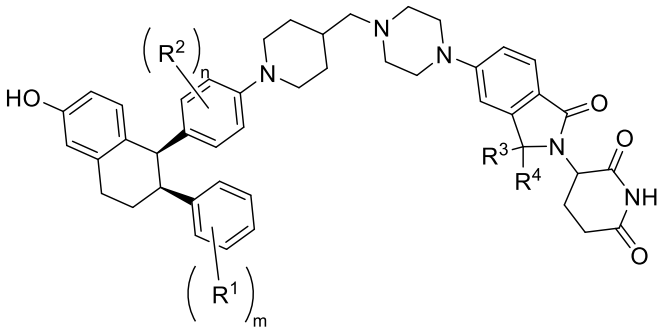
Summary of the Disclosure

[0007a] An aspect of the present disclosure provides a use of a compound of Formula (I),



(I), or a pharmaceutically acceptable salt 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;

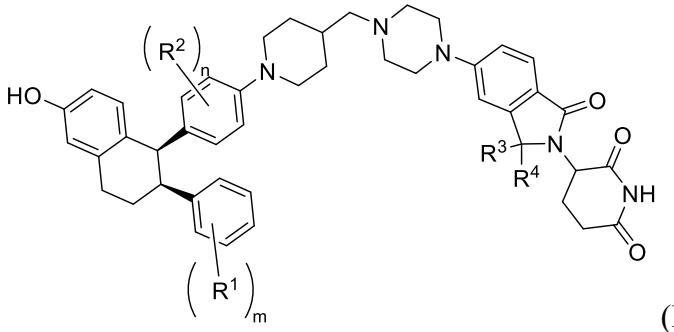
each R^5 and each R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

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

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

in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic estrogen receptor (ER) tumor mutation, and wherein about 10 mg to about 1000 mg of the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered.

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



(I), or a pharmaceutically acceptable salt, 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,

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

[0009] In one example, this application pertains to a method of treating breast cancer in a subject in need thereof, wherein the subject comprises at least one somatic ER tumor mutation; the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg. In some examples, the breast cancer comprises at least one somatic ER tumor mutation.

[0010] In one example, this application pertains to a method of treating breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation; the method comprising administering to the subject a therapeutically effective amount of a compound

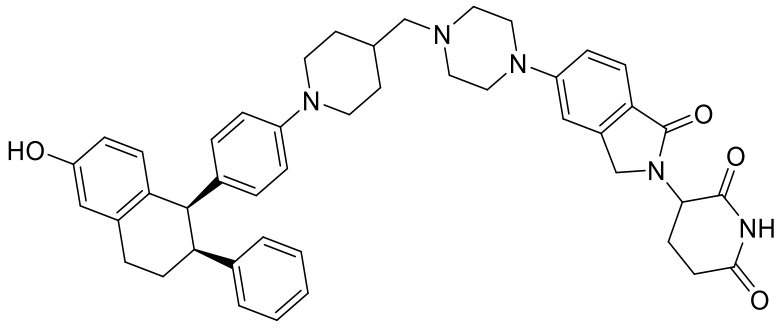
of Formula (I), wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

[0011] In one example, this application pertains to a compound of Formula (I) for use in a method of treating breast cancer in a subject in need thereof, wherein the subject comprises at least one somatic ER tumor mutation. In some examples, the subject comprises at least one somatic ER tumor mutation selected from the group consisting of Y537X, D538X, E380X, L379X, V422X, S463X, and L536X, wherein "X" refers to any amino acid residue, other than the wild-type residue at that position. In some examples, the subject comprises at least one somatic ER tumor mutation selected from the group consisting of Y537S, Y537N, D538G, E380Q, L379I, V422del, S463P, L536P and L536_D538>P.

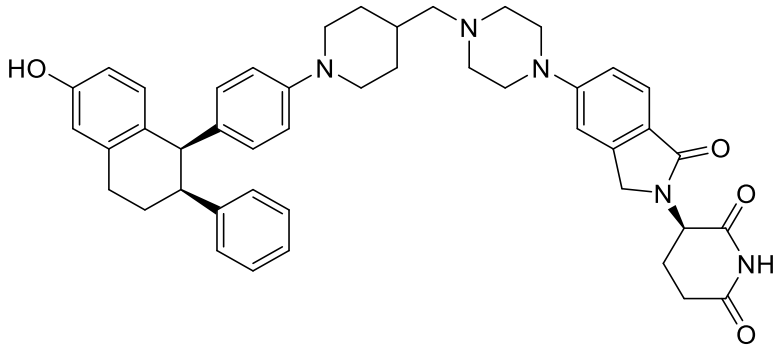
[0012] In one example, this application pertains to a compound of Formula (I) for use in a method of treating breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation. In some examples, the breast cancer comprises at least one somatic ER tumor mutation selected from the group consisting of Y537X, D538X, E380X, L379X, V422X, S463X, and L536X, wherein "X" refers to any amino acid residue, other than the wild-type residue at that position. In some examples, the breast cancer comprises at least one somatic ER tumor mutation selected from the group consisting of Y537S, Y537N, D538G, E380Q, L379I, V422del, S463P, L536P and L536_D538>P.

[0013] In some examples, the breast cancer is ER+, HER2-. In some examples, the breast cancer is metastatic or locally advanced.

[0014] In some examples, the compound of Formula (I) is:



(I-a);



(I-j);

or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof.

