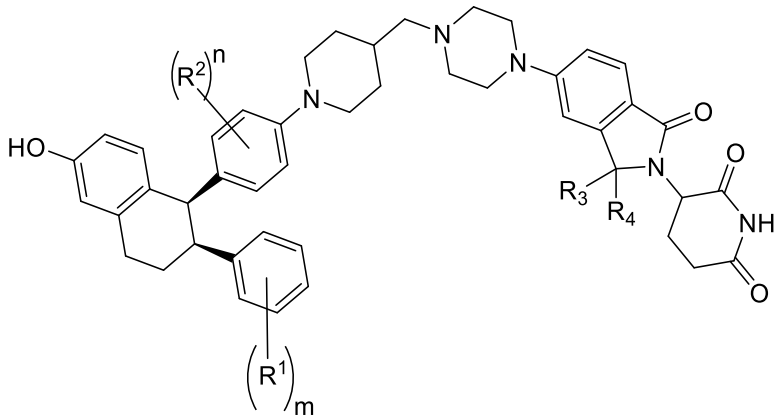
intervals [CI] 9.7-18.8%) and for the 250 mg dose was 14.6% (CI 10.5-19.4%) (Astra Zeneca Faslodex Full Prescribing Information, revised 03/2019).

Summary of the Disclosure

[0007a] In an aspect of the present disclosure, there is provided a use of a compound in the manufacture of a medicament for treating breast cancer in a subject in need thereof, the compound having a Formula (I),



(I), or a pharmaceutically acceptable salt thereof, wherein:

each R^1 and each R^2 is independently selected from halogen, OR_5, $N(R_5)(R_6)$, NO_2, CN, $SO_2(R_5)$, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R_3 and R_4 are either both hydrogen or

R_3 and R_4, taken together with the carbon to which they are attached, form a carbonyl;

each R_5 and each R_6 is independently selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

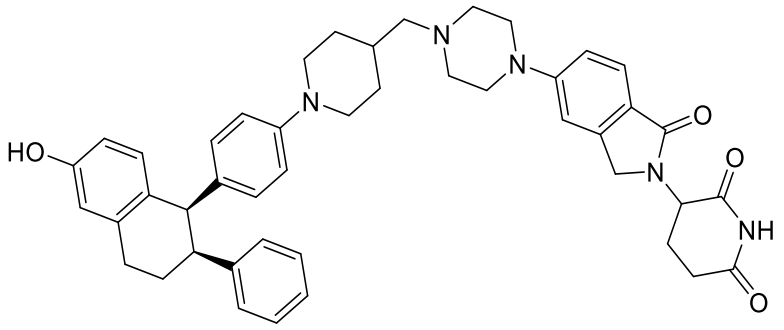
m is 0, 1, 2, 3, 4, or 5; and

n is 0, 1, 2, 3, or 4,

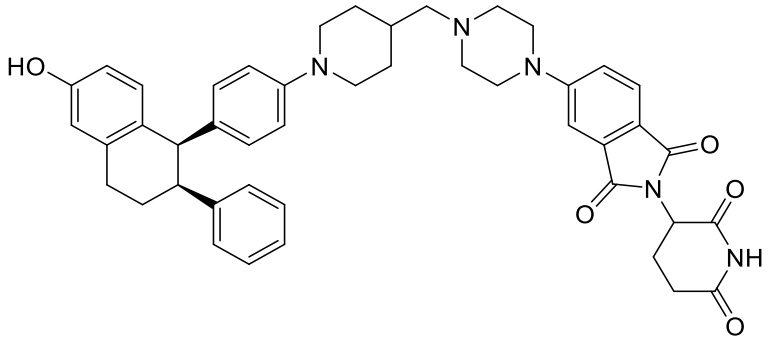
wherein an effective amount of the compound is to be administered to the subject, and

wherein the effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

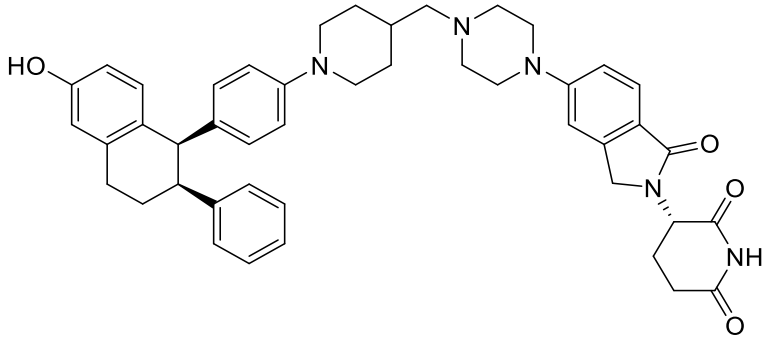
[0007b] In another aspect of the present disclosure, there is provided a use of a compound of Formula (I) in the manufacture of a medicament for treating metastatic breast cancer in a subject in need thereof, wherein an effective amount of the compound of Formula (I) is to be administered orally once a day to the subject, and wherein the compound of Formula (I) is:



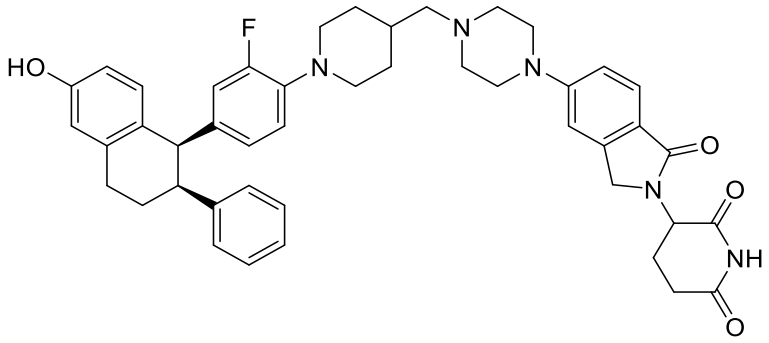
(I-a);



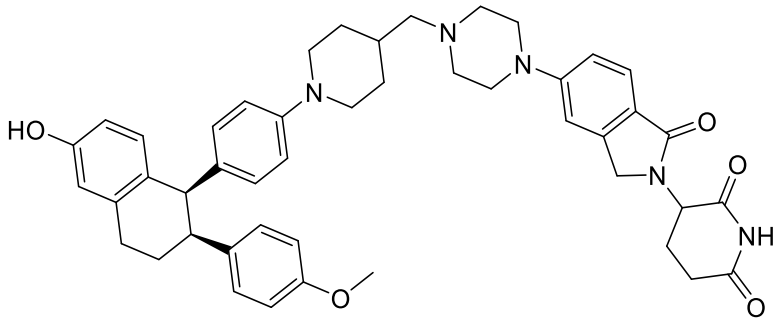
(I-b);



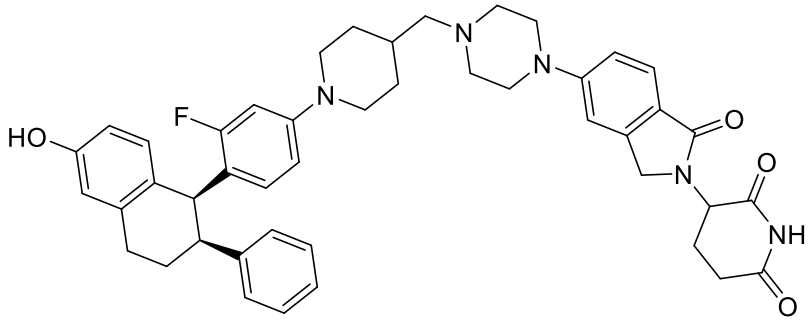
(I-c);



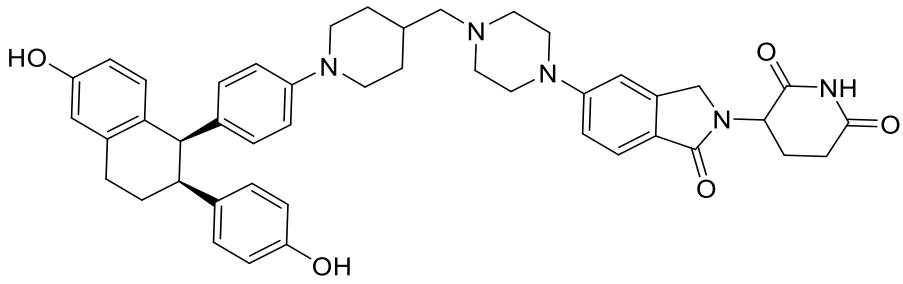
(I-d);



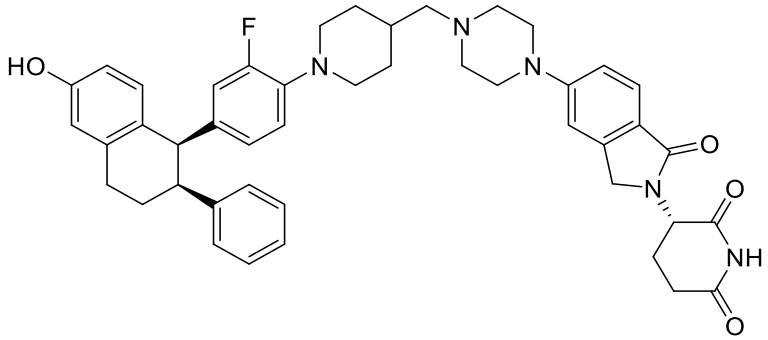
(I-e);



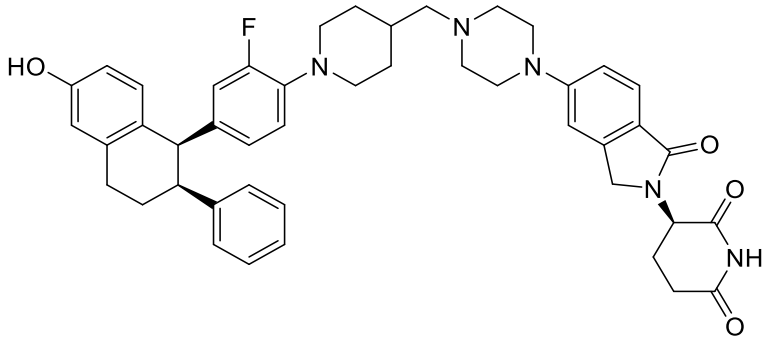
(I-f);



(I-g);



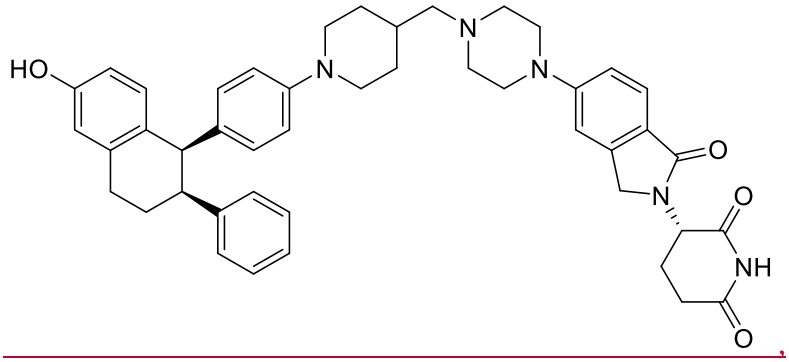
(I-h); or



(I-i);

or a pharmaceutically acceptable salt thereof.

