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

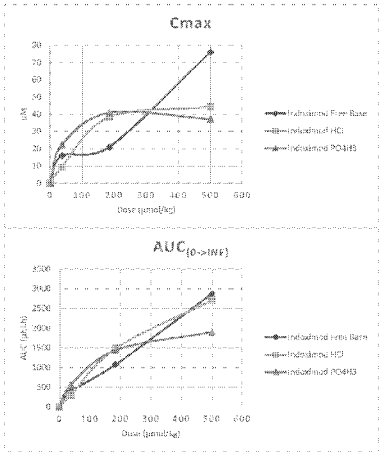


Figure 6: Dose dependency of Cmax and AUC for indoximod and its salts rats after oral dosing in capsule form

(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.

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.

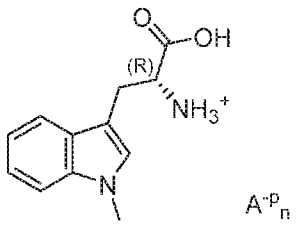
[0012] Mixed-lymphocyte response (MLR) T cell proliferation assay show that T cells that are in an IDO^{+} environment restore ~50% of their proliferative capacity at concentrations of indoximod higher than 30 μM. Murine antitumor experiments show that biological effects of indoximod are observed when 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.

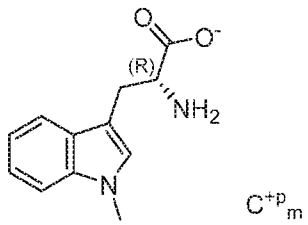
[0014] The results of these investigations showed that a few selected prodrugs resulted in increases in parameters of exposure; and that increases in in vitro solubility and in vivo exposure could be achieved by a few salts of indoximod upon oral administration.

SUMMARY OF THE INVENTION

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



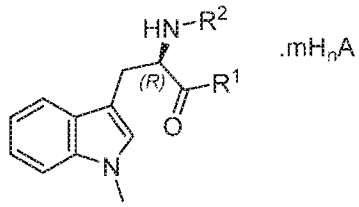
Formula 1a



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.

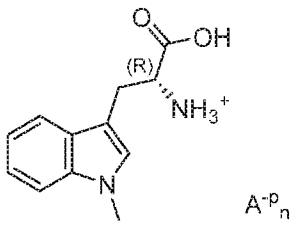
[0025] In the presence of IDO^+ dendritic cells, $CD8^+$ effector T cells become anergic and unable to proliferate. Moreover, regulatory T cells ($CD4^+$ $CD25^+$ $FoxP3^+$) are activated in the presence of IDO^+ DCs and become able to mediate systemic immunosuppression to tumor or viral antigens. Indoximod 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:



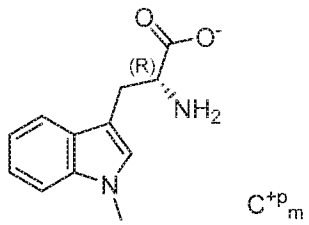
Formula 1a

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:

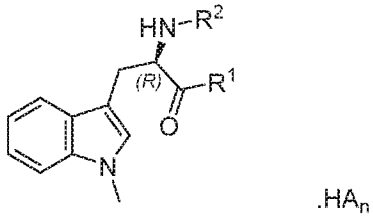


Formula 1b

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

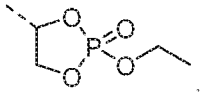
[0032] In one embodiment, a prodrug of indoximod is disclosed. In one embodiment, the structure of the prodrug, in free base or salt form, is provided in Formula 2:



Formula 2

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

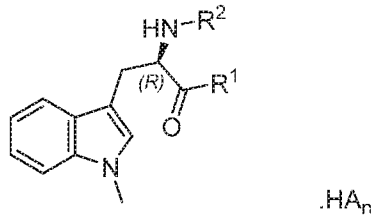
[0040] In some embodiments of the prodrug of Formula 2, R^1 cannot be –OH when R^2 is H.

[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,

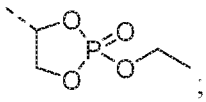


Formula 2

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

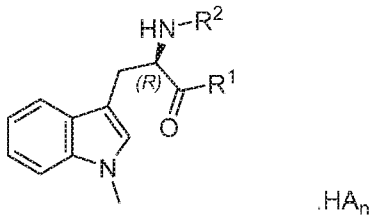
N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan

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.

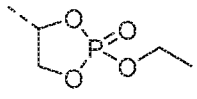
[0045] In a another embodiment, the invention provides prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,



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;

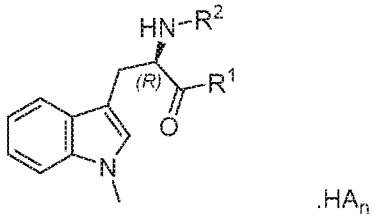
wherein each R^7 is independently halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl,C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2$R, -$S(O)_2$OR, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

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,

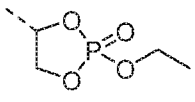


Formula 2

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;

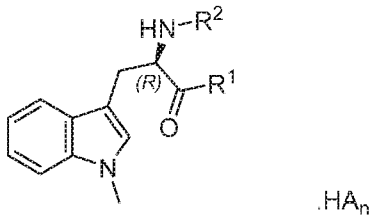
wherein R^7 is selected from halogen, cyano, nitro, -OR, -N(R)$_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -C(O)N(R)$_2$, -C(O)R, -S(O)R, -S(O)OR, -S(O)N(R)$_2$, -S(O)$_2$R, -S(O)$_2$OR, -S(O)$_2$N(R)$_2$, -OC(O)R, -OC(O)OR, -OC(O)N(R)$_2$, -N(R)C(O)R, -N(R)C(O)OR, or -N(R)C(O)N(R)$_2$;

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,

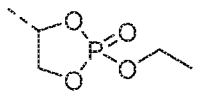


Formula 2

wherein

R^1 is -OH, -OC$_{2-3}$alkyl, -OCH$_2$CH(OH)CH$_2$OH, -O(CH$_2$)$_2$N(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$_2$CH(CH$_3$)$_2$, -$C^{(S)}$H(CH)$_3$CH$_2$CH$_3$, -(CH$_2$)$_2$SCH$_3$, -CH$_2$-R^6, -(CH$_2$)$_2$C(O)NH$_2$, -(CH$_2$)$_3$C(O)OH, or -(CH$_2$)$_4$NH$_2$;

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

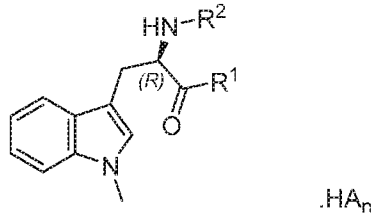
wherein R^6 is phenyl;

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.

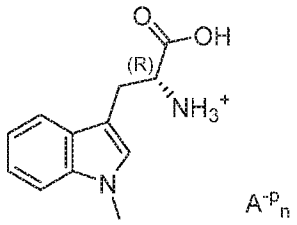
[0049] In a preferred embodiment, the invention provides prodrugs of indoximod, in their free base or as a pharmaceutically appropriate salt form, as represented by compounds of Formula 2 represented in Table 1.

[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-

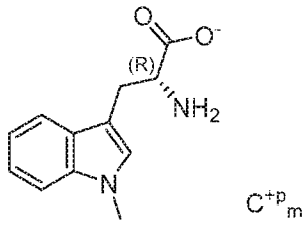
methyl-*D*-tryptophanate; (x) 2-(dimethylamino)ethyl 1-methyl-*D*-tryptophanate; (xi) (2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate; (xii) 2-(tetrahydro-2*H*-pyran-4-yl)ethyl 1-methyl-*D*-tryptophanate; (xiii) ethyl 1-methyl-*D*-tryptophanate; (xiv) isopropyl 1-methyl-*D*-tryptophanate; (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.

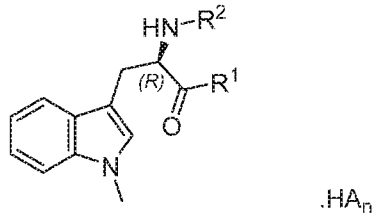
[0053] In a third embodiment of the first aspect, the invention provides a pharmaceutical composition comprising salts of indoximod, as represented by compounds of Formula 1b, wherein C^{+p}_{m} is an cation selected from the group of Li^{+}, Na^{+}, K^{+}, Mg^{+2} or Ca^{+2}, wherein positive

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,

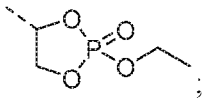


Formula 2

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

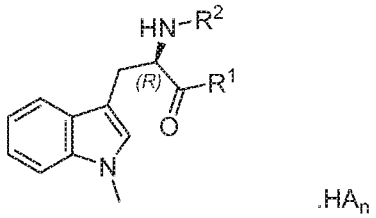
N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan

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.

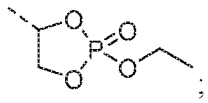
[0057] In a another embodiment of the second aspect, the invention provides a pharmaceutical composition comprising prodrugs of indoximod, in their free base or salt form, as represented by compounds of Formula 2,



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;

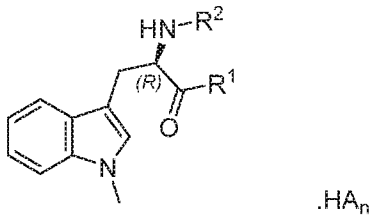
wherein each R^7 is independently halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl,C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2R$, -$S(O)_2OR$, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

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,

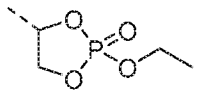


Formula 2

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;

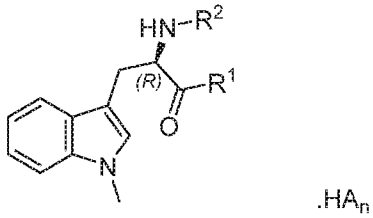
wherein R^7 is selected from halogen, cyano, nitro, -OR, -$N(R)_2$, -SR, -C(O)OR, C_{1-6}alkyl, C_{1-6}haloalkyl, -$C(O)N(R)_2$, -C(O)R, -S(O)R, -S(O)OR, -$S(O)N(R)_2$, -$S(O)_2R$, -$S(O)_2OR$, -$S(O)_2N(R)_2$, -OC(O)R, -OC(O)OR, -$OC(O)N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or -$N(R)C(O)N(R)_2$;

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,

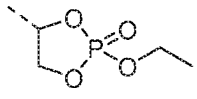


Formula 2

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 -$(CH_2)_4NH_2$;

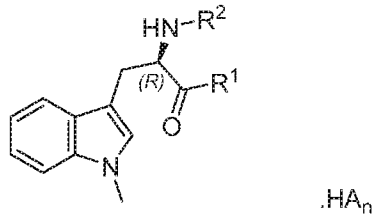
wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry;

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 $-(CH_2)_2C(O)NH_2$;

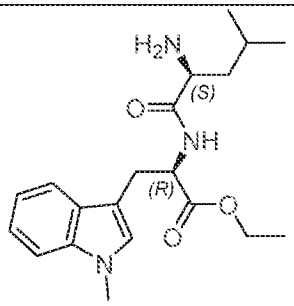
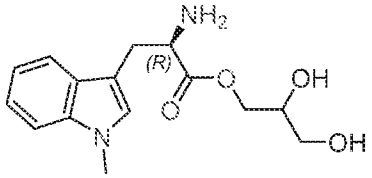
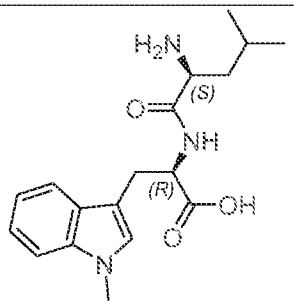
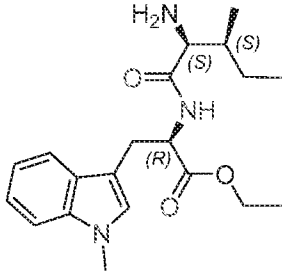
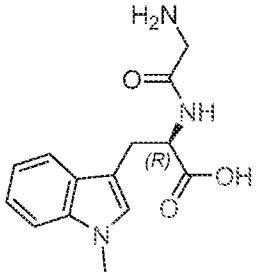
wherein $C^{(S)}$ represents a carbon with the *S* stereochemistry

