THERAPEUTIC COMPOUNDS, FORMULATIONS, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit and priority of U.S. Provisional Application No. 62/965,738, filed on January 24, 2020, the content of which is hereby incorporated by reference in their entirety.

TECHNICAL FIELD

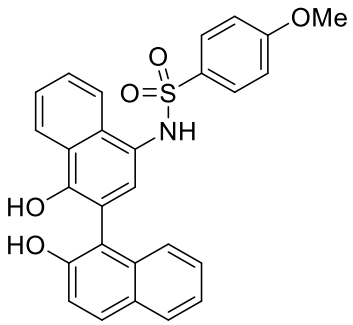
[0002] Provided herein is a compound of Formula (I), and pharmaceutical compositions and uses thereof, such as in the treatment of cancer, fibrosis, or chronic inflammation.

BACKGROUND

[0003] While great strides have been made in the treatment of cancer, a cure remains elusive. In recent years, advancements in formulation chemistry have increased the range of therapeutic compounds that can be utilized in cancer treatment.

SUMMARY

[0004] Provided in some examples herein is a compound of Formula (I):



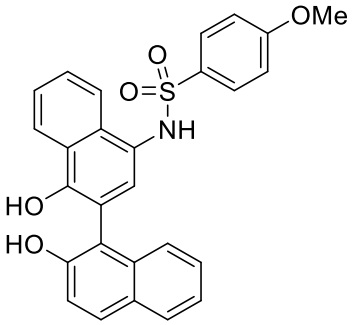
(I)

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such as for use in therapies for cancer, fibrosis, or chronic inflammation. Provided in certain examples are pharmaceutical compositions comprising a compound of Formula (I). In general instances, compounds of Formula (I) have low solubility and are very difficult to formulate in a practical and usable form. For example, in some instances, formulations, such as comprising a combination of Labrasol® and PEG400 (60:40), require unmanageable pill burden at even modest dosing. In certain instances, provided herein are compositions and formulations capable of providing good solubility of a compound of Formula (I) and/or reducing pill burden in therapies involving a compound of Formula (I).

[0004a] In one aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a. at least 50 mg of a compound of Formula (I):



(I)

;

b. a glyceride emulsifier present in the composition in a weight ratio of compound of Formula (I) to emulsifier of about 1:1 to about 1:2;

c. a solubilizer present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:2 to about 1:4, wherein the solubilizer is polyoxyl castor oil;

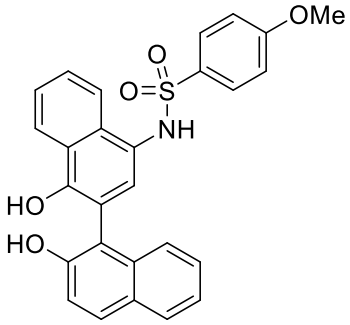
d. a polyethylene glycol (PEG) present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:3 to about 1:5;

e. a surfactant present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:1 to about 1:2, wherein the surfactant is polysorbate; and

f. an antioxidant present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 15:1 to about 25:1.

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a. at least 50 mg of a compound of Formula (I):



(I)

;

b. a glyceride emulsifier present in the composition in a weight ratio of compound of Formula (I) to emulsifier of about 1:1;

c. a solubilizer present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:3, wherein the solubilizer is polyoxyl castor oil;

d. a polyethylene glycol (PEG) present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:4;

e. a surfactant present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:2, wherein the surfactant is polysorbate; and

f. an antioxidant present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 20:1.

[0004c] In a further aspect of the present disclosure, there is provided an oral dosage form comprising the pharmaceutical composition disclosed herein contained within a capsule.

[0004d] In another aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating cancer.

[0004e] In a further aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating fibrosis.

[0004f] In another aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating chronic inflammation.

[0004g] In a further aspect of the present disclosure, there is provided a use of the oral dosage form of disclosed herein in the manufacture of a medicament for treating chemotherapy-induced peripheral neuropathy.

[0004h] In another aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating diabetic neuropathy.

[0004i] In a further aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating familial amyloid polyneuropathy.

[0004j] In another aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating cachexia.

[0004k] In a further aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein in the manufacture of a medicament for treating anaphylaxis.

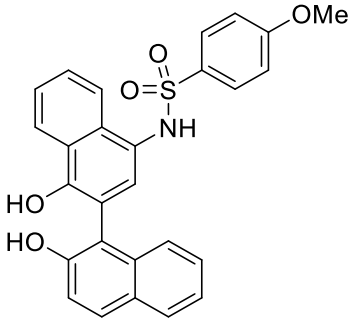
[0004l] In another aspect of the present disclosure, there is provided the oral dosage form disclosed herein for use in therapy.