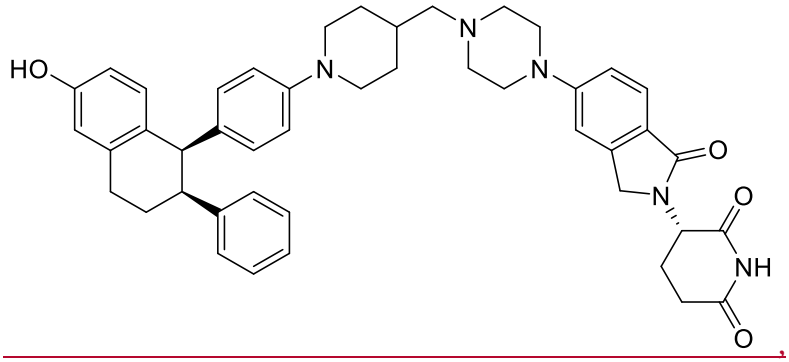
[0007c] In a further aspect of the present disclosure, there is provided a use of a compound of Formula (I-c),



,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating metastatic breast cancer in a subject in need thereof, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered orally once a day, and wherein palbociclib is to be further administered orally once a day.

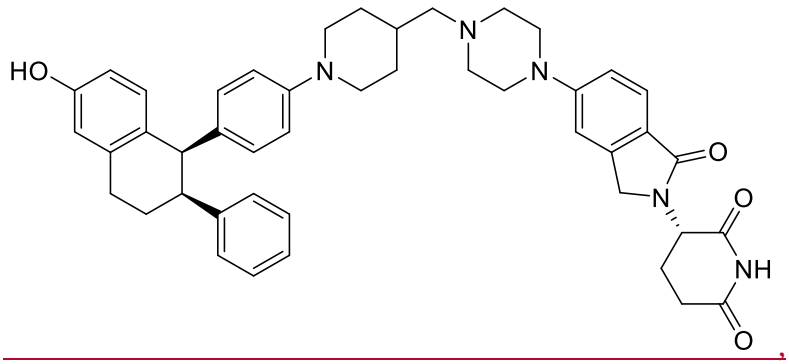
[0007d] In another aspect of the present disclosure, there is provided a use of a compound of Formula (I-c),



,

in the manufacture of a medicament for treating metastatic breast cancer in a subject in need thereof, wherein a therapeutically effective amount of the compound is to be administered orally once a day, and palbociclib is to be further administered orally once a day.

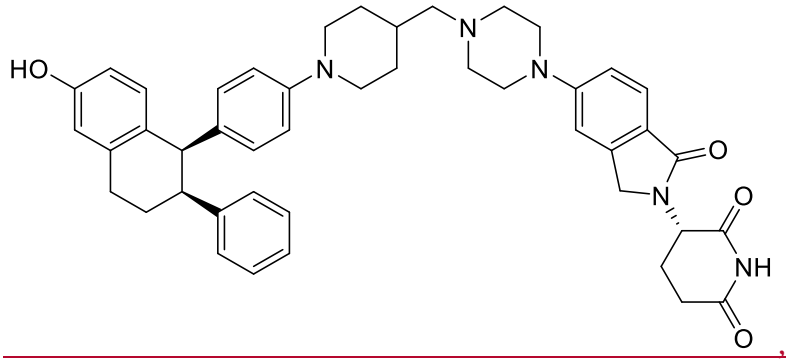
[0007e] In a further aspect of the present disclosure, there is provided a use of a compound of Formula (I-c),



,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for selective estrogen receptor degradation in a patient, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered orally once a day, and palbociclib is to be further administered orally once a day.

[0007f] In another aspect of the present disclosure, there is provided a use of a compound of Formula (I-c),

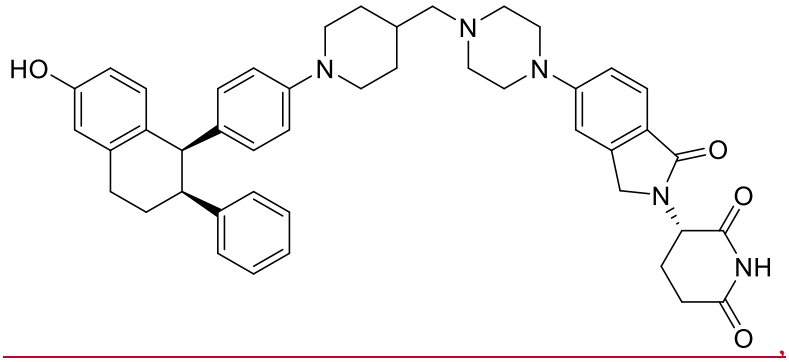


,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting a cyclin-dependent kinase in a subject in need thereof, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered orally once a day, and palbociclib is to be further administered orally once a day.

[0007g] In a further aspect of the present disclosure, there is provided a kit comprising:

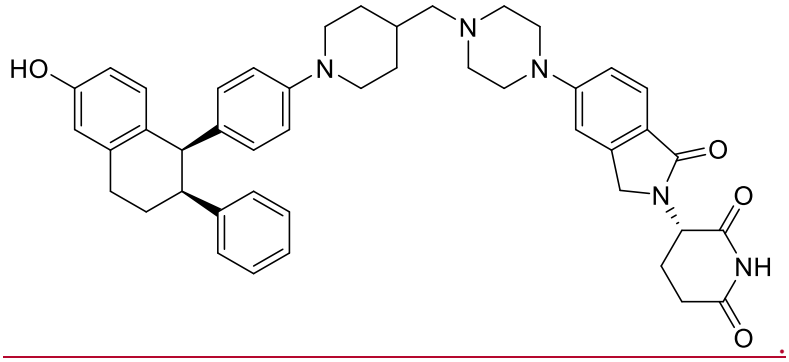
(i) a compound of Formula (I-c),



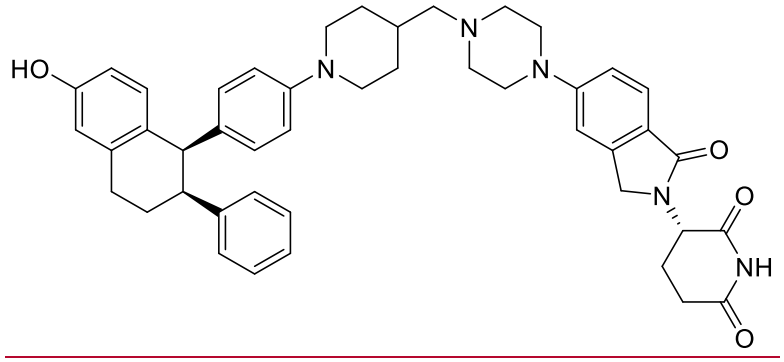
(ii) palbociclib, and

(iii) instructions for use.

[0007h] In another aspect of the present disclosure, there is provided a liquid composition comprising a surfactant, a solvent, and a compound of Formula (I-c):

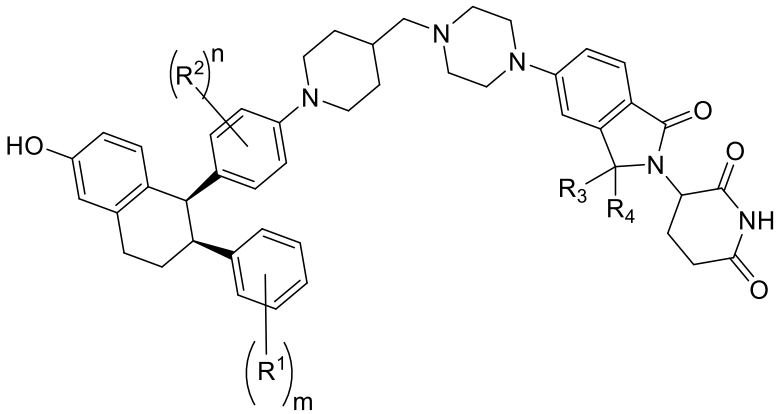


[0007i] In a further aspect of the present disclosure, there is provided a method of making a liquid composition comprising a surfactant, a solvent, and a compound of Formula (I-c):



comprising the step of adding the solvent to a pre-aliquoted volume of the surfactant.

[0008] In one ~~aspect~~example, this application pertains to a method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I),



(I), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, wherein:

each R^1 and each R^2 is independently selected from the group consisting of halo, OR_5, $N(R_5)(R_6)$, NO_2, CN, $SO_2(R_5)$, C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

R_3 and R_4 are either both hydrogen or, taken together with the carbon to which they are attached, form a carbonyl;

each R_5 and each R_6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

m is 0, 1, 2, 3, 4, or 5; and

n is 0, 1, 2, 3, or 4.

[0009] In one ~~embodiment~~example, the breast cancer is ER+, HER2-.

[0010] In one ~~embodiment~~example, the breast cancer is metastatic or locally advanced.

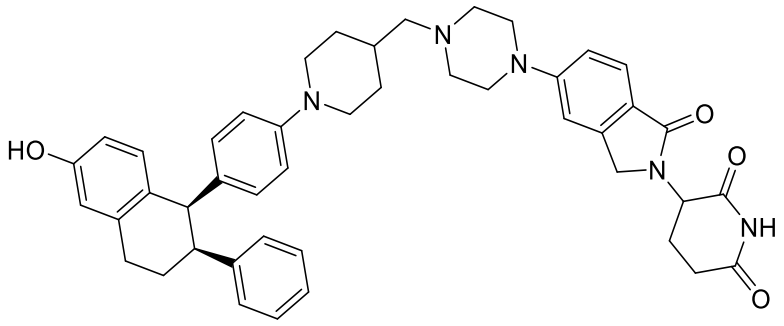
[0011] In one ~~embodiment~~example, each R^1 and each R^2 is independently selected from the group consisting of halo and OR_5.

[0012] In one ~~embodiment~~example, R_3 and R_4 are both hydrogen.

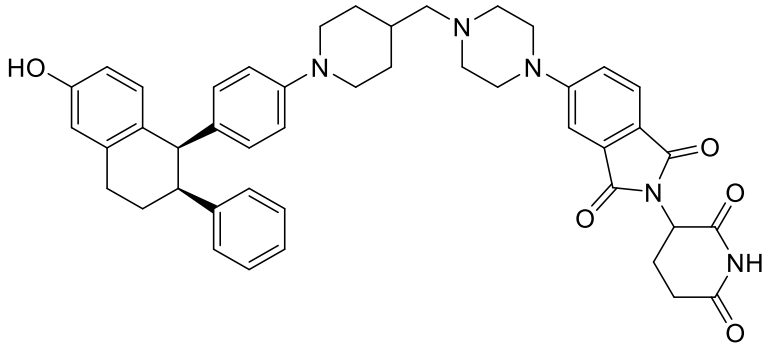
[0013] In one ~~embodiment~~example, R_3 and R_4, taken together with the carbon to which they are attached, form a carbonyl.

[0014] In one ~~embodiment~~example, m and n are each 0. In one ~~embodiment~~example, m and n are each 1. In one ~~embodiment~~example, one of m and n is 0 and the other is 1. For example, in one ~~embodiment~~example m is 0 and n is 1. In another ~~embodiment~~example, m is 0 and n is 1.