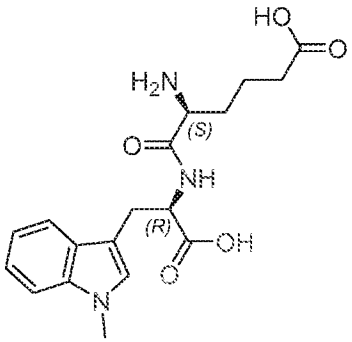
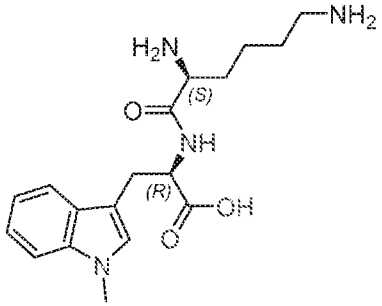
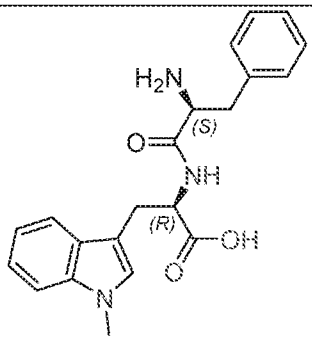
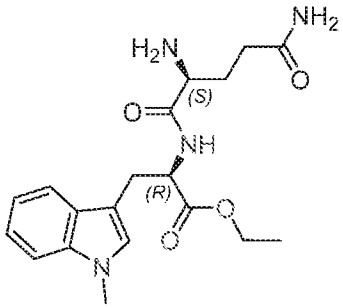
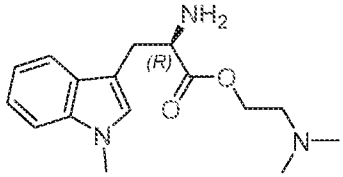
with the proviso that R^1 cannot be –OH when R^2 is H,

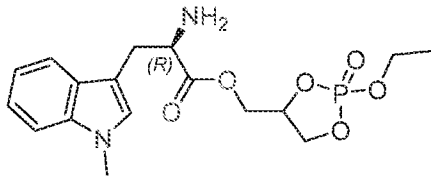
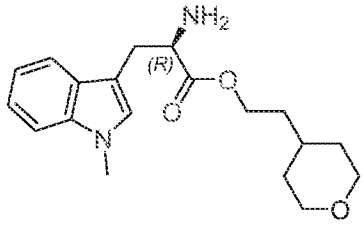
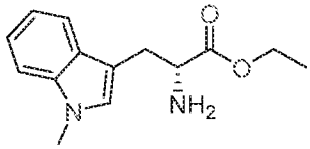
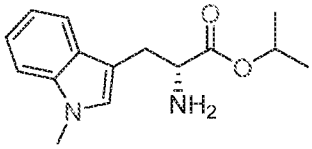
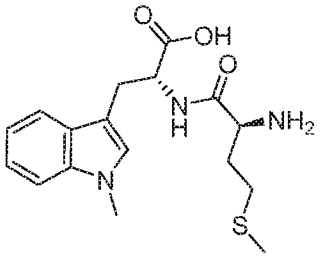
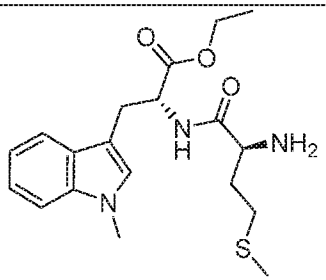
HA is an acid selected from the group of PO_4H_3 (phosphoric acid), SO_4H_2 (sulfuric acid), HCl (hydrochloric acid) HSO_3CH_3 (methyl sulfonic acid) or $C_6H_5SO_3H$ (benzyl sulfonic acid); and *n* is the stoichiometric ratio of 0, 0.5, 1 or 2 that ensure charge neutrality of the resulting salt.

[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_{1-6}alkoxycarbonyloxy and -OC(O)C_{1-6}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.

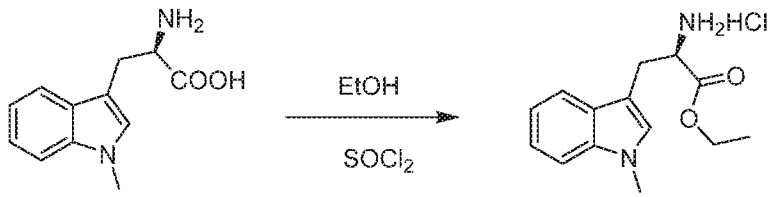
[00116] As used herein, the term "prodrug of indoximod" refers to any substance that after in vivo administration is metabolized to produce indoximod as one of the main metabolites.

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.

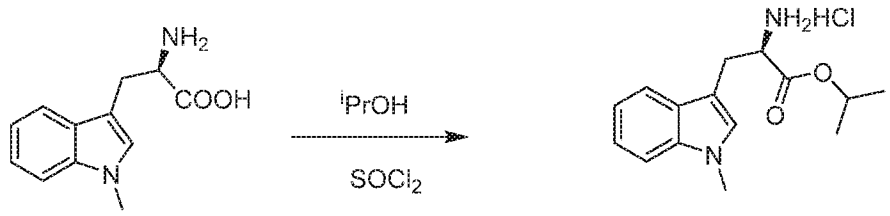
Synthesis of ethyl 1-methyl-D-tryptophanate hydrochloride (NLG-1283)



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 %).

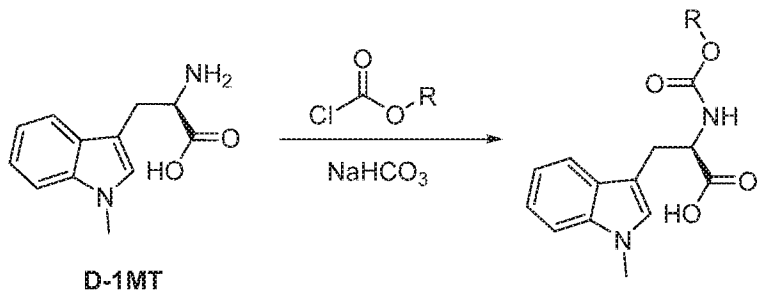
Synthesis of isopropyl 1-methyl-D-tryptophanate hydrochloride (NLG-1284)



D-1MT NLG-1284

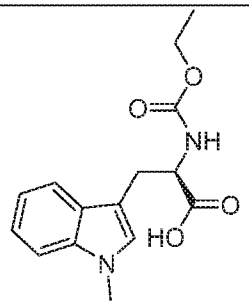
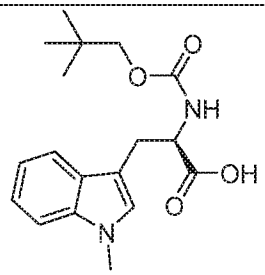
[00119] To a suspension of D-1MT (0.500 g, 2.29 mmol) in isopropanol (15 mL) at 0 °C rt, was added $SOCl_2$ (0.167 mL, 2.29 mmol) and the mixture was stirred at 80 °C overnight. After cooling to rt, the solvent was distilled-off and the crude was basified with 25 % aq $NaHCO_3$ (20 mL), the product was 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

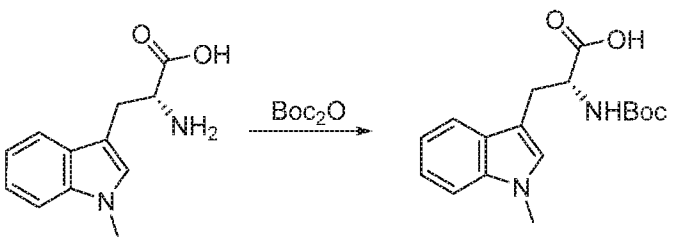


D-1MT

[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.

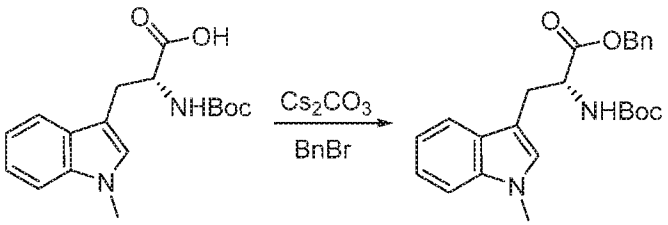
#	Compound	Name	Yield (%)
NLG-1277		N^{α}-(ethoxycarbonyl)-1-methyl-D-tryptophan	81
	1.23 (t, 3H, J = 6.8 Hz), 3.63-3.71 (m, 1H), 3.74 (s, 3H), 4.07-4.12 (m, 2H), 4.69 (dd, 1H, J = 6.7, 11.6 Hz), 5.20 (dd, 1H, J = 6.9, 11.5 Hz), 6.9 (s, 1H), 7.07 (t, 1H, 6.9 Hz), 7.21-7.48 (m, 2H), 7.57 (d, 1H, J = 7.1 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



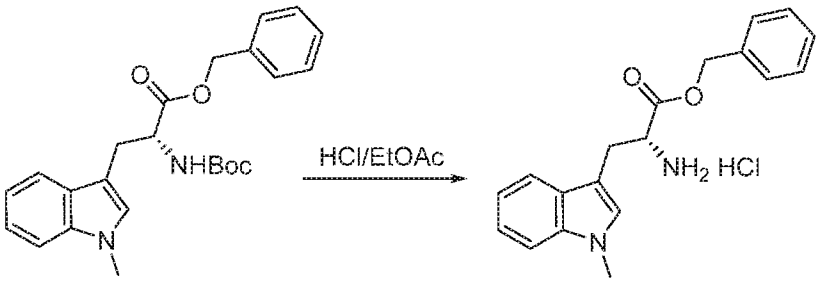
[00121] To a mixture of D-1MT (3.0 g, 13.75 mmol) in dioxane (70 mL) at 0 °C was added NaOH (550 mg dissolved in 30 mL DI water), followed by the addition of Boc_2O. The reaction was stirred at 0 °C for 4 h and stirred overnight at rt. The solution was concentrated under reduced pressure to approx. one 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



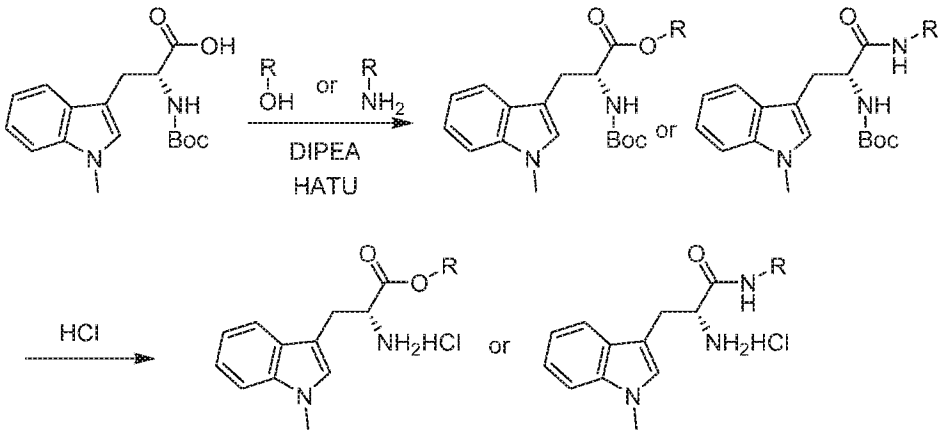
[00122] In 60 ml of DMF was dissolved N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophan (3.00 g, 9.42 mmol) to which Cs_2CO_3 (1.78 g, 5.47 mmol) and benzyl bromide (1.61 mL, 9.42 mmol) was added. The resulting suspension was allowed to stir at room temperature for 2 hours. After the end of reaction (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%).

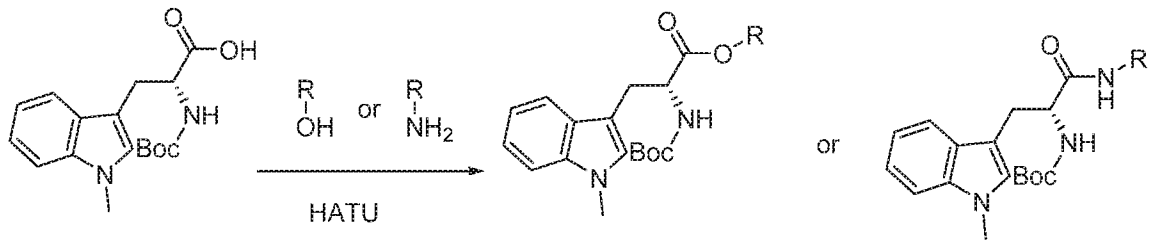
Synthesis of benzyl 1-methyl-D-tryptophanate hydrochloride (NLG-1338)



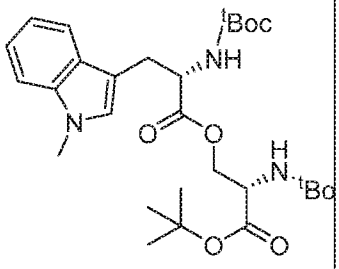
[00123] Ethyl acetate (26.9 mL) and MeOH (8.9 mL) in a RB flask equipped with a septum and a needle vent were cooled in an ice bath with stirring. Acetyl chloride (14.22 mL) was added slowly. The resulting solution was stirred at 0 °C for 20 minutes and MeOH (0.5 mL) was added. A flask containing benzyl 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).

