

Selectively Substituted Quinoline Compounds

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States provisional patent application no. 61/890,718, filed on October 14, 2013. That application is incorporated by reference herein.

BACKGROUND

[0002] Field of the Disclosure

[0003] Embodiments of the disclosure relate to selectively substituted quinoline compounds and pharmaceutical agents comprising one or more of those compounds as active ingredient(s). More particularly, embodiments of the disclosure relate to those compounds that act as an antagonist or inhibitor for Toll-like receptors (TLR) 7 and 8, and their use in a pharmaceutical composition effective for treatment of systemic lupus erythematosus (SLE) and lupus nephritis.

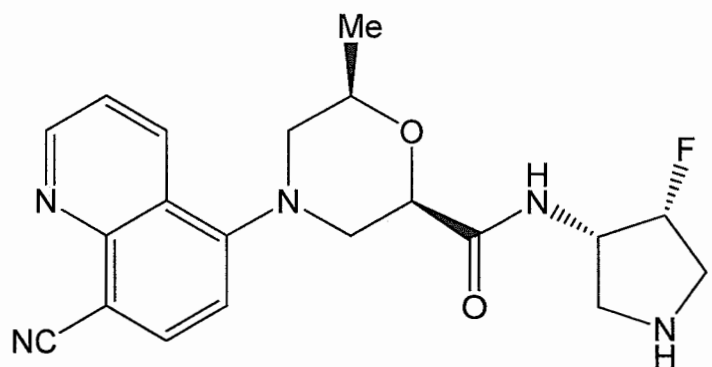
[0004] Description of Related Art

[0005] Systemic lupus erythematosus (SLE) and lupus nephritis are autoimmune diseases characterized by inflammation and tissue damage. For example, SLE may cause damage to the skin, liver, kidneys, joints, lungs, and central nervous system. SLE sufferers may experience general symptoms such as extreme fatigue, painful and swollen joints, unexplained fever, skin rash, and kidney dysfunction. Because organ involvement differs amongst patients, symptoms may vary. SLE is predominantly a disease of younger women, with peak onset between 15-40 years of age and an approximate 10-fold higher prevalence in women vs. men.

[0006] Current treatments for SLE typically involve immunomodulatory drugs such as belimumab, hydroxychloroquine, prednisone, and cyclophosphamide. All of these drugs may have dose-limiting side effects, and many patients still have poorly controlled disease.

BRIEF SUMMARY OF THE DISCLOSURE

[0007] In one aspect, the present invention refers to a compound as shown below or pharmaceutically acceptable salt thereof:

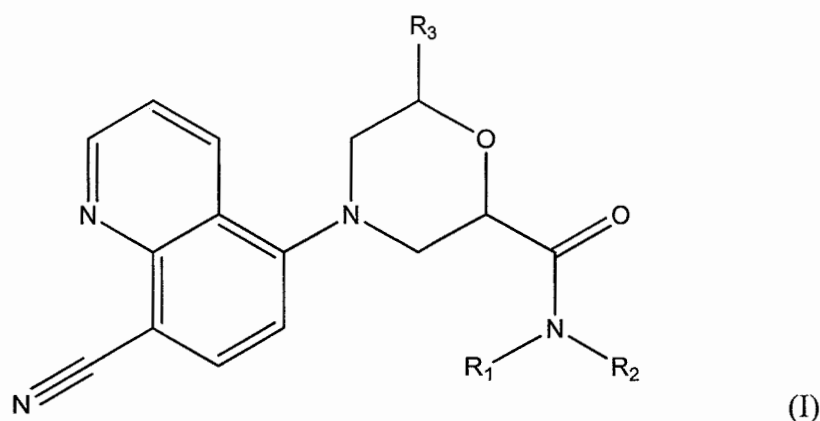


[0007a] In yet another aspect, the present invention refers to a pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt as disclosed herein and at least one pharmaceutically acceptable carrier.

[0007b] In yet another aspect, the present invention refers to a pharmaceutically acceptable salt of claim 1, wherein the pharmaceutically acceptable salt, with relative stereochemistry indicated, is (2*R*,6*R*)-4-(8-cyanoquinolin-5-yl)-*N*-((3*S*,4*R*)-4-fluoropyrrolidin-3-yl)-6-methylmorpholine-2-carboxamide hydrochloride.

[0007c] In yet another aspect, the present invention refers to a pharmaceutical composition comprising the pharmaceutically acceptable salt as disclosed herein and at least one pharmaceutically acceptable carrier.