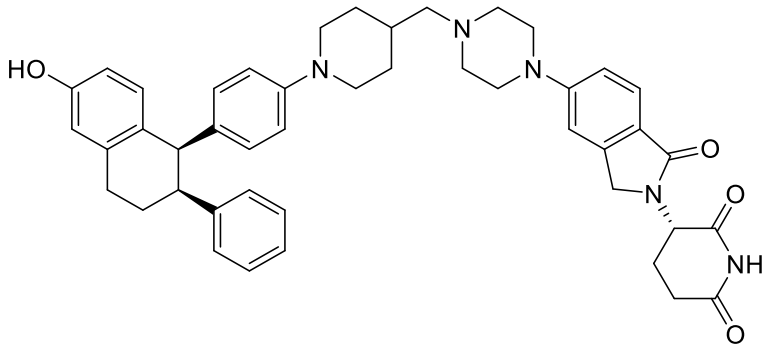
[0015] In one ~~embodiment~~example, the compound of Formula (I) is:



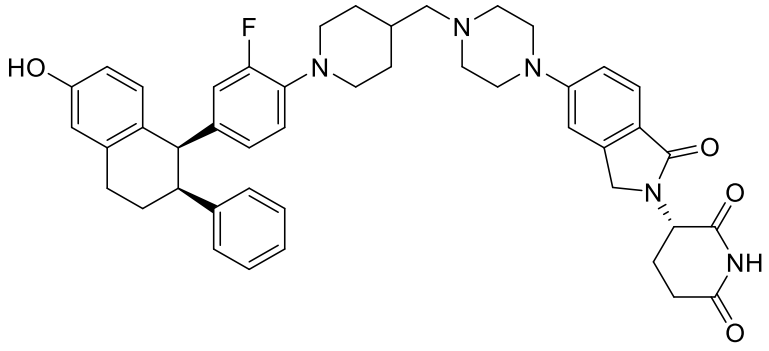
(I-a);



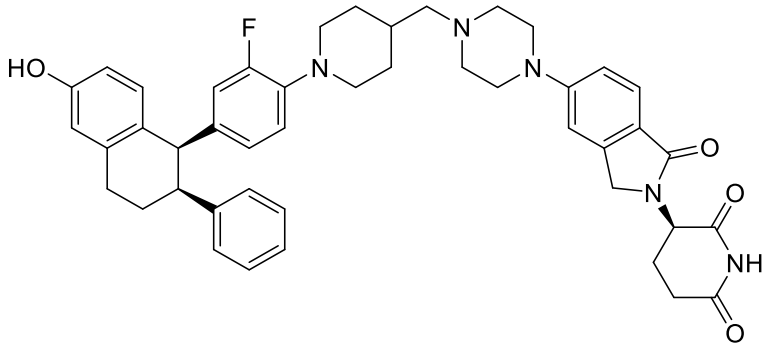
(I-b);



(I-c);



(I-h); or



(I-i);

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug of any of the foregoing.

[0016] In one ~~embodiment~~example, the method comprises administering to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, or isotopic derivative thereof.

[0017] In one ~~embodiment~~example, the compound of Formula (I) is administered orally to the subject.

[0018] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is administered to the subject once a day, twice a day, three times a day, or four times a day. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is administered to the subject once a day. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is administered to the subject all at once or is administered in two, three, or four portions.

[0019] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, or 30 mg.

[0020] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

[0021] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 20 mg to about 700 mg.

[0022] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 30 mg to about 500 mg.

[0023] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 30 mg to about 120 mg.

[0024] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 10 to about 40 mg, about 20 to about 50 mg, about 30 to about 60 mg, about 40 to about 70 mg, about 50 to about 80 mg, about 60 to about 90 mg, about 70 to about 100 mg, about 80 to about 110 mg, about 90 to about 120 mg, about 100 to about 130 mg, about 110 to about 140 mg, about 120 to about 150 mg, about 130 to about 160 mg, about 140 to about 170 mg, about 150 to about 180 mg, about 160 to about 190 mg, about 170 to about 200 mg, about 180 to about 210 mg, about 190 to about 220 mg, about 200 to about 230 mg, about 210 to about 240 mg, about 220 to about 250 mg, about 230 to about 260 mg, about 240 to about 270 mg, about 250 to about 280 mg, about 260 to about 290 mg, about 270 to about 300 mg, about 280 to about 310 mg, about 290 to about 320 mg, about 300 to about 330 mg, about 310 to about 340 mg, about 320 to about 350 mg, about 330 to about 360 mg, about 340 to about 370 mg, about 350 to about 380 mg, about 360 to about 390 mg, or about 370 to about 400 mg.

[0025] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,500 ng*hr/mL, about 3,600 ng*hr/mL, about 3,700 ng*hr/mL, about 3,800 ng*hr/mL, about 3,900 ng*hr/mL, about 4,000 ng*hr/mL, about 4,100 ng*hr/mL, about 4,200 ng*hr/mL, about 4,300 ng*hr/mL, 4,400 ng*hr/mL, about 4,500 ng*hr/mL, about 4,600 ng*hr/mL, about 4,700 ng*hr/mL, about 4,800 ng*hr/mL, about 4,900 ng*hr/mL, or about 5,000 ng*hr/mL.

[0026] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,500 ng*hr/mL and less than about 4,000 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,600 ng*hr/mL and less than about 4,100 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,700 ng*hr/mL and less than about 4,200 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,800 ng*hr/mL and less than about 4,300 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of

the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,900 ng*hr/mL and less than about 4,400 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,000 ng*hr/mL and less than about 4,500 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,100 ng*hr/mL and less than about 4,600 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,200 ng*hr/mL and less than about 4,700 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,300 ng*hr/mL and less than about 4,800 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,400 ng*hr/mL and less than about 4,900 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,500 ng*hr/mL and less than about 5,000 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,600 ng*hr/mL and less than about 5,100 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,700 ng*hr/mL and less than about 5,200 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,800 ng*hr/mL and less than about 5,300 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,900 ng*hr/mL and less than about 5,400 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 5,000 ng*hr/mL and less than about 5,500 ng*hr/mL.

[0027] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,000 ng*hr/mL and less than about 4,200 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,900 ng*hr/mL and less than about 4,300 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,800 ng*hr/mL and less than about 4,400 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the

compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,700 ng*hr/mL and less than about 4,500 ng*hr/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,600 ng*hr/mL and less than about 4,600 ng*hr/mL.

[0028] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 200 ng/mL, about 205 ng/mL, about 210 ng/mL, about 215 ng/mL, about 220 ng/mL, about 225 ng/mL, about 230 ng/mL, about 235 ng/mL, about 240 ng/mL, about 245 ng/mL, or about 250 ng/mL.

[0029] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 200 ng/mL and less than about 220 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 205 ng/mL and less than about 225 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 210 ng/mL and less than about 230 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 215 ng/mL and less than about 235 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 220 ng/mL and less than about 240 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 225 ng/mL and less than about 245 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 230 ng/mL and less than about 250 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 235 ng/mL and less than about 255 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 240 ng/mL and less than about 260 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 245 ng/mL and less than about 265 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 250 ng/mL and less than about 270 ng/mL.

[0030] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 214 ng/mL and less than about 236 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 213 ng/mL and less than about 237 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 212 ng/mL and less than about 238 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 211 ng/mL and less than about 239 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 210 ng/mL and less than about 240 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 205 ng/mL and less than about 245 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 200 ng/mL and less than about 250 ng/mL.

[0031] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 223 ng/mL and less than about 225 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 222 ng/mL and less than about 226 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 221 ng/mL and less than about 227 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 220 ng/mL and less than about 228 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 219 ng/mL and less than about 229 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 218 ng/mL and less than about 230 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 217 ng/mL and less than about 231 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 216 ng/mL and less than about 232 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a

mean day 15 C_{max} of greater than about 215 ng/mL and less than about 233 ng/mL. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 214 ng/mL and less than about 234 ng/mL.

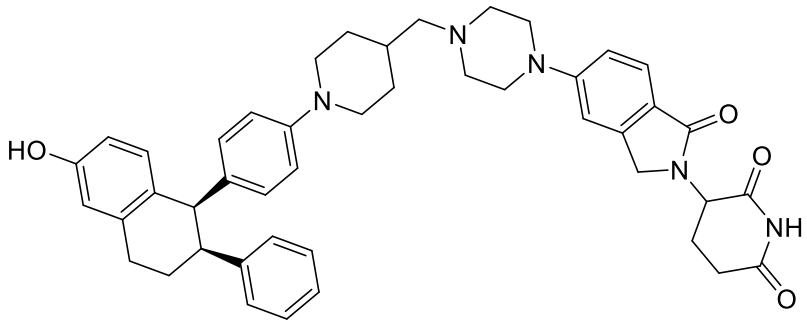
[0032] In one ~~embodiment~~example, the compound of Formula (I) is formulated as a tablet. In one ~~embodiment~~example, the tablet comprises a compound of Formula (I) and, optionally, one or more of the following: emulsifier; surfactant; binder; disintegrant; glidant; and lubricant. In one ~~embodiment~~example, the emulsifier is hypromellose. In one ~~embodiment~~example, the surfactant is Vitamin E polyethylene glycol succinate. In one ~~embodiment~~example, the binder is microcrystalline cellulose or lactose monohydrate. In one ~~embodiment~~example, the disintegrant is croscarmellose sodium. In one ~~embodiment~~example, the glidant is silicon dioxide. In one ~~embodiment~~example, the lubricant is sodium stearyl fumarate. In one ~~embodiment~~example, the subject in need of treatment is in a fed state. In one ~~embodiment~~example, the subject in need of treatment is in a fasted state.

[0033] In one ~~aspect~~example, this application pertains to a method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) as defined herein, further comprising the administration of a therapeutically effective amount of a CDK4/6 inhibitor to the subject in need thereof. In one ~~embodiment~~example, the CDK4/6 inhibitor is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, or palbociclib. In one ~~embodiment~~example, the CDK4/6 inhibitor is palbociclib.

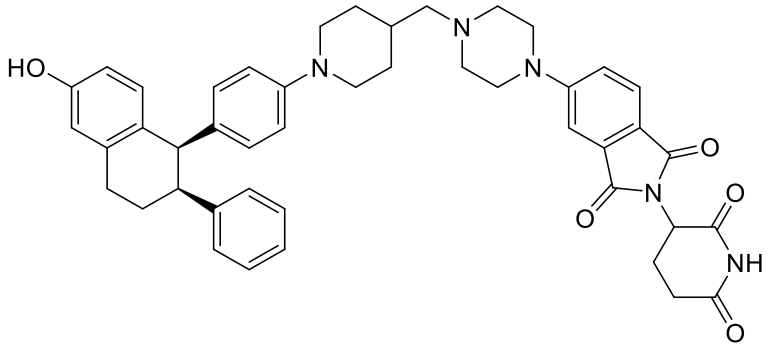
[0034] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered to the subject once a day. In one ~~embodiment~~example, the therapeutically effective amount of palbociclib is 60 mg, 75 mg, 100 mg, or 125 mg. In one ~~embodiment~~example, the palbociclib is administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with palbociclib followed by off treatment is repeated one, two, three, four, five, or more times. In one ~~embodiment~~example, the compound of formula (I) is administered once daily for 21 up to consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with the compound of formula (I) followed by off treatment is repeated one, two, three, four, five, or more times. In one ~~embodiment~~example, the administration of the compound of Formula (I) and palbociclib to the subject in need thereof occurs when the subject is in a fed state. In one

~~embodiment~~example, the administration of the compound of Formula (I) and palbociclib to the subject in need thereof occurs when the subject is in a fasted state.