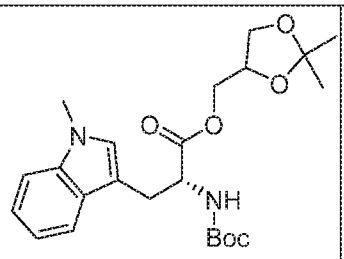
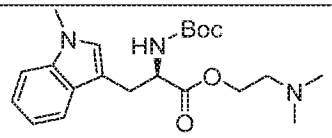
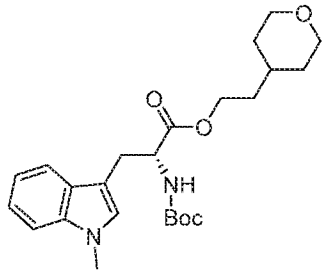
General scheme for the derivatization of –COOH group of D-1MT

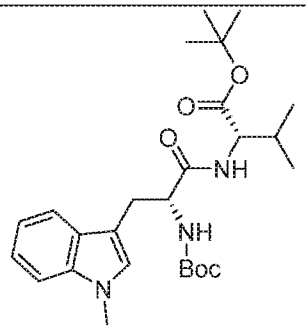
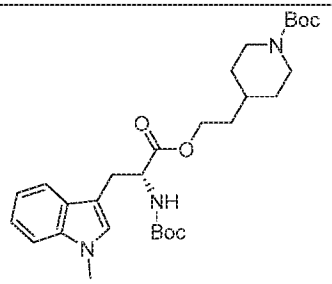
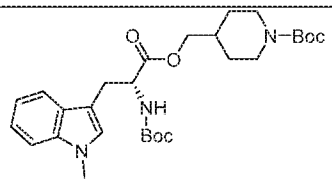


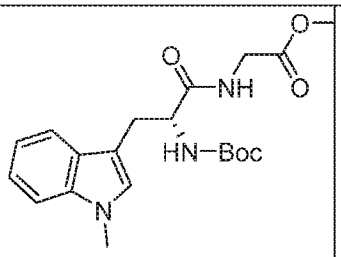


[00124] To a solution of N-(tert-butoxycarbonyl)-1-methyl-D-tryptophan (3.14 mmol), appropriate alcohol or amine (3.14 mmol) and HATU (3.14 mmol) in acetonitrile (30 mL) at 0 °C was added DIPEA (9.42 mmol) and the solution was allowed to warm to rt. After stirring overnight (17 h), the reaction was diluted 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.

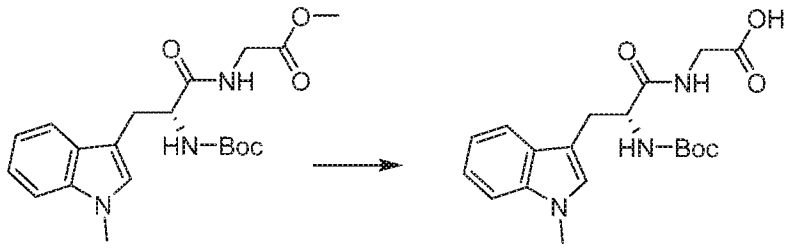
#	Compound	Name	Yield (%)
NLG-1551-B.1-E15		(S)-3-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl Na-(tert-butoxycarbonyl)-1-methyl-D-tryptophanate	40
	1.41 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H), 3.16 (dd, 1H, J = 15.3, 4.8 Hz), 3.29 (dd, 1H, J = 15.3, 4.8 Hz), 3.75 (s, 3H), 4.35-4.52 (m, 3H), 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)		

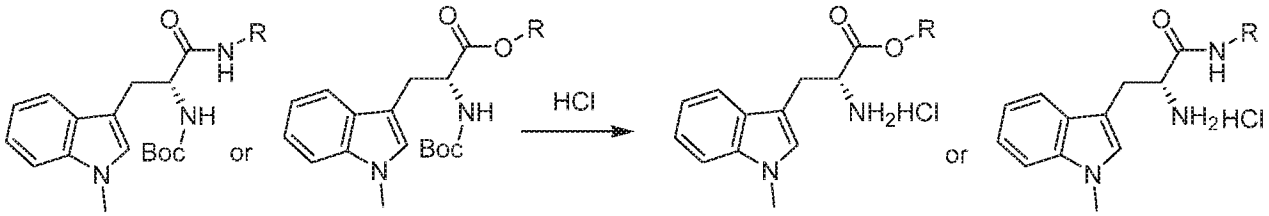
NLG-1578-A-E43		methyl N^{α}-(tert-butoxycarbonyl)-1-methyl-D-tryptophylglycinate	91
	1.25 (s, 9H), 3.15-3.25 (m, 2H), 3.67 and 3.69 (two s, 3H), 3.70 and 3.71 (two s, 3H), 3.90-3.92 (m, 2H), 5.21 and 4.48 (s, 1H), 6.54-6.52 (m, 1H), 6.93 (s, 1H), 7.13 – 7.03 (m, 1H), 7.14 – 7.30 (m, 2H), 7.59 (d, 1H,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

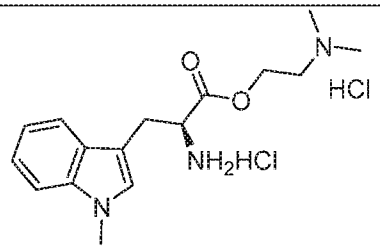


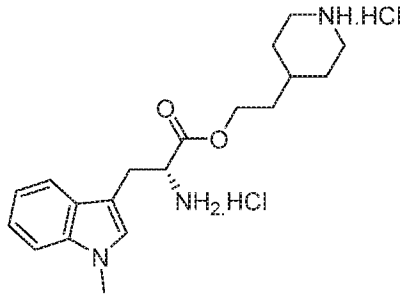
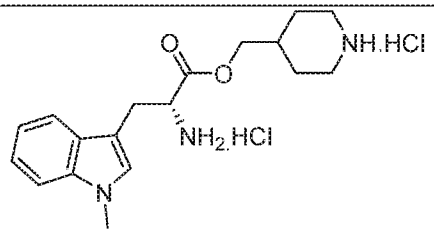
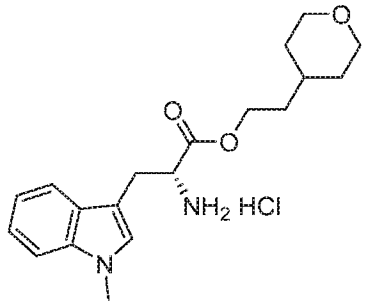
R = H, alkyl, alkylaryl

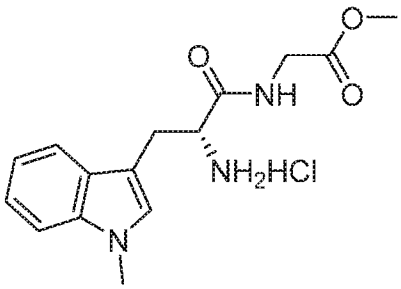
R = H, alkyl, alkylaryl

[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.

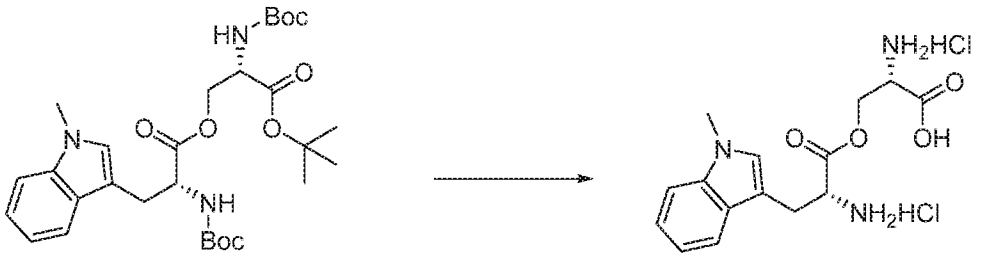
[00127] The following compounds were synthesized following procedures described in the above sections.

#	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)

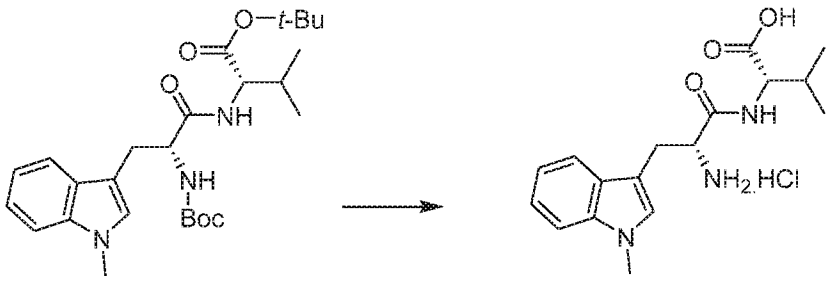


NLG-1551-B.1-E15 NLG-1551

[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).

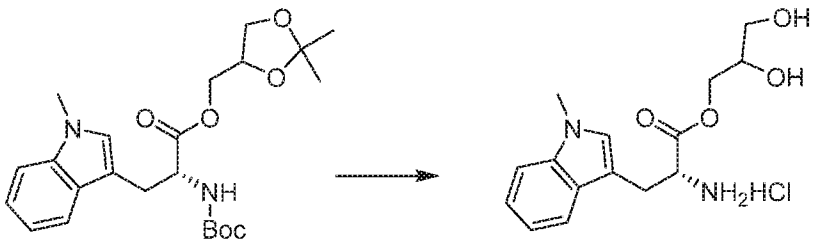
Synthesis of 1-methyl-D-tryptophyl-L-valine hydrochloride (NLG-1556)



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)

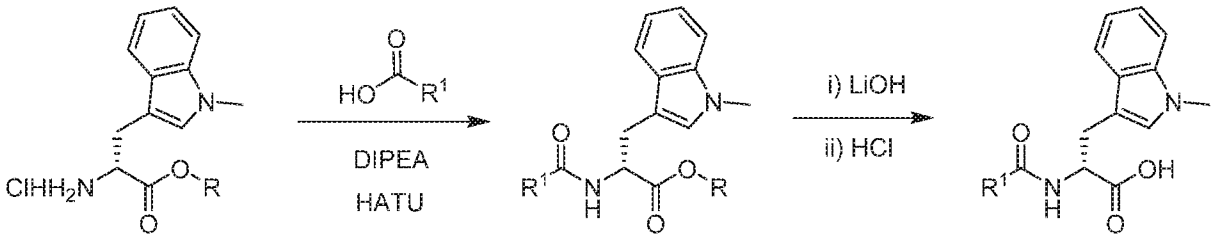
Synthesis of 2,3-dihydroxypropyl 1-methyl-D-tryptophanate hydrochloride (NLG-1558)

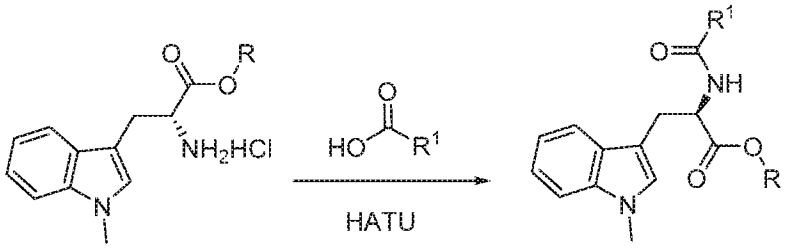


NLG1558-A-E23 **NLG-1558**

[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).

