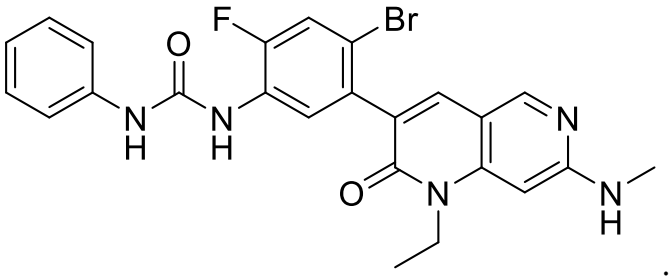
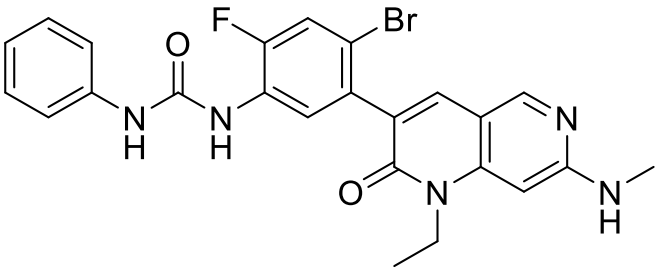
compound of Formula (I) as described herein has the following structure:



Formula (I)

[0005a] In one aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a) a solid dispersion comprising: a compound represented by Formula (I) or pharmaceutically acceptable salt thereof,



Formula (I)

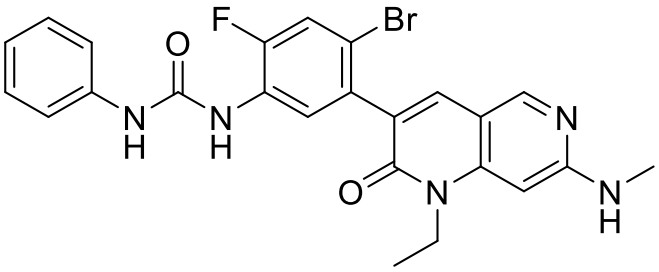
and a pharmaceutically acceptable polymer; and

b) one or more pharmaceutically acceptable carriers,

wherein no single anilinic substance is present in an amount equal to or less than about 3.0% by weight.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a) a solid dispersion comprising: an amorphous form of a compound represented by Formula (I)

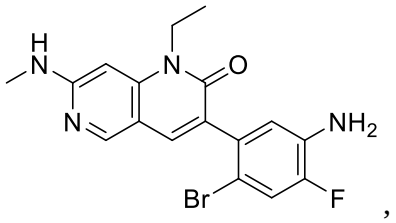


Formula (I)

and a pharmaceutically acceptable polymer; and

b) one or more pharmaceutically acceptable carriers;

wherein each of: a compound represented by Formula (II):

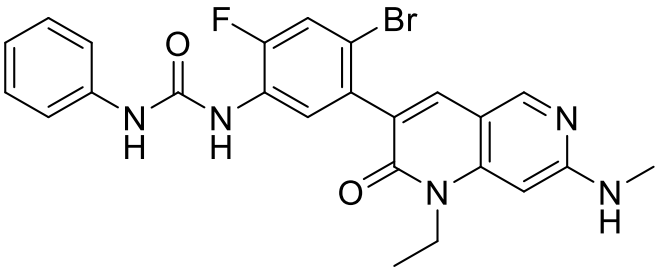


Formula (II)

aniline and diphenyl urea are present in amount equal to or less than about 1.5% by weight based on the total weight of the composition.

[0005c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising:

a) a solid dispersion comprising: an amorphous form of a compound represented by Formula (I)



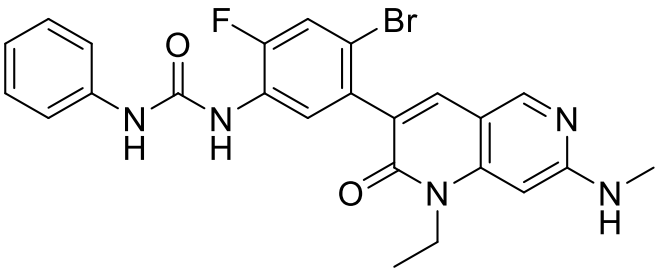
Formula (I)

and a pharmaceutically acceptable polymer; and

b) one or more pharmaceutically acceptable carriers;

wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

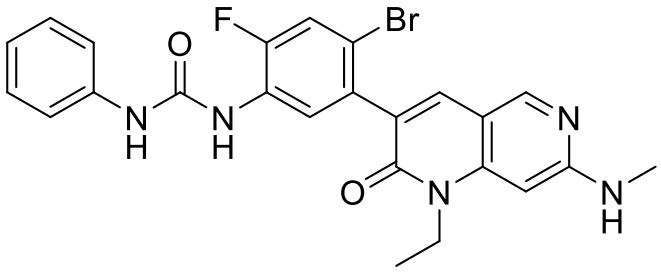
[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound represented by Formula (I)



Formula (I)

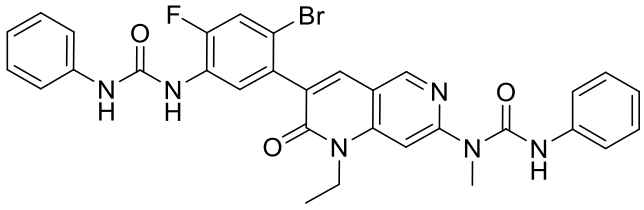
and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the composition comprises one or more anilinic substances each in an amount equal to or less than about 3.0% by weight based on the weight of the compound of Formula (I).

[0005e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound represented by Formula (I)



Formula (I)

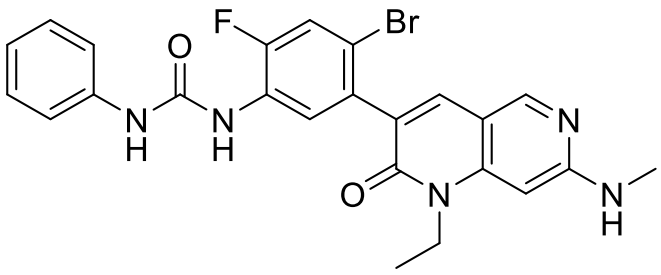
and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition comprises one or more anilinic substances and a compound represented by Formula (III):



Formula (III)

each in an amount equal to or less than 3.0% by weight based on the weight of the compound of Formula (I).

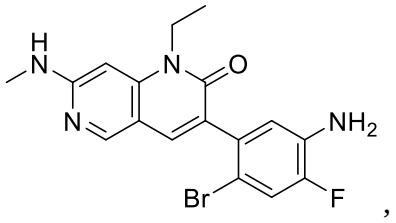
[0005f] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound represented by Formula (I)



Formula (I)

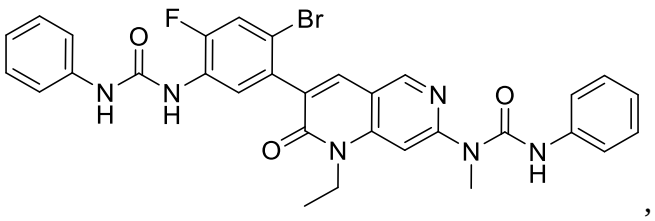
and a pharmaceutically acceptable carrier, wherein the composition has less than 3% w/w of

each of: a compound represented by Formula (II):



Formula (II)

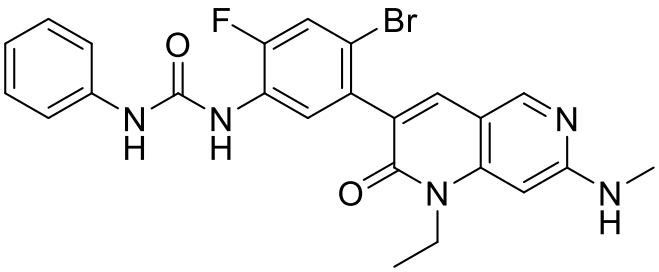
a compound represented by Formula (III):



Formula (III)

aniline, and diphenyl urea.

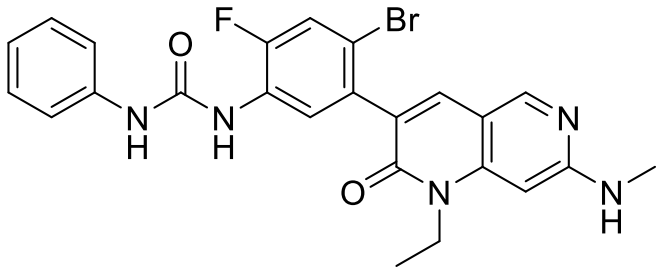
[0005g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound represented by Formula (I):



Formula (I)

and a pharmaceutically acceptable carriers, wherein the composition has less than 3% w/w of each of: 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-2(1H)-one, aniline and diphenyl urea.

[0005h] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for a 50 mg single dosage unit of a compound represented by:



;

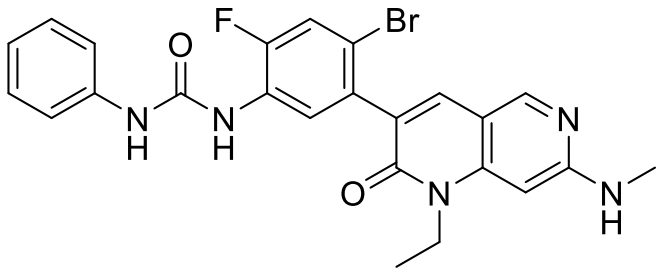
comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and

an extragranular blend comprising a glidant and/or a lubricant; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

[0005i] In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by:



;

comprising:

a solid dispersion having:

50 mg of the compound wherein the compound is present in amorphous form;

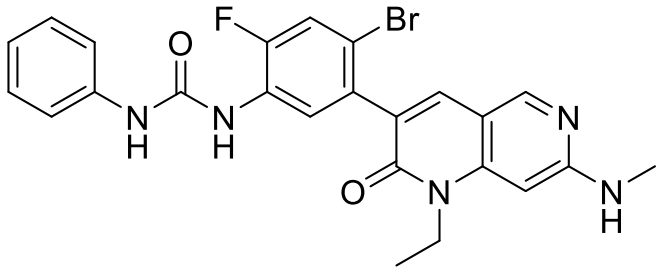
hydroxypropyl methyl cellulose acetate succinate;

a bulking agent,

a filler, and

a lubricant and/or a glidant; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

[0005j] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by:



comprising:

comprises:

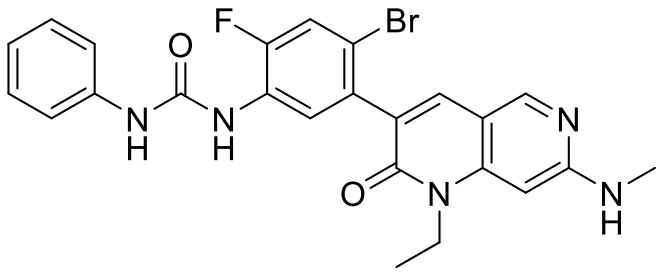
a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and a polymer;

about 25-45% by weight of a bulking agent based on the total amount of the pharmaceutical composition;

about 25-45% by weight of a filler based on the total amount of the pharmaceutical composition; and

a glidant and/or a lubricant; wherein the composition has not more than about 1.5% (w/w) of 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-2(1H)-one, when exposed to 60% relative humidity at 25 ºC for 1 month, 3 months or 6 months.