[0015] In some examples, wherein the compound of Formula (I) is a compound of Formula (I-a). In some examples, the compound of Formula (I) is a compound of Formula (I-c). In some examples, the compound of Formula (I) is a compound of Formula (I-j).

[0016] In some examples, the compound of Formula (I) is administered orally to the subject.

[0017] In some examples, 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 some examples, 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 unit doses. In some examples, 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, about 30 mg, or about 40 mg. In some examples, the therapeutically effective amount of the compound of Formula (I) is about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, or about 40 mg.

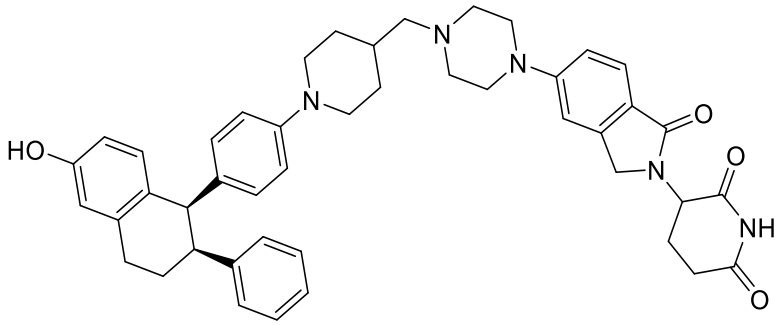
[0018] In one example, this application pertains to a method of treating breast cancer in a subject; the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I); further comprising the administration of a therapeutically effective amount of at least one additional anti-cancer agent to the subject in need thereof.

[0019] In some examples, the additional anti-cancer agent is selected from the group consisting of FLT-3 inhibitor, VEGFR inhibitor, EGFR TK inhibitor, aurora kinase inhibitor, PIK-1 modulator, Bcl-2 inhibitor, HDAC inhibitor, c-Met inhibitor, PARP inhibitor, CDK 4/6 inhibitor, anti-HGF antibody, PI3 kinase inhibitor, AKT inhibitor, mTORC1/2 inhibitor, JAK/STAT inhibitor, checkpoint 1 inhibitor, checkpoint 2 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, B7-H3 inhibitor, CTLA4 inhibitor, LAG-3 inhibitor, OX40 agonist, focal adhesion kinase inhibitor, Map

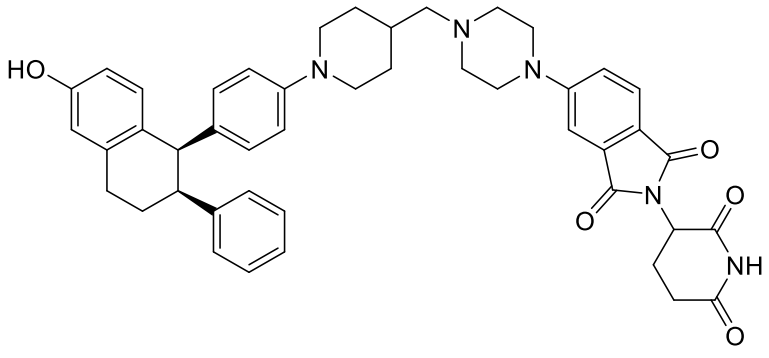
kinase kinase inhibitor, and VEGF trap antibody. In some examples, the additional anti-cancer agent is a CDK 4/6 inhibitor.

[0020] In some examples, the additional anti-cancer agent is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, palbociclib, everolimus, venetoclax, inavolisib, pazopanib, carboplatin, cisplatin, oxaliplatin, paclitaxel, epithilone B, fulvestrant, acolbifene, lasofoxifene, idoxifene, topotecan, pemetrexed, erlotinib, ticilimumab, ipilimumab, vorinostat, etoposide, gemcitabine, doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, capecitabine, camptothecin, PD0325901, irinotecan, tamoxifen, toremifene, anastrazole, letrozole, bevacizumab, goserelin acetate, raloxifene, alpelisib, trastuzumab, trastuzumab emtansine, pertuzumab, fam-trastuzumab deruxtecan-nxki (Enhertu), or eribulin (halaven). In some examples, the additional anti-cancer agent is palbociclib,

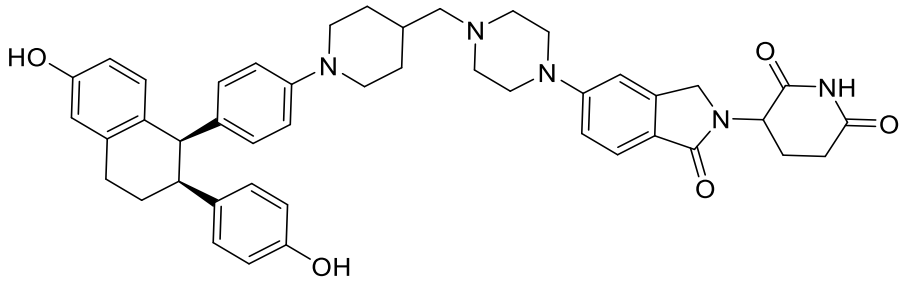
[0021] In one example, this application pertains to method of treating breast cancer in a subject in need thereof, comprising once a day, oral administration of a therapeutically effective amount of the compound of Formula (I), wherein the compound of Formula (I) is:



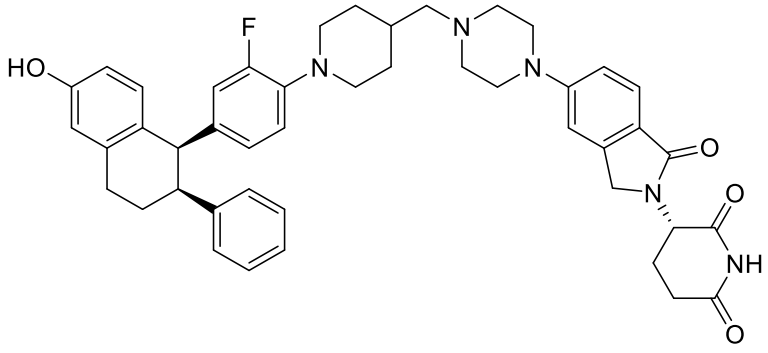
(I-a);



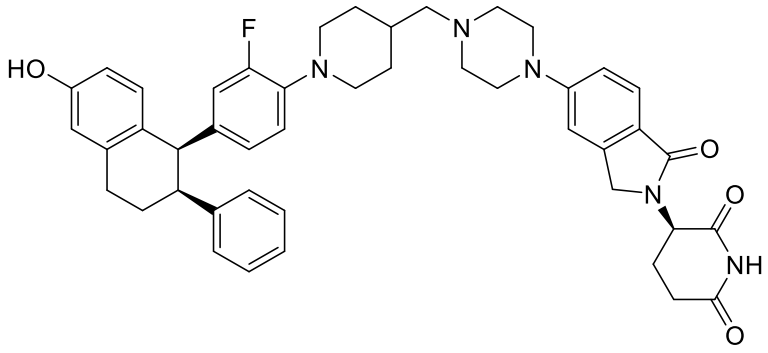
(I-b);



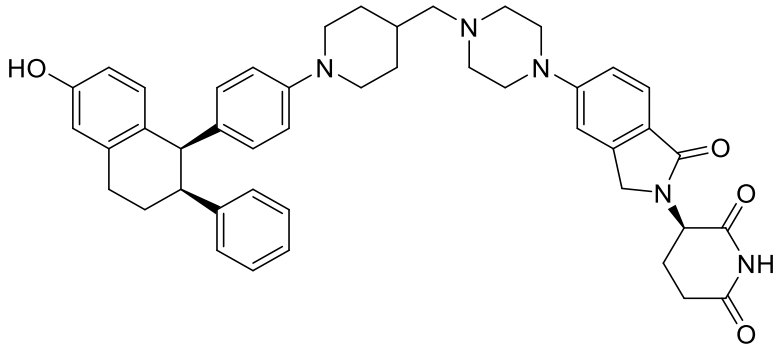
(I-g);



(I-h);



(I-i); or



(I-j);

or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, wherein the subject comprises at least one somatic ER tumor mutation. In some examples, the breast cancer comprises at least one somatic ER mutation.

[0022] In one example, this application pertains to method of treating 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), wherein the compound of Formula (I) is (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i), or (I-j), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

[0023] In one example, this application pertains to a method of treating breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation, the method comprising:

(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-a) or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and

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

[0024] In one example, this application pertains to a method of treating breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation, the method comprising:

(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-c) or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and

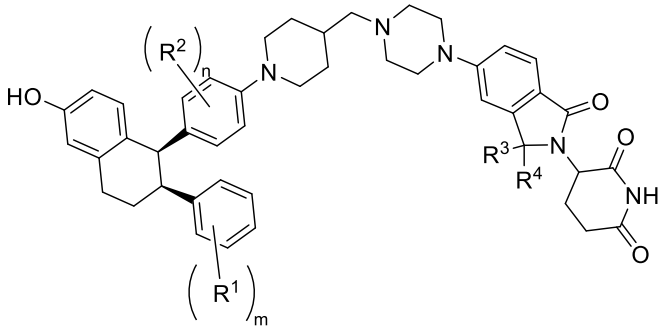
(ii) once a day, oral administration of palbociclib.

[0025] In one example, this application pertains to a method of treating breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation, the method comprising:

(i) once a day, oral administration of a therapeutically effective amount of a compound of Formula (I-j), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and

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

[0025a] Another aspect of the present disclosure provides a use of a compound of Formula



(I), (I), or a pharmaceutically acceptable salt 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

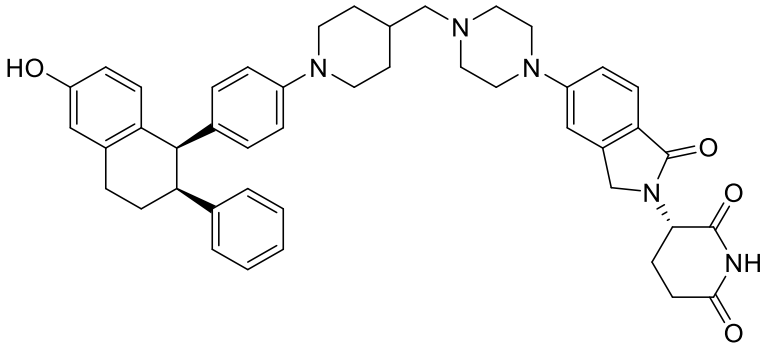
n is 0, 1, 2, 3, or 4,

in the manufacture of a medicament for the treatment of breast cancer in a subpopulation of breast cancer subjects, wherein:

a breast cancer subject is selected for treatment based on the subject's somatic estrogen receptor (ER) tumor biomarker status; and

