[10]。

[0017] 5.在体内,当在可移植的黑素瘤及可移植(4T1)和内生(mmTV-neu)乳腺癌的小鼠模型中测试时,吲哚西美德在使用环磷酰胺、紫杉醇或吉西他滨的化学-免疫治疗方案中作为抗癌剂更有效[6]。

[0018] 6.IDO1通过依赖于GCN2的机制经由Trp耗竭和Trp分解代谢物存在的综合作用也参与了将初始CD4 T细胞分化成Treg[11,12]。在吲哚西美德的存在下,这种转化在体内中断。

[0019] 7.类似地,IDO+pDC也参与体内成熟Treg的激活,这也需要在Treg群体中完整的GCN2途径。这种现象可以通过过量的Trp或吲哚西美德来防止[8]。

[0020] 8.除了防止成熟的Treg细胞的激活外,吲哚西美德可以在体外和体内介导抑制性

FoxP3$^+$Treg转化为促炎性TH17细胞。Treg至TH17细胞的这种转化需要在pDC中存在抗原或B7接合，以及在pDC中存在功能性IDO1和GCN2基因。吲哚西美德能够模拟IDO1或GCN2基因消融的表型结果[9]，因此支持其在IDO途径抑制中的作用。

[0021] 9.使用IDO1-KO小鼠或源自IDO1-KO小鼠的pDC的抗肿瘤和免疫学研究表明，在缺乏功能性IDO1的遗传背景的情况下，吲哚西美德的有益作用丧失[6]。特别地，观察到IDO1-KO小鼠发展肿瘤，其对于用吲哚西美德治疗联合化疗不敏感。另外，源自IDO1-KO小鼠的肿瘤引流淋巴结的pDC能够刺激培养物中T细胞的增殖至与IDO(-)APC相同的程度。这些观察结果被解释为IDO1作为吲哚西美德药理学靶标的遗传验证。然而，这也可以解释为吲哚西美德阻断IDO途径内的一些其它作用点。

[0022] 10.还通过施用其它有据记录的IDO1抑制剂(即在体外和基于细胞的测定中抑制IDO1的促酶活性的分子)，诸如5-Br-芸苔宁、甲萘醌、甲基-硫代乙内酰脲-色氨酸及苯基咪唑类似物(未公布)，来重现通过施用吲哚西美德获得的抗肿瘤和免疫学观察结果，从而验证了IDO1途径作为药理学靶标[4,13,14]。

[0023] 11.在临床前动物模型中，吲哚西美德的体内药效动力学作用主要在肿瘤引流淋巴结中发现，其中该作用被认为是CD8α+细胞的激活和增殖、FoxP3+Treg的数量减少、Treg(CD40L$^-$)重编程为免疫刺激T细胞(CD40L$^+$)，并将IDO$^+$抗原呈递细胞从CD11c$^+$/CD80/86$^-$重编程为CD80/86$^+$表型。

[0024] 由于这些原因，正在癌症适应症的人类临床试验中研究吲哚西美德。已经在几种癌症适应症中研究了与不同的化学治疗剂和生物学免疫治疗剂、诸如多西他赛、紫杉醇、吉西他滨、Nab-紫杉醇、替莫唑胺、伊匹单抗、西普鲁塞-T或疫苗组合的吲哚西美德。

[0025] 吲哚西美德是可经口生物利用的，具有有利的药代动力学(PK)特性(Tmax：约3h；半衰期：约10h)和优异的安全性。患者的药代动力学研究表明，吲哚西美德显示了在高达800mg/剂量的剂量下的线性PK曲线，最大血浆浓度(Cmax)为15μM且药物暴露(AUC$_{(0-最后)}$)水平为约100μM.h。然而，增加剂量超过800mg/剂量至2000mg/剂量，不会导致Cmax或药物暴露的线性或成比例增加，因此潜在地限制了该研究药物的治疗活性。

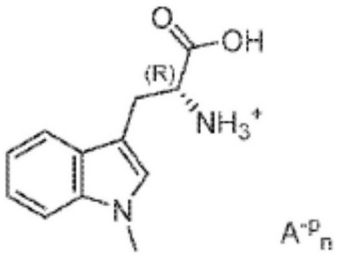
[0026] 混合淋巴细胞应答(MLR)T细胞增殖测定显示，在高于30μM的吲哚西美德浓度下，处于IDO$^+$环境中的T细胞恢复其增殖能力的约50％。鼠抗肿瘤实验表明，当向小鼠用于饮用水中的吲哚西美德以3mg/mL(约500mg/kg/天)给药或以200mg/kg bid经口给药，导致Cmax高于20μM且暴露大于300μM.h时，观察到吲哚西美德的生物学作用。由于这些原因，希望在人临床试验中将Cmax和暴露于吲哚西美德增加，以使其达到治疗活性所需的水平。然而，该药物的非线性药代动力学曲线使得不可能通过增加给予患者的剂量来解决这个问题。

[0027] 由于上述原因，我们研究了不同的吲哚西美德制剂诸如喷雾干燥分散体或盐或吲哚西美德前药(呈不同盐形式)是否会增加溶解度和吸收率，或将血液清除率降低至增加最大浓度和暴露于吲哚西美德的水平。此外，我们寻找当经口且以丸剂(胶囊剂或片剂)剂量制剂给药时可能导致暴露参数增加的前药及其盐。

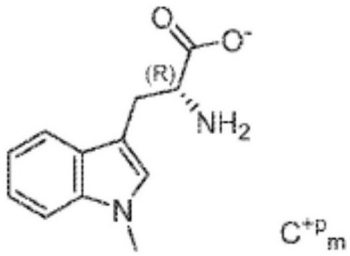
[0028] 这些研究的结果表明，几种选定前药导致暴露参数增加；并且体外溶解度和体内暴露的增加可以通过经口施用后的几种吲哚西美德盐来实现。

[0029] 发明概述

[0030] 一方面，本发明描述了根据式1a和1b的化合物和包含化合物的药物组合物

[0031] 

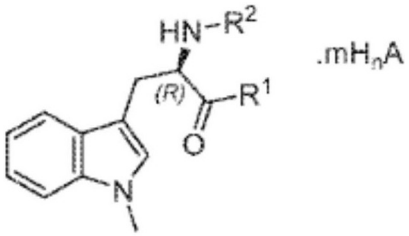
式 1a



式 1b

[0032] 其中$A^{-p}{}_n$是无机或有机阴离子且$C^{+p}{}_m$是如本文所定义的无机阳离子。

[0033] 另一方面，本发明包括根据式(2)的化合物和包含化合物的药物组合物

[0034] 

式 2

[0035] 其中R^1、R^2和mH_nA在本文中定义

[0036] 另一方面，本公开提供了

[0037] a)包含式1a、1b或式2的化合物的药物组合物，其导致在经口施用至受试者后相较于施用等摩尔剂量的配制为游离碱的吲哚西美德升高的至1-甲基-D-色氨酸(吲哚西美德)的暴露和最大浓度。

[0038] b)在有需要的受试者中使用包含式1a、1b或2的化合物的组合物调节吲哚胺-2,3-双加氧酶途径活性的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的足够量的此类组合物。

[0039] c)在有需要的受试者中使用包含式1a、1b或2的化合物的组合物治疗癌症的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的足够量的此类组合物。

[0040] d)在有需要的受试者中使用包含式1a、1b或2的化合物的组合物治疗与癌症相关的肿瘤-特异性免疫抑制的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的足够量的此类组合物。

[0041] e)在有需要的受试者中使用包含式1a、1b或2的化合物的组合物治疗与传染病(如HIV-1感染、流感)相关的免疫抑制的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的足够量的此类组合物。

[0042] 附图简述

[0043] 图1显示了呈游离碱及其盐酸盐形式的吲哚西美德的XRPD谱图。

[0044] 图2显示了吲哚西美德盐酸盐的热重(TGA)和差示扫描量热法(DSC)分析。

[0045] 图3显示了呈游离碱及其磷酸盐形式的吲哚西美德的XRPD谱图。

[0046] 图4显示了吲哚西美德磷酸盐的热重(TGA)和差示扫描量热法(DSC)分析。

[0047] 图5显示了于各种溶剂溶液和刺激生物流体中的吲哚西美德及其盐相对于pH的测量溶解度曲线。

[0048] 图6显示了以经口胶囊形式给予大鼠的吲哚西美德相对于摩尔剂量的吲哚西美德、吲哚西美德盐酸盐或吲哚西美德磷酸盐的最大血浆浓度(Cmax)和暴露(AUC_{0-inf})。

[0049] 发明详述

[0050] 吲哚西美德(1-甲基-D-色氨酸,D1mT)是研究的吲哚胺-2,3-双加氧酶(IDO)途径的抑制剂,其结合标准和实验化疗剂和免疫调节剂以及主动免疫疗法在多种癌症适应症的若干人类临床试验中进行了测试。

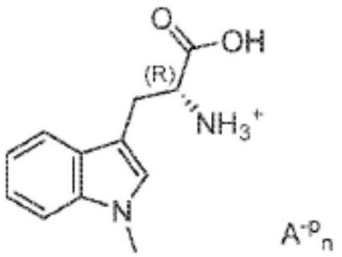
[0051] 在IDO^+树突细胞的存在下,$CD8^+$效应T细胞变得无反应性且不能增殖。此外,调节性T细胞($CD4^+CD25^+FoxP3^+$)在IDO^+DC的存在下被激活,并且能够介导对肿瘤或病毒抗原的全身免疫抑制。吲哚西美德能够恢复这些过程,从而允许效应T细胞增殖并引导Treg重新编程为TH17辅助样表型。在体外测定中,这些作用由吲哚西美德介导,EC 50为约30μM[6]。在临床前鼠肿瘤模型中,抗肿瘤作用、刺激效应T细胞和Treg在引流淋巴结中的重编程需要约500mg/kg的每日剂量,且暴露>300μM.h。

[0052] 在范围为200mg至2000mg/剂量的经口剂量下的人药代动力学实验已经显示药代动力学参数C_{max}和暴露(AUC_{0-inf})在高达约800mg/剂量的范围内随剂量线性增加。在这些剂量下,血浆中的C_{max}达到约15μM的平均值,且AUC_{0-inf}达到约100μM.h。C_{max}和AUC参数在高达2000mg/剂量的较高剂量下,不会显著增加高于这些值。因此,为了获得与在鼠模型中产生免疫调节和抗肿瘤治疗效果的那些吲哚西美德浓度和暴露水平相当的吲哚西美德浓度和暴露水平,增加吲哚西美德的C_{max}和暴露水平将是有用的。

[0053] 本发明描述了式1a、1b和式2的化合物,其在经口施用时产生相较于经口施用等摩尔剂量的吲哚西美德更高的吲哚西美德暴露和最大血清浓度。

[0054] 吲哚西美德的盐

[0055] 在一个实施方案中,公开了吲哚西美德的盐。在一个实施方案中,所述盐具有根据式1a的结构:

[0056] 

式 1a

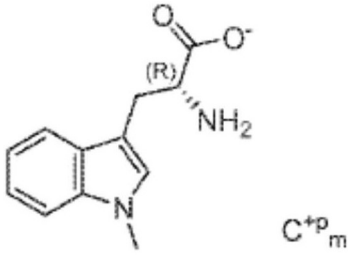
[0057] 其中$A^{-p}{}_n$是无机或有机阴离子呈电离态-p。在一个实施方案中,阴离子以确保分子电中性的化学计量比n存在。

[0058] 在一个实施方案中,阴离子$A^{-p}{}_n$选自由以下组成的组:氯离子、磷酸根、硫酸根、甲磺酸根、苯磺酸根、乙酸根、抗坏血酸根、天冬氨酸根、谷氨酸根、戊二酸根、乳酸根、马来酸根、丙二酸根、草酸根、丁二酸根、富马酸根、酒石酸根和柠檬酸根。在一个实施方案中,阴离子以化学计量比n存在,使得所得的盐是电中性的。因此,在一个实施方案中,阴离子分别具

有-1、-2或-3的电离态p，并且分别以1、1/2或1/3的化学计量比n存在，使得满足电中性的化学计量条件。在一个实施方案中，磷酸根是HPO_4^{-2}且HPO_4^{-2}以0.5的化学计量比n存在。在一个实施方案中，磷酸根是HPO_4^{-}且HPO_4^{-}以1的化学计量比n存在。在一个实施方案中，硫酸根是SO_4^{-2}且SO_4^{-2}以0.5的化学计量比n存在。在一个实施方案中，甲磺酸根是$CH_3SO_3^{-}$且$CH_3SO_3^{-}$以0.5的化学计量比n存在。

[0059] 在另一个实施方案中，阴离子$A^{-p}{}_n$是化学计量比n为1的Cl^-。在另一个优选的实施方案中，阴离子$A^{-p}{}_n$是在化学计量比n为1下的Cl^-且晶形是形式1的无水同种型。

[0060] 在一个实施方案中，所述盐具有根据式1b的结构：

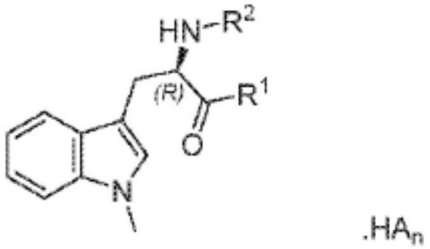
[0061] 

式 1b

[0062] 其中$C^{+p}{}_m$是呈电离态+p的阳离子。在一个实施方案中，阳离子以确保分子电中性的化学计量比m存在。在一个实施方案中，$C^{+p}{}_m$选自由以下组成的组：Li^+、Na^+、K^+、Mg^{+2}和Ca^{+2}。在一个实施方案中，当p是+1时m是1且当p是+2时m是1/2。

[0063] 吲哚西美德前药

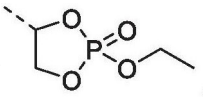
[0064] 在一个实施方案中，公开了吲哚西美德的前药。在一个实施方案中，呈游离碱或盐形式的前药的结构以式2提供：

[0065] 

式 2

[0066] 在一个实施方案中，R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$、$-OC_{1-3}$烷基$-R^3$、$-NHC^{(S)}HR^4(COOH)$、$-NHC^{(R)}HR^4(COOH)$、$-OC_{1-6}$烷基R^6、$-OC_{1-2}$烷基$-C^{(S)}H(NH_2)(COOH)$或$-OC_{1-2}$烷基$-C^{(R)}H(NH2)(COOH)$。在一个实施方案中，R^1是$-NHC^{(S)}HR^4(COOCH_3)$或$-NHC^{(R)}HR^4(COOCH_3)$。

[0067] 在一个实施方案中，R^2是-H、$-C(O)C^{(S)}H(NH_2)R^4$、$-C(O)C^{(R)}H(NH_2)R^4$、$-C(O)CH_2C^{(S)}H(NH_2)-C(O)OCH_3$、$-C(O)OR^5$或$-C(O)NHR^5$。

[0068] 在一个实施方案中，R^3是四氢吡喃或  。

[0069] 在一个实施方案中，R^4是-H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、$-C_{1-5}$烷基SC_{1-5}烷基、$-C_{1-5}$烷基OC_{1-5}烷基、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或-

$(CH_2)_{1-3}NC(=NH_2)NH_2$。

[0070] 在一个实施方案中，当R^4不是-H时，$C^{(S)}$和$C^{(R)}$分别是具有S或R立体化学的碳。

[0071] 在一个实施方案中，R^5是-H、C_{1-6}烷基R^6或R^6。在一个实施方案中，R^6是选自由以下组成的组：-H、芳基、烷基芳基、杂芳基、环烷基和杂环烷基，其中芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代。

[0072] 在一个实施方案中，每个R^7独立地是卤素、氰基、硝基、-OR、$-N(R)_2$、-SR、-C(O)OR、C_{1-6}烷基、C_{1-6}卤代烷基、-C(O)N$(R)_2$、-C(O)R、-S(O)R、-S(O)OR、-S(O)$N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、-OC(O)R、-OC(O)OR、-OC(O)$N(R)_2$、-N(R)C(O)R、-N(R)C(O)OR或-N(R)C(O)$N(R)_2$，其中R是H或C_{1-4}烷基。

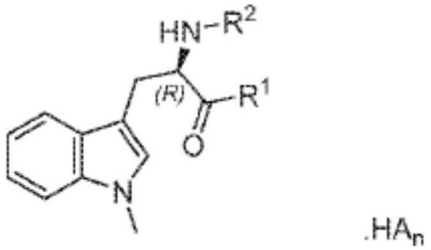
[0073] 在式2的前药的一些实施方案中，当R^2是H时R^1不能是-OH。

[0074] 此外，在所有实施方案中，前药不可能是N^{α}-叔丁氧基羰基-1-甲基-D-色氨酸、N^{α}-苄基-1-甲基-D-色氨酸乙酯或N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯。

[0075] 在一个实施方案中，HA_n是酸。在一个实施方案中，酸HA_n选自由以下组成的组：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苯基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸。

[0076] 在一个实施方案中，酸HA_n以化学计量比n存在，使得所得前药是电中性的。因此，在一个实施方案中，酸HA_n的化学计量比n是0、0.5、1或2，使得前药是电中性的。

[0077] 本发明还提供了呈其游离碱或盐形式的吲哚西美德的前药。在一个实施方案中，吲哚西美德的前药由式2的化合物表示，

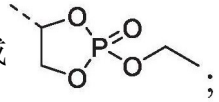
[0078] 

式 2

[0079] 其中

[0080] R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$、$-OC_{1-3}$烷基$-R^3$、$-NHC^{(S)}HR^4(COOH)$、$-NHC^{(R)}HR^4(COOH)$、$-OC_{1-6}$烷基R^6、$-OC_{1-2}$烷基、$-C^{(S)}H(NH_2)(COOH)$或$-OC_{1-2}$烷基$-C^{(R)}H(NH2)(COOH)$；

[0081] R^2是-H、$-C(O)C^{(S)}H(NH_2)R^4$、$-C(O)C^{(R)}H(NH_2)R^4$、$-C(O)CH_2C^{(S)}H(NH_2)-C(O)OCH_3$、$-C(O)OR^5$或$-C(O)NHR^5$、

[0082] R^3是四氢吡喃或 

；

[0083] 其中R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、C_{1-5}烷基SC_{1-5}烷基、$-C_{1-5}$烷基OC_{1-5}烷基、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

[0084] 其中当R^4不是-H时，$C^{(S)}$和$C^{(R)}$分别表示具有S或R立体化学的碳；其中R^5是-H、C_{1-6}烷基R^6；或R^6

[0085] 其中R^6是H、芳基、烷基芳基、杂芳基、环烷基或杂环烷基，其中此类芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

[0086] 其中每个R^7独立地选自卤素、氰基、硝基、-OR、-N(R)$_2$、-SR、-C(O)OR、C_{1-6}烷基、C_{1-6}卤代烷基、-C(O)N(R)$_2$、-C(O)R、-S(O)R、-S(O)OR、-S(O)N(R)$_2$、-S(O)$_2$R、-S(O)$_2$OR、-S(O)$_2$N(R)$_2$、-OC(O)R、-OC(O)OR、-OC(O)N(R)$_2$、-N(R)C(O)R、-N(R)C(O)OR或-N(R)C(O)N(R)$_2$；

[0087] 其中R是-H或C_{1-4}烷基；

[0088] 前提是当R^2是-H时R^1不能是-OH，并且所述化合物不能是

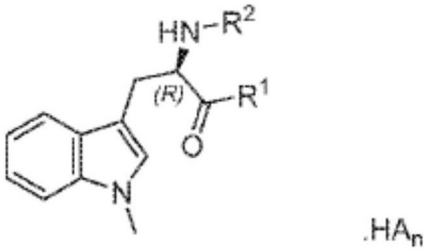
[0089] N^{α}-叔丁氧基羰基-1-甲基-D-色氨酸

[0090] N^{α}-苄基-1-甲基-D-色氨酸乙酯

[0091] N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯

[0092] HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸；且n是确保所得盐的电中性的0、0.5、1或2的化学计量比。

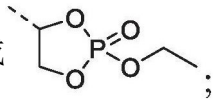
[0093] 在另一个实施方案中，本发明提供了如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药，

[0094] 

式 2

[0095] 其中R^1是-OH、-OC_{2-3}烷基、-$OCH_2CH(OH)CH_2OH$、-$O(CH_2)_2N(CH_3)_2$或-OC_{1-3}烷基-R^3，-

[0096] R^2是H或-C(O)$C^{(S)}$H(NH_2)R^4，

[0097] R^3是四氢吡喃或 

；

[0098] 其中R^4是H、-C_{1-5}烷基、-$(CH_2)_{1-2}SH$、-$(CH_2)_{1-3}SCH_3$、-$(CH_2)_{1-3}OCH_3$、-CH_2-R^6、-CH_2OH、-$CH(OH)CH_3$、-$(CH_2)_{1-2}C(O)NH_2$、-$(CH_2)_{1-3}C(O)OH$、-$(CH_2)_{1-4}NH_2$或-$(CH_2)_{1-3}NC(=NH_2)NH_2$；

[0099] 其中当R^4不是H时$C^{(S)}$表示具有S立体化学的碳；

[0100] 其中R^6是H、芳基、烷基芳基、杂芳基、环烷基、杂环烷基，其中此类芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

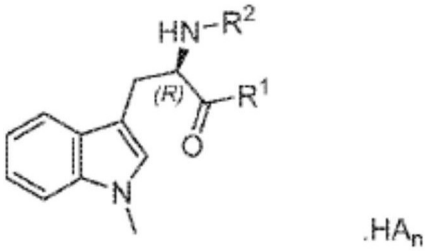
[0101] 其中每个R^7独立地是卤素、氰基、硝基、-OR、-N(R)$_2$、-SR、-C(O)OR、C_{1-6}烷基、C_{1-6}卤代烷基、-C(O)N(R)$_2$、-C(O)R、-S(O)R、-S(O)OR、-S(O)N(R)$_2$、-S(O)$_2$R、-S(O)$_2$OR、-S(O)$_2$N(R)$_2$、-OC(O)R、-OC(O)OR、-OC(O)N(R)$_2$、-N(R)C(O)R、-N(R)C(O)OR或-N(R)C(O)N(R)2；

[0102] 其中R是H或C_{1-4}烷基；

[0103] 前提是当R^2是H时R^1不能是-OH；

[0104] HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸；并且n是确保所得盐的电中性的0、0.5、1或2的化学计量比。

[0105] 在一个优选的实施方案中，本发明提供了如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药，

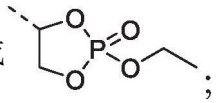
[0106] 

式 2

[0107] 其中

[0108] R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$，

[0109] R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

[0110] R^3是四氢吡喃或 

；

[0111] 其中R^4是H、$-C_{1-5}$烷基、$-CH_2-R^6$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_2SCH_3$、$-(CH_2)_{1-3}C(O)OH$或$-(CH_2)_{1-4}NH_2$

[0112] 其中当R^4不是-H时$C^{(S)}$表示具有S立体化学的碳；

[0113] 其中R^6是-H、芳基、烷基芳基或杂芳基，其中此类芳基、烷基芳基或杂芳基被一个R^7基团任选地取代；

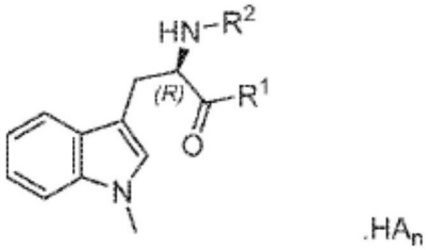
[0114] 其中R^7选自卤素、氰基、硝基、-OR、$-N(R)_2$、-SR、$-C(O)OR$、C_{1-6}烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$；

[0115] 其中R是-H或C_{1-4}烷基；

[0116] 前提是当R^2是H时R^1不能是-OH；

[0117] HA_n是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)或$C_6H_5SO_3H$(苄基磺酸)；且n是确保所得盐的电中性的0、0.5、1或2的化学计量比。

[0118] 在另一个优选的实施方案中，本发明提供了如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药，

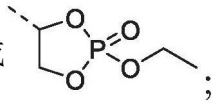
[0119] 

式 2

[0120] 其中

[0121] R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$，

[0122] R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

[0123] R^3是四氢吡喃或  ；

[0124] 其中R^4是$-CH_2CH(CH_3)_2$、$-C^{(S)}H(CH)_3CH_2CH_3$、$-(CH_2)_2SCH_3$、$-CH_2-R^6$、$-(CH_2)_2C(O)NH_2$、$-(CH_2)_3C(O)OH$或$-(CH_2)_4NH_2$；

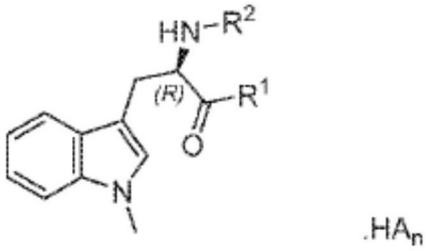
[0125] 其中$C^{(S)}$表示具有S立体化学的碳；

[0126] 其中R^6是苯基；

[0127] 前提是当R^2是H时R^1不能是-OH；

[0128] HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)HSO_3CH_3(甲基磺酸)和$C_6H_5SO_3H$(苄基磺酸)，并且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

[0129] 在最优选的实施方案中，本发明提供了如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药，

[0130] 

式 2

[0131] 其中

[0132] R^1是$-OC_{2-3}$烷基或$-OCH_2CH(OH)CH_2OH$，

[0133] R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

[0134] 其中R^4是$-CH_2CH(CH_3)_2$、$-(CH_2)_2SCH_3$或$-(CH_2)_2C(O)NH_2$；

[0135] 其中$C^{(S)}$表示具有S立体化学的碳

[0136] 前提是当R^2是H时R^1不能是-OH，

[0137] HA是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)HSO_3CH_3(甲基磺酸)或$C_6H_5SO_3H$(苄基磺酸)；且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

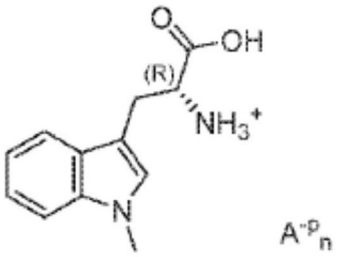
[0138] 在一个优选的实施方案中，本发明提供了如由表1中呈现的式2化合物表示的呈游离碱或药学上适当的盐形式的吲哚西美德的前药。

[0139] 在一个实施方案中，所述前药基本上包括以下化合物中的至少一种：(i)N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯；(ii)1-甲基-D-色氨酸2,3-二羟丙酯；(iii)N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸；(iv)N^{α}-(L-异亮氨酰)-1-甲基-D-色氨酸乙酯；(v)N^{α}-(L-甘氨酰)-1-甲基-D-色氨酸；(vi)(S)-5-氨基-6-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-6-氧代己酸；(vii)N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸；(viii)N^{α}-(L-苯基丙氨酰)-1-甲基-D-色氨酸；(ix)N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯；(x)1-甲基-D-色氨酸2-(二甲基氨基)乙酯；(xi)1-甲基-D-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯；(xii)1-甲基-D-色氨酸2-(四氢-2H-吡喃-4-基)乙酯；(xiii)1-甲基-D-色氨酸乙酯；(xiv)1-甲基-D-色氨酸异丙酯；(xv)N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸；或(xvi)N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯。

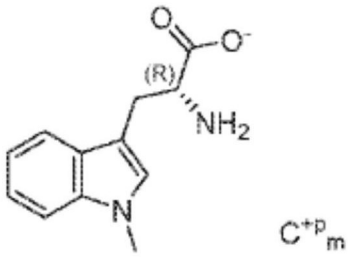
[0140] 吲哚西美德盐和前药的药物组合物

[0141] 一方面，本发明提供了包含如由式1a和1b的化合物表示的吲哚西美德的盐的药物组合物，

[0142]



式1a



式1b

[0143] 其中$A^{-}{}_{n}$是无机或有机阴离子且$C^{+p}{}_{m}$是呈电离态且在确保分子电中性的化学计量比下的无机阳离子。

[0144] 在第一方面的第二个实施方案中，本发明提供了包含如由式1a的化合物表示的吲哚西美德的盐的药物组合物，其中$A^{-p}{}_{n}$是选自由以下组成的组的阴离子：氯离子、磷酸根、硫酸根、甲磺酸根、苯磺酸根、乙酸根、抗坏血酸根、天冬氨酸根、谷氨酸根、戊二酸根、乳酸根、马来酸根、丙二酸根、草酸根、丁二酸根、富马酸根、酒石酸根和柠檬酸根，其中在化学计量比n为1、1/2或1/3下，负电荷p分别是-1、-2或-3，使得其满足电中性的化学计量条件。

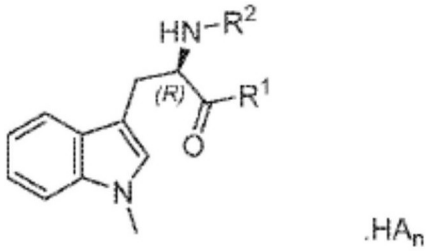
[0145] 在第一方面的第三个实施方案中，本发明提供了包含如由式1b的化合物表示的吲哚西美德的盐的药物组合物，其中$C^{+p}{}_{m}$是选自以下组的阳离子：Li^{+}、Na^{+}、K^{+}、Mg^{+2}或Ca^{+2}，其中在化学计量比m为1或1/2下，正电荷p分别是+1或+2，使得其满足电中性的化学计量条件。

[0146] 在第一方面的第四个实施方案中，本发明提供了包含如由式1a的化合物表示的吲哚西美德的盐的药物组合物，其中在化学计量比n分别为0.5、0.5、1或1下，$A^{-p}{}_{n}$是选自由以下组成的组的阴离子：HPO_4^{-2}(磷酸根)、SO_4^{-2}(硫酸根)、$H_2PO_4^{-}$(磷酸根)、Cl^{-}和$CH_3SO_3^{-}$(甲磺酸根)。

[0147] 在第一方面的优选的第五个实施方案中，本发明提供了包含如由式1a的化合物表示的吲哚西美德的盐的药物组合物，其中$A^{-p}{}_{n}$是在化学计量比n为1下的Cl^{-}。

[0148] 在第一方面的最优选的第五个实施方案中，本发明提供了包含如由式1a的化合物表示的吲哚西美德的盐的药物组合物，其中$A^{-p}{}_{n}$是在化学计量比n为1下的Cl^{-}且晶形是形式

1的无水同种型。在第二方面，本发明提供了包含呈其游离碱或盐形式的吲哚西美德的前药的药物组合物。在一个实施方案中，吲哚西美德的前药由式2的化合物表示，

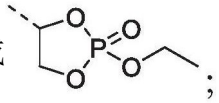
[0149] 

式 2

[0150] 其中

[0151] R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$、$-OC_{1-3}$烷基$-R^3$、$-NHC^{(S)}HR^4(COOH)$、$-NHC^{(R)}HR^4(COOH)$、$-OC_{1-6}$烷基R^6、$-OC_{1-2}$烷基、$-C^{(S)}H(NH_2)(COOH)$或$-OC_{1-2}$烷基$-C^{(R)}H(NH2)(COOH)$；

[0152] R^2是-H、$-C(O)C^{(S)}H(NH_2)R^4$、$-C(O)C^{(R)}H(NH_2)R^4$、$-C(O)CH_2C^{(S)}H(NH_2)-C(O)OCH_3$、$-C(O)OR^5$或$-C(O)NHR^5$，

[0153] R^3是四氢吡喃或  ；

[0154] 其中R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、C_{1-5}烷基SC_{1-5}烷基、$-C_{1-5}$烷基OC_{1-5}烷基、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

[0155] 其中当R^4不是-H时，$C^{(S)}$和$C^{(R)}$分别表示具有S或R立体化学的碳；其中R^5是-H、C_{1-6}烷基R^6；或R^6

[0156] 其中R^6是H、芳基、烷基芳基、杂芳基、环烷基或杂环烷基，其中此类芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

[0157] 其中每个R^7独立地选自卤素、氰基、硝基、-OR、$-N(R)_2$、-SR、$-C(O)OR$、C_{1-6}烷基、C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$；

[0158] 其中R是-H或C_{1-4}烷基；

[0159] 前提是当R^2是-H时R^1不能是-OH，且所述化合物不能是

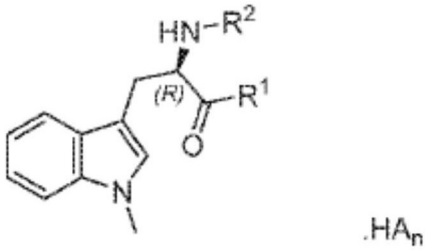
[0160] N^{α}-叔丁氧基羰基-1-甲基-D-色氨酸

[0161] N^{α}-苄基-1-甲基-D-色氨酸乙酯

[0162] N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯

[0163] HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苯基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸；且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

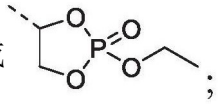
[0164] 在第二方面的另一个实施方案中，本发明提供了包含如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药的药物组合物。

[0165] 

式 2

[0166] 其中R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$、-

[0167] R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

[0168] R^3是四氢吡喃或  ;

[0169] 其中R^4是H、$-C_{1-5}$烷基、$-(CH_2)_{1-2}SH$、$-(CH_2)_{1-3}SCH_3$、$-(CH_2)_{1-3}OCH_3$、$-CH_2-R^6$、$-CH_2OH$、$-CH(OH)CH_3$、$-(CH_2)_{1-2}C(O)NH_2$、$-(CH_2)_{1-3}C(O)OH$、$-(CH_2)_{1-4}NH_2$或$-(CH_2)_{1-3}NC(=NH_2)NH_2$；

[0170] 其中当R^4不是H时，$C^{(S)}$表示具有S立体化学的碳；

[0171] 其中R^6是H、芳基、烷基芳基、杂芳基、环烷基、杂环烷基，其中此类芳基、烷基芳基、杂芳基、环烷基或杂环烷基被一个、两个或三个R^7基团任选地取代；

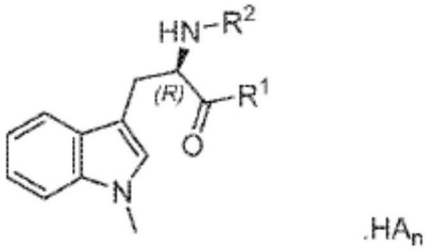
[0172] 其中每个R^7独立地是卤素、氰基、硝基、$-OR$、$-N(R)_2$、$-SR$、$-C(O)OR$、C_{1-6}烷基，C_{1-6}卤代烷基、$-C(O)N(R)_2$、$-C(O)R$、$-S(O)R$、$-S(O)OR$、$-S(O)N(R)_2$、$-S(O)_2R$、$-S(O)_2OR$、$-S(O)_2N(R)_2$、$-OC(O)R$、$-OC(O)OR$、$-OC(O)N(R)_2$、$-N(R)C(O)R$、$-N(R)C(O)OR$或$-N(R)C(O)N(R)_2$；

[0173] 其中R是H或C_{1-4}烷基；

[0174] 前提是当R^2是H时R^1不能是-OH；

[0175] HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)、$C_6H_5SO_3H$(苄基磺酸)、乙酸、抗坏血酸、天冬氨酸、谷氨酸、戊二酸、乳酸、马来酸、丙二酸、草酸、丁二酸、富马酸、酒石酸和柠檬酸；且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

[0176] 在第二方面的一个优选的实施方案中，本发明提供了包含如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药的药物组合物，

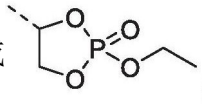
[0177] 

式 2

[0178] 其中

[0179] R^1是-OH、$-OC_{2-3}$烷基、$-OCH_2CH(OH)CH_2OH$、$-O(CH_2)_2N(CH_3)_2$或$-OC_{1-3}$烷基$-R^3$，

[0180] R^2是H或$-C(O)C^{(S)}H(NH_2)R^4$，

[0181] R^3是四氢吡喃或  ;

[0182] 其中R^4是H、-C_{1-5}烷基、-CH_2-R^6、-$(CH_2)_{1-2}C(O)NH_2$、-$(CH_2)_2SCH_3$、-$(CH_2)_{1-3}C(O)OH$或-$(CH_2)_{1-4}NH_2$

[0183] 其中当R^4不是-H时，$C^{(S)}$表示具有S立体化学的碳；

[0184] 其中R^6是-H、芳基、烷基芳基或杂芳基，其中此类芳基、烷基芳基或杂芳基被一个R^7基团任选地取代；

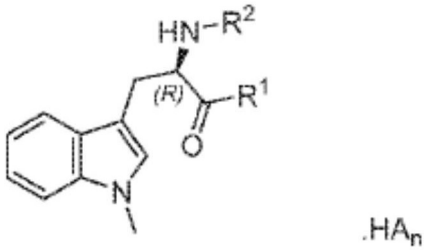
[0185] 其中R^7选自卤素、氰基、硝基、-OR、-$N(R)_2$、-SR、-C(O)OR、C_{1-6}烷基、C_{1-6}卤代烷基、-C(O)$N(R)_2$、-C(O)R、-S(O)R、-S(O)OR、-S(O)$N(R)_2$、-$S(O)_2$R、-$S(O)_2$OR、-$S(O)_2N(R)_2$、-OC(O)R、-OC(O)OR、-OC(O)$N(R)_2$、-N(R)C(O)R、-N(R)C(O)OR或-N(R)C(O)$N(R)_2$；

