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(72) Inventeurs/Inventors:
MULLER, GEORGE W., US;
CHEN, ROGER, US;
SAINDANE, MANOHAR TUKARAM, US;
GE, CHUANSHENG, US
(73) Propriétaire/Owner:
CELGENE CORPORATION, US
(74) Agent: SMART & BIGGAR

(54) Titre : PROCÉDES DE PRÉPARATION DE 2-(2,6-DIOXOPIPERIDIN-3-YL)-1-OXOISOINDOLINES SUBSTITUÉES
(54) Title: PROCESSES FOR THE PREPARATION OF SUBSTITUTED 2-(2,6-DIOXOPIPERIDIN-3-YL)-1-OXOISOINDOLINES

(57) **Abrégé/Abstract:**

The present invention concerns new processes for the preparation of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines which are useful for preventing or treating diseases or conditions related to an abnormally high level or activity of TNF α . The invention provides processes for the commercial production of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines including, but not limited to, the therapeutically active 3-(4-amino-1-oxoisoindolin-2-yl) piperidine-2,6-dione.

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(71) Applicant (for all designated States except US): **CEL-GENE CORPORATION** [US/US]; 86 Morris Avenue, Summit, NJ 07901 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MULLER, George, W.** [US/US]; 250 Windmill Court, Bridgewater, NJ 08807 (US). **CHEN, Roger** [US/US]; 110 Christie Street, Edison, NJ 08820 (US). **SAINDANE, Manohar, Tukaram** [US/US]; 20 Arbutus Way, Monmouth Junction, NJ 08852 (US). **GE, Chuansheng** [US/US]; 9 Breckenridge Court, Belle Mead, NJ 08502 (US).

(74) Agents: **INSOGNA, Anthony, M.** et al.; Jones Day, 222 East 41st Street, New York, NY 10017-6702 (US).

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(54) Title: PROCESSES FOR THE PREPARATION OF SUBSTITUTED 2-(2,6-DIOXOPIPERIDIN-3-YL)-1-OXOISOINDOLINES

(57) Abstract: The present invention concerns new processes for the preparation of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines which are useful for preventing or treating diseases or conditions related to an abnormally high level or activity of TNF α . The invention provides processes for the commercial production of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines including, but not limited to, the therapeutically active 3-(4-amino-1-oxoisoindolin-2-yl) piperidine-2,6-dione.



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**PROCESSES FOR THE PREPARATION OF SUBSTITUTED
2-(2,6-DIOXOPIPERIDIN-3-YL)-1-OXOISOINDOLINES**

1. FIELD OF THE INVENTION

[001] The present invention relates to processes for the preparation of compounds useful for reducing levels or activity of tumor necrosis factor α in a mammal. More specifically, the invention relates to processes for the synthesis of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines. In particular, the invention relates to processes useful for the preparation of 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione.

2. BACKGROUND OF THE INVENTION

[002] Excessive or unregulated production of tumor necrosis factor α , or TNF α , has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome (Tracey *et al.*, *Nature* 330, 662-664 (1987) and Hinshaw *et al.*, *Circ. Shock* 30, 279-292 (1990)), cachexia (Dezube *et al.*, *Lancet* 335 (8690), 662 (1990)), and Adult Respiratory Distress Syndrome (Millar *et al.*, *Lancet* 2 (8665), 712-714 (1989)). Certain substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines have been shown to reduce levels of TNF α (International Publication No. WO 98/03502).

[003] An oxoisoindoline that has demonstrated particular therapeutic promise is 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione (REVLIMIDTM). This compound has been shown to be useful in treating and preventing a wide range of diseases and conditions including, but not limited to, inflammatory diseases, autoimmune diseases, and cancers including both solid and homological cancers. REVLIMID has received Fast Track Designation from the Food and Drug Administration for the treatment of multiple myeloma and myelodysplastic syndromes. Furthermore, REVLIMID is in late-stage clinical trials for the treatment of hematological and solid tumor cancers and immunological and inflammatory diseases.

[004] Existing methods for synthesizing substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines are described in International Publication No. WO 98/03502 (See page 7, line 22, to page 10, line 33, and Examples 1 to 18) and Muller *et al.*, *Bioorgan. Med. Chem. Lett.* **9**,1625-1630 (1999). In one existing method, an *N*-protected glutamine is cyclized and then deprotected to generate an α -aminoglutaramide hydrochloride. The α -aminoglutaramide hydrochloride is coupled to a substituted methyl 2-bromomethylbenzoate to form a 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline. A benzo substituent can then be transformed to another substituent if desired.

[005] While these methods are enabling and useful for preparing substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines, there are possibilities for alterations that may result in a more efficient synthesis.

[006] Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application.

3. SUMMARY OF THE INVENTION

[007] The present invention provides processes for the commercial production of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines that are cost effective and readily scaleable with commercial reagents. In one embodiment, the invention provides a process for preparing a substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline comprising the steps of: (1) esterifying an *N*-protected or -unprotected glutamine; (2) deprotecting the α -amino group of the esterified glutamine if it is protected; (3) coupling the *N*-deprotected, esterified glutamine with an optionally substituted 2-haloalkylbenzoate; (4) cyclizing the coupled product ; and (5) optionally transforming one or more benzo substituents on the cyclized product into other substituent(s) in one or more steps.

[008] In another embodiment, the invention provides a process for preparing a substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline comprising the steps of: (1) esterifying an *N*-protected or -unprotected glutamine; (2) deprotecting the α -amino group of the esterified glutamine if it is protected; (3) coupling the *N*-deprotected, esterified glutamine with an optionally substituted 2-haloalkylbenzoate; (4) transforming one or more benzo substituents on the coupled product into other substituent(s) in one or more steps; and (5) cyclizing the transformed product.

[009] In yet other embodiments, the present invention provides processes for preparing substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines as set forth in Scheme 1, wherein:

R^1 - R^9 , X, and ProtG¹ are as described below. $R^{1'}$ - $R^{4'}$ denote that one or more of the R^1 - R^4 substituents may optionally be transformed to the corresponding $R^{1'}$ - $R^{4'}$ substituents, respectively, in one or more steps. One of these embodiments comprises steps 1, 2, 3, 4, and 5. Another embodiment comprises steps 1, 2, 3, 6, and 7.

[010] In still other embodiments, the invention provides processes for preparing mono-benzo-substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines as set forth in Scheme 2, wherein R^1 - R^9 , X, and ProtG¹ are as described below. The benzo substituent R^1 may be converted into R^2 if desired. One of these embodiments comprises steps 1, 2, 3, 4, and 5. Another embodiment comprises steps 1, 2, 3, 6, and 7.

[011] In yet other embodiments, the invention provides processes for synthesizing 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione as set forth in Scheme 3. One of these embodiments comprises steps 1, 2, 3, 4, and 5. Another embodiment comprises steps 1, 2, 3, 6, and 7.

[012] In still another embodiment, the processes of the present invention are useful for preparing substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines or pharmaceutically acceptable salts, hydrates, solvates, or polymorphs thereof. In yet another embodiment, the processes of the invention are useful for preparing compounds useful for preventing or treating diseases or conditions related to an abnormally high level or activity of TNF α . In yet another embodiment, the processes of the invention are useful for preparing compounds useful for treating or preventing oncological conditions.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 Terminology

[013] As used herein and unless otherwise indicated, the term "halo", "halogen", or the like means -F, -Cl, -Br, or -I.

[014] As used herein and unless otherwise indicated, the term "lower molecular weight halo" means -F or -Cl.

[015] As used herein and unless otherwise indicated, the term "higher molecular weight halo" means -Br or -I.

[016] As used herein and unless otherwise indicated, the term "alkyl" means a saturated, monovalent, unbranched or branched hydrocarbon chain. Examples of alkyl groups include, but are not limited to, (C₁-C₆)alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, *t*-butyl, pentyl, isopentyl, neopentyl, and hexyl. Longer alkyl groups include heptyl, octyl, nonyl and decyl groups. An alkyl group can be unsubstituted or substituted with one or more suitable substituents.

[017] As used herein and unless otherwise indicated, the term "alkoxy" means an alkyl group that is linked to another group via an oxygen atom (*i.e.*, -O-alkyl). An alkoxy group can be unsubstituted or substituted with one or more suitable substituents. Examples of alkoxy groups include, but are not limited to, (C₁-C₆)alkoxy groups, such as -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-2-methyl-1-propyl, -O-2-methyl-2-propyl, -O-2-methyl-1-butyl, -O-3-methyl-1-butyl, -O-2-methyl-3-butyl, -O-2,2-dimethyl-1-propyl, -O-2-methyl-1-pentyl, 3-O-methyl-1-pentyl, -O-4-methyl-1-pentyl, -O-2-methyl-2-pentyl, -O-3-methyl-2-pentyl, -O-4-methyl-2-pentyl, -O-2,2-dimethyl-1-butyl, -O-3,3-dimethyl-1-butyl, -O-2-ethyl-1-butyl, -O-butyl, -O-isobutyl, -O-*t*-butyl, -O-pentyl, -O-isopentyl, -O-neopentyl and -O-hexyl.

[018] As used herein and unless otherwise indicated, the term "lower alkyl" means alkyl having from 1 to 4 carbon atoms. Examples include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, and tertiary butyl (^tBu, or *t*-butyl).

[019] As used herein and unless otherwise indicated, the term "lower alkoxy" means a lower alkyl group that is linked to another group via an oxygen atom (*i.e.*, -O-lower alkyl). Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, and tertiary butoxy (^tOBu, or *t*-butoxy).

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[020] As used herein and unless otherwise indicated, the term "alcohol" means any compound substituted with an -OH group.

[021] Unless otherwise indicated, the compounds of the invention, including intermediates useful for the preparation of the compounds of the invention, which contain reactive functional groups (such as, without limitation, carboxy, hydroxy, and amino moieties) also include protected derivatives thereof. "Protected derivatives" are those compounds in which a reactive site or sites are blocked with one or more protecting groups (also known as blocking groups). Suitable protecting groups for carboxy moieties include benzyl, *t*-butyl, and the like. Suitable protecting groups for amino and amido groups include acetyl, *t*-butyloxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for hydroxy include benzyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art. The choice and use of protecting groups and the reaction conditions to install and remove protecting groups are described in T. W. Green, "Protective Groups in Organic Synthesis", Third Ed., Wiley, New York, 1999.

[022] As used herein and unless otherwise indicated, the term "substituted" as used to describe a compound or chemical moiety means that at least one hydrogen atom of that compound or chemical moiety is replaced with a second chemical moiety. The second chemical moiety may be any desired substituent that does not adversely affect the desired activity of the compound. Examples of substituents are those found in the exemplary compounds and embodiments disclosed herein, as well as halogen; C₁₋₈ alkyl; C₂₋₈ alkenyl; C₂₋₈ alkynyl; hydroxyl; C₁₋₆ alkoxy; amino; nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl; sulfonyl; sulfonamide; ketone; aldehyde; ester; oxygen (=O); haloalkyl (*e.g.*, trifluoromethyl); carbocyclic cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocycloalkyl, which may be monocyclic or fused or non-fused polycyclic (*e.g.*, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiazinyl); carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic aryl (*e.g.*, phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl); amino (primary, secondary,

or tertiary); o-lower alkyl; o-aryl, aryl; aryl-lower alkyl; CO₂CH₃; CONH₂; OCH₂CONH₂; NH₂; SO₂NH₂; OCHF₂; CF₃; OCF₃; -NH((C₁-C₈)alkyl); -N((C₁-C₈)alkyl)₂; -NH((C₆)aryl); -N((C₆)aryl)₂; -CHO; -CO((C₁-C₈)alkyl); -CO((C₆)aryl); -CO₂((C₁-C₈)alkyl); and -CO₂((C₆)aryl); and such moieties may also be optionally substituted by a fused-ring structure or bridge, for example -OCH₂O-. These substituents may optionally be further substituted with a substituent selected from such groups.

[023] As used herein and unless otherwise indicated, a composition that is “substantially free” of a compound means that the composition contains less than about 20% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight, and most preferably less than about 3% by weight of the compound.

[024] As used herein and unless otherwise indicated, the term “stereochemically pure” means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound.

[025] As used herein and unless otherwise indicated, the term “enantiomerically pure” means a stereomerically pure composition of a compound having one chiral center.

[026] As used herein and unless otherwise indicated, the term “racemic” or “racemate” means about 50% of one enantiomer and about 50% of the corresponding enantiomer relative to all chiral centers in the molecule. The invention encompasses all enantiomerically pure, enantiomerically enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures of the compounds of the invention.

[027] As used herein and unless otherwise indicated, the term “process(es) of the invention” refers to the methods disclosed herein which are useful for preparing a compound of the invention. Modifications to the methods disclosed herein (*e.g.*, starting materials, reagents, protecting groups, solvents, temperatures, reaction times, purification) are also encompassed by the present invention.

[028] As used herein and unless otherwise indicated, the term “adding” or the like means contacting one reactant, reagent, solvent, catalyst, or the like with another reactant, reagent, solvent, catalyst, or the like. Reactants, reagents, solvents, catalysts, or the like can be added individually, simultaneously, or separately and can be added in any order. They can

be added in the presence or absence of heat and can optionally be added under an inert atmosphere.

[029] As used herein and unless otherwise indicated, the term "coupling" or the like means covalently linking two or more reactants *via* chemical reaction(s). The linking can be facilitated by acid(s), base(s), activating agent(s), catalyst(s), and so on. The linking can occur in the presence or absence of heat, light, sound (sonication), microwave radiation, and so on and can optionally occur under an inert atmosphere.

[030] As used herein and unless otherwise indicated, a reaction that is "substantially complete" or is driven to "substantial completion" means that the reaction contains more than about 80% by percent yield, more preferably more than about 90% by percent yield, even more preferably more than about 95% by percent yield, and most preferably more than about 97% by percent yield of the desired product.

[031] As used herein and unless otherwise indicated, the term "pharmaceutically acceptable salt" refers to a salt prepared from a pharmaceutically acceptable non-toxic inorganic or organic acid. Suitable non-toxic acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, and *p*-toluenesulfonic acids. For example, specific pharmaceutically acceptable salts are hydrochloride, maleic acid, and tartaric acid salts.

[032] As used herein and unless otherwise indicated, the term "hydrate" means a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[033] As used herein and unless otherwise indicated, the term "solvate" means a solvate formed from the association of one or more solvent molecules to a compound of the present invention. The term "solvate" includes hydrates (*e.g.*, mono-hydrate, dihydrate, trihydrate, tetrahydrate, and the like).

[034] As used herein and unless otherwise indicated, the term "polymorph" means solid crystalline forms of a compound of the present invention or complex thereof. Different

polymorphs of the same compound may exhibit different physical, chemical and /or spectroscopic properties.

[035] As used herein and unless otherwise indicated, the phrase "diseases or conditions related to an abnormally high level or activity of TNF α " means diseases or conditions that would not arise, endure, or cause symptoms if the level or activity of TNF α were lower, or diseases or conditions that can be prevented or treated by a lowering of TNF α level or activity.

[036] As used herein and unless otherwise indicated, the term "treat", "treatment", "treating", or the like refers to the reduction or amelioration of the progression, severity and/or duration of a disease or condition, or the amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a disease or condition resulting from the administration of one or more therapies (*e.g.*, one or more therapeutic agents such as a compound of the invention).

[037] As used herein and unless otherwise indicated, the term "prevent", "prevention", "preventing" or the like refers to the reduction in the risk of acquiring or developing a given disease or condition, or the reduction or inhibition of the recurrence, onset, or development of one or more symptoms of a given disease or condition.

[038] Acronyms or symbols for groups or reagents have the following definition: ProtG = protecting group; Cbz = benzyloxycarbonyl; Boc = *t*-butyloxycarbonyl; Fmoc = 9-fluorenylmethoxycarbonyl; *p*-TsOH = *para*-toluenesulfonic acid; TFA = trifluoroacetic acid; TMSCl = trimethylsilyl chloride; DMAP = *N,N*-dimethylaminopyridine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; CDI = 1,1'-carbonyldiimidazole; NBS = *N*-bromosuccinimide; VAZO[®] = 1,1'-azobis-(cyclohexanecarbonitrile); DMF = *N,N*-dimethylformamide; THF = tetrahydrofuran; DCM = dichloromethane; MTBE = methyl *tert*-butyl ether.

[039] If there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. Furthermore, if the stereochemistry of a structure or a portion thereof is not indicated, *e.g.*, with bold or dashed lines, the structure or portion thereof is to be interpreted as encompassing all stereoisomers of it.

[040] The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4.2 Processes of the Invention

[041] The present invention provides cost-effective and efficient processes for the commercial production of substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines. In one embodiment, the invention provides a process for preparing a substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline comprising the steps of: (1) protecting the α -amino group of a glutamine; (2) esterifying the *N*-protected glutamine; (3) deprotecting the α -amino group of the esterified glutamine; (4) coupling the *N*-deprotected glutamine ester with an optionally substituted 2-haloalkylbenzoate; (5) cyclizing the coupled product ; and (6) optionally transforming one or more benzo substituents on the cyclized product into other substituent(s) in one or more steps. In one embodiment, the *N*-deprotected glutamine ester is a free amine. In another embodiment, the *N*-deprotected glutamine ester is an acid addition salt. In a particular embodiment, the *N*-deprotected glutamine ester is a hydrochloride salt.

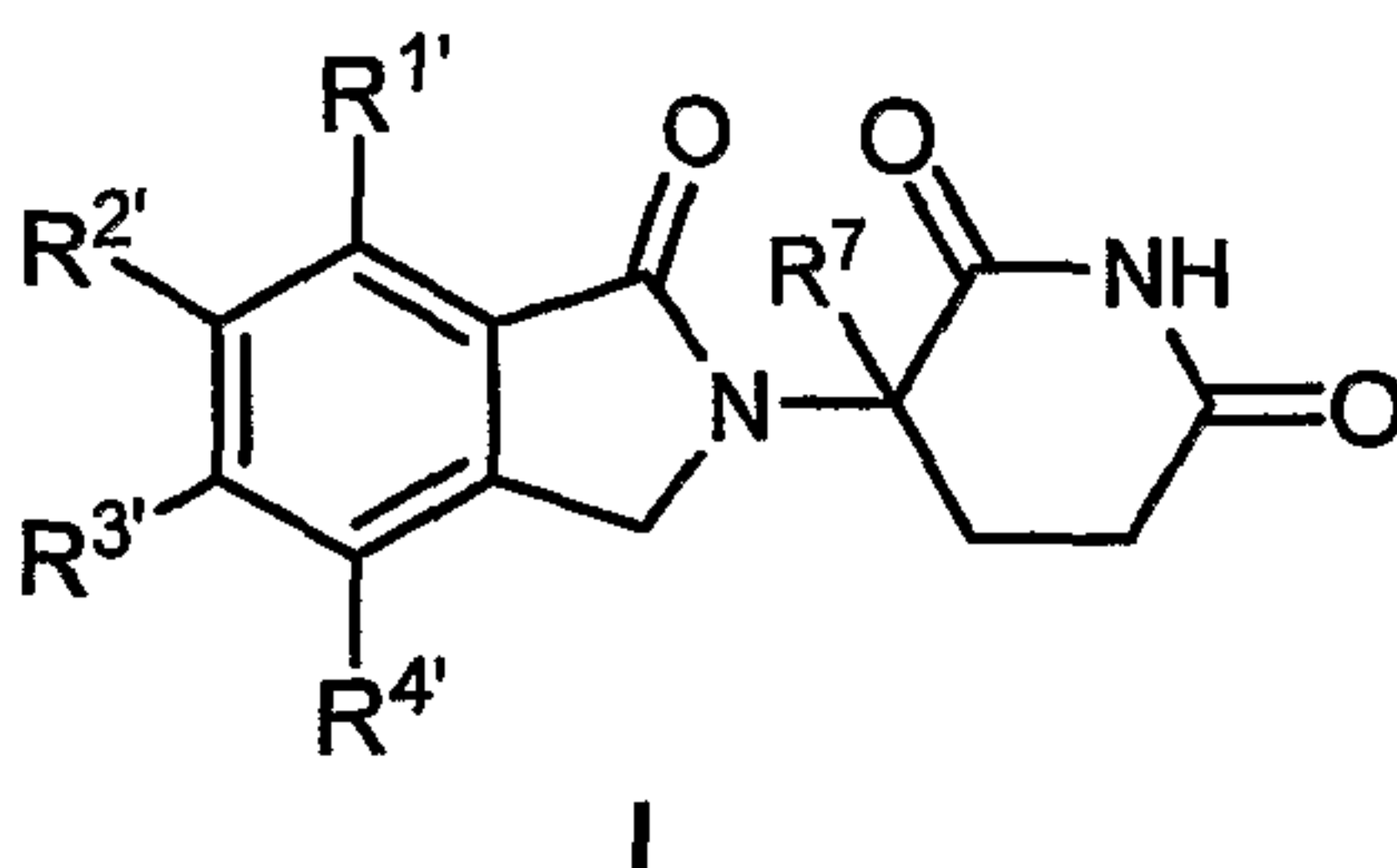
[042] In another embodiment, the invention provides a process for preparing a substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline comprising the steps of: (1) esterifying glutamine; (2) coupling the esterified glutamine with an optionally substituted 2-haloalkylbenzoate; (3) cyclizing the coupled product ; and (4) optionally transforming one or more benzo substituents on the cyclized product into other substituent(s) in one or more steps. In one embodiment, the esterified glutamine is a free amine. In another embodiment, the esterified glutamine is an acid addition salt. In a particular embodiment, the esterified glutamine is a hydrochloride salt.

[043] In yet another embodiment, the invention provides a process for preparing a substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline comprising the steps of: (1) protecting the α -amino group of a glutamine; (2) esterifying the *N*-protected glutamine; (3) deprotecting the α -amino group of the esterified glutamine; (4) coupling the *N*-deprotected glutamine ester with an optionally substituted 2-haloalkylbenzoate; (5) transforming one or more benzo substituents on the coupled product into other substituent(s) in one or more steps; and (6) cyclizing the transformed product. In one embodiment, the *N*-deprotected glutamine

ester is a free amine. In another embodiment, the *N*-deprotected glutamine ester is an acid addition salt. In a particular embodiment, the *N*-deprotected glutamine ester is a hydrochloride salt.

[044] In still another embodiment, the invention provides a process for preparing a substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoline comprising the steps of: (1) esterifying glutamine; (2) coupling the esterified glutamine with an optionally substituted 2-haloalkylbenzoate; (3) transforming one or more benzo substituents on the coupled product into other substituent(s) in one or more steps; and (4) cyclizing the transformed product. In one embodiment, the esterified glutamine is a free amine. In another embodiment, the esterified glutamine is an acid addition salt. In a particular embodiment, the esterified glutamine is a hydrochloride salt.

[045] In one embodiment, the invention relates to a process for preparing a compound of Formula I:



or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein:

each of $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ is at each occurrence independently hydrogen, halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;

R^7 is hydrogen, halo, alkyl, or benzyl; and

$ProtG^2$ is a suitable *N*-protecting group,

which comprises the alternative sequences of steps of:

(1)(a) coupling a glutamine ester or a salt thereof with an optionally substituted 2-haloalkylbenzoate;

(b) cyclizing the coupled product; and

(c) optionally transforming one or more benzo substituents of the cyclized product into other substituent(s) in one or more steps,

or:

(2)(a) coupling a glutamine ester or a salt thereof with an optionally substituted 2-haloalkylbenzoate;

(b) transforming one or more benzo substituents of the coupled product into other substituent(s) in one or more steps; and

(c) cyclizing the transformed product.

[046] For the above embodiments, the α -amino group of a glutamine can be protected as, for example, an amide (*e.g.*, a trifluoroacetamide) or as a carbamate (*e.g.*, a Cbz, Boc, or Fmoc carbamate). The *N*-protecting group can be removed in various ways, including, but not limited to, by catalytic hydrogenolysis (*e.g.*, for a Cbz carbamate), under acidic condition (*e.g.*, for a Boc carbamate), or under basic condition (*e.g.*, for a Fmoc carbamate or a trifluoroacetamide). The carboxyl group of an *N*-protected or *N*-unprotected glutamine can be esterified as, for example, an alkyl or a benzyl ester. Various methods of esterification are well known in the art. For example, esterification can occur in the corresponding alcohol under acidic condition. The corresponding alcohol can also be used in the presence of an activating agent such as, *e.g.*, a carbodiimide to esterify. Esterification can also be effected using a corresponding alkyl or benzyl halide under basic condition.

[047] A glutamine ester or a salt thereof can be coupled to an optionally substituted 2-haloalkylbenzoate under basic conditions. The optionally substituted 2-haloalkylbenzoate can be generated by halogenating the corresponding an optionally substituted 2-alkylbenzoate, *e.g.*, using an appropriate halogenating agent under free-radical condition. Cyclization to form a 2,6-piperidinedione moiety can occur under acidic or basic conditions with an ester group as the accepting group. Cyclization can also be effected in the presence of an activating agent (*e.g.*, thionyl chloride, oxalyl chloride, CDI, and the like) with a carboxyl group as the accepting group. Among the various possible kinds of transformation of benzo substituents, a benzo -NO₂ group can be reduced to an -NH₂ group and a protected benzo -NHProtG² group can be deblocked to yield an -NH₂ group.