[0005] While a compound of Formula (I) is generally considered to be highly insoluble (akin to “brick dust”), in certain instances, compositions and formulations provided herein are able to provide high loading of a compound of Formula (I), good ability to solubilize a compound of Formula (I), good ability to provide for high bioavailability of a compound of Formula (I), good stability (e.g., chemical and/or physical stability),

and/or reduce pill burden for individuals receiving therapies involving the administration of a compound of Formula (I).

[0006] In some examples, a composition, formulation or oral dosage form provided herein comprises, in addition to the compound of Formula (I), any suitable excipient or combination of excipients. In certain examples, the formulation (e.g., excipient or combination of excipients thereof) is suitable for providing good solubility of a compound of Formula (I), good physical stability (e.g., good solubility and/or dispersion of a compound of Formula (I)), good chemical stability of a compound of Formula (I), good (e.g., oral) bioavailability of a compound of Formula (I), and/or desirable or therapeutic effect, with a manageable (e.g., fewer than 25 pills per day, or other amount described herein) or reduced pill burden (e.g., relative to two-component excipient systems described herein) and/or an acceptable toxicity profile (e.g., gastrointestinal toxicity profile, such as due at least in part to the low or reduced levels of excipient(s) present in the compositions and formulations provided herein relative to alternative formulations).

[0007] Provided in certain examples herein are pharmaceutical compositions, formulations, and oral dosage forms comprising an (e.g., therapeutically effective) amount of a compound of Formula (I):



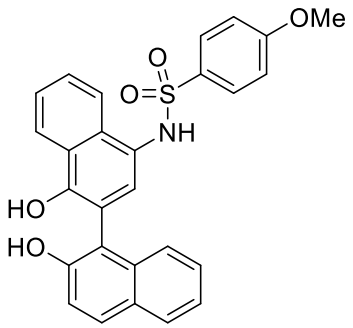
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[0008] In some examples, provided herein, are methods of using a compound of Formula (I), or a composition, formulation, or oral dosage form comprising a compound of Formula (I). In certain examples, such methods are methods for providing a therapeutic effect, such as treating a disease or disorder mediated by STAT3, cancer, fibrosis, or chronic inflammation (e.g., with a manageable or reduced pill burden). In some examples, methods provided herein comprise administering a compound of Formula (I), or a composition, formulation, or oral dosage form thereof, such as to achieve a certain pharmacokinetic profile, such as described herein.

[0009] Provided herein, in one example, is a pharmaceutical composition comprising:

a. a therapeutically effective amount of a compound of Formula (I):



(I)

;

b. an emulsifier (e.g., glyceride), the emulsifier being present in the composition in a weight ratio of compound of Formula (I) to the emulsifier of about 1:1 to about 1:2 (e.g., about 1:1.5);

c. a solubilizer, the solubilizer being present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:1 to about 1:5 (e.g., about 1:2 to about 1:4, e.g., about 1:3);

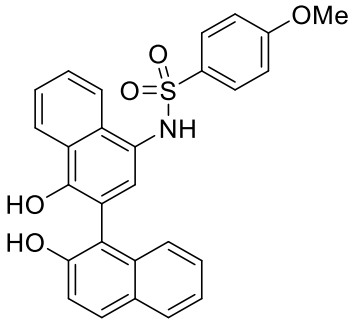
d. a polyethylene glycol (PEG), the polyethylene glycol being present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:2 to about 1:6 (e.g., about 1:3 to about 1:5, e.g., about 1:4);

e. a surfactant, the surfactant being present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 2:1 to about 1:2 (e.g., about 1:1 to about 1:2, e.g., about 1:1); and

f. an (e.g., optional) antioxidant, the antioxidant being present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 10:1 to about 30:1 (e.g., about 15:1 to about 25:1, e.g., about 20:1).

[0010] Provided herein, in one example, is a pharmaceutical composition comprising:

a. a therapeutically effective amount of a compound of Formula (I):



(I)

;

b. an emulsifier (e.g., glyceride), the emulsifier being present in the composition in a weight ratio of compound of Formula (I) to the emulsifier of about 1:3 to about 1:7;

c. a solubilizer, the solubilizer being present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:10 to about 1:20 (e.g., about 1:11 to about 1:16);

d. a polyethylene glycol (PEG), the polyethylene glycol being present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:12 to about 1:20 (e.g., about 1:15 to about 1:17);

e. a surfactant, the surfactant being present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:2 to about 1:6 (e.g., about 1:3 to about 1:5);

f. an (e.g., optional) antioxidant, the antioxidant being present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 2:1 to about 20:1 (e.g., about 5:1).

[0011] In certain examples, the composition is or is a part of a self-emulsifying drug dispersion (SEDD). In certain examples, the composition is a capsule fill formulation. In certain examples, the composition further comprises a capsule shell.