[0186] 其中R是-H或C_{1-4}烷基；

[0187] 前提是当R^2是H时，R^1不能是-OH；

[0188] HA_n是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)、HSO_3CH_3(甲基磺酸)或$C_6H_5SO_3H$(苄基磺酸)；且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

[0189] 在第二方面的一个最优选的实施方案中，本发明提供了包含如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药的药物组合物

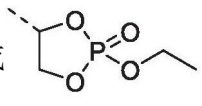
[0190] 

式 2

[0191] 其中

[0192] R^1是-OH、-OC_{2-3}烷基、-$OCH_2CH(OH)CH_2OH$、-$O(CH_2)_2N(CH_3)_2$或-OC_{1-3}烷基-R^3，

[0193] R^2是H或-C(O)$C^{(S)}H(NH_2)R^4$，

[0194] R^3是四氢吡喃或  ;

[0195] 其中R^4是-$CH_2CH(CH_3)_2$、-$C^{(S)}H(CH)_3CH_2CH_3$、-$(CH_2)_2SCH_3$、-CH_2-R^6、-$(CH_2)_2C(O)NH_2$、-$(CH_2)_3C(O)OH$或-$(CH_2)_4NH_2$；

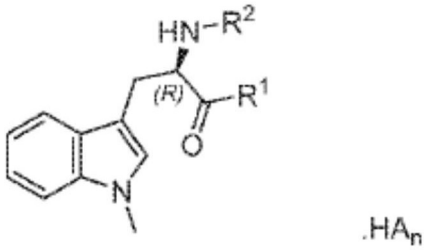
[0196] 其中$C^{(S)}$表示具有S立体化学的碳；

[0197] 其中R^6是苯基；

[0198] 前提是当R^2是H时，R^1不能是-OH；

[0199] HA_n是选自由以下组成的组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)HSO_3CH_3(甲基磺酸)和$C_6H_5SO_3H$(苄基磺酸)，且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

[0200] 在第二方面的一个最优选的实施方案中，本发明提供了包含如由式2化合物表示的呈其游离碱或盐形式的吲哚西美德的前药的药物组合物，

[0201] 

式 2

[0202] 其中

[0203] R^1是-OC_{2-3}烷基或-$OCH_2CH(OH)CH_2OH$，

[0204] R^2是H或-$C(O)C^{(S)}H(NH_2)R^4$，

[0205] 其中R^4是-$CH_2CH(CH_3)_2$、-$(CH_2)_2SCH_3$或-$(CH_2)_2C(O)NH_2$；

[0206] 其中$C^{(S)}$表示具有S立体化学的碳

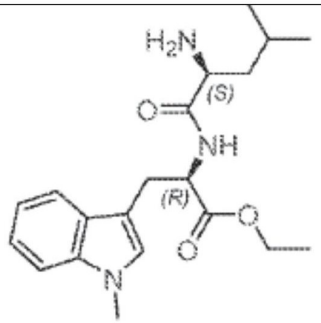
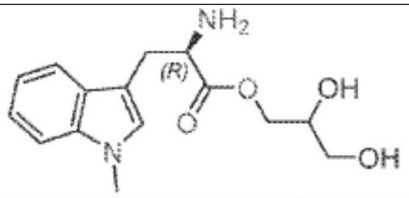
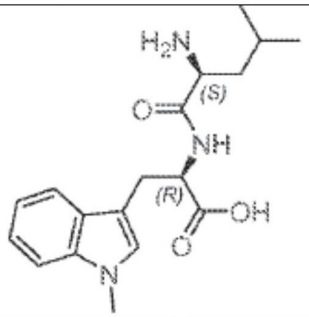
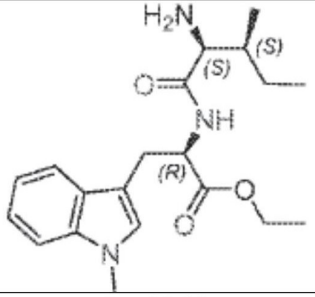
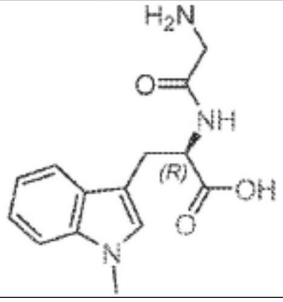
[0207] 前提是当R^2是H时R^1不能是-OH，

[0208] HA是选自以下组的酸：PO_4H_3(磷酸)、SO_4H_2(硫酸)、HCl(盐酸)HSO_3CH_3(甲基磺酸)或$C_6H_5SO_3H$(苄基磺酸)；且n是确保所得盐电中性的0、0.5、1或2的化学计量比。

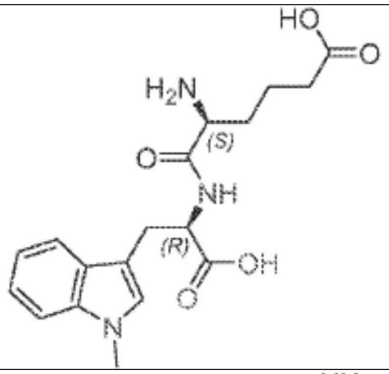
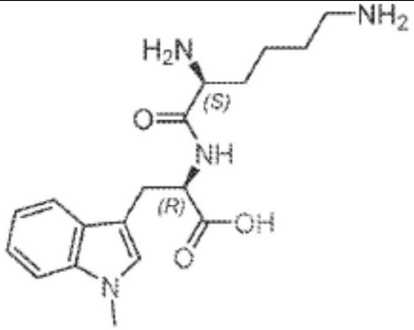
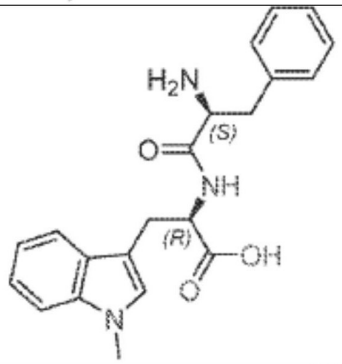
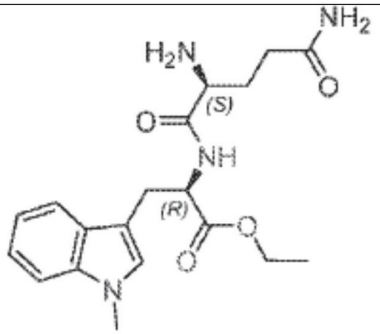
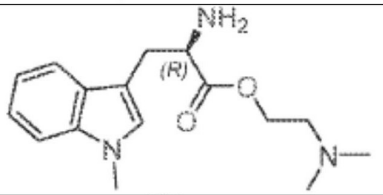
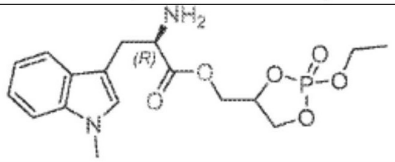
[0209] 在一个优选的实施方案中，本发明提供了包含如由表1中呈现的式2化合物表示的呈其游离碱或呈药学上适当的盐形式的吲哚西美德的前药的药物组合物。

[0210] 表1.吲哚西美德的前药

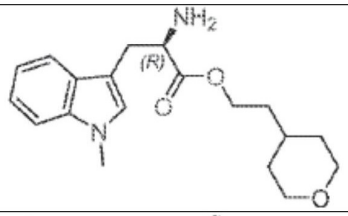
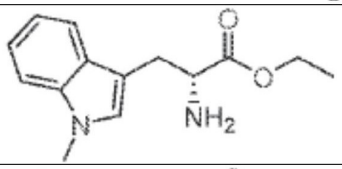
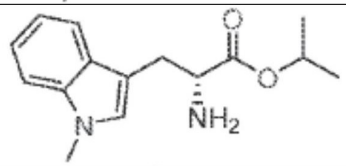
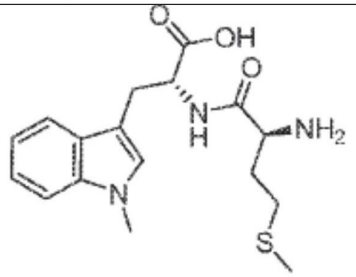
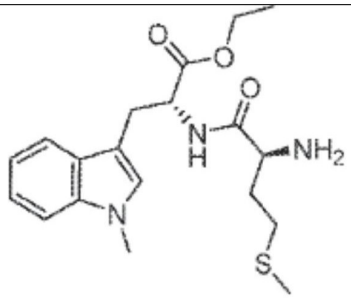
[0211]

化合物编号	结构	名称
01		N^{α}-(*L*-亮氨酰)-1-甲基-*D*-色氨酸乙酯
02		1-甲基-*D*-色氨酸 2,3-二羟丙酯
03		N^{α}-(*L*-亮氨酰)-1-甲基-*D*-色氨酸
04		N^{α}-(*L*-异亮氨酰)-1-甲基-*D*-色氨酸乙酯
05		N^{α}-(*L*-甘氨酰)-1-甲基-*D*-色氨酸

[0212]

06		(*S*)-5-氨基-6-(((*R*)-1-羧基-2-(1-甲基-1*H*-吲哚-3-基)乙基)氨基)-6-氧代己酸
07		N^{α}-(*L*-赖氨酰)-1-甲基-*D*-色氨酸
08		N^{α}-(*L*-苯基丙氨酰)-1-甲基-*D*-色氨酸
09		N^{α}-(*L*-谷酰氨基)-1-甲基-*D*-色氨酸乙酯
10		1-甲基-*D*-色氨酸 2-(二甲基氨基)乙酯
11		1-甲基-*D*-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯

[0213]

12		1-甲基-*D*-色氨酸 2-(四氢-2*H*-吡喃-4-基)乙酯
13		1-甲基-*D*-色氨酸乙酯
14		1-甲基-*D*-色氨酸异丙酯
15		N^{α}-(*L*-甲硫氨酰)-1-甲基-*D*-色氨酸
16		N^{α}-(*L*-甲硫氨酰)-1-甲基-*D*-色氨酸乙酯

[0214] 另一方面，本发明提供了在有需要的受试者中使用式1或2的组合物调节吲哚胺-2,3-双加氧酶途径活性的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的治疗有效量的此类组合物。

[0215] 另一方面，本发明提供了在有需要的受试者中使用式1a、1b和2的化合物治疗癌症的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的治疗有效量的此类组合物。

[0216] 另一方面，本发明提供了在有需要的受试者中使用式1a、1b和2的化合物治疗与癌症相关的肿瘤-特异性免疫抑制的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的足够量的此类组合物。

[0217] 另一方面，本发明提供了在有需要的受试者中使用包含式1a、1b或2的化合物的组合物治疗与传染病(如HIV-1感染、流感)相关的免疫抑制的方法，所述方法包括向此类受试者经口施用在适当的药物形式或媒介物中的足够量的此类组合物。

[0218] 在一个实施方案中，于药物组合物中包含吲哚西美德的盐和/或前药，且所述组合物被包含于固体胶囊、明胶胶囊、片剂或丸剂中。在一个实施方案中，所述盐和/或前药被包含于可溶性胶囊中。

[0219] 在特定的实施方案中，本发明的组合物可另外地含有药物组合物中常见的其领域确定的使用水平的其它辅助剂组分。因此，例如，所述组合物可以含有用于物理配制本发明组合物的各种剂型的另外材料，诸如染料、调味剂、防腐剂、抗氧化剂、遮光剂、增稠剂和稳定剂。所述制剂可以灭菌，并且如果需要，与不与制剂的一种或多种寡核苷酸有害地相互作用的辅助剂(如润滑剂、防腐剂、稳定剂、润湿剂、乳化剂、用于影响渗透压的盐、缓冲剂、着色剂、调味剂和/或芳香物等)混合。

[0220] 在某些实施方案中，本发明的药物组合物包含一种或多种赋形剂。在某些此类实施方案中，赋形剂选自水、盐溶液、醇、聚乙二醇、明胶、乳糖、乳糖一水合物、淀粉酶、硬脂酸镁、滑石、硅酸、粘性石蜡、羟甲基纤维素、微晶纤维素和聚乙烯吡咯烷酮。

[0221] 在某些实施方案中，本发明的药物组合物是使用已知技术制备的，包括但不限于混合、溶解、制粒、制糖衣丸、磨细、乳化、包封、包埋或压片过程。

[0222] 另外的实施方案涉及药物制剂，其中所述制剂选自由以下组成的组：固体、粉末、液体和凝胶。在某些实施方案中，本发明的药物组合物是液体(如，悬浮液、酏剂和/或溶液)。在某些此类实施方案中，液体药物组合物是使用本领域已知的成分制备的，包括但不限于水、二醇、油、醇、调味剂、防腐剂和着色剂。

[0223] 在某些实施方案中，本发明的药物组合物是固体的(如，粉末、片剂和/或胶囊)。在某些此类实施方案中，固体药物组合物包含本领域已知的一种或多种成分，包括但不限于淀粉、糖、稀释剂、粒化剂、润滑剂、粘合剂和崩解剂。

[0224] 在某些实施方案中，本发明的药物组合物包含递送系统。递送系统的实例包括但不限于脂质体和乳剂。某些递送系统对于制备某些药物组合物是有用的，包括那些包含疏水化合物的药物组合物。在某些实施方案中，使用某些有机溶剂诸如二甲基亚砜。

[0225] 在某些实施方案中，本发明的药物组合物包含共溶剂体系。某些此类共溶剂系统包括例如苄基醇、非极性表面活性剂、水混溶性有机聚合物和水相。在某些实施方案中，此类共溶剂系统用于疏水化合物。此类共溶剂系统的非限制性实例是VPD共溶剂系统，其是包含3％w/v苄基醇、8％w/v非极性表面活性剂聚山梨醇酯80及65％w/v聚乙二醇300的无水乙醇溶液。此类共溶剂系统的比例可以相当大地变化，而不显着改变其溶解度和毒性特征。此外，可以改变共溶剂组分的特性：例如，可以使用其它表面活性剂代替聚山梨酯80；聚乙二醇的级分大小可以变化；其它生物相容性聚合物可以代替聚乙二醇，例如聚乙烯吡咯烷酮；并且其它糖或多糖可代替葡萄糖。

[0226] 在某些实施方案中，本发明的药物组合物包含持续释放系统。此类缓释系统的非限制性实例是固体疏水型聚合物的半透性基质。在某些实施方案中，持续释放系统根据其化学性质可能会在数小时、数天、数周或数月的时间内释放试剂。

[0227] 在某些实施方案中，本发明的药物组合物经制备用于经口施用。在某些此类实施方案中，药物组合物通过合并一种或多种试剂和药学上可接受的载体来配制。某些此类载体使得药物组合物能够被配制成片剂、丸剂、糖衣丸、胶囊剂、液体剂、凝胶剂、糖浆剂、浆料、混悬剂等，用于受试者口服摄取。适合的赋形剂包括但不限于填充剂，诸如糖，包括乳糖、乳糖一水合物、蔗糖、甘露糖醇或山梨糖醇；纤维素制剂，诸如，例如玉米淀粉、小麦淀粉、大米淀粉、马铃薯淀粉、明胶、黄蓍胶、甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素钠、微晶纤维素和/或聚乙烯吡咯烷酮(PVP)。在某些实施方案中，此类混合物经任选研磨，

并且可任选地添加辅剂。在某些实施方案中，形成药物组合物以获得片剂或糖衣丸芯。在某些实施方案中，加入崩解剂(如，交联的羧甲基纤维素，诸如交联羧甲纤维素钠、交联聚乙烯吡咯烷酮、琼脂或海藻酸或其盐，诸如藻酸钠)。

[0228] 在某些实施方案中，对糖衣丸芯作包衣。在某些此类实施方案中，可以使用浓糖溶液，其可任选地含有阿拉伯胶、滑石、聚乙烯吡咯烷酮、卡波姆凝胶、聚乙二醇和/或二氧化钛、漆溶液和适合的有机溶剂或溶剂混合物。可向片剂或糖衣丸包衣中加入染料或色素。

[0229] 在某些实施方案中，用于经口施用的药物组合物是由明胶制成的推入适配胶囊。某些此类推入适配胶囊包含与一种或多种填充剂(诸如乳糖)、粘合剂(诸如淀粉)和/或润滑剂(诸如滑石或硬脂酸镁)以及任选的稳定剂掺混的本发明的一种或多种药物试剂。在某些实施方案中，用于经口施用的药物组合物是由明胶和增塑剂(诸如甘油或山梨糖醇)制成的密封软胶囊。在某些软胶囊中，将本发明的一种或多种药物试剂溶解或混悬在诸如脂肪油、液体石蜡或液体聚乙二醇的适合液体中。此外，可以加入稳定剂。

[0230] 在某些实施方案中，药物组合物经制备用于经颊施用。某些此类药物组合物是以常规方式配制的片剂或锭剂。

[0231] 在某些实施方案中，药物组合物经制备用于通过注射(如静脉内、皮下、肌肉内等)施用。在某些此类实施方案中，药物组合物包含载体并且在水溶液、诸如水或生理上相容的缓冲液、诸如汉克斯溶液(Hanks′s solution)、林格氏溶液(Ringer′s solution)或生理盐水缓冲液中配制。在某些实施方案中，包含其他成分(例如，有助于溶解性或用作防腐剂的成分)。在某些实施方案中，使用适当的液体载体、助悬剂等制备可注射的混悬液。用于注射的某些药物组合物以单位剂量形式呈现，例如在安瓿或多剂量容器中。某些用于注射的药物组合物是在油性或含水媒介物中的混悬液、溶液或乳液，并且可以含有诸如助悬剂、稳定剂和/或分散剂的配方剂。适用于注射用药物组合物的某些溶剂包括但不限于亲脂性溶剂和脂肪油，诸如芝麻油、合成脂肪酸酯，诸如油酸乙酯或甘油三酯，以及脂质体。水性注射混悬液可含有增加混悬液粘度的物质，诸如羧甲基纤维素钠、山梨糖醇或葡聚糖。任选地，此类悬浮液还可以含有适合的稳定剂或增加药物试剂的溶解度的试剂以允许制备高浓度溶液。

[0232] 在某些实施方案中，本发明的药物组合物可以是泡腾片剂或粒化剂。泡腾片剂最通常由可溶性酸源和碳酸盐源组成，以产生二氧化碳气体，后者作为崩解剂。泡腾反应所需的酸度可源自食品酸、酸酐和酸性盐。食品酸可例如是柠檬酸、酒石酸、苹果酸、富马酸、己二酸或丁二酸。酸酐可以是丁二酸酐或柠檬酸酐等。酸性盐可以是例如磷酸二氢钠(磷酸一钠)、焦磷酸二氢二钠(酸式焦磷酸钠)、柠檬酸盐(柠檬酸二氢钠和柠檬酸氢二钠)、酸式亚硫酸钠(亚硫酸氢钠)。适合的碳酸酯源是例如碳酸氢钠、碳酸钠、碳酸氢钾、碳酸钾、倍半碳酸钠(等摩尔量的碳酸钠和碳酸氢钠的混合物)、碳酸甘氨酸、碳酸L-赖氨酸、碳酸精氨酸、碳酸钙。

[0233] 也可以通过形成其它气体(诸如氧)来诱导泡腾，如从过硼酸钠中释放或从在与水混合时产生活性氧的过氧化合物(如过硼酸钠一水合物或过碳酸钠)和在与水接触时释放次氯酸根的氯化合物(如二氯异氰脲酸钠或次氯酸钙)的组合释放。

[0234] 本发明的药物组合物可根据本领域已知的标准方法制造。根据本发明的颗粒和泡腾片可通过干式压实或湿法制粒获得。这些颗粒随后可以与例如适合的崩解剂、助流剂和

润滑剂混合，并压制成片剂或填充到例如适合大小的小袋中。也可以通过直接压制适合的粉末混合物，即没有任何先前的赋形剂制粒来获得泡腾片剂。

[0235] 根据本发明的适合的粉末或颗粒混合物也可通过喷雾干燥(如，通过热法喷雾干燥或通过基础喷雾干燥)、冻干、熔融挤出、丸粒分层、包被活性药物成分或任何其它适合的方法获得。优选地，选择条件诸如以防止活性药物成分的非晶化。如此获得的粉末或颗粒可以与一种或多种适合的成分混合，并可将所得的混合物压制以形成泡腾片或填充到小袋中。

[0236] 所有出版物、专利和专利申请，包括其中的任何附图和附录，出于所有目的通过引用整体并入，其程度如同每个单独的出版物、专利和专利申请、附图或附录具体地和单独地被指示为出于所有目的通过引用整体并入。

[0237] 定义

[0238] 本文中使用的术语可以在单划线“-”或双划线“=”之前和/或之后，以表示命名的取代基与其母体部分之间的键的键顺序；单划线表示单键且双划线表示双键或在螺取代基的情况下表示一对单键。在单划线或双划线不存在下，应当理解，在取代基与其母体部分之间形成单键；此外，取代基旨在从“从左到右”读出，除非划线另有说明。例如，C_{1-6}烷氧基羰基氧基和-OC(O)C_{1-6}烷基表示相同的官能团；类似地，芳基烷基、芳基烷基-和-烷基芳基表示相同的官能团。

[0239] 此外，本文中的某些术语可用作如本领域技术人员熟悉的单价和二价连接基团，以及根据它们在两个其它部分之间呈现连接使用。例如，烷基基团可以是一价基团或二价基团；在后一种情况下，对于本领域技术人员显而易见的是，从单价烷基基团去除另外的氢原子以提供适合的二价部分。

[0240] 除非另有说明，否则如本文所用的术语“烯基”意指含有2至10碳并含有至少一个碳碳双键的直链或支链烃。烯基的代表性实例包括但不限于乙烯基、2-丙烯基、2-甲基-2-丙烯基、3-丁烯基、4-戊烯基、5-己烯基、2-庚烯基、2-甲基-1-庚烯基、3-癸烯基和3,7-二甲基辛2,6-二烯基。

[0241] 如本文所用的术语“烷氧基”意指通过氧原子附加到母体分子部分的如本文所定义的烷基基团。烷氧基的代表性实例包括但不限于甲氧基、乙氧基、丙氧基、2-丙氧基、丁氧基、叔丁氧基、戊基氧基和己基氧基。

[0242] 除非另有说明，否则如本文所用的术语“烷基”意指含有1至10个碳原子的直链或支链烃。烷基的代表性实例包括但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、异丁基、叔丁基、正戊基、异戊基、新戊基、正己基、3-甲基己基、2,2-二甲基戊基、2,3-二甲基戊基、正庚基、正辛基、正壬基和正癸基。当“烷基”基团是两个其它部分之间的连接基团时，则其也可以是直链或支链；实例包括但不限于-CH_2-、-CH_2CH_2-、-$CH_2CH_2CHC(CH_3)$-、-$CH_2CH(CH_2CH_3)CH_2$-。

[0243] 术语C_{1-5}烷基是指1至5个碳原子的直链或支链烷基。

[0244] 术语C_{1-6}烷基是指1至6个碳原子的直链或支链烷基。

[0245] 如本文所用的术语“芳基”意指苯基(即单环芳基)或含有至少一个苯基环的双环体系或在芳香族双环体系中仅含有碳原子的芳香族双环。双环芳基可以是稠合至单环环烷基、单环环烯基或单环杂环基的蒽基、萘基或苯基。双环芳基通过双环体系的苯基部分内所

含的任何碳原子或者萘基环或奠基环内的任何碳原子连接在母体分子部分上。双环芳基的稠合单环环烷基或单环杂环基部分被一个或两个氧代和/或硫杂基基团任选取代。双环芳基的代表性实例包括但不限于奠基、萘基、二氢茚-1-基、二氢茚-2-基、二氢茚-3-基、二氢茚-4-基、2,3-二氢吲哚-4-基、2,3-二氢吲哚-5-基、2,3-二氢吲哚-6-基、2,3-二氢吲哚-7-基、茚-1-基、茚-2-基、茚-3-基、茚-4-基、二氢萘-2-基、二氢萘-3-基、二氢萘-4-基、二氢萘-1-基、5,6,7,8-四氢萘-1-基、5,6,7,8-四氢萘-2-基、2,3-二氢苯并呋喃-4-基、2,3-二氢苯并呋喃-5-基、2,3-二氢苯并呋喃-6-基、2,3-二氢苯并呋喃-7-基、苯并[d][1,3]间二氧杂环戊烯-4-基、苯并[d][1,3]间二氧杂环戊烯-5-基、2H-色烯-2-酮-5-基、2H-色烯-2-酮-6-基、2H-色烯-2-酮-7-基、2H-色烯-2-酮-8-基、异吲哚啉-1,3-二酮-4-基、异吲哚啉-1,3-二酮-5-基、茚-1-酮-4-基、茚-1-酮-5-基、茚-1-酮-6-基、茚-1-酮-7-基、2,3-二氢苯并[b][1,4]二氧杂环己烯-5-基、2,3-二氢苯并[b][1,4]二氧杂环己烯-6-基、2H-苯并[b][1,4]噁嗪3(4h)-酮-5-基、2H苯并[b][1,4]噁嗪3(4h)-酮-6-基、2H苯并[b][1,4]噁嗪3(4h)-酮-7-基、2H苯并[b][1,4]噁嗪3(4h)-酮-8-基、苯并[d]噁嗪-2(3H)-酮-5-基、苯并[d]噁嗪-2(3H)-酮-6-基、苯并[d]噁嗪-2(3H)-酮-7-基、苯并[d]噁嗪-2(3H)-酮-8-基、喹唑啉-4(3H)-酮-5-基、喹唑啉-4(3H)-酮-6-基、喹唑啉-4(3H)-酮-7-基、喹唑啉-4(3H)-酮-8-基、喹噁啉-2(1H)-酮-5-基、喹噁啉-2(1H)-酮-6-基、喹噁啉-2(1H)-酮-7-基、喹噁啉-2(1H)-酮-8-基、苯并[d]噻唑-2(3H)-酮-4-基、苯并[d]噻唑-2(3H)-酮-5-基、苯并[d]噻唑-2(3H)-酮-6-基和苯并[d]噻唑-2(3H)-酮-7-基。在某些实施方案中，双环芳基是稠合至5或6元单环环烷基、5或6元单环环烯基或者5或6元单环杂环基的(i)萘基环或(ii)苯基环，其中稠合的环烷基、环烯基和杂环基基团被独立为氧代或硫杂的一个或两个基团任选取代。

[0246] 如本文所用的术语“芳基烷基”、“烷基芳基”和“芳基烷基-”意指通过如本文定义的烷基基团附加至母体分子部分的如本文所定义的芳基基团。芳基烷基的代表性实例包括但不限于苄基、2-苯基乙基、3-苯基丙基和2-萘-2-基乙基。

[0247] 如本文所用的术语“氰基”和“腈”意指-CN基团。

[0248] 如本文所用的术语“环烷基”意指单环或双环环烷基环体系。单环环体系是含有3至8个碳原子的环状烃基团，其中此类基团可以是饱和的或不饱和的，但不是芳香族的。在某些实施方案中，环烷基基团是完全饱和的。单环环烷基的实例包括环丙基、环丁基、环戊基、环戊烯基、环己基、环己烯基、环庚基和环辛基。双环环烷基环体系是桥接单环或稠合双环。桥接单环含有单环环烷基环，其中单环的两个不相邻碳原子由一个和另外三个碳原子之间的亚烷基桥(即形式$-(CH_2)_w-$的桥接基团，其中w是1、2或3)连接。双环环体系的代表性实例包括但不限于双环[3.1.1]庚烷、双环[2.2.1]庚烷、双环[2.2.2]辛烷、双环[3.2.2]壬烷、双环[3.3.1]壬烷和双环[4.2.1]壬烷。稠合的双环环烷基环体系含有稠合至苯基、单环环烷基、单环环烯基、单环杂环基或单环杂基的单环环烷基环。桥连或稠合双环环烷基通过单环环烷基环中包含的任何碳原子连接到母体分子部分。环烷基基团被一个或两个独立为氧代或硫杂的基团任选取代。在某些实施方案中，稠合双环环烷基是与苯基环、5或6元单环环烷基、5或6元单环环烯基、5或6元单环杂环基或5或6元单环杂芳基稠合的5或6元单环环烷基环，其中稠合双环环烷基被一个或两个独立地为氧代或硫杂的基团任选取代。

[0249] 如本文所用的“环烯基”是指单环或双环环烯基环体系。单环环体系是含有3至8个碳原子的环状烃基团，其中此类基团是不饱和的(即含有至少一个环形碳碳双键)，但不是

芳香族的。单环环体系的实例包括环戊烯基和环己烯基。双环环烯基环是桥接单环或稠合双环。桥接单环含有单环环烯基环，其中单环的两个不相邻的碳原子由一个和另外三个碳原子之间的亚烷基桥(即形式-$(CH_2)_w$-的桥接基团，其中w是1、2或3)连接。双环环烯基的代表性实例包括但不限于降冰片烯基和双环[2.2.2]辛-2-烯基。稠合的双环环烯基环体系含有稠合至苯基、单环环烷基、单环环烯基、单环杂环基或单环杂芳基的单环环烯基环。桥连或稠合双环环烯基通过单环烯基环中包含的任何碳原子连接到母体分子部分。环烯基基团任选被一个或两个独立地为氧代或硫杂的基团任选取代。

[0250] 如本文所用的术语“卤代”或“卤素”意指Cl、Br、I或F。

[0251] 如本文所用的术语“卤代烷基”意指通过如本文所定义的烷基基团附加到母体分子部分的如本文所定义的至少一种卤素。卤代烷基的代表性实例包括但不限于氯甲基、2-氟乙基、三氟甲基、五氟乙基和2-氯-3-氟戊基。

[0252] 如本文所用的术语“杂芳基”意指单环杂芳基或含有至少一个杂芳环的双环环体系。单环杂芳基可以是5或6元环。5元环由两个双键和一个、两个、三个或四个氮原子和任选的一个氧或硫原子组成。6元环由三个双键和一个、两个、三个或四个氮原子组成。5或6元杂芳基通过任何碳原子或杂芳基中含有的任何氮原子连接到母体分子部分。单环杂芳基的代表性实例包括但不限于呋喃基、咪唑基、吲哚基、1-甲基-吲哚基、异噁唑基，异噻唑基、噁二唑基、噁唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、吡唑基、吡咯基、四唑基、噻二唑基、噻唑基、噻吩基、三唑基和三嗪基。双环杂芳基由稠合至苯基、单环环烷基、单环环烯基、单环杂环基或单环杂芳基的单环杂芳基组成。双环杂芳基基团的稠合环烷基或杂环基部分被一个或两个独立为氧代或硫杂的基团任选取代。当双环杂芳基含有稠合环烷基环、环烯基环或杂环基环时，则双环杂芳基基团通过双环体系的单环杂芳基部分内含有的任何碳或氮原子连接至母体分子部分。当双环杂芳基是稠合至苯基环或单环杂芳基的单环杂基时，则双环杂芳基基团通过双环环体系内的任何碳原子或氮原子连接到母体分子部分。双环杂芳基的代表性实例包括但不限于苯并咪唑基、苯并呋喃基、苯并噻吩基、苯并噁二唑基、苯并噁噻二唑基、苯并噻唑基、噌啉基、5,6-二氢喹啉-2-基、5,6-二氢异喹啉-1-基、呋喃并吡啶基、吲唑基、吲哚基、异喹啉基、萘啶基、喹啉基、嘌呤基、5,6,7,8-四氢喹啉-2-基、5,6,7,8-四氢喹啉-3-基、5,6,7,8-四氢喹啉-4-基、5,6,7,8-四氢异喹啉-1-基、噻吩并吡啶基、4,5,6,7-四氢苯并[c][1,2,5]噁二唑基和6,7-二氢苯并[c][1,2,5]噁二唑-4(5H)-酮基。在某些实施方案中，稠合双环杂芳基是稠合至苯基环、5或6元单环环烷基、5或6元单环环烯基、5或6元单环杂环基或5或6元单环杂芳基的5或6元单环杂芳基环，其中稠合环烷基、环烯基和杂环基基团被一个或两个独立为氧代或硫杂的基团任选取代。

[0253] 如本文所用的术语“杂芳基烷基”和“烷基杂芳基”意指通过如本所定义的烷基基团附加至母体分子部分的如本文所定义的杂芳基。杂芳基烷基的代表性实例包括但不限于呋喃-3-基甲基、1H-咪唑-2-基甲基、1H-咪唑-4-基甲基、1-(吡啶-4-基)乙基、吡啶-3-基甲基、吡啶-4-基甲基、嘧啶-5-基甲基、2-(嘧啶-2-基)丙基、噻吩-2-基甲基和噻吩-3-基甲基。

[0254] 如本文所用的术语“杂环基”或“杂环烷基”意指单环杂环或双环杂环。单环杂环是含有至少一个独立选自由O、N和S组成的组的杂原子的3、4、5、6或7元环，其中所述环是饱和的或不饱和的，而不是芳香族的。3或4元环含有1个选自由O、N和S组成的组的杂原子。5元环

可含有零或一个双键及一个、两个或三个选自由O、N和S组成的组的杂原子。6或7元环含有零个、一个或两个双键及一个，两个或三个选自由O、N和S组成的组的杂原子。单环杂环通过单环杂环中含有的任何碳原子或任何氮原子连接到母体分子部分。单环杂环的代表性实例包括但不限于氮杂环丁基、氮杂环庚烷基、氮丙啶基、二氮杂环庚烷基、1,3-二噁烷基、1,3-二氧杂环戊烷基、1,3-二硫戊环基、1,3-二噻烷基、咪唑啉基、咪唑烷基、异噻唑啉基、异噻唑烷基、异噁唑啉基、异噁唑烷基、吗啉基、噁二唑啉基、噁二唑烷基、噁唑啉基、噁唑烷基、哌嗪基、哌啶基、吡喃基、吡唑啉基、吡唑烷基、吡咯啉基、吡咯烷基、四氢呋喃基、四氢噻吩基、噻二唑啉基、噻二唑烷基、噻唑啉基、噻唑烷基、硫代吗啉基、1,1-二氧桥硫代吗啉基(硫代吗啉砜)、硫代吡喃基和三噻烷基。双环杂环是稠合至苯基、单环环烷基、单环环烯基、单环杂环或单环杂芳基的单环杂环。将双环杂环通过双环环体系的单环杂环部分内所含的任何碳原子或任何氮原子连接至母体分子部分。双环杂环基的代表性实例包括但不限于2,3-二氢苯并呋喃-2-基、2,3-二氢苯并呋喃-3-基、吲哚啉-1-基、吲哚啉-2-基、吲哚啉-3-基、2,3-二氢苯并噻吩-2-基、十氢喹啉基、十氢异喹啉基、八氢-1H-吲哚基和八氢苯并呋喃基。杂环基基团被一个或两个独立为氧代或硫杂的基团任选取代。在某些实施方案中，双环杂环基是稠合至苯基环、5或6元单环环烷基、5或6元单环环烯基、5或6元单环杂环基或5或6元单环杂芳基的5或6元单环杂环基环，其中双环杂环基被一个或两个独立为氧代或硫杂的基团任选取代。

[0255] 如本文所用的术语“羟基”意指-OH基团。

[0256] 如本文所用的术语“硝基”意指-NO_2基团。

[0257] 如本文所用的术语“氧代”意指=O基团。

[0258] 如本文所用的术语“硫杂”意指-S-基团。

[0259] 如本文所用的术语“饱和”意指引用的化学结构不含任何多个碳-碳键。例如，如本文定义的饱和环烷基基团包括环己基、环丙基等。

[0260] 如本文所用的术语“不饱和”意指参考的化学结构含有至少一个多碳碳键，但不是芳香族的。例如，如本文所定义的不饱和环烷基基团包括环己烯基、环戊烯基、环己二烯基等。

[0261] 如本文所用，可互换使用的术语“个体”或“患者”是指任何动物，包括哺乳动物，优选小鼠、大鼠、其它啮齿动物、兔、狗、猫、猪、牛、绵羊、马或灵长类动物，且最优选人。

[0262] 如本文所用，短语“治疗有效量”是指研究人员、兽医、医师或其它临床医生在组织、系统、动物、个体或人类中寻求的引起生物或药物应答的活性化合物或试剂的量。

[0263] 在某些实施方案中，治疗有效量可以是适用于以下目的的量：

[0264] (1)预防疾病；例如，预防可能易患疾病、病状或病症但尚未经历或显示疾病的病理或症状的个体的疾病、病状或病症；

[0265] (2)抑制疾病；例如，抑制正在经历或显示疾病、病状或病症的病理或症状的个体中的疾病、病状或病症；或

[0266] (3)缓解疾病；例如，缓解正在经历或显示疾病、病状或病症的病理或症状的个体中的疾病、病状或病症(即逆转病理和/或症状)，例如降低疾病的严重程度。

[0267] 如本文所用，术语“治疗(treatment，treating)”意指(i)缓解参考的疾病状态，例如缓解正在经历或显示疾病、病状或病症的病理或症状的个体中的疾病、病状或病症(即逆