[048] In yet other embodiments, the present invention provides processes for preparing substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines as set forth in Scheme 1. In these embodiments:

(a) each of R^1 , R^2 , R^3 , R^4 , $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ is at each occurrence independently hydrogen, halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

(b) each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;

(c) R^7 is hydrogen, halo, alkyl, or benzyl;

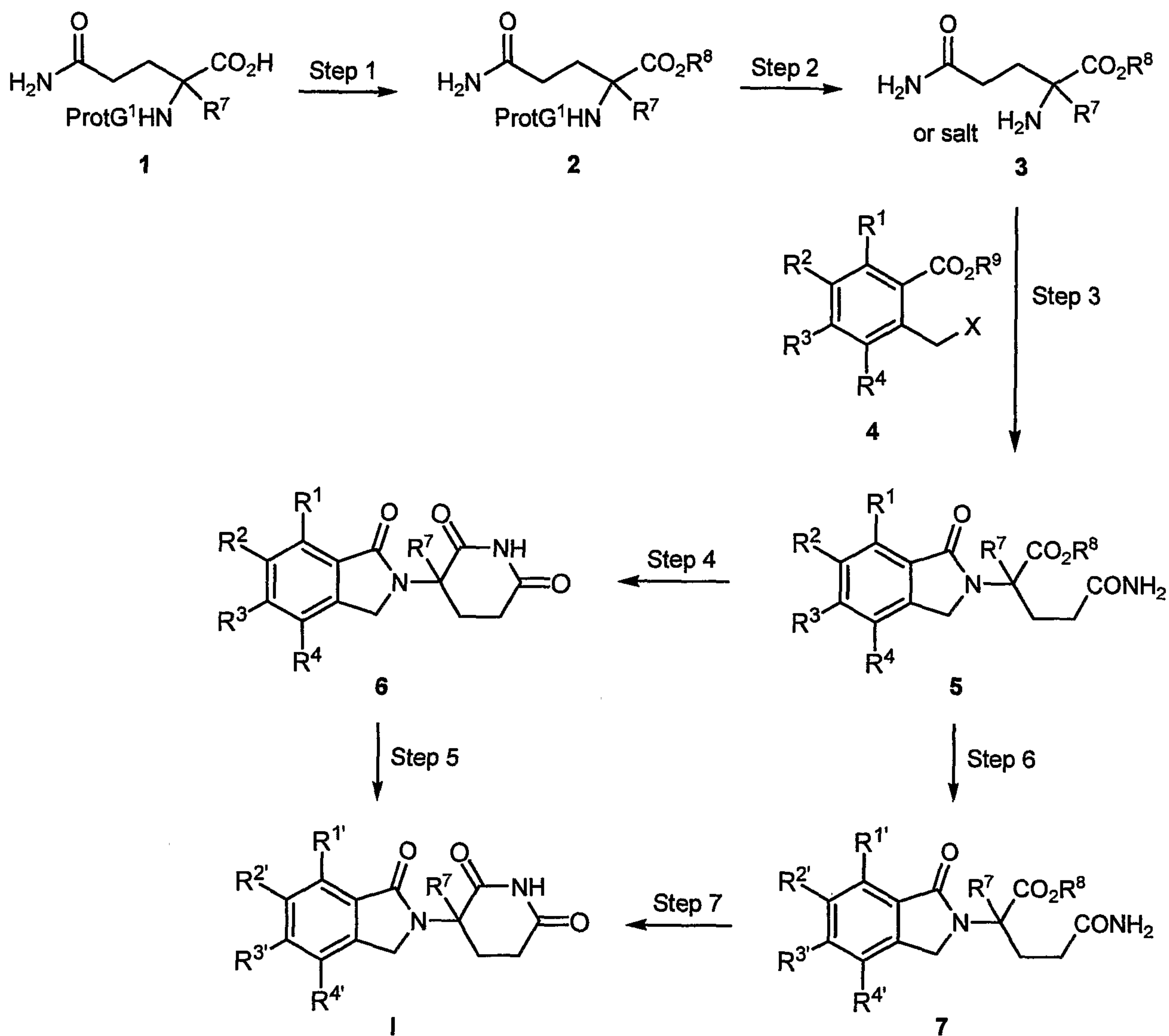
(d) R^8 is hydrogen, alkyl, or benzyl;

(e) R^9 is alkyl;

(f) X is halo; and

(g) each of $ProtG^1$ and $ProtG^2$ is at each occurrence independently a suitable *N*-protecting group.

[049] $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ denote that one or more of the R^1 , R^2 , R^3 , and/or R^4 substituents are optionally transformed to the corresponding $R^{1'}$, $R^{2'}$, $R^{3'}$, and/or $R^{4'}$ substituents, respectively, in one or more steps.



Scheme 1

[050] In one embodiment of Scheme 1:

(a) each of R^1 , R^2 , R^3 , R^4 , $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ is at each occurrence independently hydrogen, lower molecular weight halo, lower alkyl, lower alkoxy, $-\text{NO}_2$, $-\text{NHProtG}^2$, or $-\text{NR}^5\text{R}^6$;

(b) each of R^5 and R^6 is at each occurrence independently hydrogen or lower alkyl;

(c) R^7 is hydrogen or lower alkyl;

(d) R^8 is hydrogen, lower alkyl, or benzyl;

(e) R⁹ is lower alkyl;

(f) X is higher molecular weight halo; and

(g) each of ProtG¹ and ProtG² is at each occurrence independently a suitable acyl *N*-protecting group.

[051] In another embodiment of Scheme 1:

(a) each of R¹, R², R³, and R⁴ is at each occurrence independently hydrogen, -NO₂, or -NHProtG²;

(b) each of R^{1'}, R^{2'}, R^{3'}, and R^{4'} is at each occurrence independently hydrogen, -NHProtG², or -NH₂;

(c) R⁷ is hydrogen or methyl;

(d) R⁸ is hydrogen or methyl;

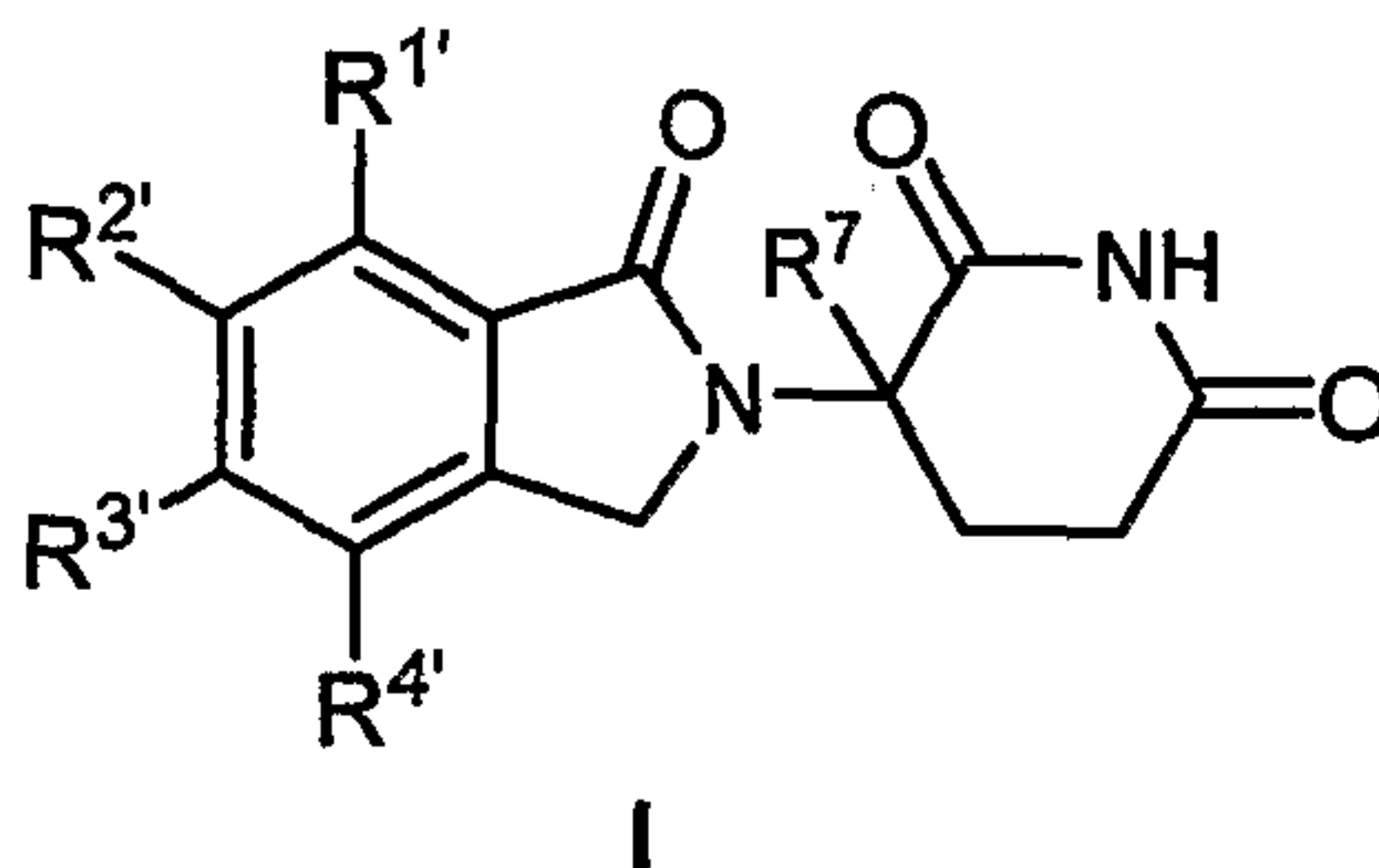
(e) R⁹ is methyl;

(f) X is bromo;

(g) ProtG¹ is Cbz or Boc; and

(h) ProtG² is Cbz, Boc, formyl, acetyl, trifluoroacetyl, or pivaloyl.

[052] In one embodiment, the invention relates to a process for preparing a compound of Formula I:



or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein:

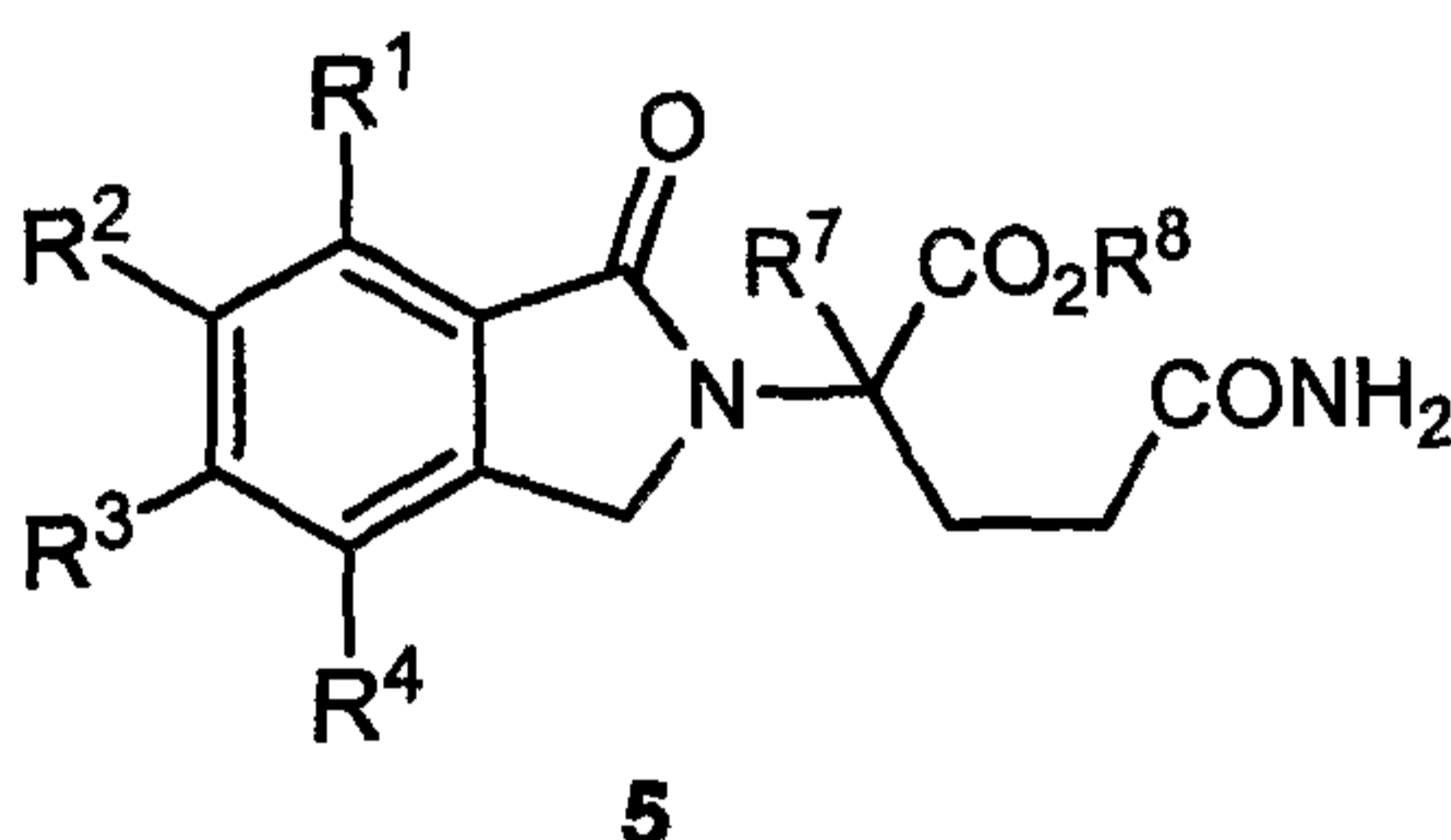
each of R^{1'}, R^{2'}, R^{3'}, and R^{4'} is at each occurrence independently hydrogen, halo, alkyl, alkoxy, -CF₃, -CN, -NO₂, -NHProtG², or -NR⁵R⁶;

each of R⁵ and R⁶ is at each occurrence independently hydrogen or alkyl;

R⁷ is hydrogen, halo, alkyl, or benzyl; and

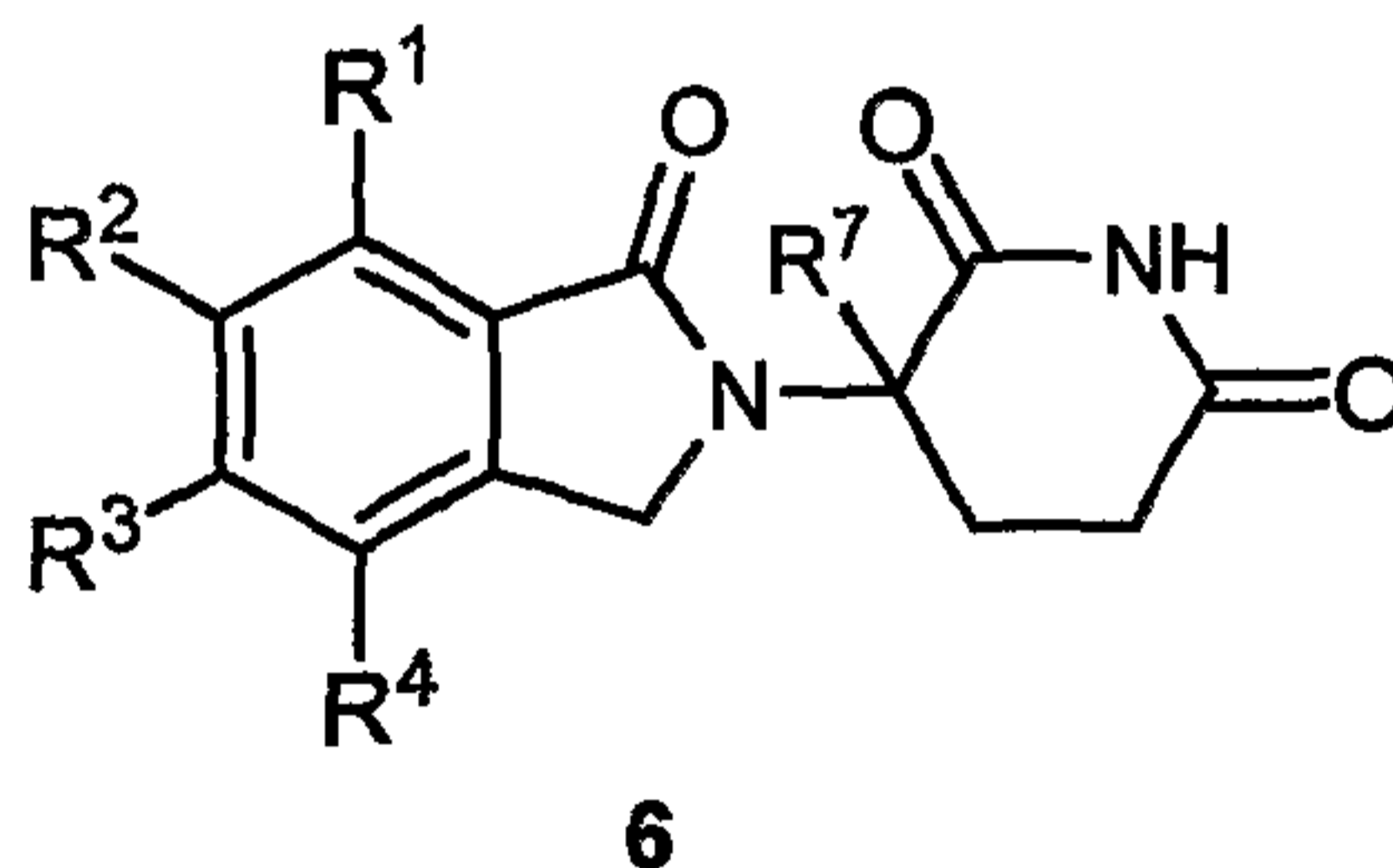
ProtG² is a suitable *N*-protecting group,
which comprises the alternative sequences of steps of:

(1)(a) cyclizing a compound of Formula 5:



and

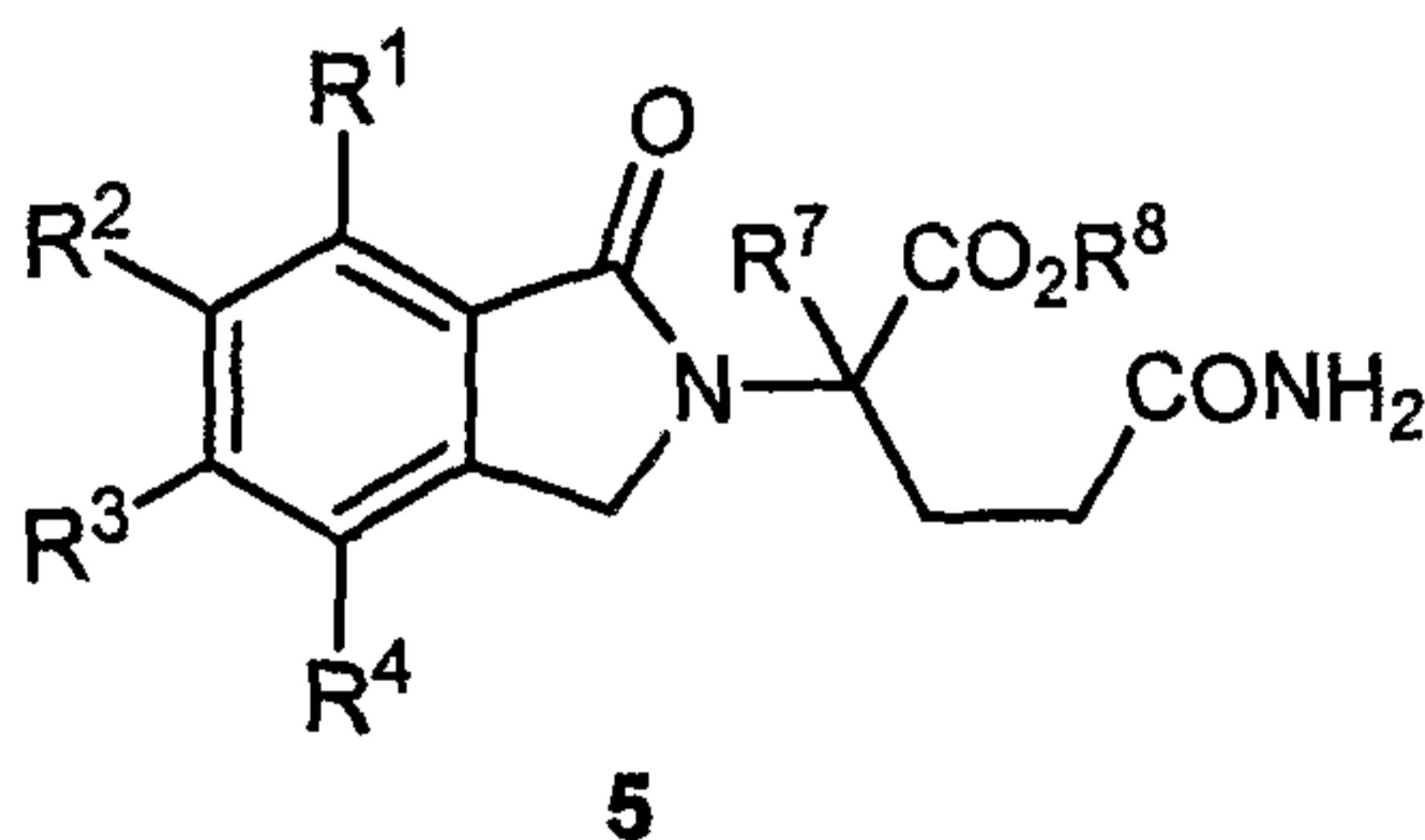
(b) optionally transforming one or more of the R¹, R², R³, and/or R⁴ substituents of the cyclized product of Formula 6:



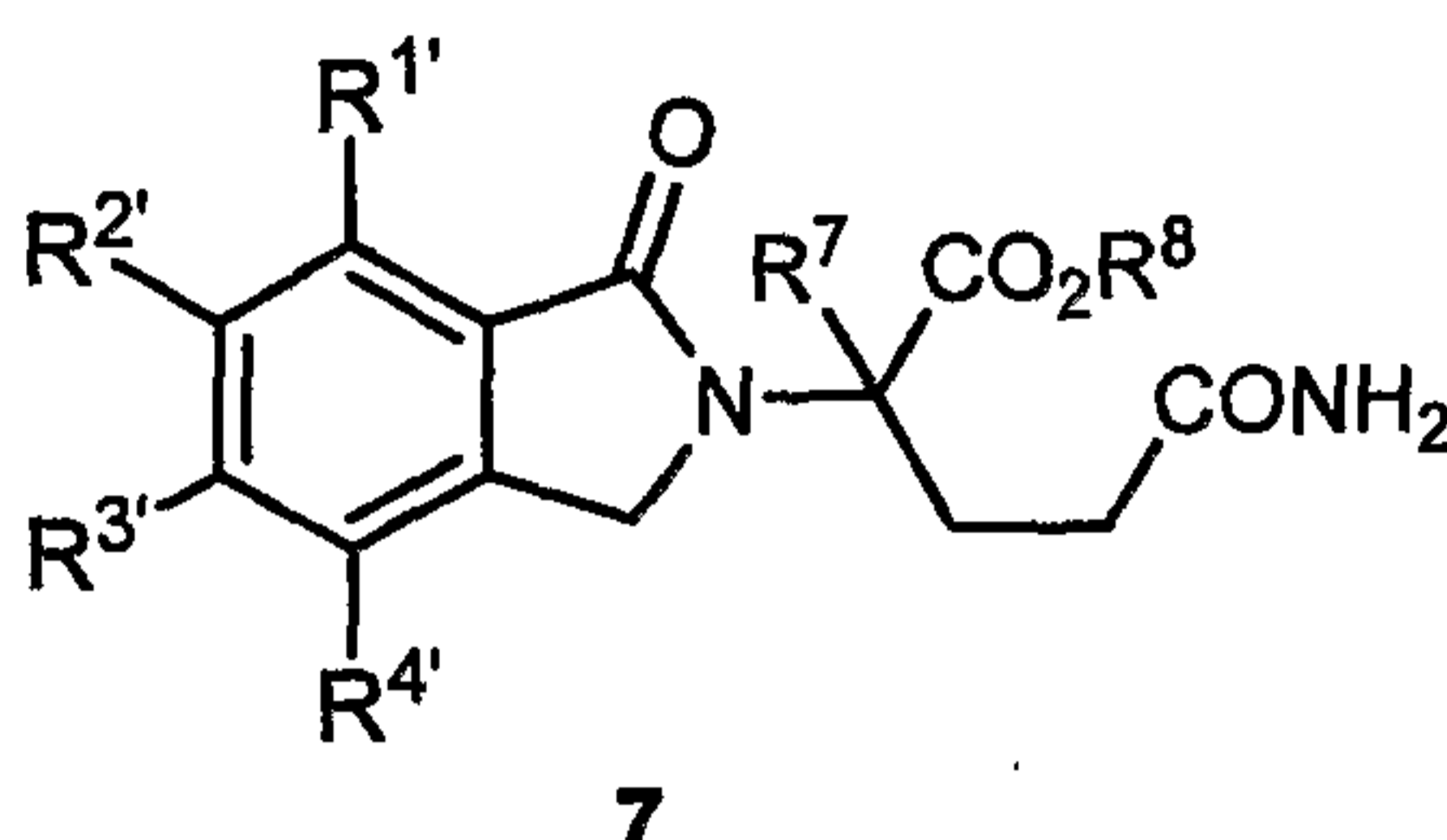
into one or more of the corresponding R^{1'}, R^{2'}, R^{3'}, and/or R^{4'} substituents, respectively, of the compound of Formula I in one or more steps,

or:

(2)(a) transforming one or more of the R¹, R², R³, and/or R⁴ substituents of a compound of Formula 5:



into one or more of the corresponding R^1 , R^2 , R^3 , and/or R^4 substituents, respectively, of a compound of Formula 7:



in one or more steps, and

(b) cyclizing the transformed product of Formula 7,

wherein, for both sequences of steps unless noted otherwise:

each of R^1 , R^2 , R^3 , R^4 , $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ is at each occurrence independently hydrogen, halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;

R^7 is hydrogen, halo, alkyl, or benzyl;

R^8 is alkyl or benzyl for sequence (1) and is hydrogen, alkyl, or benzyl for sequence (2); and

$ProtG^2$ is a suitable *N*-protecting group.

[053] In one embodiment of Scheme 1, an *N*-protected glutamine 1 is esterified in step 1. The *N*-protected glutamine may be commercially available or prepared by protecting the

α -amino group of a glutamine as is known in the art (See, *e.g.*, T. W. Green, "Protective Groups in Organic Synthesis", Third Ed., Wiley, New York, 1999). In one embodiment, $ProtG^1$ is a suitable *N*-protecting group and R^8 is lower alkyl or benzyl. In a particular embodiment, $ProtG^1$ is Cbz and R^8 is methyl. The selection of R^8 and of the conditions for esterification depends, *inter alia*, upon the nature of the *N*-blocking group. In one embodiment, $ProtG^1$ is Fmoc, R^8 is

t-butyl, and esterification is conducted employing 2-methyl-prop-1-ene and a catalytic

amount of acid. In another embodiment, ProtG¹ is Boc, R⁸ is methyl, and esterification is effected using MeI and DBU.

[054] In yet another embodiment, ProtG¹ is Cbz, R⁸ is lower alkyl, and esterification is conducted in the corresponding lower alcohol under acidic condition. In a further embodiment, esterification is conducted in the lower alcohol in the presence of catalytic amount of activating agent(s). In a particular embodiment, the activating agent is TMSCl. In another particular embodiment, the activating agent is acetyl chloride. In yet another particular embodiment, the activating agents are TMSCl and acetyl chloride. Esterification in the lower alcohol is performed at an elevated temperature in one embodiment. In a particular embodiment, esterification in the lower alcohol is performed at a temperature at which the lower alcohol refluxes. Esterification in the lower alcohol is generally conducted until the reaction is substantially complete. In an embodiment, esterification in the lower alcohol is conducted for at least about 4 hours. In a particular embodiment, ProtG¹ is Cbz, R⁸ is methyl, and esterification is conducted in methanol.

[055] In step 2 of Scheme 1, the *N*-protecting group of ester 2 is cleaved. In one embodiment, *N*-deprotected ester 3 is a free amine. In another embodiment, *N*-deprotected ester 3 is an acid addition salt. In a particular embodiment, *N*-deprotected ester 3 is a hydrochloride salt. The selection of ProtG¹ and of the conditions for the cleavage of the *N*-blocking group depends, *inter alia*, upon the nature of the ester group R⁸. In one embodiment, R⁸ is lower alkyl or benzyl, ProtG¹ is Boc, and the *N*-Boc group is cleaved under acidic condition. In a particular embodiment, the *N*-Boc group is cleaved using TFA. In another particular embodiment, the *N*-Boc group is cleaved using HCl. In another embodiment, R⁸ is *t*-butyl, ProtG¹ is Fmoc, and the *N*-Fmoc group is cleaved under basic condition. In an embodiment, the *N*-Fmoc group is cleaved using piperidine.