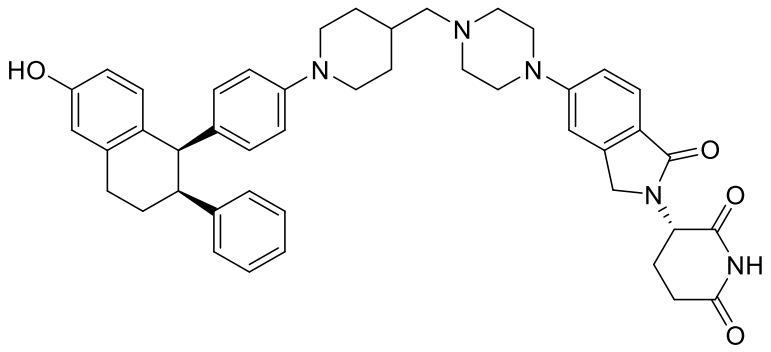
[0035] In one ~~aspect~~example, this application pertains to a method of treating metastatic breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, wherein the compound of Formula (I), is selected from the group consisting of:



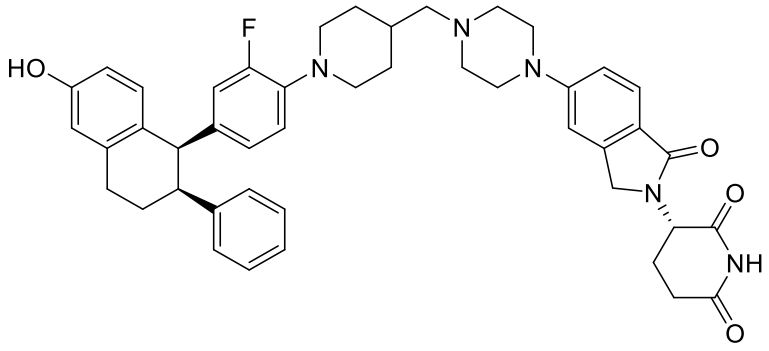
(I-a);



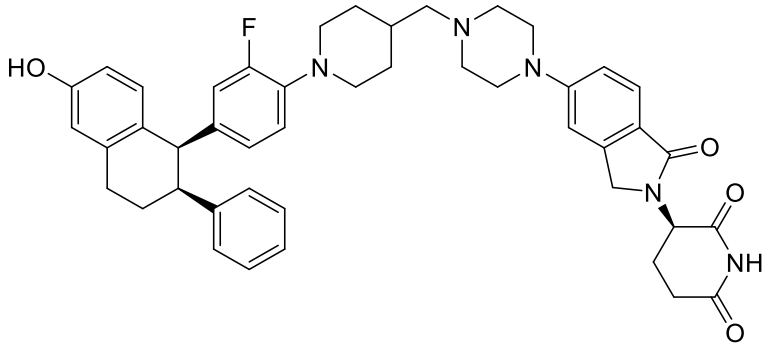
(I-b);



(I-c);



(I-h); and



(I-i).

[0036] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is administered to the subject all at once or is administered in two, three, or four portions.

[0037] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 30 mg to about 1000 mg.

[0038] In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I) is about 10 to about 40 mg, about 20 to about 50 mg, about 30 to about 60 mg, about 40 to about 70 mg, about 50 to about 80 mg, about 60 to about 90 mg, about 70 to about 100 mg, about 80 to about 110 mg, about 90 to about 120 mg, about 100 to about 130 mg, about 110 to about 140 mg, about 120 to about 150 mg, about 130 to about 160 mg, about 140 to about 170 mg, about 150 to about 180 mg, about 160 to about 190 mg, about 170 to about 200 mg, about 180 to about 210 mg, about 190 to about 220 mg, about 200 to about 230 mg, about 210 to about 240 mg, about 220 to about 250 mg, about 230 to about 260 mg, about 240 to about 270 mg, about 250 to about 280 mg, about 260 to about 290 mg, about 270 to about 300 mg, about 280 to about 310 mg, about 290 to about 320 mg, about 300 to about 330 mg, about 310 to about 340 mg, about 320 to about 350 mg, about 330 to about 360 mg, about 340 to about 370 mg, about 350 to about 380 mg, about 360 to about 390 mg, or about 370 to about 400 mg.

[0039] In one ~~embodiment~~example, the compound of Formula (I) is formulated as a tablet.

[0040] In one ~~aspect~~example, this application pertains to a method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), wherein the compound of Formula (I) is a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), Formula (I-i), or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, further comprising the administration of a therapeutically effective amount of a CDK4/6 inhibitor to the subject in need thereof. In one ~~embodiment~~example, the CDK4/6 inhibitor is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, or palbociclib. In one ~~embodiment~~example, the CDK4/6 inhibitor is palbociclib.

[0041] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered at the same time as the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered prior to the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered after the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In some ~~embodiment~~examples for the method of treating breast cancer in a subject in need thereof, comprising administering to

the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i) and the administration of palbociclib are separated in time such that the two compounds, and their respective excipients (if present), do not mix in the subject's stomach.

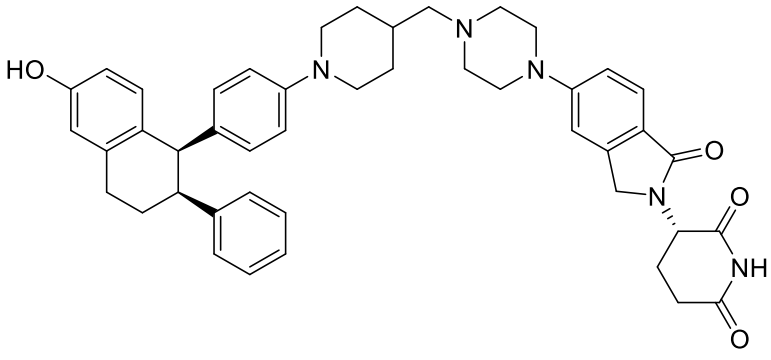
[0042] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered at least 5, at least 10, at least 15, at least 20, at least 25, or at least 30 minutes prior to the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered at least 30 minutes prior to the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered between 30 and 60 minutes prior to the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i).

[0043] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered at least 5, at least 10, at least 15, at least 20, at least 25, or at least 30 minutes after the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered at least 30 minutes after the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered between 30 and 60 minutes after the administration of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i).

[0044] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i), and further comprising the administration of a therapeutically effective amount of palbociclib, the therapeutically effective amount of palbociclib is administered to the subject once a day. In one ~~embodiment~~example, the therapeutically effective amount of palbociclib is 60 mg, 75 mg, 100 mg, or 125 mg. In one ~~embodiment~~example, the palbociclib is administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with palbociclib followed by off treatment is repeated one, two, three, four,

five, or more times. In one ~~embodiment~~example, the compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i) is administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with the compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i) followed by off treatment is repeated one, two, three, four, five, or more times. In one ~~embodiment~~example, the administration of the compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i) and palbociclib to the subject in need thereof occurs when the subject is in a fed state. In one ~~embodiment~~example, the administration of the compound of Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), Formula (I-f), Formula (I-g), Formula (I-h), or Formula (I-i) and palbociclib to the subject in need thereof occurs when the subject is in a fasted state.

[0045] In one ~~aspect~~example, this application pertains to a method of treating breast cancer in a subject in need thereof, comprising: (i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c),



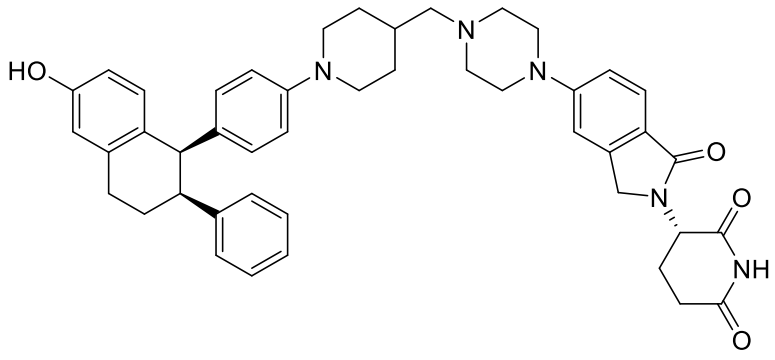
, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) once a day, oral administration of palbociclib. In one ~~aspect~~example, this application pertains to a method of treating breast cancer in a subject in need thereof, comprising: (i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and (ii) once a day, oral administration of palbociclib. In one ~~embodiment~~example, the therapeutically effective amount of the compound of Formula (I-c) is about 30 mg to about 1000 mg. In one ~~embodiment~~example, the therapeutically effective amount of palbociclib is 60 mg, 75 mg, 100 mg, or 125 mg. In one ~~embodiment~~example, the palbociclib is administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with palbociclib followed

by off treatment is repeated one, two, three, four, five, or more times. In one ~~embodiment~~example, the compound of formula (I-c) is administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with the compound of formula (I-c) followed by off treatment is repeated one, two, three, four, five, or more times. In one ~~embodiment~~example, the administration of the compound of Formula (I-c) and palbociclib to the subject in need thereof occurs when the subject is in a fed state. In one ~~embodiment~~example, the administration of the compound of Formula (I-c) and palbociclib to the subject in need thereof occurs when the subject is in a fasted state.

[0046] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the administration of a compound of Formula (I-c) and the administration of palbociclib are separated in time such that the two compounds, and their respective excipients (if present), do not mix in the subject's stomach. In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered prior to the administration of a compound of Formula (I-c). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered at least 5, at least 10, at least 15, at least 20, at least 25, or at least 30 minutes prior to the administration of a compound of Formula (I-c). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered at least 30 minutes prior to the administration of a compound of Formula (I-c). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered between 30 and 60 minutes prior to the administration of a compound of Formula (I-c).

[0047] In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered after the administration of a compound of Formula (I-c). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered at least 5, at least 10, at least 15, at least 20, at least 25, or at least 30 minutes after the administration of a compound of Formula (I-c). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered at least 30 minutes after the administration of a compound of Formula (I-c). In one ~~embodiment~~example, for the method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) and further once a day, oral administration of palbociclib, the palbociclib is administered between 30 and 60 minutes after the administration of a compound of Formula (I-c).

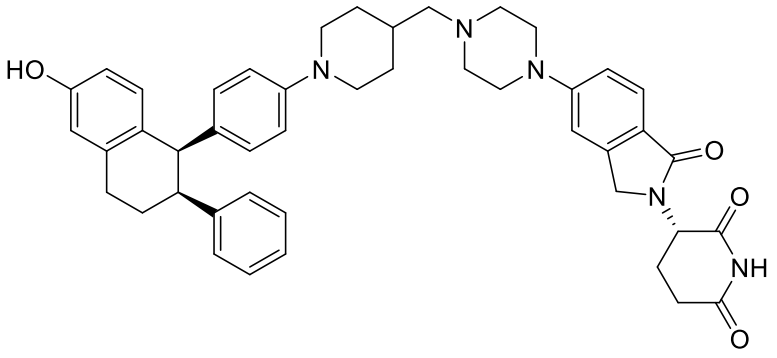
[0048] In one ~~aspect~~example, this application pertains to a method for selective estrogen receptor degradation in a patient comprising: (i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c),



, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) once a day, oral administration of palbociclib.

[0049] In one ~~aspect~~example, this application pertains to a method for inhibiting a cyclin-dependent kinase in a subject in need thereof comprising: (i) once a day, oral administration of a

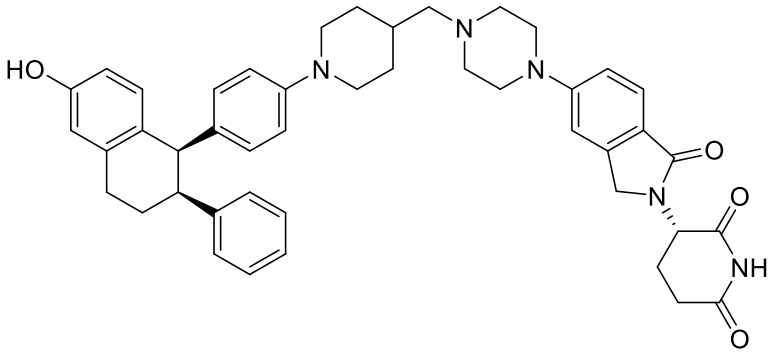
therapeutically effective amount of a compound of Formula (I-c),



, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) once a day, oral administration of palbociclib.