转或改善病理和/或症状)，诸如降低疾病的严重程度;或(ii)引发参考的生物学作用(如，IDO调节或色氨酸降解抑制)。

[0268] 使用潜在的IDO介导的免疫抑制来表现疾病状况的缓解可能需要同时或依次施用额外的治疗剂，诸如在癌症情况下的抗肿瘤剂，或者在病毒性疾病情况下的抗逆转录病毒剂。例如，当用作单一试剂时，用于治疗癌症的IDO抑制剂的施用并不总是产生直接的抗瘤作用。然而，当与化疗药物(抗肿瘤剂)组合时，观察到的抗肿瘤作用高于单独的每种试剂的作用之和。

[0269] 如本文所用，术语“催化袋”、“催化位点”、“活性位点”共同和不明确地是指酶的含有负责底物结合(电荷、疏水性、空间位阻)的氨基酸残基与作为质子供体或受体或负责结合辅因子并参与化学反应催化的催化氨基酸残基的区域。

[0270] 如本文所用，短语“药学上可接受的盐”是指药学上可接受的酸和碱加成盐和溶剂化物两者。此类药学上可接受的盐包括以下酸的盐，诸如盐酸、磷酸、氢溴酸、硫酸、亚磺酸、甲酸、甲苯磺酸、甲磺酸、硝酸、苯甲酸、柠檬酸、酒石酸、马来酸、氢碘酸、链烷酸诸如乙酸、其中n是0-4的HOOC-(CH2)n-COOH等。非毒性药用碱加成盐包括碱的盐，诸如钠盐、钾盐、钙盐、铵盐等。本领域技术人员将认识到各种各样的无毒药学上可接受的加成盐。

[0271] 如本文所用，术语“吲哚西美德”是指1-甲基-D-色氨酸，也被称为D-1MT或D1mT。

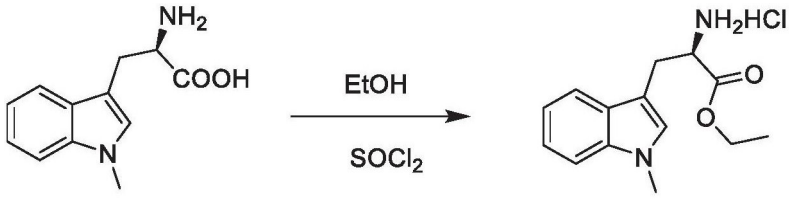
[0272] 如本文所用，术语“吲哚西美德的前药”是指在体内施用之后被代谢以产生吲哚西美德作为主要代谢物之一的任何物质。

实施例

[0273] 实施例1:试剂和合成方法

[0274] 所有试剂和溶剂均购自商业来源。所有商业试剂和溶剂无需进一步纯化直接使用。使用具有0.25mm EM Science硅胶板(60F-254)的分析薄层色谱(TLC)监测反应。将显影的TLC板通过短波UV光(254nm)或浸在高锰酸钾溶液中显色，随后在热板上加热。使用粒径为32-63μm的Selecto Scientific硅胶进行快速色谱。所有反应在氮气氛下在火焰或烘箱干燥的玻璃器皿中进行。除非另有说明，否则将所有反应物都在环境温度下磁力搅拌。使用Bruker DRX400、Varian VXR400或VXR300获得^{1}H NMR谱。相对于作为内部参照的TMS(0.0)、DMSO-d_6(2.50)或CD_3OD(4.80)，以百万分之一(δ)报道^{1}H NMR谱。除非另有说明，否则所有^{1}H NMR谱均在$CDCl_3$中取得。

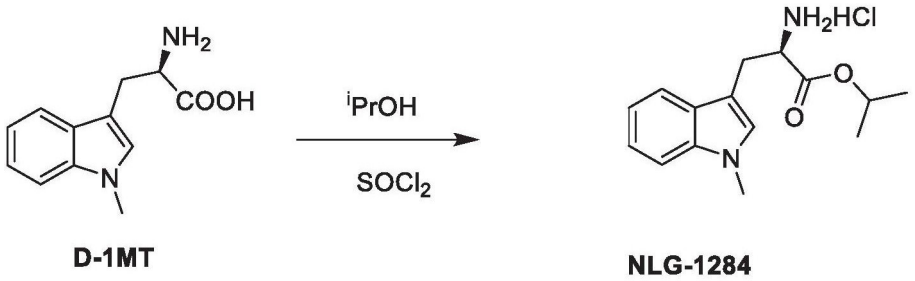
[0275] 合成1-甲基-D-色氨酸乙酯盐酸盐(NLG-1283)

[0276] 

D-1MT NLG-1283

[0277] 在0℃下向D-1MT(4.00g，18.3mmol)于乙醇(50mL)中的混悬液中加入$SOCl_2$(1.34mL，18.3mmol)，并将混合物在80℃下搅拌过夜。冷却至室温后，蒸馏除去溶剂，并将粗物质用二乙醚(100mL)稀释，将白色固体滤掉，并用无水乙醚洗涤，得到所需产物(5.1g，98%)。

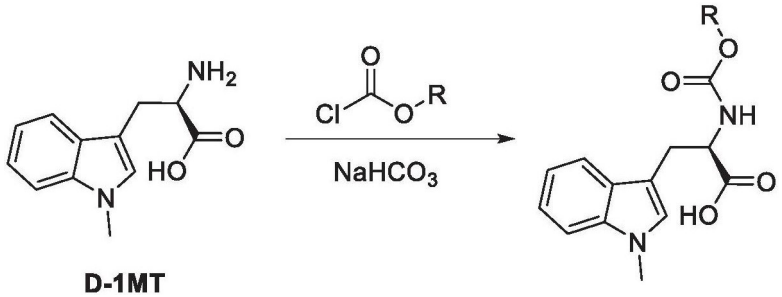
[0278] 合成1-甲基-D-色氨酸异丙酯盐酸盐(NLG-1284)

[0279] 

D-1MT NLG-1284

[0280] 在0℃室温下向D-1MT(0.500g,2.29mmol)于异丙醇(15mL)中的混悬液中加入$SOCl_2$(0.167mL,2.29mmol),并将混合物在80℃下搅拌过夜。冷却至室温后,蒸馏除去溶剂,并将粗产物用25%$NaHCO_3$水溶液(20mL)碱化,将产物用CH_2Cl_2萃取,将合并的有机萃取物经Na_2SO_4干燥,并将溶剂减压蒸馏除去。游离碱通过在二噁烷中加入无水HCl而转化为HCl盐,减压下去除溶剂,得到呈白色固体的所需产物(0.252g,37%)。

[0281] 合成氨基甲酸酯的一般方法

[0282] 

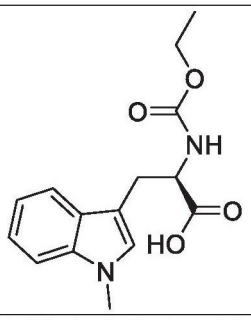
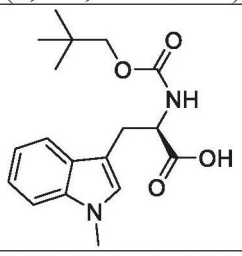
D-1MT

[0283] 向D-1MT(0.150g,0.687mmol)于1:1 THF/1M $NaHCO_3$(2.75mL,2.75mmol)中的搅拌溶液中逐滴加入适当的氯甲酸酯。将混合物搅拌30分钟,并且将溶液用水稀释并用乙醚萃取2次。将水层冷却至0℃,并加入浓HCl溶液将pH调节至约1。立即用乙酸乙酯萃取冷水层,并将合并的有机层用水、盐水洗涤并干燥。减压下去除溶剂以提供粗制氨基甲酸酯。将粗物质通过柱色谱纯化并用活性炭处理,以得到纯氨基甲酸酯。

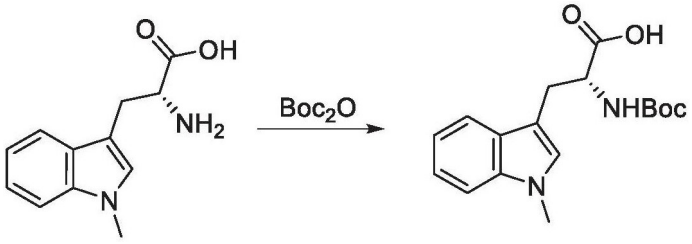
[0284]

#	化合物	名称	产率

[0285]

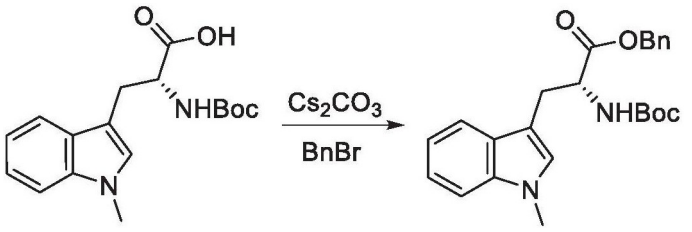
			(%)
NLG-1277		N^{α}-(乙氧基羰基)-1-甲基-D-色氨酸	81
	1.23 (t, 3H, J = 6.8 Hz), 3.63-3.71 (m, 1H), 3.74 (s, 3H), 4.07-4.12 (m, 2H), 4.69 (dd, 1H, J = 6.7, 11.6 Hz), 5.20 (dd, 1H, J = 6.9, 11.5 Hz), 6.9 (s, 1H), 7.07 (t, 1H, 6.9 Hz), 7.21-7.48 (m, 2H), 7.57 (d, 1H, J = 7.1 Hz), 9.07 (br s, 1H)		
NLG-1278		1-甲基-N^{α}-((新戊基氧基)羰基)-D-色氨酸	72
	0.90 (s, 9H), 3.34 (s, 2H), 3.64 (s, 3H), 3.73 (t, 1H, J = 6.8 Hz), 4.75 (d, 1H, J= 7.8 Hz), 5.23 (d, 1H, J = 7.9 Hz), 6.89 (s, 1H), 7.07 (t, 1H, J = 8.2 Hz), 7.25-7.59 (m 与 CHCl3 重叠, 2H), 7.58 (d, 1H, 7.8 Hz), 8.4 (br s, 2H)		

[0286] 合成N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸

[0287] 

[0288] 在0℃下向D-1MT(3.0g,13.75mmol)于二噁烷(70mL)中的混合物中加入NaOH(550mg溶解在30mL去离子水中),然后加入Boc_2O。将反应物在0℃下搅拌4小时,并在室温下搅拌过夜。将溶液在减压下浓缩至原始体积的约三分之一。将反应物在0℃下用1N HCl酸化,并将产物用EtOAc萃取。将有机萃取物用盐水洗涤,并经Na_2SO_4干燥,减压下蒸发溶剂以得到产物,其无需进一步纯化直接用于下一步(4.3g,98%)。

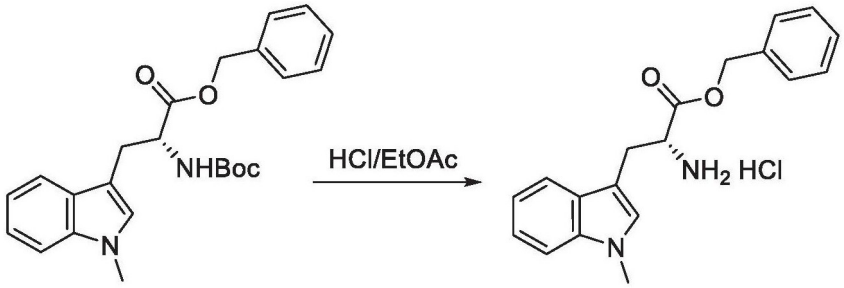
[0289] 合成N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯

[0290] 

[0291] 在60ml DMF中溶解N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸(3.00g,9.42mmol),向其中加入Cs_2CO_3(1.78g,5.47mmol)和苄基溴(1.61mL,9.42mmol)。使所得的混悬液在室温下

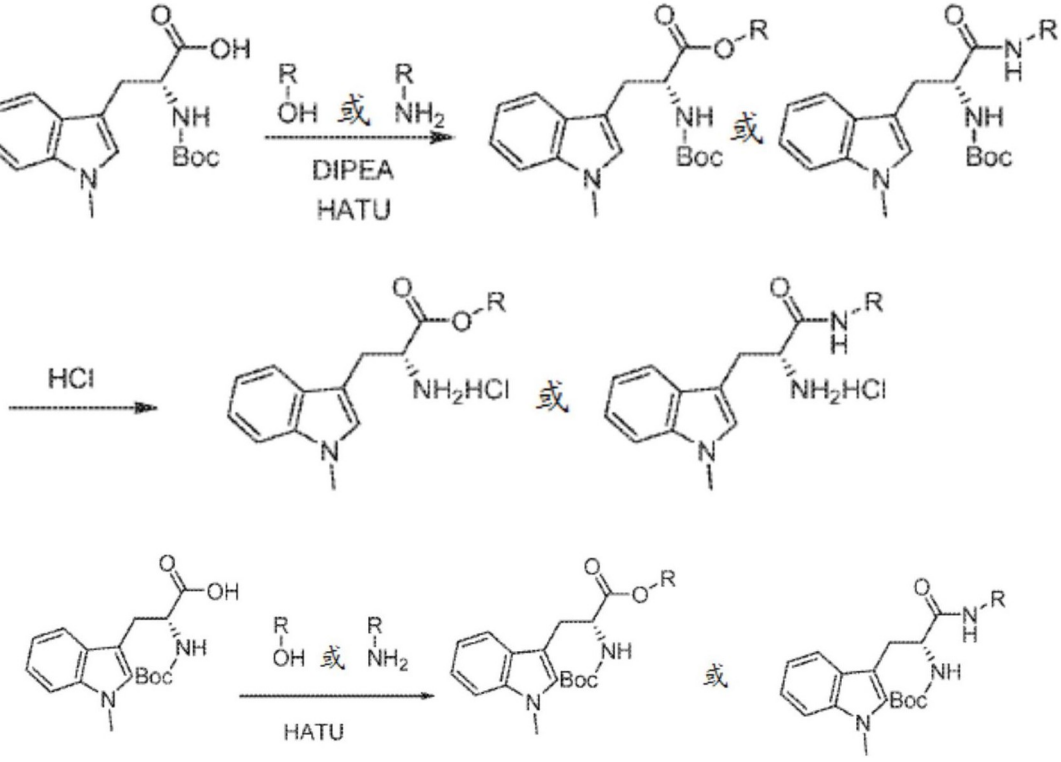
搅拌2小时。反应(TLC)结束后,减压下除去DMF,然后将残余物混悬在甲苯/乙酸乙酯中,之后用蒸馏水(3x50mL)和盐水洗涤。将有机层经无水硫酸钠干燥并真空浓缩。将残余物通过硅胶柱色谱纯化(3.5g,91%)。

[0292] 合成1-甲基-D-色氨酸苄酯盐酸盐(NLG-1338)

[0293] 

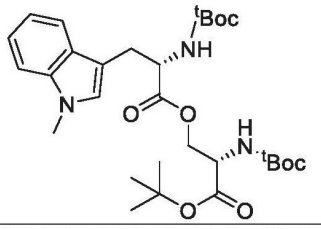
[0294] 在搅拌下,在冰浴中冷却装备有隔片和针孔的RB烧瓶中的乙酸乙酯(26.9mL)和MeOH(8.9mL)。缓慢加入乙酰氯(14.22mL)。将所得溶液在0℃下搅拌20分钟,并加入MeOH(0.5mL)。将含有N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯(3.5g,8.6mmol)的烧瓶置于冰浴中,并将冷的新鲜制备的HCl(4M于EtOAc中)慢慢倾入含有N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸苄酯的烧瓶中。在0℃下将溶液剧烈搅拌15分钟,其中观察到白色混悬液形成,并将烧瓶从冰浴中取出。将混悬液剧烈搅拌2.5小时。将溶液在用乙醚(50mL)稀释的冰浴中冷却,并且过滤悬浮液,并将固体滤饼用冷乙醚洗涤。将固体在高真空下干燥,并分离出呈无色固体的所需产物(6.45g,88%)。1H NMR(d_6-dmdso);3.28(dd,2H,J=5.6,15.2Hz),3.70(s,3H),4.26-4.29(m,1H),5.08(d,1H,J=12.4Hz),5.13(d,1H,J=12.4Hz),7.04(t,1H,J=7.6Hz),7.06(s,1H),7.10-7.18(m,3H),7.30-7.35(m,3H),7.42(d,1H,J=8Hz),7.53(d,1H,J=8Hz)。

[0295] D-1MT的-COOH基团的衍生化的一般方案

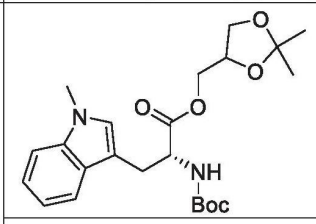
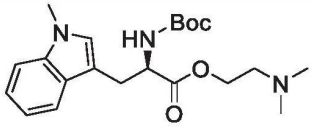
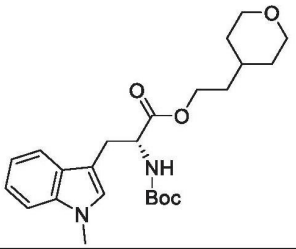
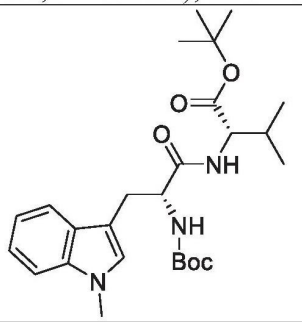
[0296] 

[0297] 向N-(叔丁氧基羰基)-1-甲基-D-色氨酸(3.14mmol)、适当的醇或胺(3.14mmol)和HATU(3.14mmol)在乙腈(30mL)中的溶液中加入DIPEA(9.42mmol)，并使溶液升温至室温。搅拌过夜(17小时)后，将反应物用水(50mL)稀释，并将产物用CH_2Cl_2(3x50mL)萃取。将合并的有机萃取物用水(25mLx1)、盐水(25mlx1)洗涤，经Na_2SO_4干燥并减压浓缩，以得到粗物质。色谱纯化得到所需产品。

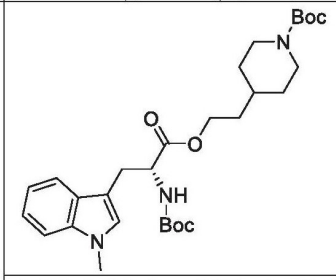
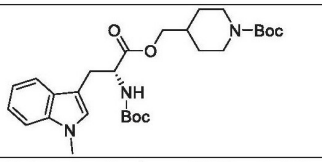
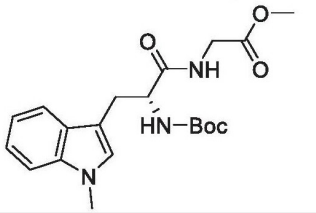
[0298]

#	化合物	名称	产率(%)
NLG-1551-B.1-E15		(S)-Na-(叔丁氧基羰基)-1-甲基-D-色氨酸 3-(叔丁氧基)-2-((叔丁氧基羰基)氨基)-3-氧代丙酯	40
	1.41 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H),3.16 (dd, 1H, J = 15.3, 4.8 Hz), 3.29 (dd, 1H, J = 15.3, 4.8 Hz),3.75 (s, 3H),4.35-4.52 (m, 3H),4.61 (d,		

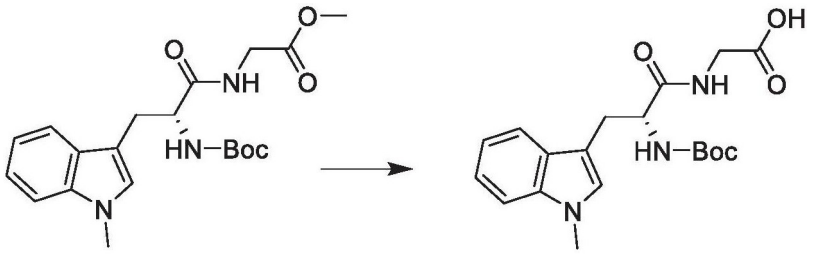
[0299]

	1H, J = 6.3 Hz),4.99 (d, 1H, J = 8.6 Hz), 5.28 (d, 1H, J = 8.7 Hz),6.87 (s, 1H), 7.11 (t, 1H , J = 7.3 Hz), 7.22 (t, 1H , J = 7.3 Hz), 7.29 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 7.8 Hz)。		
NLG-1558-A-E23		N-(叔丁氧基羰基)-1-甲基-D-色氨酸(2,2-二甲基-1,3-二氧杂环戊烷-4-基)甲酯	78
	1.27 (s, 3H), 1.33 (s, 3H), 1.35 (s, 9 H), 3.21 (d, 2H, J = 5.6 Hz),3.44-3.50 (m, 1H), 3.67 (s, 3H), 3.80-3.86 (m, 1H), 3.99-4.03 (m, 2H), 4.07-4.12 (m, 1H), 4.58 (q, 1H, J = 6.5 Hz), 4.99 (d, 1H, J = 8.2 Hz), 6.82 (s, 1H), 7.03 (t, 1H, J = 7.4 Hz), 7.14 (t, 1H, J = 7.4 Hz), 7.21 (d, 1H, J = 8.1 Hz), 7.47 (d, 1H, J = 8.0 Hz)。		
NLG-1557-B-E14		N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸 2-(二甲基氨基)乙酯	38
	1.33 (s, 1H), 1.43 (s, 8H), 2.23 (s, 5H), 2.29 (s, 1H), 2.43 – 2.60 (m, 4H), 3.27 (d, *J* = 5.6 Hz, 2H), 3.74 (s, 3H), 4.1 – 4.23 (m, 2H), 4.63 (m, 1H), 5.10 (m, 1H), 6.91 (s, 1H), 7.10 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.21 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.28 (d, *J* = 8.0, 1H), 7.54 (d, *J* = 8.0 Hz, 1H)。		
NLG-1572-A-E39		N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸 2-(四氢-2H-吡喃-4-基)乙酯	60
	1.29 – 1.35 (m, 2H), 1.42 (s, 9H), 1.60-1.67 (m, 5H), 3.17 – 3.35 (m, 4H), 3.74 (s, 3H), 3.84 – 3.93 (m, 2H), 4.10 (dq, 2H, *J* = 10.4, 6.4 Hz), 4.55 – 4.65 (m, 1H), 5.06 (d, 1H, *J* = 8.2 Hz), 6.86 (s, 1H), 7.09 (ddd, 1H, *J* = 8.0, 7.0, 1.1 Hz), 7.21 (ddd, 1H, *J* = 8.2, 6.9, 1.1 Hz), 7.28 (d, 1H, *J* = 7.4 Hz), 7.48 – 7.59 (m, 1H)		
NLG-1556-A-E22		N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酰-L-缬氨酸叔丁酯	91
	0.69 (d, 3H, J = 6.8 Hz), 0.75 (d, 3H, J = 6.8 Hz), 1.42 (s, 18H), 1.98-2.03 (m, 1H), 3.18 (dd, 1H, J = 14.4, 7.2 Hz), 3.27-3.35 (m, 1H), 3.73 (s, 3H), 4.35-4.39 (m, 1H), 4.50 (br s, 1H), 5.07 (br s, 1H), 6.31		

[0300]

	(d, 1H, J = 8.8 Hz), 6.92 (s, 1H), 7.12 (t, 1H, J = 7.2 Hz), 7.22 (t, 1H, J = 7.2 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 8.0 Hz)		
NLG-1561-A-E29		4-(2-((Nα-(叔丁氧基羰基)-1-甲基-D-色氨酰)氧基)乙基)哌啶-1-甲酸叔丁酯	92
	0.95-1.05 (m, 2H), 1.47 (s, 18H), 1.32-1.40 (m, 3H), 1.55 (d, 2H, J = 2.4 Hz), 2.59 (dt, 2H, J = 2.7, 12.8 Hz), 3.25 (d, 2H, J = 5.6 Hz), 3.74 (s, 3H), 3.99-4.05 (m, 2H), 4.94-5.00 (m, 2H), 5.08 (d, 1H, J = 8.0 Hz), 6.52 (br s, 1H), 6.86 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz)。		
NLG-1563-A-E30		4-(((Nα-(叔丁氧基羰基)-1-甲基-D-色氨酰)氧基)甲基)哌啶-1-甲酸叔丁酯	83
	0.93-1.10 (m, 2H), 1.29-1.32 (m, 1H), 1.45 (s, 18H), 1.63-1.69 (m, 2H), 2.59 (tt, 2H, J = 2.4, 13.2 Hz), 3.25 (t, 2H, J = 5.4 Hz), 3.75 (s, 3H), 3.84-3.92 (m, 2H), 4.01-4.06 (m, 2H), 5.06 (d, 1H, J = 8.0 Hz), 6.35 (br s, 1H), 6.86 (s, 1H), 7.10 (dt, 1H, J = 1.2, 6.8 Hz), 7.24 (dt, 1H, J = 1.2, 6.8 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.53 (d, 1H, J = 8.0 Hz)		
NLG-1578-A-E43		Nα-(叔丁氧基羰基)-1-甲基-D-色氨酰甘氨酸甲酯	91
	1.25 (s, 9H), 3.15-3.25 (m, 2H), 3.67 和 3.69 (两个 s, 3H), 3.70 和 3.71 (两个 s, 3H), 3.90-3.92 (m, 2H), 5.21 和 4.48 (s, 1H), 6.54-6.52 (m, 1H), 6.93 (s, 1H), 7.13 – 7.03 (m, 1H), 7.14 – 7.30 (m, 2H), 7.59 (d, 1H, *J* = 8.0 Hz)。		

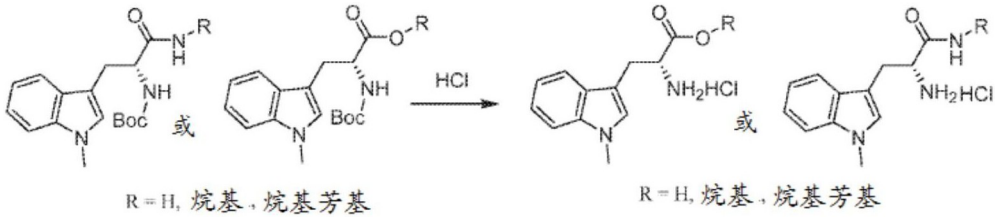
[0301] 合成Nα-(叔丁氧基羰基)-1-甲基-D-色氨酰甘氨酸(NLG-1579-A-E44)

[0302] 

NLG-1578-A-E43 **NLG-1579-A-E44**

[0303] 向NLG-1578-A-E43(300mg,0.770mmol)于THF(10mL)中的溶液添加水(2mL)和锂一水合物(49mg,1.16mmol),并将混合物在环境温度下搅拌2.0小时。将混合物用1M HCl(在0℃下)中和并倾倒至冰冷水(20mL)中。将水层用EtOAc(3x35mL)萃取。将合并的有机层经Na_2SO_4干燥并浓缩。将粗产物通过快速柱色谱纯化以得到呈白色固体的所需产物(260mg,

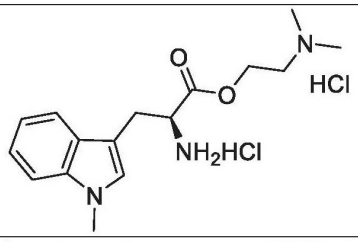
90%)。^{1}H NMR:1.25和1.39(两个s,9H).3.18-3.24(m,2H),3.70(s,3H),3.81-4.05(m,2H),4.55(s,1H),5.20-5.33(m,1H),6.63(s,1H),6.92(s,1H),7.10(t,1H,J=7.2Hz),7.15-7.25(m,2H),7.59(dt,1H,J=7.9Hz)

[0304] 

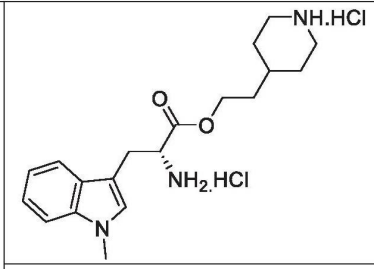
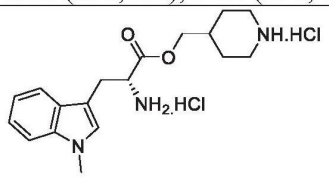
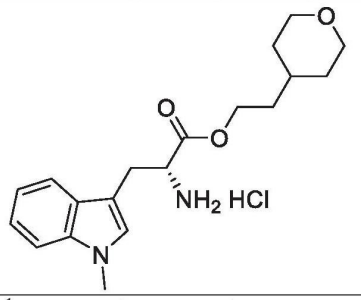
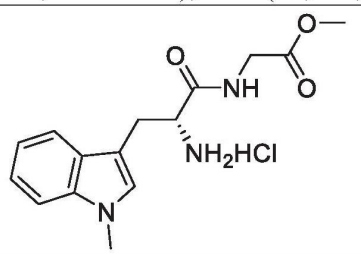
[0305] 在室温下,向于二噁烷(15mL)中的tBoc保护的胺(1.57mmol)的混合物中加入HCl(4mL,4.0M溶液于二噁烷中)。搅拌2.5小时后,减压下蒸馏除去溶剂。将残余物与甲基叔丁醚(10mL)一起搅拌,将固体过滤并在减压下干燥,以得到所需产物。

[0306] 按照以上部分所述的程序合成以下化合物。

[0307]

#	化合物	名称	产率(%)
NLG-1557		1-甲基-D-色氨酸 2-(二甲基氨基)乙酯二盐酸盐	42
	^{1}H NMR (400 MHz, 甲醇-d_4): 2.69 (s, 3H), 2.77 (s, 3H), 3.46 (dd, J = 6.7, 2.1 Hz, 2H), 3.81 (s, 3H), 4.35 (m, 1H), 4.46 (t, J = 6.6 Hz, 1H), 4.54 (m, Hz, 1H), 7.11 (dd, J = 8.0 1.2 Hz, 1H), 7.18 – 7.25 (m, 2H), 7.40 (d, J = 8.0), 7.58 (d, J = 8.0, 1H)。		

[0308]

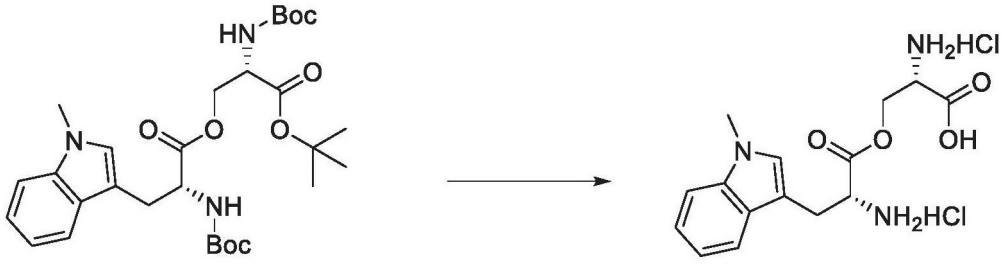
NLG-1561		1-甲基-D-色氨酸 2-(哌啶-4-基)乙酯二盐酸盐	64
	(DMSO-d6) 1.24-1.45 (m, 5H), 1.60 (d, 2H, J = 13.2 Hz), 2.64-2.72 (m, 2H), 3.11-3.14 (m, 2H), 3.25 (dd, 1H, J = 14.4, 7.6 Hz), 3.33-3.83 (m, 1H, 与来自DMSO的HO合并), 3.75 (s, 3H), 3.99-4.08 (m, 2H), 4.15 (t, 1H, J = 6.6 Hz), 7.04 (t, 1H, J = 7.4 Hz), 7.16 (t, 1H, J = 7.6 Hz), 7.24 (s, 1H), 7.42 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 8.75 (br s, 3H), 8.95 (br s, 1H), 9.16 (br s, 1H)		
NLG-1563		1-甲基-D-色氨酸哌啶-4-基甲酯二盐酸盐	50
	(DMSO-d6) 1.16-1.34 (m, 2H), 1.41 (d, 1H, J = 13.6 Hz), 1.53 (d, 1H, J = 13.6 Hz), 1.61-1.66 (m, 1H), 2.66-2.70 (m, 2H), 3.08-3.16 (m, 2H), 3.22-3.28 (m, 1H), 3.36-3.44 (m, 1H), 3.74 (s, 3H), 3.78-3.88 (m, 2H), 4.12-4.17 (m, 1H), 7.05 (t, 1H, J = 7.4 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.24 (s, 1H), 7.40 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 7.6 Hz), 8.83 (br s 3H), 9.06 (br s, 1H), 9.34 (br s, 1H)		
NLG-1572		1-甲基-D-色氨酸 2-(四氢-2H-吡喃-4-基)乙酯盐酸盐	94
	^{1}H NMR(DMSO-d_6, 400 MHz): δ = 0.93 – 1.11 (m, 2H), 1.18 (d, 1H, *J* = 6.2 Hz), 1.26 – 1.43 (m, 4H), 3.14 (d, 2H, *J* = 11.2 Hz), 3.23 (dd, 1H, *J* = 14.7, 7.7 Hz), 3.29 – 3.39 (m, 2H), 3.69-3.78 (m, 4H), 4.04 (d, 2H, *J* = 6.2 Hz), 4.17 (t, 1H, *J* = 6.6 Hz), 7.04 (ddd, 1H, *J* = 8.0, 7.1, 1.0 Hz), 7.16 (ddd, 1H, *J* = 8.3, 7.0,1.2 Hz), 7.23 (s, 1H), 7.42 (d, 1H, *J* = 8.2 Hz), 7.53 (dd, 1H, *J* = 8.1, 1.4 Hz), 8.69 (br s, 3H)。		
NLG-1578		1-甲基-D-色氨酰甘氨酸甲酯盐酸盐	93
	3.12 (dd, 1H, *J* = 14.7, 7.8 Hz,), 3.25 (dd, 1H, *J* = 14.7, 5.7 Hz),		

[0309]

	3.64 (s, 3H), 3.72 (s, 3H), 3.93 (t, 2H, *J* = 6.0 Hz), 3.97-4.06 (m, 1H), 7.03 (t, 1H, *J* = 7.5 Hz), 7.14 (t, 1H, *J* = 7.20 Hz), 7.19 (s, 1H), 7.39 (d, 1H, *J* = 8.2 Hz), 7.71 (d, 1H, *J* = 8.0 Hz), 8.21 (s, 2H), 9.15 (m, 1H)。

[0310] 合成O-(1-甲基-D-色氨酰)-L-丝氨酸二盐酸盐(NL-G1551)

[0311]

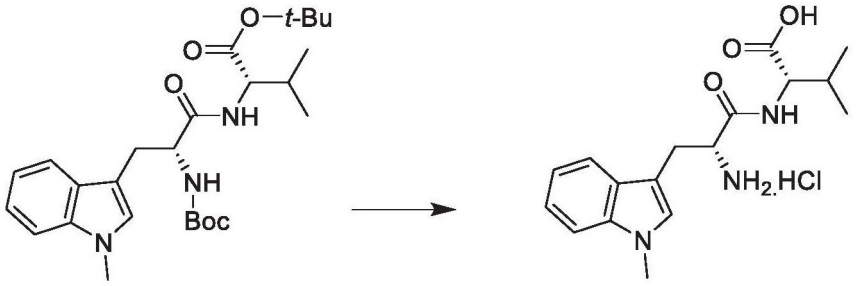


NLG-1551-B.1-E15 **NLG-1551**

[0312] 在0℃下向NLG-1551-B.1-E15(0.450g,824.66mmol)于CH_2Cl_2(10mL)中的溶液添加HCl(2mL,4M溶液于二噁烷中),并使溶液升温至室温。在搅拌5小时后,蒸发溶剂并将反应物用三氟乙酸(8mL)稀释,并将溶液在室温下搅拌7小时。在蒸发三氟乙酸后,将反应物用无水HCl溶液(1mL,4M溶液于二噁烷中)稀释并将混合物搅拌10分钟。减压下蒸发溶剂,将产物用乙醇:乙醚(10:90,15mL)研磨,并且将产物过滤并用无水乙醚(10mL)洗涤。减压下干燥产物(0.190g,61%)。^{1}H NMR(400MHz,CD_3OD):3.22-3.28(m,1H),3.43(dd,1H,J=15.4,4.7Hz),3.70(s,3H),4.23(t,1H,J=3.9Hz),4.35(dd,1H,J=8.0,4.9Hz),4.60(d,2H,J=3.8Hz),6.99-7.04(m,1H),7.05(s,1H),7.09-7.16(m,1H),7.29(d,1H,J=8.3Hz),7.50(d,1H,J=7.9Hz)。

[0313] 合成1-甲基-D-色氨酰-L-缬氨酸盐酸盐(NLG-1556)