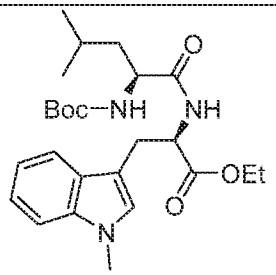
General scheme for the derivatization of the –NH_2 and –COOH group of D-1MT

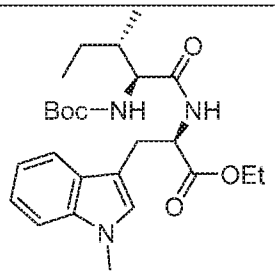
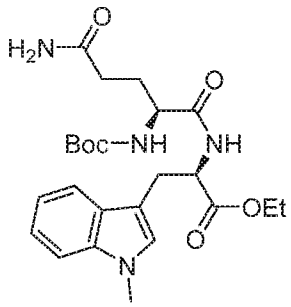
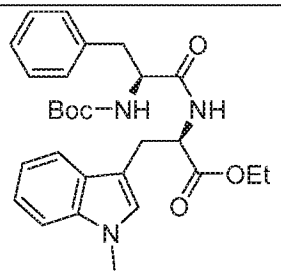


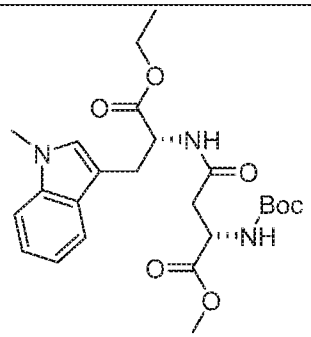
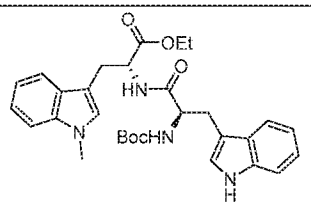
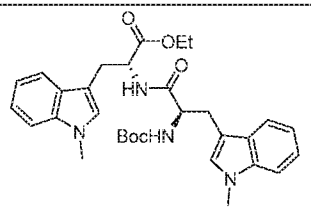


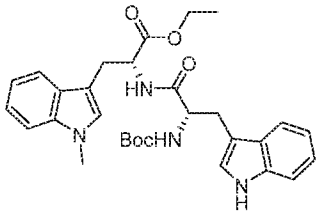
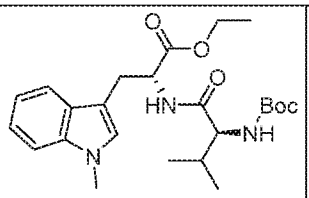
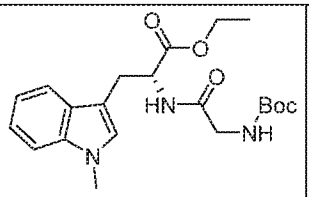
R = Et, Bn

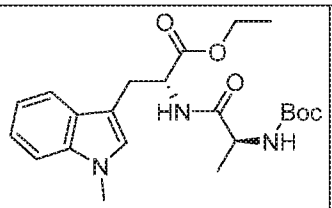
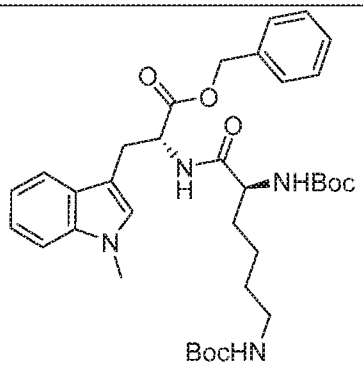
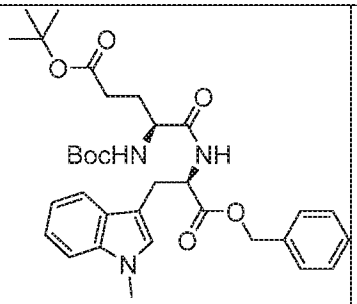
[00131] Appropriate D-tryptophanate hydrochloride ester (1.0 g, 3.54 mmol) and appropriate acid (3.54 mmol) were stirred in acetonitrile (50 mL) at 0 °C. HATU (1.48 g, 3.89 mmol) and iPr_2NEt (2.46 mL, 14.15 mmol) were added and the reaction stirred overnight at room temperature. The solvent was removed 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.

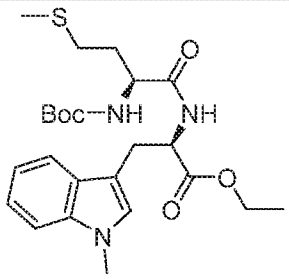
#	Compound	Name	Yield (%)
NLG-1564-B-E31		ethyl N^{α}-((tert-butoxycarbonyl)-L-leucyl)-1-methyl-D-tryptophanate	92
	0.86 (dd, 6H, J = 6.2, 2.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.39 (s, 9H), 1.55-1.58 (m, 2H), 3.29 (d, 2H, J = 5.7 Hz), 3.74 (s, 3H), 4.03-4.18 (m, 3H), 4.79-4.86 (m, 2H), 6.60 (d, 1H, J =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

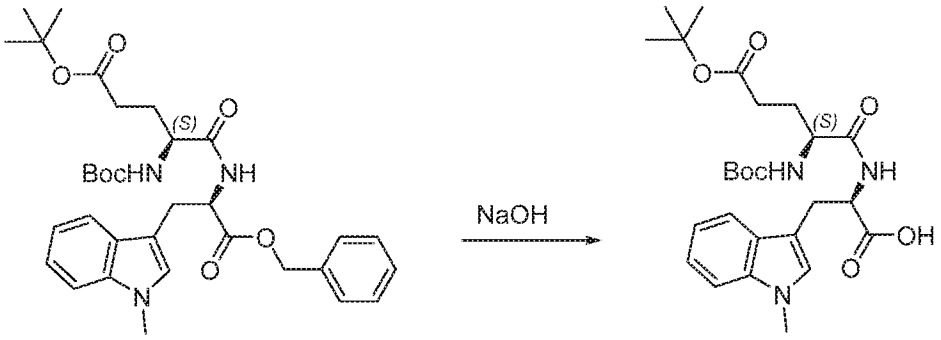
	(dd, 1H, *J* = 14.78, 5.2 Hz), 3.67 (s, 3H), 3.99 - 4.07 (m, 2H), 4.33 (br s, 1H), 4.79 (q, 1H, *J* = 6.2 Hz), 6.37 (d, 1H , *J* = 7.8 Hz), 6.57 (s, 1H), 7.06 (ddd, 1H , *J* = 8.0, 6.8, 1.2 Hz), 7.14 – 7.25 (m, 6H), 7.41 (d, 1H, *J* = 7.9 Hz).		
NLG-1585-A-E45		methyl N^2-(tert-butoxycarbonyl)-N^4-((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)-L-asparaginate	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)

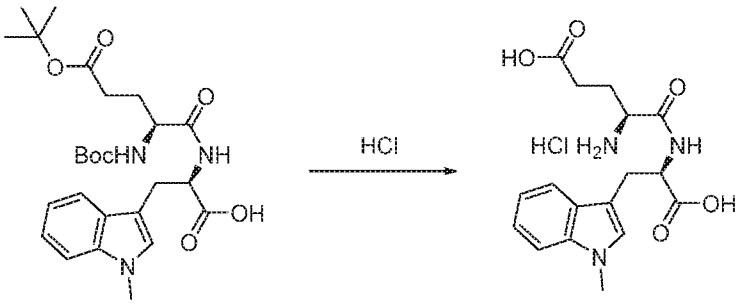


NLG-1547-D-E17 **NLG-1547-E.2-E17**

[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).

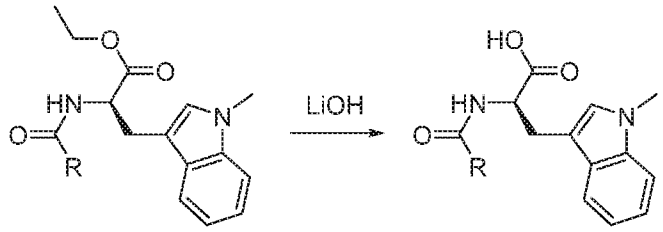
Synthesis of (S)-4-amino-5-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-5-oxopentanoic acid hydrochloride (NLG-1547)



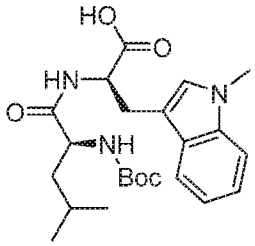
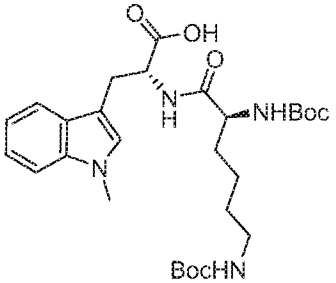
(NLG-1547-E.2-E17) (NLG-1547)

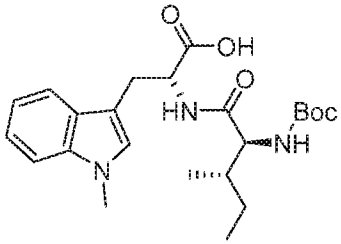
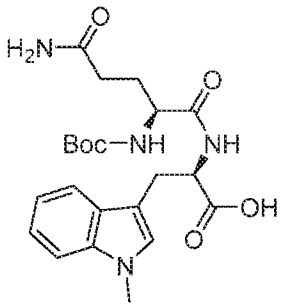
[00133] To N^{α}-((S)-5-(tert-butoxy)-2-((tert-butoxycarbonyl)amino)-5-oxopentanoyl)-1-methyl-D-tryptophan (470 mg, 0.93 mmol) was added HCl (4M in dioxane) (4.7 mL). The resulting solution was allowed to stir at room temperature for 5 hours. The solution was concentrated and the solid was dissolved 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).

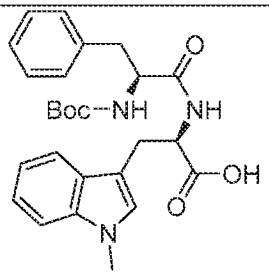
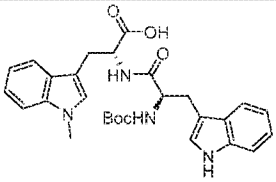
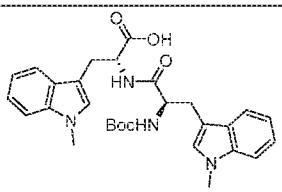
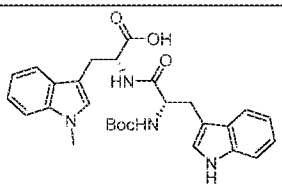
General method for the hydrolysis of substituted D-1MT ethyl esters

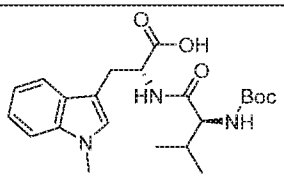
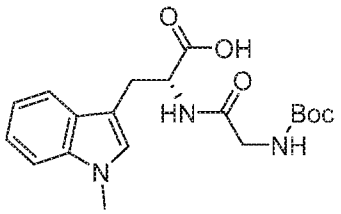
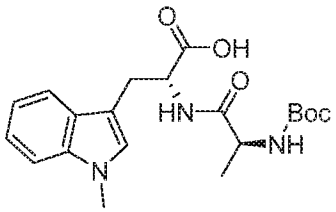


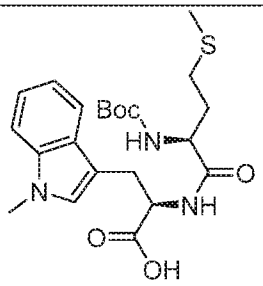
[00134] To a solution of appropriate amide (0.991 mmol) in THF (10 mL) was added water (3 mL) and lithium monohydrate (67 mg, 1.59 mmol) and the mixture stirred under ambient temperature for 2 h. The mixture was neutralized with 1M HCl (at 0 °C) and poured into ice cold water (20 mL). The aqueous layer 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).		

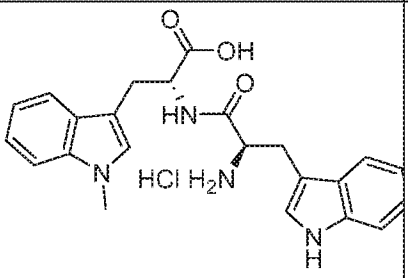
NLG1575-A-E41		N^{α}-((tert-butoxycarbonyl)-L-phenylalanyl)-1-methyl-D-tryptophan	75
	1.30 (s, 9H), 2.81-2.88 (m, 1H), 2.94-3.00 (m, 1H), 3.08 (dd, 1H, *J* = 14.8, 5.8 Hz), 3.21-3.25 (m, 1H), 3.66 (s, 3H), 4.41 (d, 1H, *J* = 6.7 Hz), 4.79-4.86 (m, 1H), 5.13 (d, 1H, *J* = 8.3 Hz), 6.56 (d, 1H, *J* = 6.5 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* =		

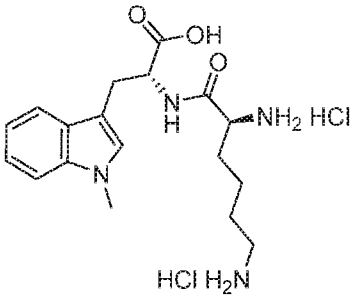
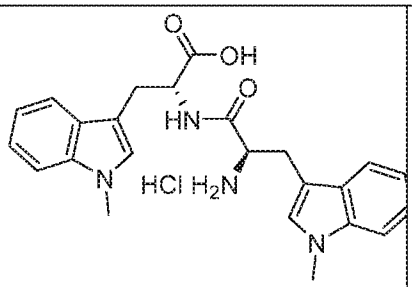
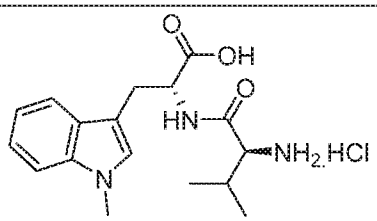
	7.5 Hz), 7.12 – 7.25 (m, 4H), 7.44 (q, 2H, *J* = 8.8 Hz), 7.56 (d, 1H, *J* = 7.9 Hz), 8.02 (br s, 1H).		
NLG-1553-C-E21		N^{α}-((tert-butoxycarbonyl)-L-valyl)-1-methyl-D-tryptophan	100
	0.77 (d, 3H, J = 6.8 Hz), 0.81 (d, 3H, J = 6.4 Hz), 1.38 (s, 9H), 1.84-1.92 (m, 1H), 3.30-3.32 (m, 1H), 3.66-3.77 (m, 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)		