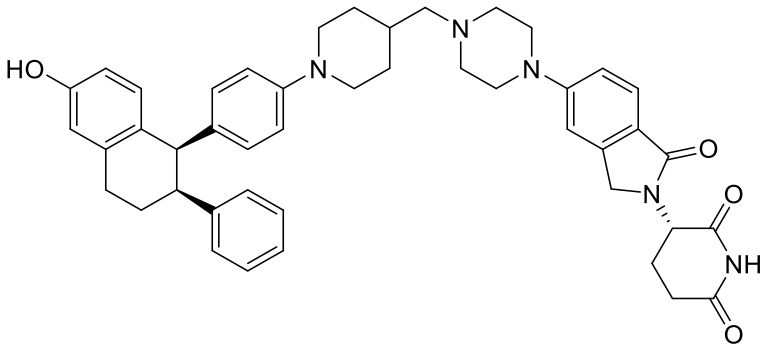
about 10 mg to about 1000 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered.

[0025b] A further aspect of the present disclosure provides a use of a compound of Formula (I-c),



(I-c), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic estrogen receptor (ER) tumor mutation, and wherein about 10 mg to about 1000 mg of the compound of Formula (I-c) or a pharmaceutically acceptable salt thereof is to be administered.

[0025c] Another aspect of the present disclosure provides a use of a compound of Formula (I-c),



(I-c), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer in a subpopulation of breast cancer subjects, wherein:

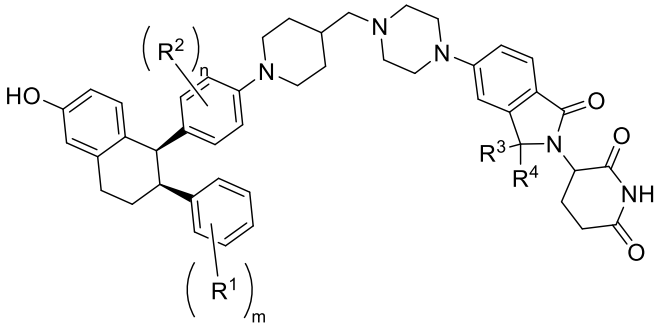
a breast cancer subject is selected for treatment based on the subject's somatic estrogen receptor (ER) tumor biomarker status; and

about 10 mg to about 1000 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered.

[0026] In one example, this application pertains to a method of treating breast cancer in a subpopulation of breast cancer subjects, comprising:

selecting a breast cancer subject for treatment based on the subject's somatic ER tumor biomarker status; and

administering a therapeutically effective amount of a compound of Formula (I),



(I), or a pharmaceutically acceptable salt, 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

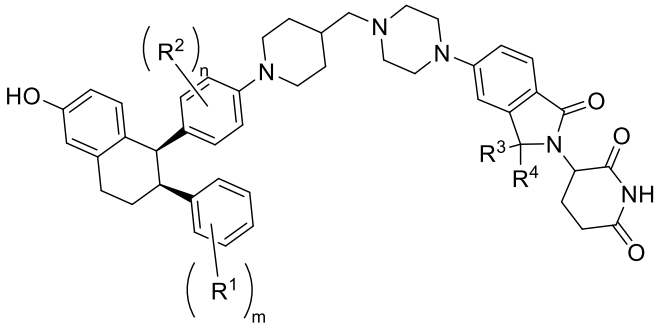
n is 0, 1, 2, 3, or 4, and

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

[0027] In one example, this application pertains to a method of treating breast cancer in a subpopulation of breast cancer subjects, comprising:

selecting a breast cancer subject for treatment based on the subject's somatic ER tumor biomarker status; and

administering a therapeutically effective amount of a compound of Formula (I),



(I), or a pharmaceutically acceptable salt, 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, and

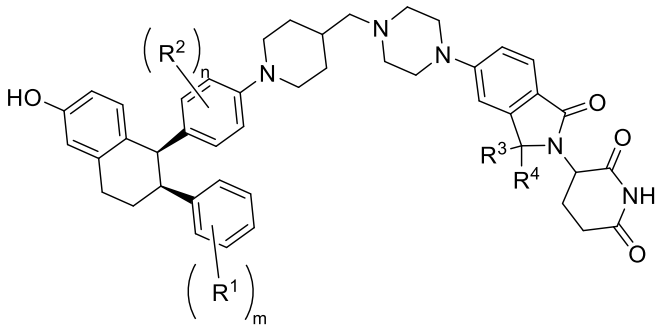
wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

[0028] In some examples, the method further comprises the administration of at least one additional anti-cancer agent. In some examples, the additional anti-cancer agent is selected from the group consisting of FLT-3 inhibitor, VEGFR inhibitor, EGFR TK inhibitor, aurora kinase inhibitor, PIK-1 modulator, Bcl-2 inhibitor, HDAC inhibitor, c-Met inhibitor, PARP inhibitor, CDK 4/6 inhibitor, anti-HGF antibody, PI3 kinase inhibitor, AKT inhibitor, mTORC1/2 inhibitor, JAK/STAT inhibitor, checkpoint 1 inhibitor, checkpoint 2 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, B7-H3 inhibitor, CTLA4 inhibitor, LAG-3 inhibitor, OX40 agonist, focal adhesion kinase inhibitor, Map kinase kinase inhibitor, and VEGF trap antibody. In some examples, the additional anti-cancer agent is a CDK 4/6 inhibitor. the additional anti-cancer agent is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, palbociclib, everolimus, venetoclax, inavolisib, pazopanib, carboplatin, cisplatin, oxaliplatin, paclitaxel, epithilone B, fulvestrant, acolbifene, lasofoxifene, idoxifene, topotecan, pemetrexed, erlotinib, ticilimumab, ipilimumab, vorinostat, etoposide, gemcitabine, doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, capecitabine, camptothecin, PD0325901, irinotecan, tamoxifen, toremifene, anastrazole, letrozole, bevacizumab, goserelin acetate, raloxifene, alpelisib, trastuzumab, trastuzumab emtansine, pertuzumab, fam-trastuzumab deruxtecan-nxki (Enhertu), or eribulin (halaven). In some examples, the additional anti-cancer agent is palbociclib,