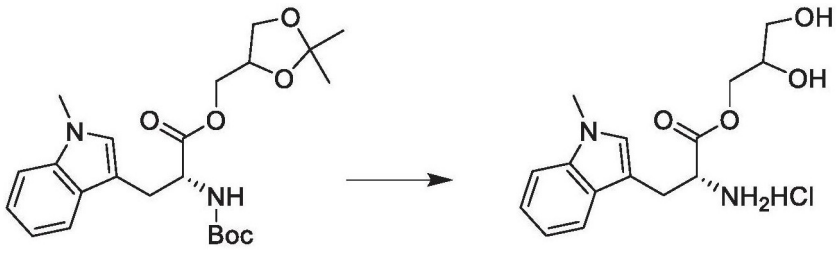
[0314]



NLG-1556-A-E22 **NLG-1556**

[0315] 将于装备有隔片和针孔的RB烧瓶中的二噁烷(7mL)和MeOH(1.20mL,28.6mmol)在冰浴中搅拌冷却。缓慢添加乙酰氯(2.00mL,28.6mmol)。将所得溶液在0℃下搅拌20分钟并添加MeOH(0.1mL)。将含有NLG-1556-A-E22(678mg,1.43mmol)的烧瓶放置于冰浴中,并将冷的新鲜制备的HCl(4M于二噁烷中)缓慢倾倒至含有NLG-1556-A-E22的烧瓶中。使溶液升温至室温并剧烈搅拌18小时。使用旋转蒸发仪去除溶剂以得到纯白色固体(205mg,40%)。(DMSO-d6)0.71-0.77(m,6H),1.91-2.00(m,1H),3.08(dd,1H,J=14.4,8.4Hz),3.23(dd,1H,J=14.4,8.4Hz),3.73(s,3H),4.12-4.17(m,2H),7.06(t,1H,J=7.4Hz),7.17(t,1H,J=7.8Hz),7.20(s,1H),7.40(d,1H,J=8.4Hz),7.74(d,1H,J=8.0Hz),8.2(br s,3H),8.74(d,1H,J=8.4Hz)

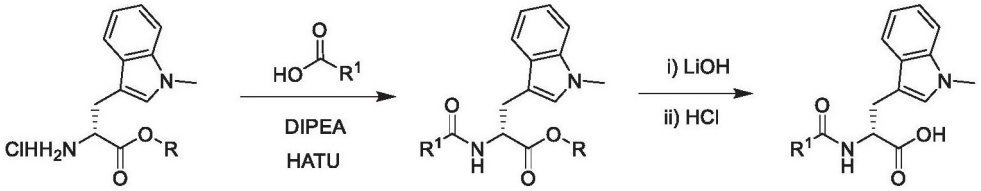
[0316] 合成1-甲基-D-色氨酸2,3-二羟丙酯盐酸盐(NLG-1558)

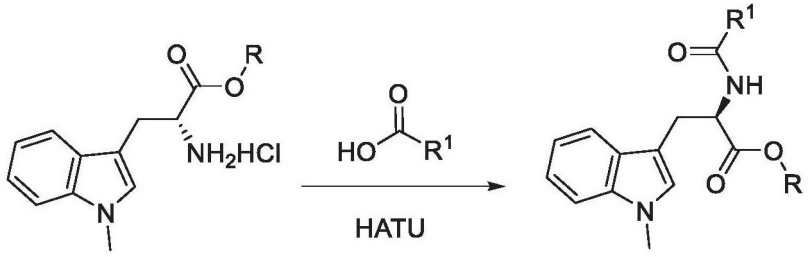
[0317] 

NLG1558-A-E23 NLG-1558

[0318] 在0℃下向NLG1558-A-E23(11.5g,26.59mmol)于THF(100mL)中的溶液添加TFA(16.3mL,212.7mmol)和水(0.958g,53.18mmol)并去除冷却浴,将混合物在室温下搅拌2小时。添加HCl(13.3mL,53.18mmol;4.0M溶液于二噁烷中)并继续搅拌1小时。将反应物在40℃下搅拌45分钟。将沉淀的白色固体过滤并用MTBE洗涤以得到盐酸盐(4.5g,51%)。^{1}H NMR(400MHz,DMSO-d_6):3.32-3.40(m,1H),3.44-3.52(m,3H),3.76-3.86(m,4H),4.16-4.37(m,3H),7.10(t,1H,J=7.4Hz),7.14(s,1H),7.19(t,1H,J=7.6Hz),7.38(d,1H,J=8.2Hz),7.58(d,1H,J=7.9Hz)。

[0319] D-1MT的-NH_2和-COOH基团的衍生化的一般方案

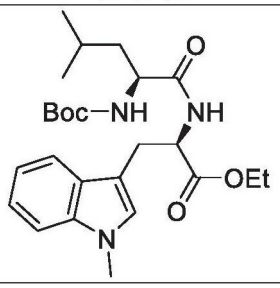


[0320] 

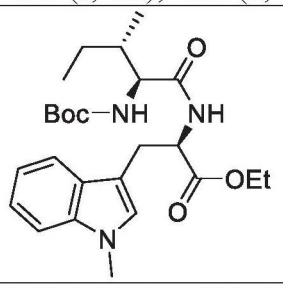
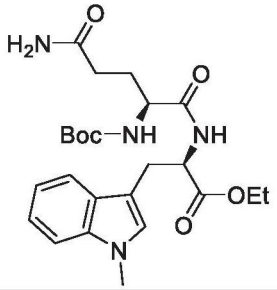
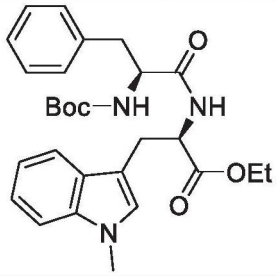
R = Et, Bn

[0321] 将适当的D-色氨酸酯盐酸盐酯(1.0g,3.54mmol)和适当的酸(3.54mmol)在0℃下在乙腈(50mL)中搅拌。添加HATU(1.48g,3.89mmol)和iPr_2Net(2.46mL,14.15mmol),并将反应物在室温下搅拌过夜。减压下去除溶剂并将粗物质用水(50mL)和二氯甲烷(50mL)稀释。分离有机层并将水层用二氯甲烷(3x50mL)萃取。将合并的有机层用盐水(50mL)洗涤、经Na_2SO_4干燥并减压浓缩。将粗产物通过快速柱色谱纯化,以得到所需产物。

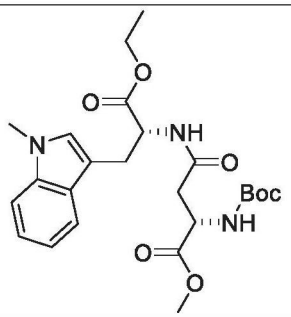
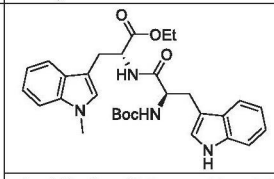
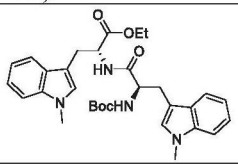
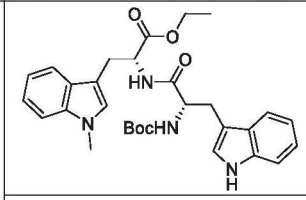
[0322]

#	化合物	名称	产率(%)
NLG-1564-B-E31		N^{α}-((叔丁氧基羰基)-L-亮氨酰)-1-甲基-D-色氨酸乙酯	92

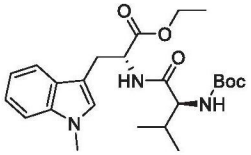
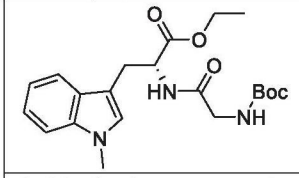
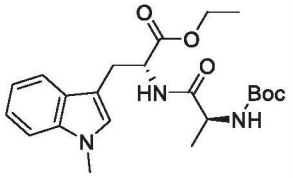
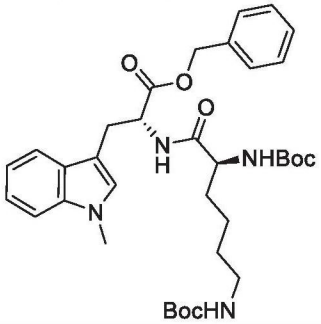
[0323]

	0.86 (dd, 6H, J = 6.2, 2.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.39 (s, 9H), 1.55-1.58 (m, 2H), 3.29 (d, 2H, J = 5.7 Hz), 3.74 (s, 3H), 4.03-4.18 (m, 3H), 4.79-4.86 (m, 2H), 6.60 (d, 1H, J = 7.8 Hz), 6.87 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.26 (s, 1H), 7.52 (d, 1H, J = 7.9 Hz)		
NLG-1565-A-E32		N^{α}-((叔丁氧基羰基)-L-异亮氨酰)-1-甲基-D-色氨酸乙酯	93
	0.80-0.84 (m, 6H), 1.02 – 0.91 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz), 1.40 (s, 9 H), 1.87 (m, 1H), 3.28 (t, 2H, *J* = 5.4 Hz), 3.72 (s, 3H), 4.00 – 4.04 (m, 1H), 4.05- 4.16 (m, 2H), 4.85 (q, 1H, *J* = 6.4 Hz), 4.95 (d, 1H, *J* = 9.0 Hz), 6.46 (d, 1H, *J* = 7.7 Hz), 6.87 (s, 1H), 7.10 (ddd, 1H, *J* = 8.0, 6.8, 1.1 Hz), 7.20 (ddd, 1H, *J* = 8.2, 6.9, 1.2 Hz), 7.26 (d, 1H, J = 8.0 Hz), 7.53 (dt, 1H, *J* = 7.9, 1.0 Hz)		
NLG-1566-A-E37		N^{α}-((叔丁氧基羰基)-L-谷酰氨基)-1-甲基-D-色氨酸乙酯	90
	1.16 (t, 3H, *J* = 7.1 H), 1.33 (s, 9H), 1.79 – 1.99 (m, 2H), 2.05 (ddd, 1H, *J* = 15.2, 6.9, 5.7 Hz), 2.18 (ddd, 1H, *J* = 14.8, 8.6, 5.9 Hz), 3.21 (d, 2H, *J* = 5.9 Hz), 3.68 (s, 3H), 4.00 – 4.14 (m, 3H), 4.75 (dt, 1H, *J* = 7.7, 5.9 Hz), 5.22 (s, 1H), 5.55 (d, 1H, *J* = 7.0 Hz), 5.90 (s, 1H), 6.85 (s, 1H), 6.87 – 6.93 (m, 1H), 7.04 (ddd, 1H, *J* = 8.0, 6.9, 1.1 Hz), 7.14 (ddd, 1H, *J* = 8.2, 6.9, 1.1 Hz), 7.17 – 7.21 (m, 1H), 7.45 (d, 1H, *J* = 7.9 Hz)。		
NLG-1574-A-E40		N^{α}-((叔丁氧基羰基)-L-苯基丙氨酰)-1-甲基-D-色氨酸乙酯	80
	1.14 (t, 3H, *J* = 7.1 H), 1.29 (s, 9H), 2.82 (s, 2H), 2.91-3.02 (m, 1H), 3.03-3.10 (m, 2H), 3.25 (dd, 1H, *J* = 14.78, 5.2 Hz), 3.67 (s, 3H), 3.99 - 4.07 (m, 2H), 4.33 (br s, 1H), 4.79 (q, 1H, *J* = 6.2 Hz), 6.37 (d, 1H , *J* = 7.8 Hz), 6.57 (s, 1H), 7.06 (ddd, 1H , *J* = 8.0, 6.8, 1.2 Hz), 7.14 – 7.25 (m, 6H), 7.41 (d, 1H, *J* = 7.9 Hz)。		

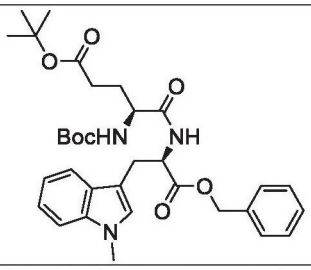
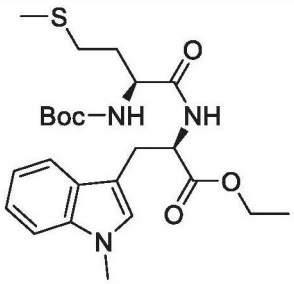
[0324]

NLG-1585-A-E45		N^2-(叔丁氧基羰基)-N^4-((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)-L-天冬酰胺甲酯	71
	1.18 (t, 3H, *J* = 7.2 Hz), 1.39 (s, 9H), 2.63 (dd, 1H, *J* = 17.1, 6.1 Hz), 2.95 (dd, 1H, J = 17.2, 4.4 Hz), 3.29 (d, 2H, *J* = 5.8 Hz), 3.62 (s, 3H), 3.74 (s, 3H), 4.03-4.13 (m, 2H), 4.53 (br s, 1H), 4.79-4.83 (m, 1H), 5.61 (d, 1H, *J* = 9.0 Hz), 6.88 (s, 1H), 7.01-7.10 (m, 2H), 7.19 (ddd, 1H, *J* = 8.2, 6.9, 1.2 Hz), 7.24-7.27 (m, 1H), 7.51 (m, 1H)。		
NLG-1546-B-E20		Nα-((叔丁氧基羰基)-D-色氨酰)-1-甲基-D-色氨酸乙酯	97
	1.18 (t, 3H, *J* = 7.1 Hz), 1.38 (s, 9H), 1.73 (br s, 1H), 3.13 (dd, 2H, *J* = 5.4, 2.5 Hz), 3.32 (s, 1H), 3.57 (s, 3H), 4.05 (dd, 2H, *J* = 17.2, 7.2 Hz), 4.43 (s, 1H), 4.72 – 4.80 (m, 1H), 5.07 (s, 1H), 6.22 (s, 1H), 6.42 (s, 1H), 6.90 (s, 1H), 6.97 (s, 1H), 7.04 – 7.25 (m, 5H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.87 (s, 1H)		
NLG-1549-A-E26		Nα-(Nα-(叔丁氧基羰基)-1-甲基-D-色氨酰)-1-甲基-D-色氨酸乙酯	95
	1.16 (t, 3H, *J* = 7.1 Hz), 1.37 (s, 9H), 3.02 – 3.20 (m, 3H), 3.35 (d, 1H, *J* = 15.0 Hz), 3.57 (s, 3H), 3.68 (s, 3H), 3.94 – 4.10 (m, 2H), 4.42 (br s, 1H), 4.75 (d, 1H, *J* = 6.8 Hz), 5.04 (s, 1H), 6.24 (br s, 1H), 6.37 (s, 1H), 6.84 (br s, 1H), 6.94 (s, 1H), 7.08-7.18 (m, 3H), 7.17 – 7.25 (m, 2H), 7.27 – 7.33 (m, 1H), 7.65 (d, 1H, *J* = 7.9 Hz)		
NLG-1560-B-E28		Nα-((叔丁氧基羰基)-L-色氨酰)-1-甲基-D-色氨酸乙酯	97
	1.12 (t, 3H, *J* = 7.1 Hz), 1.39 (s, 9H), 2.90 (d, 1H, *J* = 15.2 Hz), 3.05 – 3.32 (m, 3H), 3.56 (s, 3H), 3.91 – 4.10 (m, 2H), 4.44 (br s, 1H), 4.75 (br s, 1H), 5.15 (br s, 1H), 6.18 (d, 1H, *J* = 7.8 Hz), 6.27 (s, 1H), 6.86 (d, 1H, *J* = 2.3 Hz), 7.04 (ddd, 1H, *J* = 8.0, 6.8, 1.2 Hz), 7.14 (ddd, 1H, *J* = 8.0, 7.1, 1.2 Hz), 7.16 – 7.27 (m, 3H), 7.30 (dt, 1H, *J* = 8.1, 1.0 Hz), 7.37 (d, 1H, *J* = 8.2 Hz), 7.68 (d, 1H, *J* = 7.7 Hz), 7.80 (s, 1H)		

[0325]

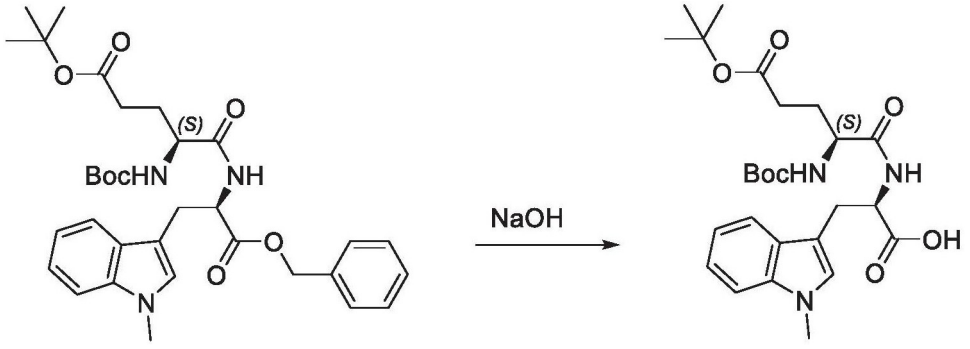
NLG-1553-B-E21		N^{α}-((叔丁氧基羰基)-L-缬氨酰)-1-甲基-D-色氨酸乙酯	95
	0.80 (d, 3H, J = 6.8 Hz), 0.87 (d, 3H, J = 6.8 Hz), 1.19 (t, 3H, J = 7.2 Hz), 1.40 (s, 9H), 2.09-2.17 (m, 1H), 3.25-3.32 (m, 2H), 3.74 (s, 3H), 3.94-3.97 (m, 1H), 4.09-4.15 (m, 2H), 4.84-4.89 (m, 1H), 4.93-4.95 (m, 1H), 6.45 (d, 1H, J = 7.6 Hz), 6.87 (s, 1H), 7.10 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 7.6 Hz), 7.53 (dd, 1H, J = 8.0, 1.2 Hz)		
NLG-1554-A-E25		N^{α}-((叔丁氧基羰基)甘氨酰)-1-甲基-D-色氨酸乙酯	94
	1.22 (t, 3H, J = 7.2 Hz), 1.42 (s, 9H), 3.31 (d, 2H, J = 5.2 Hz), 3.72-3.77 (m, 2H), 3.74 (s, 3H), 4.07-4.17 (m, 2H), 4.86-4.91 (m, 1H), 5.04 (br s, 1H), 6.50 (d, 1H, J = 7.6 Hz), 6.86 (s, 1H), 7.10 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.4 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 7.6 Hz)		
NLG-1555-A-E27		N^{α}-((叔丁氧基羰基)-L-丙氨酰)-1-甲基-D-色氨酸乙酯	95
	1.20 (t, 3H, J = 7.0 Hz), 1.29 (d, 3H, J = 7.2 Hz), 1.40 (s, 9H), 3.30 (d, 1H, J = 5.6 Hz), 3.75 (s, 3H), 4.09-4.16 (m, 3H), 4.81-4.86 (m, 1H), 4.93 (br s, 1H), 6.61 (br s, 1H), 6.87 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.27 (d, 1H, J = 8.4 Hz, 与氯仿合并), 7.52 (d, 1H, J = 8.0 Hz)		
NLG-1548-A-E18		N^{α}-(N^{2},N^{6}-双(叔丁氧基羰基)-L-赖氨酰)-1-甲基-D-色氨酸苄酯	91
	^{1}H NMR (400 MHz, 氯仿-*d*) δ 1.25 (q, *J* = 7.7 Hz, 2H), 1.39 (s, 9H), 1.44 (s, 9H), 1.47 – 1.55 (m, 1H), 1.67 – 1.80 (m, 2H), 3.02 (t, *J* = 6.7 Hz, 2H), 3.29 (d, *J* = 5.5 Hz, 2H), 3.66 (s, 3H), 4.04 (s, 1H), 4.53 (s, 1H), 4.90 (q, *J* = 6.1 Hz, 1H), 4.97 (s, 1H), 5.09 (q, *J* = 12.2 Hz, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.64 (s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.23 – 7.29 (m, 4H 与 $CHCl_3$ 重叠), 7.30 – 7.39 (m, 3H), 7.49 (d, *J* = 7.9 Hz, 1H)。		

[0326]

NLG-1547-D-E17		(S)-5-(((R)-1-(苄基氧基)-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-4-((叔丁氧基羰基)氨基)-5-氧代戊酸叔丁酯	93
	δ 1.38 (s, 9H), 1.43 (s, 9H), 1.76 – 1.91 (m, 1H), 1.94 – 2.09 (m, 1H), 2.20 (dt, *J* = 16.6, 7.0 Hz, 1H), 2.31 (dt, *J* = 16.6, 7.3 Hz, 1H), 3.19 – 3.36 (m, 2H), 3.67 (s, 3H), 4.90 (dt, *J* = 8.1, 5.6 Hz, 1H), 5.00 – 5.14 (m, 2H), 5.19 (s, 1H), 6.70 (s 重叠 m, 2H), 7.08 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.18 – 7.28 (m, 4H), 7.29 – 7.37 (m, 2H), 7.50 (dt, *J* = 8.0, 1.0 Hz, 1H)。		
DD-00508-B-E078		N^{α}-((叔丁氧基羰基)-L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	84
	δ 1.21 (t, *J*=7.2 Hz, 3H), 1.40 (s, 9H), 1.79 – 1.89 (m, 1H), 1.94 – 2.00 (m, 1H), 2.01 (s, 3H), 2.31-2.36 (m, 1H), 2.36-2.46 (m, 1H), 3.30 (dd, *J*=5.7, 3.6 Hz, 2H), 3.75 (s, 3H), 4.12 (q, *J*=7.2 Hz, 2H), 4.26 (d, *J*=7.5 Hz, 1H), 4.84 (q, *J*=6.4 Hz, 1H), 5.17 (d, *J*=8.3 Hz, 1H), 6.67 (d, *J*=7.2 Hz, 1H), 6.89 (s, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 7.21 (t, *J*=7.2 Hz, 1H), 7.28 (d, *J*=7.5 Hz, 1H), 7.53 (d, *J*=7.9 Hz, 1H)。		

[0327] 合成N^{α}-((S)-5-(叔丁氧基)-2-((叔丁氧基羰基)氨基)-5-氧代戊酰)-1-甲基-D-色氨酸(NLG-1547-E.2-E17)

[0328]

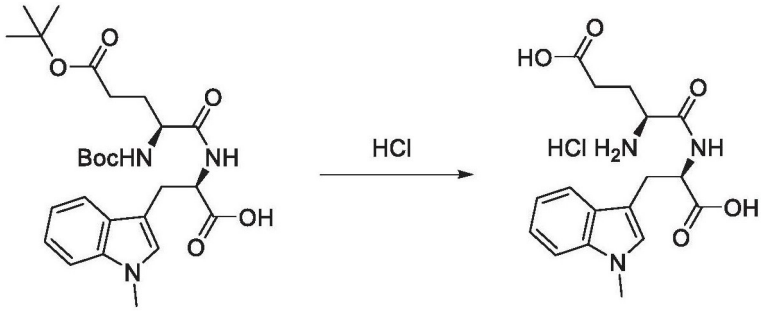


NLG-1547-D-E17 **NLG-1547-E.2-E17**

[0329] 将(S)-5-(((R)-1-(苄基氧基)-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-4-((叔丁氧基羰基)氨基)-5-氧代戊酸叔丁酯(800mg,1.38mmol)混悬于MeOH(8mL)和THF(8mL)中。冷却至0℃后,添加NaOH溶液(2.4mL,2M)并将反应物搅拌1小时。将溶液用1M HCl酸化至pH=4,并将溶剂减压(40℃)浓缩。将溶液在分液漏斗内的水和DCM之间分配,并收集有机层。将水层用DCM(2x15mL)萃取,并将合并的有机层用水和盐水洗涤。色谱纯化得

到所需产物(0.502g,72%)。^{1}H NMR(氯仿-d,400MHz):δ=1.38(s,9H),1.44(s,9H),1.68-1.81(m,1H),1.84-1.99(m,1H),2.12-2.33(m,3H),3.23-3.42(m,2H),4.23(s,3H),4.86(d,1H,J=6.9Hz),5.41(d,1H,J=8.6Hz),6.83(d,1H,J=7.5Hz),6.93(s,1H),7.09(dt,1H,J=8.0,1.2Hz),7.18(t,1H,J=7.8Hz),7.23(显著的d与$CDCl_3$重叠,1H,),7.60(d,1H,J=7.9Hz)。

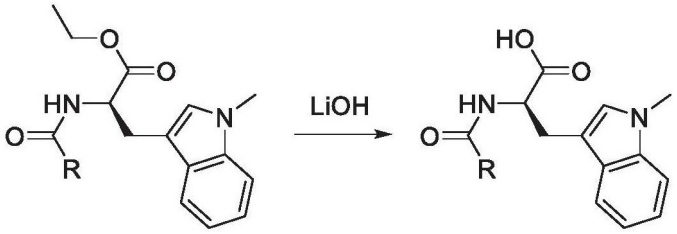
[0330] 合成(S)-4-氨基-5-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-5-氧代戊酸盐酸盐(NLG-1547)

[0331] 

(NLG-1547-E.2-E17) (NLG-1547)

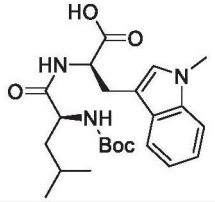
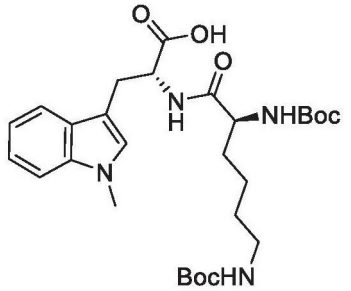
[0332] 向N^{α}-((S)-5-(叔丁氧基)-2-((叔丁氧基羰基)氨基)-5-氧代戊酰)-1-甲基-D-色氨酸(470mg,0.93mmol)添加HCl(4M于二噁烷中)(4.7mL)。将所得溶液在室温下搅拌5小时。将溶液浓缩,并将固体溶解于MeOH中,并且用活性炭处理并加热至60℃保持1小时。将溶液通过硅藻土过滤,并将滤液浓缩,以得到呈米色固体的所需产物(0.304,85%)。^{1}H NMR(DMSO-d_6,400MHz):(旋转异构体的混合物)1.73-2.21(m,4H),2.93-3.12(m,1H),3.14-3.27(m,1H),3.70(s,3H),3.83(q,1H,J=5.8Hz),4.53-4.72(m,1H),7.01(tt,1H,J=7.3,3.7Hz),7.07-7.19(m,2H),7.35(dt,1H,J=7.5,3.5Hz),7.44-7.61(m,1H),8.42(br s,3H),8.83-9.10(m,1H)。

[0333] 水解经取代的D-1MT乙酯的一般方法

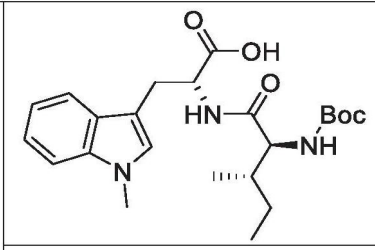
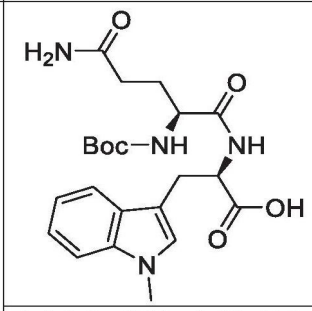
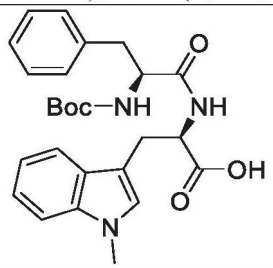
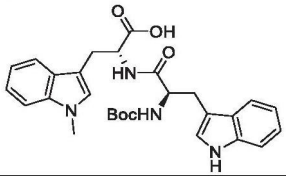
[0334] 

[0335] 向适当酰胺(0.991mmol)于THF(10mL)中的溶液中加入水(3mL)和锂一水合物(67mg,1.59mmol),并将混合物在环境温度下搅拌2小时。将混合物用1M HCl(在0℃下)中和并倾倒至冰冷水(20mL)中。将水层用EtOAc(3x35mL)萃取。将合并的有机层经Na_2SO_4干燥并浓缩。将粗产物通过快速柱色谱纯化,以得到所需产物。

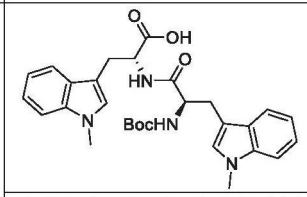
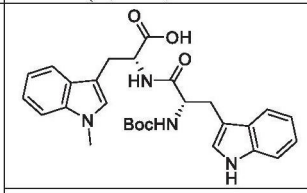
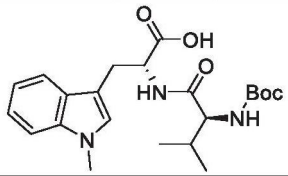
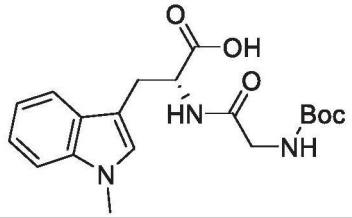
[0336]

#	化合物	名称	产率 (%)
NLG-1570-A-E33		N^{α}-((叔丁氧基羰基)-L-亮氨酰)-1-甲基-D-色氨酸	87
	0.76 – 0.96 (m, 6H), 1.39 (s, 9H), 1.40-1.54 (m, 3H), 3.29 (dd, 1H, *J* = 15.1, 5.3 Hz), 3.40 (dd,1H, *J* = 14.9, 5.7 Hz), 3.70 (s, 3H), 4.41 (td, 1H , *J* = 9.3, 5.4 Hz), 4.86 (q, 1H, *J* = 6.7, 5.8 Hz), 5.26 (d, 1H, *J* = 9.1 Hz), 6.88 (br s, 1H), 7.05 – 7.11 (m, 1H), 7.14 – 7.28 (m, 3H), 7.59 (d, 1H, *J* = 7.9 Hz)		
NLG-1548-B-E18		N^{α}-(N^{2},N^{6}-双(叔丁氧基羰基)-L-赖氨酰)-1-甲基-D-色氨酸	91
	1.05 – 1.20 (m, 2H), 1.37 (s, 9H), 1.44 (s, 9H), 1.65 – 1.80 (m, 2H), 2.98 (br d, 2H), 3.15 – 3.51 (m, 2H), 3.69 (s, 3H), 3.84 – 4.04 (m, 1H), 4.15 (d, 1H, *J* = 7.6 Hz), 4.69 (s, 1H), 4.85 (d, 1H, *J* = 6.6 Hz), 5.43 (s, 1H), 5.73 – 6.18 (m, 2H), 6.91 (s, 1H), 7.06 (t, 1H, *J*=7.4 Hz), 7.18 (t, 1H, *J* = 7.5 Hz), 7.24 (d, 1H, *J* = 8.3 Hz), 7.60 (d, 1H, *J* = 7.9 Hz)。		

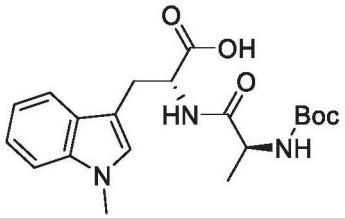
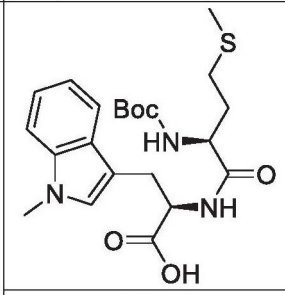
[0337]

NLG1571-A-E34		N^{α}-((叔丁氧基羰基)-L-异亮氨酰)-1-甲基-D-色氨酸	88
	0.75-0.88 (m, 8 H), 1.37 (s, 9H), 1.62-1.70 (m, 1H), 3.13-3.17 和 3.30-3.32 (两个 m, 2H), 3.65 和 3.70 (两个 s, 3H), 4.89-4.92 (m, 1H), 5.33 (d, 1H, *J* = 9.2 Hz), 6.79 (t, 1H, *J* = 7.1 Hz), 6.92 (s, 1H), 7.08 (t, 1H, *J* = 7.4 H), 7.19 (t, 1H, *J* = 7.7 Hz), 7.25 (d, 1H, *J* = 6.8 Hz), 7.56 和 7.62 (两个 d, 1H, *J* = 8.0 Hz)。		
NLG1569-A-E38		N^{α}-((叔丁氧基羰基)-L-谷酰氨基)-1-甲基-D-色氨酸	83
	1.34 (s, 9H), 1.59 (dd, 1H, *J* = 14.1, 7.9 Hz), 1.73-1.77 (m, 1H), 1.94-2.04 (m, 2H), 3.02 (dd, 1H , *J* = 14.6, 7.9 Hz), 3.13 (dd, 1H, *J* = 14.5, 5.2 Hz,), 3.69 (s, 3H), 3.90-3.96 (m, 1H), 4.40-4.45 (m, 1H), 6.72 (s, 1H), 6.80 (d, 1H, *J* = 8.3 Hz), 6.96-7.02 (m, 1H), 7.05 (s, 1H), 7.10 (ddd, 1H, *J* = 8.2, 7.0, 1.1 Hz), 7.18 (s, 1H), 7.34 (d, 1H, *J* = 8.2 Hz), 7.51 (d, 1H, *J* = 7.9 Hz), 7.98 (d, 1H, *J* = 7.9 Hz), 12.70 (br s, 1H)。		
NLG1575-A-E41		N^{α}-((叔丁氧基羰基)-L-苯基丙氨酰)-1-甲基-D-色氨酸	75
	1.30 (s, 9H), 2.81-2.88 (m, 1H), 2.94-3.00 (m, 1H), 3.08 (dd, 1H, *J* = 14.8, 5.8 Hz), 3.21-3.25 (m, 1H), 3.66 (s, 3H), 4.41 (d, 1H, *J* = 6.7 Hz), 4.79-4.86 (m, 1H), 5.13 (d, 1H, *J* = 8.3 Hz), 6.56 (d, 1H, *J* = 6.5 Hz), 6.63 (s, 1H), 6.95-7.25 (m, 8H), 7.46 (d, 1H, *J* = 7.9 Hz)。		
NLG-1546-C-E20		N^{α}-((叔丁氧基羰基)-D-色氨酰)-1-甲基-D-色氨酸	84
	1.31 (s, 9H), 3.05-3.13 (m, 3H), 3.29 (s, 1H), 3.55 (s, 3H), 4.44 (s, 1H), 4.75 (q, *J* = 6.1 Hz, 1H), 5.10 (s, 1H), 6.26 (s, 1H), 6.58 (s, 1H), 6.89 (s, 2H), 7.07 – 7.24 (m, 5H), 7.31 (d, 1H, *J* = 8.0		

[0338]

	Hz), 7.64 (d, 1H, *J* = 6.6 Hz), 8.09 – 8.35 (m, 1H)		
NLG-1549-B-E26		N^{α}-(N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酰)-1-甲基-D-色氨酸	40
	1.27 (s, 9H), 2.99 (dd, 1H, *J* = 14.7, 5.4 Hz), 3.09 (dd, 1H, *J* = 14.3, 6.7 Hz), 3.16 (dd, 1H, *J* = 14.8, 5.2 Hz), 3.25 – 3.44 (m, 1H), 3.57 (s, 3H), 3.69 (s, 3H), 4.39 (br s, 1H), 4.76 (dt, 1H, *J* = 8.1, 5.5 Hz), 5.01 (br s, 1H), 6.29 (br s, 1H), 6.53 (s, 1H), 6.79 (br s, 1H), 6.91 (s, 1H), 6.97 (br s, 2H), 7.07 – 7.18 (m, 2H), 7.20 (d, 1H, *J* = 8.2 Hz), 7.21 – 7.34 (m 与 $CDCl_3$ 重叠, 2H), 7.62 (d, 1H, *J* = 7.9 Hz)		
NLG-1560-C.1-E28		N^{α}-((叔丁氧基羰基)-L-色氨酰)-1-甲基-D-色氨酸	91
	1.35 (s, 9H), 3.08 (2.79 – 3.25, 4H), 3.50 (s, 3H), 3.71 – 3.79 (m, 1H), 4.31 – 4.55 (m, 1H), 4.62 – 4.96 (m, 1H), 6.45 (s, 1H), 6.70 – 6.91 (m, 1H), 6.98 – 7.06 (m, 1H), 7.08 (t, 1H, *J* = 7.5 Hz), 7.12 – 7.25 (m, 4H), 7.44 (q, 2H, *J* = 8.8 Hz), 7.56 (d, 1H, *J* = 7.9 Hz), 8.02 (br s, 1H)。		
NLG-1553-C-E21		N^{α}-((叔丁氧基羰基)-L-缬氨酰)-1-甲基-D-色氨酸	100
	0.77 (d, 3H, J = 6.8 Hz), 0.81 (d, 3H, J = 6.4 Hz), 1.38 (s, 9H), 1.84-1.92 (m, 1H), 3.30-3.32 (m, 1H), 3.66-3.77 (m, 4H), 4.08-4.12 (m, 1H), 4.88-4.92 (m, 1H), 5.23 (d, 1H, J = 9.2 Hz), 6.66 (d, 1H, J = 7.2 Hz), 6.92 (s, 1H), 7.09 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.26 (d, 1H, J = 8.4 Hz, 与氯仿合并), 7.62 (d, 1H, J = 8.0 Hz)		
NLG-1554-B-E25		N^{α}-((叔丁氧基羰基)甘氨酰)-1-甲基-D-色氨酸	83
	1.39 (s, 9H), 3.25-3.35 (m, 2H), 3.2-3.74 (m, 5H), 4.85-4.90 (m, 1H), 5.21 (br s, 1H), 6.63 (br s, 1H), 6.90 (s, 1H), 7.08 (t, 1H, J = 7.4 Hz), 7.17-7.27 (m, 2H, 与氯仿合并), 7.55 (d, 1H, J = 7.6 Hz)		

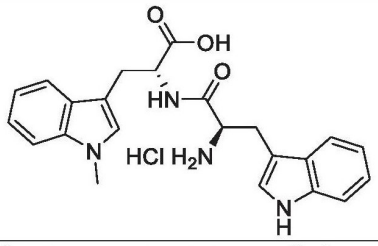
[0339]

NLG-1555-B-E27		N^{α}-((叔丁氧基羰基)-L-丙氨酰)-1-甲基-D-色氨酸	86
	1.21 (d, 3H, J = 7.2 Hz), 1.38 (s, 9H), 3.19-3.38 (m, 3H), 3.73 (s, 3H), 4.22-4.27 (m, 1H), 4.84 (br s, 1H), 6.77 (br s, 1H), 6.87 (s, 1H), 7.08 (t, 1H, J = 7.4 Hz), 7.19 (t, 1H, J = 7.4 Hz), 7.24 (d, 1H, J = 8.8 Hz, 与氯仿合并), 7.57 (d, 1H, J = 7.6 Hz)		
DD00510-A-E079		N^{α}-((叔丁氧基羰基)-L-甲硫氨酰)-1-甲基-D-色氨酸	92
	1.36 (s, 9H), 1.68 – 1.87 (m, 2H), 1.94 和 2.01 (s, 3H), 2.25-2.43 (两个 m, 2H), 3.23 (dd, *J*=14.9, 6.5 Hz, 1H), 3.36 (dd, *J*=14.6, 4.8 Hz, 1H), 3.71 (s, 3H), 4.23-4.34 (两个 m, 1H), 4.82-4.94 (两个 m, 1H), 5.52 (d, *J*=6.7 Hz, 1H), 6.79 – 6.99 (m, 2H), 7.09 (t, *J*=7.4 Hz, 1H), 7.19 (t, *J*=7.4 Hz, 1H), 7.25 (d, *J*=6.1 Hz, 1H), 7.58 (d, *J*=8.0 Hz 1H)		

[0340] ^{t}Boc脱保护的一般方法.