[056] In a further embodiment, R⁸ is lower alkyl, ProtG¹ is Cbz, and the *N*-Cbz group is cleaved by catalytic hydrogenolysis under hydrogen. In one embodiment, the *N*-Cbz group is cleaved using a metal catalyst. In a further embodiment, the metal catalyst is a Pd catalyst. In a particular embodiment, the catalyst is 5% Pd/C. In another particular embodiment, the catalyst is 10% Pd/C. The hydrogenolysis is generally conducted under a hydrogen pressure that drives the reaction to substantial completion. In an embodiment, the hydrogenolysis is

conducted under a hydrogen pressure of about 40 to 50 psi. The hydrogenolysis is done in a protic solvent in one embodiment. In a further embodiment, the protic solvent is a lower alcohol. In a particular embodiment, the solvent is methanol. In another particular embodiment, the solvent is ethanol. The hydrogenolysis is done in an aprotic solvent in another embodiment. In a particular embodiment, the aprotic solvent is ethyl acetate. The hydrogenolysis is done in a mixture of protic solvent and aprotic solvent in yet another embodiment. In an embodiment, the mixture of protic and aprotic solvents comprises a lower alcohol and ethyl acetate. In a particular embodiment, the mixture of protic and aprotic solvents comprises methanol and ethyl acetate. In another particular embodiment, the mixture of protic and aprotic solvents comprises ethanol and ethyl acetate. The hydrogenolysis is performed in the absence of added acid in one embodiment. In another embodiment, the hydrogenolysis is performed in the presence of added acid. In a particular embodiment, the added acid is HCl. The hydrogenolysis is generally conducted until the reaction is substantially complete. In one embodiment, the hydrogenolysis is conducted for at least about 3 hours.

[057] In another embodiment of Scheme 1, ester 3 may be formed directly from a glutamine whose amino and carboxyl groups are unprotected. Ester 3 is a free amine in one embodiment. In another embodiment, ester 3 is an acid addition salt. In a particular embodiment, ester 3 is a hydrochloride salt. In one embodiment, R⁸ is lower alkyl and esterification occurs in the corresponding lower alcohol under acidic condition. In a further embodiment, esterification is conducted in the lower alcohol in the presence of catalytic amount of activating agent(s). In a particular embodiment, the activating agent is TMSCl. In another particular embodiment, the activating agent is acetyl chloride. In yet another particular embodiment, the activating agents are TMSCl and acetyl chloride. Esterification in the lower alcohol is performed at an elevated temperature in one embodiment. In a particular embodiment, esterification in the lower alcohol is performed at a temperature at which the lower alcohol refluxes. Esterification in the lower alcohol is generally conducted until the reaction is substantially complete. In an embodiment, esterification in the lower alcohol is conducted for at least about 4 hours. In a particular embodiment, R⁸ is methyl, and esterification is conducted in methanol. Furthermore, an acid addition salt of ester 3 may be commercially available, such as glutamine methyl ester hydrochloride.

[058] In step 3 of Scheme 1, a benzyl halide 4 is coupled to a free amine 3 in one embodiment or to an acid addition salt 3 in another embodiment. The coupling occurs in the presence of a base in one embodiment. In one embodiment, the base is an alkyl amine. In a particular embodiment, the base is NEt_3 . In a further embodiment, the base is iPrEt_2N . In another embodiment, the base is a carbonate or bicarbonate. In a particular embodiment, the base is NaHCO_3 . In yet another embodiment, the base is a pyridine. In a particular embodiment, the base is 4-DMAP. The coupling is conducted in a polar solvent in one embodiment. In a further embodiment, the polar solvent is aprotic. In a particular embodiment, the solvent is DMF. In another particular embodiment, the solvent is acetonitrile. In yet another particular embodiment, the solvent is THF. The coupling is performed at ambient temperature in one embodiment. In another embodiment, the coupling is performed at elevated temperature. In a particular embodiment, the coupling is performed at a temperature at which the solvent refluxes. The coupling is generally conducted until the reaction is substantially complete. In one embodiment, the coupling is conducted for at least about 1 hour.

[059] Benzyl halide 4 can be generated by halogenating the corresponding optionally substituted 2-alkylbenzoate. X is halo in one embodiment. In another embodiment, X is higher molecular weight halo. In a particular embodiment, X is bromo and benzyl bromide 4 is prepared by brominating the corresponding optionally substituted 2-alkylbenzoate with a brominating agent in the presence of a radical initiator. In a particular embodiment, the brominating agent is NBS. The radical initiator is light in a particular embodiment and VAZO[®] (*i.e.*, 1,1'-azobis-(cyclohexanecarbonitrile)) in another particular embodiment. R^9 is lower alkyl in an embodiment. In a particular embodiment, R^9 is methyl.

[060] From common intermediate 5 in Scheme 1, cyclization to form the 2,6-piperidinedione ring and optional transformation of one or more benzo substituents R^1 , R^2 , R^3 , and/or R^4 in one or more steps can occur in different order. In one embodiment, cyclization transpires in step 4 prior to optional transformation of one or more benzo substituents in step 5 (which may comprise one or more steps). Both compounds 6 and I are substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines.

[061] In one embodiment, cyclization in step 4 of Scheme 1 occurs with an ester group as the accepting group. In an embodiment, R^8 is lower alkyl. In a particular

embodiment, R⁸ is methyl. Cyclization is effected in the presence of an acid in one embodiment. In a further embodiment, a catalytic amount of acid is used. In a particular embodiment, the acid is *p*-TsOH. Cyclization under acidic condition is conducted in an aprotic solvent in one embodiment. In a further embodiment, the aprotic solvent is apolar. In a particular embodiment, the solvent is toluene. Cyclization occurs at ambient temperature in an embodiment. In another embodiment, cyclization occurs at elevated temperature. In a particular embodiment, cyclization occurs at a temperature at which the solvent refluxes.

[062] Cyclization with an ester group as the accepting group occurs in the presence of a base in another embodiment. In one embodiment, the base is an alkoxide. In a further embodiment, the base is a sterically bulky alkoxide. In a particular embodiment, the base is KO^tBu. In another embodiment, the base is a carbonate. In a particular embodiment, the base is K₂CO₃. Cyclization under basic condition is conducted in an aprotic solvent in one embodiment. In a further embodiment, the aprotic solvent is polar. In a particular embodiment, the solvent is THF. In another particular embodiment, the solvent is acetonitrile. Cyclization is generally conducted at a temperature that drives the reaction to substantial completion. In an embodiment, cyclization is conducted at ambient temperature. In another embodiment, cyclization is conducted at a temperature below ambient temperature. In a particular embodiment, cyclization is conducted at between about 0 and 5 °C. Cyclization is conducted at elevated temperature in yet another embodiment. In a particular embodiment, cyclization is conducted at a temperature at which the solvent refluxes. Cyclization is generally performed until the reaction is substantially complete. In an embodiment, cyclization is performed for at least about 0.5 hour.

[063] In another embodiment, cyclization occurs with a carboxyl group as the accepting group (*i.e.*, R⁸ is hydrogen). In one embodiment, cyclization is effected with an activating agent that activates the carboxyl group. In a particular embodiment, the activating agent is thionyl chloride. In another particular embodiment, the activating agent is CDI. Cyclization is effected in the presence of a second activating agent in another embodiment. In a particular embodiment, the second activating agent is 4-DMAP. Cyclization occurs in the presence of a base in one embodiment. In an embodiment, the base is an alkyl amine. In a particular embodiment, the base is NEt₃. In a further embodiment, the base is *i*PrEt₂N. In another embodiment, the base belongs to the pyridine family of amines. In a particular

embodiment, the base is pyridine. Cyclization occurs in the presence of a mixture of bases in another embodiment. In an embodiment, the mixture of bases comprises an alkyl amine and an amine belonging to the pyridine family of amines. In a particular embodiment, the mixture of bases is NEt_3 and pyridine. Cyclization is conducted in an aprotic solvent in one embodiment. In a further embodiment, the aprotic solvent is polar. In a particular embodiment, the solvent is DCM. In another particular embodiment, the solvent is THF. Cyclization is generally conducted at a temperature that drives the reaction to substantial completion. In an embodiment, cyclization is conducted at a range of temperature below and including ambient temperature. In a particular embodiment, cyclization is conducted from about $-30\text{ }^\circ\text{C}$ to ambient temperature. Cyclization is conducted at elevated temperature in another embodiment. In a particular embodiment, cyclization is conducted at a temperature at which the solvent refluxes. Cyclization is generally performed until the reaction is substantially complete. In an embodiment, cyclization is performed for at least about 3 hours.

[064] If cyclization with a carboxyl group as the accepting group is desired, the carboxyl group can be generated from an ester group in various ways after coupling of amine or acid addition salt 3 to benzyl halide 4, depending upon, *inter alia*, the nature of the ester group and the nature of the other functional groups in intermediate 5. In one embodiment, R^8 is benzyl, and the benzyl ester is converted to a carboxyl group by hydrogenolysis with a catalyst. In an embodiment, the catalyst is a metal catalyst. In a further embodiment, the catalyst is a Pd catalyst and, in a particular embodiment, a Pd/C catalyst. In another embodiment, R^8 is *t*-butyl, and the *t*-butyl ester is converted to a carboxyl group in the presence of an acid. The acid is TFA in a particular embodiment and HCl in another particular embodiment. In yet another embodiment, R^8 is lower alkyl. R^8 is methyl in a particular embodiment. In an embodiment, the lower alkyl ester is converted to a carboxyl group in the presence of acid and water. In another embodiment, the lower alkyl ester is converted to a carboxyl group (after appropriate acidifying workup) in the presence of a base. In an embodiment, the base is a hydroxide. The base is LiOH in a particular embodiment, NaOH in another particular embodiment, and KOH in yet another particular embodiment.

[065] If a racemic substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline is desired, conducting the cyclization with an ester group as the accepting group under basic condition

offers an advantage. Base may racemize any chiral stereocenter to which R^7 is attached, where R^7 is hydrogen. Conversely, if an enantiomerically pure substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline is desired, conducting the cyclization with an ester group as the accepting group under acidic condition or with a carboxyl group as the accepting group in the presence of activating agent(s) may be beneficial. In these two latter scenarios, the reaction conditions may result in retention of the stereochemistry of any chiral stereocenter to which R^7 is attached.

[066] After cyclization to form the glutarimide ring, one or more benzo R^1 , R^2 , R^3 , and/or R^4 substituents may optionally be transformed to the corresponding $R^{1'}$, $R^{2'}$, $R^{3'}$, and/or $R^{4'}$ substituents, respectively, in one or more steps (summarized as step 5 of Scheme 1). In one embodiment, one of R^1 , R^2 , R^3 , or R^4 is $-\text{NO}_2$ and it is reduced to $-\text{NH}_2$ for the corresponding $R^{1'}$, $R^{2'}$, $R^{3'}$, or $R^{4'}$, respectively. In a particular embodiment, R^4 is $-\text{NO}_2$ and it is reduced to $-\text{NH}_2$ for $R^{4'}$. The reduction of $-\text{NO}_2$ to $-\text{NH}_2$ is effected under hydrogen with a metal catalyst in one embodiment. In a further embodiment, the catalyst is a Pd catalyst. In a particular embodiment, the catalyst is 10% Pd/C. In another particular embodiment, the catalyst is 5% Pd/C. The reduction is conducted in a protic solvent in one embodiment. In a further embodiment, the protic solvent is an alcohol, in one embodiment a lower alcohol. The solvent is ethanol in a particular embodiment and methanol in another particular embodiment. In another embodiment the solvent is propanol, isopropanol, butanol, isobutanol or *t*-butanol. In another embodiment, the reduction is conducted in an apolar, aprotic solvent. The solvent is 1,4-dioxane in a particular embodiment. In yet another embodiment, the reduction is conducted in a polar, aprotic solvent. The solvent is acetone in a particular embodiment. In another embodiment, the solvent is DMSO, DMF or THF. The reduction is generally carried out at a hydrogen pressure that drives the reaction to substantial completion. In a particular embodiment, the reduction is carried out at a hydrogen pressure between about 40 and 50 psi. In an embodiment, the reduction is run at ambient temperature. The reduction is generally performed until the reaction is substantially complete. In an embodiment, the reduction is performed for at least about 2 hours.

[067] In another embodiment, one of R^1 , R^2 , R^3 , or R^4 is $-\text{NHProtG}^2$ and it is deprotected to give $-\text{NH}_2$ for the corresponding $R^{1'}$, $R^{2'}$, $R^{3'}$, or $R^{4'}$, respectively. In a particular embodiment, R^4 is $-\text{NHProtG}^2$ and it is deprotected to give $-\text{NH}_2$ for $R^{4'}$. In one

embodiment, the protecting group ProtG² for a benzo -NHProtG² substituent is an acyl group which is selectively removable under mild condition. ProtG² is formyl in a particular embodiment and acetyl in another particular embodiment. In a further embodiment, ProtG² is a lower alkanoyl group which is branched in the position α to the carbonyl group. ProtG² is pivaloyl in a particular embodiment and trifluoroacetyl in another particular embodiment. In a particular embodiment, a benzo -NHC(O)CF₃ group is deblocked under basic condition. In another embodiment, -NHProtG² is a carbamate. ProtG² is Boc in a particular embodiment and Cbz in another particular embodiment. In particular embodiments, a benzo -NHBoc group is deprotected under acidic condition and a benzo -NHCbz group is deblocked by hydrogenolysis with a catalyst.

[068] The choice of ProtG² depends, *inter alia*, upon the stability of the protecting group under reaction conditions where its cleavage is not desired and upon the stability of other functional groups under the conditions required to remove the protecting group. The various choices for ProtG² and the conditions to remove it are well known in the art, as, *e.g.*, described in T. W. Green, "Protective Groups in Organic Synthesis", Third Ed., Wiley, New York, 1999. Substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines with benzo -NHProtG² substituent(s) intact may also exhibit biological properties, and thus the removal of ProtG² may not be desired.

[069] From common intermediate 5 in Scheme 1, one or more benzo R¹, R², R³, and/or R⁴ substituents can alternatively be transformed to the corresponding R^{1'}, R^{2'}, R^{3'}, and/or R^{4'} substituents, respectively, in one or more steps (summarized as step 6) before cyclization of oxoisindoline 7 in step 7 produces substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoline I. The above description of cyclization in step 4 and transformation of benzo substituent(s) in step 5 and further embodiments described herein for steps 4 and 5 generally apply to transformation of benzo substituent(s) in step 6 and cyclization in step 7. Furthermore, if cyclization is done in step 7 with a carboxyl group as the accepting group, compound 7 having R⁸ as hydrogen can be generated from the corresponding compound 7 having R⁸ as alkyl or benzyl.

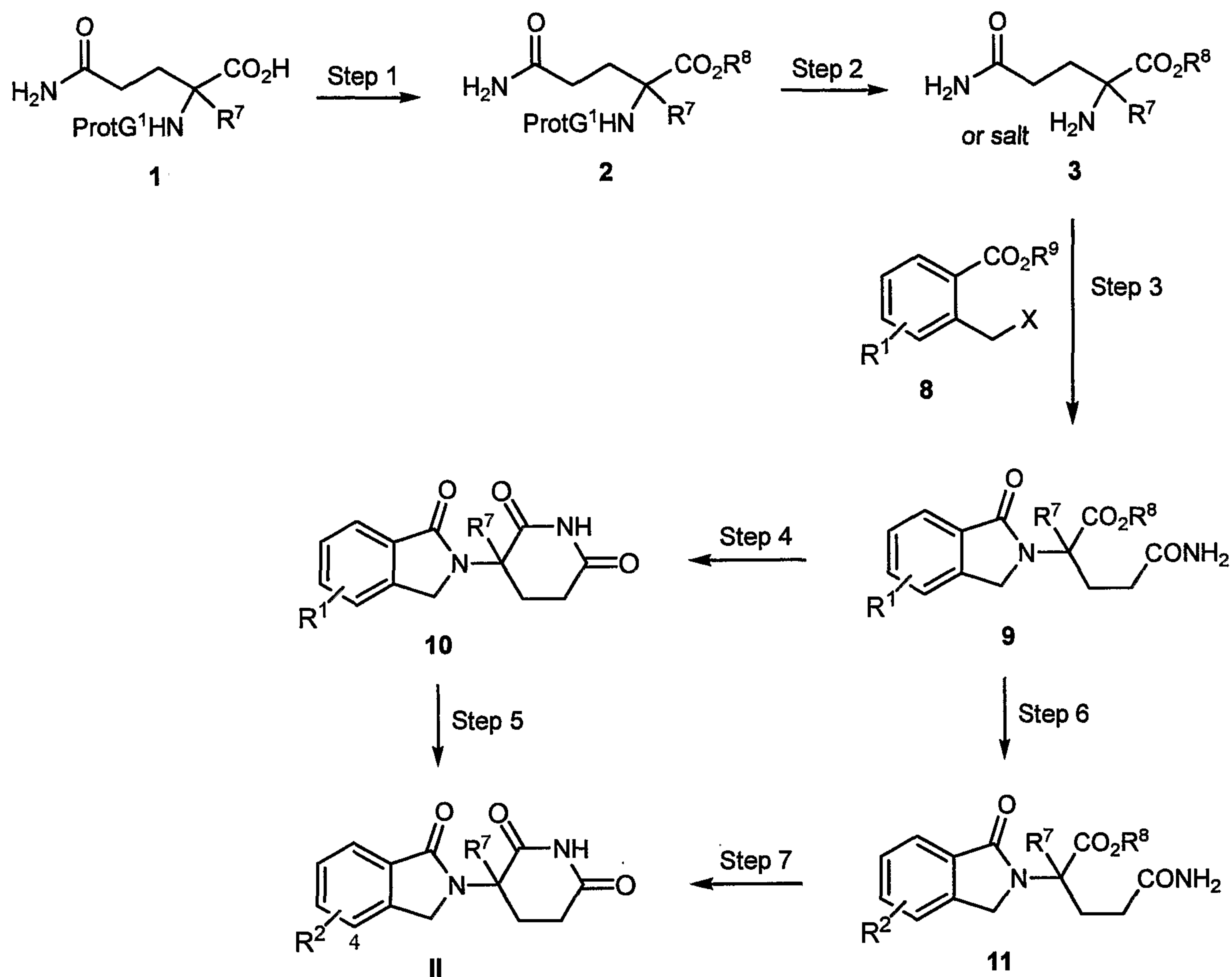
[070] Whether cyclization is performed prior to conversion of benzo substituent(s) or conversion of benzo substituent(s) is performed prior to cyclization may depend upon various factors. For example, if transformation of a benzo substituent results in another substituent

that is not compatible with desired conditions for cyclization, then conducting cyclization in step 4 prior to transformation of the benzo substituent in step 5 may be desired.

[071] Scheme 2 illustrates particular embodiments of the synthesis of mono-benzo-substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines. In these embodiments:

- (a) each of R^1 and R^2 is at each occurrence independently halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$, and can occupy any position on the benzo ring;
- (b) each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;
- (c) R^7 is hydrogen, halo, alkyl, or benzyl;
- (d) R^8 is hydrogen, alkyl, or benzyl;
- (e) R^9 is alkyl;
- (f) X is halo; and
- (g) each of $ProtG^1$ and $ProtG^2$ is at each occurrence independently a suitable *N*-protecting group.

R^2 denotes that R^1 may optionally be transformed to R^2 .



Scheme 2

[072] In one embodiment of Scheme 2:

(a) each of R^1 and R^2 is at each occurrence independently lower molecular weight halo, lower alkyl, lower alkoxy, $-\text{NO}_2$, $-\text{NHProtG}^2$, or $-\text{NR}^5\text{R}^6$, and can occupy any position on the benzo ring;

(b) each of R^5 and R^6 is at each occurrence independently hydrogen or lower alkyl;

(c) R^7 is hydrogen or lower alkyl;

(d) R^8 is hydrogen, lower alkyl, or benzyl;

(e) R^9 is lower alkyl;

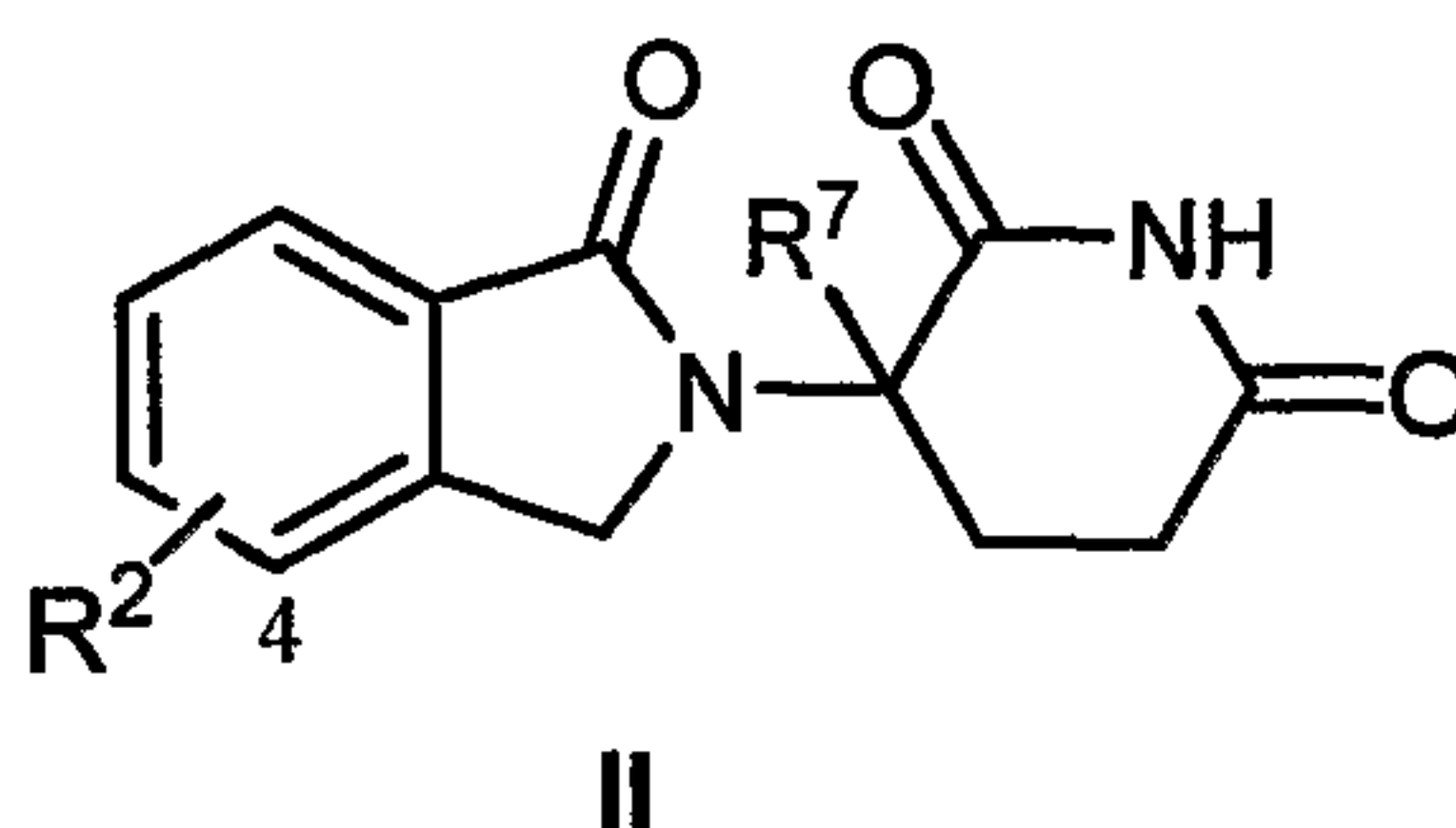
(f) X is higher molecular weight halo; and

(g) each of ProtG¹ and ProtG² is at each occurrence independently a suitable acyl *N*-protecting group.

[073] In another embodiment of Scheme 2:

- (a) R¹ is -NO₂ or -NHProtG² and can occupy any position on the benzo ring;
- (b) R² is -NH₂ and occupies the same position on the benzo ring as R¹;
- (c) R⁷ is hydrogen or methyl;
- (d) R⁸ is hydrogen or methyl;
- (e) R⁹ is methyl;
- (f) X is bromo;
- (g) ProtG¹ is Cbz or Boc; and
- (h) ProtG² is Cbz, Boc, formyl, acetyl, trifluoroacetyl, or pivaloyl.