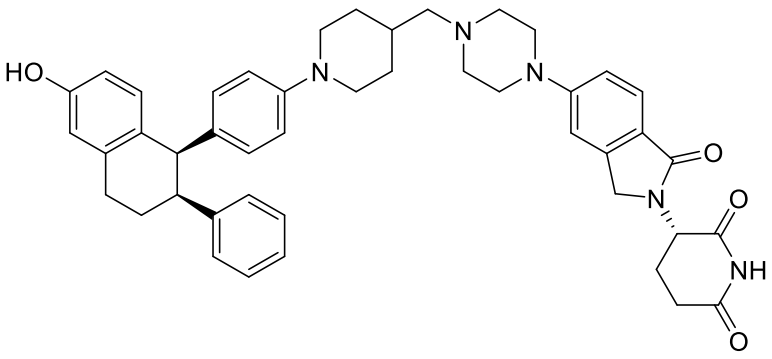
[0050] In one ~~aspect~~example, this application pertains to a kit comprising: a compound of Formula

(I-c),



, palbociclib, and instructions for use.

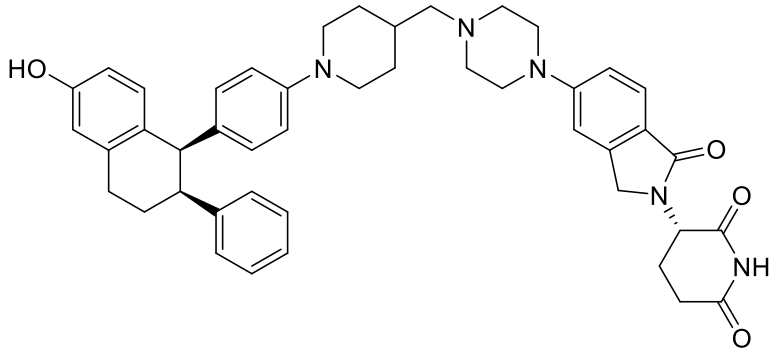
[0051] In one ~~aspect~~example, this application pertains to a liquid composition comprising a surfactant, a solvent, and a compound of Formula (I-c),



. In some ~~embodiment~~examples, the surfactant is a sorbitan derivative. In some ~~embodiment~~examples, the surfactant is Tween 80. In some

~~embodiment~~examples, the solvent is a low molecular weight polyethylene glycol (PEG). In some ~~embodiment~~examples, the solvent is polyethylene glycol (PEG)-400.

[0052] In one ~~aspect~~example, this application pertains to method of making a liquid composition comprising a surfactant, a solvent, and a compound of Formula (I-c):



comprising the step of adding the solvent to a pre-aliquoted volume of the surfactant. In some ~~embodiment~~examples, the method further comprises the step of adding a compound of Formula (I-c) to a mixture of the solvent and the surfactant. In some ~~embodiment~~examples, the surfactant is a sorbitan derivative. In some ~~embodiment~~examples, the surfactant is Tween 80. In some ~~embodiment~~examples, the solvent is a low molecular weight polyethylene glycol (PEG). In some ~~embodiment~~examples, the solvent is polyethylene glycol (PEG)-400.

Brief Description of the Figures

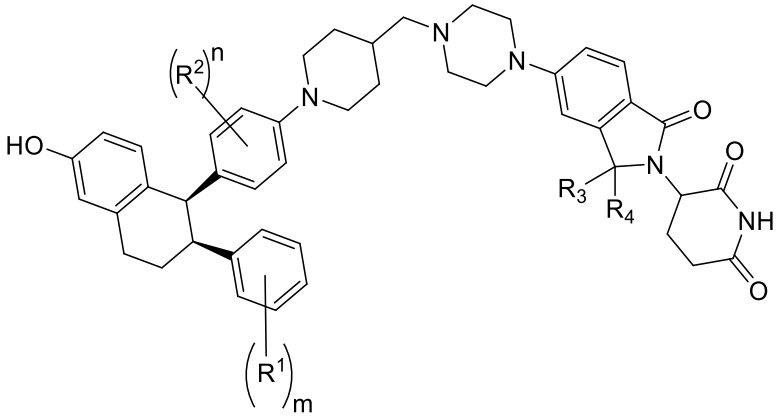
[0053] FIG. 1 shows the results of tumor growth inhibition experiments (mean tumor volume (mm^3) vs. time) associated with oral, once daily administration of Compound (I-c) at doses of 3 mg/kg, 10 mg/kg, and 30 mg/kg compared to vehicle. At doses of 3 mg/kg, 10 mg/kg, and 30 mg/kg of Compound (I-c), tumor growth inhibition (TGI) of 85%, 98%, and 124%, respectively, was observed compared to a control group in a MCF7 xenograft model.

[0054] FIG. 2 is a Western Blot experiment that shows the reduction of ER in MCF7 xenograft tumors in response to dosing of Compound (I-c) of 3 mg/kg, 10 mg/kg, and 30 mg/kg (oral, once daily).

[0055] FIG. 3 is a pair of line graphs which show the mean concentration of the compound of Formula (I-c) (ng/mL) over the course of 24 hours post-dosing on both day 1 and day 15 in a Phase I clinical trial.

What is claimed is:

1. Use of a compound in the manufacture of a medicament for~~A method of~~ treating breast cancer in a subject in need thereof, ~~comprising administering to~~ the ~~subject a therapeutically effective amount of a~~ compound having a~~of~~ Formula (I),



(I), or a pharmaceutically acceptable salt~~, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug~~ thereof, wherein:

each R^1 and each R^2 is independently selected from halogen~~the group consisting of halo~~, OR_5, $N(R_5)(R_6)$, NO_2, CN, $SO_2(R_5)$, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R_3 and R_4 are either both hydrogen or

R_3 and R_4, taken together with the carbon to which they are attached, form a carbonyl;

each R_5 and each R_6 is independently selected from ~~the group consisting of~~ hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

m is 0, 1, 2, 3, 4, or 5; and

n is 0, 1, 2, 3, or 4,

wherein an effective amount of the compound is to be administered to the subject, and wherein the~~therapeutically~~ effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

2. The use~~method~~ of claim 1, wherein the breast cancer is ER+, HER2-.

3. The use~~method~~ of claim 1 or 2, wherein the breast cancer is metastatic or locally advanced.

4. The use~~method~~ of any one of claims 1-3, wherein R^1 and R^2 are each independently ~~selected from the group consisting of~~ halo or~~and~~ OR_5.

5. The use~~method~~ of any one of claims 1-4, wherein R_3 and R_4 are both hydrogen.

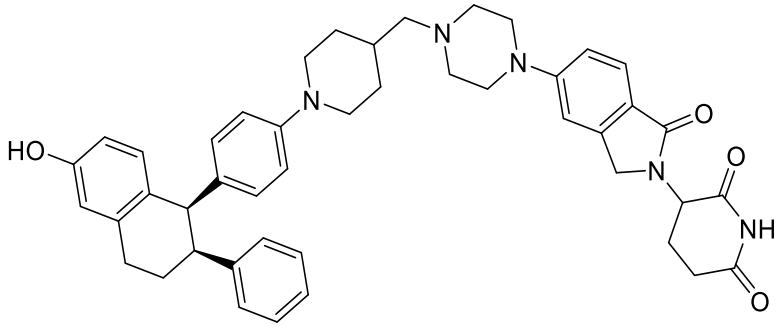
6. The use~~method~~ of any one of claims 1-4, wherein R_3 and R_4, taken together with the carbon to which they are attached, form a carbonyl.

7. The use~~method~~ of any one of claims 1-3, 5, or 6, wherein m and n are each 0.

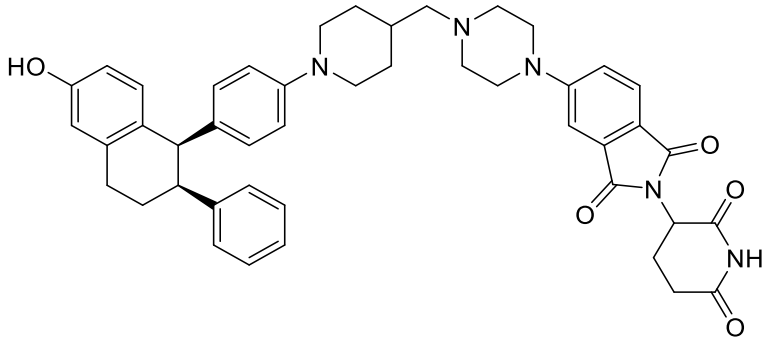
8. The use~~method~~ of any one of claims 1-6, wherein m and n are each 1.

9. The use~~method~~ of any one of claims 1-3, 5, or 6, wherein one of m and n is 0 and the other is 1.

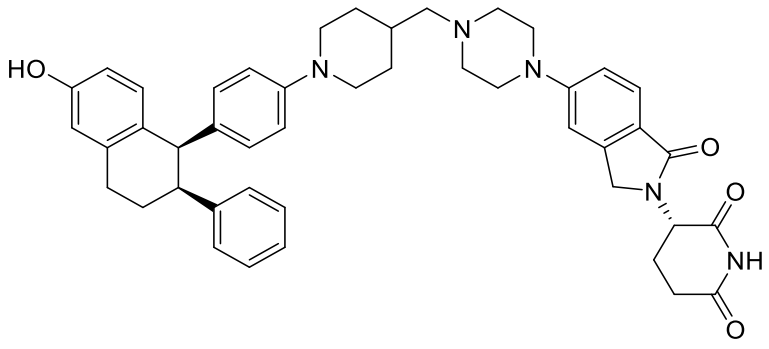
10. The use~~method~~ of any one of claims 1-3, wherein the compound of Formula (I) is:



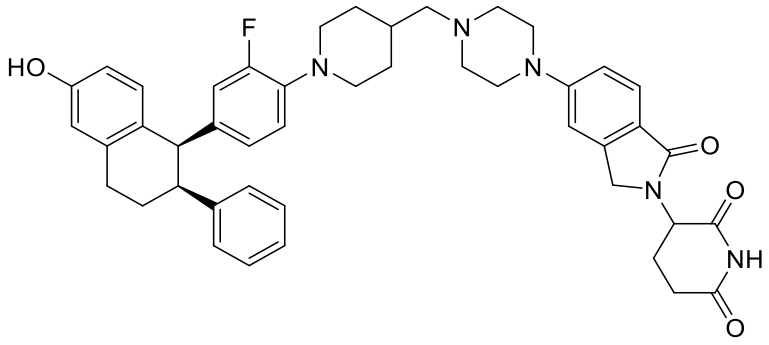
(I-a);



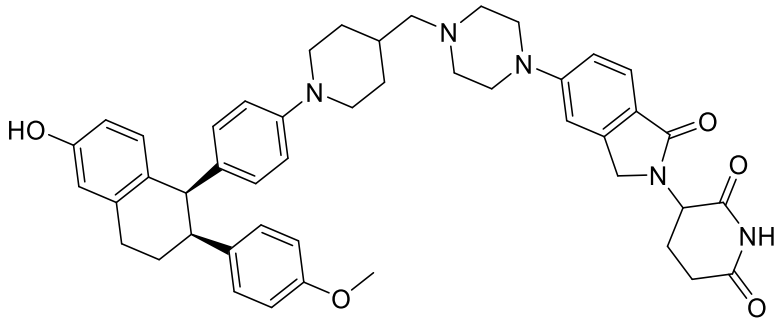
(I-b);



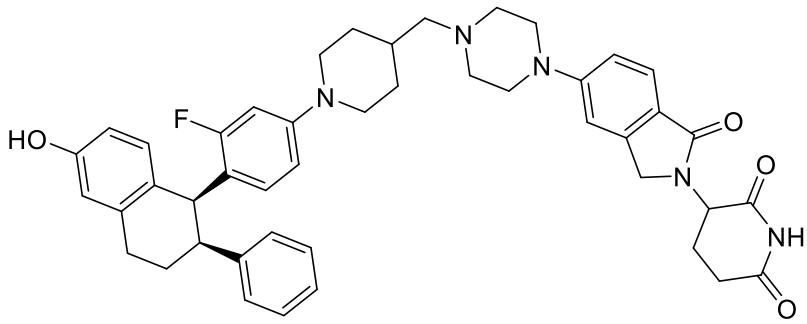
(I-c);