[0007d] The disclosure provide compounds and methods of use for preventing or treating diseases or conditions characterized by Toll-like receptor 7 or 8 activation in patients. One example features a compound of formula (I):



wherein at least one of R_1 and R_2 is $-H$, methyl, or ethyl, and the other is $-H$; or the other is

C_1 - C_6 alkyl that is optionally substituted with:

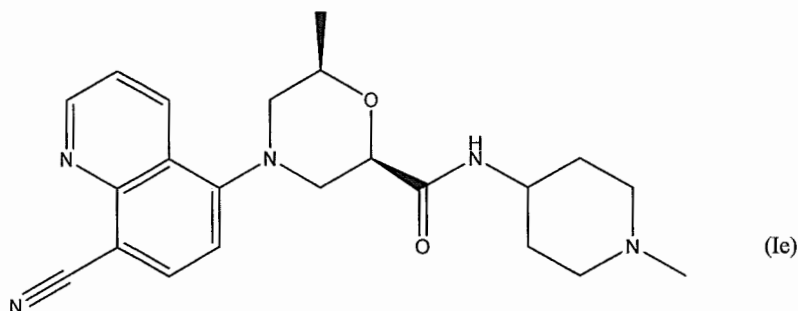
$-OH$, methoxy, ethoxy, $-OCH(CH_3)_2$, $-O(CH_2)_2CH_3$, phenyl, furanyl, $-O(CH_2)_2OH$, phenoxy, methylthio, $-F$, $-N(CH_3)_2$, cyano, pyridinyloxy, fluorophenoxy, isochromanyl, phenol, benzylamino, $-NHCH_3$, oxo-, amino, carboxyl, 7-member spiroaminyl, a three to six member cycloalkyl, saturated or unsaturated and optionally including one or more heteroatoms selected from O and N , and optionally substituted at one or more C or N atoms by methyl, cyano, fluoro, methylamino, or trifluoromethyl; or the other is

C_3 - C_7 cycloalkane, saturated or unsaturated, optionally bridged, optionally including one or more heteroatoms selected from O , S , and N , and optionally substituted at one or more C or N atoms by methyl, ethyl, pyridinyl, azetidyl, acetamidyl, carboxamidyl, cyano, fluoro, methylamino, or trifluoromethyl; or

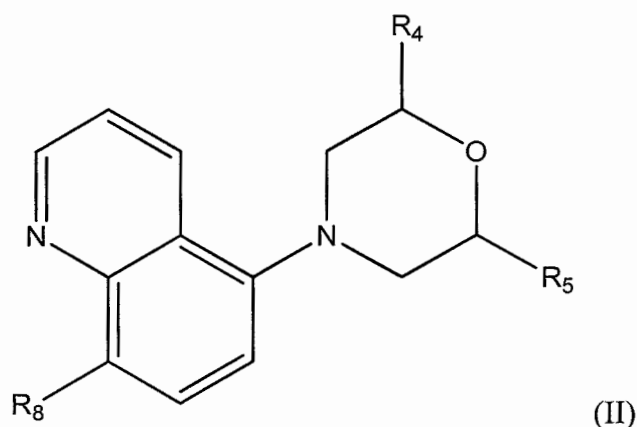
R_1 and R_2 , together with the nitrogen atom to which they are attached, form an 8 to 11 member spirodiamine, an 8 member bicyclodiamine, a 7 member spiroxamine, a piperidinyl optionally substituted with ethyl, or a four to six member cycloalkyl, optionally substituted with at least one of carboxamidyl, aminomethyl, methyl, (ethylamino)methyl, (dimethylamino)methyl, dimethylamino, (methylamino)methyl, and amino; and wherein R_3 is $-H$ or methyl.