[0341] 在0℃下,向适当的^{t}Boc保护的胺(0.707mmol)于二噁烷(2mL)中的溶液加入HCl溶液(1.77mL,4.0M溶液于二噁烷中)。使溶液升温至室温并剧烈搅拌2.5-18小时。使用旋转蒸发仪除去溶剂。将固体用无水乙醚(15mL)稀释,并过滤产物以得到粗产物。将粗物质在高真空下干燥,得到所需产物。

[0342]

#	化合物	名称	产率(%)
NLG-1546		N^{α}-(D-色氨酰)-1-甲基-D-色氨酸盐酸盐	95
	^{1}H NMR (400 MHz, 甲醇-d_4) δ 3.15 (d, *J* = 8.5 Hz, 1H), 3.19 (d, *J* = 8.5 Hz, 1H), 3.36 (d, 1H, *J* = 4.9 Hz), 3.37 – 3.41 (m, 1H), 3.71 (s, 3H), 4.06 (t, 1H, *J* = 3.6 Hz), 4.74 (s, 1H), 6.93 (s, 1H), 7.02 (t, 1H, *J* = 6.2 Hz), 7.04 – 7.07 (m, 1H), 7.14 (td, 2H, *J* = 7.9, 1.7 Hz), 7.20 (s, 1H),		

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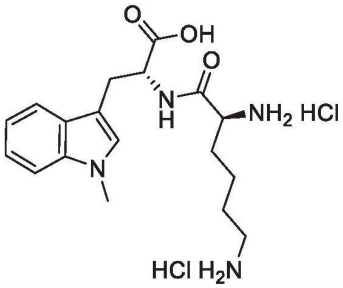
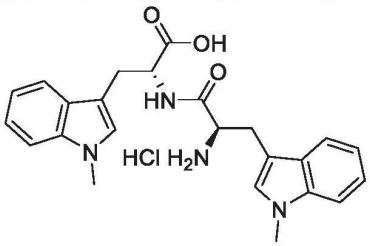
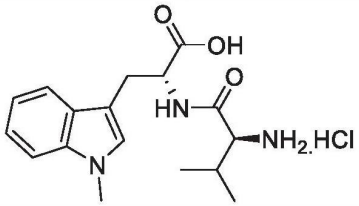
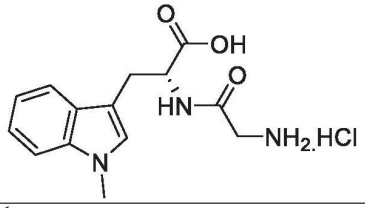
	7.22 (d, *J* = 8.1 Hz, 1H), 7.30 (d, 1H, *J* = 8.2 Hz), 7.38 (d, 1H, *J* = 8.1 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 7.65 (d, 1H, *J* = 7.9 Hz), 7.70 (d, 1H, *J* = 8.2 Hz)		
NLG-1548		N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸二盐酸盐	87
	^{1}H NMR (400 MHz, DMSO-d_6): 0.88 – 1.13 (m, 2H), 1.33 – 1.56 (m, 4H), 2.54 (t, 2H, *J* = 7.1 Hz), 2.95 – 3.10 (m, 1H), 3.15 – 3.24 (m, 1H), 3.42 (显著的 q 与 H_2O 重叠, 1H, *J* = 7.0 Hz), 3.73 (s, 3H), 4.50 – 4.67 (m, 1H), 7.01 (t, 1H, *J* = 7.5 Hz), 7.06 – 7.18 (m, 2H), 7.38 (d, 1H, *J* = 8.3 Hz), 7.55 (d, 1H, *J* = 7.9 Hz), 8.02 (br s, 3H), 8.20 (br s, 3H), 8.83 (d, 1H, *J* = 8.1 Hz), 12.93 (br s, 1H)		
NLG-1549		1-甲基-N^{α}-(1-甲基-D-色氨酰)-D-色氨酸盐酸盐	92
	^{1}H NMR (400 MHz, DMSO-d_6): 3.10 (td, 2H, *J* = 15.5, 7.9 Hz), 3.24 (ddd, 2H, *J* = 17.5, 15.1, 5.9 Hz), 3.72 (s, 2H), 3.73 (s, 4H), 4.02 (dd, 1H, *J* = 8.3, 5.1 Hz), 4.58 (q, 1H, *J* = 7.0 Hz), 7.04 (td, 2H, *J* = 7.4, 4.2 Hz), 7.09 – 7.23 (m, 4H), 7.40 (t, 2H, *J* = 8.1 Hz), 7.58 (d, 1H, *J* = 7.9 Hz), 7.74 (d, 1H, *J* = 7.9 Hz), 8.11 (s, 1H), 8.97 (d, 1H, *J* = 7.7 Hz), 12.82 (br s, 1H)		
NLG-1553		N^{α}-(L-缬氨酰)-1-甲基-D-色氨酸盐酸盐	92
	^{1}H NMR (400 MHz, DMSO-d_6): 0.54 (d, 3H, J = 7.2 Hz), 0.72 (d, 3H, J = 6.8 Hz),1.89-1.94 (m, 1H), 3.01 (dd, 1H, J = 14.8, 9.6 Hz), 3.22 (dd, 1H, J = 14.6, 5.0 Hz), 3.56-3.65 (m, 1H), 3.70 (s, 3H), 4.61-4.66 (m, 1H), 7.01 (t, 1H, J = 7.6 Hz), 7.12 (s, 1H), 7.12 (t, 1H, J = 7.6 Hz), 7.36 (t, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 8.09 (br s, 3H), 8.78 (d, 1H, J = 8.4 Hz), 12.8 (br s, 1H)		
NLG-1554		N^{α}-甘氨酰-1-甲基-D-色氨酸盐酸盐	87
	^{1}H NMR (400 MHz, DMSO-d_6): 3.02-3.08 (m, 1H), 3.17-3.22 (m, 1H),		

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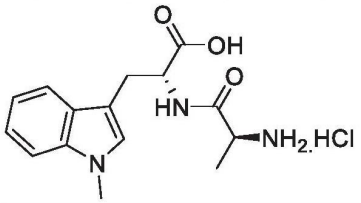
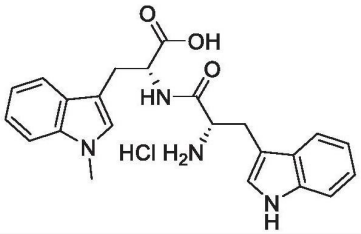
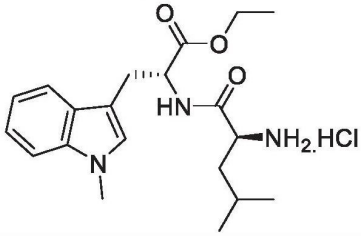
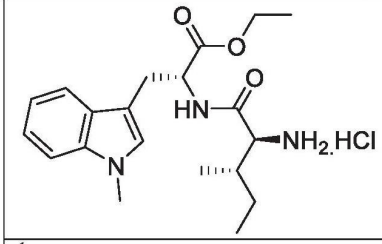
	3.48-3.60 (m, 2H), 3.74 (s, 3H), 4.55-4.58 (m, 1H), 7.03 (t, 1H, J = 7.8 Hz), 7.12-7.18 (m, 2H), 7.38 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 8.13 (br s, 3H), 8.76 (d, 1H, J = 8.0 Hz), 12.87 (br s, 1H)		
NLG-1555		N^{α}-(L-丙氨酰)-1-甲基-D-色氨酸盐酸盐	44
	^{1}H NMR (400 MHz, DMSO-d_6): 1.18 (d, 3H), 3.02-3.06 (m, 1H), 3.17-3.23 (m, 1H), 3.72 (s, 3H), 4.05-4.09 (m, 1H), 4.57-4.62 (m, 1H), 7.02 (t, 1H, J = 7.6 Hz), 7.12-7.15 (m, 2H), 7.38 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 7.6 Hz), 8.16 (br s, 3H), 8.88-8.92 (m, 1H)		
NLG-1560		N^{α}-(L-色氨酰)-1-甲基-D-色氨酸盐酸盐	90
	^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.88 (dd, 1H, *J* = 14.7, 8.2 Hz), 2.98 (dd, 1H, *J* = 14.5, 7.9 Hz), 3.08 (dt, 2H, *J* = 14.7, 5.0 Hz), 3.63 (s, 3H), 4.06 (br s, 1H), 4.55 (q, 1H, *J* = 7.9), 6.87 (dd, 1H, *J* = 8.0, 7.0 Hz), 6.97 (s, 1H), 7.01 (t, 1H, *J* = 7.4 Hz), 7.06 (t, 1H, *J* = 7.4 Hz), 7.08 – 7.15 (m, 2H), 7.34 (d, 2H, *J* = 8.2 Hz), 7.56 (dd, 2H, *J* = 8.0, 5.1 Hz), 8.09 (s, 3H), 8.95 (d, 1H, *J* = 8.1 Hz), 11.02 (s, 1H)		
NLG-1564		N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯盐酸盐	93
	^{1}H NMR (400 MHz, DMSO-d_6): 0.70 (t, 6H, *J* = 5.7 Hz). 1.13 (t, 3H, *J* = 7.1 Hz), 1.38 – 1.23 (m, 3H), 3.01 (dd, 1H , *J* = 14.5, 9.4 Hz), 3.18 (dd, 1H , *J* = 14.5, 5.2 Hz), 3.70 (s, 3H), 4.08 (q, 2H , *J* = 7.1 Hz), 4.62 – 4.53 (m, 1H), 7.00 (ddd, 1H, *J* = 7.8, 7.0, 1.0 Hz), 7.09-7.13 (m, 2H), 7.36 (d, 1H , *J* = 8.2 Hz), 7.50 (dd, 1H, *J* = 7.6, 1.1 Hz), 8.18 (br s, 3H), 8.99 (d, 1H, *J* = 8.1 Hz)。		
NLG-1565		N^{α}-(L-异亮氨酰)-1-甲基-D-色氨酸乙酯盐酸盐	93
	^{1}H NMR (400 MHz, DMSO-d_6): 0.60 – 0.66 (m, 6H), 0.75 – 0.82 (m, 2H), 1.12 (t, 3H, *J* = 7.1 Hz, 4H), 1.63 (br s, 1H), 3.02 (dd, 1H, *J* = 14.6, 9.4 Hz), 3.17 (dd, 1H, J = 14.6, 5.2 Hz), 3.61 (br s, 1H), 3.69 (s,		

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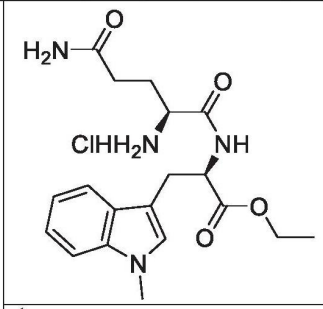
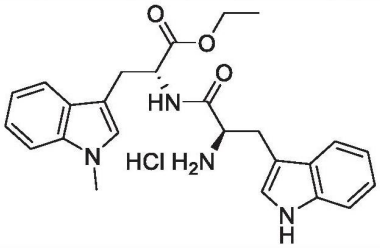
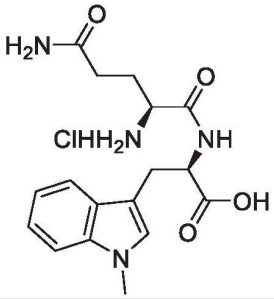
	3H), 4.07 (q, 2H, *J* = 7.1 Hz), 4.62 (br s, 1H), 7.01 (t, 1H, *J* = 7.5 Hz), 7.10 – 7.14 (m, 2H), 7.36 (d, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 7.9 Hz), 8.00 (br s, 2H), 8.85 (br s, 1H)。		
NLG-1566		N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯盐酸盐	59
	^{1}H NMR (400 MHz, DMSO-d_6): 1.08 (t, 3H, *J* = 7.1 Hz),1.81-1.97 (m, 2H), 2.01-2.12 (m, 2H), 3.07 (dd, 1H, *J* = 14.4, 8.4 Hz), 3.16 (dd, 1H, *J* = 14.4, 6.0 Hz), 3.70 (s, 3H), 3.82 (t, 1H, *J* = 6.0 Hz), 4.03 (q, 2H, *J* = 7.1 Hz), 4.53 (q, 1H, *J* = 7.0 Hz), 6.93 (s, 1H), 7.02 (ddd, 1H, *J* = 7.9, 7.0, 1.0 Hz), 7.09-7.14 (m, 2H), 7.35 (d, 1H, *J* = 8.2 Hz), 7.40 (s, 1H), 8.24 (br s, 3H), 9.01 (d, 1H, *J* = 7.2 Hz)。		
NLG-1567		N^{α}-(D-色氨酰)-1-甲基-D-色氨酸乙酯盐酸盐	97
	^{1}H NMR (400 MHz, DMSO-d_6): 1.19 (t, 3H, *J* = 7.1 Hz), 1.91 (br s, 2H), 2.87 (m, 1H), 3.25 (d, 2H, *J* = 5.6 Hz), 3.33 (dd, 1H, *J* = 14.5, 4.4 Hz), 3.66 (s, 3H), 3.70 (dd, 1H, *J* = 9.0, 4.7 Hz), 4.10 (m, 1H), 4.87 (dt, 1H, *J* = 8.5, 5.5 Hz), 6.71 (d, 1H, *J* = 8.5 Hz), 6.95 (d, 1H, *J* = 2.6 Hz), 7.00 – 7.10 (m, 2H), 7.12 – 7.22 (m, 2H), 7.24 (d, 2H, *J* = 6.1 Hz), 7.32 (d, 1H, *J* = 8.1 Hz), 7.51 (d, 1H, *J* = 7.7 Hz), 7.60 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 8.3 Hz), 8.15 (s, 1H)。		
NLG-1569		N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸盐酸盐	97
	^{1}H NMR (400 MHz, DMSO-d_6): 1.79-1.84 (m, 2H), 1.95-2.06 (m, 2H), 3.04 (dd, 1H, *J* = 14.6, 8.5 Hz), 3.19 (dd, 1H, *J* = 14.6, 5.2 Hz), 3.49 – 3.35 (m, 2H), 3.70 (s, 3H), 3.78 – 3.88 (m, 1H), 4.53 (td, 1H, *J* = 8.3, 5.2 Hz), 6.93 (s, 1H), 7.00 (ddd, 1H, *J* = 8.0, 7.0, 1.0 Hz), 7.16 – 7.07 (m, 2H), 7.35 (dt, 1H, *J* = 8.3, 0.9 Hz), 7.38 (s, 1H), 7.54 (dt, 1H, *J* = 7.9, 1.0 Hz), 8.28 (d, 2H, *J* = 4.2 Hz), 8.87 (d, 1H, *J* = 8.1 Hz)		

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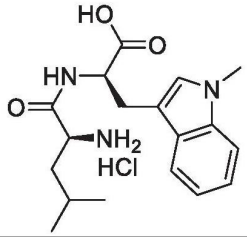
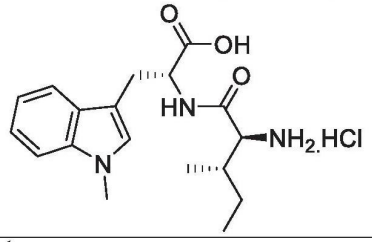
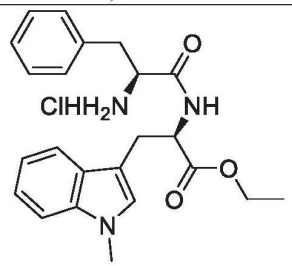
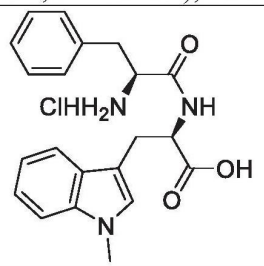
NLG-1570		N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸盐酸盐	95
	^{1}H NMR (400 MHz, DMSO-d_6): 0.68 (t, 6H, J = 5.5 Hz). 1.34 – 1.17 (m, 3H), 2.99 (dd, 1H , J = 14.5, 9.6 Hz), 3.20 (dd, 1H, J = 14.6, 4.7 Hz), 3.34 – 3.40 (m, 3H), 3.68 (s, 3H), 4.52 – 4.62 (m, 1H), 6.99 (t, 1H, J = 7.4 Hz), 7.16 – 7.08 (m, 2H), 7.35 (d, 1H, J = 8.2 Hz), 7.54 (d, 1H, J = 7.9 Hz), 8.17 (br s, 2H), 8.85 (d, 1H, J = 8.3 Hz)		
NLG-1571		N^{α}-(L-异亮氨酰)-1-甲基-D-色氨酸盐酸盐	94
	^{1}H NMR (400 MHz, DMSO-d_6): 0.55-0.65 (m, 6 H), 0.71 – 0.75 (m, 1H), 1.03-1.12 (m, 1H), 1.57 – 1.63 (m, 1H), 2.99 (dd, 1H, J = 14.6, 9.8 Hz), 3.19 (dd, 1H, J = 14.6, 4.7 Hz), 3.61-3.63 (m, 1H), 3.69 (s, 3H), 4.58-4.64 (m, 1H), 7.0 (t, 1H, J = 7.6 Hz), 7.08 – 7.13 (m, 2H), 7.35 (d, 1H, J = 8.2 Hz), 7.53 (d, 1H, J = 7.9 Hz), 8.10 (br s, 3H), 8.72 (d, 1H, J = 8.1 Hz)。		
NLG-1574		N^{α}-(L-苯基丙氨酰)-1-甲基-D-色氨酸乙酯盐酸盐	60
	^{1}H NMR (400 MHz, DMSO-d_6): 1.15 (t, 3H, J = 7.1 Hz), 2.52 (dd, 1H, J = 13.7, 9.9 Hz), 3.17 – 3.23 (m, 3H), 3.46 (dd, 1H, J = 9.9, 4.1 Hz), 3.64 (s, 3H), 4.03-4.11 (m, 2H), 4.83 (dt,1H, J = 8.4, 5.6 Hz), 6.72 (s, 1H), 6.99 (ddd, 1H, J = 8.0, 6.9, 1.1 Hz), 7.31 – 7.05 (m, 7H), 7.45 (d, 1H, J = 7.9 Hz), 7.61 (d, 1H, J = 8.4 Hz)		
NLG-1575		N^{α}-(L-苯基丙氨酰)-1-甲基-D-色氨酸盐酸盐	91
	^{1}H NMR (400 MHz, DMSO-d_6): 2.78 (dd, 1H, J = 13.9, 7.1 Hz), 2.89-2.97 (m, 2H), 3.10 (dd, 1H, J = 14.5, 5.3 Hz), 3.35 (br s, 3H), 3.47 (s, 3H), 4.05 (dd, 1H, J = 7.1, 5.6 Hz), 4.51 (td, 1H, J = 8.2, 5.3 Hz), 6.92 – 6.94 (m, 2H), 6.99 – 7.18 (m, 6H), 7.36 (dt, J = 8.3, 0.9 Hz, 1H), 7.56 (dt, J = 8.0, 0.9 Hz, 1H), 8.89 (d, J = 8.1 Hz, 1H)。		

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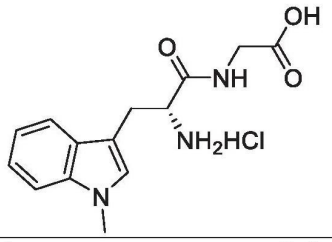
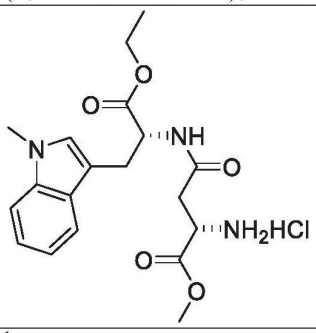
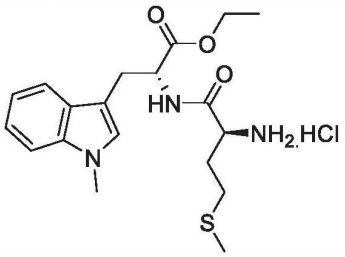
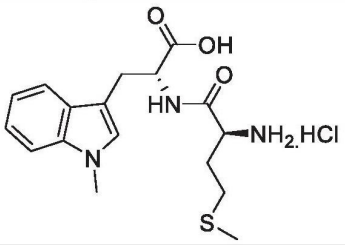
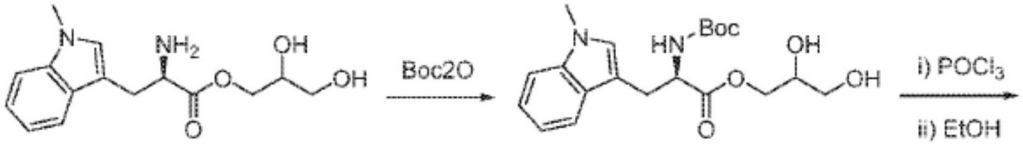
NLG-1579		1-甲基-D-色氨酰甘氨酸盐酸盐	90
	^{1}H NMR (400 MHz,甲醇-d_4): 3.25 (dd, 2H , J = 14.8, 7.9 Hz), 3.43 (dd, 1H, J = 14.8, 6.1 Hz), 3.77 (s, 3H), 3.92 (d, 2H, J = 5.5 Hz), 4.14-4.19(m, 1H), 7.09 (t, 1H, J = 7.5 Hz), 7.16- 7.24 (m, 2H), 7.36 (d, 1H , J = 8.1 Hz), 7.67 (d, 1H, J = 7.9 Hz)。		
NLG-1585		N^4-((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)-L-天冬酰胺甲酯盐酸盐	92
	^{1}H NMR (400 MHz, DMSO-d_6): 1.12 (t, 3H, J = 7.1 Hz), 2.64-2.76 (m, 2H), 3.06 (dd, 1H, J = 14.5, 8.2 Hz), 3.17 (dd, 1H, J = 14.6, 5.9 Hz), 3.58 (s, 3H), 3.73 (s, 3H), 4.04-4.13 (m, 3H), 4.57 (td, 1H, J = 8.0, 5.9 Hz), 7.02 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz), 7.12-7.16 (m, 2H), 7.39 (dt, 1H, J = 8.3, 0.9 Hz), 7.51 (dt, 1H, J = 8.0, 1.0 Hz), 8.27 (s, 3H), 9.00 (d, 1H, J = 7.8 Hz)		
NLG-3272-01		N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯盐酸盐	90
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.69 (t, J=7.1 Hz, 3H), 2.44 (s, 3H), 2.61 – 2.82 (m, 2H), 3.59 (dd, J=14.5, 9.5 Hz, 1H), 3.74 (dd, J=14.6, 5.0 Hz, 1H), 4.27 (s, 3H), 4.37 (s, 1H), 4.63 (q, J=7.1 Hz, 2H), 5.05 – 5.22 (m, 1H), 7.56 (t, J=7.4 Hz, 1H), 7.62 – 7.75 (m, 2H), 7.91 (d, J=8.2 Hz, 1H), 8.05 (d, J=7.8 Hz, 1H), 8.86 (s, 2H), 9.60 (d, J=7.8 Hz, 1H)。		
NLG-3380-01		N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸盐酸盐	76
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.73-1.77 (m, 2H), 1.88 (s, 3H), 2.11-2.17 (m, 2H), 3.03 (dd, J=14.6, 9.3 Hz, 1H), 3.24 (dd, J=14.6, 4.7 Hz, 1H), 3.73 (s, 3H), 3.78 (t, J=5.7 Hz, 1H), 4.51 – 4.67		

[0348]		(m, 1H), 7.02 (t, *J*=7.4 Hz, 1H), 7.11-7.15 (m, 2H), 7.37 (d, *J*=8.1 Hz, 1H), 7.56 (d, *J*=8.1 Hz, 1H), 8.78 (br s, 1H)

[0349] 合成1-甲基-D-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯盐酸盐(NLG-1559)



NLG-1558 游离碱 NLG-1559-A-E24

[0350]

NLG-1559-B-E24 NLG-1559

[0351] N^{α}-(叔丁氧基羰基)-1-甲基-D-色氨酸2,3-二羟丙酯(NLG-1559-A-E24)

[0352] 在0℃下向NLG-1558游离碱(0.750mg,2.57mmol)于乙腈(10mL)中的溶液中添加Boc_2O(560mg,2.57mmol),并使反应物升温至室温并搅拌4小时。减压下去除溶剂并将粗产物通过柱色谱纯化,得到所需产物(760mg,75%)。^1H NMR:1.34(s,9H),3.13-3.23(m,2H),3.35-3.38(m,1H),3.42-3.45(m,1H),3.67-3.72(m,4H),4.01-4.08(m,2H),5.01-5.04(m,1H),6.83(s,1H),7.05(t,1H,J=7.4Hz),7.16(t,1H,J=7.3Hz),7.23(d,1H,J=8.2Hz),7.49(d,1H,J=7.9Hz)。

[0353] Na-(叔丁氧基羰基)-1-甲基-D-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯(NLG-1559-B-E24)

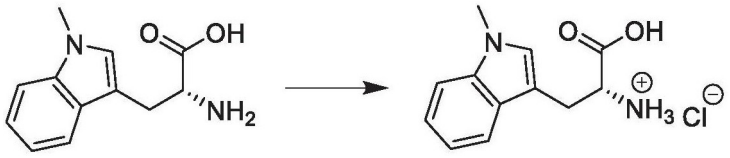
[0354] 在0℃下向NLG-1559-A-E24(650mg,1.66mmol)于无水吡啶(2mL)中的溶液中加入$POCl_3$,并使溶液升温至室温。搅拌过夜(18小时)后,加入乙醇(1.5mL),并且继续反应4小时。减压下去除溶剂,并将粗产物通过柱色谱纯化(460mg,57%)。^1H NMR:1.13(t,3H,J=7.0Hz),1.30(s,9H),3.10-3.20(m,2H),3.47-3.55(m,1H),3.60(s,3H),41.9-4.44(m,3H),4.55-4.57(m,1H),5.23-5.27(m,1H),6.79和6.83(两个s,1H),7.01(t,1H,J=7.4Hz),7.12(t,1H,J=7.2Hz),7.18(d,1H,J=9.2Hz),7.46(d,1H,J=7.7Hz)。

[0355] 1-甲基-D-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯盐酸盐(NLG-1559)

[0356] 在0℃下向NLG-1559-B-E24(550mg,1.14mmol)于无水CH_2Cl_2(10mL)中的溶液中加入无水HCl(1.4mL,4M溶液于二噁烷中),并使混合物升温至室温。搅拌2小时后,减压下去除溶剂并将粗物质用无水乙醚(3x15mL)洗涤。过滤白色固体并减压干燥产物(0.241g,61%)。(CD_3OD-d_4)1.20(td,3H,J=7.1,4.3Hz),3.26-3.42(m,2H),3.44(dd,1H,J=5.1,3.0Hz),3.48-3.56(m,1H),3.71(s,3H),3.95(h,2H,J=7.1Hz),4.21-4.36(m,3H),4.37-4.53(m,1H),7.02(t,1H,J=7.4Hz),7.07(d,1H,J=4.0Hz),7.10-7.17(m,1H),7.30(d,1H,J=8.2Hz),7.49(d,1H,J=7.4Hz)。

[0357] 一种或多种药学上可接受的盐组合物

[0358] 合成(R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙-1-铵氯化物(NLG-1607)

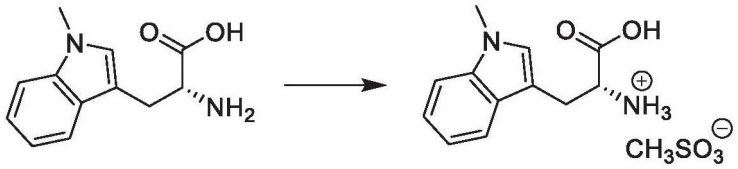
[0359] 

D-1MT NLG-1607

[0360] 向冰冷HCl(15.5mL,30.9mmol;2M)水溶液添加D1MT(4.5g,20.6mmol)。搅拌30分钟后,减压下蒸发澄清溶液,并将粗物质用乙醇(40mL)蒸发三次。将粗物质在乙醇和叔丁基甲基醚中搅拌并过滤得到所需产物(4.25g,81%)。

[0361] 开发了一种可替代的方法,其中将约10g D-1MT混悬于具有100mL乙腈的250mL玻璃瓶中。将10mL预先溶解在乙腈中的HCl溶液(511.2mg/mL)根据游离碱:酸的1:1摩尔比加入到D-1MT游离形式溶液中,然后在室温下保持振摇以形成盐。将过滤的固体在30℃下真空干燥过夜。通过上述工艺获得白色粉末(11.1g),并用XRPD、DSC和TGA表征(图1-2)。基于HPLC分析,纯度为99.7%面积,并且通过ELSD分析化学计量,计算出的摩尔比(API:HCl酸)为1:1.0。如通过偏振光显微术(PLM)和X射线粉末分散光谱(XRPD,图1)所评估,该粉末是结晶。如通过热重分析(TGA)和差示扫描量热法(DSC)(图2)所评估,所述盐是无水的。

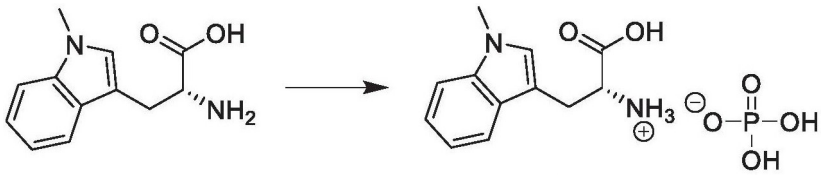
[0362] 合成(R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙-1-铵甲磺酸盐(NLG-1619)

[0363] 

D-1MT NLG-1619

[0364] 向甲磺酸(1.50mL,22.9mmol)于DI水(50mL)中的搅拌溶液中以100mg分批加入D-1MT(1.0g,4.48mmol)。将溶液在75℃下剧烈搅拌3小时,直到溶液均匀。将溶液减压浓缩,并收集固体(1.38g,96%)。^{1}H NMR(甲醇-d_4,400MHz):δ=2.69(s,3H),3.32-3.39(m,1H),3.49(dd,1H,J=15.3,4.9Hz),3.80(s,3H),4.25(dd,1H,J=7.8,4.9Hz),7.10(ddd,1H,J=8.0,7.0,1.0Hz),7.14(s,1H),7.21(ddd,1H,J=8.2,7.0,1.1Hz),7.38(dd,1H,J=8.3,1.1Hz),7.62(dt,1H,J=8.0,0.9Hz)

[0365] 合成(R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙-1-铵磷酸二氢盐(NLG-1660)

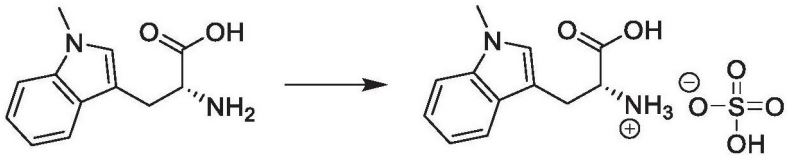
[0366] 

D-1MT NLG-1660

[0367] 在50℃下向磷酸(0.673g,6.87mmol)于去离子水(30mL)中的溶液中分批加入D-1MT(0.5g,2.29),并使混合物在50℃下搅拌过夜。然后将溶液浓缩至其原始体积的一半,并使其在室温下静置过夜。将所得沉淀过滤、用冷乙醇洗涤并干燥以得到呈白色固体的NLG-1660(0.250,34%)。^{1}H NMR(400MHz,DMSO-d_6)δ2.95(dd,1H,J=15.1,8.6Hz),3.22-3.29(m,1H),3.46(dd,1H,J=8.6,4.2Hz),3.71(s,3H),7.00(ddd,1H,J=8.0,7.1,1.0Hz),7.09-7.15(m,2H),7.37(d,1H,J=8.4Hz),7.55(d,1H,J=7.9Hz)。

[0368] 开发了一种可替代的方法，其中将约10g D-1MT混悬在具有100mL THF的500mL玻璃瓶中。将20ml预先溶解在THF中的H_3PO_4溶液(792.3mg/mL)根据1:3的游离碱:酸摩尔比加入到D-1MT游离形式溶液中，然后在室温下保持振摇过夜，以形成盐。将过滤的固体在30℃下真空干燥过夜，通过XRPD、DSC、TGA和ELSD检查。获得白色粉末(11.1g)，其通过PLM和XRPD图案显示为结晶(图3)。基于DSC和TGA数据，盐是无水的(图4)。纯度为99.8%，并通过ELSD分析化学计量，计算的摩尔比(游离碱:磷酸)为1:0.57。

[0369] 合成(R)-1-羧基-2-(1-甲基-1H-吲哚-3.基)乙-1-铵硫酸氢盐(NLG-1667)

[0370] 

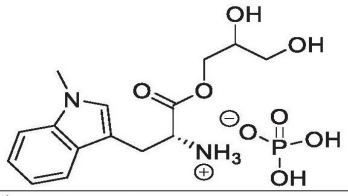
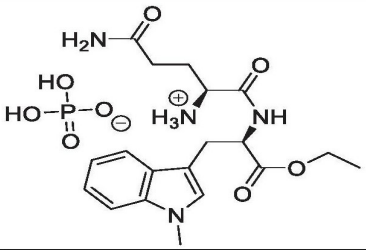
D-1MT NLG-1667

[0371] 在室温下向D-1MT(1.00g，4.58mmol)于水/THF(4:1，100mL)中的混悬液中加入0.5M H_2SO_4(9.16mL，4.58mmol)，并将混合物在室温下搅拌过夜。将白色固体滤掉，并用冷THF洗涤，得到D-1MT的硫酸盐(0.429g，34%)。(DMSO-d_6)3.17(dd，1H，J＝15.1，7.2Hz)，3.27(dd，1H，J＝15.0，5.3Hz)，3.74(s，3H)，3.96(t，1H，J＝6.2Hz)，7.04(t，1H，J＝7.4Hz)，7.12-7.21(m，2H)，7.41(d，1H，J＝8.2Hz)，7.58(d，1H，J＝8.0Hz)，8.52(br s，4H)。