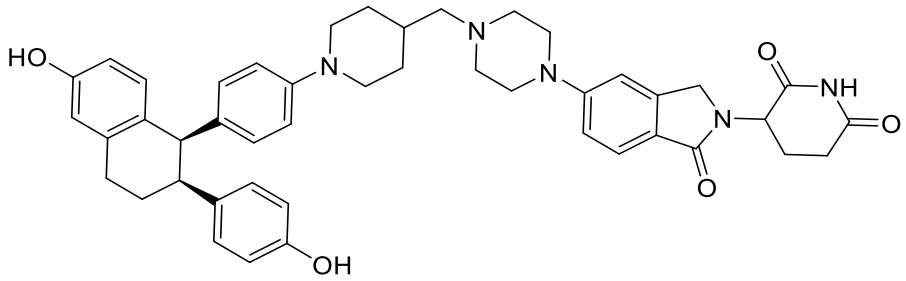
(I-d);



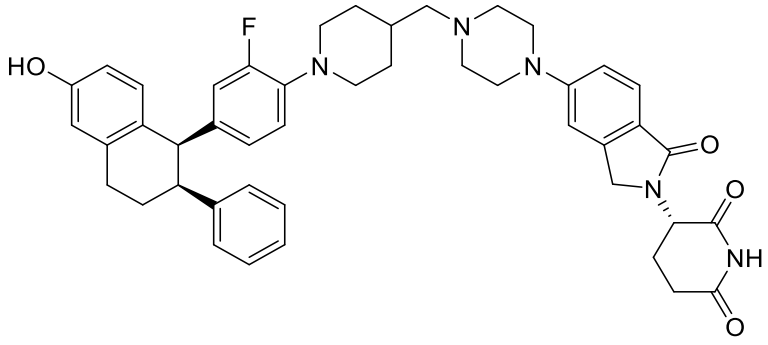
(I-e);



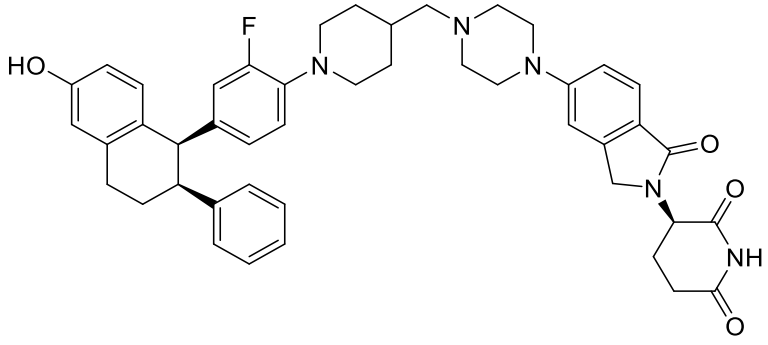
(I-f);



(I-g);



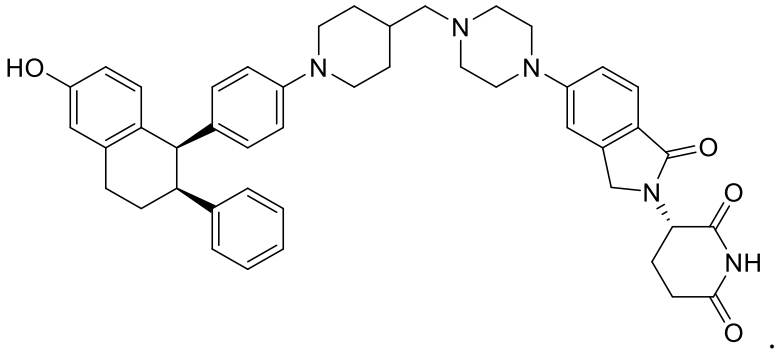
(I-h); or



(I-i);

or a pharmaceutically acceptable salt thereof~~, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug of any of the foregoing~~.

11. The use~~method~~ of any one of claims 1-3, wherein the compound of Formula (I) is a compound of Formula (I-c):



.

12. The use~~method~~ of any one of claims 1-11, wherein the compound of Formula (I) is to be administered orally to the subject.

13. The use~~method~~ of any one of claims 1-12, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is to be administered to the subject once a day, twice a day, three times a day, or four times a day.

14. The use~~method~~ of any one of claims 1-13, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is to be administered to the subject once a day.

15. The use~~method~~ of claims 1-12, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is to be administered to the subject all at once or is to be administered in two, three, or four portions.

16. The use~~method~~ of any one of claims 1-15, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is about 3 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, or about 30 mg.

17. The use~~method~~ of any one of claims 1-15, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is about 20 mg to about 750 mg.

18. The use~~method~~ of any one of claims 1-15, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is about 30 mg to about 500 mg.

19. The use~~method~~ of any one of claims 1-15, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) is about 30 mg to about 120 mg.

20. The use~~method~~ of any one of claims 1-19, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 3,500 ng*hr/mL, greater than about 3,600 ng*hr/mL, greater than about 3,700 ng*hr/mL, greater than

about 3,800 ng*hr/mL, greater than about 3,900 ng*hr/mL, greater than about 4,000 ng*hr/mL, greater than about 4,100 ng*hr/mL, greater than about 4,200 ng*hr/mL, greater than about 4,300 ng*hr/mL, greater than about 4,400 ng*hr/mL, greater than about 4,500 ng*hr/mL, greater than about 4,600 ng*hr/mL, greater than about 4,700 ng*hr/mL, greater than about 4,800 ng*hr/mL, greater than about 4,900 ng*hr/mL, or greater than about 5,000 ng*hr/mL.

21. The use~~method~~ of any one of claims 1-19, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) results in a mean day 15 AUC_{TAU} of greater than about 4,000 ng*hr/mL and less than about 4,500 ng*hr/mL.

22. The use~~method~~ of any one of claims 1-21, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 200 ng/mL, greater than about 205 ng/mL, greater than about 210 ng/mL, greater than about 215 ng/mL, greater than about 220 ng/mL, greater than about 225 ng/mL, greater than about 230 ng/mL, greater than about 235 ng/mL, greater than about 240 ng/mL, greater than about 245 ng/mL, or greater than about 250 ng/mL.

23. The use~~method~~ of any one of claims 1-21, wherein the ~~therapeutically~~ effective amount of the compound of Formula (I) results in a mean day 15 C_{max} of greater than about 215 ng/mL and less than about 235 ng/mL.

24. The use~~method~~ of any one of claims 1-23, wherein the compound of Formula (I) is formulated as a tablet.

25. The use~~method~~ of claim 24, wherein the tablet further comprises ~~a compound of Formula (I) and, optionally,~~ one or more of an~~the following:~~ emulsifier; a surfactant; a binder; a disintegrant; a glidant; or~~and~~ lubricant.

26. The use~~method~~ of claim 25, wherein the emulsifier is hypromellose.

27. The use~~method~~ of claim 25, wherein the surfactant is vitamin E polyethylene glycol succinate.

28. The use~~method~~ of claim 25, wherein the binder is microcrystalline cellulose or lactose monohydrate.

29. The use~~method~~ of claim 25, wherein the disintegrant is croscarmellose sodium.

30. The use~~method~~ of claim 25, wherein the glidant is silicon dioxide.

31. The use~~method~~ of claim 25, wherein the lubricant is sodium stearyl fumarate.

32. The use~~method~~ of any one of claims 1-31, wherein~~further comprising the administration of~~ a therapeutically effective amount of a CDK4/6 inhibitor is to be further administered to the subject in need thereof.

33. The use~~method~~ of claim 32, wherein the CDK4/6 inhibitor is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, or palbociclib.

34. The use~~method~~ of claim 32, wherein the CDK4/6 inhibitor is palbociclib.

35. The use~~method~~ of claim 34, wherein the ~~therapeutically~~ effective amount of palbociclib is to be administered to the subject once a day.

36. The use~~method~~ of claims 34 or 35, wherein the ~~therapeutically~~ effective amount of palbociclib is 60 mg, 75 mg, 100 mg, or 125 mg.

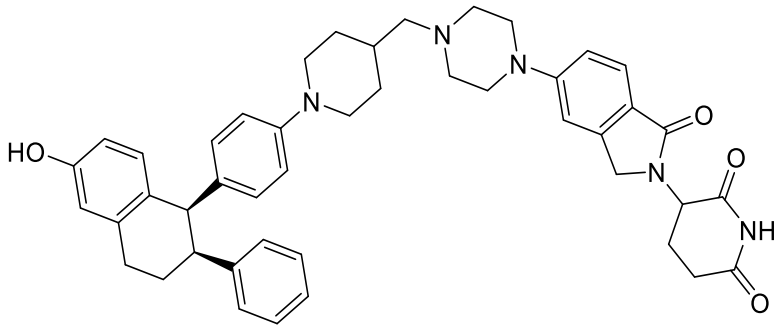
37. The use~~method~~ of any one of claims 33-36, wherein the palbociclib is to be administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with palbociclib followed by off treatment is repeated one, two, three, four, five, or more times.

38. The use~~method~~ of any one of claims 1-37, wherein the compound of Formula (I) is to be administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with the compound of Formula (I) followed by off treatment is repeated one, two, three, four, five, or more times.

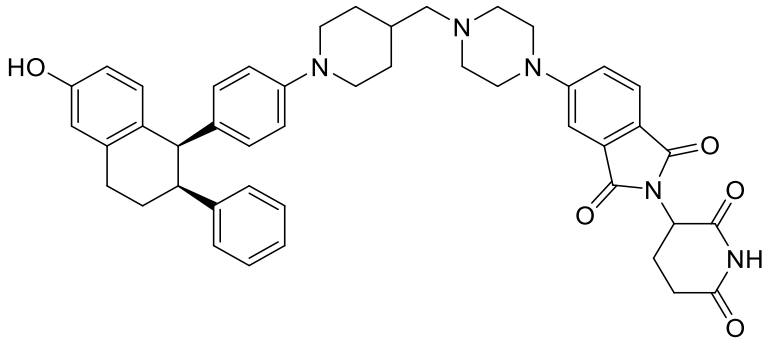
39. The use~~method~~ of any one of claims 1-38, wherein the subject is in a fed state.