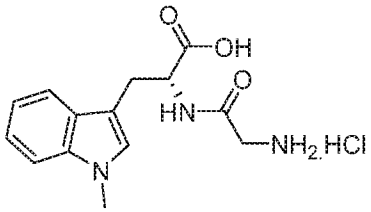
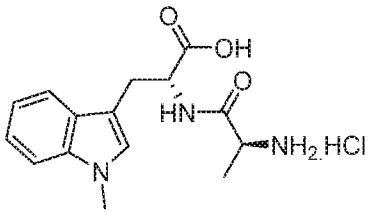
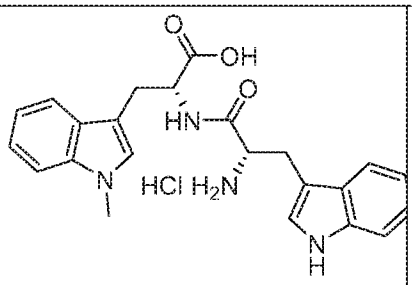
DD00510-A-E079		N^{α}-((tert-butoxycarbonyl)-L-methionyl)-1-methyl-D-tryptophan	92
	1.36 (s, 9H), 1.68 – 1.87 (m, 2H), 1.94 and 2.01 (s, 3H), 2.25-2.43 (two m, 2H), 3.23 (dd, *J*=14.9, 6.5 Hz, 1H), 3.36 (dd, *J*=14.6, 4.8 Hz, 1H), 3.71 (s, 3H), 4.23-4.34 (two m, 1H), 4.82-4.94 (two m, 1H), 5.52 (d, *J*=6.7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

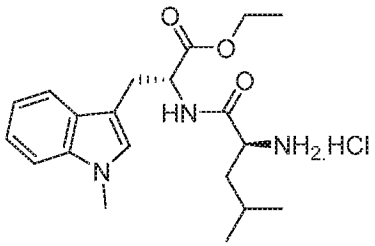
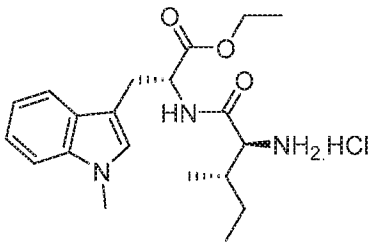
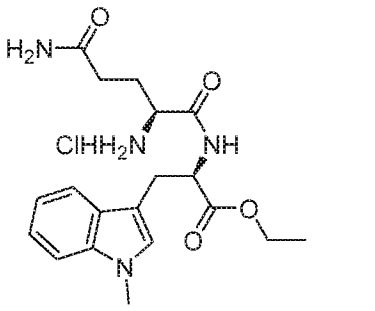
General method for ^{t}Boc deprotection.

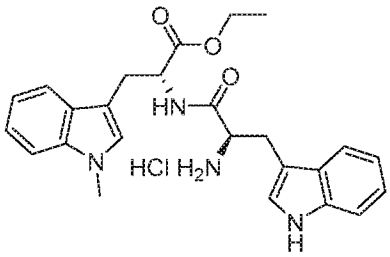
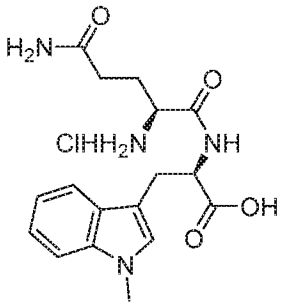
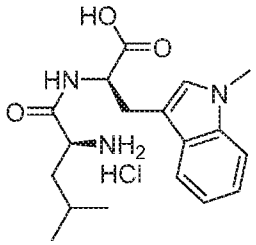
[00135] To a solution of appropriate ^{t}Boc protected amine (0.707 mmol) in dioxane (2 mL) was added HCl solution (1.77 mL, 4.0 M solution in dioxane) at 0 °C. The solution was allowed to warm to rt and stirred vigorously for 2.5-18 h. The solvent was removed using rotary evaporator. The solid was diluted 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.

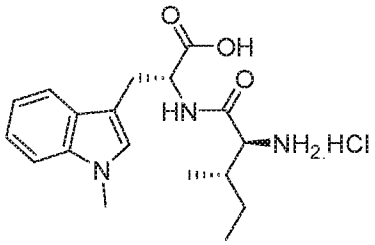
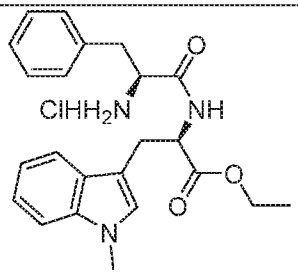
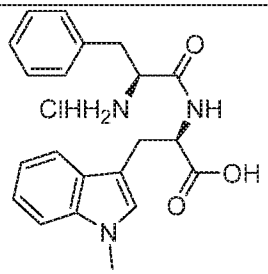
#	Compound	Name	Yield (%)
NLG-1546		N^{α}-(D-tryptophyl)-1-methyl-D-tryptophan hydrochloride	95
	^{1}H NMR (400 MHz, Methanol-d_4) δ 3.15 (d, *J* = 8.5 Hz, 1H), 3.19 (d, *J* = 8.5 Hz, 1H), 3.36 (d, 1H, *J* = 4.9 Hz), 3.37 – 3.41 (m, 1H), 3.71 (s, 3H), 4.06 (t, 1H, *J* = 3.6 Hz), 4.74 (s, 1H), 6.93 (s,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

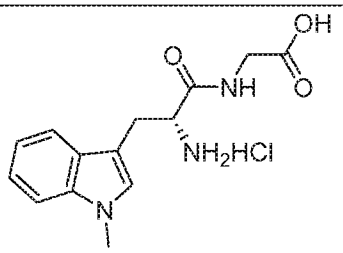
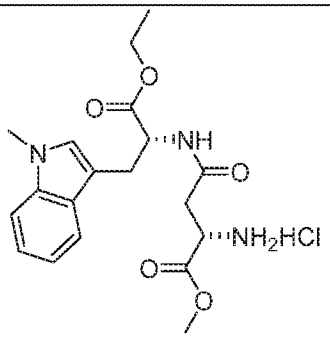
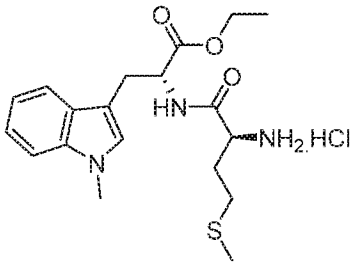
	(d, J = 8.1 Hz, 1H), 7.30 (d, 1H, J = 8.2 Hz), 7.38 (d, 1H, J = 8.1 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.65 (d, 1H, J = 7.9 Hz), 7.70 (d, 1H, J = 8.2 Hz)		
NLG-1548		N^{α}-(L-lysyl)-1-methyl-D-tryptophan dihydrochloride	87
	^{1}H NMR (400 MHz, DMSO-d_6): 0.88 – 1.13 (m, 2H), 1.33 – 1.56 (m, 4H), 2.54 (t, 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,		

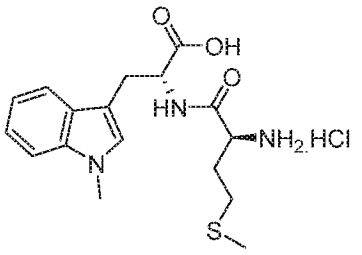
	J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 8.09 (br s, 3H), 8.78 (d, 1H, J = 8.4 Hz), 12.8 (br s, 1H)		
NLG-1554		N^{α}-glycyl-1-methyl-D-tryptophan hydrochloride	87
	^{1}H NMR (400 MHz, DMSO-d_6): 3.02-3.08 (m, 1H), 3.17-3.22 (m, 1H), 3.48-3.60 (m, 2H), 3.74 (s, 3H), 4.55-4.58 (m, 1H), 7.03 (t, 1H, J = 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).		

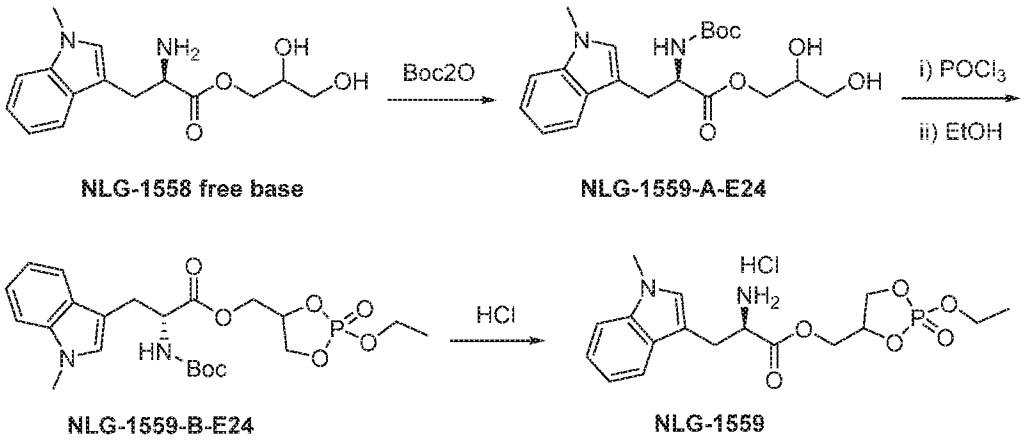
NLG-1567		ethyl N^{α}-(D-tryptophyl)-1-methyl-D-tryptophanate hydrochloride	97
	^{1}H NMR (400 MHz, DMSO-d_6): 1.19 (t, 3H, J = 7.1 Hz), 1.91 (br s, 2H), 2.87 (m, 1H), 3.25 (d, 2H, J = 5.6 Hz), 3.33 (dd, 1H, J = 14.5, 4.4 Hz), 3.66 (s, 3H), 3.70 (dd, 1H, J = 9.0, 4.7 Hz), 4.10 (m, 1H), 4.87 (dt, 1H, 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)

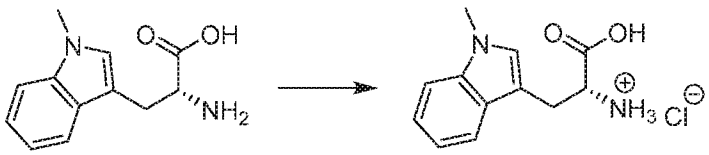
[00137] To a solution of **NLG-1559-A-E24** (650 mg, 1.66 mmol) in dry pyridine (2 mL) at 0 °C was added $POCl_3$ and the solution was allowed to warm to rt. After stirring overnight (18 h), ethanol (1.5 mL) was added and the reaction continued for 4 h. The solvent was removed under reduced pressure 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)

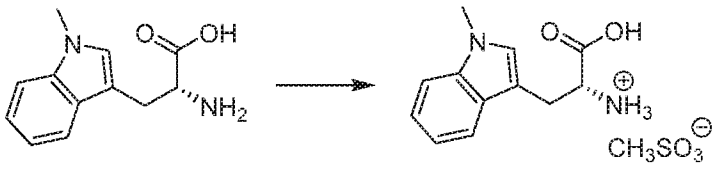


D-1MT NLG-1607

[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).

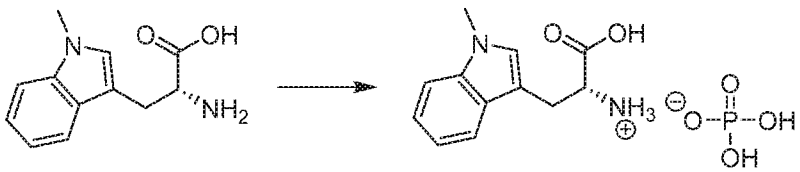
Synthesis of (R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethan-1-aminium methanesulfonate (NLG-1619)



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)



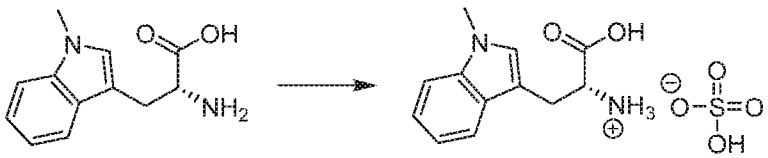
D-1MT NLG-1660

[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

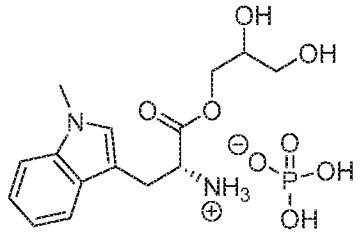
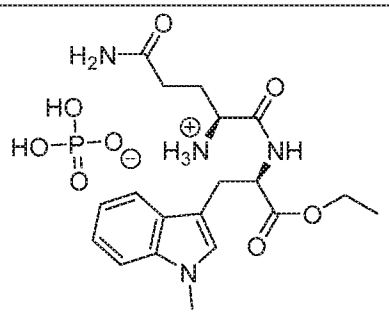
[00144] To a suspension of D-1MT (1.00 g, 4.58 mmol) in water/THF (4:1, 100 mL) at rt, was added 0.5M H_2SO_4 (9.16 mL, 4.58 mmol) and the mixture was stirred at rt overnight. The white solid was filtered-off and washed with cold THF to afford the sulfate salt of D-1MT (0.429 g, 34%). (DMSO-d_6) 3.17 (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).