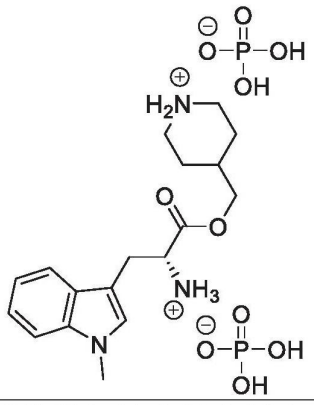
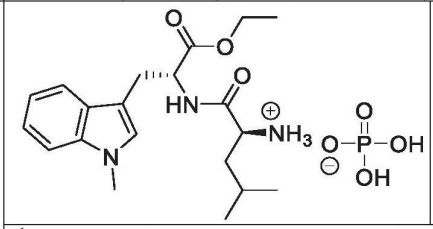
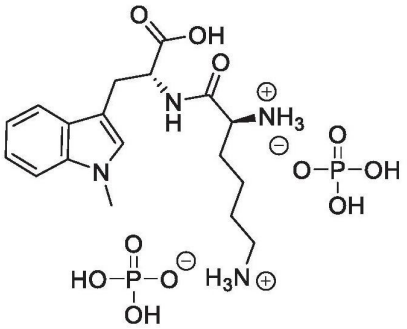
[0372] 产生吲哚西美德前药的单磷酸盐和二磷酸盐的一般方法。

[0373] 在0℃下向游离碱(0.747mmol)于EtOH(5ml)中的溶液添加磷酸(0.747mmol；于EtOH中的溶液1mL)或(在二胺的情况下，1.494mmol)，并使混合物升温至室温并搅拌5-18小时。减压下去除溶剂并将残余物用甲基叔丁醚(10mL)稀释，搅拌1-5小时后，将固体过滤并在减压下干燥，得到所需产物。对于NLG-03380-02，使用离子交换树脂从NLG-03380-01产生游离碱。

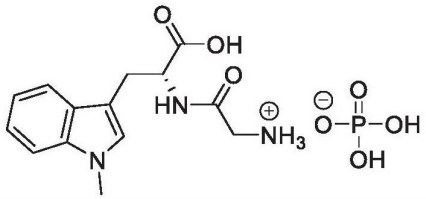
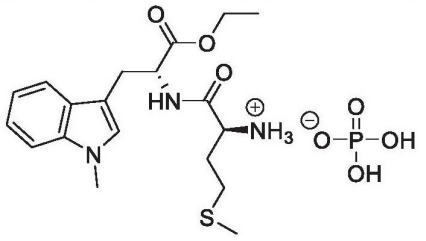
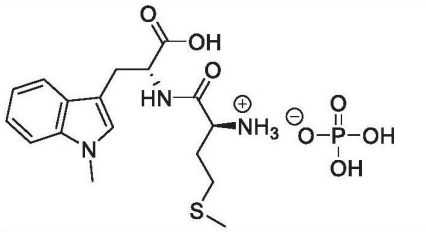
[0374]

#	化合物	名称	产率(%)
NLG-1626		(2R)-1-(2,3-二羟基丙氧基)-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-铵磷酸二氢盐	44
	^{1}H NMR (DMSO-d_6, 400 MHz): 3.07-3.15 (m, 2H), 3.27-3.38 和 3.43-3.50 (m, 2H), ^{1}H NMR (400 MHz, DMSO-d_6): 3.60-3.68 (m, 1H), 3.73 (s, 3H), 3.84 (br s, 1H), 3.90-3.96 (m, 1H), 4.02-4.12 (m, 1H), 6.95 (br s, 3H), 7.02 (ddd, 1H, J = 8.0. 70. 1.0 Hz), 7.11-7.19 (m, 2H), 7.38 (dt, 1H, J = 8.3, 0.9 Hz), 7.49-7.56 (m, 1H)。		
NLG-1629		(S)-5-氨基-1-(((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-1,5-二氧代戊-2-铵磷酸二氢盐	59
	^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (t, 3H, J =7.0 Hz), 1.64-1.70 (m, 1H), 1.75-1.85 (m, 1H), 2.06 (t, 2H, J = 7.9 Hz), 3.06-3.18 (m, 2H), 3.44 (br s 1H), 3.72 (s, 3H), 4.04 (q, 2H , J =		

[0375]

	7.1 Hz), 4.52 (q, 1H , *J* = 7.1 Hz), 6.80 (s, 1H), 7.02 (t, 1H , *J* = 7.5 Hz), 7.11– 7.16 (m, 2H), 7.32-7.38 (m, 2H), 7.50 (d, 1H , *J* = 7.9 Hz), 7.82 (br s, 3H), 8.57 (s, 1H)。		
NLG-1664		(R)-4-(((2-铵基-3-(1-甲基-1H-吲哚-3-基)丙酰基)氧基)甲基)哌啶-1-鎓磷酸二氢盐	31
	(DMSO-d_6) 1.35-1.56 (m, 4H), 1.63-1.68 (m, 1H), 2.61-2.73 (m, 2H), 3.09-3.26 (m, 4H), 3.73 (s, 3H), 3.81 (dd, 1H, J = 5.1, 10.9 Hz), 3.88 (dd, 1H, J = 5.1, 11.1 Hz), 3.95 (t, 1H, J = 6.7 Hz), 7.02 (t, 1H, J = 7.4 Hz), 7.09-7.17 (m, 1H), 7.21 (s, 1H), 7.38 (d, 1H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.9 Hz), 8.44 (br s, 10H)		
NLG-1665		(S)-1-(((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-4-甲基-1-氧代戊-2-铵磷酸二氢盐	59
	^{1}H NMR (400 MHz, DMSO-d_6): 0.77 (dd, 6H, *J* = 6.5, 6H, 2.2 Hz), 1.1 (t, 3H, *J* = 7.1, 7.1 Hz), 1.18-1.32 (m, 1H), 1.39-1.50 (m, 1H), 1.39 - 1.49 (m, 1H), 3.06 (dd, 1H, *J* = 14.5, 8.4 Hz), 3.17 (dd, 1H, *J* = 14.4, 5.4 Hz), 3.40 (dd, 1H, *J* = 8.6, 5.7 Hz), 3.72 (s, 3H), 4.06 (q, 2H, *J* = 7.1, 7.1, 7.1 Hz), 4.55 (td, 1H, *J* = 8.1, 8.1, 5.5 Hz), 5.52 (bs, 8H), 7.02 (t, 1H, *J* = 7.2 Hz), 7.10 – 7.15 (m, 2H), 7.38 (d, 1H, *J* = 8.3 Hz), 7.51 (d, 1H, *J* = 7.9 Hz), 8.62 (d, 1H, *J* = 7.9 Hz)。		
NLG-1670		(S)-6-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-6-氧代己-1,5-二铵磷酸二氢盐	81
	^{1}H NMR(氧化氘, 400 MHz): δ = 0.39 – 0.78 (m, 2H), 1.21 (ddd, 2H, *J* = 9.1, 6.8, 2.6 Hz), 1.28 – 1.49 (m, 2H), 2.39 (td, 2H, *J* = 7.4, 3.8 Hz), 3.08 (dd, 1H, *J* = 15.0, 10.9 Hz), 3.45 (ddd, 1H, *J* = 15.1, 4.5, 1.0 Hz), 3.74 (s, 3H), 3.79 (t, 1H, *J* = 6.7 Hz), 4.68 – 4.77 (m, 1H), 7.14 (d, 1H, *J* = 0.8 Hz), 7.14 – 7.20 (m, 1H), 7.28		

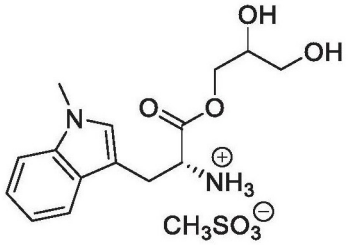
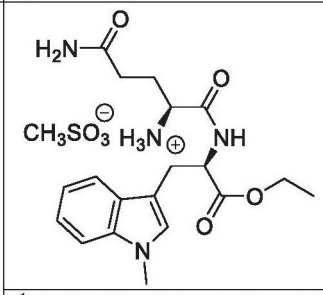
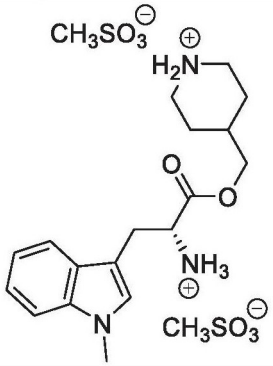
[0376]

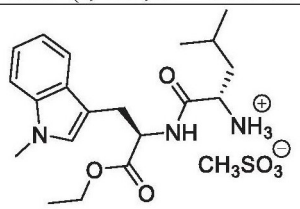
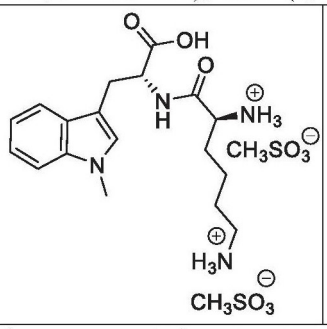
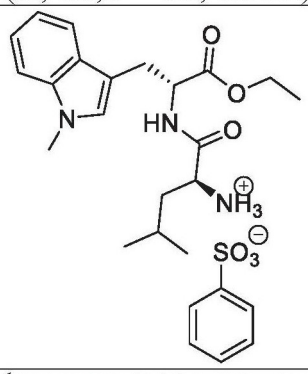
	(ddd, 1H, *J* = 8.3, 7.1, 1.1 Hz), 7.41 – 7.47 (m, 1H), 7.70 (dd, 1H, *J* = 7.9, 0.9 Hz) ppm		
NLG-1677		(R)-2-((1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-2-氧代乙-1-铵磷酸二氢盐	80
	(DMSO-d6) 3.01-3.05 (m, 1H), 3.18-3.22 (m, 1H), 3.42-3.56 (m, 2H), 3.72 (s, 3H), 4.42-4.50 (m, 1H), 7.01-7.14 (m, 3H), 7.33-7.37 (m, 1H), 7.51-7.55 (m, 1H), 8.44 (br s, 9H), 8.65 (s, 1H)		
NLG-03272-02		(S)-1-(((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-4-(甲基硫基)-1-氧代丁-2-铵磷酸二氢盐	75
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.13 (t, *J*=7.1 Hz, 3H), 1.64-1.72 (m, 1H), 1.73 – 1.84 (m, 1H), 1.93 (s, 3H), 2.28 (t, *J*=7.9 Hz, 2H), 3.08 (dd, *J*=14.6, 8.5 Hz, 1H), 3.18 (dd, *J*=14.5, 5.2 Hz, 1H), 3.54 (t, *J*=6.0 Hz, 1H), 3.73 (s, 3H), 4.07 (q, *J*=7.1 Hz, 2H), 4.56 (q, *J*=6.8, 6.1 Hz, 1H), 7.02 (t, *J*=7.4 Hz, 1H), 7.07 – 7.23 (m, 2H), 7.38 (d, *J*=8.2 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 1H), 7.98 (br s, 5H), 8.68 (d, *J*=7.7 Hz, 1H)		
NLG-03380-02		(S)-1-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-4-(甲基硫基)-1-氧代丁-2-铵磷酸二氢盐	78
	^{1}H NMR(DMSO-d_6, 400 MHz): δ (ppm) 1.63 – 1.79 (m, 2H), 1.85 (s, 3H), 2.13 (t, *J*=8.1 Hz, 2H), 3.01 (dd, *J*=14.6, 9.0 Hz, 1H), 3.23 (dd, *J*=14.7, 4.6 Hz, 1H), 3.72 (s, 4H), 4.51 (s, 1H), 7.00 (t, *J*=7.5 Hz, 1H), 7.06 – 7.20 (m, 2H), 7.36 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=7.9 Hz, 1H), 8.63 (s, 6H)		

[0377] 产生吲哚西美德前药的单甲磺酸盐和二甲磺酸盐以及苯磺酸盐的一般方法。

[0378] 在室温下向游离碱(0.25g,0.723mmol)于乙醇(10mL)中的溶液中加入甲磺酸或苯磺酸(在二胺的情况下,0.723mmol或1.446mmol),并将混合物在室温下搅拌过夜。将乙醇蒸发,并将粗产物在甲基叔丁醚中搅拌1-5小时。将沉淀过滤并干燥,得到相应的甲磺酸盐或苯磺酸盐。

[0379]

#	化合物	名称	产率(%)
NLG-1627		(2R)-1-(2,3-二羟基丙氧基)-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-铵甲磺酸盐	41
	^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (s, 3H), 3.24- 3.29 (m, 2H), 3.29 -3.41 (m, 2H), 3.65-3.68 (m, 1H), 3.75 (s, 3H), 4.04 (dd, 1H, J = 11.1, 6.3 Hz), 4.16 (dd, 1H, J = 11.0, 4.0 Hz), 4.28 (br s, 1H), 7.06 (ddd, 1H , J = 8.0, 7.1, 1.0 Hz), 7.17 (ddd, 1H , J = 8.2, 7.1, 1.1 Hz), 7.21 (s, 1H), 7.39-7.46 (m, 1H), 7.54 (dt, 1H, J= 8.1, 0.9 Hz), 8.29 (br s, 3H)。		
NLG-1631		((S)-5-氨基-1-(((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-1,5-二氧代戊-2-铵甲磺酸盐	78
	^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (t, 3H, J = 7.1 Hz), 1.80-1.86 (m, 2H), 1.97- 2.13 (m, 2H), 2.31 (s, 3H), 3.08 (dd, 1H , J = 14.5, 8.2 Hz), 3.18 (dd, 1H , J = 14.5, 6.0 Hz), 3.72 (s, 3H), 3.85 (q, 1H , J = 5.6 Hz), 4.06 (q, 2H , J = 7.1 Hz), 4.59 (td, 1H , J = 8.0, 6.0 Hz), 6.98 (s, 1H), 7.03 (ddd, 1H, J = 8.0, 6.9, 1.0 Hz), 7.09-7.18 (m, 2H), 7.34-7.42 (m, 2H), 7.52 (dt, 1H , J = 7.9, 1.0 Hz), 8.12 (d, 3H, J = 5.6 Hz), 8.93 (d, 1H, J = 7.9 Hz)。		
NLG-1662		(R)-4-(((2-铵基-3-(1-甲基-1H-吲哚-3-基)丙酰基)氧基)甲基)哌啶-1-鎓甲磺酸盐	32
	(DMSO-d$_6$) 1.25 (dt, 2H, J = 8.3, 34.3 Hz), 1.49 (ddd, 3H, J = 8.0, 12.1, 23.2 Hz), 2.50 (s, 6H), 2.54-2.69 (m, 2H), 3.01-3.15 (m, 2H), 3.58 (s, 3H), 3.70 (dd, 1H, J = 4.2, 11.0 Hz), 3.79 (dd, 1H, J = 4.1, 11.0 Hz), 3.96-4.07 (m ,1H), 6.88 (t, 1H, J = 7.5 Hz), 6.95-7.03 (m, 2H), 7.12 (d, 1H, J = 8.1 Hz), 7.31 (d, 1H, J = 7.9 Hz), 8.13-8.33 (m, 3H),		

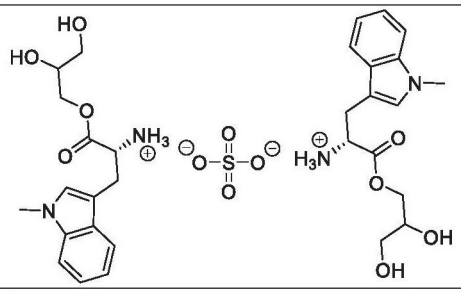
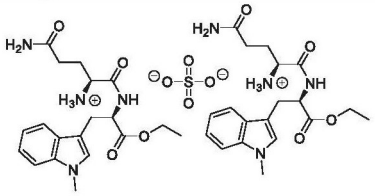
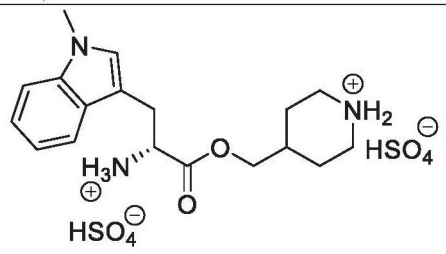
	8.59 (t, 1H, J = 10.5 Hz)		
NLG-1666		(S)-1-(((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-4-甲基-1-氧代戊-2-铵甲磺酸盐	69
	^{1}H NMR (400 MHz, DMSO-d_6): 0.73 (dd, 6H, J = 8.2, 6.3 Hz, 6H), 1.16 (t, 3H, J = 7.1, 7.1 Hz, 3H), 1.24 (t, 2H, J = 7.1, 7.1 Hz, 2H), 1.32 (dt, 1H, J = 13.0, 6.7, 6.7 Hz, 1H), 2.29 (s, 3H), 3.03 (dd, 1H, J = 14.5, 9.3 Hz, 1H), 3.20 (dd,1H, J = 14.5, 5.3 Hz), 3.72 (s, 3H), 4.11 (q, 2H, J = 7.1, 7.1, 7.1 Hz), 4.64 (td, 1H, J = 8.8, 8.8, 5.5 Hz), 7.02 (t, 1H, J = 7.5, 7.5 Hz), 7.13 (d, 2H, J = 9.8 Hz), 7.38 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 7.9 Hz), 8.01 (s, 3H), 8.92 (d, 1H, J = 8.2 Hz, 1H)。		
NLG-1668		(S)-6-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-6-氧代己-1,5-二铵甲磺酸盐	79
[0380]	^{1}H NMR(甲醇-d4, 400 MHz): δ = 0.82 – 0.98 (m, 2H), 1.26 – 1.40 (m, 2H), 1.42 – 1.56 (m, 2H), 1.73 (dt, 1H, J = 15.3, 7.5 Hz), 1.96 (dddd, 1H, J = 26.4, 16.4, 12.9, 6.1 Hz), 2.53 (ddd, 2H, J = 13.0, 6.6, 4.6 Hz), 2.71 (s, 6H), 3.14 (dd, 1H, J = 14.9, 10.0 Hz), 3.44 (ddd, 1H, J = 14.9, 4.6, 1.0 Hz), 3.78 (s, 3H), 3.81 (t, 1H, J = 6.5 Hz), 7.03 – 7.11 (m, 2H), 7.19 (ddd, 1H, J = 8.3, 7.1, 1.2 Hz), 7.36 (dt, 1H, J = 8.3, 0.9 Hz), 7.60 (dt, 1H, J = 8.0, 1.0 Hz) ppm		
NLG-1671		N^{α}-((S)-2-(λ^4-氮烷基)-4-甲基戊酰基)-1-甲基-D-色氨酸乙酯苯磺酸盐	68
	^{1}H NMR (400 MHz, DMSO-d_6): 0.73 (dd, 6H, J = 8.2, 6.3 Hz), 1.16 (t, 3H, J = 7.1, 7.1 Hz), 1.24 (t, 2H, J = 7.3, 7.3 Hz), 1.32 (dt, 1H, J = 13.0, 6.5, 6.5 Hz), 2.98 – 3.09 (m, 1H), 3.20 (dd, 1H, J = 14.5, 5.2 Hz), 3.72 (s, 3H), 4.11 (q, 2H, J = 7.1, 7.1, 7.1 Hz), 4.64 (td, 1H, J = 8.9, 8.9, 5.4 Hz), 6.99 – 7.05 (m, 1H), 7.09 – 7.17 (m, 2H), 7.26 – 7.35 (m, 3H), 7.38 (d, 1H, J = 8.2 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.59 (dd, 2H, J = 7.7, 1.9 Hz), 8.00 (s, 3H), 8.92 (d, 1H, J = 8.2 Hz)。		

[0381] 产生吲哚西美德前药的单硫酸盐、二硫酸盐和硫酸氢盐的一般方法。

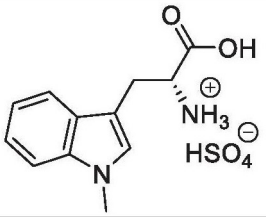
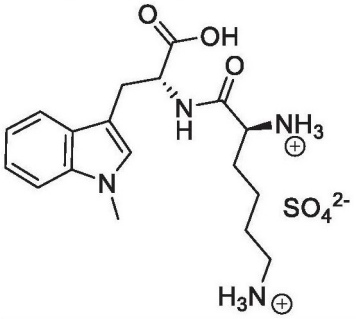
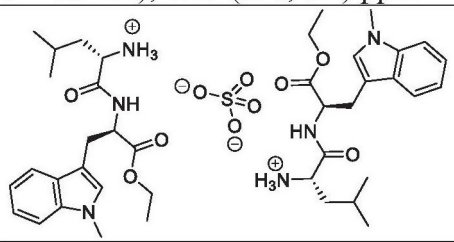
[0382] 在0℃下向游离碱(1.22mmol)于无水THF(10mL)中的溶液中加入作为于THF中的溶

液(2mL)形式的硫酸(0.611mmol或1.22mmol),并将溶液升温至室温。搅拌2-6小后,蒸馏除去溶剂,并将粗物质用甲基叔丁醚搅拌,将固体过滤并真空干燥以产生所需产物。

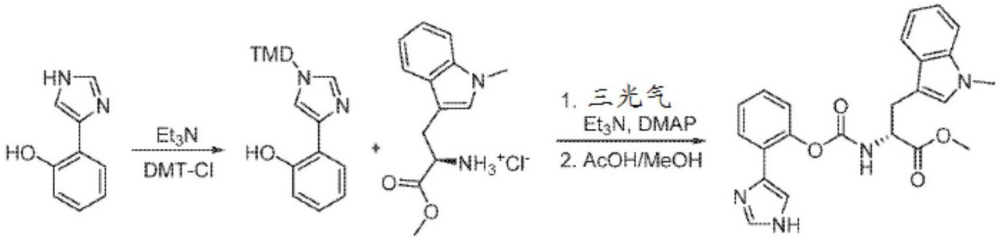
[0383]

#	化合物	名称	产率(%)
NLG-1628		(2R)-1-(2,3-二羟基丙氧基)-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-铵硫酸盐	43
	^{1}H NMR (400 MHz, DMSO-d_6): 3.05-3.19 (m, 2H), 3.29 - 3.40 和 3.44-3.55 (两个 m, 2H), 3.62-3.69 (m, 1H), 3.74 (s, 3H), 3.89-3.99 (m, 2H), 4.07 – 4.12 (m, 1H), 6.25 (br s, 2H), 7.03 (t, 1H, J = 7.7 Hz), 7.11-7.21 (m, 2H), 7.40 (d, 1H, J = 8.1 Hz), 7.51-7.57 (m, 1H)。		
NLG-1630		(S)-5-氨基-1-(((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)氨基)-1,5-二氧代戊-2-铵硫酸盐	83
	^{1}H NMR (400 MHz, DMSO-d_6) : 1.10 (t, 3H , J = 7.1 Hz), 1.63-1.74 (m, 1H), 1.75-1.86 (m, 1H), 2.02-2.07 (m, 2H), 3.13 (qd, 2H , J = 14.5, 6.8 Hz), 3.52 (dd, 1H , J = 7.4, 5.0 Hz), 3.72 (s, 3H), 4.04 (q, 2H, J = 7.1 Hz), 4.55 (q, 1H, J = 1.6 Hz), 6.47 (br s, 2H), 6.85 (s, 1H), 7.03 (t, 1H, J = 7.5 Hz), 7.10 -7.19 (m, 2H), 7.29 (s, 1H), 7.38 (d,1H, J = 8.2 Hz), 7.51 (d, 1H, J = 7.9 Hz), 8.59 (d, 1H, J = 7.9 Hz)。		
NLG-1663		(R)-4-(((2-铵基-3-(1-甲基-1H-吲哚-3-基)丙酰基)氧基)甲基)哌啶-1-鎓硫酸氢盐	25
	(DMSO-d_6) 1.08-1.30 (m, 2H), 1.42-1.59 (m, 2H), 1.64-.178 (m, 1H), 2.64-2.84 (m, 2H), 3.11-3.35 (m, 4H), 3.75 (s, 3H), 3.81-3.90 (m, 2H), 4.22-4.27 (m, 1H), 5.79 (br s, 7H), 7.06 (t, 1H, J = 7.4 Hz), 7.11-7.24 (m, 2H), 7.43 (d, 1H, J = 8.1 Hz), 7.51 (d, 1H, J = 7.7 Hz), 8.17 (s, 1H), 8.39 (s, 2H), 8.51 (s, 1H)		

[0384]

NLG-1667		(R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙-1-铵硫酸氢盐	30
	(DMSO-d_6) 3.17 (dd, 1H, J = 15.1, 7.2 Hz), 3.27 (dd, 1H, J = 15.0, 5.3 Hz), 3.74 (s, 3H), 3.96 (t, 1H, J = 6.2 Hz), 7.04 (t, 1H, J = 7.4 Hz), 7.12-7.21 (m, 2H), 7.41 (d, 1H, J = 8.2 Hz), 7.58 (d, 1H, J = 8.0 Hz), 8.52 (br s, 4H)		
NLG-1669		(S)-6-(((R)-1-羧基-2-(1-甲基-1H-吲哚-3-基)乙基)氨基)-6-氧代己-1,5-二铵硫酸盐	82
	^{1}H NMR(DMSO-d_6, 400 MHz): δ = 1.08 – 1.58 (m, 7H), 2.55 – 2.71 (m, 2H), 3.03 (dd, 1H, *J* = 14.6, 8.8 Hz), 3.21 (dd, 1H, *J* = 14.6, 4.9 Hz), 3.63 (s, 1H), 3.72 (s, 3H), 4.53 (d, 1H, *J* = 7.9 Hz), 7.02 (t, 1H, *J* = 7.4 Hz), 7.09 – 7.18 (m, 2H), 7.37 (d, 1H, *J* = 8.2 Hz), 7.56 (d, 1H, *J* = 7.9 Hz), 8.25 (br s, 6H) ppm		
NLG-1691		N^{α}-((S)-2-(λ^4-氮烷基)-4-甲基戊酰基)-1-甲基-D-色氨酸乙酯硫酸盐	29
	^{1}H NMR (400 MHz, DMSO-d_6): 0.72 – 0.78 (m, 6H), 1.11 (t, 3H, *J* = 7.2, 7.2 Hz), 1.14 – 1.18 (m, 1H), 1.22 – 1.30 (m, 1H), 1.45 (dt, 1H, *J* = 13.5, 6.8, 6.8 Hz), 3.00 – 3.08 (m, 1H), 3.15 (dd, 1H, *J* = 14.5, 5.6 Hz), 3.70 (s, 3H), 4.05 (q, 2H, *J* = 7.1, 7.1, 7.1 Hz), 4.54 (q, 1H, *J* = 7.5, 7.5, 7.4 Hz), 7.00 (t, 1H, *J* = 7.5, 7.5 Hz), 7.11 (m, 2H), 7.36 (d, 1H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 7.9 Hz), 8.48 (d, 1H, *J* = 7.9 Hz)。		

[0385]



[0386] 合成(R)-2-(((2-(1H-咪唑-4-基)苯氧基)羰基)氨基)-3-(1-甲基-1H-吲哚-3-基)丙酸甲酯(NLG-1264)

[0387] 向2-(1H-咪唑-4-基)苯酚(1.0mmol)(根据J.Med.Chem.,2008,51(16),第4968-4977页制备)于DMF(3mL)中的溶液添加三乙胺(1.1mmol)。搅拌10分钟后,滴加4,4′--二甲

氧基三苯甲基氯(1.0mmol)于DMF中的溶液(2mL)。在氮气氛下搅拌过夜后,将反应混合物倾入冰水(10mL)中。将固体滤掉,用冷水洗涤并溶于乙酸乙酯中。将有机层经Na2SO4干燥并浓缩,粗产物不经进一步纯化就用于下一步。在0℃下向(R)-2-氨基-3-(1-甲基-1H-吲哚-3-基)丙酸甲酯(0.5mmol)(如根据Paul Cox,Donald Craig,Stephanos Ioannidis,Volker S.Rahn,Tetrahedron Letters 2005,46,4687所述制备)于DCM(3mL)中的混悬液中,加入三光气(0.5mmol)和Et3N(2.0mmol)。将溶液搅拌1小时,并浓缩至干。将粗残余物立即用于下一步而不进行纯化。将粗残余物溶于DCM(5mL)中,加入苯基咪唑衍生物(0.5mmol)和DMAP(1.5mmol)。将所得溶液在室温下搅拌过夜。减压下去除溶剂,并将粗残余物通过硅胶塞过滤并浓缩。向残余物中加入MeOH(3mL)和AcOH(2mL),并将溶液在室温下搅拌30分钟。将溶液用水稀释,并用固体K2CO3制成碱性(pH约8-9)。用EtOAc萃取水层,将合并的有机层用水、盐水洗涤并干燥(Na2SO4)。将粗残余物通过硅胶柱色谱纯化,得到化合物(21%产率)。1H NMR:3.20-3.48(m,2H),3.66(s,3H),3.70(s,3H),4.61-4.75(m,1H),6.57(d,1H,J=7.2Hz),6.90-7.30(m,7H),7.50-7.58(m,1H),7.10-7.76(m,2H)。

[0388] 实施例2:吲哚西美德游离碱的固体形式的表征

[0389] D-1MT(HPLC纯度99.6%)游离碱为白色粉末,并且其在偏振光显微镜(PLM)下且通过X射线粉末分散光谱(XRPD)显示为双折射针状和结晶外观(图1)。其仅显示了通过热重分析(TGA)和差示扫描量热法(DSC)获得的在293.8℃下开始的单熔体吸热峰,和30-200℃的约0.01%重量损失,表明其是一种无水形式。该晶形是非吸湿性(从0-80%RH有0.09%重量增加),并且在动态蒸汽吸附法(DVS)之后不显示变化。此外,固体粉末形式的稳定性研究表明,D-1MT在测试条件(25℃/60%RH,40℃,40℃/75%RH,60℃和70℃)下持续4周是化学稳定的。另外,其在25℃下在24小时内在含0.1N HCl和50mM磷酸盐缓冲液pH 2-8的溶液中也是稳定的而其在含0.3%H_2O_2的pH 2和pH 8缓冲液中显示出较少的降解(0.45%-3.3%)(大部分杂质是RRT=0.58)。

[0390] 实施例3:吲哚西美德游离碱溶解度的表征

[0391] 呈游离碱的吲哚西美德在缓冲或非缓冲溶液以及模拟生物流体(SGF、FaSSIF或FeSSIF)中的溶解度示于图5中(开放式符号)。吲哚西美德在pH 2-8的水溶液中的溶解度为1.8-2.0mg/mL,其中在pH<1.5或>10下溶解度较高。在中性pH范围内的这种低溶解度可能是由于呈晶体的吲哚西美德的高分子堆积能(packing energy),这由293.8℃的非常高的熔点反映。吲哚西美德在对应于肠pH的pH范围内的这种低溶解度可能部分地解释了人体内在高于800mg的剂量下有限的剂量吸收。因此,我们研究了吲哚西美德的盐或喷雾无水分散体在口服给药后可以增加溶解度和暴露。

[0392] 实施例4:吲哚西美德盐及其溶解度的表征

[0393] 制造若干种吲哚西美德盐并评价其物理化学性质(表2)。盐酸盐、硫酸盐、磷酸盐、半-磷酸盐、甲磺酸盐和半-甲磺酸盐是白色固体粉末,其显示结晶性质(通过PLM和XRPD)且是无水的(通过TGA)。这些盐显示比游离碱更低的熔点,表明在>1.5至<10的pH范围内水中溶解度增加。这些盐中的大多数显示出于水中的溶解度增加至约4.7-8.6mg/mL和于SGF中的溶解度增加至5.5-10.6mg/mL,其中盐酸盐显示出于水或SGF中非常显著增加至>200mg/mL。

[0394] 测试的另一种吲哚西美德盐是马来酸盐,其显示194℃的低熔点和较差结晶度(通

过PLM和XRPD)。这种盐具有水合物或溶剂化物形式的粘性白色粉末的外观(4.5%重量损失,通过TGA)。

[0395] 甲苯磺酸盐显示了褐色油状物的外观,这可能是有利的,因为这可能提高活性成分的肠吸收。

[0396] 其它盐具有不太有利的物理化学性质。例如,乳酸盐和N-甲基葡糖胺不与吲哚西美德形成盐,并且该晶体显示了吲哚西美德游离碱晶体和N-甲基葡糖胺或乳酸盐晶体的混合物。

[0397] 钠盐不显示结晶形态,它是具有非常低熔点和多个分解峰(通过TGA或DSC)的水合物或溶剂化物,因此没有对其进行进一步表征。

[0398] 表2:吲哚西美德及其盐的物理化学性质

[0399]

盐	外观	DSC (熔点或分解点)	TGA (重量损失)	化学计量比 (API:酸)	纯度	结晶度		吸水性 (0-80% RH)	溶解度 (25℃, mg/mL)	
						PLM	XRPD		水(pH)	SGF (pH)
游离碱	无水白色粉末	293.80℃	约 0.01% (30 - 200℃)	-	99.6	是	是(游离碱)	0.09	1.8 (6.03)	3.6 (2.32)
HCl 盐	无水白色粉末	230.59℃	约 0.13% (30 - 120℃)	1:1.05	99.7	是	HCl 盐形式 1	0.017	> 200 (1.06)	> 200 (1.03)
硫酸盐	无水白色粉末	225.86℃	约 1.89% (26 - 120℃)	1:0.51	99.6	是	硫酸盐形式 1	3.4	4.7 (2.03)	5.5 (1.68)
半 - 磷酸盐	无水白色粉末	216.1℃	约 0.6% (30 - 150℃)	1:0.60	99.0	是	磷酸盐形式 1	-	8.6 (2.42)	10.6 (2.05)
磷酸盐	无水白色粉末	225.09℃	约 0.15% (30 - 150℃)	1:1.01	98.9	是	磷酸盐形式 1	1.7	8.32 (NA)	9.83 (NA)
半 - 甲磺酸盐	无水白色粉末	266.2℃	约 0.3% (30 - 150℃)	1:0.56	99.7	是	不良结晶	-	5.5 (2.34)	6.0 (1.84)
甲磺酸盐	无水白色粉末	209.71℃	约 0.18% (30 - 150℃)	1:0.98	99.5	是	甲磺酸盐 + 游离碱	0.12*	5.1 (1.84)	6.0 (1.43)
马来酸盐	水合物或溶剂化物	102.6℃ 194.3℃	约 4.5% (25 - 150℃)	1:0.50	99.3	是	马来酸盐形式 1	-	-	-

[0400]

甲苯磺酸盐	褐色油状物	-	-	-	97.3	无	NA	-	-	-
乳酸盐	白色混悬液			1:01			乳酸 + 游离碱			
N - 甲基葡糖胺	白色混悬液			1:01			葡糖胺 + 游离碱			
钠盐	水合物或溶剂化物	63.82℃	约 16.9% (30 - 100℃)	1:1.03	98.8	No	Na 盐形式 1	-	-	-

[0401] 实施例4:吲哚西美德的喷雾无水分散体

[0402] 制出吲哚西美德喷雾无水分散体(SDD)制剂的列表,以评估任何SDD制剂是否能够

通过在胃肠道流体中产生和维持吲哚西美德的过饱和状态来增加分子吸收，使得其吸收可以增强。在本研究中，通过两种方法制备SDD制剂：热法喷雾干燥-制剂溶液在喷雾干燥前加热至110℃，和基础喷雾干燥-制剂pH在喷雾干燥前升高至约11.5(室温)。通过模拟胃缓冲液(GB)和模拟肠液(SIF)的体外溶出测试研究了每种SDD制剂的表现。如表3所示，C_{maxGB}表示当足够的SDD制剂在GB中溶解30分钟时吲哚西美德在溶液中的最大浓度；C_{max90}表示当SDD在SIF中溶解90分钟时的最大吲哚西美德浓度；$UltraC_{90}$表示溶解90分钟后接着通过超速离心除去任何颗粒的SIF中的浓度且$UltraC_{1200}$表示溶解1200分钟后接着通过超速离心除去任何颗粒的SIF中的浓度。预期当用SDD制剂在动物以及人类中给药时，GB和SIF中吲哚西美德的浓度提高增加了吲哚西美德吸收。评价这些SDD制剂的另一个标准是这些制剂中吲哚西美德的物理和化学稳定性。发现通过热法喷雾药物方法制备的SDD制剂通常比通过基础处理喷雾干燥制成的那些制剂更稳定。此外，粉末中较高的载药量是优选的，因为它可能降低最终制剂的剂量。基于所有这些标准，选择两种SDD制剂用于猴中的进一步体内PK研究。第一种是50％吲哚西美德/50％PVPVA-64，其显示预测的肠浓度是吲哚西美德的1.8倍($UltraC_{90}$3293ng/mL对1849ng/mL)；且第二种是50％吲哚西美德/50％Affinisol 126，其显示预测的肠浓度是吲哚西美德的2.3倍($UltraC_{90}$4340ng/mL对1849ng/mL)。这些SDD通过热法喷雾干燥制备，其显示出更佳的稳定性性质。

[0403] 表3：吲哚西美德的喷雾无水分散体制剂的溶出测试

[0404]

组成	处理方法	C_{maxGB} (μg/mL)	C_{max90} (μg/mL)	$UltraC_{90}$ (μg/mL)	$UltraC_{1200}$ (μg/mL)
吲哚西美德 API (对照)	NA	5,154	2,213	1,849	1,854

[0405]