40. The use~~method~~ of any one of claims 1-38, wherein the subject is in a fasted state.

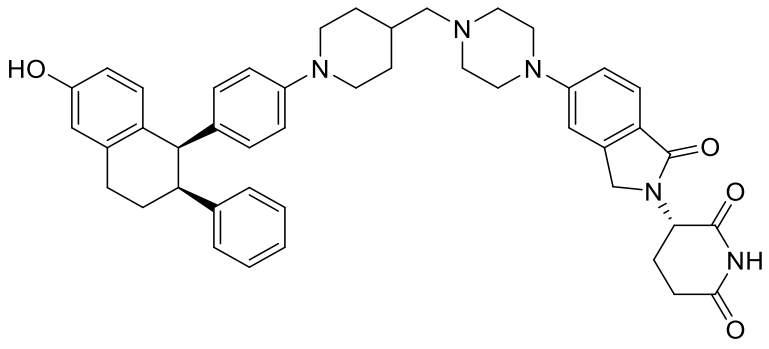
41. Use of a compound of Formula (I) in the manufacture of a medicament for~~A method of~~ treating metastatic breast cancer in a subject in need thereof, wherein an~~comprising once a day, oral administration of a therapeutically~~ effective amount of the compound of Formula (I) is to be administered orally once a day to the subject, and wherein the compound of Formula (I) is:



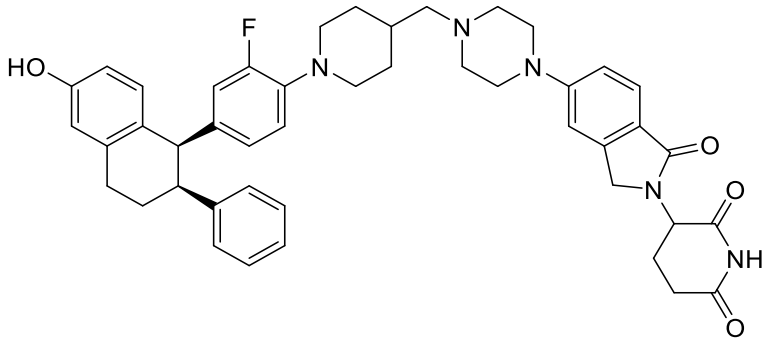
(I-a);



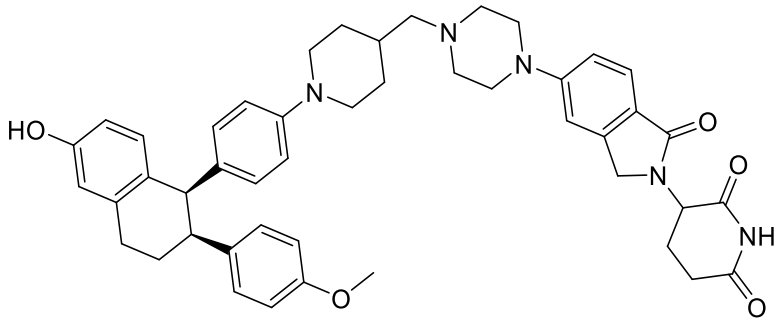
(I-b);



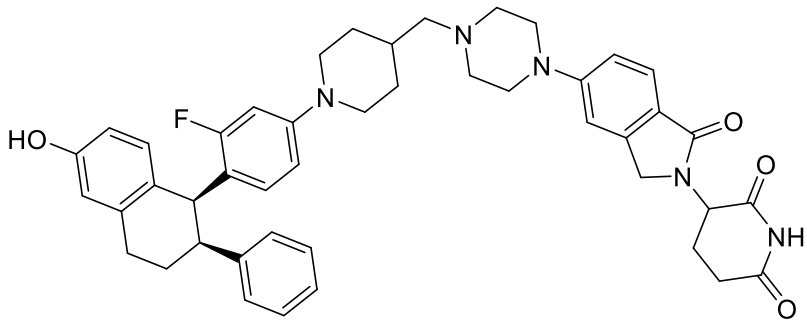
(I-c);



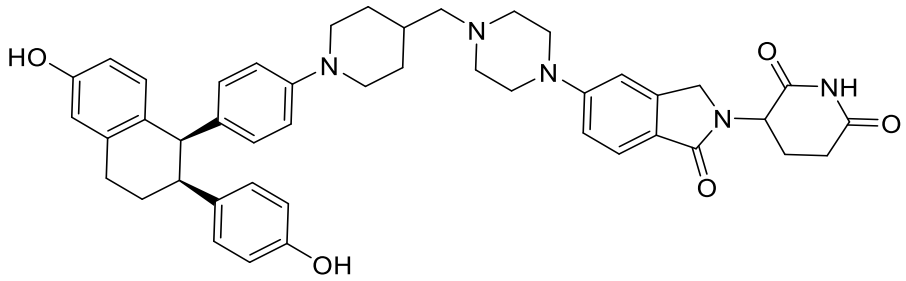
(I-d);



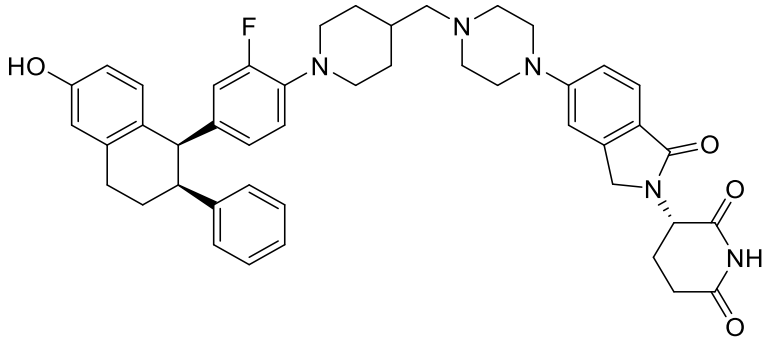
(I-e);



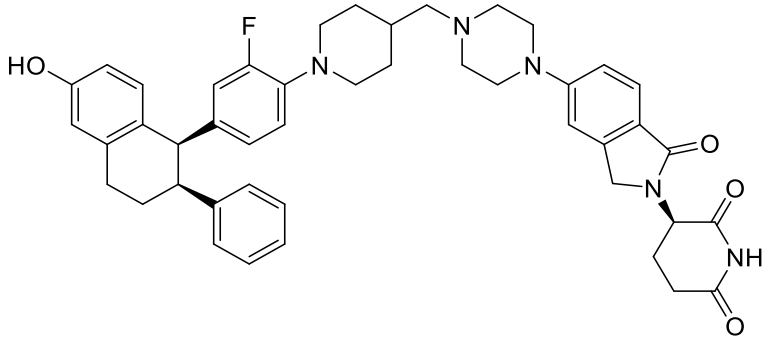
(I-f);



(I-g);



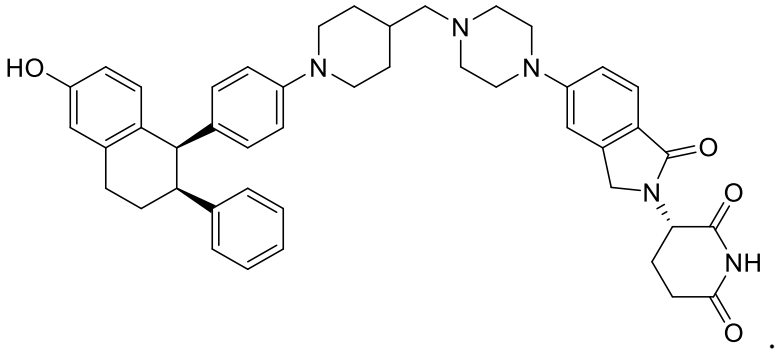
(I-h); or



(I-i);

or a pharmaceutically acceptable salt thereof~~, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug of any of the foregoing~~.

42. The use~~method~~ of claim 41, wherein the compound of Formula (I) is a compound of Formula (I-c):



.

43. The usemethod of claim 41 or 42, wherein the therapeutically effective amount of the compound of Formula (I) is to be administered to the subject all at once or is to be administered in two, three, or four portions.

44. The usemethod of any one of claims 41-43, wherein the therapeutically effective amount of the compound of Formula (I) is about 30 mg to about 1000 mg.

45. The usemethod of any one of claims 41-44, wherein the compound of Formula (I) is formulated as a tablet.

46. The usemethod of any one of claims 41-45, wherein a further comprising the administration of a therapeutically effective amount of a CDK4/6 inhibitor is to be further administered to the subject in need thereof.

47. The usemethod of claim 46, wherein the CDK4/6 inhibitor is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, or palbociclib.

48. The usemethod of claim 46, wherein the CDK4/6 inhibitor is palbociclib.

49. The usemethod of claim 48, wherein the therapeutically effective amount of palbociclib is to be administered to the subject once a day.

50. The usemethod of claims 48 or 49, wherein the therapeutically effective amount of palbociclib is 60 mg, 75 mg, 100 mg, or 125 mg.

51. The usemethod of any one of claims 48-50, wherein the palbociclib is to be administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with palbociclib followed by off treatment is repeated one, two, three, four, five, or more times.

52. The use~~method~~ of any one of claims 41-51, wherein the compound of Formula (I) is to be administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with the compound of Formula (I) followed by off treatment is repeated one, two, three, four, five, or more times.

53. The use~~method~~ of any one of claims 41-52, wherein the subject is in a fed state.

54. The use~~method~~ of any one of claims 41-52, wherein the subject is in a fasted state.

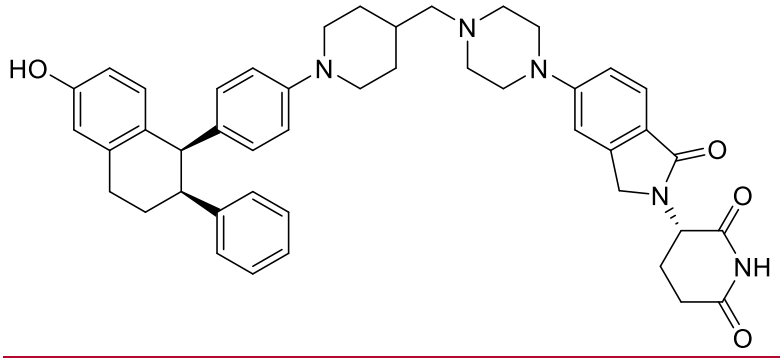
55. The use~~method~~ of any one of claims 46-54, wherein the ~~administration of the~~ CDK4/6 inhibitor is to be administered~~occurs~~ before the ~~administration of the~~ compound of Formula (I) is to be administered.

56. The use~~method~~ of claim 55, wherein the ~~administration of the~~ CDK4/6 inhibitor is to be administered~~occurs~~ at least 30 minutes before the ~~administration of the~~ compound of Formula (I) is to be administered.

57. The use~~method~~ of any one of claims 46-54, wherein the ~~administration of the~~ CDK4/6 inhibitor is to be administered~~occurs~~ after the ~~administration of the~~ compound of Formula (I) is to be administered.

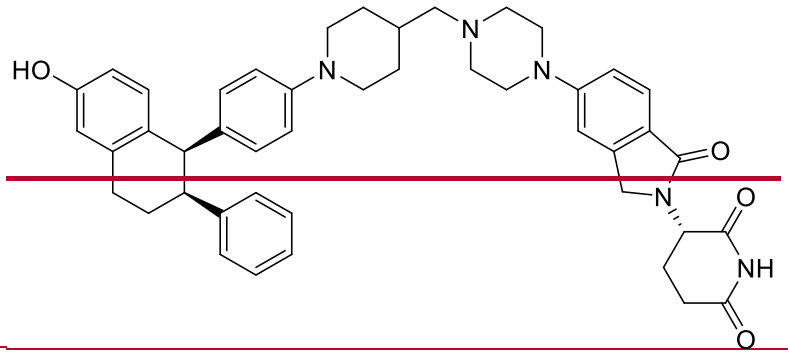
58. The use~~method~~ of claim 57, wherein the ~~administration of the~~ CDK4/6 inhibitor is to be administered~~occurs~~ at least 30 minutes after the ~~administration of the~~ compound of Formula (I) is to be administered.