[0008] In a further example the compound is a compound of Formula (I), having the stereochemistry set forth in one of Formula (Ia), (Ib), (Ic), or (Id), having the same substituent options as set forth above for Formula (Ia):

[0009] A further example provides a compound of Formula (Ie) (relative stereochemistry indicated):



[0010] In a further example the compound is a compound of Formula (II):



wherein

R_4 is -H or methyl;

R_5 is C_1 - C_5 alkyl that is saturated, partially saturated, or unsaturated, and that is optionally substituted with:

-H, -Cl, -F, -OH, -NH₂, oxo-, -N(CH₂CH₃)₂, phenyl, cyclohexyl, phenyltriazolyl, cyclohexyltriazolyl, pyridinyl, pyrrolidinyl,

morpholinyl optionally substituted with methyl or hydroxymethyl,

-O-, substituted with:

C_1 - C_6 alkyl, methylphenyl, methylcyclohexyl, pyridinyl, diazinyl, or phenyl optionally substituted with -F or methyl,

-NH-, substituted with:

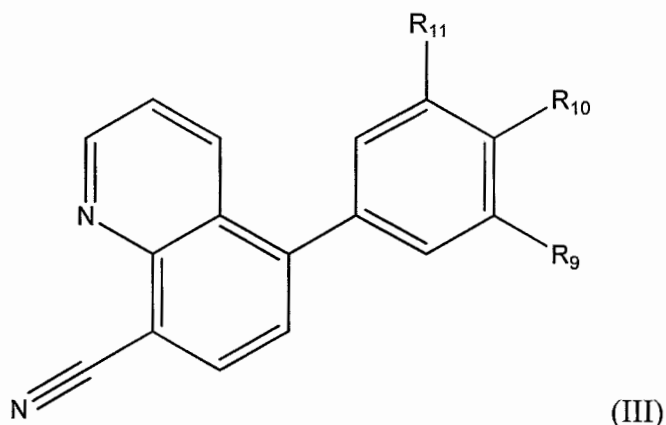
C_2 - C_7 alkyl that is linear, branched, or cyclic, saturated or unsaturated, and optionally substituted with oxo-, phenyl, methyl, or -OH,

pyridinyl optionally substituted with methyl, methoxy, phenyl, or amino,

diazinyl optionally substituted with ethyl,

[0011]

A further example provides a compound of Formula (III):



wherein

R₁₁ is H or methyl;

R₁₀ is H or, when both R₁₁ and R₉ are H, is methyl-1,4'-bipiperidinyl;

R₉ is -H or is -CH₂- substituted by 1,4'-bipiperidinyl, oxo-, hydroxyl, methylpyridinyl, or piperidinyl optionally substituted with hydroxyl, -N(CH₃)₂, or piperidinyl.

[0012]

In a further example the compound is selected from rel-(2*R*,6*R*)-4-(8-cyanoquinolin-5-yl)-N-((3*R*,4*S*)-4-fluoropyrrolidin-3-yl)-6-methylmorpholine-2-carboxamide hydrochloride, (2*R*,6*R*)-4-(8-cyanoquinolin-5-yl)-6-methyl-N-(1-methylpiperidin-4-yl)morpholine-2-carboxamide, 5-((2*S*,6*R*)-2-([1,4'-bipiperidin]-1'-ylmethyl)-6-methylmorpholino)quinoline-8-carbonitrile, and 5-((2*R*,7*R*)-2-(hydroxymethyl)-7-methyl-1,4-oxazepan-4-yl)quinoline-8-carbonitrile.

[0013]

In a further example the compound or pharmaceutically effective salt thereof of the preceding paragraph has an IC₅₀ less than or equal to 20 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further example the compound or pharmaceutically effective salt thereof of the preceding paragraph of this disclosure has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further example the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10 % fetal bovine serum at a density of 2.22X10⁵ cells/ml into a 384-well plate and incubating for 2 days at 37 °C, 5 % CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3ug/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

[0014] In further examples of the disclosure, compounds have an IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line less than or equal to 200 nM, less than or equal to 180 nM, less than or equal to 160 nM, less than or equal to 140 nM, less than or equal to 120 nM, less than or equal to 100 nM, less than or equal to 80 nM, less than or equal to 60 nM, less than or equal to 40 nM, or less than or equal to 20 nM. In further examples of the disclosure, compounds have an IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line from 10 nM to 30 nM, from 10 nM to 50 nM, from 10 nM to 100 nM, from 30 nM to 50 nM, from 30 nM to 100 nM, or from 50 nM to 100 nM. In further examples the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10 % fetal bovine serum at a density of 2.22X10⁵ cells/ml into a 384-well plate and incubating for 2 days at 37 °C, 5 % CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3ug/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

[0015] Further examples provide methods for treatment of lupus, including but not limited to treatment of systemic lupus erythematosus, cutaneous lupus, neuropsychiatric lupus, fetal heart block, and antiphospholipid syndrome, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[0016] Further examples provide methods for antagonizing TLR7, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[0017] Further examples provide methods for antagonizing TLR8, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[0018] Further examples provide pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable salt of the disclosure and at least one pharmaceutically acceptable carrier.