[0012] In certain examples, the compound of Formula (I) is present in the formulation in a concentration of at least 50 mg/g (e.g., at least 60 mg/g, at least 70 mg/g, at least 80 mg/g, or at least 90 mg/g) (e.g., excluding the mass of a capsule shell). In certain examples, the compound of Formula (I) is present in the formulation in a concentration of at least 60 mg/mL (e.g., at least 70 mg/mL, at least 80 mg/mL, at least 90 mg/mL, or at least 100 mg/mL) (e.g., excluding the volume of a capsule shell). In certain examples, at least 60 wt. % (e.g., at least 80 wt. %, at least 90 wt. %, or at least 95 wt. %) of the compound of Formula (I) is soluble (dissolved) in the composition.

[0013] In certain examples, the emulsifier is a glyceride emulsifier. In certain examples, the emulsifier comprises optionally polyglycolyzed medium- and/or long-chain mono-, di-, and/or tri-glyceride(s).

[0014] In certain examples, the solubilizer is a polyoxyl castor oil or a vitamin E polyethylene glycol succinate (TPGS).

[0015] In certain examples, the polyethylene glycol (PEG) has an average molecular weight of about 200 to about 1000 (e.g., about 500 to about 700, or about 550 to about 650, or about 600).

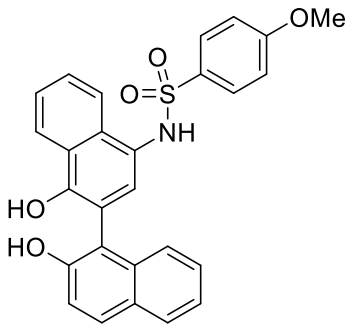
[0016] In certain examples, the surfactant is polysorbate (e.g., polysorbate 20).

[0017] In certain examples, the antioxidant is vitamin E. In certain examples, the antioxidant is ascorbyl palmitate. In certain examples, the antioxidant is butylated hydroxytoluene. In certain examples, the antioxidant is triethyl citrate. In certain examples, the antioxidant is citric acid.

[0018] In certain examples, the composition further comprises a co-solvent (e.g., Transcutol®).

[0019] Provided herein, in another example, is an oral dosage form comprising a pharmaceutical composition, the pharmaceutical composition comprising:

a. at least 40 mg (e.g., at least 50 mg, at least 60 mg, or at least 75 mg) of a compound of Formula (I):



(I)

;

b. an emulsifier (e.g., glyceride), the emulsifier being present in the composition in a weight ratio of compound of Formula (I) to emulsifier of about 1:1 to about 1:2 (e.g., about 1:1.5);

c. a solubilizer, the solubilizer being present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:1 to about 1:5 (e.g., about 1:2 to about 1:4, e.g., about 1:3);

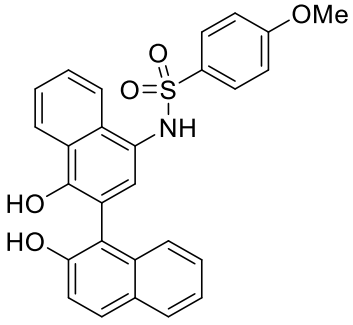
d. a polyethylene glycol (PEG), the polyethylene glycol being present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:2 to about 1:6 (e.g., about 1:3 to about 1:5, e.g., about 1:4);

e. a surfactant, the surfactant being present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 2:1 to about 1:2 (e.g., about 1:1 to about 1:2, e.g. about 1:2); and

f. an (e.g., optional) antioxidant, the antioxidant being present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 10:1 to about 30:1 (e.g., about 15:1 to about 25:1, e.g., about 20:1).

[0020] Provided herein, in another example, is an oral dosage form comprising a pharmaceutical composition, the pharmaceutical composition comprising:

a. at least 40 mg (e.g., at least 50 mg, at least 60 mg, or at least 75 mg) of a compound of Formula (I):



(I)

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b. an emulsifier (e.g., glyceride), the emulsifier being present in the composition in a weight ratio of compound of Formula (I) to emulsifier of about 1:3 to about 1:7;

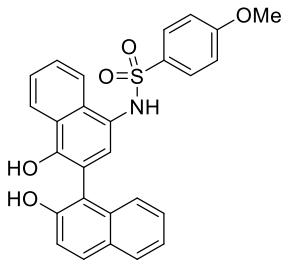
c. a solubilizer, the solubilizer being present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:10 to about 1:20 (e.g., about 1:11 to about 1:16);

d. a polyethylene glycol (PEG), the polyethylene glycol being present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:12 to about 1:20 (e.g., about 1:15 to about 1:17);

e. a surfactant, the surfactant being present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:2 to about 1:6 (e.g., about 1:3 to about 1:5);

f. an (e.g., optional) antioxidant, the antioxidant being present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 2:1 to about 20:1 (e.g., about 5:1).