[0005k] In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable tablet having 50 mg of a compound represented by:



;

wherein the tablet comprises:

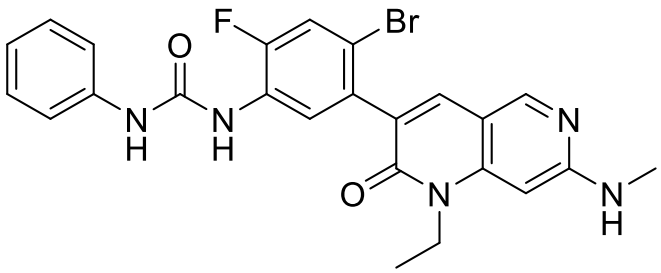
a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and

about 25-35% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

[0005l] In another aspect of the present disclosure, there is provided a use of the composition disclosed herein, or the pharmaceutically acceptable tablet disclosed herein, in the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

[0005m] In a further aspect of the present disclosure, there is provided a solid dispersion comprising the compound represented by Formula (I)



Formula (I)

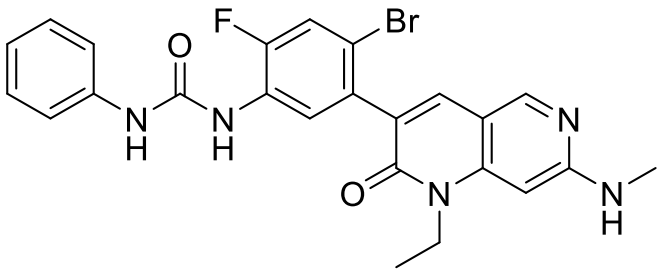
and a pharmaceutically acceptable polymer, wherein the solid dispersion comprises one or more anilinic substances each in an amount equal to or less than about 3.0% by weight based on the weight of the compound of Formula (I).

[0005n] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the solid dispersion disclosed herein and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0005o] In a further aspect of the present disclosure, there is provided a use of the composition disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient

gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

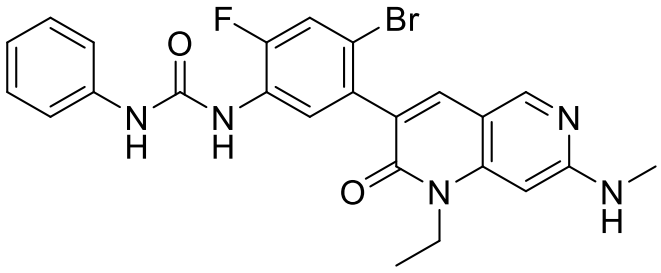
[0005p] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound represented by Formula (I)



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition has less than about 0.05% of diphenyl urea.

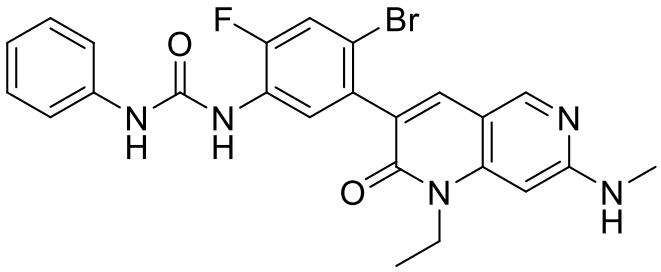
[0005q] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound represented by Formula (I)



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition has less than about 0.05% of diphenyl urea as detected by HPLC.

[0005r] In another aspect of the present disclosure, there is provided a solid dispersion comprising the compound represented by Formula (I)



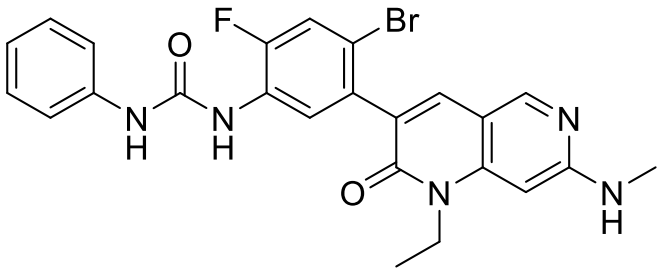
Formula (I)

and a pharmaceutically acceptable polymer, wherein the compound has a purity by HPLC of greater than about 90%.

[0005s] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the solid dispersion disclosed herein and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0005t] In another aspect of the present disclosure, there is provided a use of the composition disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

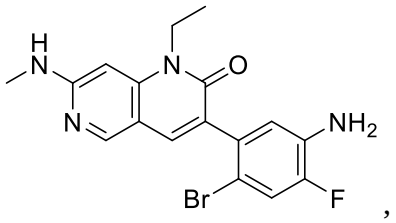
[0005u] In a further aspect of the present disclosure, there is provided a substantially purified compound represented by Formula (I)



Formula (I)

having less than about 3.0% by weight of an impurity selected from the group consisting of a

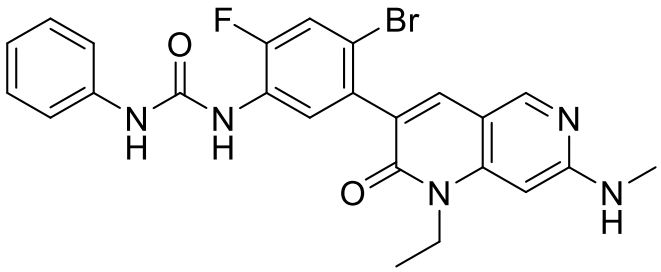
compound represented by Formula (II):



Formula (II)

aniline, and combinations thereof.

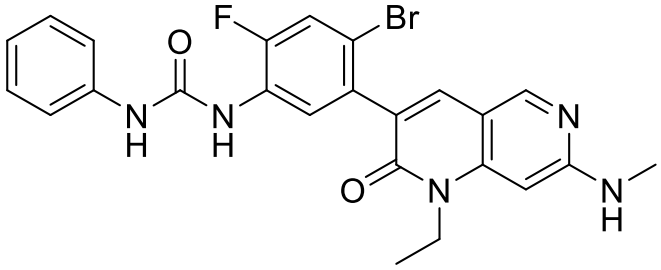
[0005v] In another aspect of the present disclosure, there is provided a high purity compound represented by Formula (I)



Formula (I)

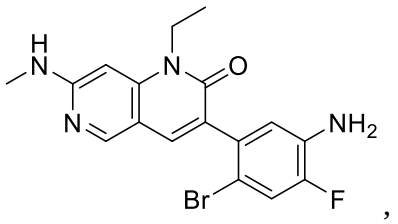
having less than about 3.0% of anilinic substance impurities.

[0005w] In a further aspect of the present disclosure, there is provided a substantially purified compound represented by Formula (I)



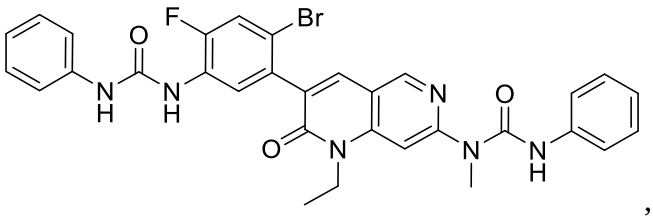
Formula (I)

having less than about 3.0% by weight of an impurity selected from the group consisting of a compound represented by Formula (II):



Formula (II)

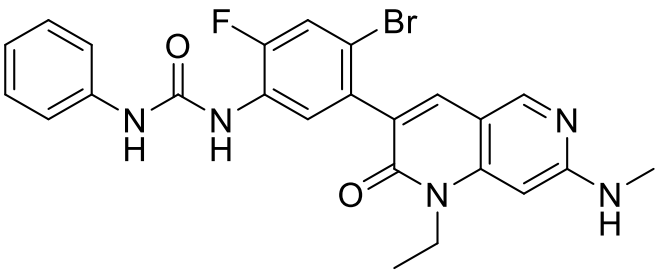
a compound represented by Formula (III):



Formula (III)

and combinations thereof.

[0005x] In another aspect of the present disclosure, there is provided a high purity compound represented by Formula (I)



Formula (I)

having less than about 0.05% of a diphenyl urea impurity.

[0005y] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising any one of the compounds disclosed herein and one or more pharmaceutically acceptable excipients, carriers or diluents.

[0005z] In another aspect of the present disclosure, there is provided a use of the composition disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal

stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

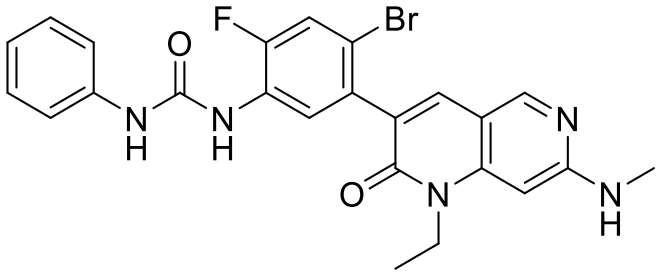
[0005aa] In a further aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, and hypereosinophilic syndrome.

[0005ab] In another aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of KIT driven germ cell tumor, KIT driven skin cancer, or KIT driven renal cell carcinoma.

[0005ac] In a further aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer.

[0005ad] In another aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein in the manufacture of a medicament for treating a disease selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma, wherein the disease comprises a PDGFRAB mutation.

[0005ae] In a further aspect of the present disclosure, there is provided a process for the preparation of the solid dispersion comprising a compound of Formula (I)



Formula (I)

disclosed herein, the process comprising:

(a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension;

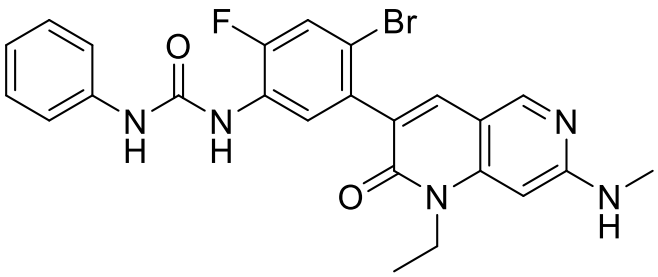
(b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 ºC;

(c) heating the suspension to dissolve the suspended particles prior to introduction into a spray-dryer; and

(d) spray-drying the suspension to obtain a spray-dried dispersion;

(e) drying the spray-dried dispersion; thereby obtaining the solid dispersion.