[074] In one embodiment, the invention relates to a process for preparing a compound of Formula II:



or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein:

R² is halo, alkyl, alkoxy, -CF₃, -CN, -NO₂, -NHProtG², or -NR⁵R⁶;

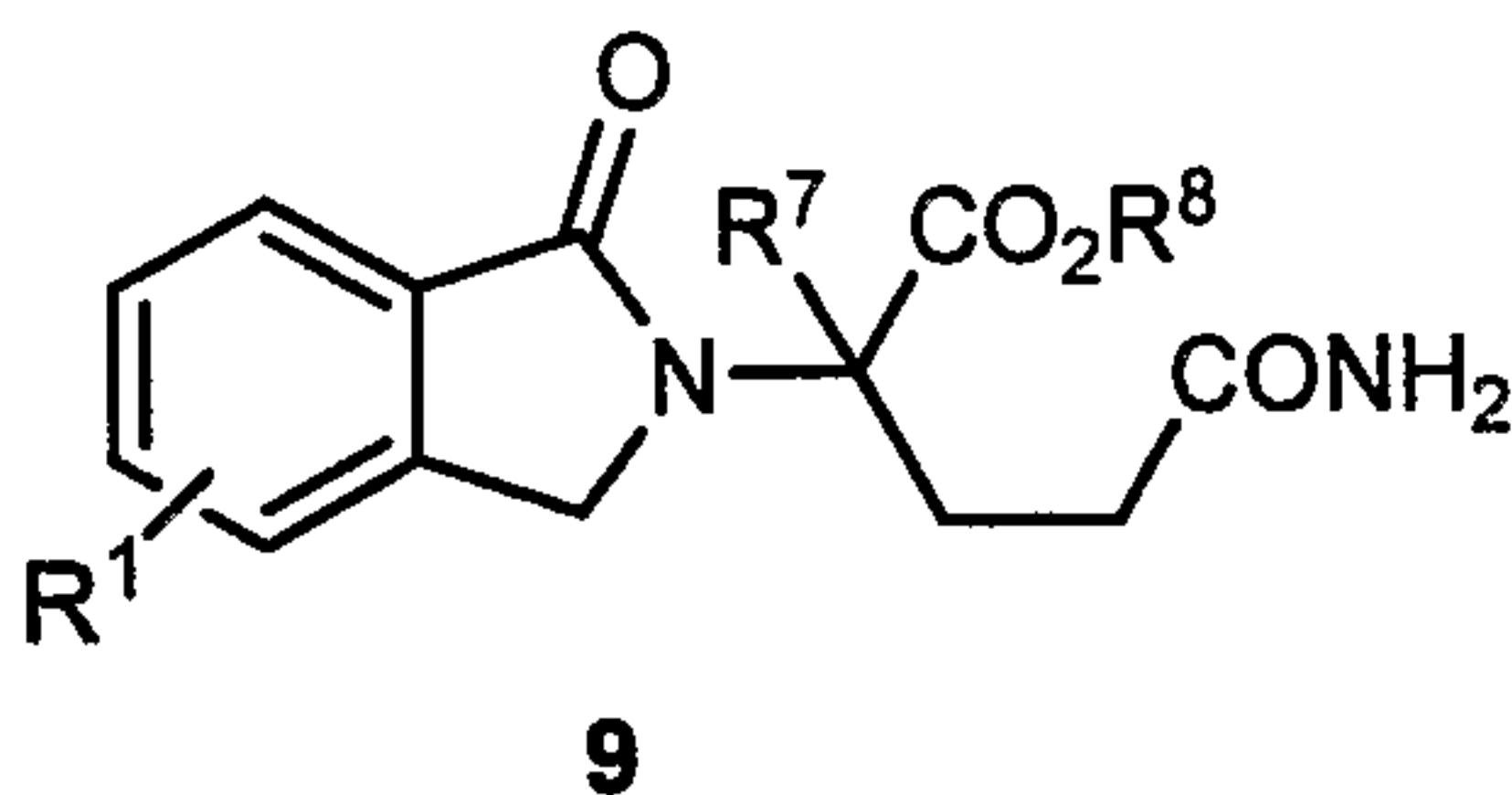
each of R⁵ and R⁶ is at each occurrence independently hydrogen or alkyl;

R⁷ is hydrogen, halo, alkyl, or benzyl; and

ProtG² is a suitable *N*-protecting group,

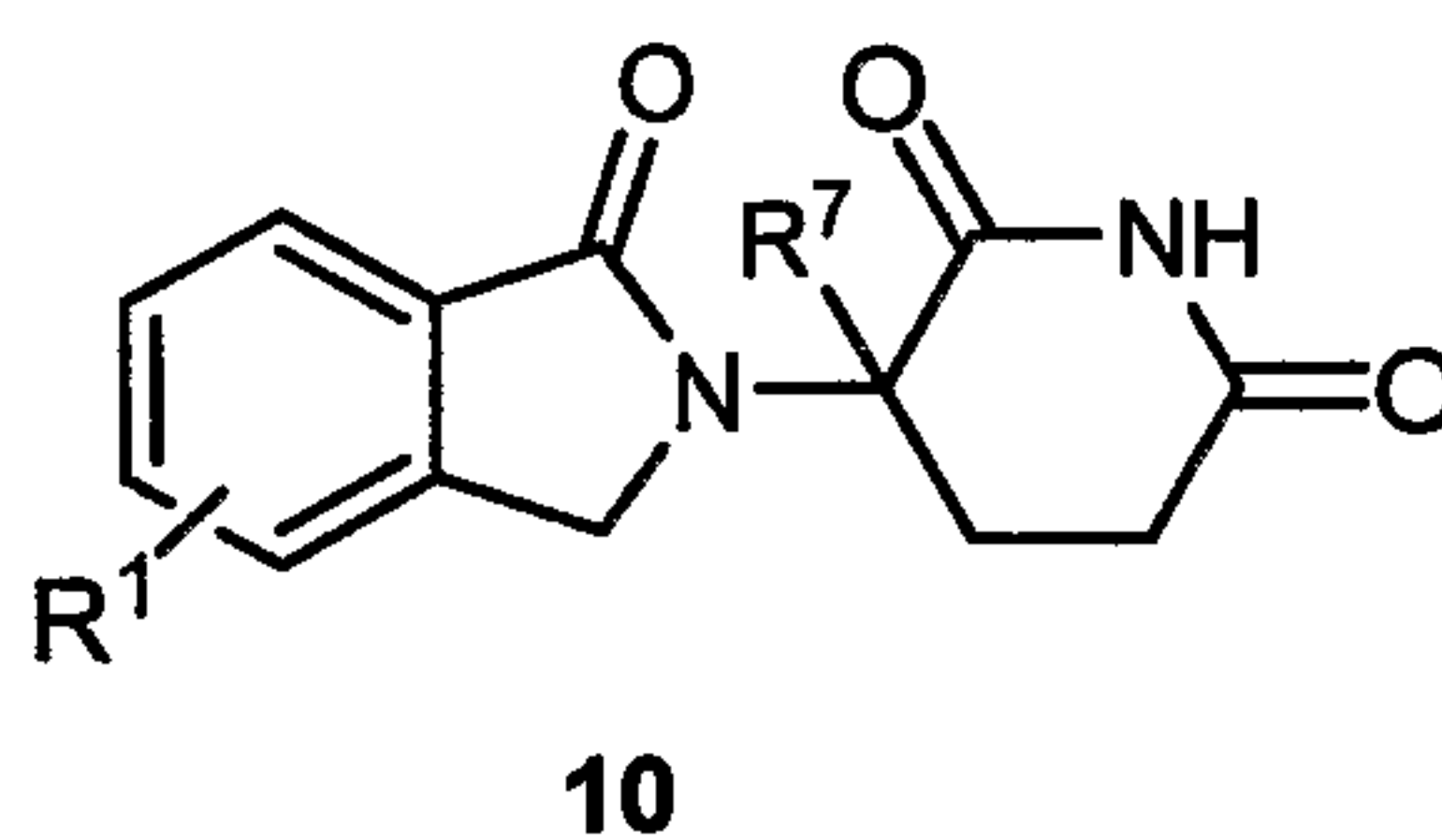
which comprises the alternative sequences of steps of:

(1)(a) cyclizing a compound of Formula 9:



and

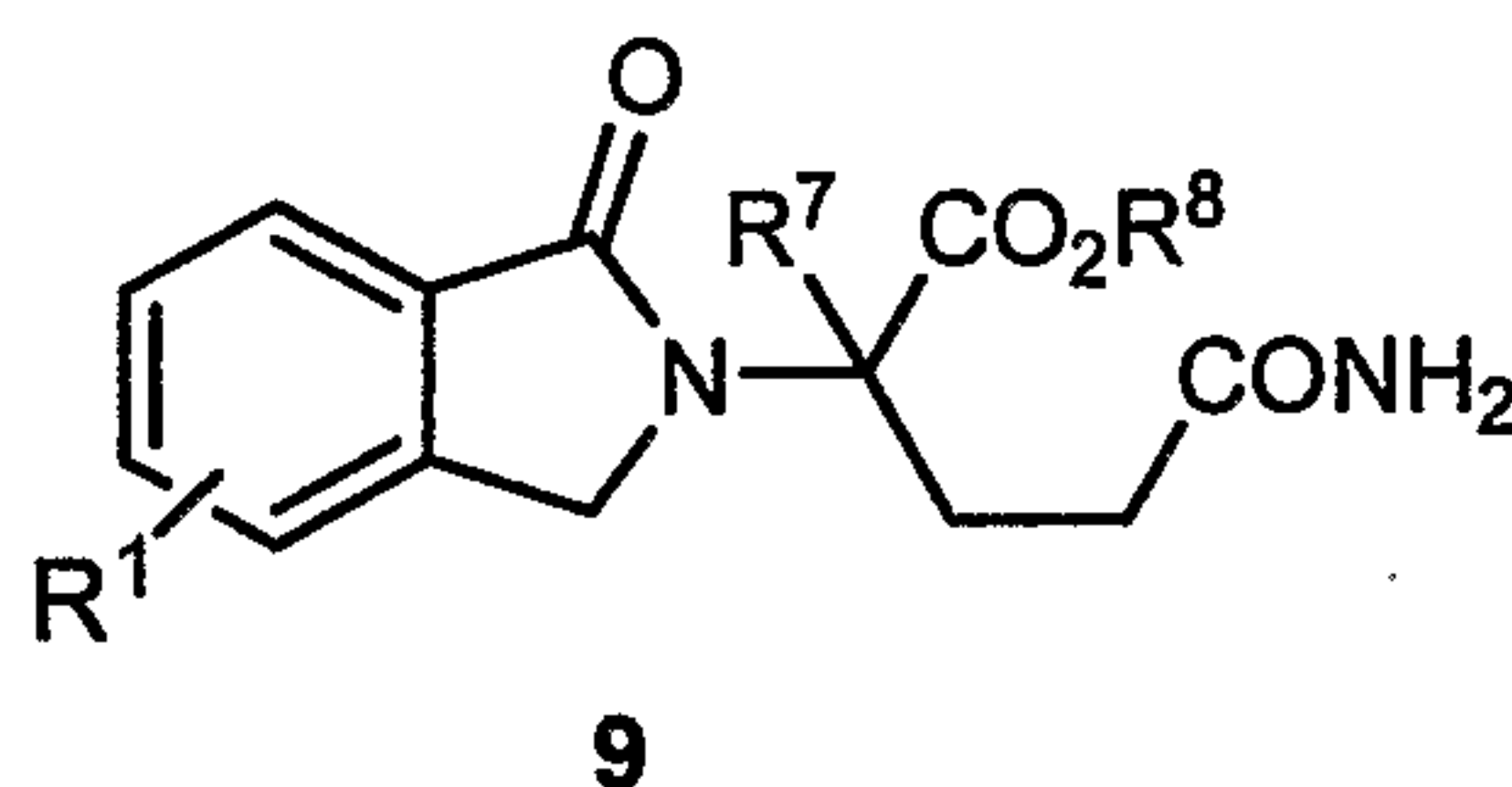
(b) optionally transforming the R¹ substituent of the cyclized product of Formula 10:



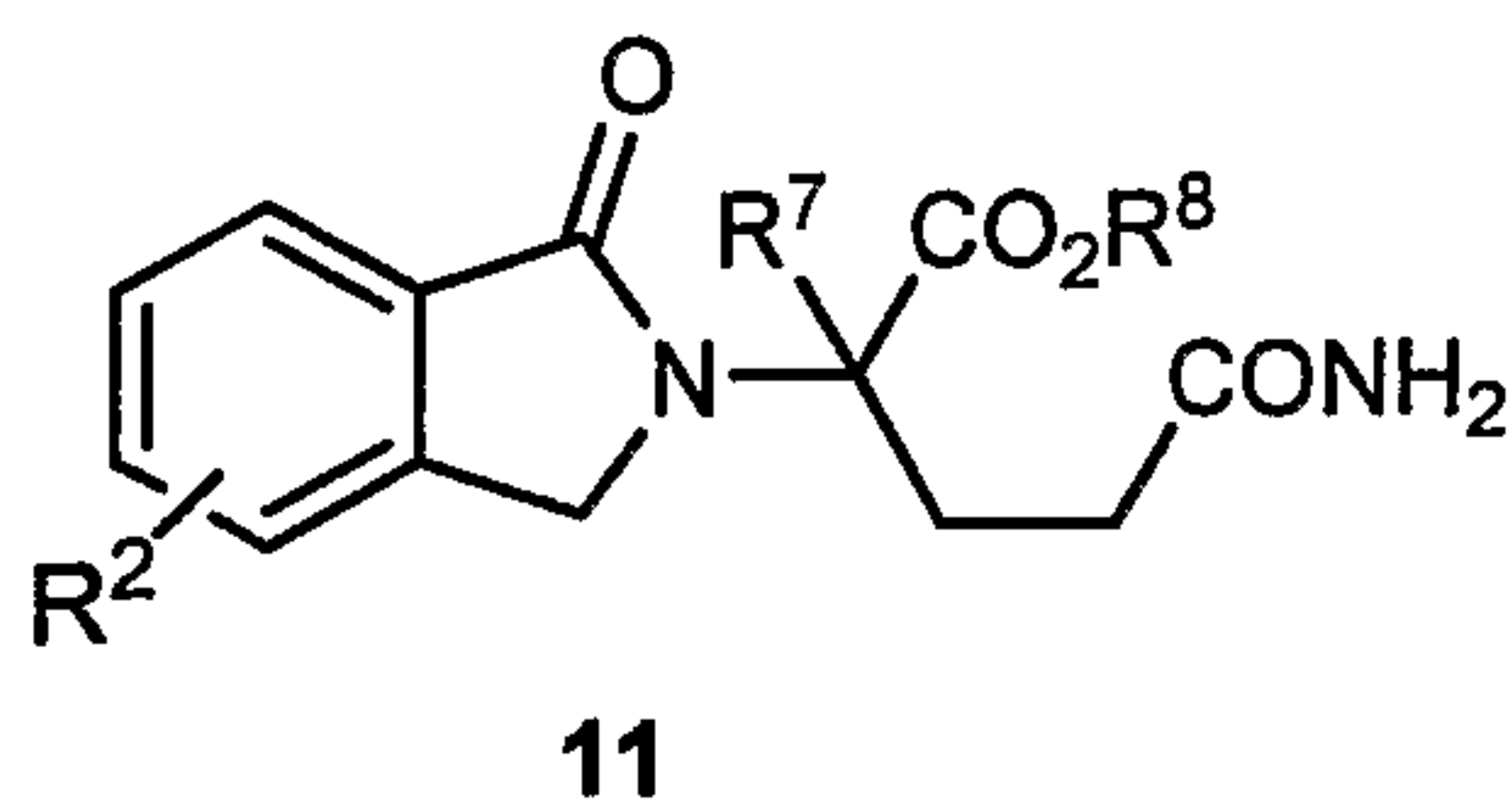
into the R² substituent of the compound of Formula II,

or:

(2)(a) transforming the R¹ substituent of a compound of Formula 9:



into the R² substituent of a compound of Formula 11:



and

(b) cyclizing the transformed product of Formula 11, wherein, for both sequences of steps unless noted otherwise:

each of R¹ and R² is at each occurrence independently halo, alkyl, alkoxy, -CF₃, -CN, -NO₂, -NHProtG², or -NR⁵R⁶;

each of R⁵ and R⁶ is at each occurrence independently hydrogen or alkyl;

R⁷ is hydrogen, halo, alkyl, or benzyl;

R⁸ is alkyl or benzyl for sequence (1) and is hydrogen, alkyl, or benzyl for sequence (2); and

ProtG² is a suitable *N*-protecting group.

[075] The description of Scheme 1 and further embodiments described herein for Scheme 1 generally apply to Scheme 2. Specifically, the description of steps 1, 2, 3, 4, 5, 6, and 7 in Scheme 1 and further embodiments described herein for Scheme 1 generally apply to the corresponding steps 1, 2, 3, 4, 5, 6, and 7, respectively, in Scheme 2.

[076] Cyclization to form the 2,6-piperidinedione ring and optional transformation of benzo substituent R¹ to R² can occur in different order from common intermediate 9 in Scheme 2. In one embodiment, cyclization transpires in step 4 prior to transformation of the benzo substituent in step 5. Both compounds 10 and II are mono-benzo-substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines. In another embodiment, the benzo substituent is transformed in step 6 before cyclization in step 7 produces II.

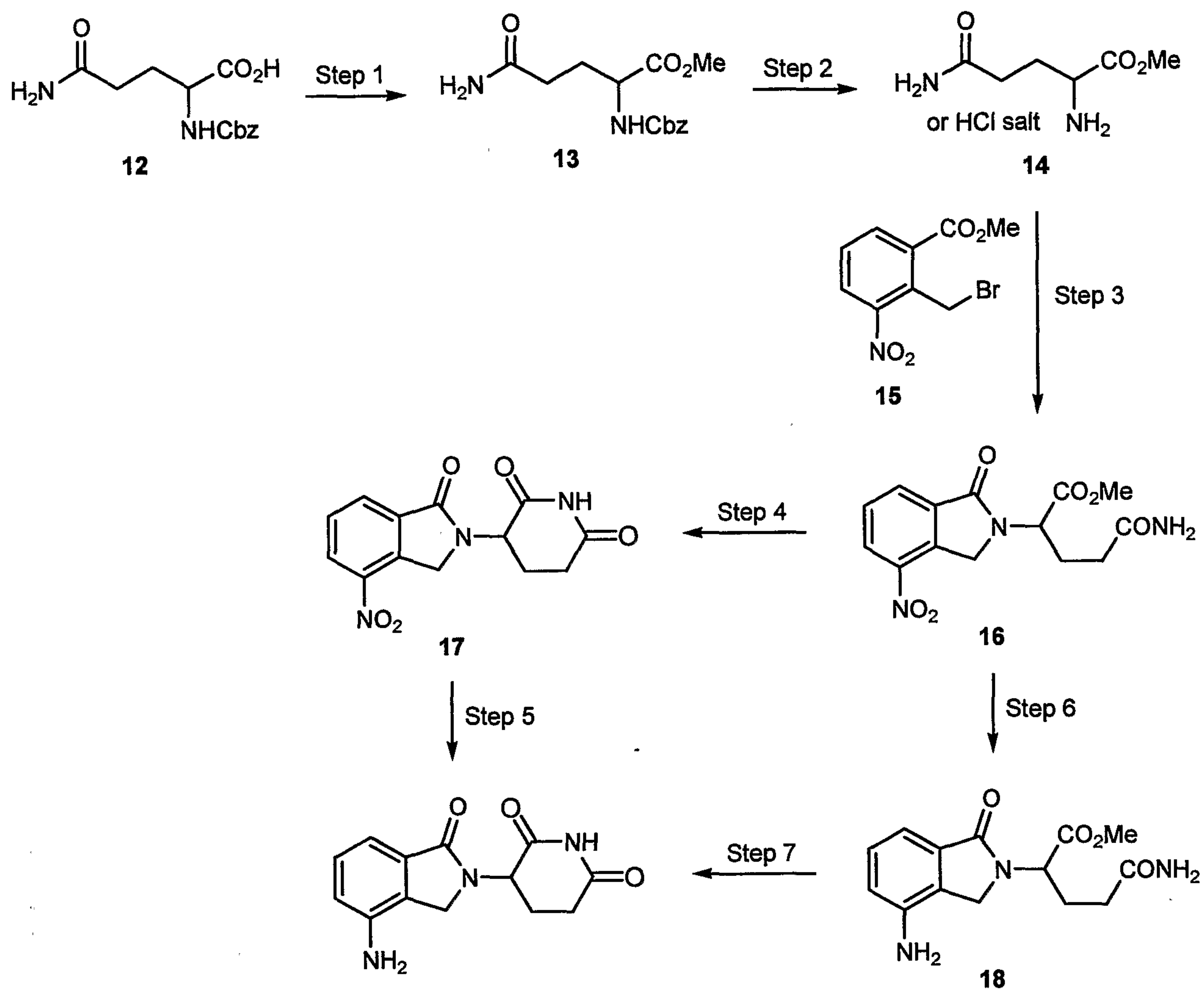
[077] Cyclization of the glutamine side chain in step 4 or step 7 of Scheme 2 can be effected in various ways. In one embodiment, cyclization occurs under acidic condition with an ester group (*e.g.*, R⁸ is lower alkyl) as the accepting group. In another embodiment, cyclization occurs under basic condition with an ester group (*e.g.*, R⁸ is lower alkyl) as the accepting group. Under acidic or basic condition, R⁸ is methyl in a particular embodiment. In yet another embodiment, cyclization occurs in the presence of activating agent(s) with a carboxyl group (*i.e.*, R⁸ is hydrogen) as the accepting group.

[078] The choice of cyclization conditions may depend, *inter alia*, upon the desired stereochemistry of the cyclized product. Cyclization with an ester group as the accepting group under basic conditions may result in racemization of any chiral stereocenter to which R⁷ is attached, where R⁷ is hydrogen. By contrast, cyclization with an ester group as the accepting group under acidic conditions or with a carboxyl group as the accepting group in

the presence of activating agent(s) may lead to retention of the stereochemistry of any chiral stereocenter to which R⁷ is attached.

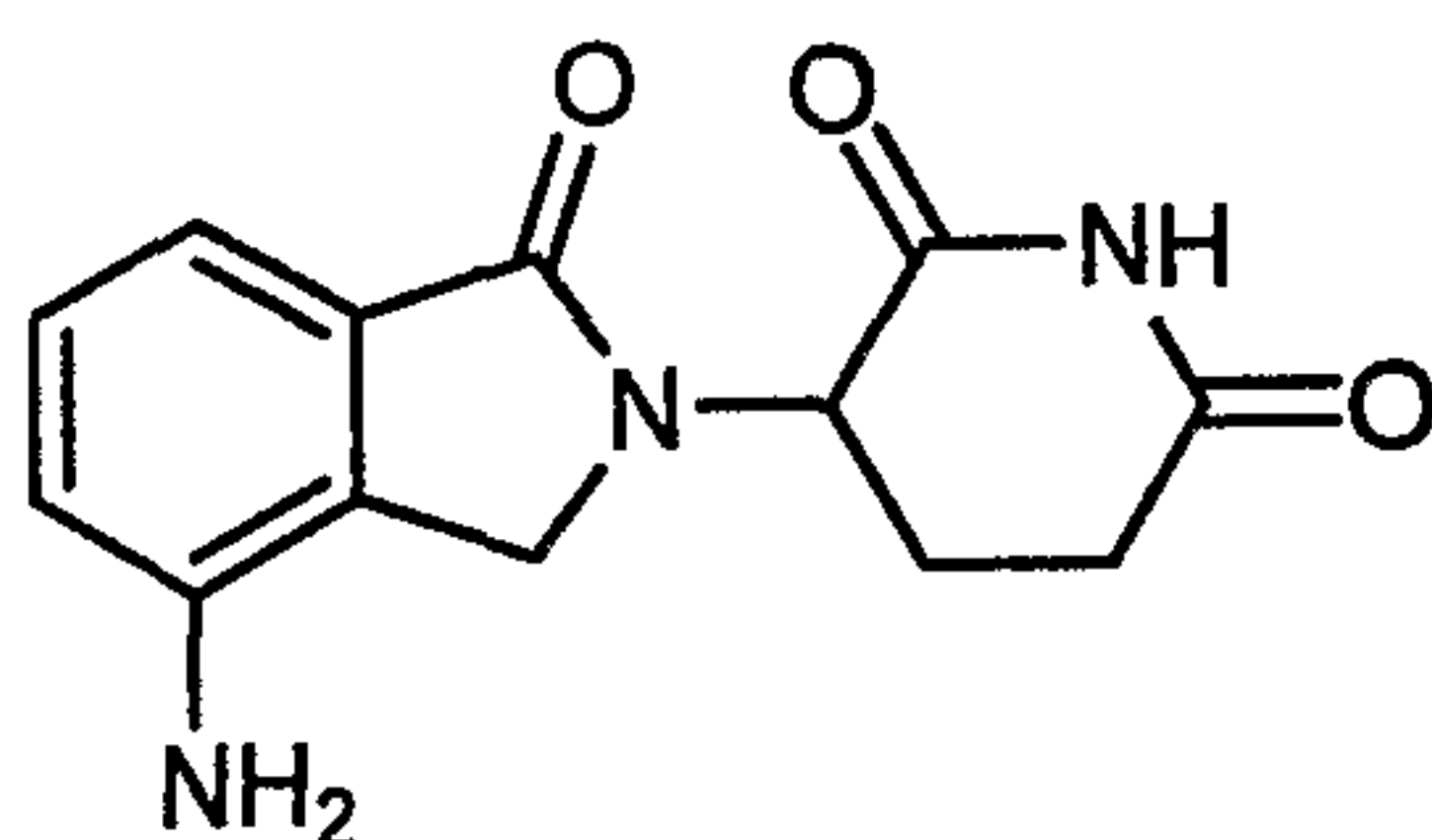
[079] There are numerous possible kinds of conversion of benzo substituent R¹ to R², if desired. In one embodiment, R¹ is -NO₂ and it is reduced to -NH₂. In a particular embodiment, R¹ is 4-NO₂ and it is reduced to 4-NH₂. Reduction of the benzo nitro group is facilitated by a metal catalyst in one embodiment. The catalyst is a Pd catalyst in a further embodiment and a Pd/C catalyst in a particular embodiment. In another embodiment, R¹ is -NHProtG² and the protecting group ProtG² is cleaved to give -NH₂. R¹ is 4-NHProtG² and ProtG² is removed to give 4-NH₂ in a particular embodiment. In yet another embodiment, ProtG² is Cbz and it is removed by hydrogenolysis with a metal catalyst. The catalyst is a Pd catalyst in a further embodiment and a Pd/C catalyst in a particular embodiment. If a benzo -NO₂ group is reduced to -NH₂ with a metal catalyst or if a benzo -NHCbz group is deblocked with a metal catalyst, one potential advantage of performing either transformation in step 6 prior to cyclization in step 7 of Scheme 2 is that less residual metal may bind to the final product II thereby than if cyclization occurred in step 4 prior to the transformation in step 5.

[080] Particular embodiments of the present invention are illustrated by the synthesis of the therapeutically active 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione in Scheme 3. The description of Scheme 1 and further embodiments described herein for Scheme 1 generally apply to Scheme 3. Specifically, the description of steps 1, 2, 3, 4, 5, 6, and 7 in Scheme 1 and further embodiments described herein for Scheme 1 generally apply to the corresponding steps 1, 2, 3, 4, 5, 6, and 7, respectively, in Scheme 3. Modifications of variables including, but not limited to, reaction solvents, reaction times, reaction temperatures, reagents, starting materials, and functional groups in the particular embodiments of the synthesis of 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione will be apparent to those of ordinary skill in the art.