59. Use of a compound of Formula (I-c),



, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating metastatic breast cancer in a subject in need thereof, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered orally once a day, and wherein palbociclib is to be further administered orally once a day~~A method of treating metastatic breast cancer in a subject in need thereof, comprising:~~

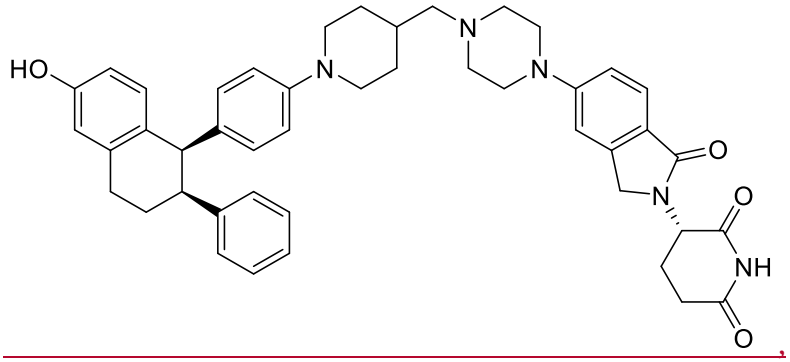
~~(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula~~



~~(I-c),~~ , ~~or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, and~~

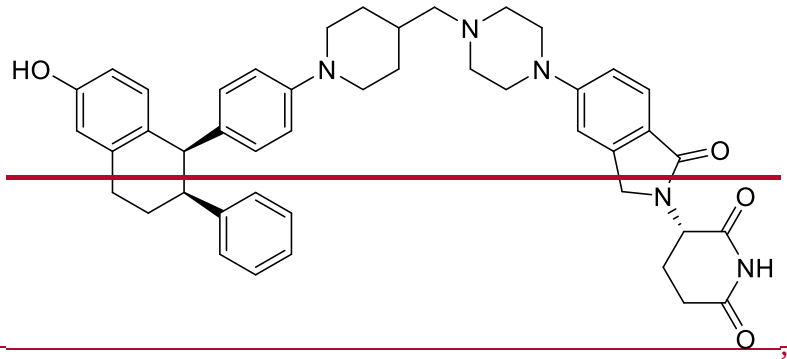
~~(ii) once a day, oral administration of palbociclib~~.

60. Use of a compound of Formula (I-c),



in the manufacture of a medicament for treating metastatic breast cancer in a subject in need thereof, wherein a therapeutically effective amount of the compound is to be administered orally once a day, and palbociclib is to be further administered orally once a day~~A method of treating metastatic breast cancer in a subject in need thereof, comprising:~~

~~(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula~~



~~(I-c),~~ , ~~and~~

~~(ii) once a day, oral administration of palbociclib~~.

61. The use~~method~~ of claim 59 or claim 60, wherein the therapeutically effective amount of the compound of Formula (I-c) is about 30 mg to about 1000 mg.

62. The use~~method~~ of any one of claims 59-61, wherein the therapeutically effective amount of palbociclib is 60 mg, 75 mg, 100 mg, or 125 mg.

63. The use~~method~~ of any one of claims 59-62, wherein the palbociclib is to be administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with palbociclib followed by off treatment is repeated one, two, three, four, five, or more times.

64. The use~~method~~ of any one of claims 59-62, wherein the compound of Formula (I-c) is to be administered once daily for up to 21 consecutive days, followed by up to 7 consecutive days off treatment, wherein the cycle of treatment with the compound of Formula (I-c) followed by off treatment is repeated one, two, three, four, five, or more times.

65. The use~~method~~ of any one of claims 59-64, wherein the subject is in a fed state.

66. The use~~method~~ of any one of claims 59-64, wherein the subject is in a fasted state.

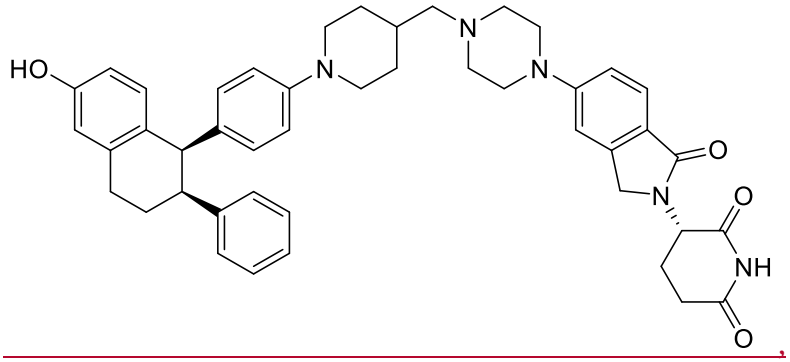
67. The use~~method~~ of any one of claims 59-66, wherein ~~the administration of~~ palbociclib is to be administered~~occurs~~ before the ~~administration of the~~ compound of Formula (I-c) is to be administered.

68. The use~~method~~ of claim 67, wherein ~~the administration of~~ palbociclib is to be administered~~occurs~~ at least 30 minutes before the ~~administration of the~~ compound of Formula (I-c) is to be administered.

69. The use~~method~~ of any one of claims 59-66, wherein ~~the administration of~~ palbociclib is to be administered~~occurs~~ after the ~~administration of the~~ compound of Formula (I-c) is to be administered.

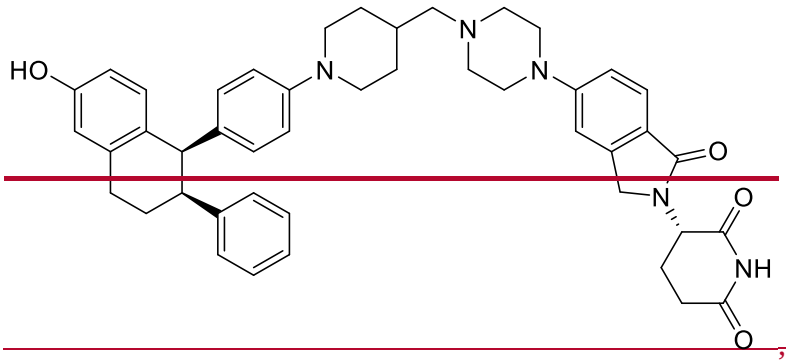
70. The use~~method~~ of claim 69, wherein ~~the administration of~~ palbociclib is to be administered~~occurs~~ at least 30 minutes after the ~~administration of the~~ compound of Formula (I-c) is to be administered.

71. Use of a compound of Formula (I-c),



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for selective estrogen receptor degradation in a patient, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered orally once a day, and palbociclib is to be further administered orally once a day~~A method for selective estrogen receptor degradation in a patient comprising:~~

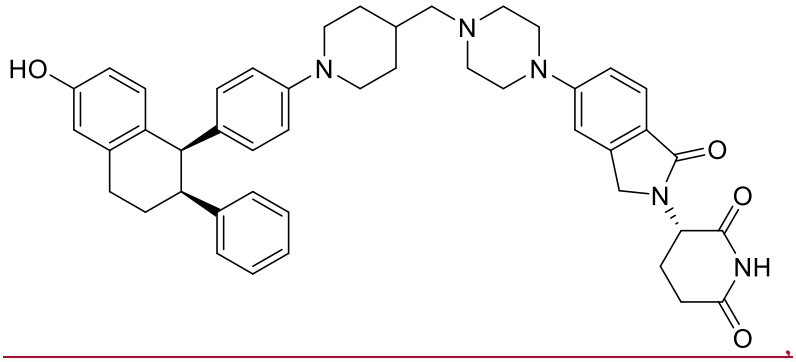
~~(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c),~~



~~or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, and~~

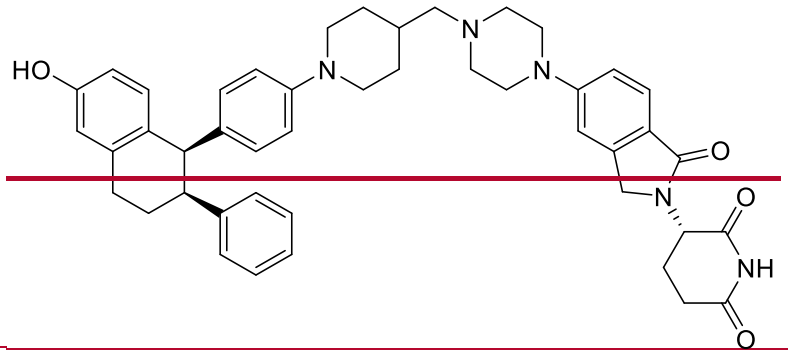
~~(ii) once a day, oral administration of palbociclib~~.

72. Use of a compound of Formula (I-c),



, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting a cyclin-dependent kinase in a subject in need thereof, wherein a therapeutically effective amount of the compound, or a pharmaceutically acceptable salt thereof, is to be administered orally once a day, and palbociclib is to be further administered orally once a day~~A method for inhibiting a cyclin-dependent kinase in a subject in need thereof comprising:~~

~~(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula~~

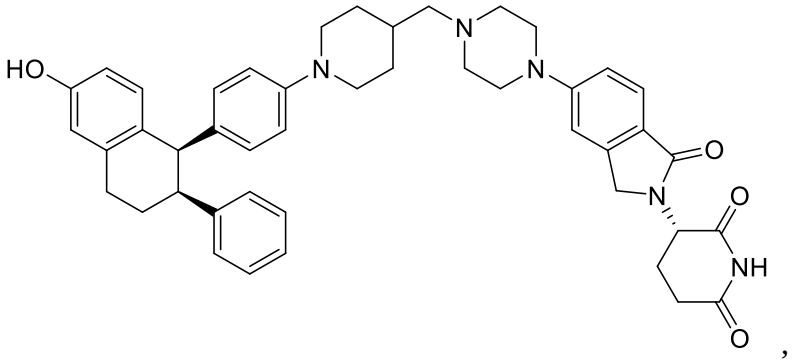


~~(I-c),~~ ~~, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph, isotopic derivative, or prodrug thereof, and~~

~~(ii) once a day, oral administration of palbociclib~~.

73. A kit comprising:

(i) a compound of Formula (I-c),

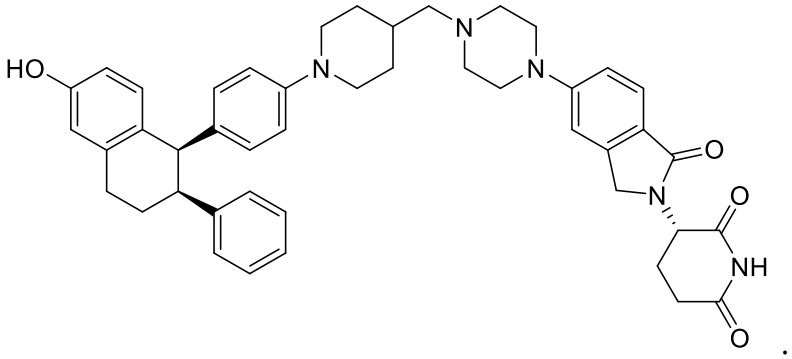


,

(ii) palbociclib, and

(iii) instructions for use.

74. A liquid composition comprising a surfactant, a solvent, and a compound of Formula (I-c):

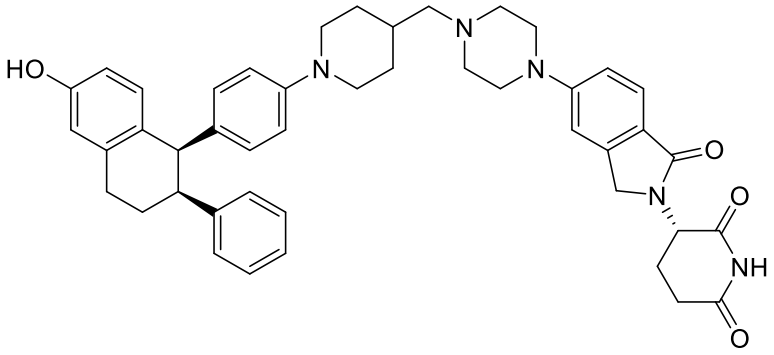


.

75. The liquid composition of claim 74, wherein the surfactant is Tween 80.

76. The liquid composition of claim 74 or 75, wherein the solvent is PEG-400.

77. A method of making a liquid composition comprising a surfactant, a solvent, and a compound of Formula (I-c):



comprising the step of adding the solvent to a pre-aliquoted volume of the surfactant.

78. The method of claim 77, wherein the surfactant is Tween 80.

79. The method of claim 77 or 78, wherein the solvent is PEG-400.