[0005af] In another aspect of the present disclosure, there is provided a solid dispersion comprising a compound of Formula (I)

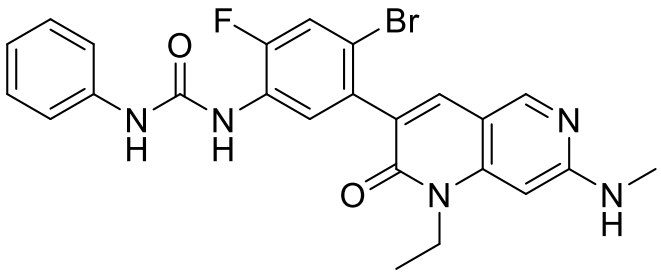


Formula (I)

produced by the process disclosed herein.

[0005ag] In a further aspect of the present disclosure, there is provided a composition or one or more of the tablets disclosed herein, for use in therapy.

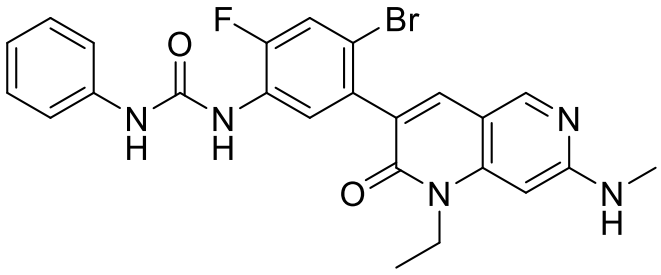
[0006] Provided herein, in part, are pharmaceutical compositions comprising a compound of Formula (I):



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition comprises one or more anilinic substances, each in an amount equal to or less than 3.0% by weight based on the weight of the compound of Formula (I).

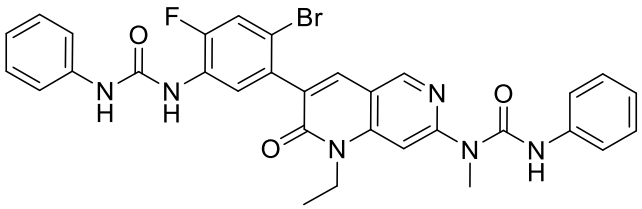
[0007] Provided herein, in part, are pharmaceutical compositions comprising a compound of Formula (I):



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the

pharmaceutical composition comprises one or more anilinic substances and a compound represented by Formula (III):



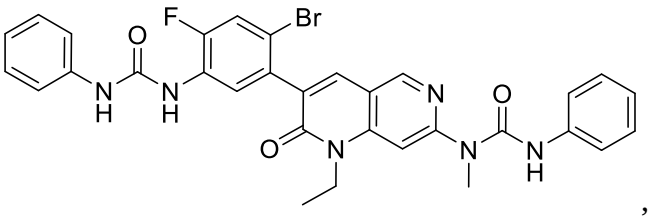
Formula (III)

each in an amount equal to or less than 3.0% by weight based on the weight of the compound of Formula (I).

[0008] In some embodiments, provided herein is the solid dispersion comprising a compound of Formula (I) and a polymer, wherein the pharmaceutical composition comprises one or more anilinic substances, each in an amount equal to or less than 3.0% by weight based on the weight of the compound of Formula (I).

[0009] In some examples, provided herein is a pharmaceutical composition comprising the compound of Formula (I) and a pharmaceutically acceptable carrier, wherein the composition has less than 3% w/w of each of: 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-2(1H)-one (the compound of Formula (II)), aniline and diphenyl urea.

[0010] In an example, provided herein is a pharmaceutical composition comprising the compound of Formula (I) and a pharmaceutically acceptable carrier, wherein the composition has less than 3% w/w of each of: 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-2(1H)-one (the compound of Formula (II)), a compound represented by Formula (III):



,

Formula (III)

aniline and diphenyl urea.

[0011] In an example, described herein is a substantially purified compound represented by Formula (I) having less than about 3.0% by weight of an impurity selected from the group consisting of the compound of Formula (II), aniline, and combinations thereof. In some examples, the compound comprises less than 0.5% of the impurity.

[0012] In an example, described herein is a substantially purified compound represented by Formula (I) having less than about 3.0% by weight of an impurity selected from the group consisting of the compound of Formula (II), the compound of Formula (III), and combinations thereof. In some examples, the compound comprises less than 0.5% of the impurity.

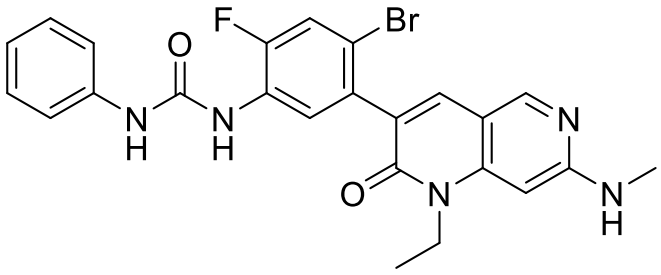
[0013] In an example, described herein is a high purity compound represented by the compound of Formula (I) having less than about 3.0% of anilinic substance impurities. In some examples, the compound comprises less than 0.5% of each of one or more anilinic substances.

[0014] In another example, provided herein is a high purity compound represented by the compound of Formula (I) having less than about 0.05% of a diphenyl urea impurity.

[0015] Described herein, in an example, is a pharmaceutical composition comprising the of Formula (I) and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition has less than about 0.05% of diphenyl urea.

[0016] Described herein, in an example, is a pharmaceutical composition comprising the of Formula (I) and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition has less than about 0.05% of diphenyl urea as detected by HPLC.

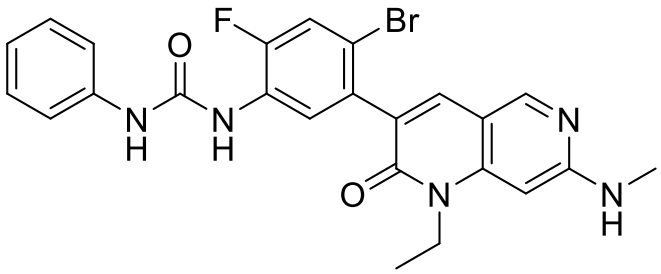
[0017] Described herein, in an example, is a pharmaceutical composition comprising: a) a solid dispersion comprising: a compound represented by Formula (I) or pharmaceutically acceptable salt thereof,



Formula (I)

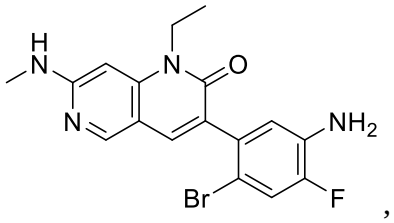
and a pharmaceutically acceptable polymer; and b) one or more pharmaceutically acceptable carriers, wherein no single anilinic substance is present in an amount equal to or less than about 3.0% by weight.

[0018] Described herein, in an example, pharmaceutical composition comprising: a) a solid dispersion comprising: an amorphous form of a compound represented by Formula (I)



Formula (I)

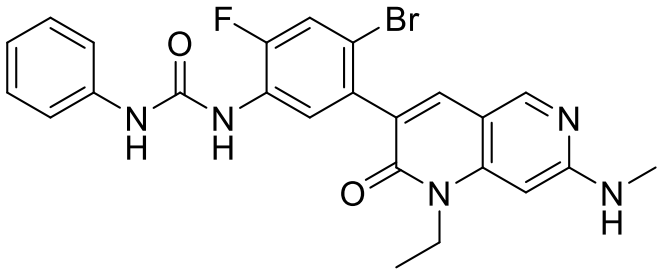
and a pharmaceutically acceptable polymer; and b) one or more pharmaceutically acceptable carriers; wherein each of: a compound represented by Formula (II):



Formula (II)

aniline and diphenyl urea are present in amount equal to or less than about 1.5% by weight based on the total weight of the composition.

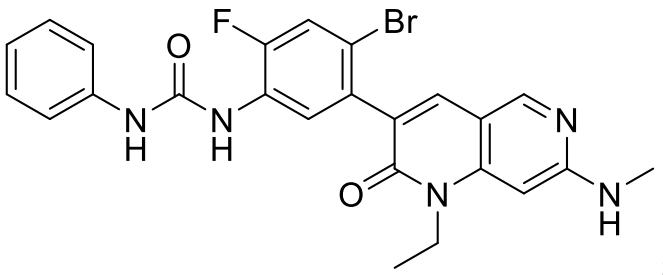
[0019] Described herein, in an example, is a pharmaceutical composition comprising: a) a solid dispersion comprising: an amorphous form of a compound represented by Formula (I)



Formula (I)

and a pharmaceutically acceptable polymer; and b) one or more pharmaceutically acceptable carriers; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

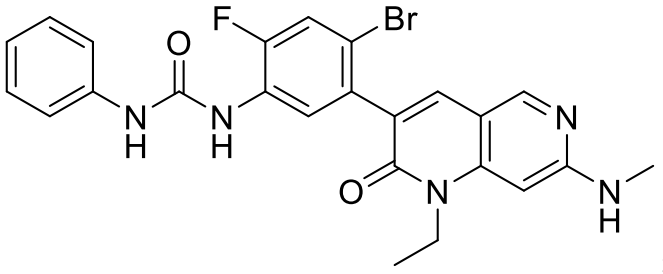
[0020] Described herein, in an example, is a pharmaceutically acceptable composition for a 50 mg single dosage unit of a compound represented by:



;

comprising: an intragranular blend, wherein the intragranular blend comprises: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and an extragranular blend comprising a glidant and/or a lubricant; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

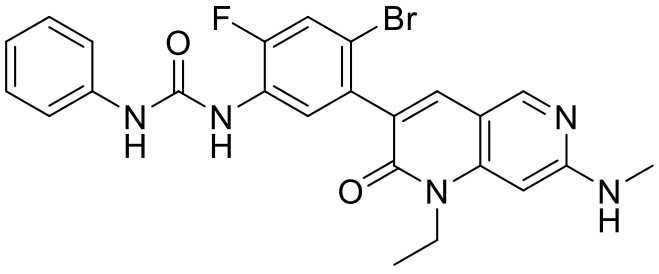
[0021] Described herein, in an example, is a pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by:



;

comprising: a solid dispersion having: 50 mg of the compound wherein the compound is present in amorphous form;hydroxypropyl methyl cellulose acetate succinate; a bulking agent, a filler, and a lubricant and/or a glidant; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

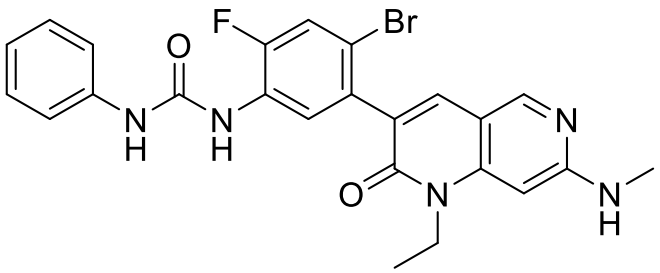
[0022] Described herein, in an example, is a pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by:



comprising:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and a polymer; about 25-45% by weight of a bulking agent based on the total amount of the pharmaceutical composition; about 25-45% by weight of a filler based on the total amount of the pharmaceutical composition; and a glidant and/or a lubricant; wherein the composition has not more than about 1.5% (w/w) of 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-2(1H)-one, when exposed to 60% relative humidity at 25 ºC for 1 month, 3 months or 6 months.