[0021] Provided herein, in another example, is an oral dosage form comprising a pharmaceutical composition, the pharmaceutical composition comprising at least 40 mg (e.g., at least 50 mg, at least 60 mg, or at least 75 mg) of a compound of Formula (I):



(I)

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[0022] In certain examples, the oral dosage form further comprises a capsule. In certain examples, the composition is configured entirely within the capsule. In certain examples, the capsule is size 00 or smaller.

[0023] In certain examples, the pharmaceutical composition further comprises an emulsifier (e.g., glyceride). In certain examples, the emulsifier is present in the composition in a weight ratio of compound of Formula (I) to the emulsifier of about 1:1 to about 1:2 (e.g., about 1:1.5). In certain examples, the emulsifier is present in the composition in a weight ratio of compound of Formula (I) to the emulsifier of about 1:3 to about 1:7.

[0024] In certain examples, the pharmaceutical composition further comprises a solubilizer. In certain examples, the solubilizer is present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:1 to about 1:5 (e.g., about 1:2 to about 1:4, e.g., about 1:3). In certain examples, the solubilizer is present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:10 to about 1:20 (e.g., about 1:11 to about 1:16).

[0025] In certain examples, the pharmaceutical composition further comprises a polyethylene glycol (PEG). In certain examples, the polyethylene glycol is present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:2 to about 1:6 (e.g., about 1:3 to about 1:5, e.g.,

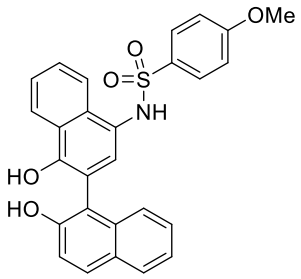
about 1:4). In certain examples, the polyethylene glycol is present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:12 to about 1:20 (e.g., about 1:15 to about 1:17).

[0026] In certain examples, the pharmaceutical composition further comprises a surfactant. In certain examples, the surfactant is present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 2:1 to about 1:2 (e.g., about 1:1 to about 1:2, e.g. about 1:2). In certain examples, the surfactant is present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:2 to about 1:6 (e.g., about 1:3 to about 1:5).

[0027] In certain examples, the pharmaceutical composition further comprises an antioxidant. In certain examples, the antioxidant is present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 10:1 to about 30:1 (e.g., about 15:1 to about 25:1, e.g., about 20:1). In certain examples, the antioxidant is present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 2:1 to about 20:1 (e.g., about 5:1).

[0028] In certain examples, the composition is as described in any of the previously described examples.

[0029] Provided herein, in another example, is a method of treating fibrosis, cancer, or chronic inflammation in an individual in need thereof, the method comprising administering to the individual a high dose of a compound of Formula (I):



(I)

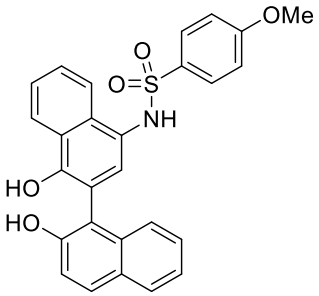
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the high dose of the compound of Formula (I) comprising administration of at least 15 mg/kg/day of the compound of Formula (I) to the individual.

[0030] In certain examples, administering the compound of Formula (I) comprises administering any pharmaceutical composition, formulation, or oral dosage form described herein. In certain examples, the method comprises administering the compound of Formula (I) in any suitable dose. In certain examples, the method comprises administering the compound of Formula (I) in any suitable number of oral dosage forms per day. In certain examples, the method comprises administering the compound of Formula (I) in a total of no more than 50 oral dosage forms per day. In certain examples, the method comprises administering the compound of Formula (I) in a total of no more than 25 oral dosage forms per day. In certain examples, the method comprises administering the compound of Formula (I) in a total of no more than 15 oral dosage forms per day.

[0031] In certain examples, the method comprises administering the compound of Formula (I) in a total of no more than 0.3 oral dosage forms per 1 kg of mass of the individual per day. In certain examples, the method comprises administering the compound of Formula (I) in a total of no more than 0.35 oral dosage forms per 1 kg of mass of the individual per day. For example, in an individual weighing 75 kg, the number of oral dosage forms administered per day would not exceed about 26 (i.e., 0.35 oral dosage forms per 1 kg of mass * 75 kg of mass = 26.25 oral dosage forms).