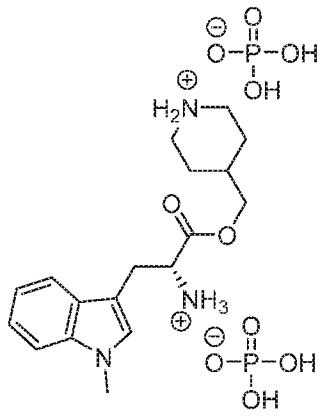
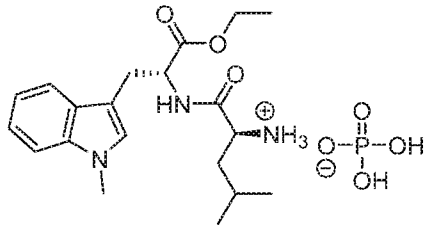
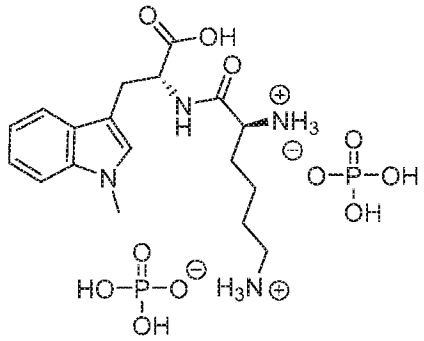
General method for the generation of mono and di phosphate salts of indoximod prodrugs.

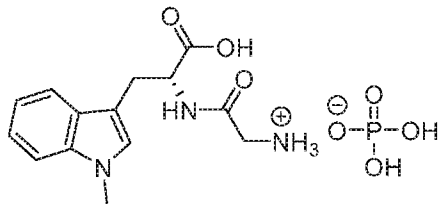
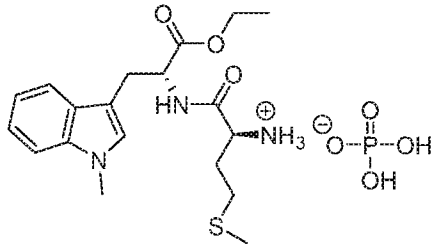
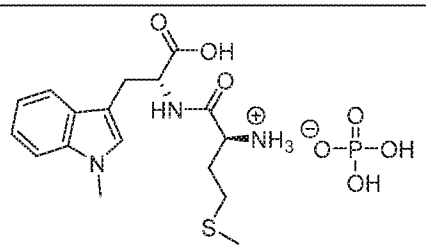
To a solution of free base (0.747 mmol) in EtOH (5ml) at 0 °C was added phosphoric acid (0.747 mmol; a solution in EtOH 1 mL) or (1.494 mmol in case of diamine) and the mixture was allowed

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).		

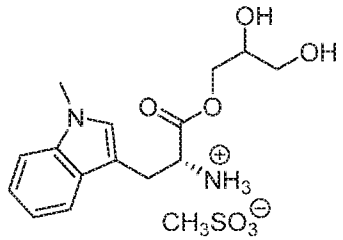
NLG-1664		(R)-4-(((2-ammonio-3-(1-methyl-1H-indol-3-yl)propanoyl)oxy)methyl)piperidin-1-ium dihydrogen phosphate	31
	(DMSO-d_6) 1.35-1.56 (m, 4H), 1.63-1.68 (m, 1H), 2.61-2.73 (m, 2H), 3.09-3.26 (m, 4H), 3.73 (s, 3H), 3.81 (dd, 1H, J = 5.1, 10.9 Hz), 3.88 (dd, 1H, J = 5.1, 11.1 Hz), 3.95 (t, 1H, J = 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

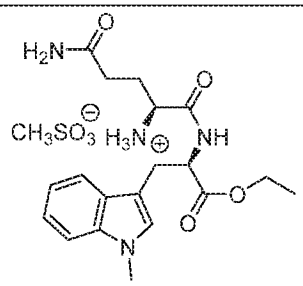
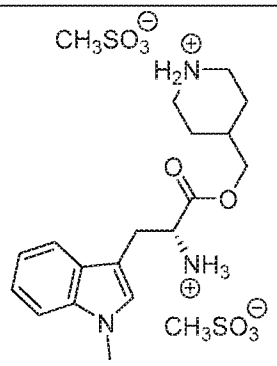
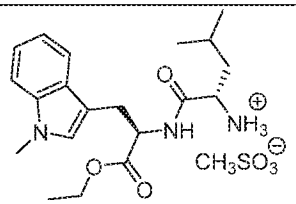
	^{1}H NMR(Deuterium Oxide, 400 MHz): δ = 0.39 – 0.78 (m, 2H), 1.21 (ddd, 2H, *J* = 9.1, 6.8, 2.6 Hz), 1.28 – 1.49 (m, 2H), 2.39 (td, 2H, *J* = 7.4, 3.8 Hz), 3.08 (dd, 1H, *J* = 15.0, 10.9 Hz), 3.45 (ddd, 1H, *J* = 15.1, 4.5, 1.0 Hz), 3.74 (s, 3H), 3.79 (t, 1H, *J* = 6.7 Hz), 4.68 – 4.77 (m, 1H), 7.14 (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		

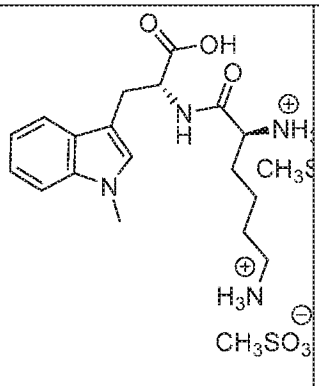
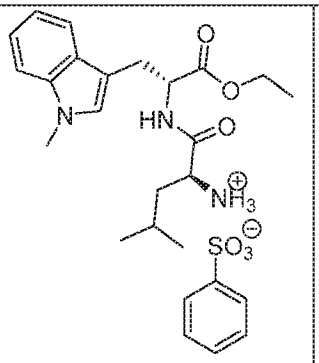
	Hz, 2H), 3.01 (dd, *J*=14.6, 9.0 Hz, 1H), 3.23 (dd, *J*=14.7, 4.6 Hz, 1H), 3.72 (s, 4H), 4.51 (s, 1H), 7.00 (t, *J*=7.5 Hz, 1H), 7.06 – 7.20 (m, 2H), 7.36 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=7.9 Hz, 1H), 8.63 (s, 6H)

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.

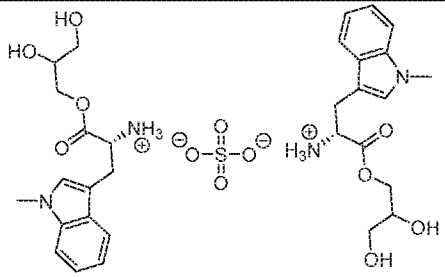
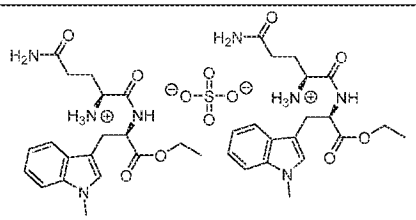
#	Compound	Name	Yield (%)
NLG-1627		(2R)-1-(2,3-dihydroxypropoxy)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-aminium methanesulfonate	41
	^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (s, 3H), 3.24- 3.29 (m, 2H), 3.29 -3.41 (m, 2H), 3.65-3.68 (m, 1H), 3.75 (s, 3H), 4.04 (dd, 1H, *J* = 11.1, 6.3 Hz), 4.16 (dd, 1H, *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).		

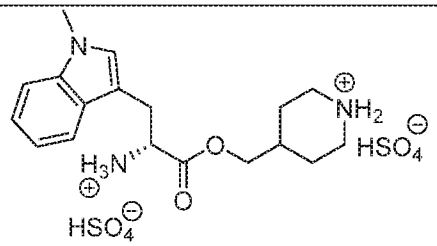
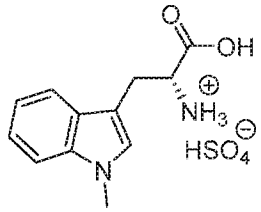
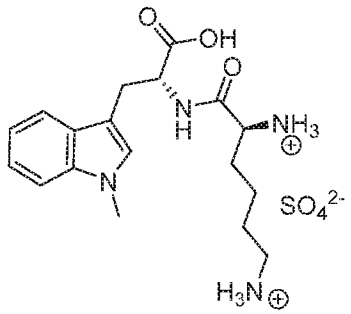
NLG-1631		((S)-5-amino-1-(((R)-1-ethoxy-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-yl)amino)-1,5-dioxopentan-2-aminium methanesulfonate	78
	^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (t, 3H, J = 7.1 Hz), 1.80-1.86 (m, 2H), 1.97- 2.13 (m, 2H), 2.31 (s, 3H), 3.08 (dd, 1H , J = 14.5, 8.2 Hz), 3.18 (dd, 1H , J = 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,		

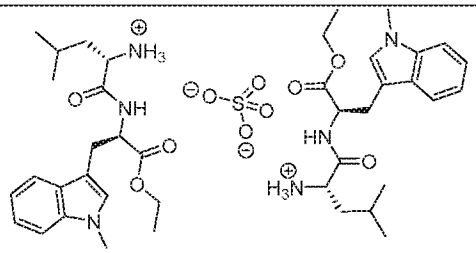
	7.1, 7.1 Hz), 4.64 (td, 1H, *J* = 8.8, 8.8, 5.5 Hz), 7.02 (t, 1H, *J* = 7.5, 7.5 Hz), 7.13 (d, 2H, *J* = 9.8 Hz), 7.38 (d, 1H, *J* = 8.2 Hz), 7.52 (d, 1H, *J* = 7.9 Hz), 8.01 (s, 3H), 8.92 (d, 1H, *J* = 8.2 Hz, 1H).		
NLG-1668		(S)-6-(((R)-1-carboxy-2-(1-methyl-1H-indol-3-yl)ethyl)amino)-6-oxohexane-1,5-diaminium 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^{α}-((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).		

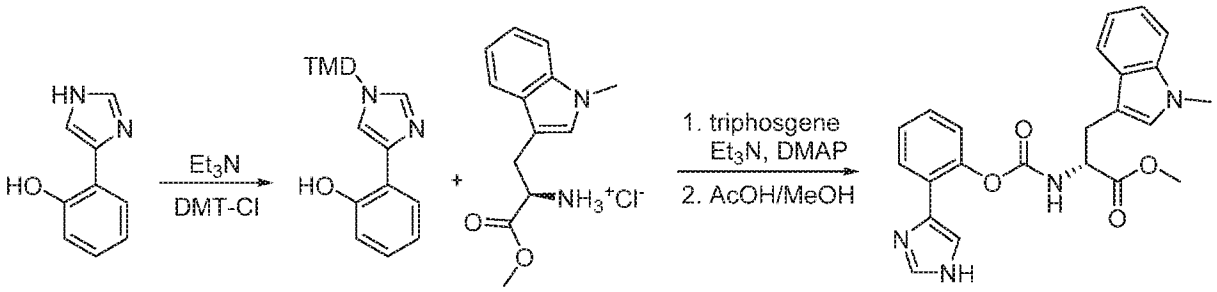
General method for the generation of mono, disulfate and hydrogen sulfate salts of indoximod and indoximod prodrugs.

[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	225.69°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 $AUC_{(0-48h)}$ 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)	# 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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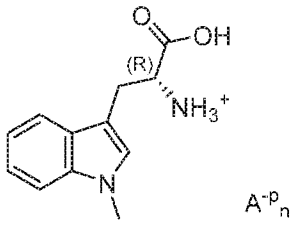
11. Munn, D.H., et al., *GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase.* Immunity, 2005. **22**(5): p. 633-42.
12. Fallarino, F., et al., *The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell 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:

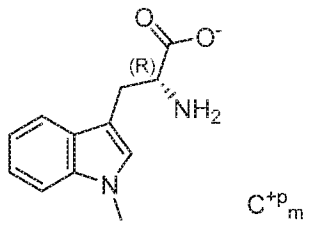
1. A salt of indoximod according to Formula 1a:



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.