[0023] Described herein, in an example, is a pharmaceutically acceptable tablet having 50 mg of a compound represented by:



;

wherein the tablet comprises: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate; about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and about 25-35% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

[0024] In an example, provided herein is a pharmaceutical composition comprising: (a) an intragranular blend comprising: (i) a solid dispersion comprising a compound represented by Formula (I), wherein the pharmaceutical composition is comprises one or more anilinic substance, each in an amount equal to or less than 3% by weight based on the weight of the compound of Formula (I), and a pharmaceutically acceptable polymer; (ii) one or more fillers; (iii) a disintegrant; (iv) a glidant; and (v) a lubricant; and (b) an extragranular blend comprising: (i) a glidant; and (ii) a lubricant. In some examples, each anilinic substance is present in an amount equal to or less than about 5.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 4.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 2.0% by weight based on the weight of the compound of

Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 1.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.7% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.5% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.3% by weight based on the weight of the compound of Formula (I).

[0025] In an example, the disclosure provides a pharmaceutical composition comprising: (a) an intragranular blend comprising: (i) about 33% by weight of a solid dispersion based on the total weight of the composition, the solid dispersion comprising a compound represented by Formula (I) and hydroxypropyl methyl cellulose acetate succinate, wherein the solid dispersion comprises about 25% by weight of the compound represented by Formula (I) based on the total weight of the solid dispersion; (ii) about 30% by weight of microcrystalline cellulose based on the total amount of the of the composition; (iii) about 30% by weight of lactose monohydrate based on the total amount of the of the composition; (iv) about 5% by weight of crospovidone based on the total amount of the of the composition; (v) about 0.5% by weight of silicon dioxide based on the total amount of the of the composition; and (vi) about 0.5% by weight of magnesium stearate based on the total amount of the of the composition; and (b) an extragranular blend comprising: (i) about 0.5% by weight of silicon dioxide based on the total amount of the of the composition; and (ii) about 0.5% by weight of magnesium stearate based on the total amount of the composition.

[0026] In an example, provided herein is a pharmaceutical composition comprising: (a) an intragranular blend comprising: (i) about 200 mg of a solid dispersion comprising a compound represented by Formula (I), wherein the pharmaceutical composition comprisesone or more anilinic substance, each in an amount equal to or less than 3% by weight based on the weight of the compound of Formula (I) and hydroxypropyl methyl cellulose acetate succinate, wherein the solid dispersion comprises about 50 mg of the compound represented by Formula (I); (ii) about 179 mg of microcrystalline cellulose; (iii) about 179 mg of lactose monohydrate; (iv) about 30 mg of crospovidone; (v) about 3 mg of silicon dioxide; and (vi) about 3 mg of magnesium stearate; and (b) an extragranular blend comprising: (i) about 3 mg of silicon dioxide; and (ii) about 3 mg of magnesium stearate. In some examples, each anilinic substance is present in an amount equal to or less than about 5.0% by weight based on the weight of the compound of Formula (I). In some

examples, each anilinic substance is present in an amount equal to or less than about 4.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 2.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 1.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.7% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.5% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.3% by weight based on the weight of the compound of Formula (I).

[0027] In an example, provided herein is a tablet providing about 50 mg of a compound represented by Formula (I), wherein the tablet comprises one or more anilinic substance impurities, each in an amount equal to or less than 3% by weight based on the weight of the compound of Formula (I), wherein the tablet comprises: (a) an intragranular blend comprising: (i) about 195 mg to about 205 mg of a solid dispersion that comprises about 50 mg of the compound and hydroxypropyl methyl cellulose acetate succinate; (ii) about 177 mg to about 181 mg of microcrystalline cellulose; (iii) about 177 mg to about 181 mg of lactose monohydrate; and (iv) about 28 mg to about 32 mg of crospovidone; and (b) an extragranular blend comprising: (i) about 2 mg to about 4 mg of silicon dioxide; and (ii) about 2 mg to about 4 mg of magnesium stearate. In some examples, each anilinic substance is present in an amount equal to or less than about 5.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 4.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 2.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 1.0% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.7% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.5% by weight based on the weight of the compound of Formula (I). In some examples, each anilinic substance is present in an amount equal to or less than about 0.3% by weight based on the weight of the compound of Formula (I).

[0028] In an example, provided herein are methods for treating a disease caused by the kinase activity of c-KIT or PDGFRA, and oncogenic forms thereof, wherein the disease is gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma (e.g., cutaneous melanoma, noncutaneous melanoma, KIT driven melanoma or PGDFRA driven melanoma), acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, or non-small cell lung cancer. In some examples, melanoma is cutaneous melanoma or noncutaneous melanaoma. In some examples, melanoma is cutaneous melanoma. In some examples, cutaneous melanoma is superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, or amelanotic and desmoplastic melanoma. In some examples, melanoma is noncutaneous (non-skin) melanoma. In some examples, noncutaneous melanoma is ocular melanoma or mucosal melanoma.

[0029] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition described herein.

[0030] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, and hypereosinophilic syndrome in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition described herein.

[0031] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer, or KIT driven renal cell carcinoma in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition described herein.

[0032] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein.

[0033] Also provided herein, in another example, is a method of treating a disease comprising a PDGFRB mutation selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition described herein.

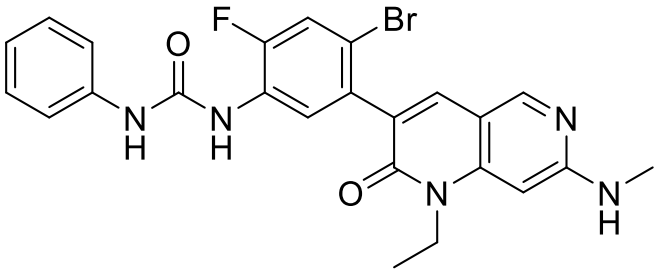
[0034] In some examples, provided herein is a method for treating diseases driven by KIT mutations or PDGFRA mutations in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, provided herein is a method for treating diseases driven by KIT mutations and PDGFRA mutations in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, provided herein is a method for treating diseases driven by KIT mutations or PDGFRA mutations, comprising passenger PDGFRB mutations in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, provided herein is a method for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma (e.g., KIT driven melanoma or PGDFRA driven melanoma or PGDFR driven melanoma), acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric

glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, the melanoma is cutaneous melanoma or noncutaneous melanaoma. In some examples, the melanoma is cutaneous melanoma. In some examples, the cutaneous melanoma is superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, or amelanotic and desmoplastic melanoma. In some examples, the melanoma is noncutaneous (non-skin) melanoma. In some examples, the noncutaneous melanoma is ocular melanoma or mucosal melanoma. In some examples, the disease is caused by the kinase activity of c-KIT and/or PDGFRA, and/or oncogenic forms thereof. In some examples, the disease is selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer (e.g., KIT driven cutaneous squamous cell carcinoma, KIT driven Merkel cell carcinoma, uveal melanoma, non-melanoma skin cancer), or KIT driven renal cell carcinoma (e.g., renal cell carcinoma, chromophobe renal cell carcinoma). In some examples, the disease is selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer. In some examples, the disease comprising a PDGFRB mutation is selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma.

[0035] Also provided herein, in another example, is a use of a composition or tablets described herein for the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

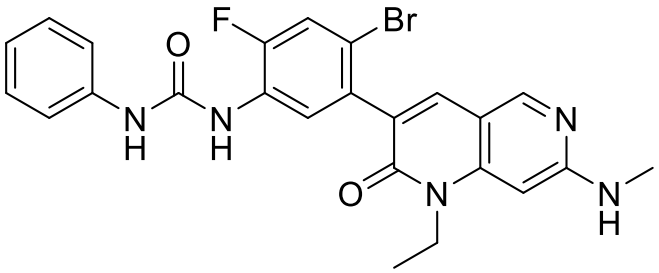
[0036] In another example, described herein is a process for the preparation of the

solid dispersion comprising a compound of Formula (I)



Formula (I)

e.g., a solid dispersion described herein, the process comprising: (a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension; (b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 ºC; (c) heating the suspension to dissolve the suspended particles prior to introduction into a spray-dryer; and (d) spray-drying the suspension to obtain a spray-dried dispersion; (e) drying the spray-dried dispersion; thereby obtaining the solid dispersion. In some examples, a solid dispersion comprising a compound of Formula (I)



Formula (I)

e.g., a solid dispersion described herein, is produced by said process.

DETAILED DESCRIPTION

[0037] The features and other details of the disclosure will now be more particularly described. Certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

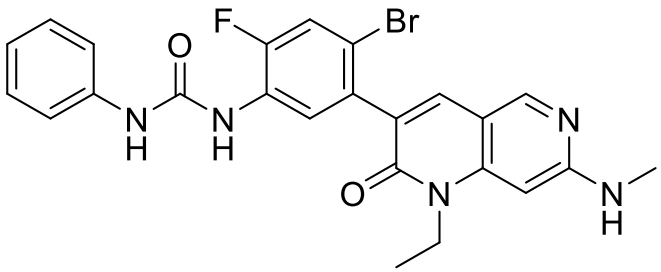
Definitions

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a) a solid dispersion comprising: a compound represented by Formula (I) or pharmaceutically acceptable salt thereof,



Formula (I)

and a pharmaceutically acceptable polymer; and

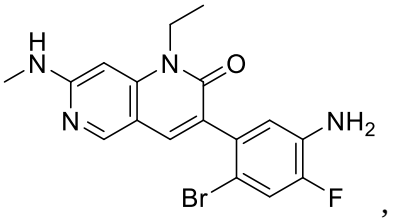
b) one or more pharmaceutically acceptable carriers,

wherein no single anilinic substance is present in an amount equal to or less than about 3.0% by weight.