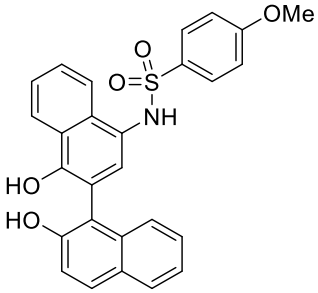
[0032] Provided herein, in another example, is a method of treating fibrosis, cancer, or chronic inflammation in an individual in need thereof, the method comprising administering to the individual a plurality of oral dosage forms, the plurality of oral dosage forms collectively comprising a therapeutically effective amount of a compound of Formula (I):



(I)

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[0033] Provided herein, in another example, is a method of treating fibrosis, cancer, or chronic inflammation in an individual in need thereof, the method comprising administering to the individual a plurality of oral dosage forms, the plurality of oral dosage forms collectively comprising a therapeutically effective amount of a compound of Formula (I):



(I)

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the plurality of oral dosage forms comprising no more than 0.35 oral dosage forms for every 1 kg of mass of the individual per day (e.g., on average or maximum).

[0034] In some examples, any suitable (e.g., therapeutically effective) amount of a compound of Formula (I) is provided to an individual, such as an individual in need thereof. In certain examples, the amount of compound of Formula (I) varies depending on the disease treated. For example, in some instances, higher doses are utilized in cancer therapies relative to fibrosis or chronic inflammation diseases. In some examples, the method comprises administering at least 1 mg/kg/day of the compound of Formula (I) to the

individual. In specific examples, the method comprises administering at least 2 mg/kg/day of the compound of Formula (I) to the individual. In more specific examples, the method comprises administering at least 5 mg/kg/day of the compound of Formula (I) to the individual. In certain examples, the method comprises administering at least 10 mg/kg/day of the compound of Formula (I) to the individual. In certain examples, the method comprises administering at least 15 mg/kg/day of the compound of Formula (I) to the individual. In certain examples, the method comprises administering at least 20 mg/kg/day of the compound of Formula (I) to the individual. In certain examples, the method comprises administering at least 25 mg/kg/day of the compound of Formula (I) to the individual. In certain examples, the method comprises administering at least 30 mg/kg/day of the compound of Formula (I) to the individual.

[0035] In certain examples, a cancer treated according to a method provided herein is a liver cancer, lung cancer, head and neck cancer, breast cancer, skin cancer, kidney cancer, testicular cancer, colon cancer, rectal cancer, gastric cancer, metastatic melanoma, prostate cancer, ovarian cancer, cervical cancer, bone cancer, spleen cancer, gall bladder cancer, brain cancer, pancreatic cancer, stomach cancer, anal cancer, prostate cancer, multiple myeloma, post-transplant lymphoproliferative disease, restenosis, myelodysplastic syndrome, leukemia, lymphoma, or acute myelogenous leukemia. In some examples, a cancer treated according to a method provided herein is a liver cancer, lung cancer, hepatocellular carcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer, or estrogen receptor-positive breast cancer. In some examples, a cancer treated according to a method provided herein is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, leukemia, or pancreatic cancer. In some examples, the leukemia is acute myelogenous leukemia.

[0036] In some examples, chronic inflammation treated herein is inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, asthma, anaphylaxis, cancer cachexia, chronic kidney disease cachexia, nonalcoholic steatohepatitis (NASH), psoriasis, uveitis, scleritis, multiple sclerosis, or pancreatitis. In some examples, chronic inflammation treated herein is inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, asthma, anaphylaxis, cancer cachexia, chronic kidney disease cachexia, or nonalcoholic steatohepatitis (NASH). In some examples, the anaphylaxis comprises anaphylactic shock.

[0037] In certain examples, the fibrosis is skin fibrosis (or dermal fibrosis), cardiac fibrosis, cirrhosis, pulmonary fibrosis, bone marrow fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneum, renal fibrosis, myelofibrosis, non-alcoholic fatty liver disease, steatohepatitis, systemic sclerosis (including diffuse systemic sclerosis or limited systemic sclerosis), endomyocardial fibrosis, myocardial infarction, atrial fibrosis, mediastinal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Keloid, arthrofibrosis, adhesive capsulitis, or cystic fibrosis. In certain examples, the fibrosis is skin fibrosis (scleroderma), cardiac fibrosis, cirrhosis, pulmonary fibrosis, bone marrow fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneum, myelofibrosis, non-alcoholic fatty

liver disease, steatohepatitis, or systemic sclerosis. In certain examples, the fibrosis is skin fibrosis (scleroderma), cardiac fibrosis, cirrhosis, or pulmonary fibrosis.

[0038] In certain examples, the fibrosis is fibrosis following exposure to certain drugs such as chemotherapy, fibrosis following exposure to environmental or other toxins or allergens, fibrosis occurring after an ischemia/reperfusion injury such as myocardial infarction or hypotension, fibrosis occurring after radiation, fibrosis following hepatitis induced by alcohol, toxins, drugs or infections, primary biliary cirrhosis, fibrosis following viral infections involving the heart, liver, or lung, and/or idiopathic retroperitoneal fibrosis.