[0029] In some examples, the administration of the additional anti-cancer agent occurs before the administration of the compound of Formula (I). In some examples, the administration of the additional anti-cancer agent occurs at least 30 minutes before the administration of the compound of Formula (I). In some examples, the administration of the

additional anti-cancer agent occurs after the administration of the compound of Formula (I). In some examples, the administration of the additional anti-cancer agent occurs at least 30 minutes after the administration of the compound of Formula (I).

[0030] In one example, this application pertains to a compound of Formula (I),



(I), or a pharmaceutically acceptable salt, 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;

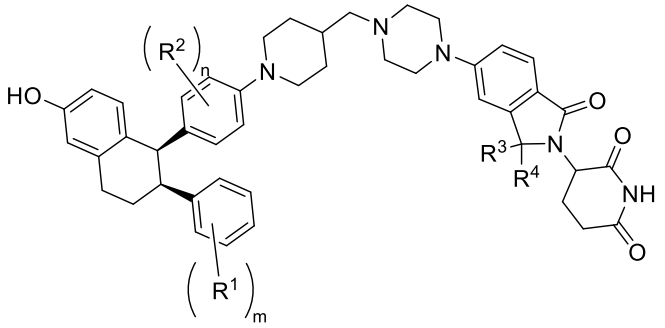
m is 0, 1, 2, 3, 4, or 5; and

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

for use in the treatment of breast cancer in a subject in need thereof, wherein the subject comprises at least one somatic ER tumor mutation; and

wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg. In some examples, the breast cancer comprises at least one somatic ER mutation.

[0031] In one example, this application pertains to a compound of Formula (I),



(I), or a pharmaceutically acceptable salt, 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;

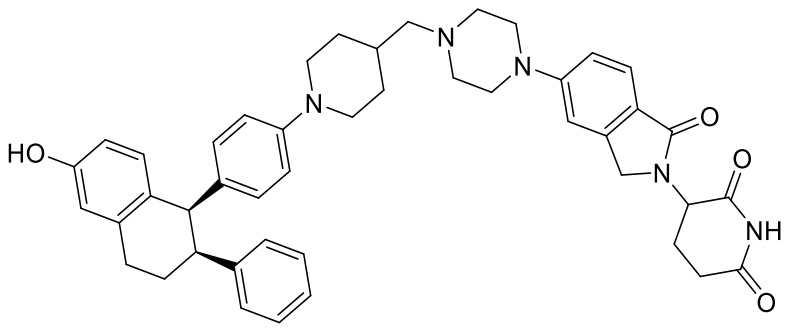
m is 0, 1, 2, 3, 4, or 5; and

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

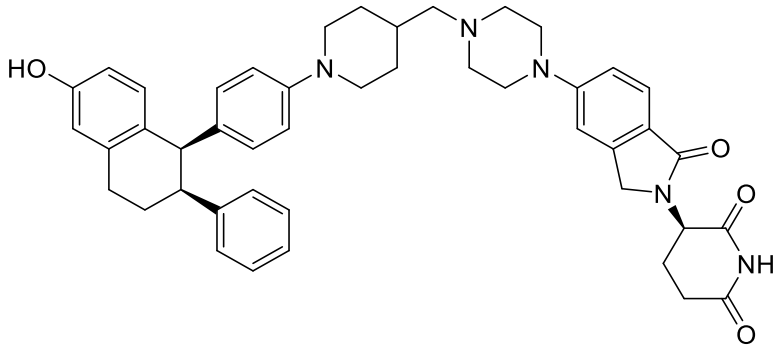
for use in the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation; and

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

[0032] In one example, this application pertains to a compound of Formula (I):

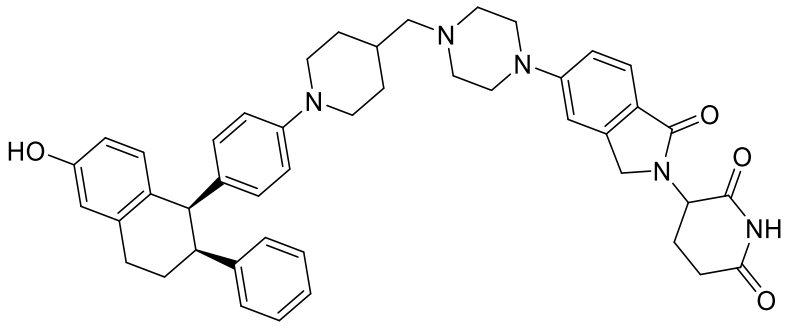


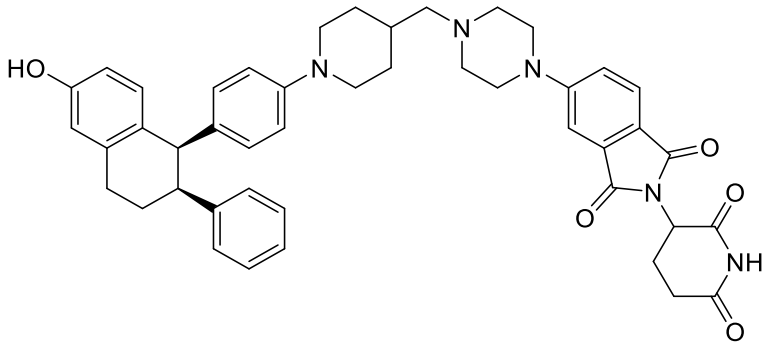
(I-a);


(I-j);

or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, for use in the treatment of breast cancer in a subject in need thereof, wherein the subject comprises at least one somatic ER tumor mutation. In some examples, the breast cancer comprises at least one somatic ER tumor mutation.