2. The pharmaceutical composition of claim 1, wherein the anilinic substance is present in amount equal to or less than about 0.5% by weight based on the total weight of the compound of Formula (I) present in the composition.

3. The pharmaceutical composition of claim 1 or 2, wherein the anilinic substance is present in an amount equal to or less than about 0.3% by weight based on the total weight of the compound of Formula (I) present in the composition.

4. The pharmaceutical composition of any one of claims 1-3, wherein the anilinic substance is one of : the compound of Formula (II)



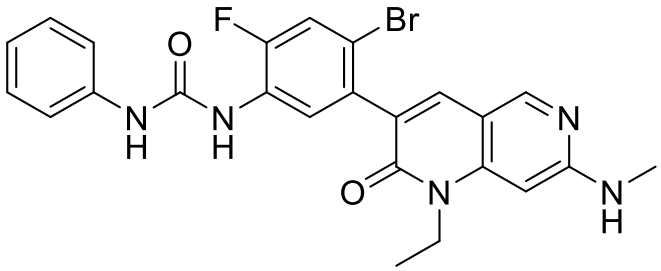
Formula (II)

aniline, or a combination thereof.

5. The pharmaceutical composition of any one of claims 1-4, wherein the compound is present in the solid dispersion as a free base in substantially amorphous form.

6. A pharmaceutical composition comprising:

a) a solid dispersion comprising: an amorphous form of a compound represented by Formula (I)

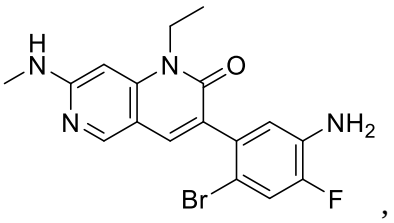


Formula (I)

and a pharmaceutically acceptable polymer; and

b) one or more pharmaceutically acceptable carriers;

wherein each of: a compound represented by Formula (II):

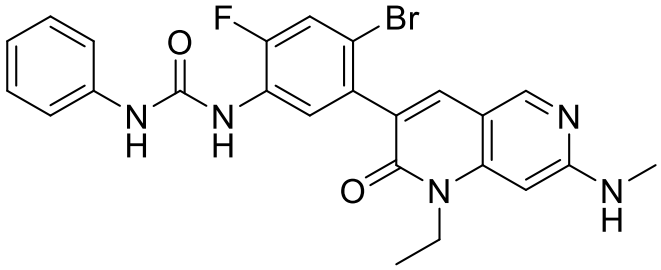


Formula (II)

aniline and diphenyl urea are present in amount equal to or less than about 1.5% by weight based on the total weight of the composition.

7. A pharmaceutical composition comprising:

a) a solid dispersion comprising: an amorphous form of a compound represented by Formula (I)



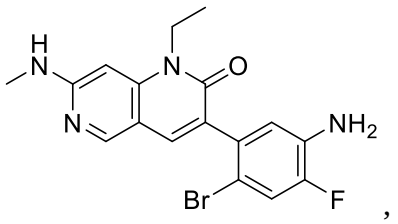
Formula (I)

and a pharmaceutically acceptable polymer; and

b) one or more pharmaceutically acceptable carriers;

wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

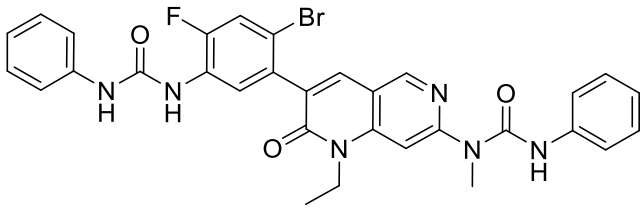
8. The pharmaceutical composition of any one of claims claim 1-6, wherein each of: a compound represented by Formula (II)



Formula (II)

aniline and diphenyl urea are present in amount equal to or less than about 0.5% by weight based on the total weight of the compound of Formula (I).

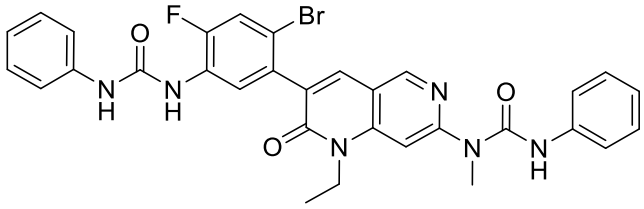
9. The pharmaceutically acceptable composition of any one of claims 1-8, further comprising less than about 10% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

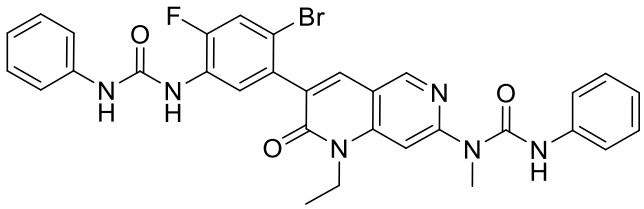
10. The pharmaceutically acceptable composition of any one of claims 1-9, further comprising less than about 3% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

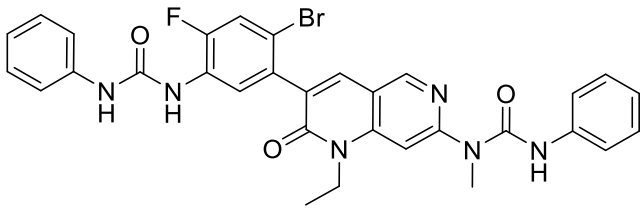
11. The pharmaceutically acceptable composition of any one of claims 1-10, further comprising less than about 1% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

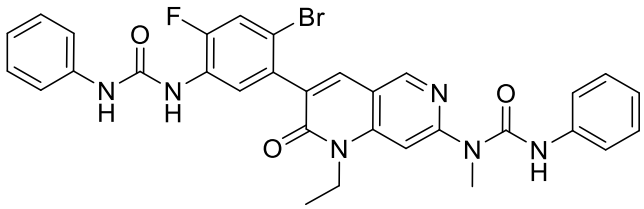
12. The pharmaceutically acceptable composition of any one of claims 1-11, further comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

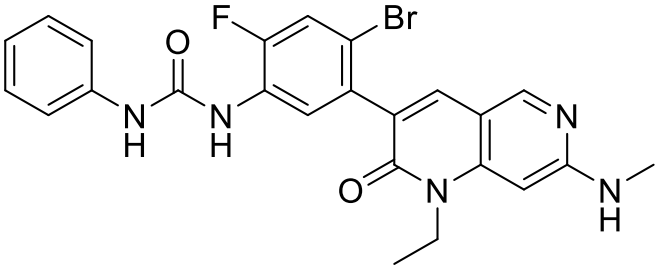
13. The pharmaceutically acceptable composition of any one of claims 1-12, further comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

14. A pharmaceutical composition comprising the compound represented by Formula (I)



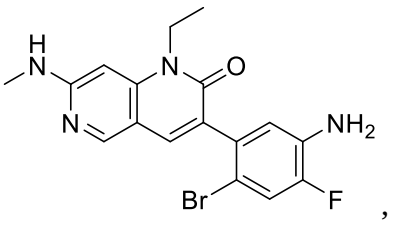
Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the composition comprises one or more anilinic substances each in an amount equal to or less than about 3.0% by weight based on the weight of the compound of Formula (I).

15. The composition of claim 14, wherein the composition has equal to or less than about 0.5% by weight one or more anilinic substances based on the weight of the compound of Formula (I).

16. The composition of claim 14 or 15, wherein the composition equal to or less than about 0.3% by weight anilinic substances based on the weight of the compound of Formula (I).

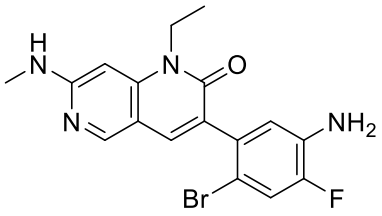
17. The composition of any one of claims 1-16, wherein the one or more anilinic substances is selected from the group consisting of a compound represented by Formula (II):



Formula (II)

aniline, and a combination thereof.

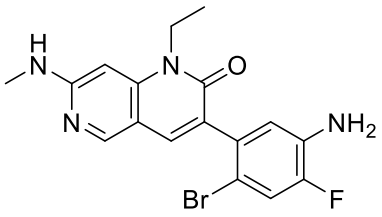
18. The pharmaceutically acceptable composition of any one of claims 1-17, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 1 % by weight based on the weight of the compound of Formula (I).

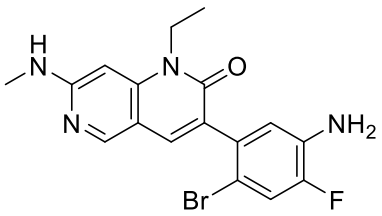
19. The pharmaceutically acceptable composition of any one of claims 1-18, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 0.1 % by weight to about 0.5% by weight based on the weight of the compound of Formula (I).

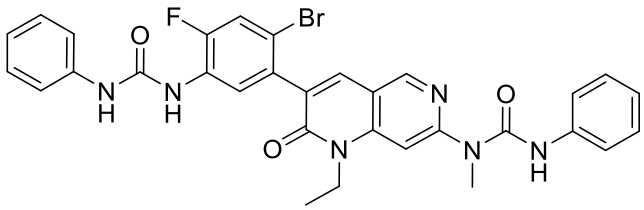
20. The pharmaceutically acceptable composition of any one of claims 1-19, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 0.01 % by weight to about 0.1% by weight based on the weight of the compound of Formula (I).