[0039] In certain examples, any method provided herein is a method of treating muscle wasting, muscle weakness, or cachexia. The muscle weakness and/or muscle wasting and/or cachexia may have an unknown cause or it may be associated with an underlying condition. The underlying condition may be a catabolic condition. In some examples, the underlying medical condition associated with cachexia is least renal failure, cancer, AIDS, HIV infection, chronic obstructive lung disease (including emphysema), multiple sclerosis, congestive heart failure, tuberculosis, familial amyloid polyneuropathy, acrodynia, hormonal deficiency, metabolic acidosis, infectious disease, chronic pancreatitis, autoimmune disorder, celiac disease, Crohn's disease, electrolyte imbalance, Addison's disease, sepsis, burns, trauma, fever, long bone fracture, hyperthyroidism, prolonged steroid therapy, surgery, bone marrow transplant, atypical pneumonia, brucellosis, endocarditis, Hepatitis B, lung abscess, mastocytosis, paraneoplastic syndrome, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, myositis, polymyositis, dematomyosytis, rheumatological diseases, autoimmune disease, collagen-vascular disease, visceral leishmaniasis, prolonged bed rest, and/or addiction to drugs, such as amphetamine, opiates, or barbitutates.

[0040] In certain examples, any method provided herein is a method of treating, preventing, or reducing the risk or severity of an allergic reaction. In some examples, the allergic reaction is induced following an exposure to an allergen. In some examples, the allergen is a food allergen (such as milk, legumes, shellfish, tree nuts, eggs, fish, soy, and wheat), an environmental allergen or seasonal allergen (such as pollen or mold), a venom allergen (such as from wasp, bee, ant, hornet, yellow jacket, or asp), a medication allergen (such as anesthetics, β-lactam antibiotics, aspirin, non-steroidal anti-inflammatory drug, chemotherapy, vaccine, protamine, or herbal preparations), or latex. In some examples, the allergic reaction is anaphylaxis, anaphylactic shock, allergic rhinitis, urticaria, food allergy, drug allergy, hymenoptera allerga, bronchial constriction, asthma, or eczema.

[0041] In certain examples, any method provided herein is a method of treating a viral infection. In some examples, the viral infection is a chronic viral infection. In some examples, the chronic viral infection is AIDS, HIV infection, Hepatitis B infection, Hepatitis C virus infection, or Epstein-Barr virus infection.

[0042] In certain examples, any method provided herein is a method of treating graft-versus-host diseases, pulmonary lymphangioleiomyomatosis, chagasic cardiomyopathy, age-related macular degeneration,

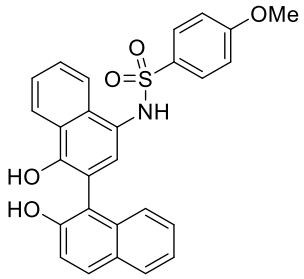
amyloidosis, astrogliosis in Alzheimer's or other neurodegenerative diseases, or familial amyloid polyneuropathy.

[0043] In certain examples, any method provided herein is a method of treating a neurodegenerative disease. In some examples, the neurodegenerative disease is chemotherapy-induced peripheral neuropathy, diabetic neuropathy, or chemobrain.

[0044] In certain examples, any method provided herein is a method of treating or reducing the risk or severity of insulin resistance. In some examples, the insulin resistance is a result of an underlying condition. In some examples, the insulin resistance is associated with muscle of the individual being treated. In some examples, the insulin resistance is caused by any reason for the individual, such as elevated free fatty acids in the blood, obesity, being overweight, having visceral fat, having a high fructose intake, having inflammation, being inactive, dysbiosis of the gut microbiota, and/or being genetically predisposed. In certain examples, any method provided herein is a method of treating or reducing the risk or severity of medical conditions associated with insulin resistance or that are complications of insulin resistance at least in part, such as severe high blood sugar; severe low blood sugar; heart attack; stroke; kidney disease (including chronic, for example, chronic kidney disease (CKD)); eye problems; cancer; non-alcoholic fatty liver disease (NAFLD); polycystic ovarian syndrome (PCOS); metabolic syndrome; diabetes; or Alzheimer's disease, for example. In certain examples, the insulin resistance is a hallmark of metabolic syndrome and type 2 diabetes. Metabolic syndrome is a group of risk factors associated with type 2 diabetes and heart disease. Its symptoms include high blood triglycerides, blood pressure, belly fat, and blood sugar, as well as low HDL (good) cholesterol levels.