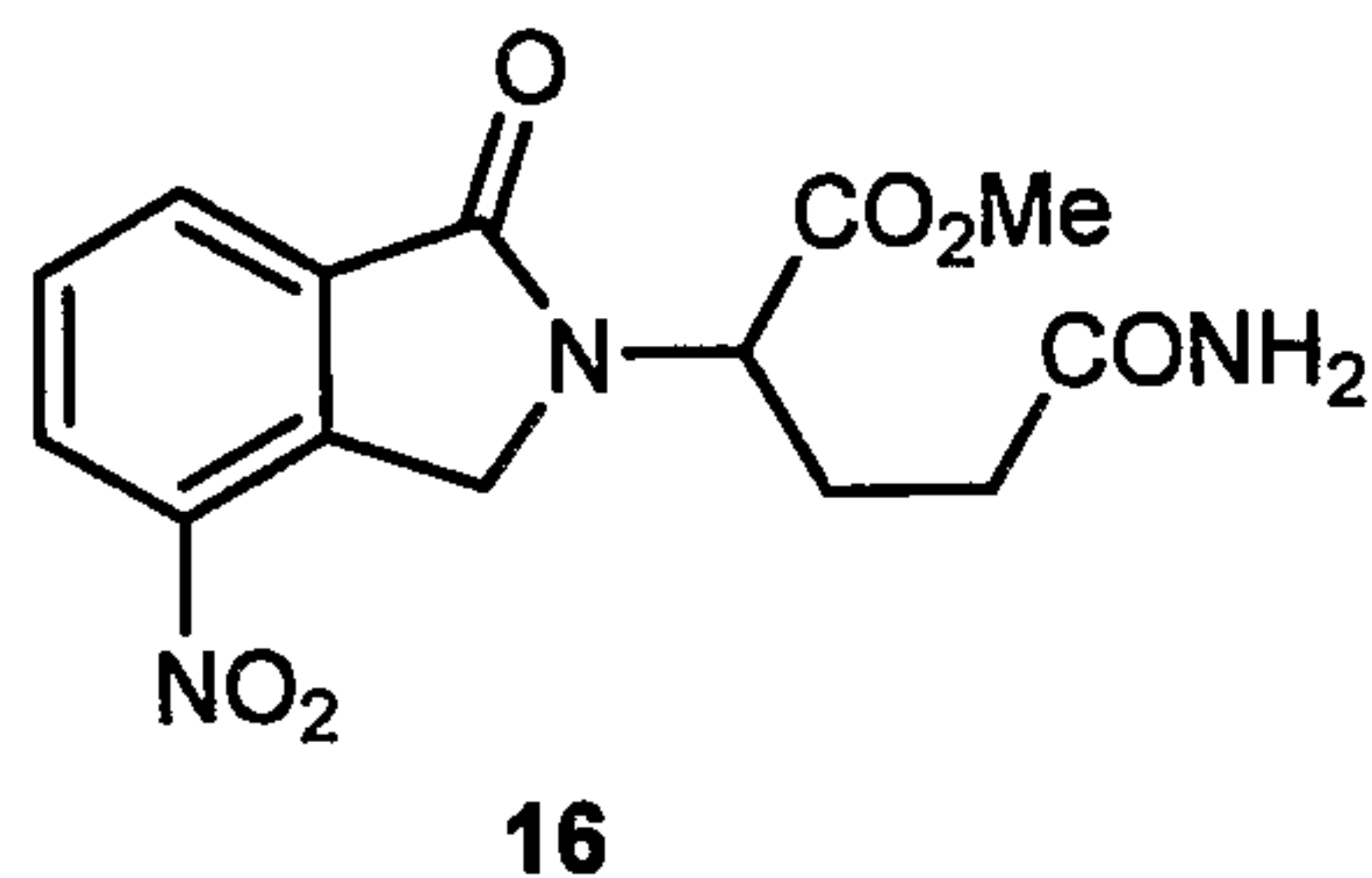
Scheme 3

[081] In one embodiment, the invention relates to a process for preparing 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione:



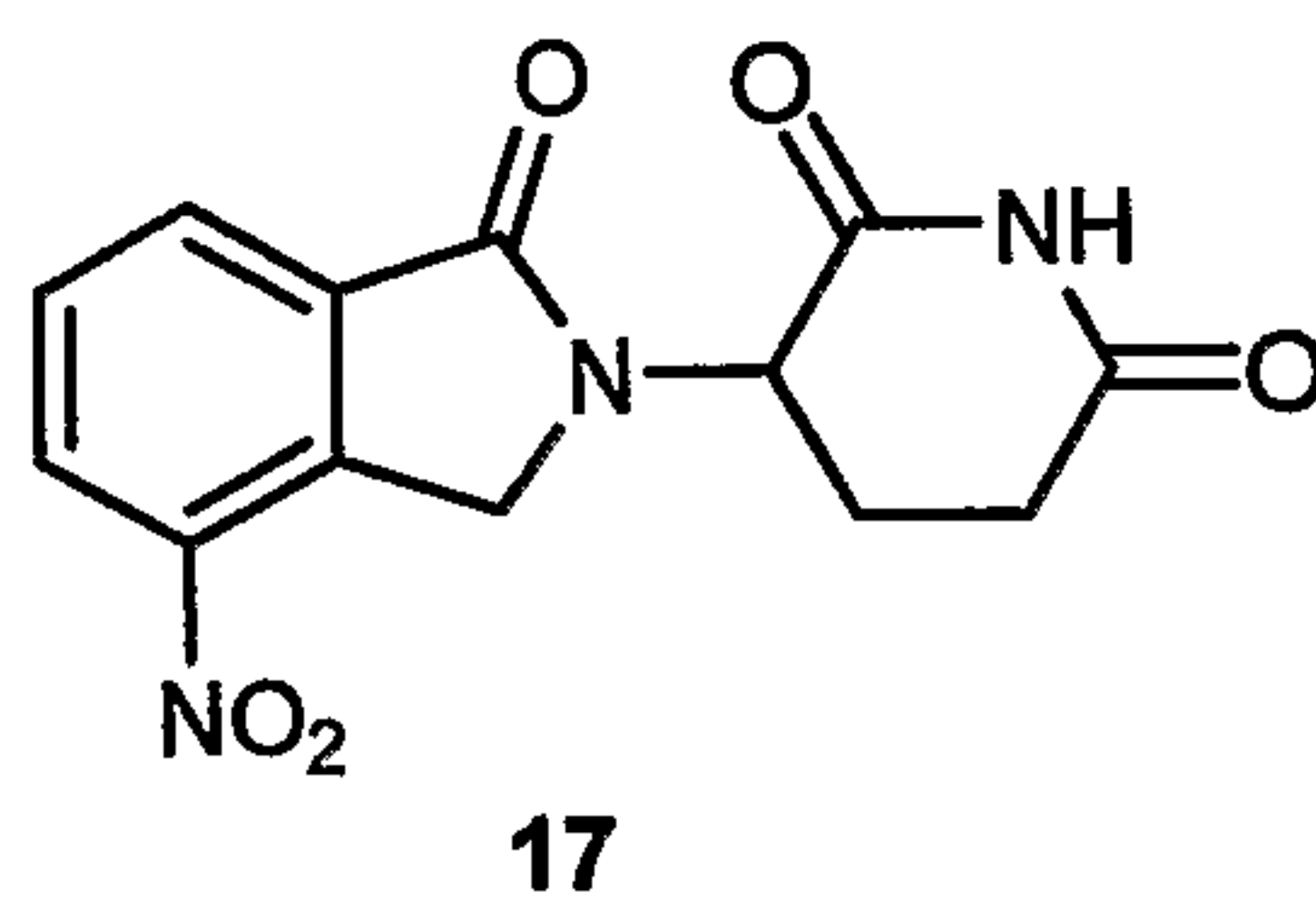
or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, which comprises the alternative sequences of steps of:

(1)(a) cyclizing a compound of Formula 16:



and

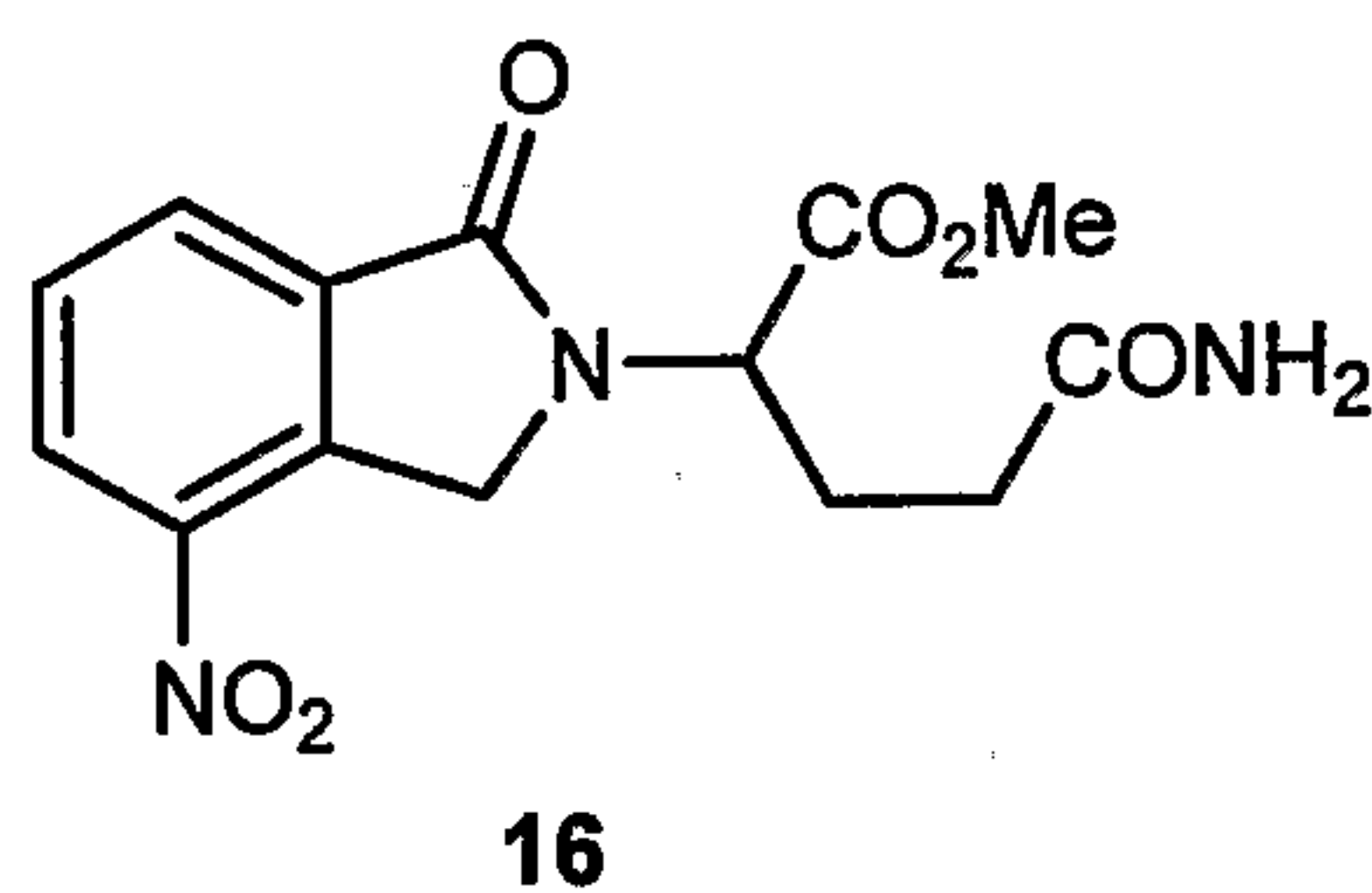
(b) reducing the -NO₂ group of the cyclized product of Formula 17:



to an -NH₂ group,

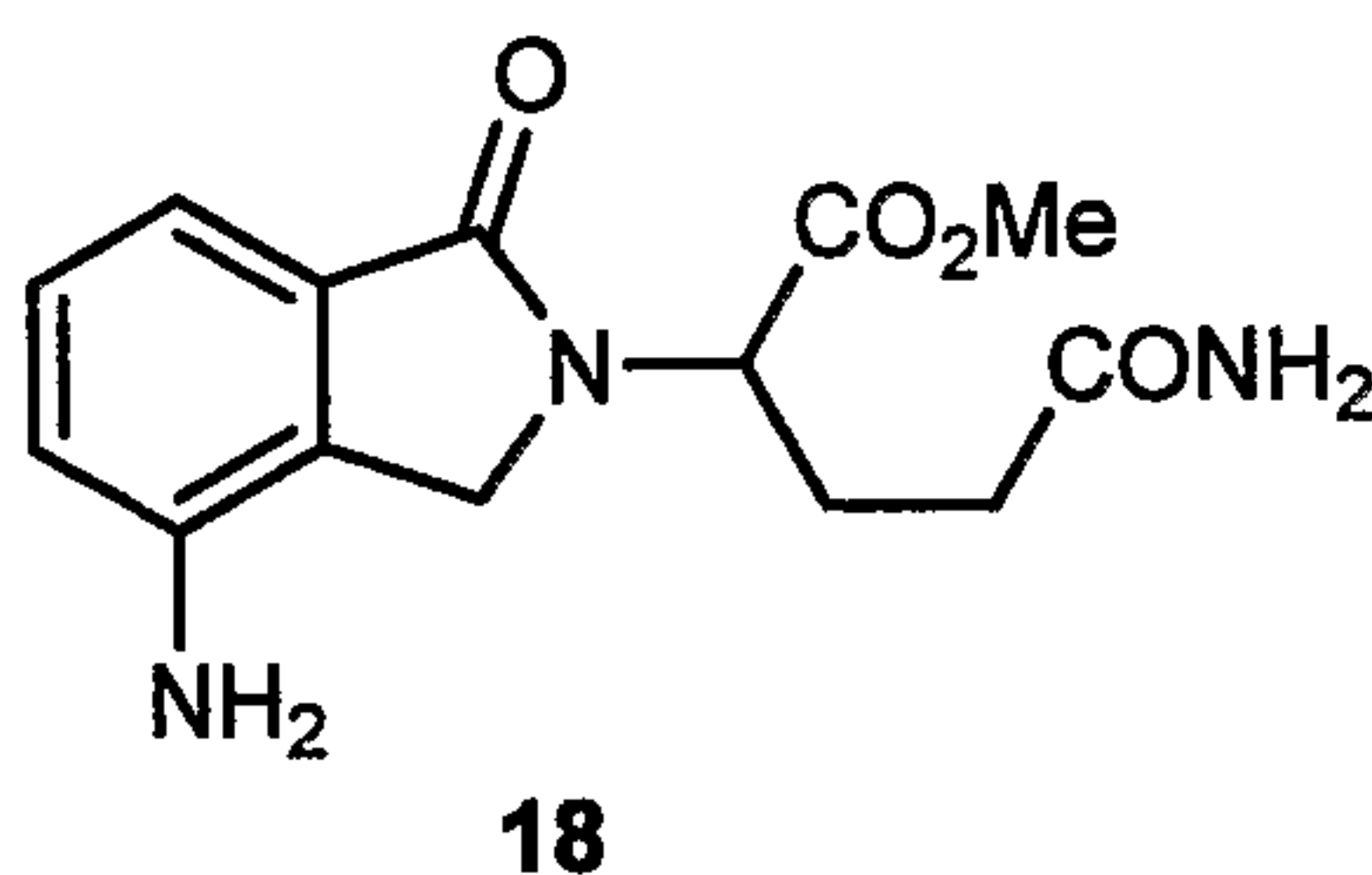
or:

(2)(a) reducing the -NO₂ group of a compound of Formula 16:



to an -NH₂ group, and

(b) cyclizing the reduced product of Formula 18:



[082] In the particular embodiments of the synthesis of 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione depicted in Scheme 3, *N*-Cbz-glutamine 12 (both enantiomers and the racemate are commercially available) is converted to methyl ester 13 with catalytic amounts of acetyl chloride and TMSCl in refluxing methanol. The *N*-Cbz blocking group is removed by hydrogenolysis over 5% Pd/C in methanol in step 2 to furnish free amine 14. The HCl salts of both enantiomers and the racemate of glutamine methyl ester 14 are also commercially available or can be made directly from the corresponding enantiomer or racemate of glutamine in methanol in the presence of an HCl source, as is well known in the art. The free amine or HCl salt of glutamine methyl ester 14 is then coupled to benzyl bromide 15 in triethylamine/refluxing acetonitrile or NaHCO₃/refluxing acetonitrile to afford oxoisoindoline 16. The synthesis of benzyl bromide 15 is described in International Publication No. WO 98/03502 (See Example 11, page 19).

[083] From common intermediate 16 in Scheme 3, 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione can be generated in two different ways. Cyclization to form the glutarimide ring can transpire under acidic conditions (*e.g.*, catalytic *p*-TsOH/refluxing toluene) or basic conditions (*e.g.*, KO^tBu/THF or K₂CO₃/acetonitrile) in step 4 prior to reduction of the nitro group to the final product over 10% Pd/C in methanol in step 5. Alternatively, the nitro group of oxoisoindoline 16 can be reduced to aniline 18 over 5% Pd/C in methanol in step 6, and then cyclization is effected under acidic conditions (*e.g.*, catalytic *p*-TsOH/refluxing toluene) or basic conditions (*e.g.*, KO^tBu/THF or K₂CO₃/refluxing acetonitrile) to afford the final product in step 7.

[084] The choice of cyclization conditions may be determined by the desired stereochemistry of 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione. If enantiomerically pure 3-(4-amino-1-oxoisoindolin-2-yl)-piperidine-2,6-dione is desired, cyclization in step 4 or step 7 of Scheme 3 may be conducted under acidic conditions (*e.g.*, catalytic *p*-TsOH/refluxing toluene) to afford the (*S*) or (*R*) final product in a synthesis using

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L- or D-glutamine methyl ester 14, respectively. On the other hand, if racemic 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione is desired, cyclization in step 4 or step 7 may be conducted under basic conditions (*e.g.*, KO^tBu/THF or K₂CO₃/acetonitrile) to furnish the racemic final product in a synthesis using less expensive L-glutamine methyl ester hydrochloride 14.

[085] In one embodiment, the processes of the invention are useful for preparing substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines or pharmaceutically acceptable salts, hydrates, solvates, or polymorphs thereof. In another embodiment, the processes of the invention are useful for preparing compounds useful for preventing or treating diseases or conditions related to an abnormally high level or activity of TNF α , including, but not limited to, cancers, inflammatory diseases, and autoimmune diseases.

[086] Polymorphs of 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione can be prepared according to the methods described in U.S. Patent No. 7,465,800.

In one embodiment, Form A of 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione is an unsolvated, crystalline solid that melts at about 270 °C and is weakly or not hygroscopic. It can be obtained by crystallization from various non-aqueous solvents including, but not limited to,

1-butanol, butyl acetate, ethanol, ethyl acetate, methanol, methyl ethyl ketone, and THF. In another embodiment, Form B of 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione is a hemihydrated, crystalline solid that melts at about 267 °C. It can be obtained by crystallization from various solvents including, but not limited to, hexane, toluene, and water. In yet another embodiment, Form C of 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione is a hemisolvated, crystalline solid that melts at about 269 °C. It can be obtained from evaporations, slurries, and slow cools in solvent systems including, but not limited to, acetone solvent systems. Other polymorphs of 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione are also obtainable, as described in the above cited patent application.

5. EXAMPLE

Synthesis of Chiral and Racemic 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione

[087] Preparation of L-N-benzyloxycarbonyl-glutamine methyl ester (13):

A solution of L-N-Cbz-glutamine, acetyl chloride (0.1 equiv.), and catalytic TMSCl in methanol was refluxed for 4-6 hours, generating the title compound (70-80% yield).

[088] Preparation of L-glutamine methyl ester (14):

A mixture of L-N-Cbz-glutamine methyl ester and 5% Pd/C in methanol was stirred under hydrogen (40 psi). The catalyst was filtered and the solvent removed *in vacuo*. The crude product was used in the ensuing coupling reaction.

[089] Preparation of methyl N-(1-oxo-4-nitroisindolin-2-yl)-L-glutamine (16):

To a mixture of L-glutamine methyl ester (0.010 mmol) and methyl 2-bromomethyl-3-nitrobenzoate (0.010 mmol) in acetonitrile (30 mL) was added triethyl amine (0.021 mmol). After the mixture was refluxed for one hour, water (2 mL) was added and acetonitrile was removed *in vacuo*. Water (50 mL) was added to the resulting residue, giving a solid which was filtered, washed with water, and dried (2.5 g, 56% yield).

[090] Preparation of (S)- or racemic 3-(4-nitro-1-oxoisindolin-2-yl)-piperidine-2,6-dione (17) from (S)- or racemic methyl N-(1-oxo-4-nitroisindolin-2-yl)-L-glutamine:

(A) To a solution of methyl N-(1-oxo-4-nitroisindolin-2-yl)-L-glutamine (0.2 g, 1.78 mmol) in THF was added 10 mL 0-5°C KO^tBu under N₂. The solution was stirred for 30 minutes and allowed to warm to room temperature over one hour followed by quenching with water. THF was removed *in vacuo*. The resulting residue was triturated with CH₂Cl₂/H₂O giving an off-white solid which was filtered, washed with water and dried under reduced pressure (0.45 g, 85% yield).

(B) Alternatively, a mixture of methyl N-(1-oxo-4-nitroisindolin-2-yl)-L-glutamine (0.2 g, 1.78 mmol) and catalytic *p*-TsOH in toluene is refluxed for 16 hours and cooled to room temperature. An off-white solid is isolated by filtration and washed with water, 10% NaHCO₃ and methanol and dried *in vacuo* (0.40 g, 91 % yield).

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[091] Preparation of (*S*)- or racemic 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione from (*S*)- or racemic 3-(4-nitro-1-oxoisindolin-2-yl)-piperidine-2,6-dione, respectively:

A mixture of (*S*)- or racemic 3-(4-nitro-1-oxoisindolin-2-yl)-piperidine-2,6-dione (1.0 g, 3.5 mmol) and 10% Pd/C (0.3 g) in methanol (600 mL) was hydrogenated in a Parr-Shaker apparatus at 50 psi of hydrogen for 5 hours. The mixture was filtered through Celite™ and the filtrate was concentrated *in vacuo*. The solid was slurried in hot ethyl acetate for 30 min, filtered, and dried to afford 0.46 g (51%) of (*S*) or racemic 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione, respectively, as a white solid.

[092] Preparation of methyl *N*-(1-oxo-4-aminoisindolin-2-yl)-L-glutamine (18):

A mixture of methyl *N*-(1-oxo-4-nitroisindolin-2-yl)-L-glutamine (6.4 g, 0.02 mmol) and 5% Pd/C (0.6 g) in methanol (100 mL) was stirred under hydrogen (40 psi) at ambient temperature for two hours. The Pd catalyst was filtered off through a pad of Celite. After concentration of the filtrate, the resulting oily residue was triturated with MTBE (30 mL), which yielded a solid after standing at ambient temperature for one hour. The off-white solid was filtered, washed with MTBE (30 mL), and dried to furnish the title compound (5.4 g, 93% yield).

[093] Preparation of racemic 3-(4-amino-1-oxoisindolin-2-yl)-piperidine-2,6-dione from methyl *N*-(1-oxo-4-aminoisindolin-2-yl)-L-glutamine:

(A) To a solution of methyl *N*-(1-oxo-4-aminoisindolin-2-yl)-L-glutamine in THF at 0 °C was added KO^tBu portionwise. The resulting mixture was stirred at 0-5 °C for 30 minutes, warmed to ambient temperature, and quenched with water (2 mL). THF was removed *in vacuo* and the resulting residue was triturated with H₂O. The resulting off-white solid was filtered, washed with water, and dried. The product had a 4% ee by chiral HPLC and contained 68 ppm of residual Pd.

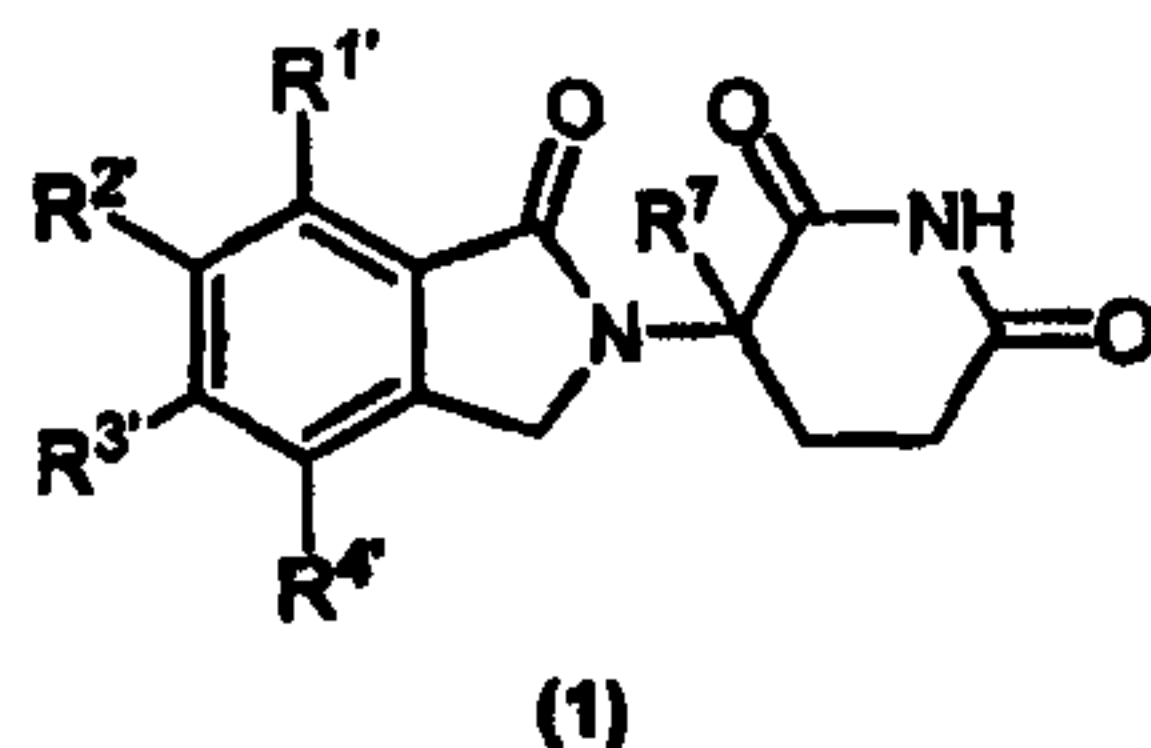
(B) Alternatively, a solution of methyl *N*-(1-oxo-4-aminoisindolin-2-yl)-L-glutamine (0.0295 mmol) and K₂CO₃ (0.0295 mmol) in acetonitrile (85 mL) was refluxed for one hour. The reaction was then quenched with water (20 mL) and acetonitrile was removed

in vacuo, giving an off-white solid. The solid was filtered, washed with water, and dried at ambient temperature for 18 hours to yield the desired compound (65% yield). The solid was slurried in acetonitrile (30 mL) for 15 minutes, filtered, and air-dried for six hours to provide the desired compound that contained less than 1 ppm of residual Pd. The Pd content was determined by inductively coupled plasma (ICP) spectroscopy.

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CLAIMS:

1. A process for preparing a compound of Formula 1:



or a pharmaceutically acceptable salt thereof, wherein:

- 5 each of R^{1'}, R², R³, and R⁴ is at each occurrence independently hydrogen, halo, alkyl, alkoxy, -CF₃, -CN, -NO₂, -NHProtG², or -NR⁵R⁶;

each of R⁵ and R⁶ is at each occurrence independently hydrogen or alkyl;

R⁷ is hydrogen, halo, alkyl, or benzyl; and

ProtG² is a suitable *N*-protecting group,

- 10 which comprises the alternative sequences of steps of:

(1)(a) coupling a glutamine ester or a salt thereof with an optionally substituted 2-halomethylbenzoate;

(b) direct cyclizing the coupled product; and

- 15 (c) optionally transforming one or more benzo substituents of the cyclized product into other substituent(s) in one or more steps,

or:

(2)(a) coupling a glutamine ester or a salt thereof with an optionally substituted 2-halomethylbenzoate;

- 20 (b) transforming one or more benzo substituents of the coupled product into other substituent(s) in one or more steps; and

(c) direct cyclizing the transformed product.