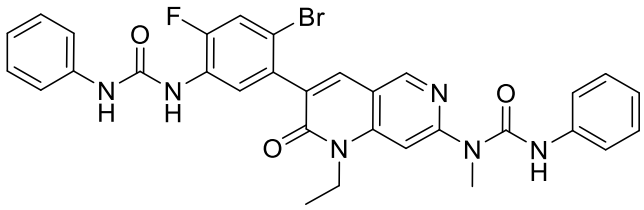
21. The pharmaceutically acceptable composition of any one of claims 1-20, further comprising less than about 10% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

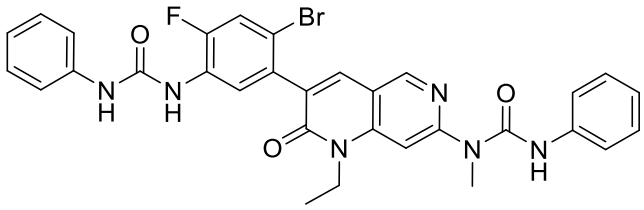
22. The pharmaceutically acceptable composition of any one of claims 1-21, further comprising less than about 3% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

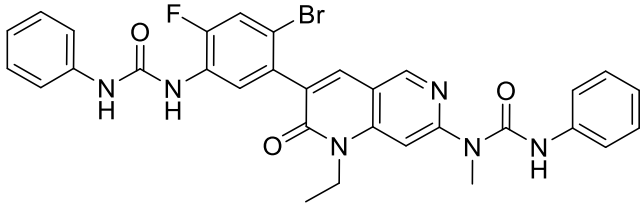
23. The pharmaceutically acceptable composition of any one of claims 1-22, further comprising less than about 1% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

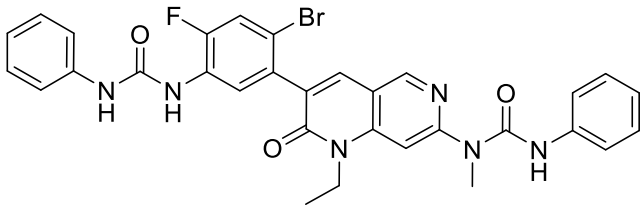
24. The pharmaceutically acceptable composition of any one of claims 1-23, further comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

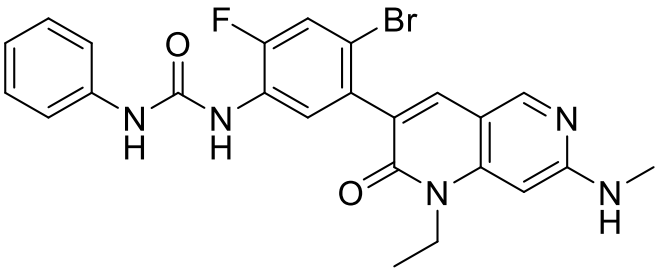
25. The pharmaceutically acceptable composition of any one of claims 1-24, further comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (III):



Formula (III)

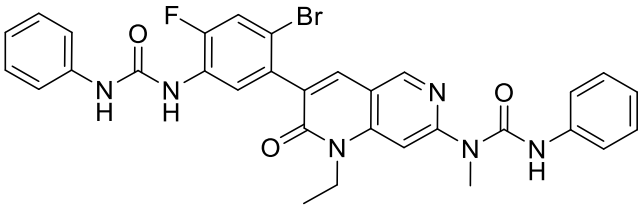
based on the weight of the compound of Formula (I).

26. A pharmaceutical composition comprising the compound represented by Formula (I)



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition comprises one or more anilinic substances and a compound represented by Formula (III):



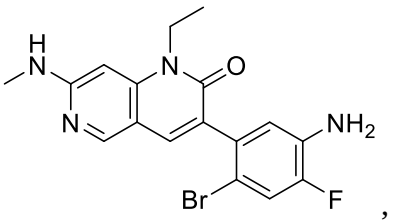
Formula (III)

each in an amount equal to or less than 3.0% by weight based on the weight of the compound of Formula (I).

27. The composition of claim 26, wherein the composition has equal to or less than about 0.5% by weight one or more anilinic substances based on the weight of the compound of Formula (I).

28. The composition of claim 26 or 27, wherein the composition equal to or less than about 0.3% by weight anilinic substances based on the weight of the compound of Formula (I).

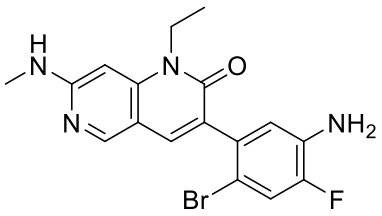
29. The composition of any one of claims 26-28, wherein the one or more anilinic substances is selected from the group consisting of a compound represented by Formula (II):



Formula (II)

aniline, and a combination thereof.

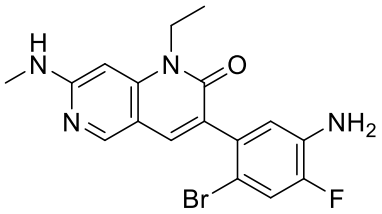
30. The pharmaceutically acceptable composition of any one of claims 26-29, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 1 % by weight based on the weight of the compound of Formula (I).

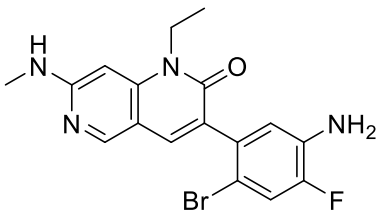
31. The pharmaceutically acceptable composition of any one of claims 26-30, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 0.1 % by weight to about 0.5% by weight based on the weight of the compound of Formula (I).

32. The pharmaceutically acceptable composition of any one of claims 26-31, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

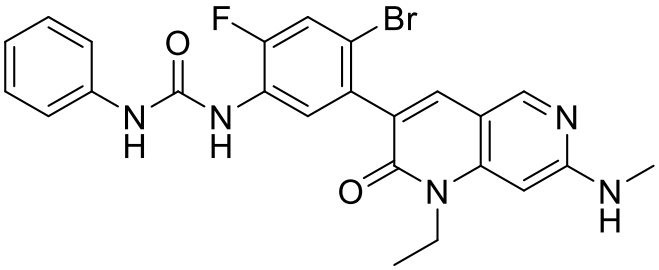
and is present in the composition in an amount of less than about 0.01 % by weight to about 0.1% by weight based on the weight of the compound of Formula (I).

33. The pharmaceutically acceptable composition of any one of claims 26-32, wherein the compound of Formula (III) is present in the composition in an amount of less than about 1% by weight based on the weight of the compound of Formula (I).

34. The pharmaceutically acceptable composition of any one of claims 26-33, wherein the compound of Formula (III) is present in the composition in an amount of less than about 0.1 % by weight to about 0.5% by weight by weight based on the weight of the compound of Formula (I).

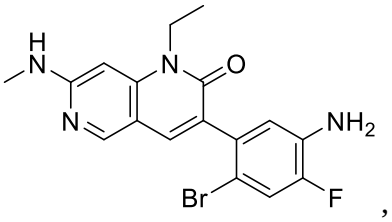
35. The pharmaceutically acceptable composition of any one of claims 26-34, wherein the compound of Formula (III) is present in the composition in an amount of less than about 0.01 % by weight to about 0.1 % by weight by weight based on the weight of the compound of Formula (I).

36. A pharmaceutical composition comprising a compound represented by Formula (I)



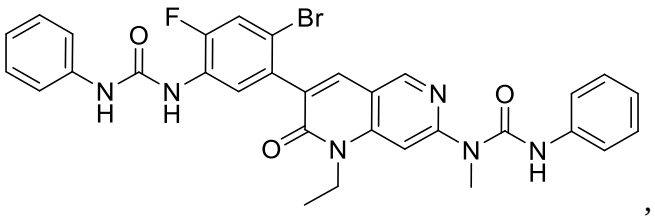
Formula (I)

and a pharmaceutically acceptable carrier, wherein the composition has less than 3% w/w of each of: a compound represented by Formula (II):



Formula (II)

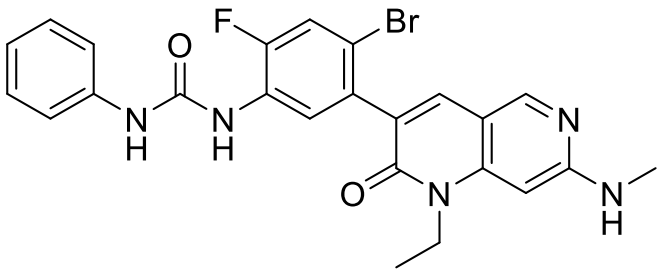
a compound represented by Formula (III):



Formula (III)

aniline, and diphenyl urea.

37. A pharmaceutical composition comprising a compound represented by Formula (I):



Formula (I)

and a pharmaceutically acceptable carriers, wherein the composition has less than 3% w/w of each of: 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-2(1H)-one, aniline and diphenyl urea.

38. The composition of any one of claims 1-37, wherein the composition comprises about 10% to about 50% by weight of the compound based on the total weight of the composition.

39. The composition of any one of claims 1-38, wherein the composition comprises about 10% to about 30% by weight of the compound, based on the total weight of the composition

40. The composition of any one of claims 1-39, wherein the composition comprises about 20% to about 30% by weight of the compound based on the total weight of the composition.

41. The composition of any one of claims 1-40, wherein the composition comprises about 25% by weight of the compound based on the total weight of the composition.

42. The composition of any one of claims 1-41, wherein the compound has a purity of at least 98% as determined by HPLC.

43. The composition of any one of claims 1-42, wherein the compound is substantially in amorphous form.

44. The composition of any one of claims 1-43, wherein the pharmaceutically acceptable carrier is selected from the group consisting of polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate

succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, hydroxyethyl cellulose, methyl cellulose and hydroxy propyl cellulose, poly methacrylic acid-ethyl acrylate, poly methacrylic acid-methyl methacrylate, poly methyl methacrylate-ethyl acrylate, poly trimethylammonioethyl methacrylate chloride-methyl methacrylate-ethyl acrylate and poly(butylmethacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate), and mixtures thereof.

45. The composition of any one of claims 1-44, wherein the pharmaceutically acceptable carrier is selected from the group consisting of polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2,

poly(methacrylic acid-co-ethyl acrylate) 1:1, and mixtures thereof.

46. The composition of any one of claims 1-45, wherein the pharmaceutically acceptable carrier is hydroxypropyl methyl cellulose acetate succinate.

47. The composition of any one of claims 1-46, wherein the ratio of the compound represented by Formula (I) and the one or more pharmaceutically acceptable carrier is from about 40:60 to about 10:90.

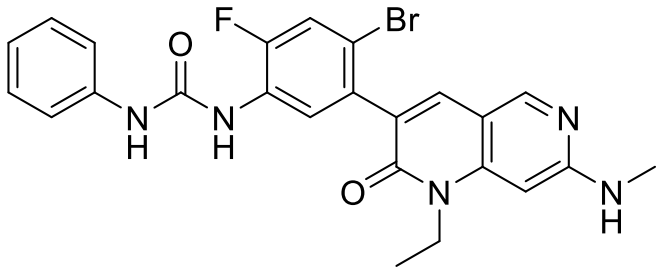
48. The composition of any one of claims 1-47, wherein the ratio of the compound represented by Formula (I) and one or more pharmaceutically acceptable carrier is from about 30:70 to about 20:80.