[0045] In specific examples, any method provided herein is a method of treating cancer, such as a cancer described herein. In some other specific examples, any method provided herein is a method for treating fibrosis, such as a type of fibrosis or disease or disorder associated therewith described herein. In some other specific examples, any method provided herein is a method for treating chronic inflammation, such as any type of chronic inflammation described herein. In certain alternative examples, any therapeutic method provided herein is a method of treating a STAT3-mediated disorder, such as by administering a compound of Formula (I) using any administrative method or formulation described herein.

[0046] Provided herein, in another example, is a method of providing to an individual an improved C_{max} or $AUC_{0-\infty}$ of a compound of Formula (I):



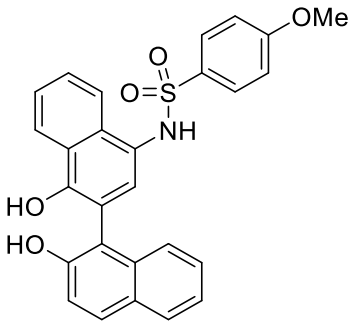
(I)

,

the improved C_{max} or $AUC_{0-\infty}$ being at least 1.1 times (e.g., at least 1.2 times, at least 1.3 times, or more) greater than the effect obtained by administering an otherwise identical amount of a compound of Formula (I) in a formulation of PEG400 and Labrasol® (40:60 by weight).

[0047] In certain examples, the method has an administration protocol of any of the previously described examples. In certain examples, the compound of Formula (I) is administered in a pharmaceutical composition or in one or more oral dosage forms of any of the previously described examples.

[0048] Provided herein, in another example, is a crystalline form of a compound of Formula (I):



(I)

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[0049] In certain examples, the crystalline form is characterized by an X-ray powder diffraction pattern comprising peaks at 8.13 ± 0.2°, 16.50 ± 0.2°, 18.41 ± 0.2°, 21.77 ± 0.2°, and 22.64 ± 0.2° two theta. In certain examples, the X-ray powder diffraction pattern further comprises at least one peak selected from 9.56 ± 0.2°, 11.43 ± 0.2°, 12.75 ± 0.2°, and 14.66 ± 0.2° two theta. In certain examples, the X-ray powder diffraction pattern further comprises at least one peak selected from 19.70 ± 0.2°, 20.21 ± 0.2°, 20.81 ± 0.2°, and 24.43 ± 0.2° two theta. In certain examples, the X-ray powder diffraction pattern further comprises at least one peak selected from 26.10 ± 0.2°, 29.29 ± 0.2°, and 30.75 ± 0.2° two theta. In certain examples, the crystalline form is characterized by an X-ray powder diffraction pattern comprising peaks at 8.13 ± 0.2°, 9.56 ± 0.2°, 11.43 ± 0.2°, 12.75 ± 0.2°, 14.66 ± 0.2°, 16.50 ± 0.2°, 18.41 ± 0.2°, from 19.70 ± 0.2°, 20.21 ± 0.2°, 20.81 ± 0.2°, 21.77 ± 0.2°, 22.64 ± 0.2°, 24.43 ± 0.2°, 26.10 ± 0.2°, 29.29 ± 0.2°, and 30.75 ± 0.2° two theta.

[0050] In certain examples, the crystalline form is characterized by an X-ray powder diffraction pattern substantially as set forth in **FIG. 1**.

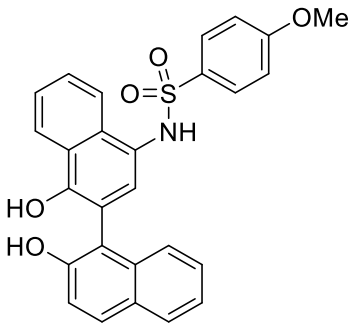
[0051] In certain examples, any method provided herein comprises administering a compound of Formula (I) having a crystalline form described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] Various features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the

CLAIMS

1. A pharmaceutical composition comprising:
    a. at least 50 mg of a compound of Formula (I):



(I)

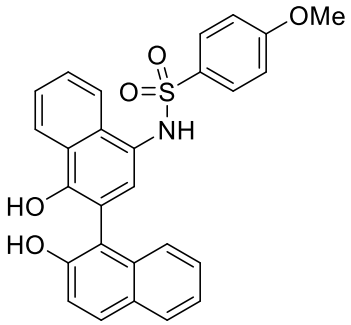
;

