

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.

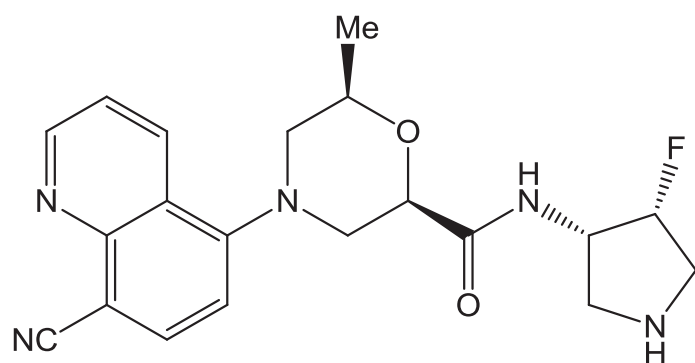
[0004] Description of Related Art

[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 disclosure refers to the use of a compound as shown below or pharmaceutically acceptable salt thereof:



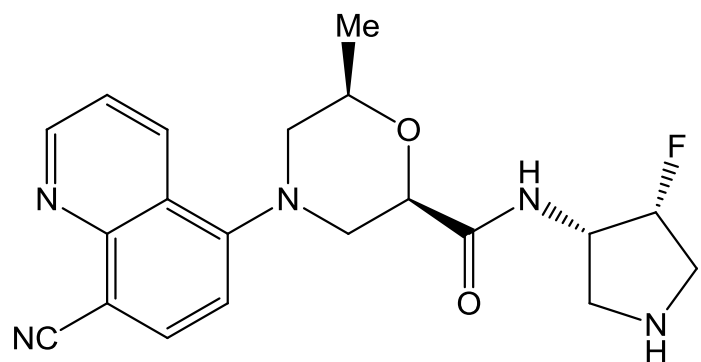
in the manufacture of a medicament for treating lupus.

[0007a] 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):

We claim:

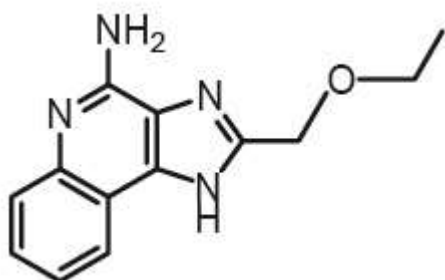
1. Use of a compound as shown below or pharmaceutically acceptable salt thereof:



in the manufacture of a medicament for treating lupus.

2. The use of claim 1, wherein said compound is to be administered as a pharmaceutically acceptable salt.
3. The use of claim 1, 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.
4. The use of claim 3, 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.
5. The use of claim 3, 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.
6. The use of any one of claims 3-5, 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 2.22×10^5 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)



at 3µg/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

7. The use of claim 1 or 2 wherein lupus is selected from the group consisting of a systemic lupus erythematosus, cutaneous lupus, and neuropsychiatric lupus.

8. The use 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.