[0033] In one example, this application pertains to a compound of Formula (I):


(I-a);


(I-b);

[0034] In one example, this application pertains to a combination for use in the treatment of breast cancer in a subject in need thereof, comprising a compound of Formula (I) as disclosed herein further comprising at least one additional anti-cancer agent.

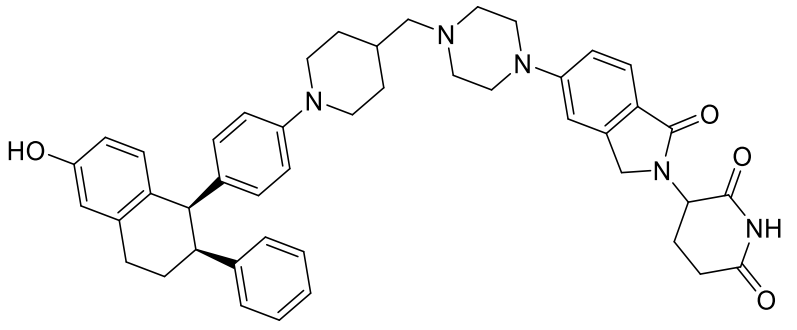
[0035] In one example, this application pertains to a combination comprising (i) a compound of Formula (I-a), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) palbociclib, for use in the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

[0036] In one example, this application pertains to a combination comprising (i) a compound of Formula (I-c), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) palbociclib, for use in the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

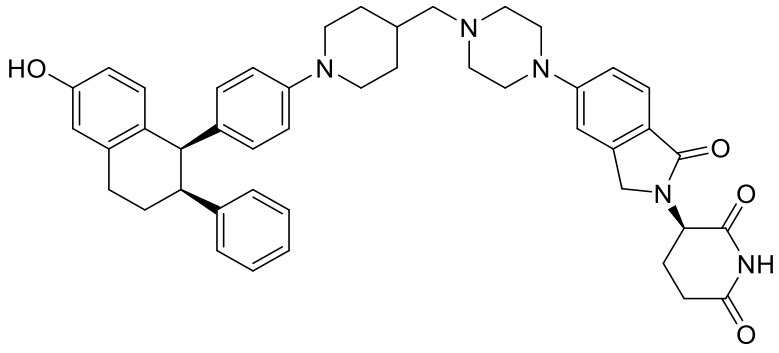
[0037] In one example, this application pertains to a combination comprising (i) a compound of Formula (I-j), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) palbociclib, for use in the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

[0038] In one example, this application pertains to a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, for use in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation; and wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

[0039] In one example, this application pertains to a compound of Formula (I):

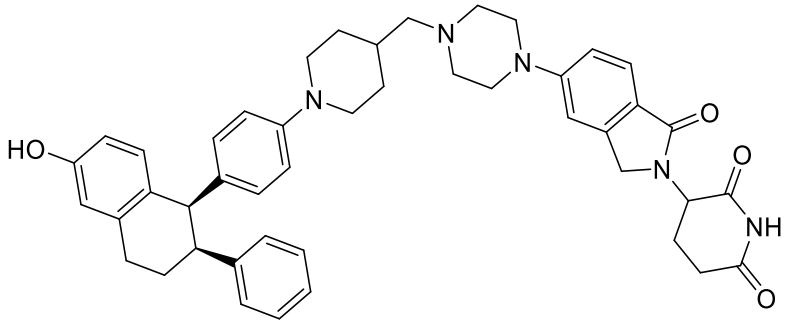


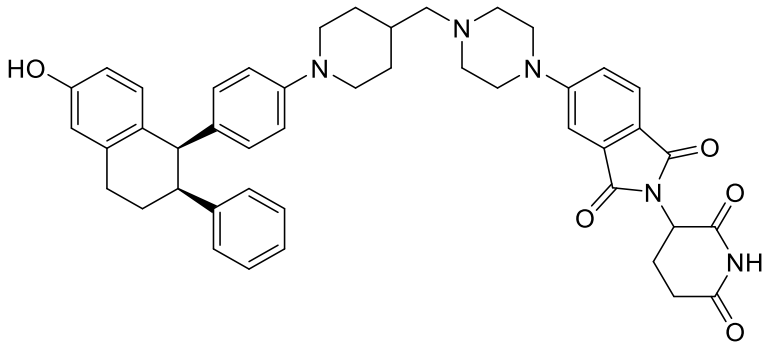
(I-a);


(I-j),

or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, for use in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the subject comprises at least one somatic ER tumor mutation; and wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg. In some example, the breast cancer comprises at least one somatic ER tumor mutation.