    b. a glyceride emulsifier present in the composition in a weight ratio of compound of Formula (I) to emulsifier of about 1:1 to about 1:2;
    c. a solubilizer present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:2 to about 1:4, wherein the solubilizer is polyoxyl castor oil;
    d. a polyethylene glycol (PEG) present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:3 to about 1:5;
    e. a surfactant present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:1 to about 1:2, wherein the surfactant is polysorbate; and
    f. an antioxidant present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 15:1 to about 25:1.
2. The pharmaceutical composition of claim 1, wherein the polyoxyl castor oil is PEG-40 hydrogenated castor oil.
3. The pharmaceutical composition of claim 1, wherein the PEG has an average molecular weight of about 200 to about 1000 Da.
4. The pharmaceutical composition of claim 1, wherein the polysorbate is polysorbate 20.
5. The pharmaceutical composition of claim 1, wherein the antioxidant is citric acid.
6. The pharmaceutical composition of claim 1, wherein at least 50 mg of the glyceride emulsifier, at least 100 mg of the solubilizer, at least 150 mg PEG, at least 50 mg of surfactant, and at least 2 mg of the antioxidant are present in the pharmaceutical composition.
7. An oral dosage form comprising the pharmaceutical composition of claim 1 contained within a capsule.
8. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating cancer.
9. The use of claim 8, wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, prostate cancer, cervical cancer, brain cancer,

pancreatic cancer, myelodysplastic syndrome, leukemia, lymphoma, kidney cancer, or metastatic melanoma.

10. The use of claim 8, wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, leukemia, or pancreatic cancer.
11. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating fibrosis.
12. The use of claim 11, wherein the fibrosis is associated with pulmonary fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneal fibrosis, myelofibrosis, dermal fibrosis, non-alcoholic fatty liver disease, steatohepatitis, or systemic sclerosis.
13. The use of claim 11, wherein the fibrosis is associated with pulmonary fibrosis, non-alcoholic fatty liver disease, steatohepatitis, or systemic sclerosis.
14. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating chronic inflammation.
15. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating chemotherapy-induced peripheral neuropathy.
16. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating diabetic neuropathy.
17. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating familial amyloid polyneuropathy.
18. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating cachexia.
19. Use of the oral dosage form of claim 7 in the manufacture of a medicament for treating anaphylaxis.
20. A pharmaceutical composition comprising:

a. at least 50 mg of a compound of Formula (I):



(I)

;

b. a glyceride emulsifier present in the composition in a weight ratio of compound of Formula (I) to emulsifier of about 1:1;

c. a solubilizer present in the composition in a weight ratio of compound of Formula (I) to solubilizer of about 1:3, wherein the solubilizer is polyoxyl castor oil;

d. a polyethylene glycol (PEG) present in the composition in a weight ratio of compound of Formula (I) to polyethylene glycol of about 1:4;

e. a surfactant present in the composition in a weight ratio of compound of Formula (I) to surfactant of about 1:2, wherein the surfactant is polysorbate; and

f. an antioxidant present in the composition in a weight ratio of compound of Formula (I) to antioxidant of about 20:1.

21. The pharmaceutical composition of claim 20, wherein the polyoxyl castor oil is PEG-40 hydrogenated castor oil.

22. The pharmaceutical composition of claim 20, wherein the PEG has an average molecular weight of about 200 to about 1000 Da.

23. The pharmaceutical composition of claim 20, wherein the polysorbate is polysorbate 20.

24. The pharmaceutical composition of claim 20, wherein the antioxidant is citric acid.

25. The pharmaceutical composition of claim 20, wherein at least 50 mg of the glyceride emulsifier, at least 150 mg of the solubilizer, at least 200 mg PEG, at least 100 mg of surfactant, and at least 2.5 mg of the antioxidant are present in the pharmaceutical composition.

26. An oral dosage form comprising the pharmaceutical composition of claim 20 contained within a capsule.

27. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating cancer.

28. The use of claim 27, wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, prostate cancer, cervical cancer, brain cancer, pancreatic cancer, myelodysplastic syndrome, leukemia, lymphoma, kidney cancer, or metastatic melanoma.

29. The use of claim 27, wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, ovarian cancer, colon cancer, multiple myeloma, leukemia, or pancreatic cancer.

30. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating fibrosis.

31. The use of claim 30, wherein the fibrosis is associated with pulmonary fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneal fibrosis, myelofibrosis, dermal fibrosis, non-alcoholic fatty liver disease, steatohepatitis, or systemic sclerosis.

32. The use of claim 30, wherein the fibrosis is associated with pulmonary fibrosis, non-alcoholic fatty liver disease, steatohepatitis, or systemic sclerosis.

33. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating chronic inflammation.

34. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating chemotherapy-induced peripheral neuropathy.

35. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating diabetic neuropathy.

36. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating familial amyloid polyneuropathy.

37. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating cachexia.

38. Use of the oral dosage form of claim 26 in the manufacture of a medicament for treating anaphylaxis.

39. The oral dosage form of claim 7 or 26 for use in therapy.