10% 吲哚西美德/ 90% Affinisol 126	热法喷雾干燥	6,253	3,027	2,982	3,392
25% 吲哚西美德/ 75% Affinisol 126	基础喷雾干燥	7,466	4,064	3,023	3,096
25% 吲哚西美德/ 75% HPMC-E3	基础喷雾干燥	17,281	7,313	3,943	3,171
25% 吲哚西美德/ 75% PVPVA-64	基础喷雾干燥	20,116	9,349	2,531	2,908
25% 吲哚西美德/ 75% Affinisol 126	热法喷雾干燥	6,831	3,932	3,892	3,976
25% 吲哚西美德/ 75% Eudragit L100	热法喷雾干燥	4,015	2,487	2,494	2,598
25% 吲哚西美德/ 75% PVPVA-64	热法喷雾干燥	8,488	3,623	3,372	2,840
50% 吲哚西美德/ 50% PVPVA-64	基础喷雾干燥	10,442	4,745	4,828	2635
50% 吲哚西美德/ 50% HPMC E3	基础喷雾干燥	9,967	4,630	4,802	3,067
50% 吲哚西美德/ 50% Affinisol 126	热法喷雾干燥	6,078	3,455	3,690	3,471
50% 吲哚西美德/ 50% Affinisol 912	热法喷雾干燥	5,931	3,352	3,599	3,228
50% 吲哚西美德/ 50% PVPVA-64	热法喷雾干燥	8,481	3,695	3,293	3,018
50% 吲哚西美德/ 50% Affinisol 126	热法喷雾干燥	8,995	4,187	4,340	4,194

[0406] 实施例5：吲哚西美德游离碱、吲哚西美德盐和吲哚西美德SDD在食蟹猴中的药代动力学比较

[0407] 为了确定与吲哚西美德游离碱相比显示溶解度增加的盐或SDD是否导致吲哚西美德的最大浓度(Cmax)和总暴露($AUC_{0->\infty}$)增加，我们在食蟹猴中进行了比较性交叉药代动力学研究，食蟹猴是用于预测人类口服生物利用度的常见物种。向每组4只猴子的两组(全是

雄性)以275μmol/kg(组1)或825μmol/kg(组2)经口给药:1)吲哚西美德游离碱胶囊;2)吲哚西美德盐酸盐胶囊;3)吲哚西美德半磷酸盐胶囊;4)SDD1混悬液(吲哚西美德50%/50% PVPVA-64,(w/w))和5)SDD2混悬液(吲哚西美德50%/Affinisol 126 50%(w/w))。每7天一次用5个剂量制剂的每一种向每只猴子给药,并且在0、0.25小时、0.5小时、1小时、2小时、4小时、6小时、8小时、12小时、24小时、36小时和48小时获得血液样品。通过经过验证的LC-MS/MS分析方法从血浆中测定吲哚西美德的浓度。C_{max}和$AUC_{(0-48h)}$通过使用WinNonLin软件(Certara)的非隔室分析计算。对于胶囊制剂中的吲哚西美德,向组1中的动物用3粒胶囊A经口给药,并向组2中的动物用4粒胶囊B给药。胶囊A和B的组成示于表4中。对于SDD制剂中的吲哚西美德,向组1中的动物用4mL/kg的15mg吲哚西美德/mL混悬液给药,并向组2中的动物用4mL/kg的45mg吲哚西美德/mL混悬液给药。在0.5%甲基纤维素(Methocel)中制备SDD混悬液制剂。

[0408] 表4:用于经口给药至食蟹猴的含呈其游离碱或盐形式的吲哚西美德的胶囊的组成

[0409]

	吲哚西美德游离碱		吲哚西美德 HCl		吲哚西美德 0.5 PO_4H_3	
MW (g/mol)	218.26		254.76		267.3	
成分(mg)	Cap A	Cap B	Cap A	Cap B	Cap A	Cap B
活性成分(mg)	100	225	116.7	262.5	122.4	275.5
Avicel PH101(mg)	17.9	40.2	20.8	46.9	21.9	49.2
甘露醇(mg)	17.9	40.2	20.8	46.9	21.9	49.2
交联羧甲纤维素钠(mg)	7.1	16.1	8.3	18.8	8.7	19.7

[0410]

总计	142.9	321.4	166.7	375	174.9	393.6

[0411] 表5中显示了在用每种吲哚西美德制剂给药后获得的每组中观察到的平均Cmax和$AUC_{(0-48h)}$参数值。表5中显示了获得的用于每种制剂相对吲哚西美德游离碱的比较的这些值的增加百分比以及P值。相较于吲哚西美德游离碱胶囊的给药,吲哚西美德HCl胶囊的给药导致在测试的两种剂量水平下,Cmax(31-65%)和暴露(37-53%)显著增加。类似地,吲哚西美德半磷酸盐胶囊产生显著的Cmax(7-44%)和暴露(27-34%)增加。相反,SDD1或SDD2制剂中的吲哚西美德产生相较于吲哚西美德游离碱胶囊显著的Cmax(15-94%)增加,但是不能增加总暴露。出于这些原因,呈其盐酸盐、半-磷酸盐或磷酸盐的吲哚西美德盐优于呈其游离碱形式的吲哚西美德,无论是呈胶囊还是呈喷雾无水分散体。

[0412] 表5:猴中吲哚西美德游离碱相对于其盐或喷雾元水分散体的Cmax和总暴露(AUC0->∞)的比较

[0413]

	吲哚西美德游离碱	吲哚西美德 HCl	吲哚西美德 0.5.H_3PO_4	吲哚西美德 PVPVA-64	吲哚西美德 Affinisol 126
剂量	275 μmol/kg				
动物数	4	4	4	4	4
Cmax，平均值(μM)	12.9±3.3	21.3±8.9	18.5±4.8	25±5	21.3±5
相对于吲哚西美德 FB 的增加%	NA	65	44	94	65
P 值	NA	0.047	0.033	0.010	0.017
AUC(0->48h)(μM.h)	66±17	101±18	89±15	72.5±18	83±25
相对于吲哚西美德 FB 的增加%	NA	53	34	9	26
P 值	NA	0.043	0.065	0.36	0.2
剂量	825 μmol/kg				

[0414]

动物数	4	4	4	4	4
Cmax，平均值(μM)	25.6±12.8	33.4±12	23.4±12.7	29.4±10	33.7±8.4
相对于吲哚西美德 FB 的增加%	NA	31	7	15	32
P 值	NA	0.010	0.042	0.041	0.025
AUC(0->48h)(μM.h)	127±73	173±75	161±81	141±61	136±57
相对于吲哚西美德 FB 的增加%	NA	37	27	11	7
P 值	NA	0.012	0.015	0.18	0.29

[0415] 本研究显示，在275-825μmol/kg的剂量范围内，吲哚西美德的盐酸盐和磷酸盐相对于游离碱可以产生Cmax和AUC药代动力学参数的增加。

[0416] 实施例6：大鼠中胶囊制剂内的吲哚西美德盐的药代动力学测试

[0417] 为了确定盐形成是否增加大鼠中吲哚西美德的最大浓度(Cmax)和总暴露($AUC_{0->\infty}$)，我们测试了吲哚西美德的盐酸盐、磷酸盐、硫酸盐和甲磺酸盐，并通过将它们与适当的赋形剂混合将其配制成胶囊。研究了三个剂量水平：37、185或500μmol/kg。

[0418] 以表6.1-6.3中显示的比例制备明胶胶囊(Torpac，20mg容量)，其含有11.4、28.6或50μmol吲哚西美德或其盐/胶囊，有或没有由微晶纤维素、乳糖一水合物、交联羧甲纤维素钠和硬脂酸镁组成的赋形剂。手动填充胶囊，并通过重量和LC-MS/MS验证来自每批的代

表性胶囊样品的组成均匀性以确定平均吲哚西美德含量。

[0419] 表6.1:用于以37μmol/kg向大鼠经口给药的含呈其游离碱或盐形式的吲哚西美德的胶囊A的组成

[0420]

	吲哚西美德游离碱	吲哚西美德HCl	吲哚西美德H_3PO_4	吲哚西美德H_2SO_4	吲哚西美德CH_3SO_3H

[0421]

MW (g/mol)	218.26		254.76		316.25		316.33		314.36	
	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)
活性成分	2.50	12.50	2.92	14.59	3.62	18.11	3.62	18.11	3.60	18.00
微晶纤维素	7.45	37.25	7.3	36.50	7.1	35.50	7.1	35.49	7.1	35.50
乳糖一水合物	7.45	37.25	7.3	36.50	7.1	35.50	7.1	35.49	7.1	35.50
交联羧甲纤维素钠	2.4	12.00	2.28	11.40	1.98	9.90	1.98	9.90	2	10.00
硬脂酸镁	0.2	1.00	0.2	1.00	0.2	1.00	0.2	1.00	0.2	1.00
总计	20.00	100	20.00	100	20.00	100	20.00	100	20.00	100
μmol/胶囊	11.4		11.4		11.4		11.4		11.4	
胶囊/动物	1		1		1		1		1	
μmol/kg	37		37		37		37		37	
mg 游离碱/kg	8		8		8		8		8	

[0422] 表6.2:用于以185μmol/kg向大鼠经口给药的含呈其游离碱或盐形式的吲哚西美德的胶囊B的组成

[0423]

MW (g/mol)	吲哚西美德游离碱 218.26		吲哚西美德HCl 254.76		D1mT 0.5. H_3PO_4 267.3	
	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)
活性成分	6.25	31%	7.3	37%	7.65	38%
微晶纤维素	5.55	28%	5.1	26%	5.05	25%
乳糖一水合物	5.55	28%	5.1	26%	5.05	25%
交联羧甲纤维素钠	2.45	12%	2.3	12%	2.05	10%
硬脂酸镁	0.2	1%	0.2	1%	0.2	1%
总计	20.00	100	20.00	100	20.00	100
μmol/胶囊	28.6		28.6		28.6	
胶囊/动物	2		2		2	
μmol/kg	185		185		185	
mg 游离碱/kg	40		40		40	

[0424] 表6.3:用于以500μmol/kg向大鼠经口给药的含呈其游离碱或盐形式的吲哚西美

德的胶囊C的组成

[0425]

MW (g/mol)	吲哚西美德游离碱 218.26		吲哚西美德 HCl 254.76		D1mT 0.5. H_3PO_4 267.3	
	(mg)	%(w/w)	(mg)	%(w/w)	(mg)	%(w/w)
活性成分	10.83	100%	12.6	100%	13.27	100%
总计	10.83	100	12.6	100	13.27	100
μmol/胶囊	50		50		50	
胶囊/动物	3		3		3	
μmol/kg	500		500		500	
mg 游离碱/kg	110		110		110	

[0426] 为了测试通过以呈其游离碱或盐形式的吲哚西美德给药而获得的药代动力学曲线，通过用1粒胶囊A、2粒胶囊B或3粒胶囊C胃内递送来给药以达到37、185和500μmol/kg的剂量水平(分别相当于8、40和110mg/kg吲哚西美德)。在给药前，将大鼠禁食16小时以消除任何混杂的食物影响，并在给药后2小时返回食物。在给药后0分钟、15分钟、30分钟、1小时、2小时、4小时、6小时、10小时、24小时、48小时和72小时，从每只大鼠获得血液样品。通过LC-MS/MS测定血浆中吲哚西美德的浓度，并使用软件WinNonLin(Certara)计算药代动力学参数。

[0427] 评价的最相关的药代动力学参数是吲哚西美德的最大浓度(Cmax)和总暴露($AUC_{0->\infty}$)。表7.1-7.3和图6显示了实验结果的概述。

[0428] 吲哚西美德盐酸盐形式导致在低剂量水平下Cmax非统计学上显著降低，在中间剂量下统计学上显著增加和在高水平下统计学显著降低。盐酸盐的药物暴露(AUC)在低剂量和高剂量水平下没有显示出显著变化，但在中间水平下显示出显著增加。与灵长类动物相比，吲哚西美德盐酸盐在啮齿类动物中的不同行为基于该盐的溶解度和溶出曲线是意想不到的，并且其不遵循剂量依赖性趋势，这突出了进行物种特异性和剂量依赖性测试对于预测人体内的药代动力学曲线的重要性。

[0429] 吲哚西美德磷酸盐和半磷酸盐在低和中等剂量水平下显示出Cmax和AUC显著增加，但在最高剂量水平下显示出Cmax显著降低和暴露非统计学上显著降低。

[0430] 图6中显示了游离碱、HCl和PO_4H_3形式的吲哚西美德的Cmax和AUC的剂量依赖性相关性。该图显示了HCl和PO_4H_3盐相对于游离碱在低和中等剂量水平下的Cmax增加，但是在最高剂量水平下在Cmax剂量-响应曲线中饱和，这未在游离碱中看到。AUC的剂量-响应曲线显示了AUC随着剂量更线性地增加，除了在测试的最高剂量水平下似乎不太与剂量成比例增加的PO_4H_3盐外。

[0431] 类似地，其它盐形式的吲哚西美德诸如硫酸盐或甲磺酸盐当以37μmol/kg测试时将Cmax和AUC增加了约30-40％。

[0432] 这些测试表明，吲哚西美德的盐酸盐和磷酸盐相对于游离碱形式增加了溶解度，并展现出增加的Cmax和AUC参数值。

[0433] 表7.1：以37μmol/kg给药的大鼠中吲哚西美德游离碱相对于其盐形式的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0434]

剂量: 37 μmol/kg	吲哚西美德游离碱	吲哚西美德 HCl	吲哚西美德 H_3PO_4	吲哚西美德 H_2SO_4	吲哚西美德 CH_3SO_3H
动物数	11	4	10	4	4
Cmax，平均值(μM)	15.9±8	9.5±2	22.3±9	22.6±7	20.3±2
相对于吲哚西美德游离碱的增加%	NA	-40	40	42	28
P 值	NA	0.069	0.044	0.077	0.18
AUC(0->∞)(μM.h)	390±166	299±77	558±185	553±196	537±194
相对于吲哚西美德游离碱的增加%	NA	-23	43	42	38
P 值	NA	0.159	0.018	0.065	0.2

[0435] 表7.2:以185μmol/kg给药的大鼠中吲哚西美德游离碱相对于其盐形式的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0436]

剂量: 185 μmol/kg	吲哚西美德游离碱	吲哚西美德 HCl	吲哚西美德 H_3PO_4
动物数	8	6	6
Cmax，平均值(μM)	20.8±4	38.4±10	40.9±5
相对于吲哚西美德游离碱的增加%	NA	84	96
P 值	NA	<0.0001	<0.0001
AUC(0->∞)(μM.h)	1080±478	1493±728	1446±645
相对于吲哚西美德游离碱的增加%	NA	38	34
P 值	NA	<0.0001	<0.0001

[0437] 表7.3:以500μmol/kg给药的大鼠中吲哚西美德游离碱相对于其盐形式的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0438]

剂量：500 μmol/kg	吲哚西美德游离碱	吲哚西美德 HCl	吲哚西美德 H_3PO_4
动物数	6	5	6
Cmax，平均值(μM)	76.2±25	44.4±8	37.2±10
相对于吲哚西美德游离碱的增加%	NA	-42	-51
P值	NA	0.012	0.0027
AUC(0->∞)(μM.h)	2871±1379	2706±847	1902±1288
相对于吲哚西美德游离碱的增加%	NA	-6	-34
P值	NA	0.41	0.12

[0439] 实施例7:液体制剂中的吲哚西美德前药的药代动力学测试

[0440] 在经口施用几种吲哚西美德前药后获得的吲哚西美德的药代动力学曲线以以下这样的方式进行测试:仅反映肠通透性和前药向吲哚西美德体内转化的差异而不反映固态形式的差异,诸如可能影响不同前药的溶解度或增溶率的多晶型晶体或无定形固体的差异。因此,吲哚西美德及其每种前药溶出于适当的媒介物中,所述媒介物为盐水溶液、Cremaphor®:乙醇:盐水(10:10:80)或Chremaphor:EtOH:盐水:HCl(10:10:80:0.1N)。吲哚西美德或其前药以1mg/mL的浓度溶解并通过经口灌胃以10mL/kg向大鼠给药以达到最终剂量为10mg/kg;或以25mg/mL溶解,并通过经口灌胃以2mL/kg向大鼠给药以达到最终剂量为50mg/kg;或以10mg/mL的浓度溶解并且以5mL/kg经口向小鼠给药以达到最终剂量为50mg/kg。从大鼠的股动脉端口,或者通过眼窝后抽血从小鼠收集血液样品(0.1-0.2mL),并通过离心立即收集血浆,并将其储存在干冰上,以避免血浆收集后的前药水解。在给药后0分钟、15分钟、30分钟、1小时、2小时、4小时、6小时、10小时、24小时、48小时和72小时从大鼠收集血液样品,或在给药后0分钟、30分钟、1小时、2小时、4小时、6小时、16小时和24小时从小鼠收集血液样品。通过LC-MS/MS测定血浆中吲哚西美德和每种前药的浓度,并计算吲哚西美德及其前药的药代动力学参数。药代动力学参数反映了从每只单独的大鼠(n)获得的各参数值的平均值,或从由一组小鼠(n)获得的血液样品的单个药代动力学曲线推断出的一个常见的参数。

[0441] 表8.1和8.2显示了在用吲哚西美德或每一种测试前药给药后获得的吲哚西美德Cmax和$AUC_{(0->\infty)}$。由于所有大鼠以相同剂量10mg/kg经口给药,但每种前药具有不同的分子重量,为了比较用每种前药给药相对于用呈游离碱的吲哚西美德给药后获得的Cmax和$AUC_{(0->\infty)}$的值,将测量的Cmax和$AUC_{(0->\infty)}$通过将它们乘以$MW_{前药}/MW_{吲哚西美德}$的比例归一化,因此假定在约2倍剂量范围内的线性药代动力学。

[0442] 表8.1显示一些前药导致Cmax、AUC或两种药代动力学参数有效增加。由于前药以完全可溶形式施用,这表明那些显示血浆中吲哚西美德提高的Cmax和/或AUC的前药是通过涉及包括前药通过肠细胞壁的通透性增强、前药相对于吲哚西美德清除率降低及前药至吲哚西美德体内转化率良好在内的因素的组合的机制来实现的。并不是每一种吲哚西美德前药形式相较于施用吲哚西美德都导致吲哚西美德的最大浓度和暴露提高。特别地,当用NLG-1563、NLG-1564、NLG-1566、NLG-1548、NLG-1572、NLG-1557、NLG-1559、NLG-1570、NLG-

1565、NLG-1554、NLG-1558、NLG-1551和NLG-1547给药时，对吲哚西美德的暴露(AUC)似乎提高，而当用NLG-1557、NLG-1558、NLG-1554、NLG-1566、NLG-1570、NLG-1283和NLG-1263给药时，吲哚西美德Cmax似乎提高。

[0443] 表8.2显示当以10mg/kg向大鼠经口给药时不会导致吲哚西美德Cmax或吲哚西美德暴露有效增加的前药，表明这些化学取代中的一些可能通过不导致转化为吲哚西美德的途径来降低吲哚西美德的通透性或转化率或者增加前药清除率或这些作用的组合。

[0444] 表8.3显示通过以50mg/kg向大鼠口服给药进行测试的前药。NLG-1283当以50mg/kg向大鼠给药时，引起Cmax和AUC增加。然而，这种前药当以50mg/kg向小鼠给药时导致Cmax和AUC降低。相反，高度相似的分子NLG-1284当以50mg/kg向大鼠口服给药时，不产生显著的Cmax或AUC增加，但是其确实在小鼠中产生显著的Cmax或AUC增加，表明不同的物种对这些前药具有不同的吸收速率、消除速率和代谢速率并且分子结构的最小变化可影响不同物种的结果。在小鼠中进行剂量依赖性PK，向小鼠用10、50和100mg/kg的吲哚西美德或类似剂量的前药NLG-1626或NLG-1665给药。对于给药前药相对于呈游离碱的吲哚西美德之间的比较，值得注意的是，前药完全溶于给药制剂中，而吲哚西美德在50和100mg/kg的剂量下不溶。这可能导致吲哚西美德的时间依赖性控制释放效应，这可能导致比以完全可溶形式给药时更低的Cmax、但更高的AUC。相较于当用于混悬液中的所有测试剂量的吲哚西美德给药时的观察结果，NLG-1626和NLG-1665导致吲哚西美德Cmax显著增加。然而，NLG-1626显示对于吲哚西美德，AUC剂量依赖性增加，其中AUC增加的百分比在较高的剂量下降低。表8.3还表明，在吲哚西美德的氨基基团上形成氨基甲酸盐，其产生针对吲哚西美德的药代动力学参数显著降低的前药。

[0445] 实施例8:大鼠中固体胶囊制剂中的吲哚西美德前药盐的药代动力学测试

[0446] 为了测试哪种前药具有在以胶囊制剂经口给药后达到更大的吲哚西美德血浆浓度和增加的吲哚西美德暴露所需的最佳的药理学性质(对吲哚西美德的溶解速率、溶解度、肠通透性、清除率和代谢速率)组合，将当呈溶液给药时显示出提高的吲哚西美德Cmax或暴露的前药制备为呈几种盐形式，并与赋形剂混合以形成粉末掺混物。配制这些混合物使得每粒胶囊含有与每种前药相同的摩尔剂量。在由微晶纤维素、乳糖一水合物、交联羧甲纤维素钠和硬脂酸镁组成的赋形剂掺混物中，以表9.1a和9.1b所示比例，制备含11μmol/胶囊A、28μmol/胶囊B或50μmol/胶囊C的吲哚西美德游离碱(分别为2.5、6.3或11.4mg/胶囊)或呈多种盐形式的其前药的明胶胶囊(Torpac，20mg容量)。通过重量和LC-MS/MS验证来自每批的胶囊的代表性样品的组成和均匀性，以确定平均吲哚西美德或前药含量。

[0447] 为了测试通过用呈不同的盐形式的吲哚西美德前药给药获得的药代动力学曲线，通过胃内递送用1粒胶囊A(11μmol/胶囊)或2粒胶囊B(28μmol/胶囊)或3粒胶囊C(50μmol/胶囊)向大鼠给药。测试的剂量水平等效于当用1粒11μmol/胶囊的胶囊A给药时8mg/kg(37μmol/kg)的吲哚西美德等效物，当用2粒28μmol/胶囊的胶囊B给药时40mg/kg(185μmol/kg)的吲哚西美德等效物及当用3粒50μmol/胶囊的胶囊C给药时110mg/kg(500μmol/kg)的吲哚西美德等效物。在给药前，将大鼠禁食16小时以消除任何混杂的食物影响，并在给药后2小时返回食物。在给药后0分钟、15分钟、30分钟、1小时、2小时、4小时、6小时、10小时、24小时、48小时和72小时，从每只大鼠获得血液样品。通过LC-MS/MS测定血浆中吲哚西美德的浓度，并使用软件WinNonLin(Certara)计算药代动力学参数。

[0448] 最相关的经评价的药代动力学参数是吲哚西美德的最大浓度(Cmax)和总吲哚西美德暴露($AUC_{0->\infty}$)。表10.1和10.2显示了实验结果的概述。

[0449] 药代动力学参数的统计学比较表明,以37-185μmol/kg给药的呈其盐酸盐(NLG-1564)、磷酸盐(NLG-1665)、甲磺酸根盐(NLG-1666)或苯磺酸盐(NLG-1671)形式的N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯能将吲哚西美德暴露显著(p＜0.05)增加33-127%,而其硫酸盐(NLG-1691)在那些剂量下没有导致Cmax或AUC显著增加。类似地,观察到NLG-1564、NLG-1665和NLG-1666的Cmax显著增加。在500μmol/kg的剂量下,与吲哚西美德相比,NLG-1564盐酸盐显示出Cmax和AUC略有增加。

[0450] 表10.2显示呈其磷酸盐(NLG-1626)的1-甲基-D-色氨酸2,3-二羟丙酯导致Cmax(37-153%)和AUC(46-75%)显著增加,而其盐酸盐(NLG-1558)和硫酸盐(NLG-1628)导致Cmax和AUC不太显著增加。有趣的是,1-甲基-D-色氨酸2,3-二羟丙酯(NLG-1627)的甲磺酸盐导致Cmax和AUC降低,尽管这种降低没有统计学意义。

[0451] 表10.2还显示N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯(HCl和磷酸盐,NLG-3272)显示出在37-500μmol/kg的剂量下Cmax和AUC统计学上显著增加。

[0452] 研究的其它前药包括:a)N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯(游离碱,HCl,磷酸盐或甲磺酸盐),b)N^{α}-甘氨酰-1-甲基-D-色氨酸(HCl或磷酸盐),c)N^{4}-((R)-1-乙氧基-3-(1-甲基-1H-吲哚-3-基)-1-氧代丙烷-2-基)-L-天冬酰胺甲酯(HCl形式)和d)N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸(游离碱,HCl,硫酸盐或磷酸盐)。与等摩尔剂量的吲哚西美德相比,这些前药导致吲哚西美德的Cmax或AUC略微变化和非统计学上显著变化(表10.3)。

[0453] 有趣的是,呈其HCl或磷酸盐形式(NLG-1563和NLG-1664)的1-甲基-D-色氨酸哌啶-4-基甲酯导致吲哚西美德的Cmax(69-79%,p＜0.004)和AUC(54-64%,p＜0.014)的统计学上显著降低。由于当通过经口溶液施用时该化合物显示出Cmax(24%)和AUC(75%)增加,增溶速率或最终溶解度的差异可以解释当以粉末形式施用时观察到的差异。

[0454] 实施例9:食蟹猴中固体胶囊制剂中的吲哚西美德前药盐的药代动力学测试

[0455] 由于随着吲哚西美德的剂量高达100mg/kg,大鼠显示出暴露的不饱和线性增加,而人类在高于10mg/kg剂量下显示出可饱和暴露,我们决定在灵长类动物中评价前药中的两种,其可能构成预测人类药代动力学的更好模型。在交叉研究设计中,以92、275或875μmol/kg的剂量,用吲哚西美德、NLG-1564HCl或NLG-3272 HCl向食蟹猴(4.5-5kg)给药,其中每只动物每7天接受相同的摩尔剂量的吲哚西美德、NLG1564 HCl或NLG-3272 HCl。根据表9.2所述的配方制备胶囊。用1粒或3粒胶囊A(458μmol/胶囊)或4粒胶囊B(1032μmol/胶囊)向猴子经口给药。在给药后0分钟、5分钟、15分钟、30分钟、1小时、2小时、4小时、8小时、12小时、24小时、26小时和48小时时收集血液样品,并通过经验证的LC-MSMS方法分析前药和吲哚西美德的浓度。

[0456] 表11.1中的数据显示,NLG-1564 HCl以统计学显著的方式将吲哚西美德的Cmax从约230-500%提高,并将AUC从195-518%提高。类似地,NLG-3272HCl以统计学显著的方式将Cmax从约305-411%提高,并将AUC从136-393%提高。灵长类动物中的药效动力学指标的增加出乎意料地优于在大鼠中观察到的结果,表明在灵长类动物中,本发明的吲哚西美德的前药可提供最大浓度和对吲哚西美德的暴露的显著提高,并预期在人类患者中提高对药物的暴露和治疗效能。

[0457] 表8.1:用吲哚西美德或其前药的溶液向大鼠经口给药后吲哚西美德的Cmax和AUC

[0458]

前药ID	名称	盐形式	MW (g/mol)	剂量 (mg/kg)	n	Cmax (μM)	归一化Cmax (μM)	归一化Cmax变化%	$AUC_{(0->\infty)}$ (μM.h)	归一化$AUC_{(0->\infty)}$ (μM.h)	归一化AUC变化%
吲哚西美德	1-甲基-*D*-色氨酸	HCl	218	10	5	17.3	17.3	0	508	508	0
NLG-1563	1-甲基-*D*-色氨酸哌啶-4-基甲酯	HCl	389	10	5	12.1	21.5	24	500	889	75
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-*D*-色氨酸乙酯	HCl	396	10	3	9.3	16.2	-6	490	888	75
NLG-1566	N^{α}-(L-谷酰氨基)-1-甲基-*D*-色氨酸乙酯	HCl	411	10	5	13	24.4	41	428	806	58
NLG-1548	N^{α}-(L-赖氨酰)-1-甲基-*D*-色氨酸	HCl	419	10	5	8.7	16.7	-3	414	795	56
NLG-1572	1-甲基-*D*-色氨酸 2-(四氢-2*H*-吡喃-4-基)乙酯	HCl	367	10	3	8.9	15	-14	460	774	52
NLG-1557	1-甲基-*D*-色氨酸 2-(二甲基氨基)乙酯	HCl	362	10	3	23.8	39.5	128	440	731	44
NLG-1559	1-甲基-*D*-色氨酸(2-乙氧基-2-氧桥-1,3,2-二氧杂磷杂环戊烷-4-基)甲酯	HCl	419	10	3	8.8	16.9	-2	327	628	23
NLG-1570	N^{α}-(*L*-亮氨酰)-1-甲基-*D*-色氨酸	HCl	368	10	3	14.5	24.4	41	366	617	21
NLG-1565	N^{α}-(*L*-异亮氨酰)-1-甲基-*D*-色氨酸乙酯	HCl	396	10	3	7.1	12.8	-26	334	606	19
NLG-1554	N^{α}-甘氨酰-1-甲基-*D*-色氨酸盐酸盐	HCl	312	10	3	19.6	28	62	419	599	18
NLG-1558	1-甲基-D-色氨酸 2,3-二羟丙酯	HCl	329	10	5	22.1	33.3	92	395	595	17
NLG-1551	*O*-(1-甲基-*D*-色氨酰)-*L*-丝氨酸	HCl	378	10	3	7.7	13.3	-23	339	588	16
NLG-1547	N^{α}-(*L*-谷氨酰氨基)-1-甲基-*D*-色氨酸	HCl	384	10	3	10	17.6	2	326	574	13
NLG-1283	1-甲基-*D*-色氨酸乙酯	HCl	283	10	3	17	22	27	350	454	-11

[0459] 表8.2:用吲哚西美德或其前药的溶液向大鼠经口给药后吲哚西美德的Cmax和AUC

[0460]

前药ID	名称	盐形式	MW (g/mol)	剂量 (mg/kg)	n	Cmax (μM)	归一化Cmax (μM)	归一化Cmax变化%	$AUC_{(0->\infty)}$ (μM.h)	归一化$AUC_{(0->\infty)}$ (μM.h)	归一化AUC变化%
吲哚西美德	1-甲基-*D*-色氨酸	HCl	218	10	5	17.3	17.3	0	508	508	0
NLG-1575	N^{α}-(L-苯基丙氨酰)-1-甲基-*D*-色氨酸	HCl	402	10	3	6.4	11.9	-31	231	425	-16
NLG-1560	N^{α}-(*L*-色氨酰)-1-甲基-*D*-色氨酸	HCl	368	10	3	7.1	12	-31	246	415	-18
NLG-1569	N^{α}-(L-谷酰氨基)-1-甲基-*D*-色氨酸	HCl	383	10	3	4.8	8.5	-51	212	372	-27
NLG-1553	N^{α}-(*L*-缬氨酰)-1-甲基-*D*-色氨酸	HCl	354	10	3	8.8	14.2	-18	209	338	-33
NLG-1574	N^{α}-(L-苯基丙氨酰)-1-甲基-*D*-色氨酸乙酯	HCl	430	10	3	4	7.9	-54	167	329	-35
NLG-1571	N^{α}-(*L*-异亮氨酰)-1-甲基-*D*-色氨酸	HCl	368	10	3	7.4	12.5	-28	187	316	-38
NLG-1555	N^{α}-(*L*-丙氨酰)-1-甲基-*D*-色氨酸	HCl	326	10	3	9	13.4	-22	207	310	-39
NLG-1549	1-甲基-N^{α}-(1-甲基-D-色氨酰)-D-色氨酸	HCl	455	10	3	1.5	3	-83	126	262	-48
NLG-1556	1-甲基-*D*-色氨酰-L-缬氨酸	HCl	354	10	3	1	1.6	-91	125	202	-60
NLG-1546	N^{α}-(*D*-色氨酰)-1-甲基-*D*-色氨酸	HCl	441	10	3	1.6	3.2	-82	90	182	-64
NLG-1561	1-甲基-*D*-色氨酸 2-(哌啶-4-基)乙酯	HCl	402	10	3	1.3	2.4	-86	59.9	110	-78
NLG-1567	N^{α}-(*D*-色氨酰)-1-甲基-*D*-色氨酸乙酯	HCl	469	10	3	0	0	-100	0	0	-100

[0461] n:用于测定平均药代动力学参数的大鼠数。

[0462] Cmax(μM):血浆中观察到的吲哚西美德的最大浓度。值是n值的平均值。

[0463] 归一化Cmax(μM):通过将观察到的血浆中吲哚西美德的Cmax乘以每种前药MW与吲哚西美德MW的比以及吲哚西美德与前药的剂量比(以mg/kg计)来计算吲哚西美德的最大平均浓度。这将Cmax归一化为相同的摩尔剂量(μmol/kg)。

[0464] 归一化Cmax变化%:计算为[Cmax(来自前药的吲哚西美德)/Cmax(来自吲哚西美德的吲哚西美德)-1]x100

[0465] $AUC_{(0->\infty)}$(μM.h):曲线下的面积[吲哚西美德]相对于血浆中观察到的时间。值是n值的平均值。

[0466] 归一化$AUC_{(0->\infty)}$(μM.h):通过将观察到的血浆中吲哚西美德的$AUC_{(0->\infty)}$乘以每种前药MW与吲哚西美德MW的比以及吲哚西美德与前药的剂量比(以mg/kg计)来计算平均AUC。这将AUC归一化为相同的摩尔剂量(μmol/kg)。

[0467] $AUC_{(0->\infty)}$变化%:计算为[$AUC_{(0->\infty)}$(来自前药的吲哚西美德)/$AUC_{(0->\infty)}$(来自吲哚西美德的吲哚西美德)-1]x100

[0468] 表8.3:用吲哚西美德或其前药的溶液向小鼠或大鼠经口给药后吲哚西美德的药代动力学参数

[0469]

药物/前药	名称	盐形式	MW (g/mol)	剂量 (mg/kg)	途径	物种	n	Tmax (h)	$t_{1/2}$ (h)	Cmax (μM)	剂量归一化 Cmax (μM)	归一化 Cmax 变化%	$AUC_{(0->\infty)}$(μM.h)	剂量归一化 $AUC_{(0->\infty)}$(μM.h)	归一化 AUC 增加%
吲哚西美德	1-甲基-*D*-色氨酸	HCl	218	50	PO	大鼠	1	8	28	27	27	0%	1323	1323	0%
NLG-1277	N^{α}-(乙氧基羰基)-1-甲基-*D*-色氨酸	FB	290	50	PO	大鼠	1	4	25	4.5	6.0	-78%	172	229	-83%
NLG-1278	1-甲基-N^{α}-((新戊基氧基)羰基)-*D*-色氨酸	FB	333	50	PO	大鼠	1	2	27.4	0.10	0.15	-99%	3.6	5.5	-100%

[0470]

NLG-1280	1-甲基-N^{α}-((新戊基氧基)羰基)-*D*-色氨酸	FB	290	50	PO	大鼠	1	8	30	5.4	7.2	-73%	281	374	-72%
NLG-1283	1-甲基-*D*-色氨酸乙酯	HCl	246	50	PO	大鼠	1	6	27	58	66	143%	2645	2988	126%
NLG-1284	1-甲基-*D*-色氨酸异丙酯	FB	261	50	PO	大鼠	1	6	21	23.4	28	4%	877	1051	-21%
NLG-1338	1-甲基-D-色氨酸苄酯	HCl	345	50	PO	大鼠	1	8	20	17.8	28	4%	650	1028	-22%
NLG-1546	N^{α}-(*D*-色氨酰)-1-甲基-*D*-色氨酸	HCl	441	50	PO	大鼠	3	10	58	1.6	3.2	-88%	90	182	-86%
吲哚西美德	1-甲基-*D*-色氨酸	FB	218	10	PO	小鼠	10	0.5	1.8	9	9	0%	34	34	0%
吲哚西美德	1-甲基-*D*-色氨酸	FB	218	50	PO	小鼠	10	1	2.7	30	30	0%	137	137	0%
吲哚西美德	1-甲基-*D*-色氨酸	HCl	218	50	PO	小鼠	7	1	2.2	16	16	-47%	61	61	-55%
吲哚西美德	1-甲基-*D*-色氨酸	FB	218	100	PO	小鼠	10	1	3.5	43	43	0%	325	325	0%
NLG-1626	1-甲基-D-色氨酸2,3-二羟丙酯	H_3PO_4	390	13.3	PO	小鼠	10	0.5	4.6	13.3	18	99%	44	59	74%
NLG-1626	1-甲基-D-色氨酸2,3-二羟丙酯	H_3PO_4	390	66.5	PO	小鼠	10	0.75	4.4	49.1	66	120%	162	218	59%
NLG-1626	1-甲基-D-色氨酸2,3-二羟丙酯	H_3PO_4	390	133	PO	小鼠	10	0.75	3.7	71	96	122%	242	326	0%
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	457	14	PO	小鼠	10	0.5	1.5	6.5	10	8%	19	28	-18%
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	457	70	PO	小鼠	10	0.75	2.3	33.3	50	66%	98	147	7%
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	457	140	PO	小鼠	10	0.5	2.7	77.6	116	170%	168	252	-23%
NLG-1277	N^{α}-(乙氧基羰基)-1-甲基-*D*-色氨酸	FB	290	50	PO	小鼠	7	0.5	1.1	0.13	0.17	-99%	0.29	0.39	-100%
NLG-1280	1-甲基-N^{α}-((新戊基氧基)羰基)-*D*-色氨酸	FB	290	50	PO	小鼠	7	NA	NA	BLQ	BLQ	-100%	0	0.0	-100%
NLG-1283	1-甲基-*D*-色氨酸乙酯	HCl	246	50	PO	小鼠	7	0.25	3.9	24	27.1	-10%	27	30.5	-78%
NLG-1284	1-甲基-*D*-色氨酸异丙酯	FB	261	50	PO	小鼠	7	0.5	4.4	70	84	180%	218	261	91%