[0019] Further examples provide methods for treatment of systemic lupus erythematosus or lupus, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[0020] Further examples provide methods for antagonizing TLR7, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[0021] Further examples provide methods for antagonizing TLR8, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[0022] Further examples provide pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable salt of the disclosure and at least one pharmaceutically acceptable carrier.

[0023] The term “optionally substituted,” as used herein, means that the subject structure may include, but is not required to include, one or more substituents independently selected from lower alkyl, methoxy-, -OH, -NH₂, -CH₂-NH-CH₂, -OCH₂CH₂CH₃, or -OCH(CH₃)₂. If the optionally substituted moiety is cyclic, then the optional substitution may be a methyl bridge between two atoms in the ring.

[0024] The symbol “C(O)” as used herein refers to a carbonyl group having the formula C=O.

[0025] Unless otherwise specified, “a” and “an” as used in this disclosure, including the claims, mean “one or more.”

[0026] As used herein, “lower alkyl” refers to straight, or, in the case of three- and four-carbon groups, straight, branched, or cyclic saturated hydrocarbons having between one and four carbon atoms.

[0027] As used herein, the term “attached through a nitrogen” when referring to a heterocyclic moiety including nitrogen, means that a point of attachment of the moiety to another structure is through a nitrogen that is part of the heterocycle.

[0028] As used herein, the term “TLR7/8” means “TLR7 and TLR8” or “TLR7 or TLR8” or “TLR7 and/or TLR8.” The particular meaning can be understood by a person skilled in the art based upon the context in which “TLR7/8” appears.

[0029] Heterocyclic moieties recited herein include azetidiny, pyrrolidinyl, piperidinyl, methylazetidiny, pyrazolyl, piperazinyl, morpholinyl, thiazolyl, pyrrolopyrrolyl, imidazolidinyl, and isothiazolyl. Where a heterocyclic group is mentioned, unless otherwise indicated it will be understood that the heterocyclic atom(s) in the group may be at any position in the group. It will further be understood that imidazolyl, pyrazolyl, thiazolyl, and pyrrolyl may be unsaturated or partially unsaturated. An example of the disclosure may include a pharmaceutical composition that includes one or more compounds of the disclosure

with a pharmaceutically acceptable excipient. These pharmaceutical compositions may be used to treat or prevent a disease or condition characterized by TLR7/8 activation in a patient, typically a human patient, who has or is predisposed to have such a condition or disease. Examples of diseases or conditions characterized by TLR7/8 activation include systemic lupus erythematosus (SLE) and lupus nephritis.

[0030] As used herein, “effective amount” of a compound of an example of the disclosure is effective amount of the above-identified compounds in an amount sufficient to treat or prevent SLE and lupus nephritis.

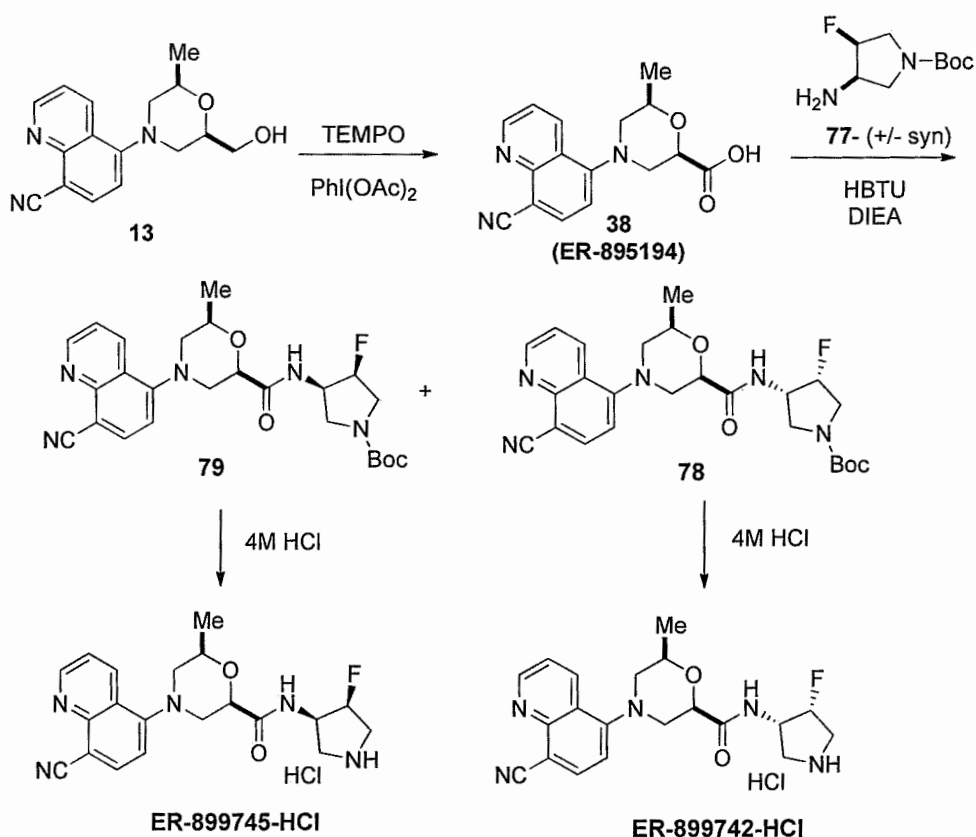
[0031] Examples presented herein may include asymmetric or chiral centers. Examples include the various stereoisomers and mixtures thereof. Individual stereoisomers of compounds of examples of the disclosure may be prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers, or by preparation of mixtures of enantiomeric compounds followed by resolution of those compounds. Suitable methods of resolution include attachment of a racemic mixture of enantiomers, designated (+/-), to a chiral auxiliary, separation of the resulting diastereomer by chromatography or recrystallization and separation of the optically pure product from the auxiliary; or direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