49. The composition of any one of claims 1-48, wherein the ratio of the compound represented by Formula (I) and one or more pharmaceutically acceptable carrier is about 25:75.

50. The composition of any one of claims 1-49, wherein the composition is a solid oral formulation.

51. The composition of claim 50, wherein the solid oral formulation is a tablet.

52. A pharmaceutically acceptable composition for a 50 mg single dosage unit of a compound represented by:



;

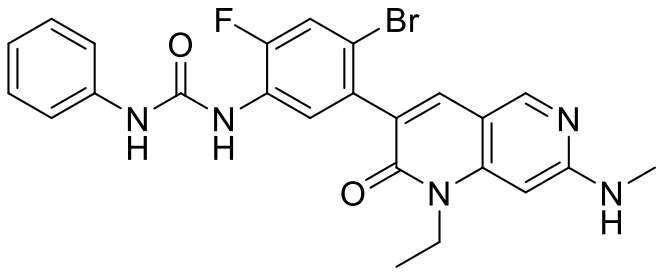
comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and

an extragranular blend comprising a glidant and/or a lubricant; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

53. A pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by:



;

comprising:

a solid dispersion having:

50 mg of the compound wherein the compound is present in amorphous form;

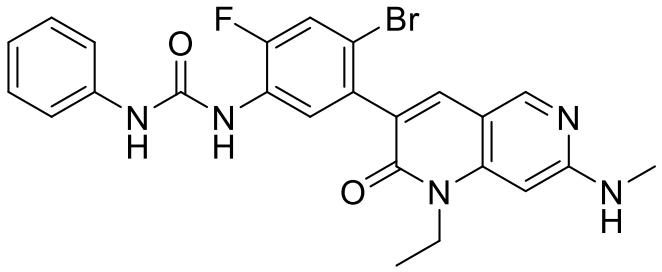
hydroxypropyl methyl cellulose acetate succinate;

a bulking agent,

a filler, and

a lubricant and/or a glidant; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

54. A pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by:



comprising:

comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and a polymer;

about 25-45% by weight of a bulking agent based on the total amount of the pharmaceutical composition;

about 25-45% by weight of a filler based on the total amount of the pharmaceutical composition; and

a glidant and/or a lubricant; wherein the composition has not more than about 1.5% (w/w) of 3-(5-amino-2-bromo-4-fluorophenyl)-1-ethyl-7-(methylamino)-1,6-naphthyridin-

2(1H)-one, when exposed to 60% relative humidity at 25 ºC for 1 month, 3 months or 6 months.

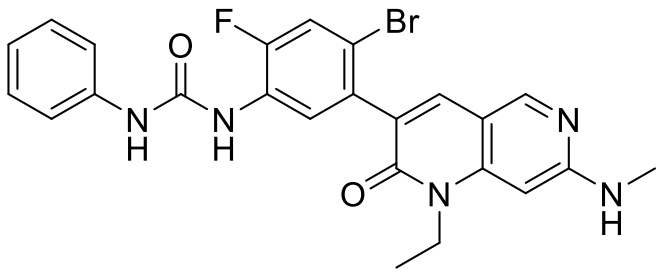
55. The pharmaceutically acceptable composition of claim 54, wherein the polymer is hydroxypropyl methyl cellulose acetate succinate.

56. The pharmaceutically acceptable composition of claim 54 or 55, wherein the bulking agent is microcrystalline cellulose.

57. The pharmaceutically acceptable composition of any one of claims 54-56, wherein the filler is lactose or a hydrate thereof.

58. The pharmaceutically acceptable composition of any one of claims 54-57, wherein the composition is in the form of a tablet.

59. A pharmaceutically acceptable tablet having 50 mg of a compound represented by:



;

wherein the tablet comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and

about 25-35% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition; wherein diphenyl urea is present in amount equal to or less than about 0.5% by weight based on the total weight of the composition.

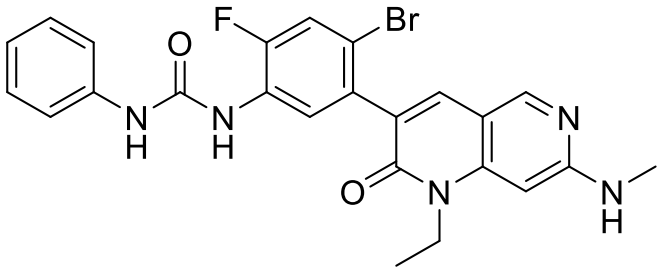
60. The pharmaceutically acceptable tablet of claim 59, further comprising at least one of: magnesium stearate, crospovidone and silicon dioxide.

61. Use of the composition of any one of claims 1-58, or the pharmaceutically acceptable tablet of claims 59-60, in the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung

cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

62. The use of claim 61, wherein the disease is gastrointestinal stromal tumors (GIST).

63. A solid dispersion comprising the compound represented by Formula (I)



Formula (I)

and a pharmaceutically acceptable polymer, wherein the solid dispersion comprises one or more anilinic substances each in an amount equal to or less than about 3.0% by weight based on the weight of the compound of Formula (I).

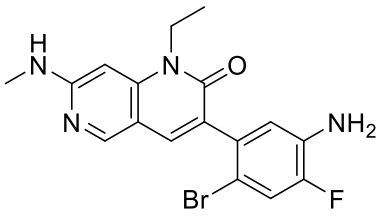
64. The solid dispersion of claim 63, wherein the pharmaceutically acceptable polymer is selected from the group consisting of polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate,

dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, hydroxyethyl cellulose, methyl cellulose and hydroxy propyl cellulose, poly methacrylic acid-ethyl acrylate, poly methacrylic acid-methyl methacrylate, poly methyl methacrylate-ethyl acrylate, poly trimethylammonioethyl methacrylate chloride-methyl methacrylate-ethyl acrylate and poly(butylmethacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate), and mixtures thereof.

65. The solid dispersion of claim 63 or 64, wherein the pharmaceutically acceptable polymer is selected from the group consisting of polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, and mixtures thereof.

66. A pharmaceutical composition comprising the solid dispersion of any one of claims 63-65 and one or more pharmaceutically acceptable carriers, excipients or diluents.

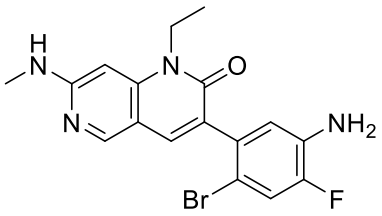
67. The solid dispersion of any one of claims 63-65 or the pharmaceutically acceptable composition of claim 66, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 1 % by weight based on the weight of the compound of Formula (I).

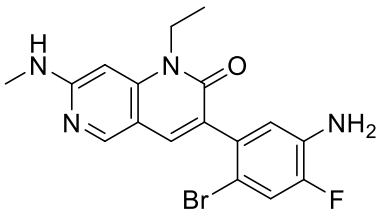
68. The solid dispersion of any one of claims 63-65 and 67 or the pharmaceutically acceptable composition of claim 66 or 67, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 0.1 % by weight to about 0.5% by weight based on the weight of the compound of Formula (I).

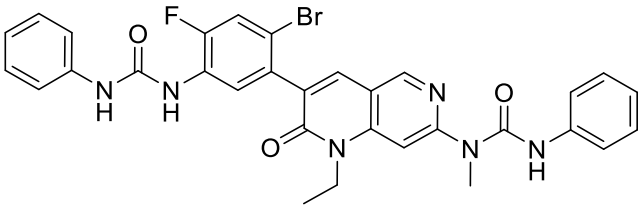
69. The solid dispersion of any one of claims 63-65 and 67-68 or the pharmaceutically acceptable composition of any one of claims 66-68, wherein the one or more anilinic substances is a compound represented by Formula (II):



Formula (II)

and is present in the composition in an amount of less than about 0.01 % by weight to about 0.1% by weight based on the weight of the compound of Formula (I).

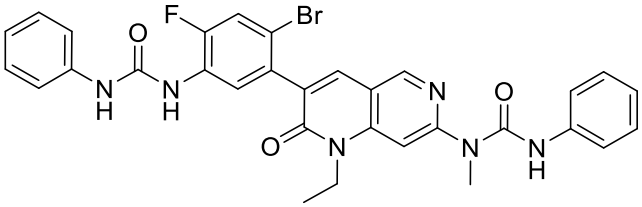
70. The solid dispersion of any one of claims 63-65 and 67-69 or the pharmaceutically acceptable composition of any one of claims 67-69, further comprising less than about 10% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

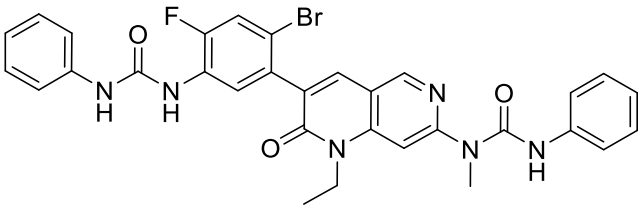
71. The solid dispersion of any one of claims 63-65 and 67-70 or the pharmaceutically acceptable composition of any one of claims 67-70, further comprising less than about 3% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

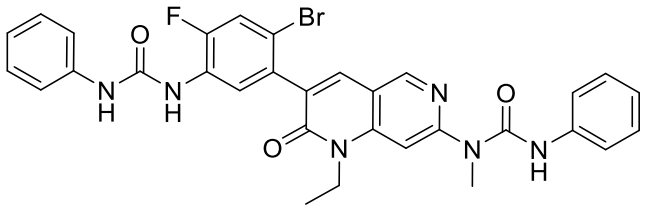
72. The solid dispersion of any one of claims 63-65 and 67-71 or the pharmaceutically acceptable composition of any one of claims 67-71, further comprising less than about 1% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

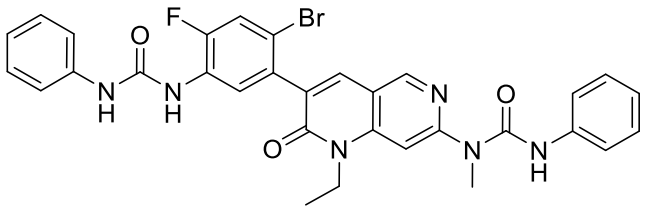
73. The solid dispersion of any one of claims 63-65 and 67-72 or the pharmaceutically acceptable composition of any one of claims 67-72, further comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

74. The solid dispersion of any one of claims 63-65 and 67-73 or the pharmaceutically acceptable composition of any one of claims 67-73, further comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (III):



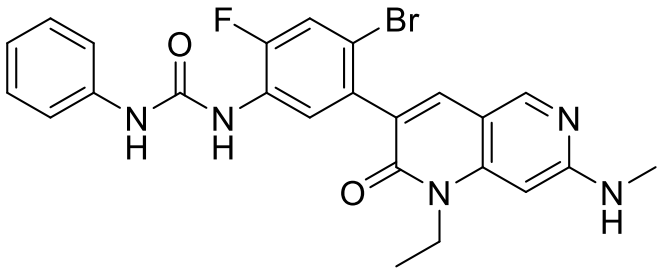
Formula (III)

based on the weight of the compound of Formula (I).