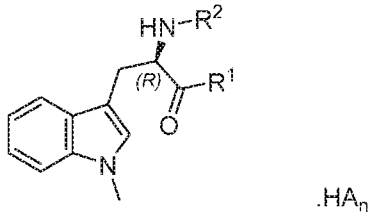
2. The salt of claim 1, wherein $A^{-p}{}_n$ is an anion selected from the group consisting of chloride, phosphate, sulfate, mesylate, besylate, acetate, ascorbate, aspartate, glutamate, glutarate, lactate, maleate, malonate, oxalate, succinate, fumarate, tartrate and citrate, wherein the ionization 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:

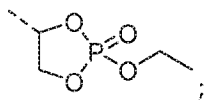


Formula 2

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;

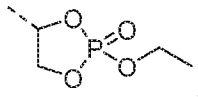
with the proviso that R^1 cannot be –OH when R^2 is H, and the compound cannot be N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan, ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate, or benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate; and

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;

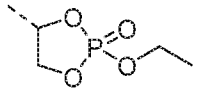
with the proviso that R^1 cannot be –OH when R^2 is H; and

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, -$S(O)N(R)_2$, -$S(O)_2$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 -$N(R)C(O)N(R)_2$, whereinR is H or C_{1-4}alkyl;

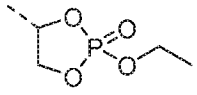
with the proviso that R^1 cannot be –OH when R^2 is H;

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;

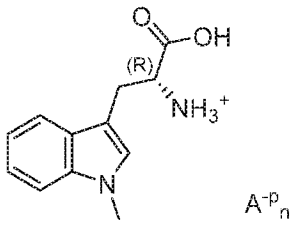
(2-ethoxy-2-oxido-1,3,2-dioxaphospholan-4-yl)methyl 1-methyl-*D*-tryptophanate;

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:

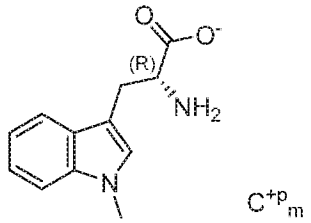


Formula 1a

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:

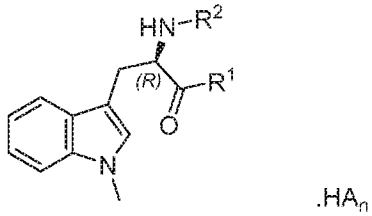


Formula 1b

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:

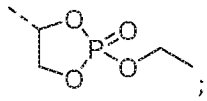


Formula 2

wherein:

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

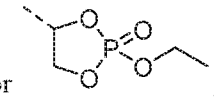
with the proviso that R^1 cannot be –OH when R^2 is H, and the compound cannot be N^{α}-tert-butoxycarbonyl-1-methyl-*D*-tryptophan, ethyl N^{α}-benzyl-1-methyl-*D*-tryptophanate, or benzyl N^{α}-(*tert*-butoxycarbonyl)-1-methyl-*D*-tryptophanate; and

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;

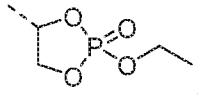
with the proviso that R^1 cannot be –OH when R^2 is H; and

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;

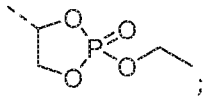
with the proviso that R^1 cannot be –OH when R^2 is H;

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.