[0032] Examples of the disclosure also include a pharmaceutical composition including any compound of the disclosure as well as a pharmaceutically acceptable excipient. The pharmaceutical compositions can be used to treat or prevent SLE and lupus nephritis. Therefore, examples of the disclosure may also feature a method for treating or preventing SLE or lupus nephritis in a human patient having or predisposed to having lupus nephritis or SLE.

[0033] Examples of the disclosure include pharmaceutically acceptable salts of the compounds presented herein. The term “pharmaceutically acceptable salt” refers to those salts that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al., describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* 66:1-19, 1977. Salts can be prepared in situ during final isolation and purification of a compound or separately by reacting a free base group with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate,

[0403]

Scheme 19



[0404]

[0405] **ER-895194** or **38**: To a stirred solution of **13** (231.0 g, 815.3 mmol) in DCM (3.93 L) at 0 – 5 °C was added iodobenzene diacetate (525 g, 1630.6 mmol) while maintaining the temperature at < 5 °C. TEMPO (25.4 g, 162.8 mmol) was added followed by water (151 mL) after which time the resulting reaction mixture was warmed to 10 °C, stirred for 30 minutes and then allowed to warm to rt and stirred for 15 h. The completed reaction was cooled to < 15 °C and quenched by the slow addition of 1.34 L of a 10 % (w/v) solution of sodium thiosulfate in water while maintaining the reaction temperature $\leq$ 15 °C followed by additional stirring at rt for 45 min. The pH of the quenched reaction was adjusted to pH 9 by the slow addition of 1M sodium hydroxide in water while maintaining the temperature at $\leq$ 25 °C. The stirring layers were separated and the organic layer was washed with water (560 mL). 1-Butanol (2.31 L) was added to the combined aqueous layers after which time the mixture was cooled to 10 – 15 °C followed by the slow addition of 5 M sulfuric acid (231 mL) maintaining the temperature at $\leq$ 25 °C to obtain an approximate pH 5. The resultant layers were separated and the aqueous layer was extracted 3 times with 1-butanol (2.31 L) while maintaining the pH of the aqueous layer approximately pH 5 between extractions. The combined aqueous layers were concentrated while warming to 50 – 55 °C after which time the resultant yellow solid-slurry was concentrated via azeotroping three times with *n*-heptane

(693 mL each) to a volume of 1.5 L followed by the addition of DCM (2.31 L). The yellow solid suspension was stirred at rt for 1 h followed by filtration, washing the filter pad two times with DCM (462 mL). The collected yellow cake was dried under vacuum overnight at 40 °C followed by suspending in toluene (1.16 L) and concentrated to complete dryness at 45 °C in vacuo to provide **38** or **ER-895194** (187 g, 629 mmol, 77% yield) as a yellow solid.