75. Use of the composition of any one of claims 67-74 in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

76. The use of claim 75, wherein the disease is gastrointestinal stromal tumors (GIST).

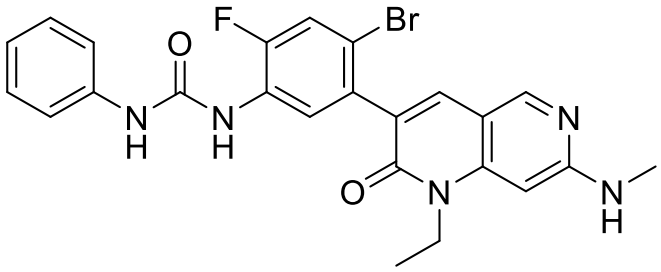
77. A pharmaceutical composition comprising a compound represented by Formula (I)



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition has less than about 0.05% of diphenyl urea.

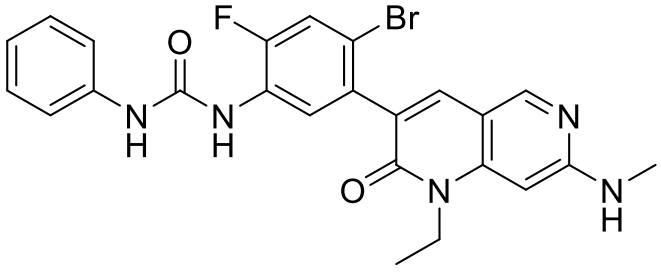
78. A pharmaceutical composition comprising a compound represented by Formula (I)



Formula (I)

and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutical composition has less than about 0.05% of diphenyl urea as detected by HPLC.

79. A solid dispersion comprising the compound represented by Formula (I)



Formula (I)

and a pharmaceutically acceptable polymer, wherein the compound has a purity by HPLC of greater than about 90%.

80. The solid dispersion of claim 79, having a purity by HPLC of greater than about 95%.

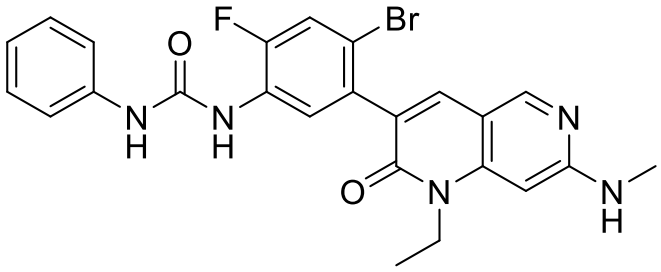
81. A pharmaceutical composition comprising the solid dispersion of claim 79 and one or more pharmaceutically acceptable carriers, excipients or diluents.

82. A pharmaceutical composition comprising the solid dispersion of claim 80 and one or more pharmaceutically acceptable carriers, excipients or diluents.

83. Use of the composition of claim 81 or 82, in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

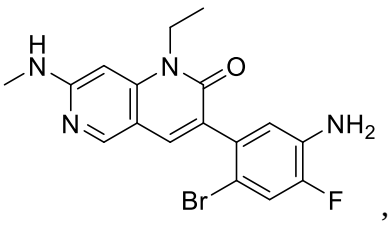
84. The use of claim 83, wherein the disease is gastrointestinal stromal tumors (GIST).

85. A substantially purified compound represented by Formula (I)



Formula (I)

having less than about 3.0% by weight of an impurity selected from the group consisting of a compound represented by Formula (II):



,

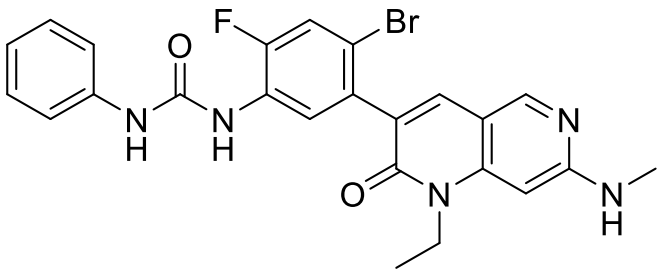
Formula (II)

aniline, and combinations thereof.

86. The compound of claim 85, wherein each of the impurities is in an amount equal to or

less than about 0.5% by weight based on the weight of the compound of Formula (I).

87. A high purity compound represented by Formula (I)



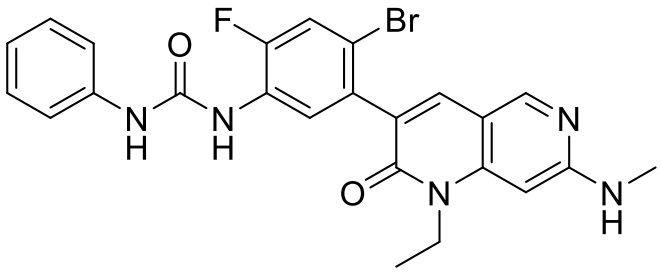
Formula (I)

having less than about 3.0% of anilinic substance impurities.

88. The compound of claim 87, wherein the compound comprises less than 0.5% of each of one or more anilinic substances.

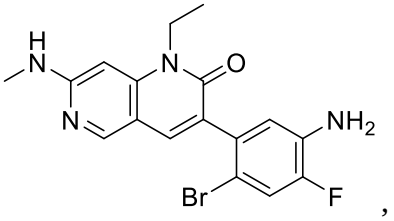
89. The compound of claim 88, wherein each of the impurities is in an amount equal to or less than about 0.5% by weight based on the weight of the compound of Formula (I).

90. A substantially purified compound represented by Formula (I)



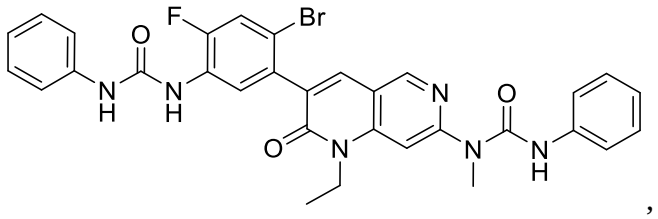
Formula (I)

having less than about 3.0% by weight of an impurity selected from the group consisting of a compound represented by Formula (II):



Formula (II)

a compound represented by Formula (III):

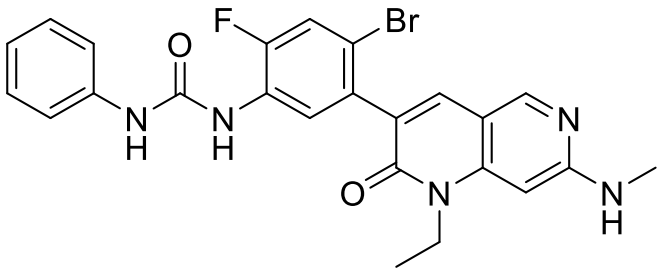


Formula (III)

and combinations thereof.

91. The compound of claim 90, wherein the impurity is in an amount equal to or less than about 0.5% by weight based on the weight of the compound of Formula (I).

92. A high purity compound represented by Formula (I)



Formula (I)

having less than about 0.05% of a diphenyl urea impurity.

93. The compound of claim 92, wherein the compound comprises less than 0.5% of each of one or more anilinic substances.

94. A pharmaceutical composition comprising any one of the compounds of claims 85-93 and one or more pharmaceutically acceptable excipients, carriers or diluents.

95. Use of the composition of claim 94 in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

96. Use of the composition or one or more of the tablets of any one of claims 1-60, 66-74, 77-78, 81-82, and 94 in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, and hypereosinophilic syndrome.

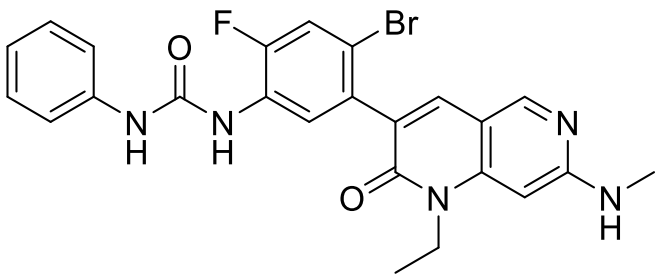
97. Use of the composition or one or more of the tablets of any one of claims 1-60, 66-74, 77-78, 81-82, and 94 in the manufacture of a medicament for treating a disease selected from the group consisting of KIT driven germ cell tumor, KIT driven skin cancer, or KIT driven renal cell carcinoma.

98. Use of the composition or one or more of the tablets of any one of claims 1-60, 66-74, 77-78, 81-82, and 94 in the manufacture of a medicament for treating a disease selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer.

99. Use of the composition or one or more of the tablets of any one of claims 1-60, 66-74, 77-78, 81-82, and 94 in the manufacture of a medicament for treating a disease selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma, wherein the disease comprises a PDGFRAB mutation.

100. The use of claim 99, wherein the disease is gastrointestinal stromal tumors (GIST).

101. A process for the preparation of the solid dispersion comprising a compound of Formula (I)



Formula (I)

according to any one of claims 63-65, 67-74, and 79-80, the process comprising:

(a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension;

(b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 ºC;

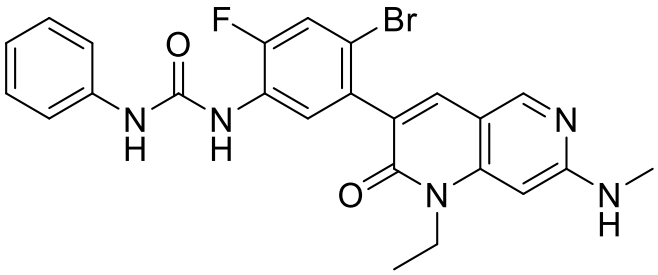
(c) heating the suspension to dissolve the suspended particles prior to introduction into a spray-dryer; and

(d) spray-drying the suspension to obtain a spray-dried dispersion;

(e) drying the spray-dried dispersion; thereby obtaining the solid dispersion.

102. The process of claim 101, wherein heating comprises passing the suspension through an in-line heat exchanger.

103. A solid dispersion comprising a compound of Formula (I)



Formula (I)

produced by the process of claim 101 or 102.

104. The composition or one or more of the tablets of any one of claims 1-60, 66-74, 77-78, 81-82, and 94, for use in therapy.