[0471] 表9.1a:胶囊组合物-大鼠经口给药

[0472]

活性成分	名称	盐形式	剂量(μmol/胶囊)	胶囊数/大鼠	% w/w				
					活性成分	微晶纤维素	乳糖一水合物	交联羧甲基纤维素	硬脂酸镁
吲哚西美德	1-甲基-D-色氨酸	游离碱	11	1	12.5	37.3	37.3	12.0	1.0
吲哚西美德	1-甲基-D-色氨酸	游离碱	28	2	31.3	27.8	27.8	12.3	1.0
吲哚西美德	1-甲基-D-色氨酸	游离碱	50	3	100	0	0	0	0
NLG-1676	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	游离碱	11	1	19.8	33.0	33.0	13.2	1.0
NLG-1548	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	HCl	11	1	24.0	32.5	32.5	10.0	1.0
NLG-1669	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	H_2SO_4	11	1	25.5	31.5	31.5	10.5	1.0
NLG-1670	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	H_3PO_4	11	1	31.1	29.0	29.0	9.9	1.0
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	11	1	22.7	32.0	32.0	12.3	1.0
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	28	2	57.6	16.2	16.2	10.0	1.0
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	50	3	100	0	0	0	0
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	11	1	26.0	30.8	30.8	11.5	1.0
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	28	2	53.1	17.7	17.7	10.5	1.0
NLG-1666	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	CH_3SO_3H	11	1	25.3	31.3	31.3	11.2	1.0
NLG-1671	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	苯磺酸盐	11	1	29.6	30.0	30.0	9.4	1.0
NLG-1691	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_2SO_4	11	1	23.4	31.5	31.5	12.6	1.0
NLG-1558	1-甲基-D-色氨酸2,3-二羟丙酯	HCl	11	1	18.8	33.5	33.5	13.2	1.0
NLG-1626	1-甲基-D-色氨酸2,3-二羟丙酯	H_3PO_4	11	1	22.4	32.5	32.5	11.6	1.0
NLG-1626	1-甲基-D-色氨酸2,3-二羟丙酯	H_3PO_4	28	2	55.9	16.7	16.7	9.6	1.0
NLG-1627	1-甲基-D-色氨酸2,3-二羟丙酯	CH_3SO_3H	11	1	22.2	32.3	32.3	12.3	1.0
NLG-1628	1-甲基-D-色氨酸2,3-二羟丙酯	H_2SO_4	11	1	19.6	33.5	33.5	12.4	1.0

[0473]

活性成分	名称	盐形式	剂量(μmol/胶囊)	胶囊数/大鼠	% w/w 活性成分	微晶纤维素	乳糖一水合物	交联羧甲基纤维素	硬脂酸镁
NLG-1672	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	游离碱	11	1	21.4	32.5	32.5	12.5	1.0
NLG-1566	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	HCl	11	1	23.5	31.3	31.3	13.0	1.0
NLG-1629	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	H_3PO_4	11	1	27.1	30.5	30.5	10.9	1.0
NLG-1630	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	H_2SO_4	11	1	24.3	31.2	31.2	12.2	1.0
NLG-1631	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	CH_3SO_3H	11	1	26.9	30.0	30.0	12.1	1.0

[0474] 表9.1b:胶囊组合物-大鼠经口给药

[0475]

活性成分	名称	盐形式	剂量(μmol/胶囊)	胶囊数/大鼠	% w/w 活性成分	微晶纤维素	乳糖一水合物	交联羧甲基纤维素	硬脂酸镁
NLG-1563	1-甲基-D-色氨酸哌啶-4-基甲酯	HCl	11	1	22.2	32.0	32.0	12.8	1.0
NLG-1664	1-甲基-D-色氨酸哌啶-4-基甲酯	H_3PO_4	11	1	29.3	28.8	28.8	12.2	1.0
NLG-1663	1-甲基-D-色氨酸哌啶-4-基甲酯	H_2SO_4	11	1	27.6	29.5	29.5	12.5	0.9
NLG-1585	N^{d}-((R)-1-乙氧基-3-(1-甲基-1*H*-吲哚-3-基)-1-氧代丙烷-2-基)-*L*-天冬酰胺甲酯	HCl	11	1	23.6	31.5	31.5	12.4	1.0
NLG-1554	N^{α}-甘氨酰-1-甲基-D-色氨酸盐酸盐	HCl	11	1	17.9	33.5	33.5	14.1	1.0
NLG-1677	N^{α}-甘氨酰-1-甲基-D-色氨酸盐酸盐	H_3PO_4	11	1	22.2	31.7	31.7	13.4	0.9
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	11	1	27.2	30.4	30.4	11.0	1.0
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	28	2	48.3	21.6	21.6	7.8	0.7
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	11	1	23.7	31.9	31.9	11.5	1.0
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基	HCl	28	2	43.7	23.5	23.5	8.5	0.8

[0476]

活性成分	名称	盐形式	剂量(μmol/胶囊)	胶囊数/大鼠	% w/w 活性成分	微晶纤维素	乳糖一水合物	交联羧甲基纤维素	硬脂酸镁
	-D-色氨酸乙酯								
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	50	3	100	0	0	0	0
NLG-3380	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸	HCl	11	1	23.3	32.0	32.0	11.5	1.0
NLG-3380	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸	HCl	28	2	42	24.2	24.2	8.8	0.8
NLG-3380	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸	H_3PO_4	28	2	45.6	22.7	22.7	8.2	0.7

[0477] 表9.2:胶囊组合物-猴经口给药

[0478]

活性成分	名称	盐形式	剂量(μmol/胶囊)	给药的胶囊数	% w/w 活性成分	微晶纤维素	甘露醇	交联羧甲基纤维素	硬脂酸镁
吲哚西美德	1-甲基-D-色氨酸	游离碱	458	1,3	70	12.5	12.5	5.0	0.0
吲哚西美德	1-甲基-D-色氨酸	游离碱	1032	4	70	12.5	12.5	5.0	0.0
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	458	1,3	70	12.5	12.5	5.0	0.0
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	1032	4	70	12.5	12.5	5.0	0.0
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	458	1,3	70	12.5	12.5	5.0	0.0
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	1032	4	70	12.5	12.5	5.0	0.0

[0479] 表10.1:用胶囊向大鼠经口给药后吲哚西美德游离碱相对于呈不同盐形式的其前药的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0480]

药物/前药 ID	名称	盐形式	剂量 (μmol/kg)	n	Cmax (μM)	Cmax 变化%	p 值	$AUC_{(0->\infty)}$ (μM.h)	AUC 变化%	p 值
吲哚西美德	1-甲基-D-色氨酸	游离碱	37	11	15.9±8	0		390±166	0	
吲哚西美德	1-甲基-D-色氨酸	游离碱	185	8	20.8±4	0		1080±478	0	
吲哚西美德	1-甲基-D-色氨酸	游离碱	500	6	76.2±25	0		2871±1379	0	
NLG-1676	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	游离碱	37	4	13.3±2	-17	0.26	340±57	-13	0.28
NLG-1548	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	HCl	37	4	17.2±9	8	0.39	350±83	-10	0.33
NLG-1669	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	H_2SO_4	37	4	15.3±5	-4	0.44	446±101	10	0.27
NLG-1670	N^{α}-(L-赖氨酰)-1-甲基-D-色氨酸	H_3PO_4	37	4	11.5±4	4	0.15	325±61	-17	0.23
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	37	4	30.4±10	92	0.005	664±134	70	0.006
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	185	8	44.2±10	112	<0.0001	1860±609	87	<0.0001
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	500	6	80.0±22	5	0.39	3300±391	15	0.26

[0481]

药物/前药 ID	名称	盐形式	剂量 (μmol/kg)	n	Cmax (μM)	Cmax 变化%	p 值	$AUC_{(0->\infty)}$ (μM.h)	AUC 变化%	p 值
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	37	7	29.2±13	84	0.008	628±145	61	0.003
NLG-1665	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	185	10	35.3±7	69	0.0001	1433±858	33	0.024
NLG-1666	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	CH_3SO_3H	37	4	33.6±3	111	0.0004	886±273	127	0.0004
NLG-1671	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	苯磺酸盐	37	4	20.5±2	29	0.14	565±82	45	0.034
NLG-1691	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	H_2SO_4	37	4	12.2±4	-23	0.19	369±145	-5	0.41

[0482] 表10.2:用胶囊向大鼠经口给药后吲哚西美德游离碱相对于呈不同盐形式的其前药的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0483]

药物/前药 ID	名称	盐形式	剂量 (μmol/kg)	n	Cmax (μM)	Cmax 变化%	p 值	$AUC_{(0->\infty)}$ (μM.h)	AUC 变化%	P 值
吲哚西美德	1-甲基-D-色氨酸	游离碱	37	11	15.9±8	0		390±166	0	
吲哚西美德	1-甲基-D-色氨酸	游离碱	185	8	20.8±4	0		1080±478	0	
吲哚西美德	1-甲基-D-色氨酸	游离碱	500	6	76.2±25	0		2871±1379	0	
NLG-1558	1-甲基-D-色氨酸 2,3-二羟丙酯	HCl	37	4	20.2±5	28	0.16	472±58	21	0.18
NLG-1626	1-甲基-D-色氨酸 2,3-二羟丙酯	H_3PO_4	37	8	21.7±3	37	0.032	571±95	46	0.0067
NLG-1626	1-甲基-D-色氨酸 2,3-二羟丙酯	H_3PO_4	185	7	52.8±23	153	0.0002	1896±765	75	0.014

[0484]

药物/前药 ID	名称	盐形式	剂量 (μmol/kg)	n	Cmax (μM)	Cmax 变化%	p 值	$AUC_{(0->\infty)}$ (μM.h)	AUC 变化%	P 值
NLG-1627	1-甲基-D-色氨酸 2,3-二羟丙酯	CH_3SO_3H	37	4	11.6±5	-27	0.16	285±39	-27	0.12
NLG-1628	1-甲基-D-色氨酸 2,3-二羟丙酯	H_2SO_4	37	4	17.6±2	2	0.34	472±120	21	0.19
NLG-3380	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸	HCl	37	8	18.4±7	16	0.25	485±130	24	0.099
NLG-3380	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸	HCl	185	8	92.7±69	345	0.005	3043±2700	181	0.003
NLG-3380	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸	H_3PO_4	185	2	45.4±15	118	0.0009	1794±761	66	0.00002
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	37	8	21.0±11	32	0.13	400±136	2	0.45
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	H_3PO_4	185	8	31.1±8	49	0.003	1236±498	14	0.27
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	37	8	19.2±6	21	0.16	439±114	13	0.24
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	185	8	52.4±15	152	<0.0001	1898±852	76	0.017
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	500	6	121±46	59	0.031	4269±1255	49	0.048

[0485] 表10.3:用胶囊向大鼠经口给药后吲哚西美德游离碱相对于呈不同盐形式的其前药的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0486]

药物/前药 ID	名称	盐形式	剂量 (μmol/kg)	n	Cmax (μM)	Cmax 变化%	p 值	$AUC_{(0->\infty)}$ (μM.h)	AUC 变化%	P 值
吲哚西美德	1-甲基-D-色氨酸	游离碱	37	11	15.9±8			390±166		
吲哚西美德	1-甲基-D-色氨酸	游离碱	185	8	20.8±4			1080±478		
吲哚西美德	1-甲基-D-色氨酸	游离碱	500	6	76.2±25			2871±1379		
NLG-1672	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	游离碱	37	4	16.7±9	5	0.43	327±12	-16	0.24
NLG-1566	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	HCl	37	4	17.8±4	12	0.33	386±89	-1	0.48
NLG-1629	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	H_3PO_4	37	4	10.9±3	-32	0.12	280±21	-28	0.11
NLG-1630	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	H_2SO_4	37	4	19±8	20	0.25	314±105	-20	0.21
NLG-1631	N^{α}-(L-谷酰氨基)-1-甲基-D-色氨酸乙酯	CH_3SO_3H	37	4	16.5±6	4	0.45	342±97	-12	0.3
NLG-1563	1-甲基-D-色氨酸哌啶-4-基甲酯	HCl	37	4	4.9±0.4	-69	0.008	180±18	-54	0.014
NLG-1664	1-甲基-D-色氨酸哌啶-4-基甲酯	H_3PO_4	37	4	3.3±1	-79	0.004	141±45	-64	0.006
NLG-1585	N^{4}-((R)-1-乙氧基-3-(1-甲基-1*H*-吲哚-3-基)-1-氧代丙烷-2-基)-*L*-天冬酰胺甲酯	HCl	37	4	19.9±6	25	0.18	409±72	5	0.41
NLG-1554	N^{α}-甘氨酰-1-甲基-D-色氨酸盐酸盐	HCl	37	4	17.5±2	10	0.35	394±103	1	0.48
NLG-1677	N^{α}-甘氨酰-1-甲基-D-色氨酸盐酸盐	H_3PO_4	37	4	15.4±5	-3	0.45	403±153	3	0.45

[0487] 表11.1:用胶囊向食蟹猴经口给药后吲哚西美德游离碱相对于呈不同盐形式的其前药的Cmax和总暴露($AUC_{0->\infty}$)的比较

[0488]

药物/前药 ID	名称	盐形式	剂量 (μmol/kg)	n	Cmax (μM)	Cmax 变化%	p 值	$AUC_{(0->\infty)}$ (μM.h)	AUC 变化%	P 值
吲哚西美德	1-甲基-D-色氨酸	游离碱	92	3	8.2±0.4			38.5±4		
吲哚西美德	1-甲基-D-色氨酸	游离碱	275	3	17.5±3			74.9±5		
吲哚西美德	1-甲基-D-色氨酸	游离碱	875	3	27.8±8			165±52		
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	92	3	50.6±8	518	0.0004	114±2	195	<0.0001
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	275	3	101±28	476	0.003	463±36	518	<0.0001
NLG-1564	N^{α}-(L-亮氨酰)-1-甲基-D-色氨酸乙酯	HCl	875	2	92±17	230	0.005	853±349	416	0.017
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	92	3	33±5	305	0.0005	90.7±11	136	0.0007
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	275	3	88±32	402	0.009	370±113	393	0.005
NLG-3272	N^{α}-(L-甲硫氨酰)-1-甲基-D-色氨酸乙酯	HCl	875	3	142±57	411	0.013	761±516	369	0.059

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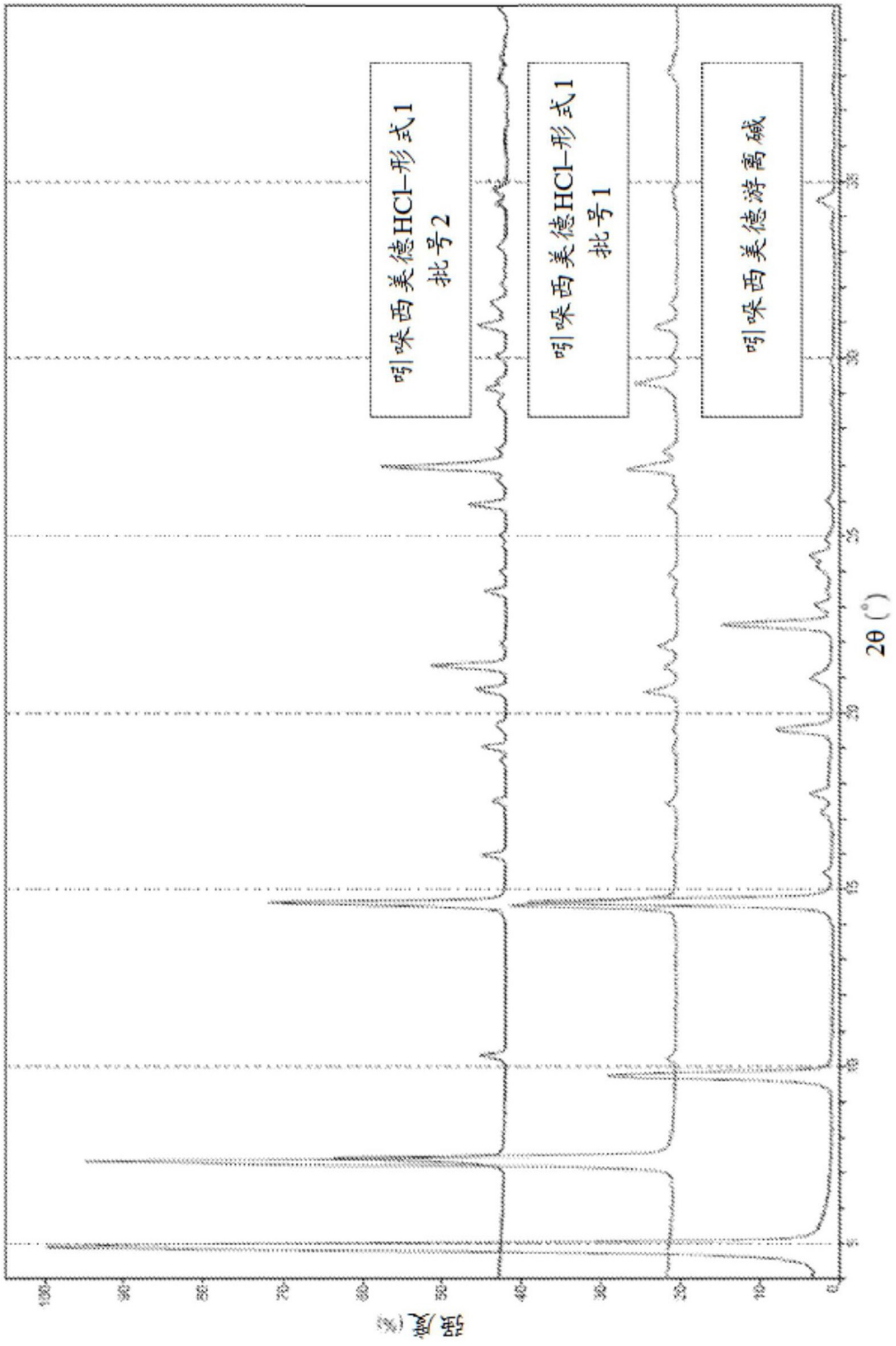

图1:吲哚西美德和吲哚西美德HCl的XRPD

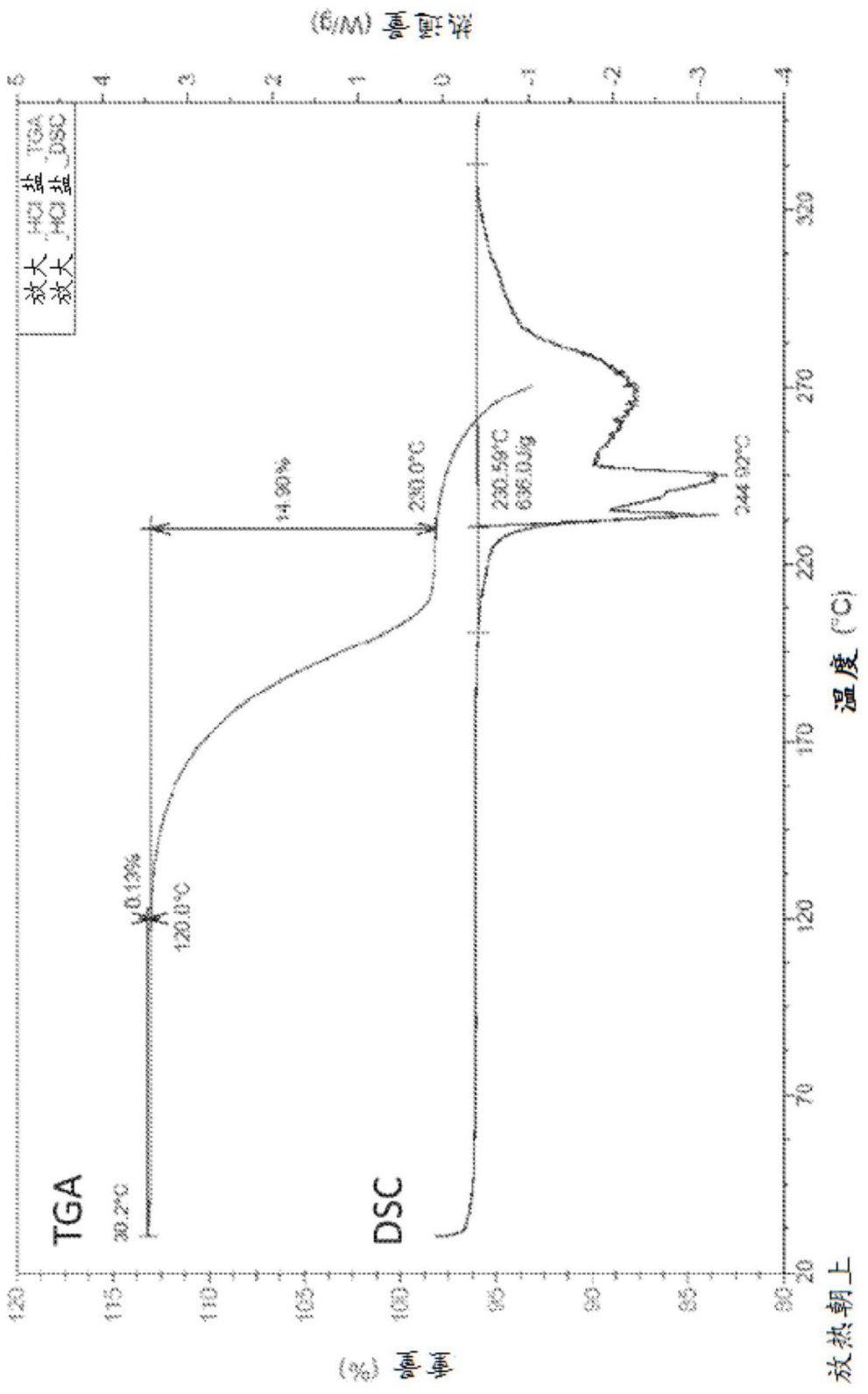

图2:吲哚西美德HCl的TGA和DSC分析

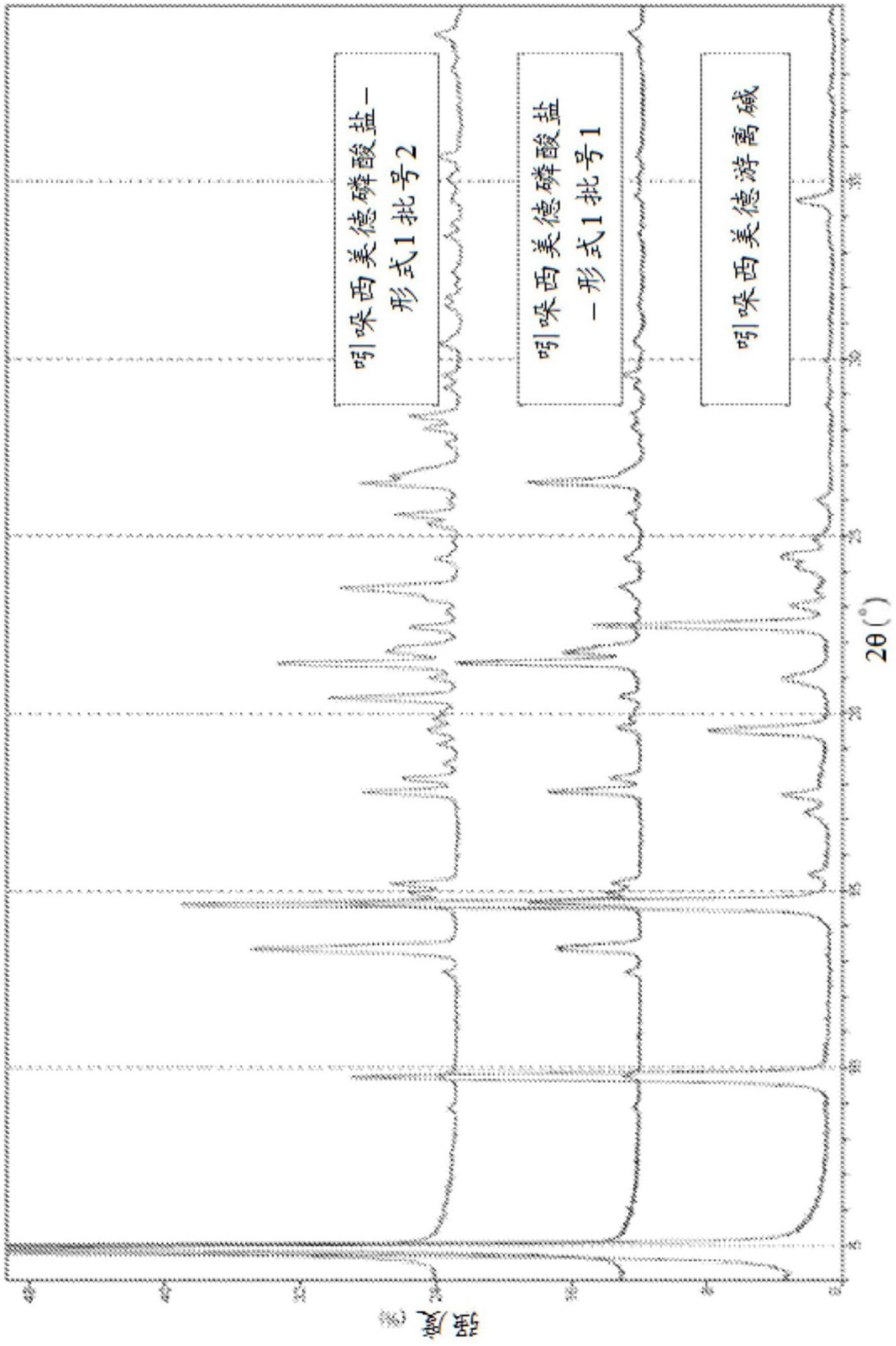

图3:吲哚西美德和吲哚西美德磷酸盐的XRPD

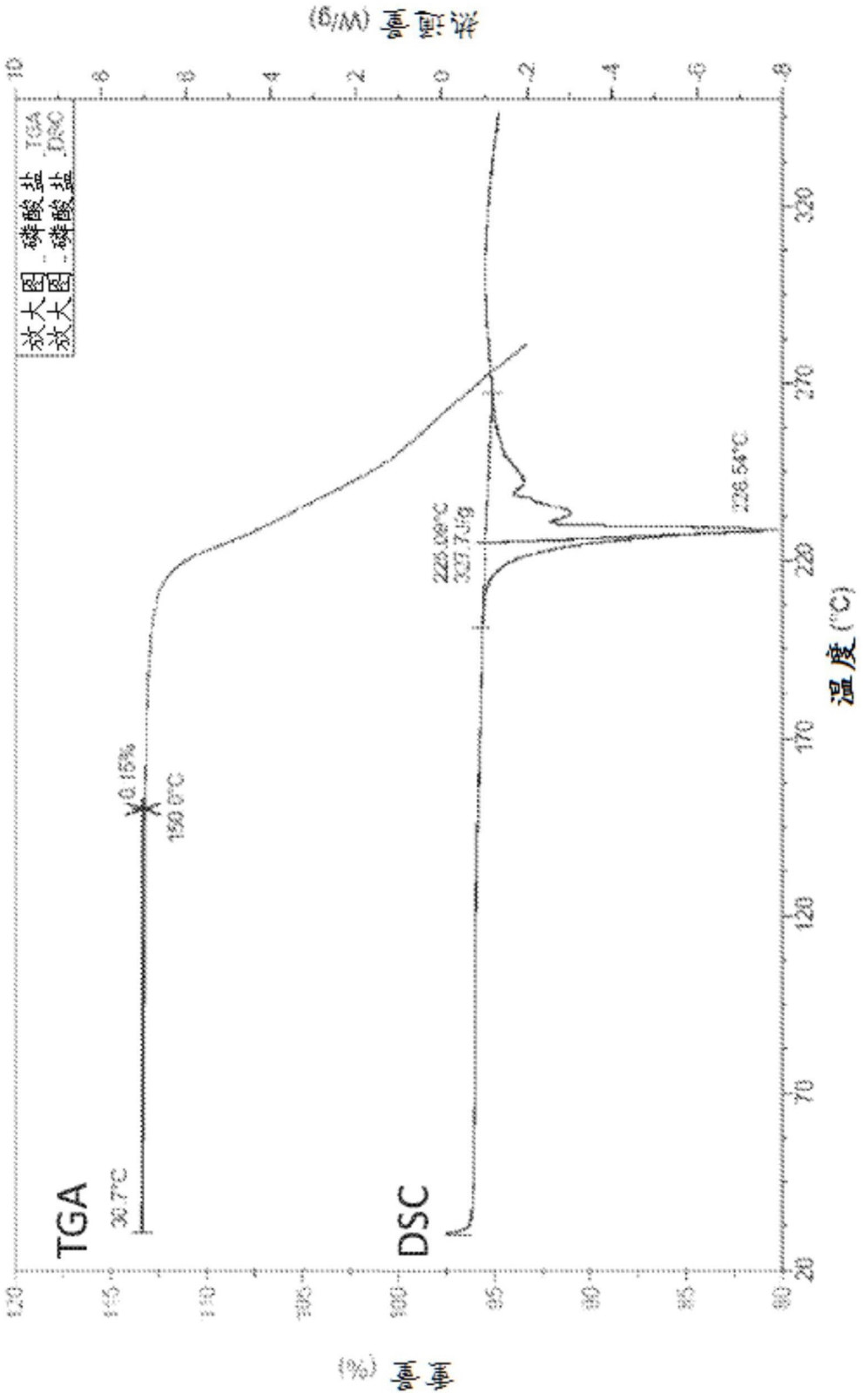

图4:吲哚西美德磷酸盐的TGA和DSC分析

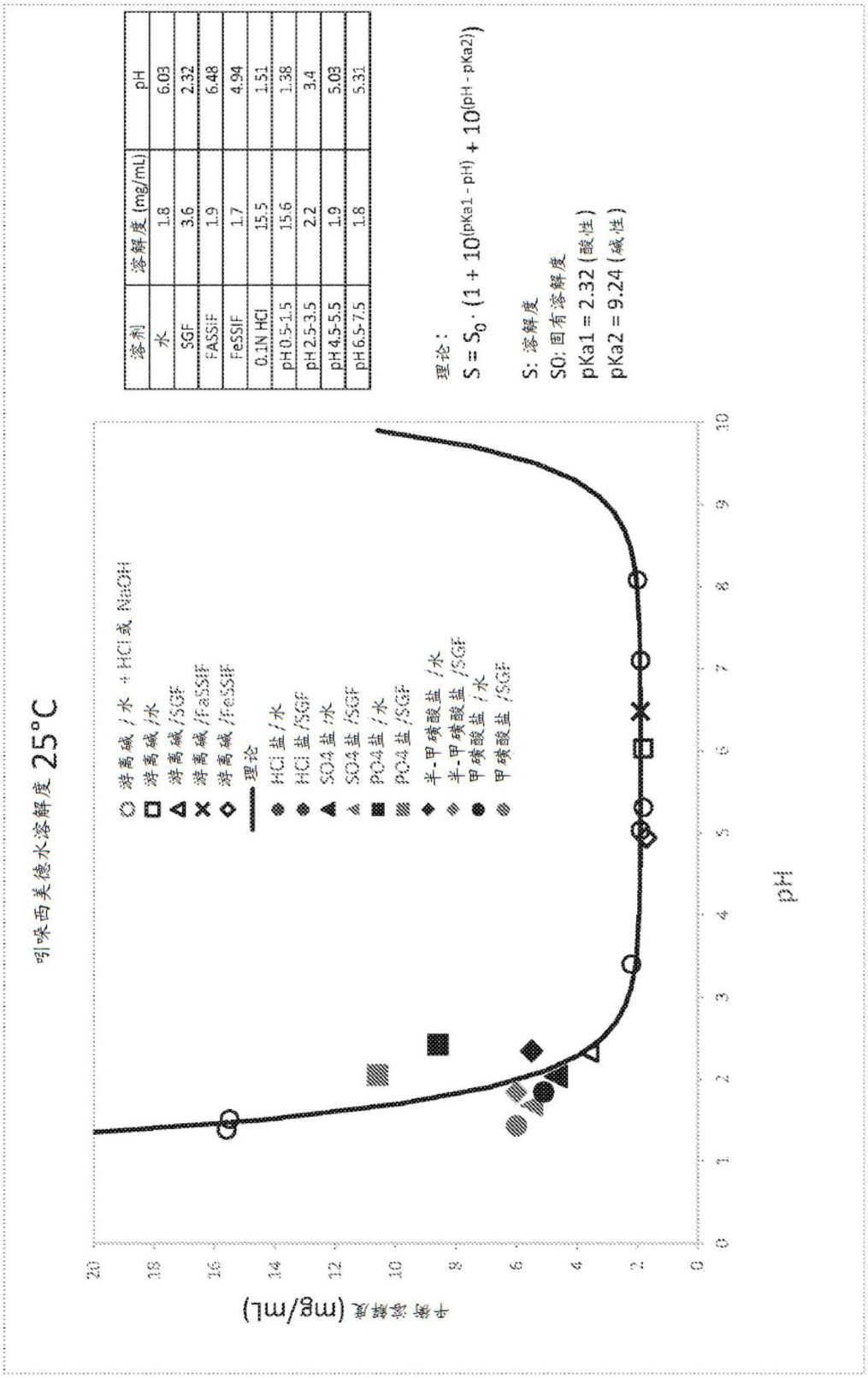

图5:吲哚西美德及其盐在不同溶剂中的溶解度

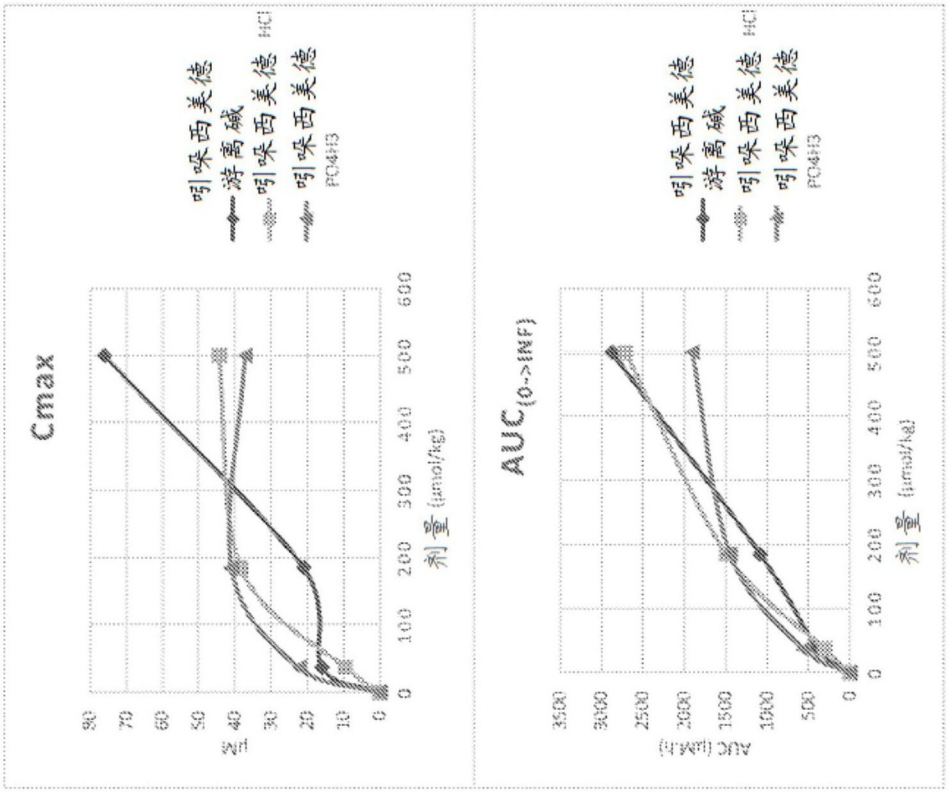

图6:以胶囊形式经口给药后大鼠中吲哚西美德及其盐的Cmax和AUC的剂量依赖性