[0040] In one example, this application pertains to a compound of Formula (I):


(I-a);


(I-b);

[0041] In one example, this application pertains to a combination for use in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, comprising a compound of Formula (I) as disclosed herein further comprising at least one additional anti-cancer agent.

[0042] In one example, this application pertains to a combination comprising (i) a compound of Formula (I-a), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) palbociclib, for use in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

[0043] In one example, this application pertains to a combination comprising (i) a compound of Formula (I-c), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) palbociclib, for use in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

[0044] In one example, this application pertains to a combination comprising (i) a compound of Formula (I-j), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, and (ii) palbociclib, for use in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation.

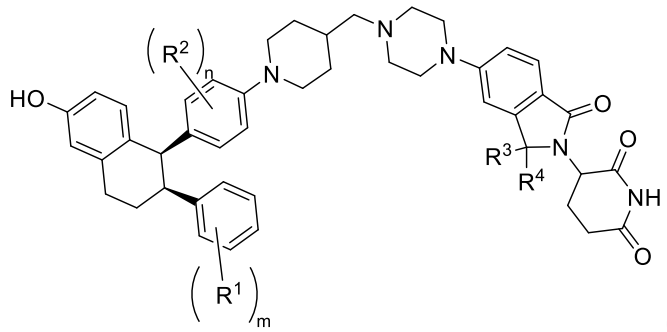
[0045] In one example, this application pertains to a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, polymorph, isotopic derivative, or prodrug thereof, for use in the manufacture of a medicament for the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic ER tumor mutation; and wherein the therapeutically effective amount of the compound of Formula (I) is about 10 mg to about 1000 mg.

Brief Description of the Figures

[0046] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

What is claimed is:

1. Use of a compound of Formula (I),



(I), or a pharmaceutically acceptable salt 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,

in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic estrogen receptor (ER) tumor mutation, and wherein about 10 mg to about 1000 mg of the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered.

2. The use of claim 1, wherein the at least one somatic ER tumor mutation is selected from the group consisting of Y537X, D538X, E380X, L379X, V422X, S463X, and L536X, wherein "X" refers to any amino acid residue, other than the wild-type residue at that position.

3. The use of claim 1 or 2, wherein the at least one somatic ER tumor mutation is selected from the group consisting of Y537S, Y537N, D538G, E380Q, L379I, V422del, S463P, L536P and L536_D538>P.

4. The use of any one of claims 1-3, wherein the breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

5. The use of any one of claims 1-4, wherein the breast cancer is metastatic or locally advanced.

6. The use of any one of claims 1-4, wherein the breast cancer is metastatic.

7. The use of any one of claims 1-6, wherein R^1 and R^2 are each independently selected from the group consisting of halo and OR^5.

8. The use of any one of claims 1-7, wherein R^3 and R^4 are both hydrogen.

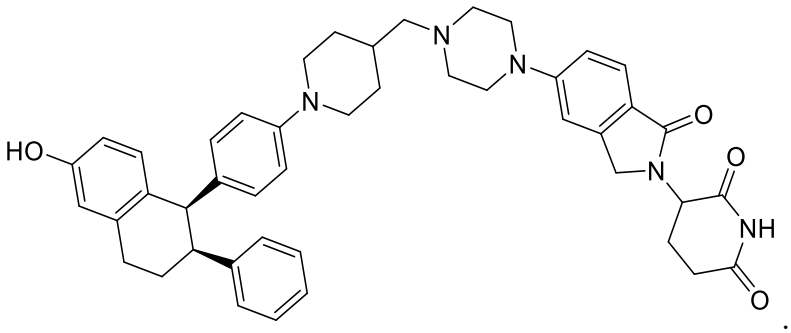
9. The use of any one of claims 1-7, wherein R^3 and R^4, taken together with the carbon to which they are attached, form a carbonyl.

10. The use of any one of claims 1-6, 8, or 9, wherein m and n are each 0.

11. The use of any one of claims 1-9, wherein m and n are each 1.

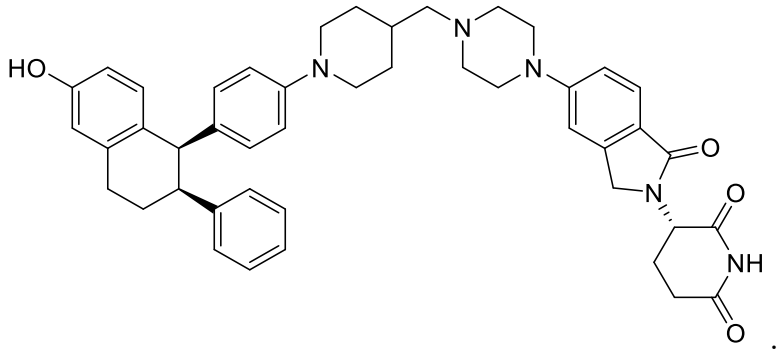
12. The use of any one of claims 1-6, 8, or 9, wherein one of m and n is 0 and the other is 1.