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2. The process of claim 1, wherein the compound of Formula 1 is racemic.
3. The process of claim 1, wherein the compound of Formula 1 is the (+)- or (-)-enantiomer.
4. The process of claim 1, wherein the glutamine ester or a salt thereof is
5 prepared by esterifying a glutamine.
5. The process of claim 1, wherein the glutamine ester or a salt thereof is prepared by:
- protecting the α -amino group of a glutamine;
- esterifying the *N*-protected glutamine; and
- 10 deprotecting the α -amino group of the esterified glutamine.
6. The process of claim 1, wherein the optionally substituted 2-halomethylbenzoate is prepared by halogenating an optionally substituted 2-methylbenzoate.
7. The process of claim 1, wherein the coupling occurs under basic condition.
- 15 8. The process of claim 1, wherein the direct cyclizing occurs under basic condition.
9. The process of claim 1, wherein the direct cyclizing occurs under acidic condition.
10. The process of claim 1, wherein the transforming comprises reducing a benzo
20 -NO₂ group to a benzo -NH₂ group.
11. The process of claim 1, wherein the transforming comprises deprotecting a benzo -NHProtG² group to yield a benzo -NH₂ group.
12. The process according to claim 1:
- wherein:

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each of R^1 , R^2 , R^3 , and R^4 is at each occurrence independently hydrogen, halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

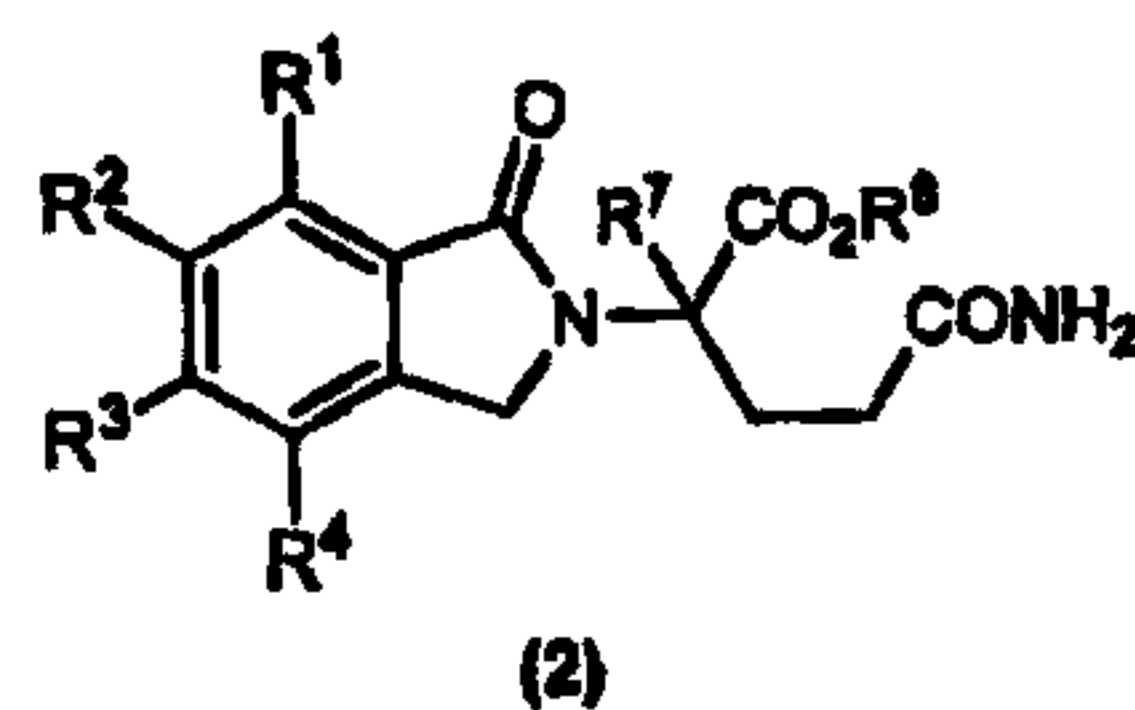
each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;

R^7 is hydrogen, halo, alkyl, or benzyl; and

5 $ProtG^2$ is a suitable *N*-protecting group,

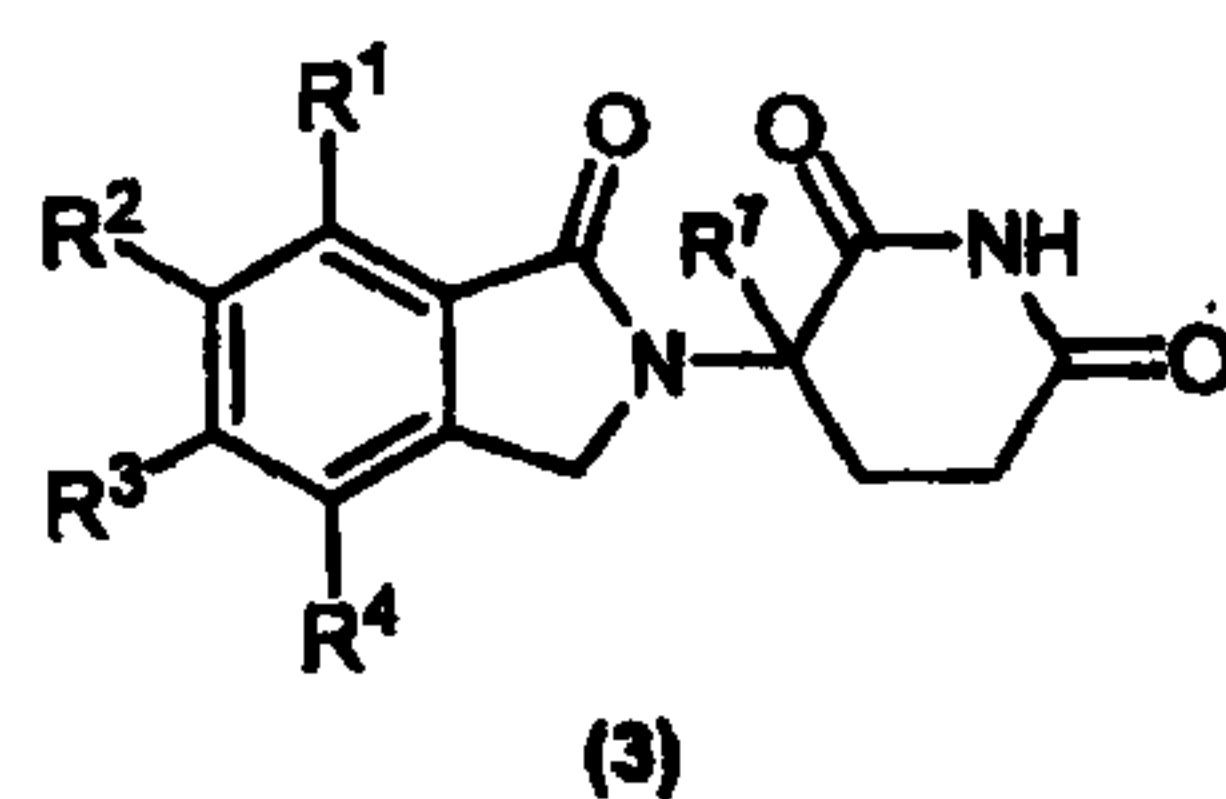
which comprises the alternative sequences of steps of:

(1)(b) direct cyclizing a compound of Formula 2:



and

10 (c) optionally transforming one or more of the R^1 , R^2 , R^3 , and/or R^4 substituents of the cyclized product of Formula 3:

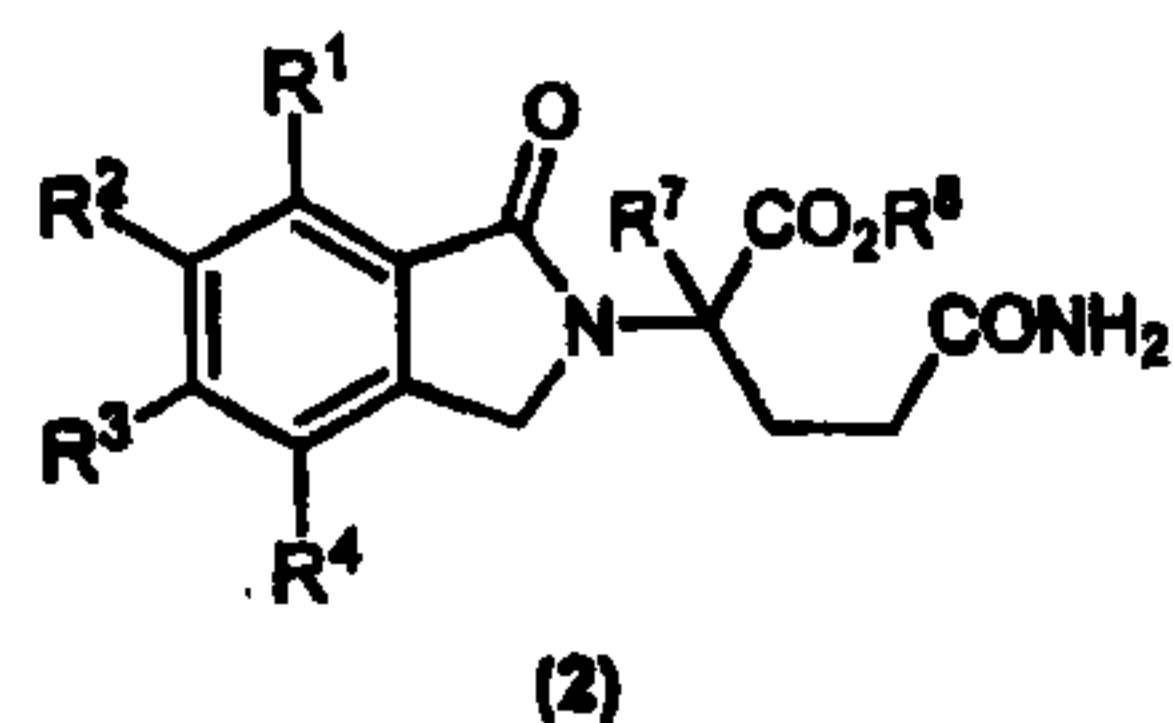


into one or more of the corresponding R^1 , R^2 , R^3 , and/or R^4 substituents, respectively, of the compound of Formula 1 in one or more steps,

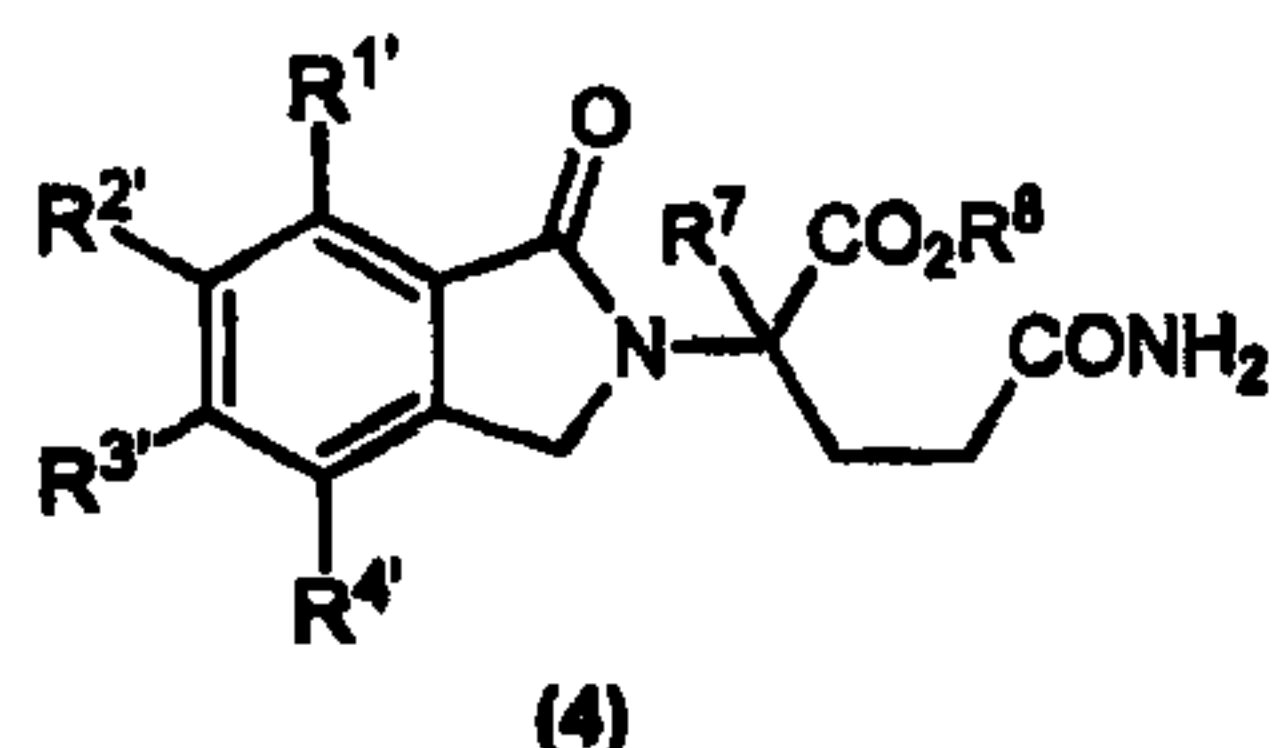
15 or:

(2)(b) transforming one or more of the R^1 , R^2 , R^3 , and/or R^4 substituents of a compound of Formula 2:

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into one or more of the corresponding R¹, R², R³, and/or R⁴ substituents, respectively, of a compound of Formula 4:



5 in one or more steps, and

(c) direct cyclizing the transformed product of Formula 4,

wherein, for both sequences of steps unless noted otherwise:

each of R¹, R², R³, R⁴, R¹', R²', R³', and R⁴' is at each occurrence independently hydrogen, halo, alkyl, alkoxy, -CF₃, -CN, -NO₂, -NHProtG², or -NR⁵R⁶;

10 each of R⁵ and R⁶ is at each occurrence independently hydrogen or alkyl;

R⁷ is hydrogen, halo, alkyl, or benzyl;

R⁸ is alkyl or benzyl for sequence (1) and is hydrogen, alkyl, or benzyl for sequence (2); and

ProtG² is a suitable *N*-protecting group.

15 13. The process of claim 12, wherein the compound of Formula 1 is racemic.

14. The process of claim 12, wherein the compound of Formula 1 is the (+)- or (-)-enantiomer.

15. The process of claim 12, wherein, for both sequences of steps unless noted otherwise:

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each of R¹, R², R³, and R⁴ is at each occurrence independently hydrogen, lower molecular weight halo, lower alkyl, lower alkoxy, -NO₂, -NHProtG², or -NR⁵R⁶;

each of R^{1'}, R^{2'}, R^{3'}, and R^{4'} is at each occurrence independently hydrogen, lower molecular weight halo, lower alkyl, lower alkoxy, -NO₂, -NHProtG², or -NR⁵R⁶;

5 each of R⁵ and R⁶ is at each occurrence independently hydrogen or lower alkyl;

R⁷ is hydrogen or lower alkyl;

R⁸ is lower alkyl for sequence (1) and hydrogen or lower alkyl for sequence (2); and

10 ProtG² is a suitable acyl *N*-protecting group.

16. The process of claim 15, wherein, for both sequences of steps unless noted otherwise:

each of R¹, R², R³, and R⁴ is at each occurrence independently hydrogen, -NO₂, or -NHProtG²;

15 each of R^{1'}, R^{2'}, R^{3'}, and R^{4'} is at each occurrence independently hydrogen, -NHProtG², or -NH₂;

R⁷ is hydrogen or methyl;

R⁸ is methyl for sequence (1) and hydrogen or methyl for sequence (2); and

ProtG² is Cbz, Boc, formyl, acetyl, trifluoroacetyl, or pivaloyl.

20 17. The process of claim 12, wherein, if R⁸ is alkyl, the direct cyclizing occurs under acidic condition.

18. The process of claim 17, wherein the direct cyclizing occurs in the presence of *p*-toluenesulfonic acid.

25 19. The process of claim 12, wherein, if R⁸ is alkyl, the direct cyclizing occurs under basic condition.

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20. The process of claim 19, wherein the direct cyclizing occurs in the presence of KO^tBu.
21. The process of claim 19, wherein the direct cyclizing occurs in the presence of K₂CO₃.
- 5 22. The process of claim 12, wherein, if R⁸ is hydrogen for sequence (2), the direct cyclizing occurs in the presence of an activating agent.
23. The process of claim 22, wherein the activating agent is thionyl chloride.
24. The process of claim 12, wherein the transforming one or more of the R¹, R², R³, and/or R⁴ substituents of the compound of Formula 2 or 3 into one or more of the
10 corresponding R^{1'}, R^{2'}, R^{3'}, and/or R^{4'} substituents, respectively, of the compound of Formula 4 or 1, respectively, comprises reducing one or more benzo -NO₂ groups to one or more benzo -NH₂ groups.
25. The process of claim 24, wherein the reducing is facilitated by a catalyst.
26. The process of claim 25, wherein the metal catalyst is a Pd catalyst.
- 15 27. The process of claim 12, wherein the transforming one or more of the R¹, R², R³, and/or R⁴ substituents of the compound of Formula 2 or 3 into one or more of the corresponding R^{1'}, R^{2'}, R^{3'}, and/or R^{4'} substituents, respectively, of the compound of Formula 4 or 1, respectively, in one or more steps comprises deprotecting one or more benzo -NHProtG² groups to yield one or more benzo -NH₂ groups in one or more steps.
- 20 28. The process of claim 27, wherein the deprotecting cleaves one or more benzo -NHCbz groups by hydrogenolysis with a catalyst to yield one or more benzo -NH₂ groups.
29. The process of claim 27, wherein the deprotecting cleaves one or more benzo -NHBoc groups under acidic condition to give one or more benzo -NH₂ groups.
30. The process of claim 12, further comprising, for sequence (2), generating a
25 compound of Formula 2 or Formula 4 in which R⁸ is hydrogen from a compound of Formula 2 or Formula 4, respectively, in which R⁸ is alkyl or benzyl.

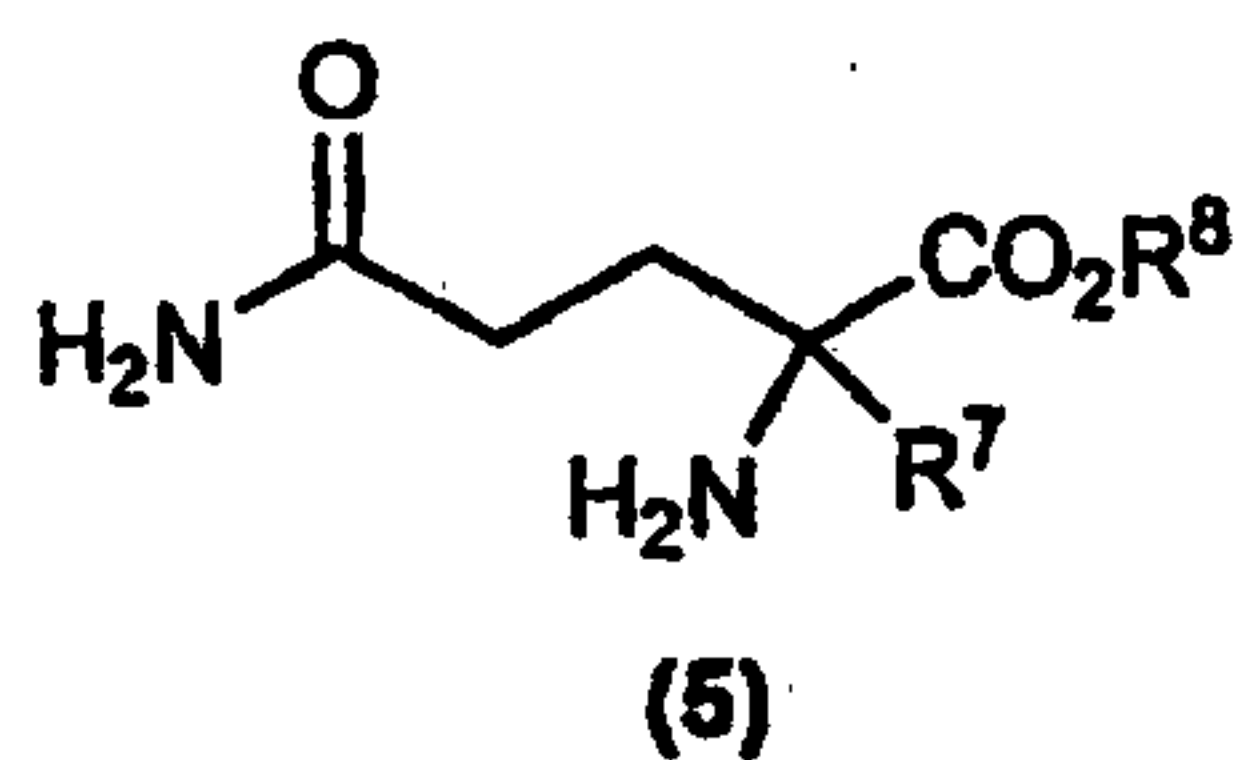
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31. The process of claim 30, wherein the compound of Formula 2 or 4 in which R⁸ is hydrogen is generated under acidic condition from a compound of Formula 2 or 4, respectively, in which R⁸ is alkyl.

32. The process of claim 30, wherein the compound of Formula 2 or 4 in which R⁸ is hydrogen is generated under basic condition from a compound of Formula 2 or 4, respectively, in which R⁸ is alkyl.

33. The process of claim 30, wherein the compound of Formula 2 or 4 in which R⁸ is hydrogen is generated by hydrogenolysis with a catalyst from a compound of Formula 2 or 4, respectively, in which R⁸ is benzyl.

34. The process of claim 12, wherein the compound of Formula 2 is prepared by coupling a compound of Formula 5:

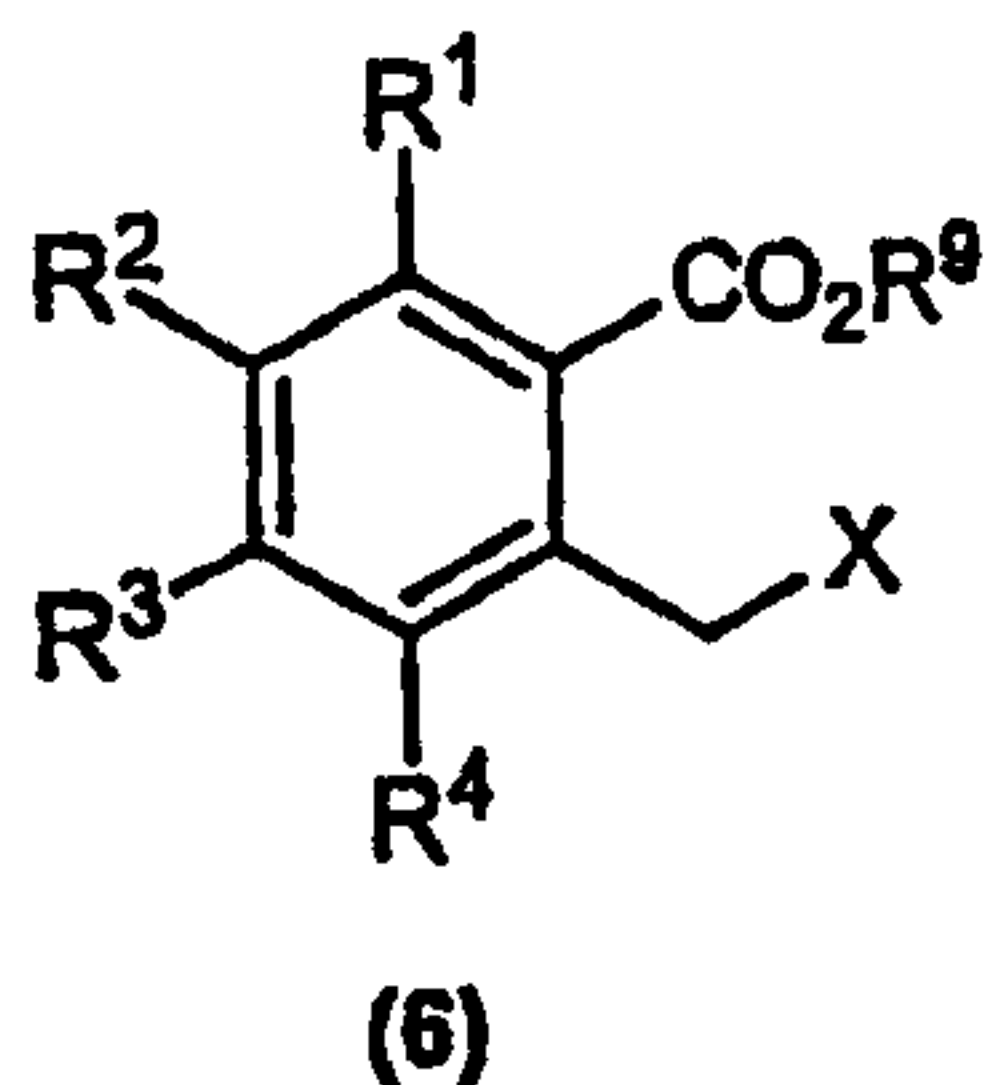


or a salt thereof, wherein:

R⁷ is hydrogen, halo, alkyl, or benzyl, and

R⁸ is alkyl or benzyl,

with a compound of Formula 6:



wherein:

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each of R^1 , R^2 , R^3 , and R^4 is at each occurrence independently hydrogen, halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;

R^9 is alkyl;

X is halo; and

$ProtG^2$ is a suitable *N*-protecting group.

35. The process of claim 34, wherein:

each of R^1 , R^2 , R^3 , and R^4 is at each occurrence independently hydrogen, lower molecular weight halo, lower alkyl, lower alkoxy, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

each of R^5 and R^6 is at each occurrence independently hydrogen or lower alkyl;

R^7 is hydrogen or lower alkyl;

R^8 is lower alkyl or benzyl;

R^9 is lower alkyl;

X is higher molecular weight halo; and

$ProtG^2$ is a suitable acyl *N*-protecting group.

36. The process of claim 35, wherein:

each of R^1 , R^2 , R^3 , and R^4 is at each occurrence independently hydrogen, $-NO_2$, or $-NHProtG^2$;

R^7 is hydrogen or methyl;

R^8 is methyl;

R^9 is methyl;

X is bromo; and

$ProtG^2$ is Cbz, Boc, formyl, acetyl, trifluoroacetyl, or pivaloyl.