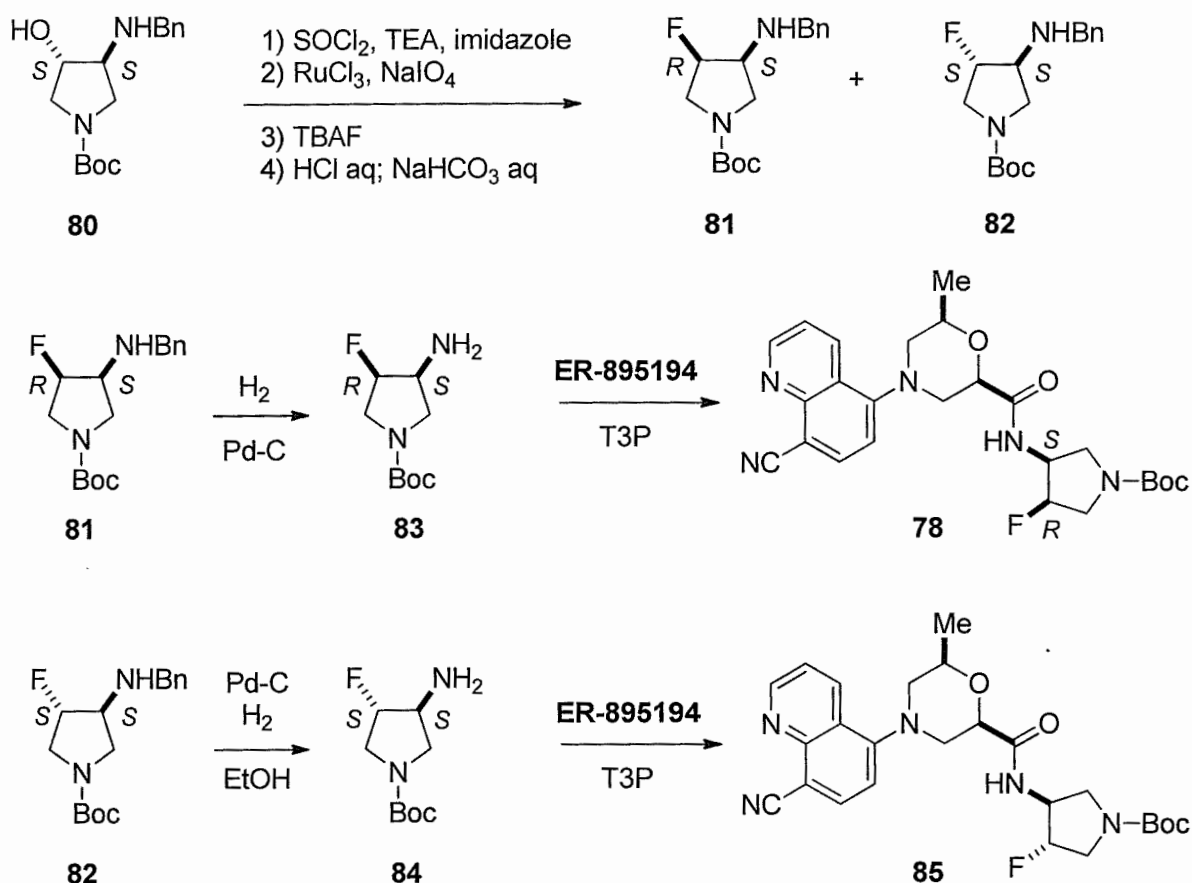
[0406] To a stirred solution of **38** (300 mg, 1.01 mmol) in DCM (2 mL) was added the mixture of (3*S*,4*R*)-*tert*-butyl 3-amino-4-fluoropyrrolidine-1-carboxylate and (3*R*,4*S*)-*tert*-butyl 3-amino-4-fluoropyrrolidine-1-carboxylate, **77** (205.3 mg, 1.005 mmol), HBTU (247 mg, 1.211 mmol) and DIEA (0.70 mL, 4.04 mmol) followed by stirring at rt for 16 h. The reaction was found complete and concentrated to dryness followed by dissolving in EtOAc (20 mL), washed 1 time with water (10 mL), 2 N citric acid in water (10 mL), saturated NaHCO₃ (10 mL), and brine (10 mL). The combined aqueous layers were extracted 3 times with EtOAc (10 mL ea.) after which time the combined organic fractions were dried over MgSO₄, filtered and concentrated to dry. The crude product was purified over a 25 g Biotage silica gel column eluting with 0-10% MeOH in DCM (200 mL total) to provide the diastereomeric mixture of **78** and **79**.