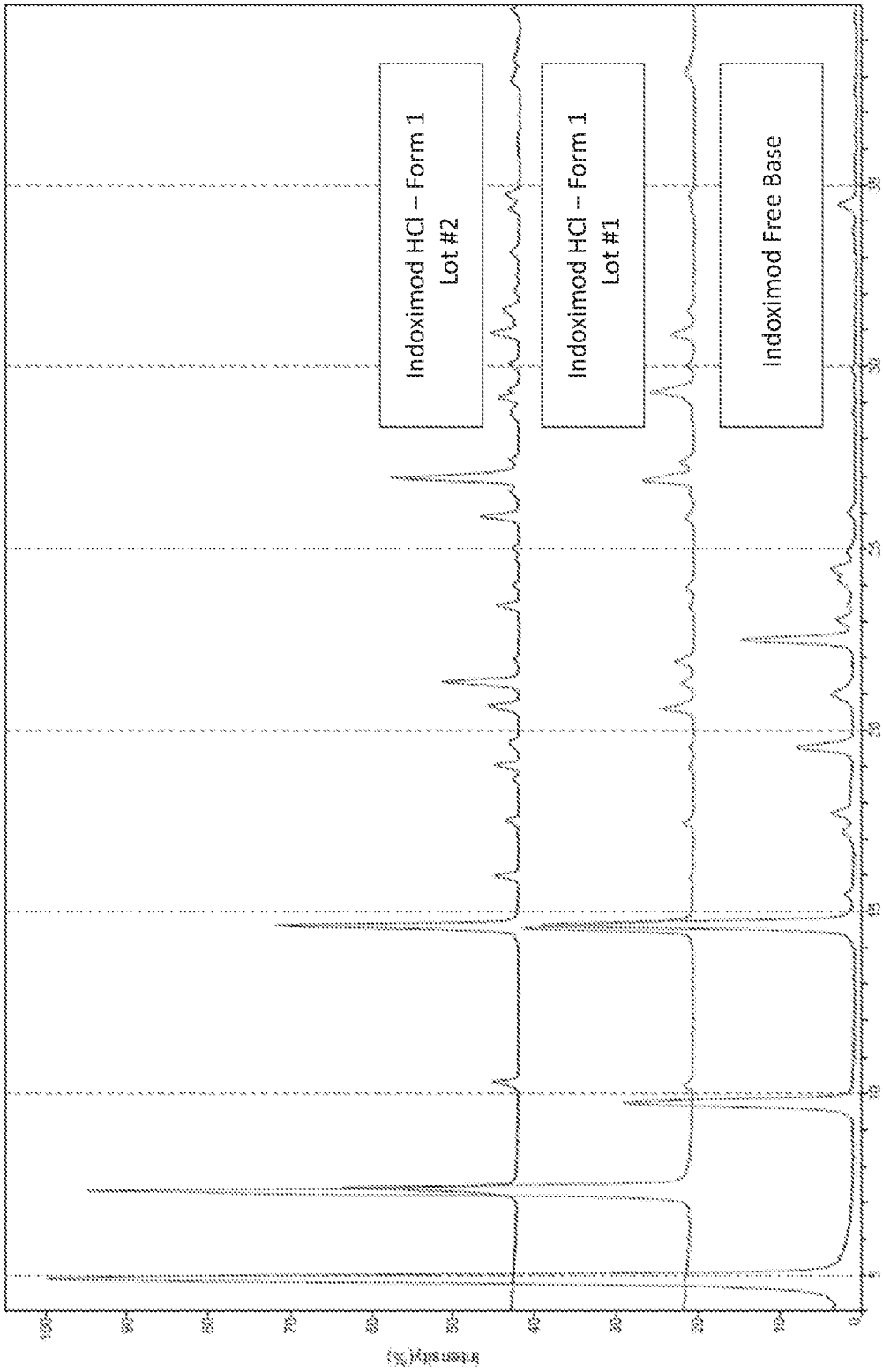


Figure 1: XRPD of indoximod and indoximod HCl

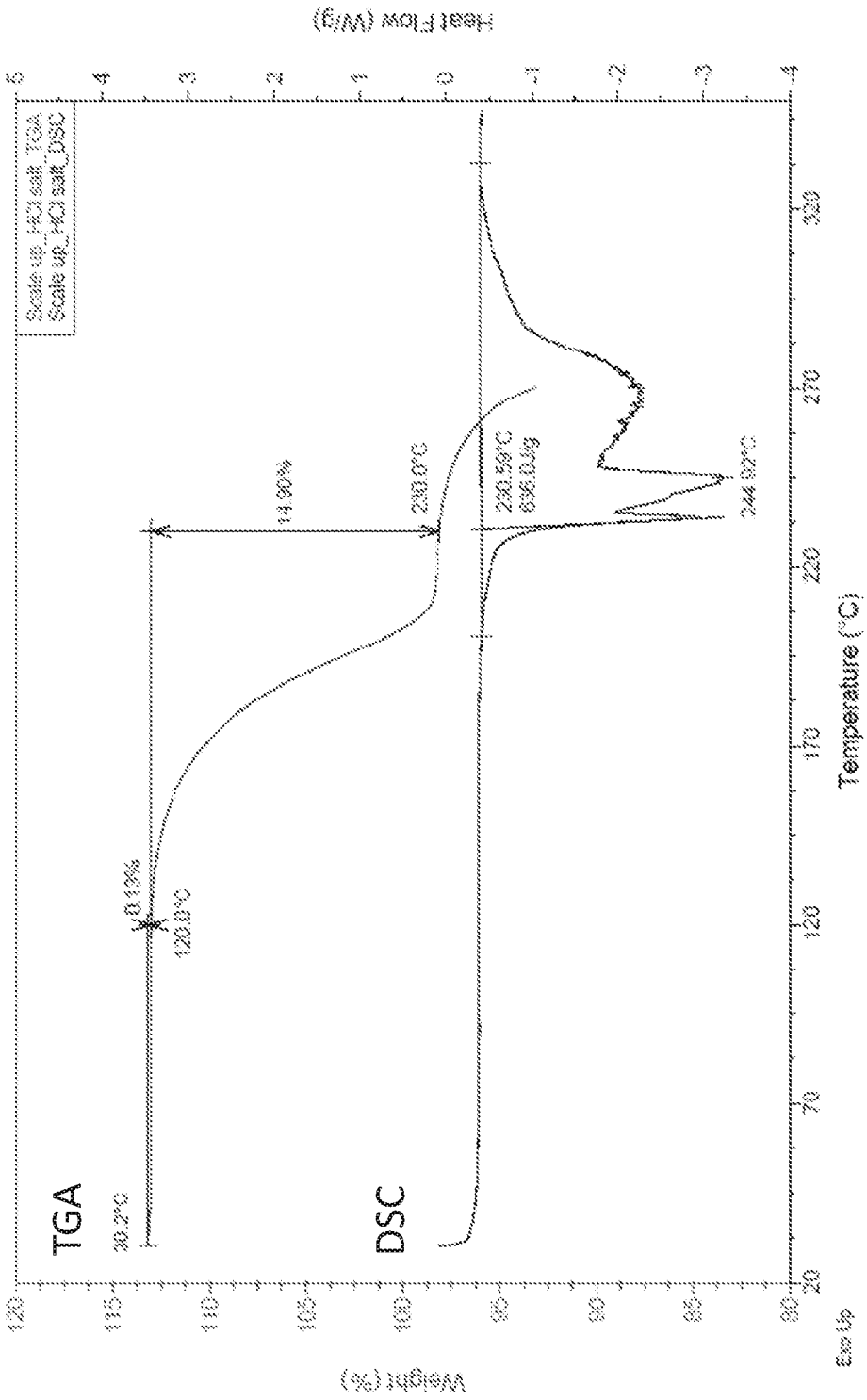


Figure 2: TGA and DSC analysis of indoximod HCl

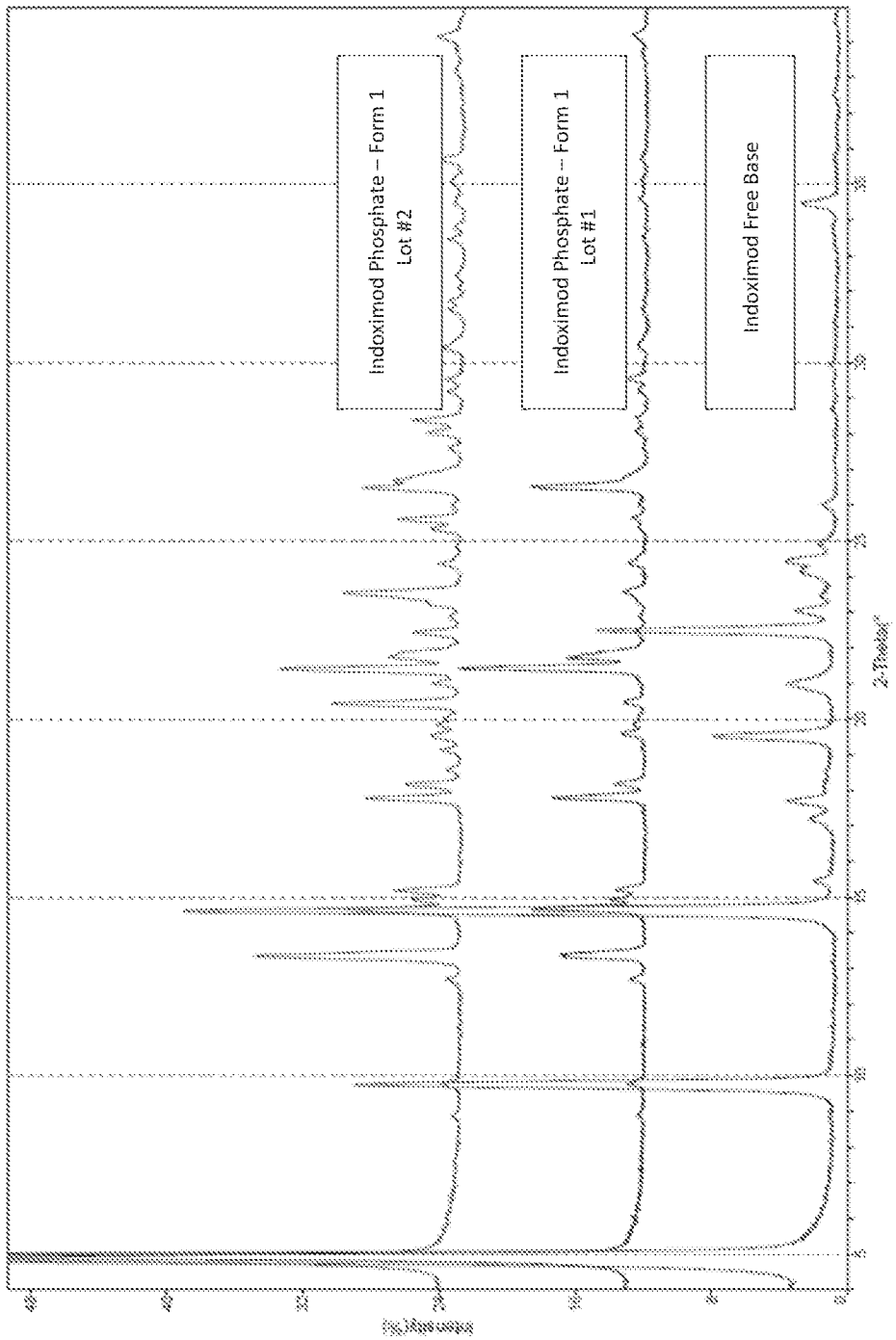


Figure 3: XRPD of indoximod and indoximod phosphate

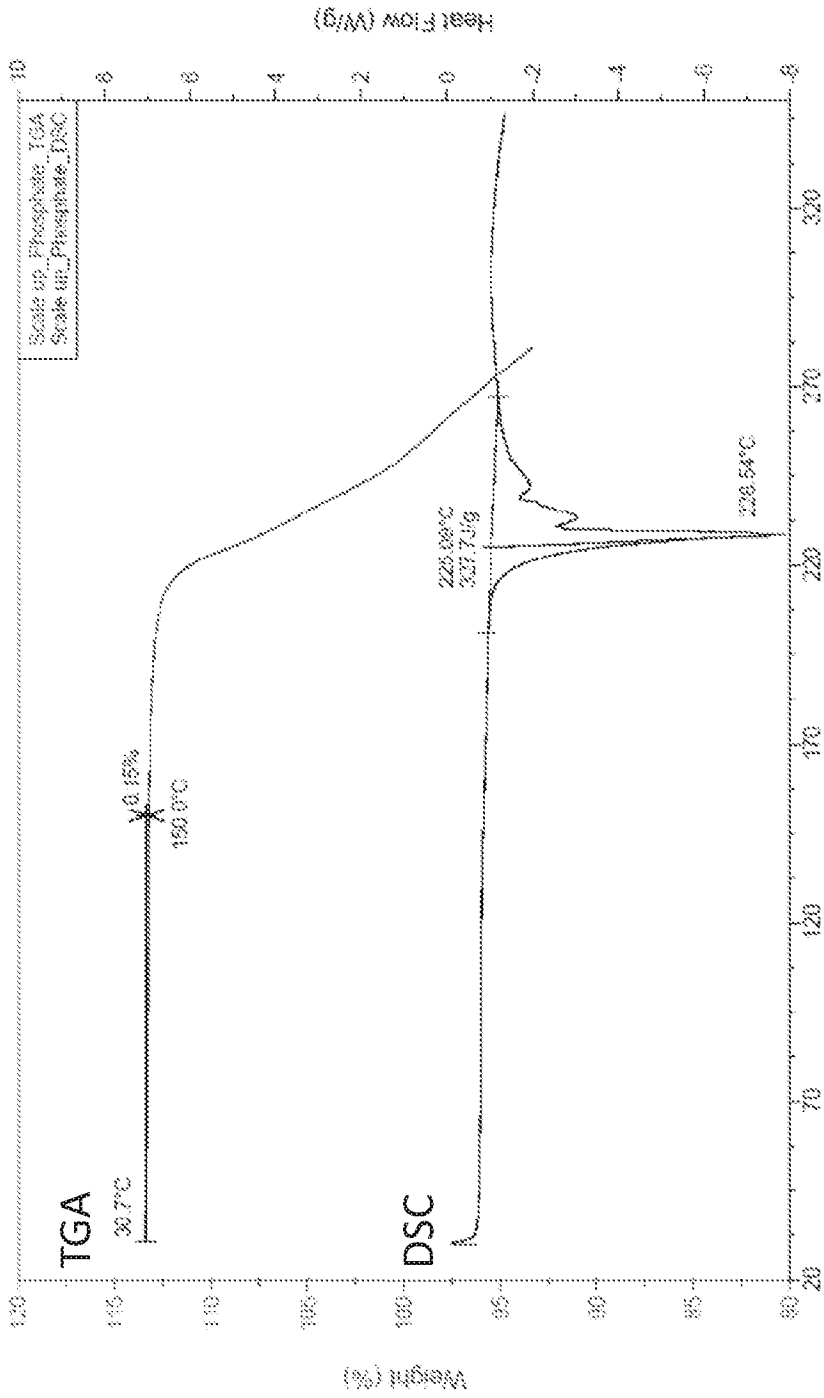
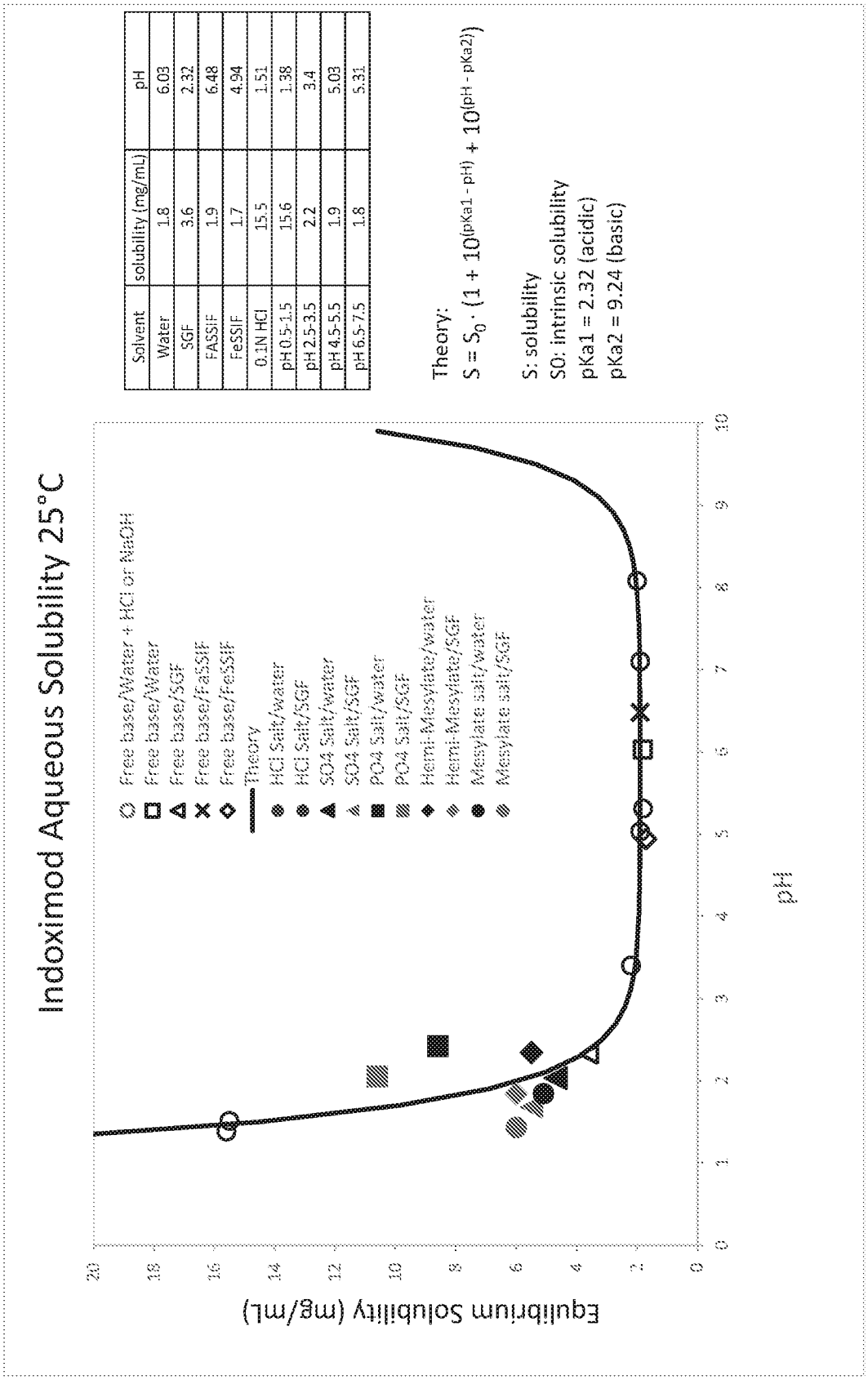


Figure 4: TGA and DSC analysis of indoximod phosphate



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

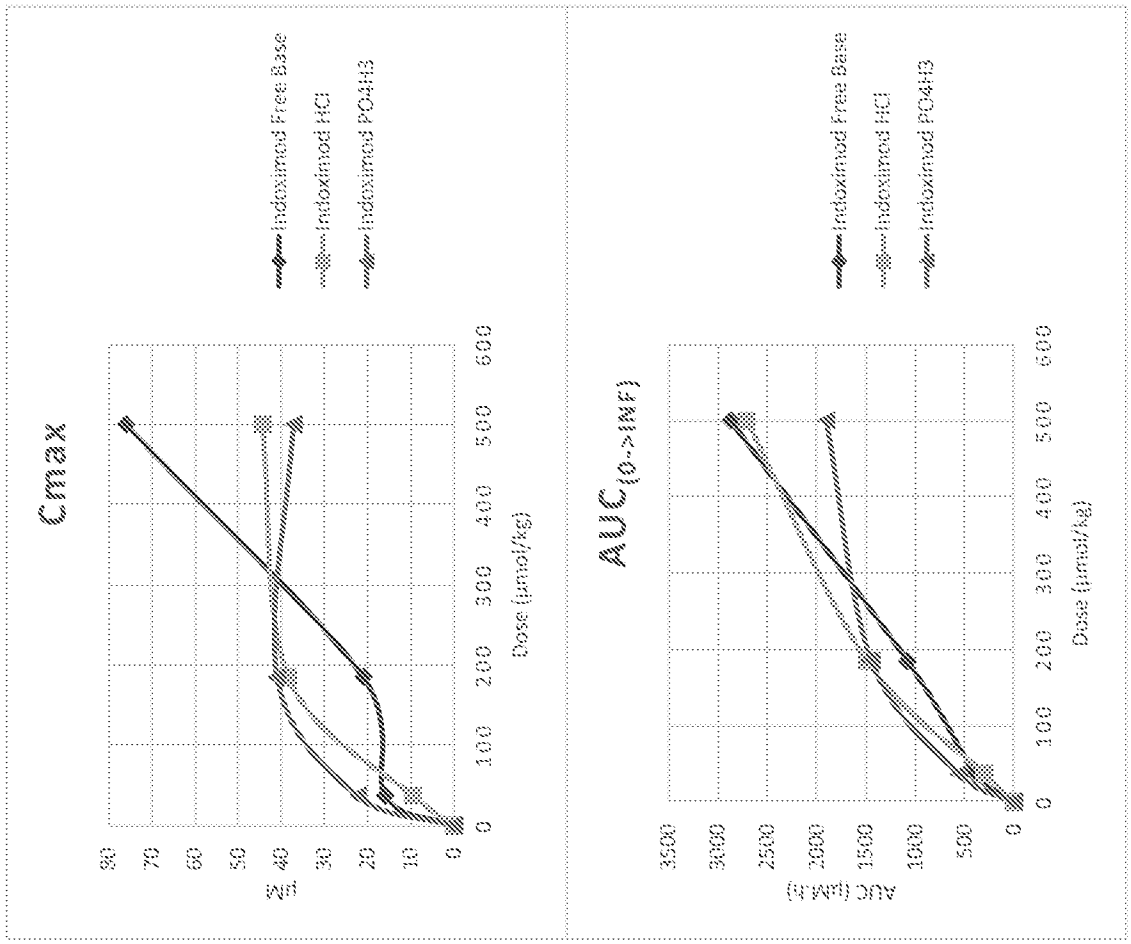


Figure 6: Dose dependency of Cmax and AUC for indoximod and its salts rats after oral dosing in capsule form

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	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	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.