37. The process of claim 34, wherein the coupling occurs under basic condition.

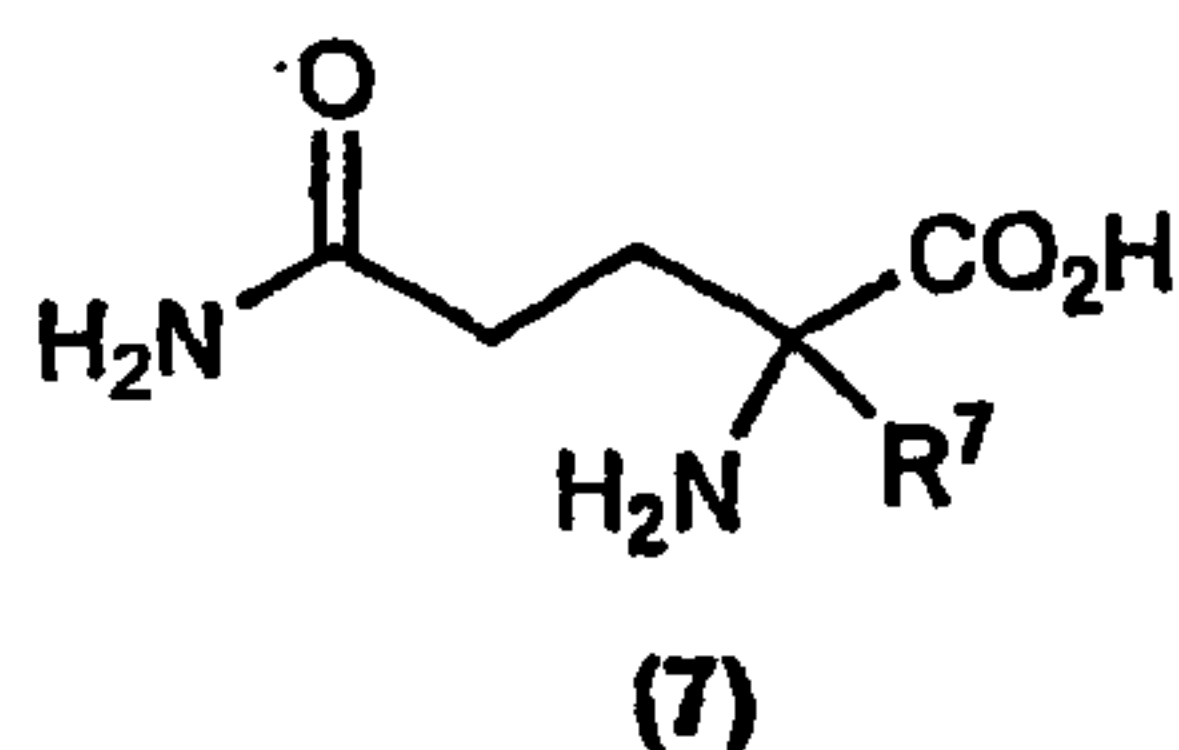
38. The process of claim 37, wherein the coupling occurs in the presence of NEt_3 .

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39. The process of claim 37, wherein the coupling occurs in the presence of $i\text{PrEt}_2\text{N}$.

40. The process of claim 37, wherein the coupling occurs in the presence of NaHCO_3 .

41. The process of claim 34, wherein the compound of Formula 5 or a salt thereof is prepared by esterifying a compound of Formula 7:

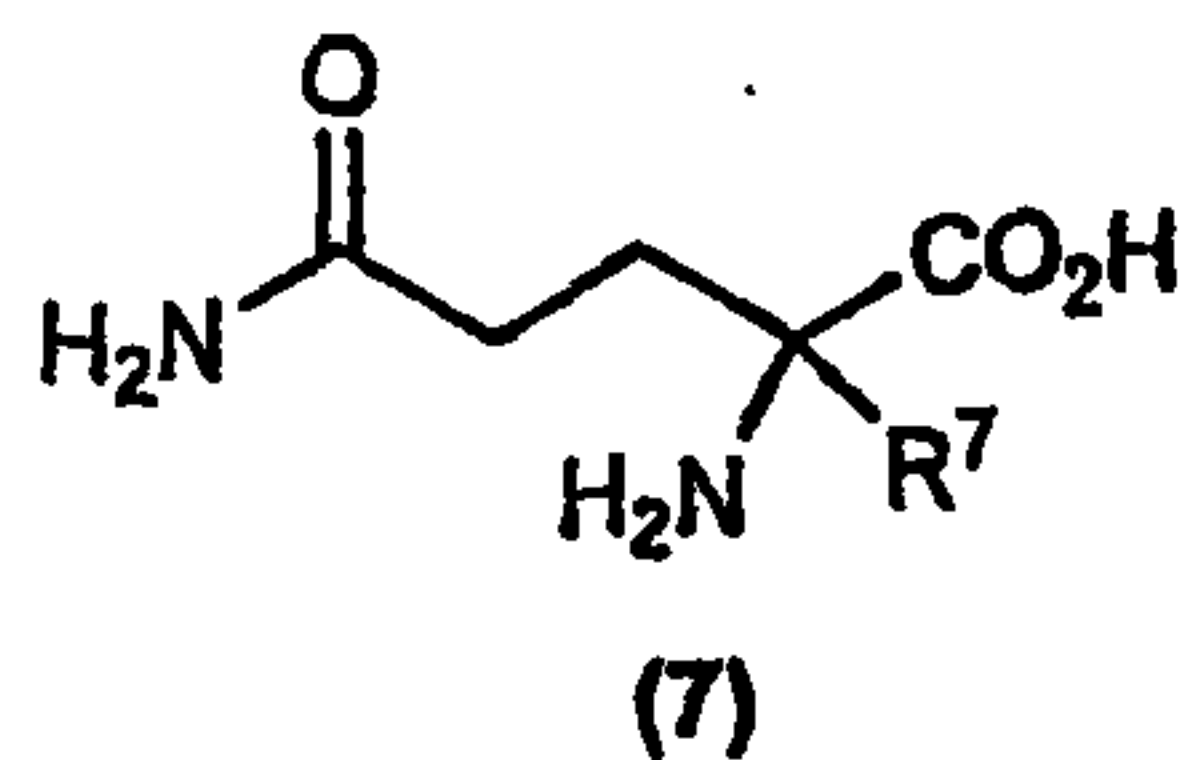


or a salt thereof, wherein R^7 is hydrogen, halo, alkyl, or benzyl.

42. The process of claim 41, wherein the esterifying occurs under acidic condition in an alcohol of the formula of R^8OH .

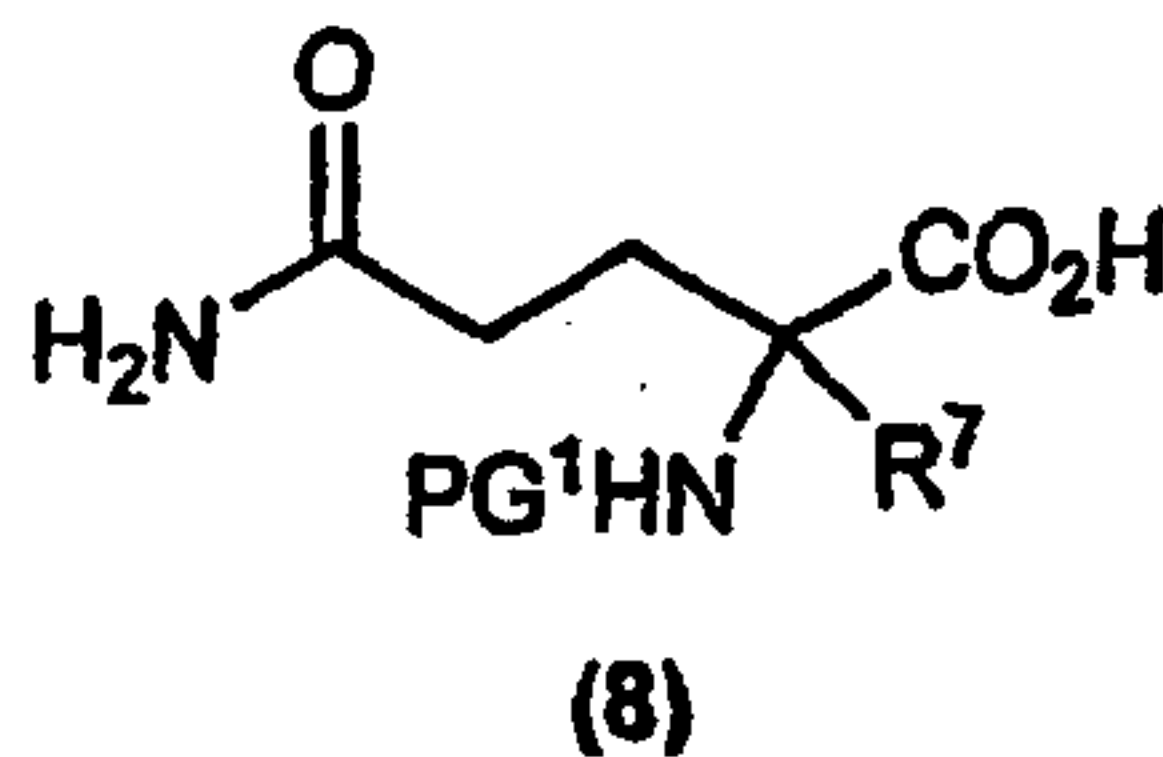
43. The process of claim 34, wherein the compound of Formula 5 or a salt thereof is prepared by:

protecting the α -amino group of a compound of Formula 7:



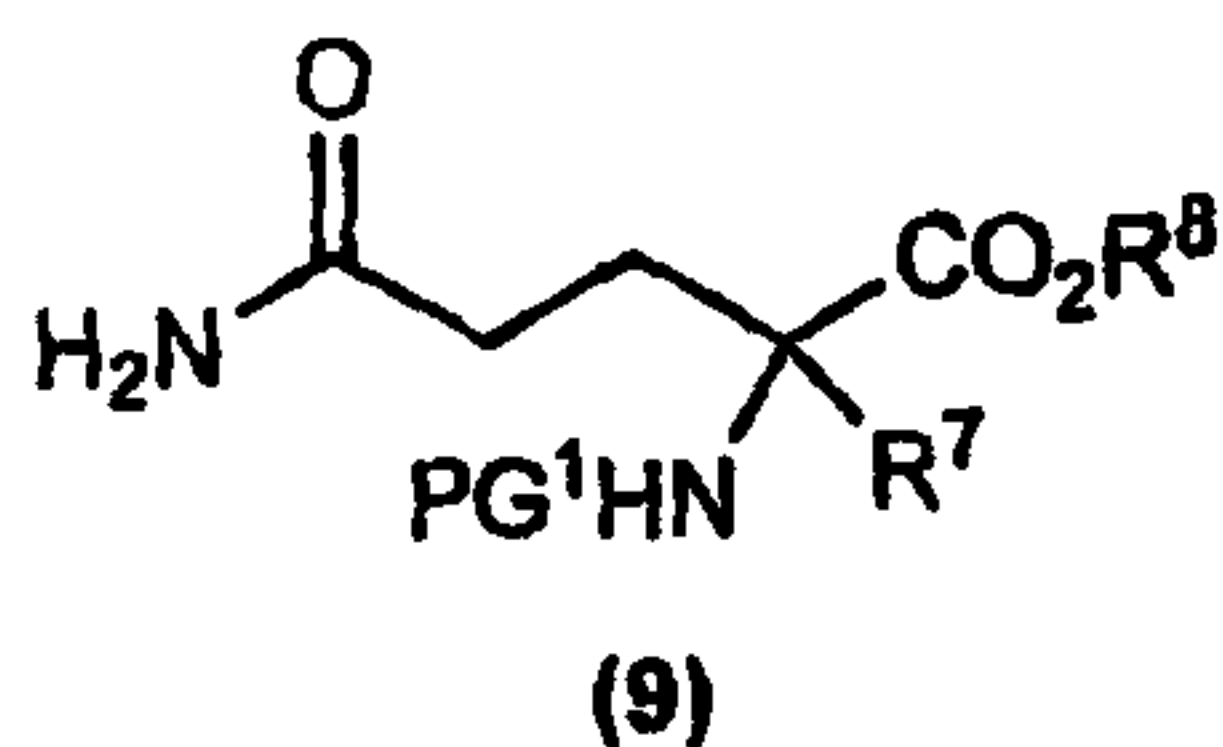
or a salt thereof;

esterifying the N -protected compound of Formula 8:



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and deprotecting the α -amino group of the esterified compound of Formula 9:



wherein:

R^7 is hydrogen, halo, alkyl, or benzyl;

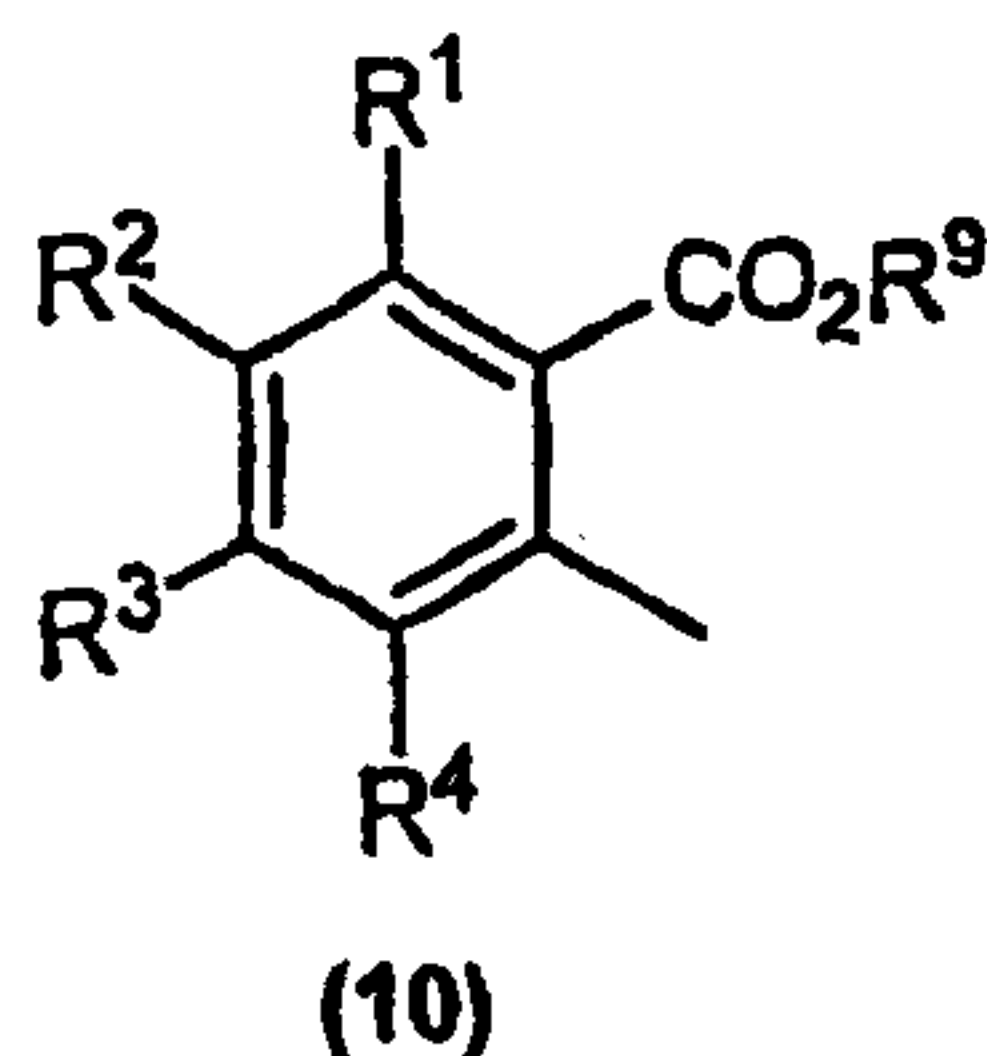
R^8 is alkyl or benzyl; and

ProtG¹ is a suitable *N*-protecting group.

44. The process of claim 43, wherein the esterifying occurs under acidic condition in an alcohol of the formula of R^8OH .

45. The process of claim 43, wherein the deprotecting comprises removing a Cbz group by hydrogenolysis with a catalyst.

46. The process of claim 34, wherein the compound of Formula 6 is prepared by halogenating a compound of Formula 10:



wherein:

each of R^1 , R^2 , R^3 , and R^4 is at each occurrence independently hydrogen, halo, alkyl, alkoxy, $-CF_3$, $-CN$, $-NO_2$, $-NHProtG^2$, or $-NR^5R^6$;

each of R^5 and R^6 is at each occurrence independently hydrogen or alkyl;

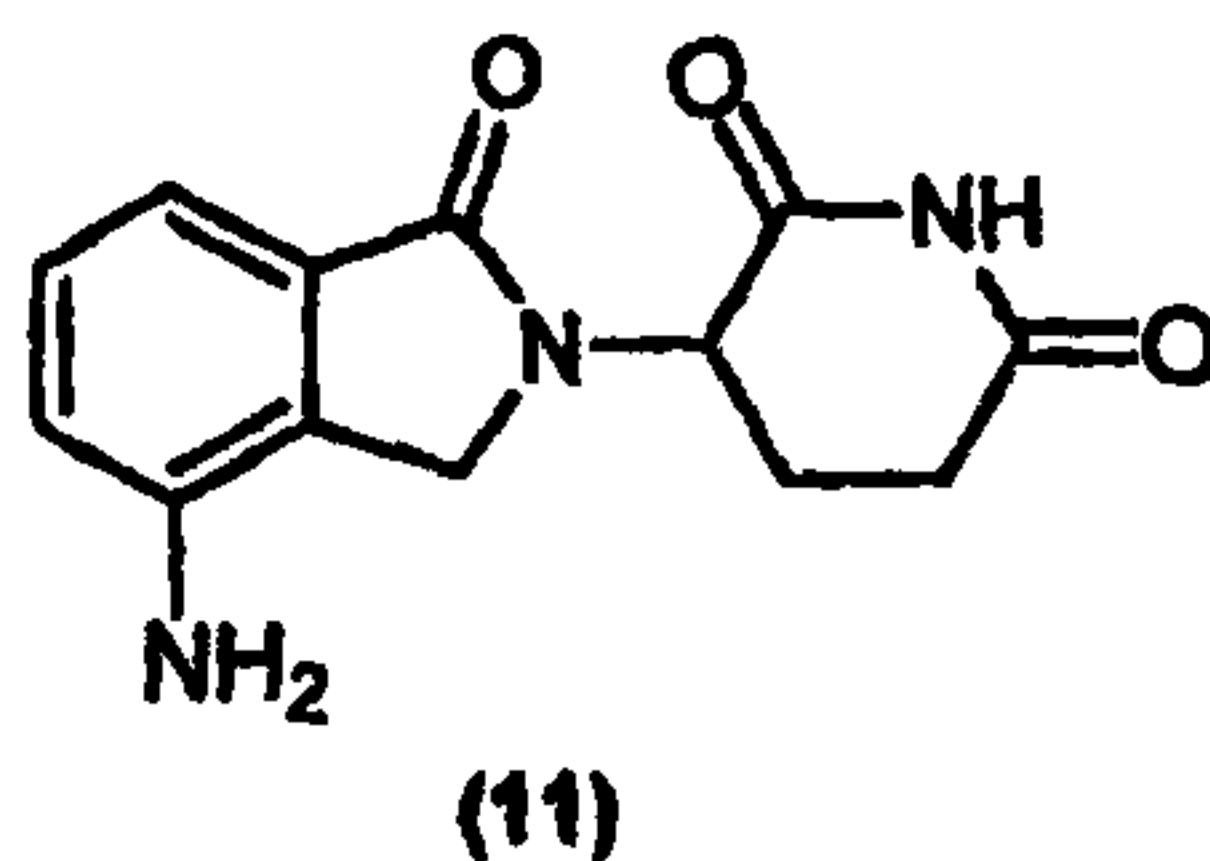
R^9 is alkyl; and

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ProtG² is a suitable *N*-protecting group.

47. The process of claim 46, wherein the halogenating comprises brominating with a brominating agent under free-radical condition.

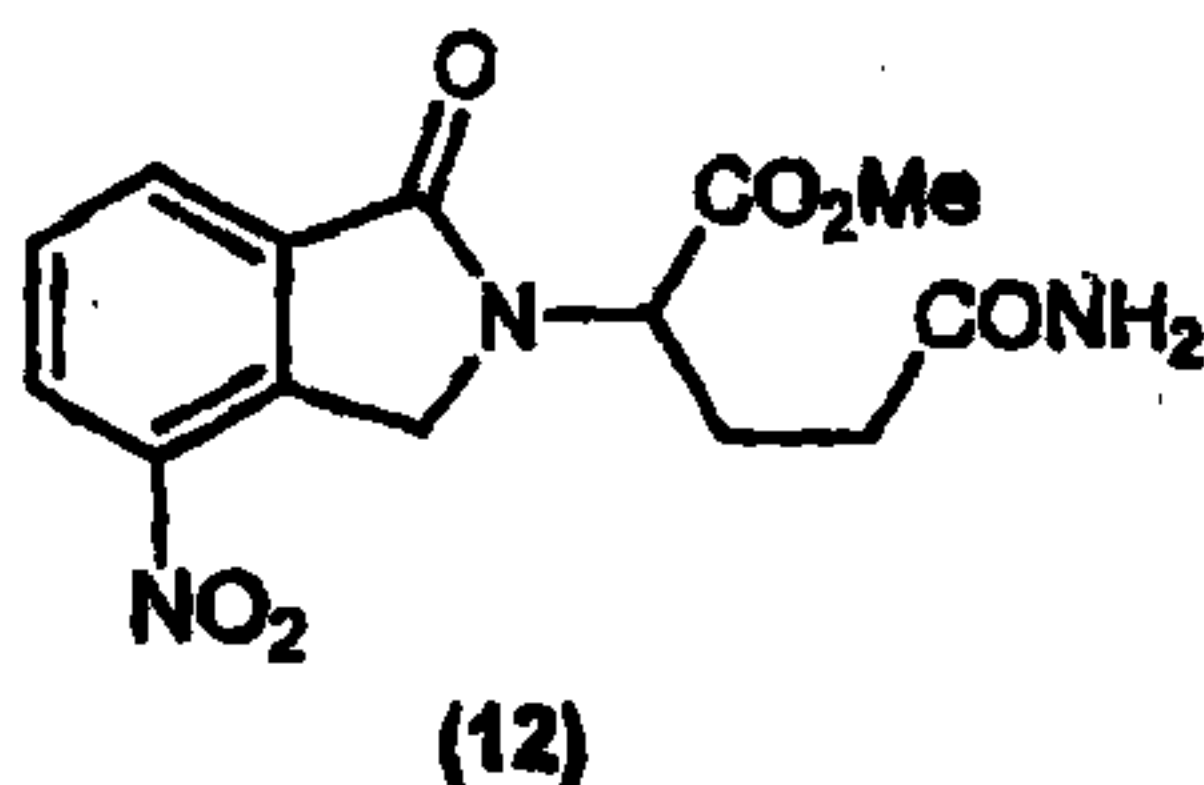
48. The process according to claim 1, for preparing a compound of Formula 11:



5

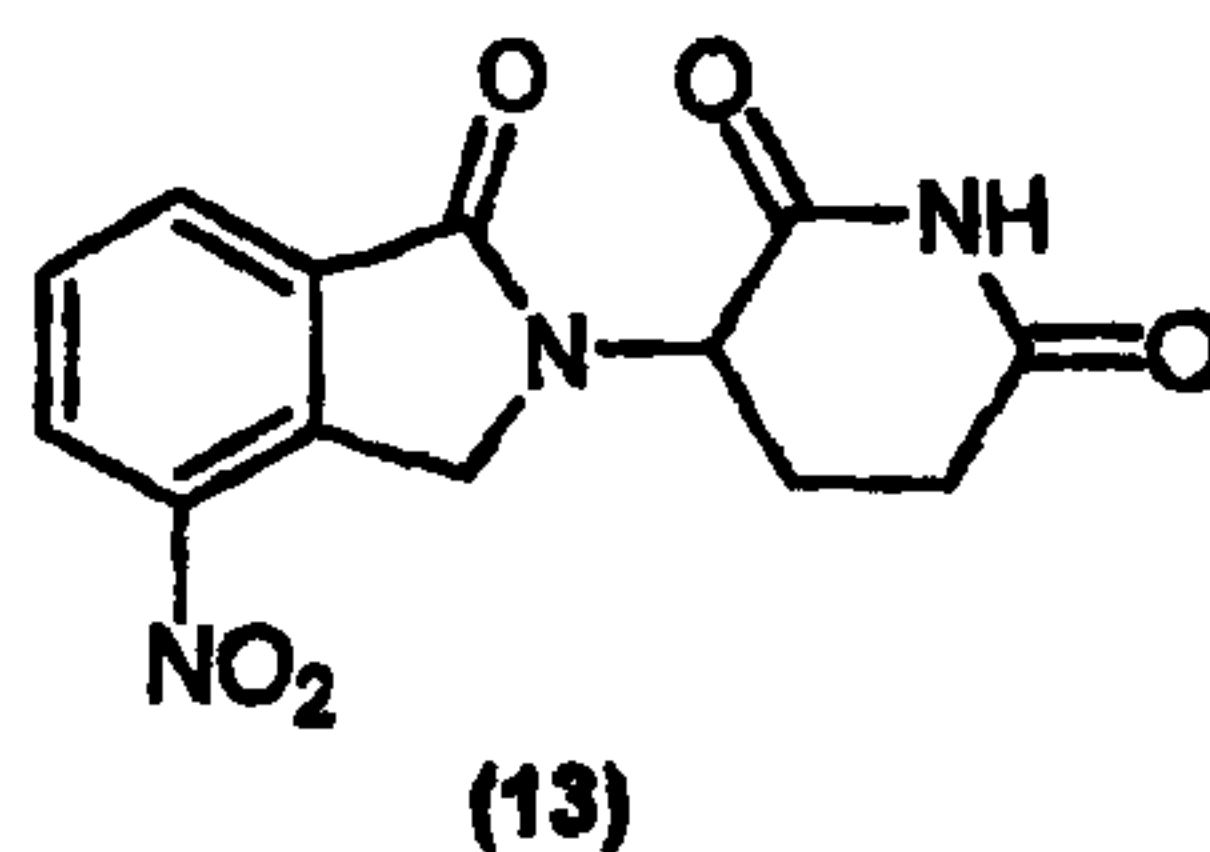
or a pharmaceutically acceptable salt thereof, which comprises the alternative sequences of steps of:

(1)(b) direct cyclizing a compound of Formula 12:



10 and

(c) reducing the -NO₂ group of the cyclized product of Formula 13:

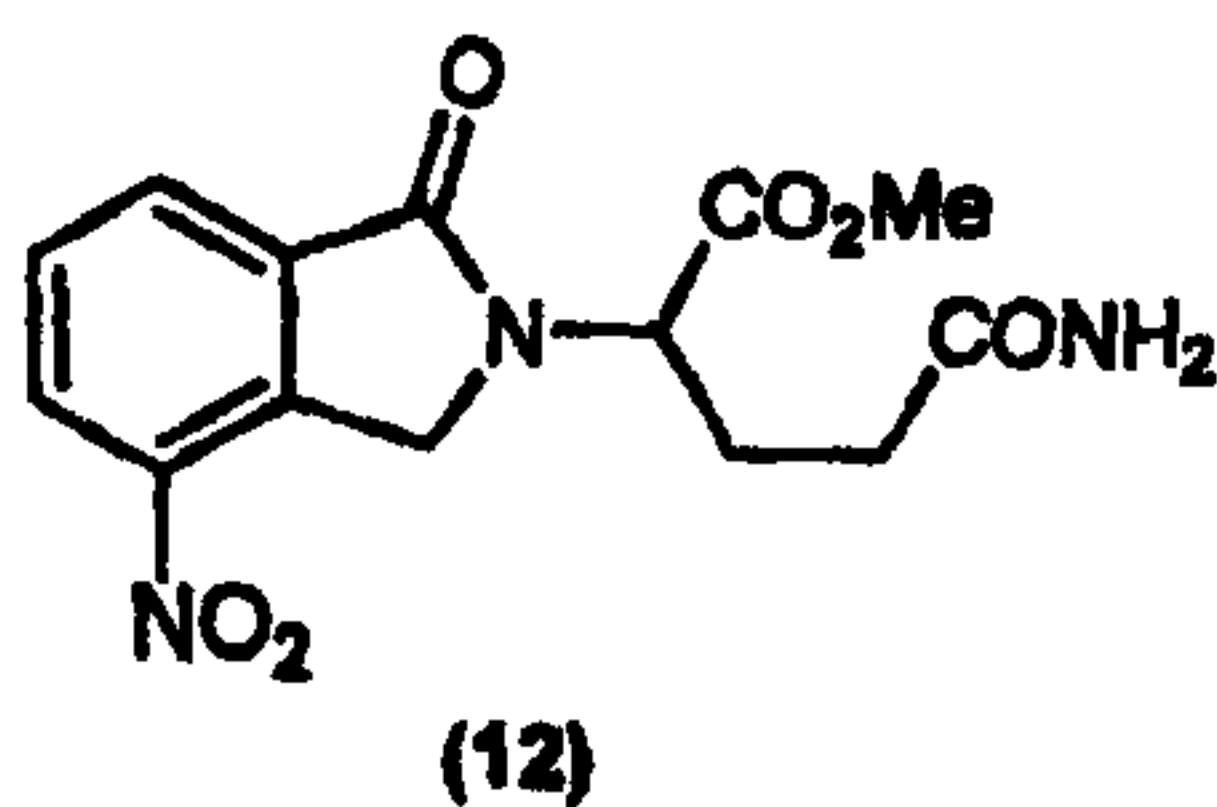


to an -NH₂ group,

or:

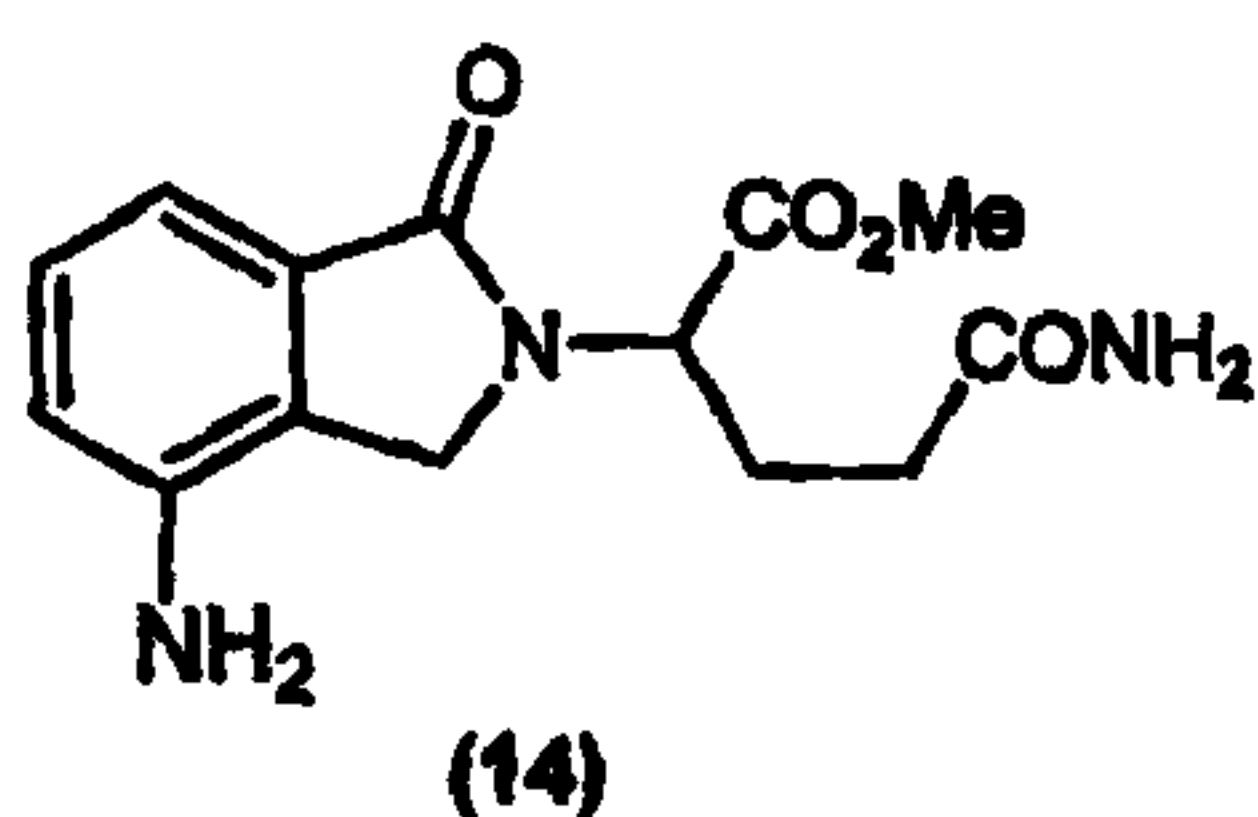
15 (2)(b) reducing the -NO₂ group of a compound of Formula 12:

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to an -NH₂ group, and

(c) direct cyclizing the reduced product of Formula 14:

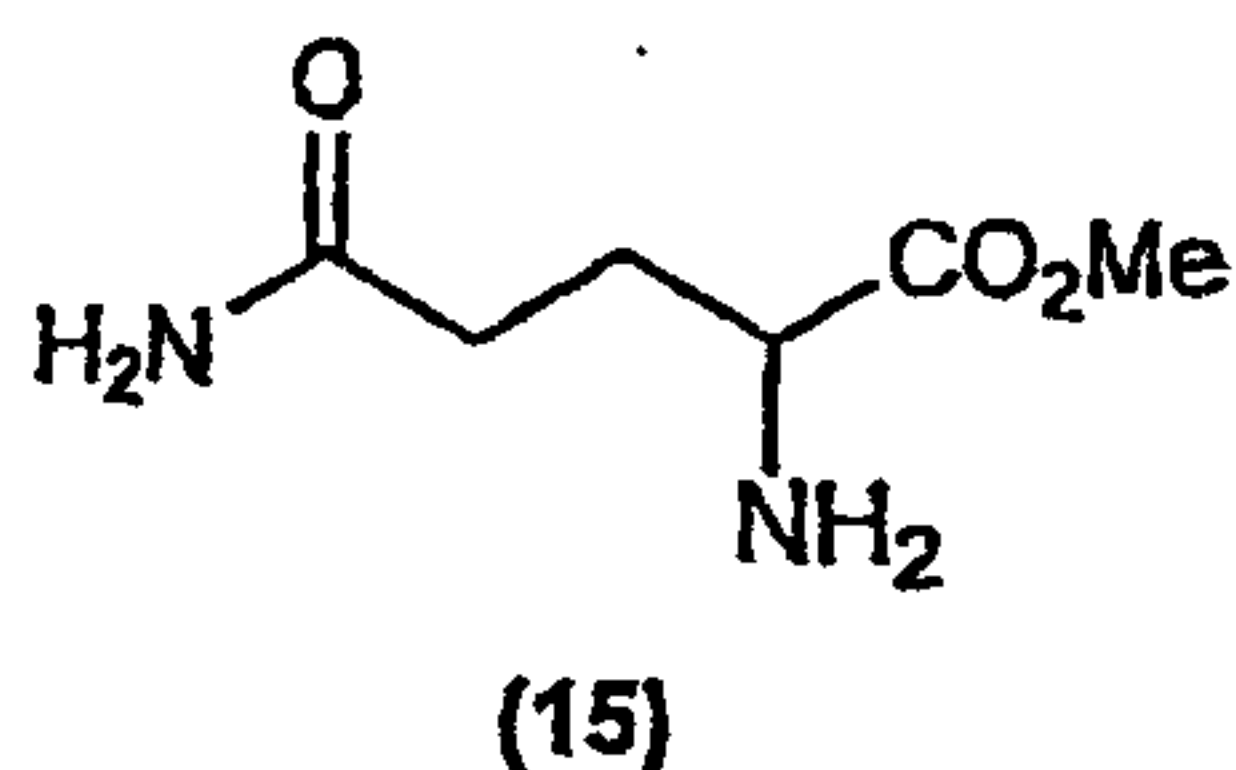


- 5 49. The process of claim 48, wherein the compound of Formula 11 is racemic.
50. The process of claim 48, wherein the compound of Formula 11 is the (+)- or (-)-enantiomer.
51. The process of claim 48, wherein the direct cyclizing occurs under acidic condition.
- 10 52. The process of claim 51, wherein the direct cyclizing occurs in the presence of *p*-toluenesulfonic acid.
53. The process of claim 48, wherein the direct cyclizing occurs under basic condition.
54. The process of claim 53, wherein the direct cyclizing occurs in the presence of
15 KO^tBu.
55. The process of claim 53, wherein the direct cyclizing occurs in the presence of K₂CO₃.
56. The process of claim 48, wherein the reducing is facilitated by a catalyst.

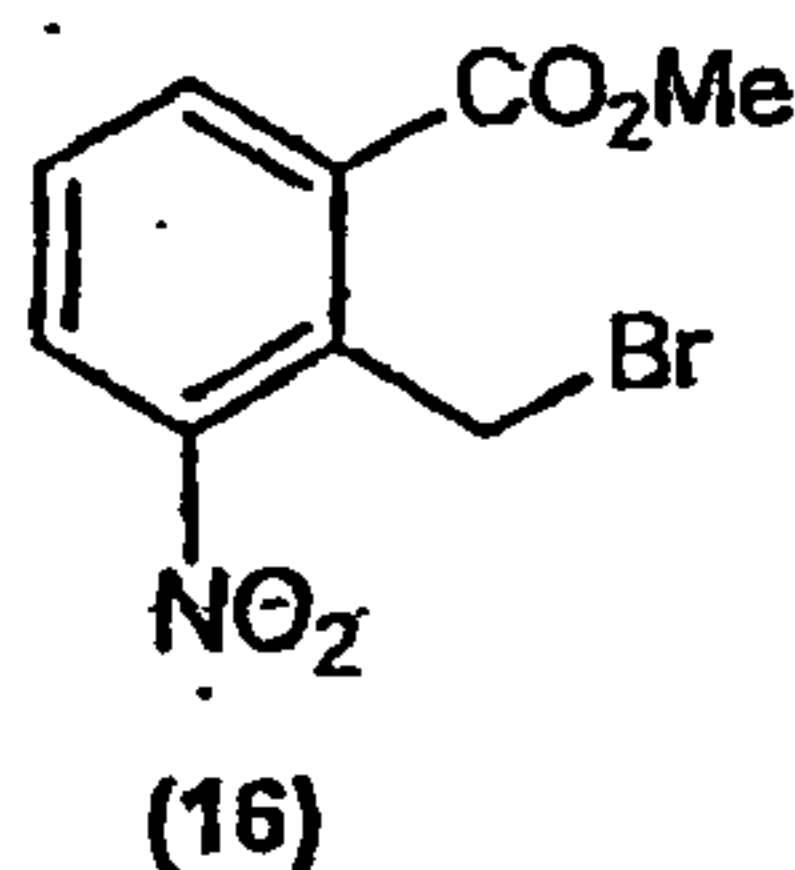
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57. The process of claim 56, wherein the catalyst is a Pd catalyst.

58. The process of claim 48, wherein the compound of Formula 12 is prepared by coupling a compound of Formula 15:



or a salt thereof with a compound of Formula 16:

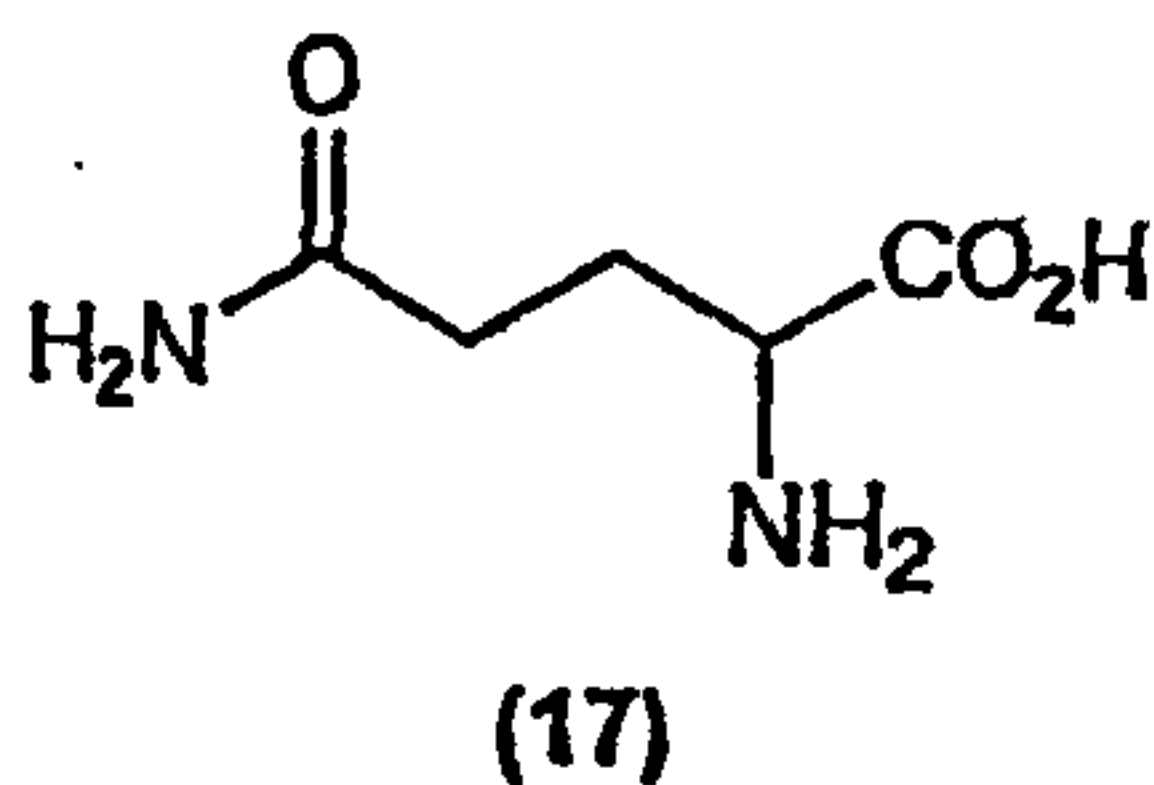


59. The process of claim 58, wherein the coupling occurs under basic condition.

60. The process of claim 59, wherein the coupling occurs in the presence of NEt_3 .

61. The process of claim 59, wherein the coupling occurs in the presence of NaHCO_3 .

62. The process of claim 58, wherein the compound of Formula 15 or a salt thereof is prepared by esterifying a compound of Formula 17:



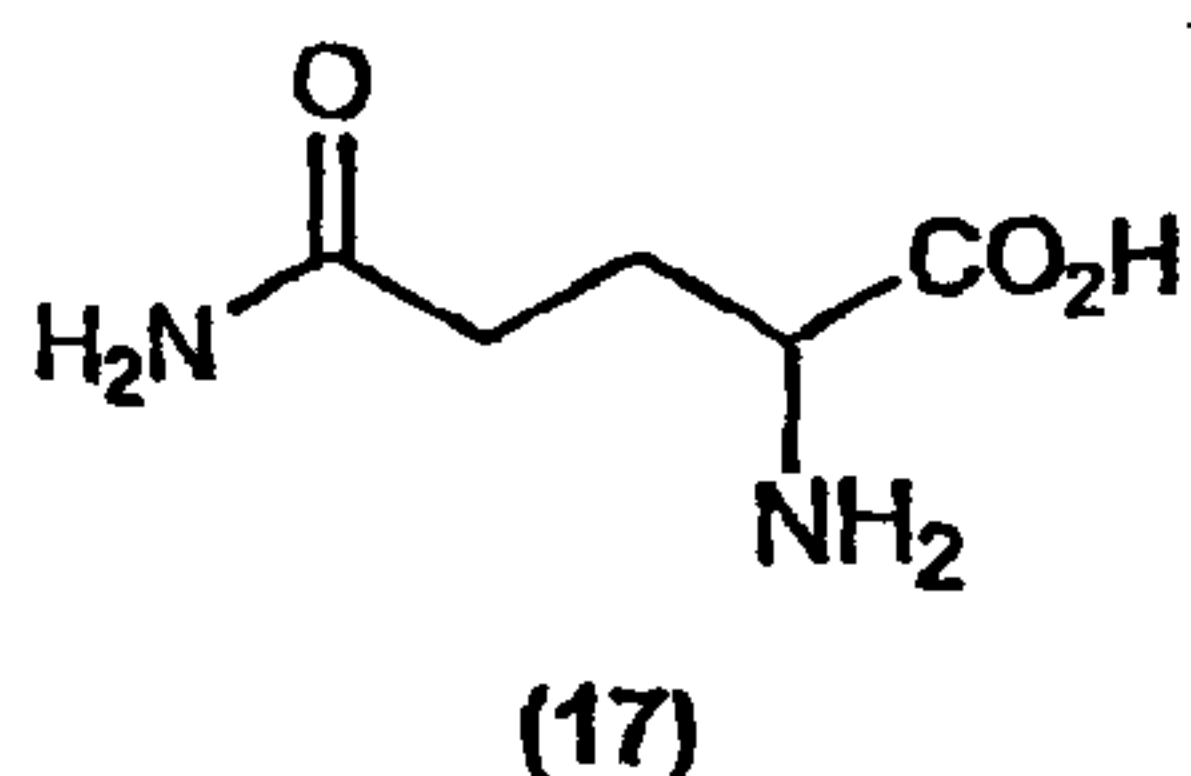
or a salt thereof as a methyl ester.

63. The process of claim 62, wherein the esterifying occurs in methanol under acidic condition.

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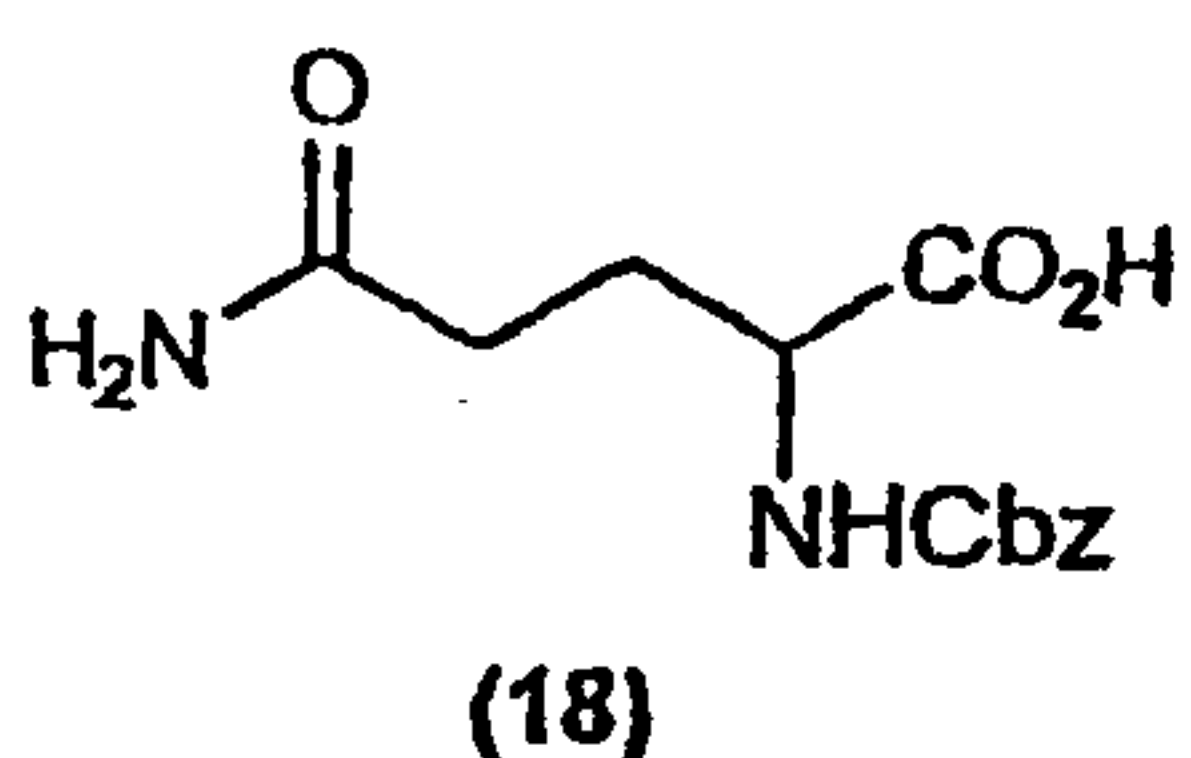
64. The process of claim 58, wherein the compound of Formula 15 or a salt thereof is prepared by:

protecting the α -amino group of a compound of Formula 17:



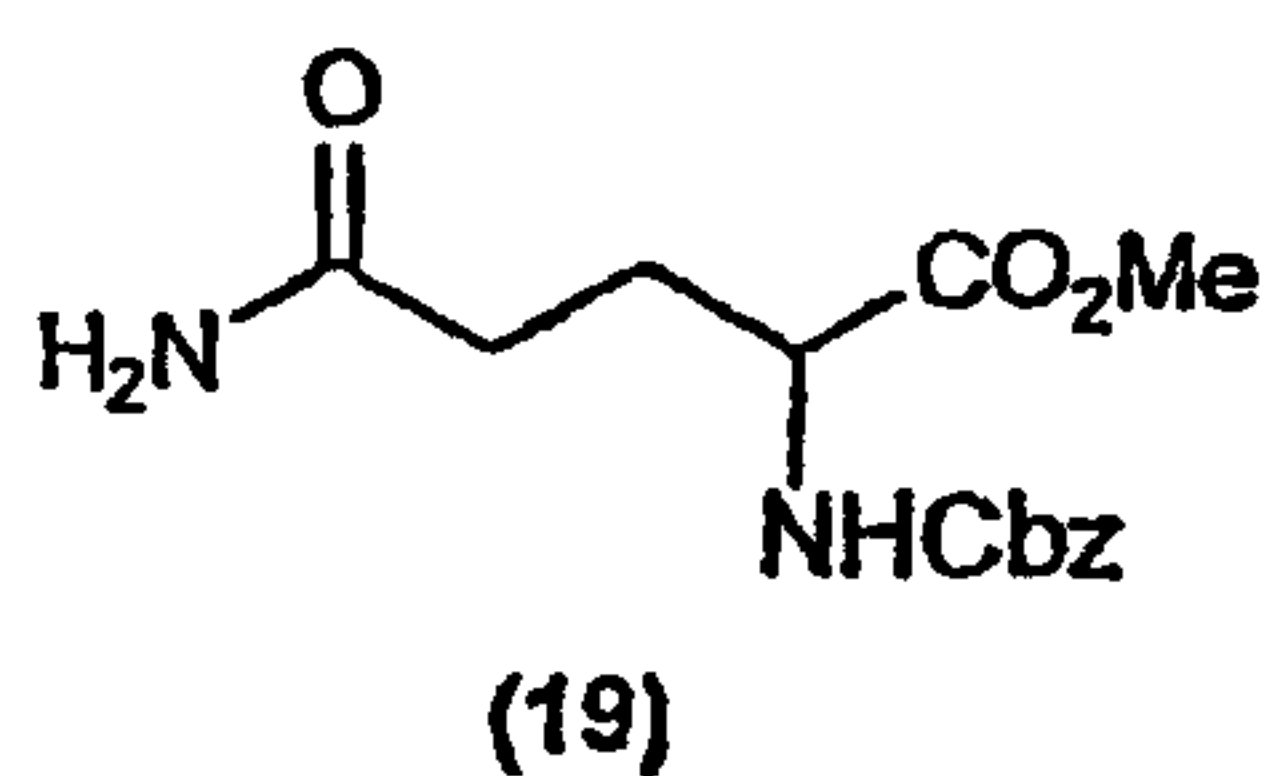
or a salt thereof as a benzyloxycarbonyl carbamate;

esterifying the *N*-protected compound of Formula 18:



as a methyl ester; and

deprotecting the α -amino group of the esterified compound of Formula 19:



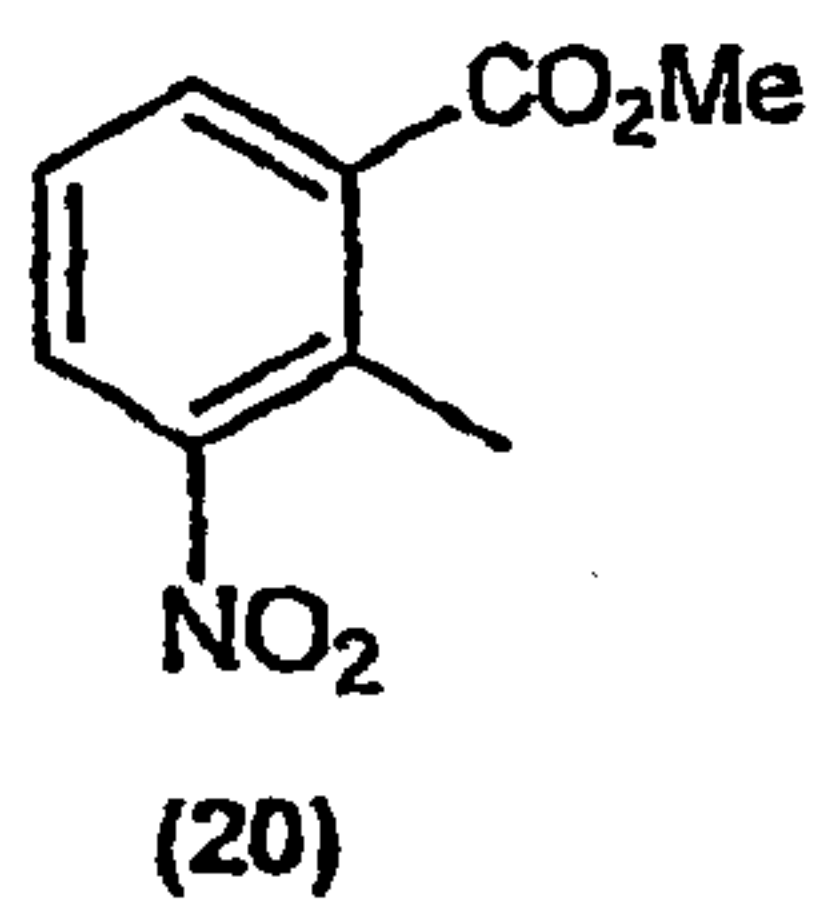
65. The process of claim 64, wherein the esterifying occurs in methanol under acidic condition.

66. The process of claim 64, wherein the deprotecting comprises removing the benzyloxycarbonyl group by hydrogenolysis with a catalyst.

67. The process of claim 66, wherein the catalyst is a Pd catalyst.

68. The process of claim 58, wherein the compound of Formula 16 is prepared by brominating a compound of Formula 20:

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69. The process of claim 68, wherein the brominating is effected by a brominating agent in the presence of a free-radical initiator.

70. The process of claim 69, wherein the brominating agent is *N*-bromosuccinimide.

71. The process of claim 69, wherein the free radical initiator is light.

72. The process of claim 69, wherein the free radical initiator is 1,1'-azobis-(cyclohexanecarbonitrile).