[0407] **78** and **79** were separated using Chiral Technologies' 5 uM Chiralpak IA column of appropriate size eluting with a Heptane:EtOH:MeOH:DEA (70:15:15:0.1) solvent system. Obtained after concentration and bringing to a dry solid via house vacuum: **78** (95 mg, 0.196 mmol, 19.5 % yield) as the first eluted fraction; and **79** (75 mg, 0.155 mmol, 15.4% yield) as the second eluted fraction.

[0408] **78** (95 mg, 0.196 mmol) was dissolved with stirring in dioxane (17 uL) followed by a dropwise addition of 4 N HCl in dioxane (0.49 mL 1.97 mmol, 10 equivalents) over a 3-minute period at rt. The reaction was stirred for an additional 4 h after which time the completed reaction was concentrated and azeotroped 3 times using toluene (10 mL each) to dryness and then high vacuumed dried to obtain **ER-899742-HCl** (69 mg, 0.164 mmol, 84% yield) as the HCl salt that did not require further purification.

[0409] **Indirect determination of the absolute stereochemistry of ER-899742**

[0410] **Scheme 20**



[0411] An indirect method was used to determine the absolute stereochemistry of **ER-899742** using the confirmed chiral starting material that described by Tsuzuki, et. al., in *Tetrahedron Asymmetry* **2001**, 12, 2989 to provide the chiral compound **81** in Scheme 20.

[0412] To a stirred solution of (3*S*,4*S*)-*tert*-butyl 3-(benzylamino)-4-hydroxypyrrolidine-1-carboxylate, **80** (3.091 g, 10.57 mmol) and imidazole (3.60 g, 52.9 mmol) in DCM (185 ml) was added triethylamine (4.42 ml, 31.7 mmol). The resultant mixture was cooled to 1-2 °C, and then a solution of thionyl chloride (1.16 ml, 15.9 mmol) in DCM (46 ml) was added dropwise over 30-min period. The mixture was stirred at 1-2 °C for 6 h, warm up to rt and stirred overnight after which time the reaction was quenched with water (46 ml). The organic layer was separated, concentrated to give crude product as white solid/foam, which was subjected to silica gel column chromatography (*n*-heptane/EtOAc 2:1) to give (3*S*,6*S*)-*tert*-butyl 3-benzyltetrahydropyrrolo[3,4-**d**][1,2,3]oxathiazole-5(3*H*)-carboxylate 2-oxide (2.10 g, 6.21 mmol, 58.7 % yield) as white solid.

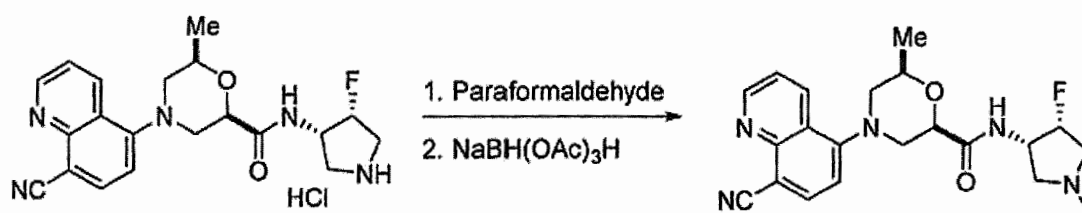
[0413] To stirred solution of (3*S*,6*S*)-*tert*-butyl 3-benzyltetrahydropyrrolo[3,4-**d**][1,2,3]oxathiazole-5(3*H*)-carboxylate 2-oxide (2.10 g, 6.21 mmol) in 1,2-dichloroethane (10 ml) diluted with acetonitrile (10 ml) and water (10 ml) cooled down to 2-3 °C was added

[0557] **ER-899477** (78 mg, 0.196 mmol, 58.3 % yield as a diastereomeric mixture) was prepared in a similar manner to **ER-899464** starting with **38** (100 mg, 0.336 mmol) and a racemic mixture of (3*S*,4*R*)-*tert*-butyl 3-amino-4-fluoropiperidine-1-carboxylate and (3*R*,4*S*)-*tert*-butyl 3-amino-4-fluoropiperidine-1-carboxylate (220 mg, 1.009 mmol).

[0558] **ER-895415** as an example for **Compound 41** in **Scheme 11**: To a stirred solution of **38** (1.10 g, 3.70 mmol) in DCM (5 mL) at 0 °C was added oxalyl chloride (1.0 mL, 11.42 mmol) dropwise over 2 min. The reaction mixture was allowed to warm to rt and stir for 1 h after which time the reaction was concentrated and dried in vacuo. The dried syrup was cooled to 0 °C followed by the slow addition of MeOH (5 mL) with stirring. The completed reaction was concentrated to dry, diluted with DCM (10 mL), washed with saturated sodium sulfite (3 mL), brine (3 mL) and then dried over Na₂SO₄, filtered and concentrated to dry. The crude product was purified over silica gel (eluting w a 0 – 50 % EtOAc in heptane gradient) to provide **ER-895415** (894 mg, 2.81 mmol, 76 % yield) after combining the desired fractions, concentrating and drying in vacuo.

[0559] Preparation of example **ER-899332** following **Scheme 21**:

[0560] **Scheme 21**

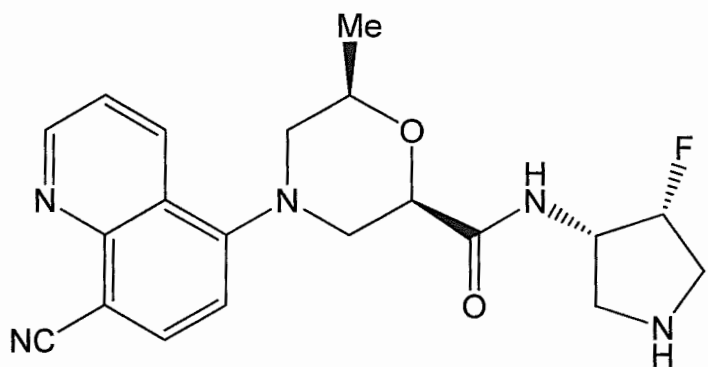


[0561] **ER-899742**

ER-899332

We claim:

1. A compound as shown below or pharmaceutically acceptable salt thereof:



2. The compound or pharmaceutically acceptable salt of any of claim 1 for use in the treatment of lupus.
3. The compound of claim 2, wherein said compound is to be administered as a pharmaceutically acceptable salt.
4. The compound or pharmaceutically acceptable salt of claim 1 for use in antagonizing TLR7.
5. The compound or pharmaceutically acceptable salt of claim 1 for use in antagonizing TLR8.
6. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of claim 1 and at least one pharmaceutically acceptable carrier.
7. The pharmaceutical composition of claim 6, wherein said compound or pharmaceutically acceptable salt thereof has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors in a HEK-293 cell line.

8. The pharmaceutical composition of claim 6, wherein said compound or pharmaceutically acceptable salt thereof has an IC₅₀ less than or equal to 20 nM against human TLR7 receptors expressed in a HEK-293 cell line.

9. The pharmaceutical composition of claim 6, wherein said compound or pharmaceutically acceptable salt thereof has an IC₅₀ less than or equal to 5 nM against human TLR7 receptors expressed in a HEK-293 cell line.

10. The pharmaceutical composition of any one of claims 7-9, wherein the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in a Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at a density of 2.22X10⁵ cells/ml into a 384-well plate and incubating for 2 days at 37°C, 5% CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3ug/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

11. The compound or pharmaceutically acceptable salt of claim 1 for use in the treatment of a systemic lupus erythematosus, cutaneous lupus, or neuropsychiatric lupus.

12. The compound of claim 11, wherein said compound is to be administered as a pharmaceutically acceptable salt.

13. A pharmaceutically acceptable salt of claim 1, wherein the pharmaceutically acceptable salt, with relative stereochemistry indicated, is (2*R*,6*R*)-4-(8-cyanoquinolin-5-yl)-*N*-((3*S*,4*R*)-4-fluoropyrrolidin-3-yl)-6-methylmorpholine-2-carboxamide hydrochloride.

14. The pharmaceutically acceptable salt of claim 13 for use in the treatment of lupus.

15. A pharmaceutical composition comprising the pharmaceutically acceptable salt of claim 13 and at least one pharmaceutically acceptable carrier.

16. The pharmaceutically acceptable salt of claim 13 for use in treating systemic lupus erythematosus, cutaneous lupus, or neuropsychiatric lupus.

17. The pharmaceutically acceptable salt of claim 13 for use in antagonizing TLR7.
18. The pharmaceutically acceptable salt of claim 13 for use in antagonizing TLR8.