13. The use of any one of claims 1-5, wherein the compound of Formula (I) is a compound of Formula (I-a):

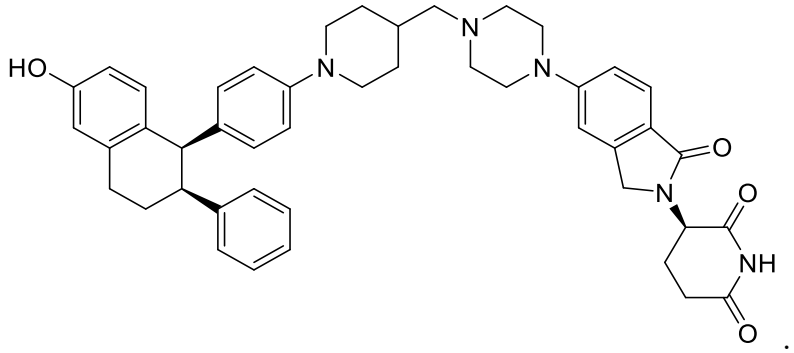


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14. The use of any one of claims 1-5, wherein the compound of Formula (I) is a compound of Formula (I-c):



15. The use of any one of claims 1-5, wherein the compound of Formula (I) is a compound of Formula (I-j):



16. The use of any one of claims 1-15, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered orally to the subject.

17. The use of any one of claims 1-16, wherein at least one additional anti-cancer agent is to be further administered.

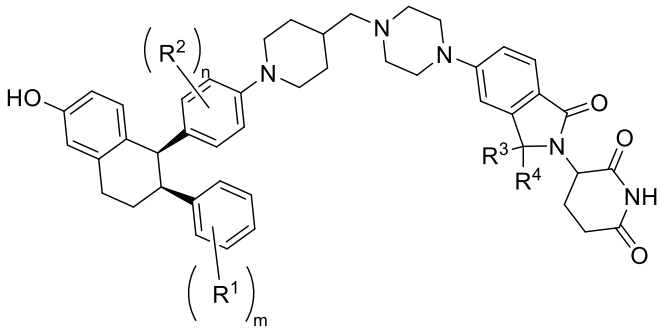
18. The use of claim 17, wherein the additional anti-cancer agent is selected from the group consisting of FLT-3 inhibitor, VEGFR inhibitor, EGFR TK inhibitor, aurora kinase inhibitor, PIK-1 modulator, Bcl-2 inhibitor, HDAC inhibitor, c-Met inhibitor, PARP inhibitor, CDK 4/6 inhibitor, anti-HGF antibody, PI3 kinase inhibitor, AKT inhibitor, mTORC1/2 inhibitor, JAK/STAT inhibitor, checkpoint 1 inhibitor, checkpoint 2 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, B7-H3

inhibitor, CTLA4 inhibitor, LAG-3 inhibitor, OX40 agonist, focal adhesion kinase inhibitor, Map kinase kinase inhibitor, and VEGF trap antibody.

19. The use of claim 17 or 18, wherein the additional anti-cancer agent is a CDK 4/6 inhibitor.

20. The use of claim 17, wherein the additional anti-cancer agent is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, palbociclib, everolimus, venetoclax, inavolisib, pazopanib, carboplatin, cisplatin, oxaliplatin, paclitaxel, epithilone B, fulvestrant, acolbifene, lasofoxifene, idoxifene, topotecan, pemetrexed, erlotinib, ticilimumab, ipilimumab, vorinostat, etoposide, gemcitabine, doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, capecitabine, camptothecin, PD0325901, irinotecan, tamoxifen, toremifene, anastrazole, letrozole, bevacizumab, goserelin acetate, raloxifene, alpelisib, trastuzumab, trastuzumab emtansine, pertuzumab, fam-trastuzumab deruxtecan-nxki (Enhertu), or eribulin (halaven).

21. The use of claim 20, wherein the additional anti-cancer agent is palbociclib.

22. Use of a compound of Formula (I),  (I), or a pharmaceutically acceptable salt 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,

in the manufacture of a medicament for the treatment of breast cancer in a subpopulation of breast cancer subjects, wherein:

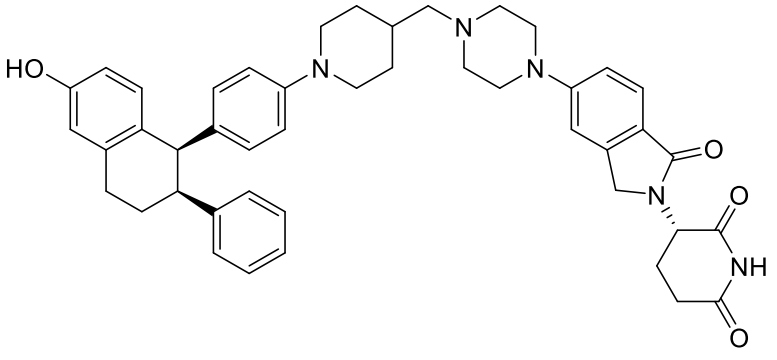
a breast cancer subject is selected for treatment based on the subject's somatic estrogen receptor (ER) tumor biomarker status; and

about 10 mg to about 1000 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered.

23. The use of claim 22, wherein the subject's somatic ER tumor biomarker status comprises at least one somatic ER tumor mutation selected from the group consisting of Y537X, D538X, E380X, L379X, V422X, S463X, and L536X, wherein "X" refers to any amino acid residue, other than the wild-type residue at that position.

24. The use of claim 22 or 23, wherein the subject's somatic ER tumor biomarker status comprises at least one somatic ER tumor mutation selected from Y537S, Y537N, D538G, E380Q, L379I, V422del, S463P, L536P and L536_D538>P.

25. The use of any one of claims 22-24, wherein the compound of Formula (I) is



(I-c).

26. The use of any one of claims 22-25, wherein the breast cancer is estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-).

27. The use of any one of claims 22-26, wherein the breast cancer is metastatic or locally advanced.

28. The use of any one of claims 22-27, wherein the breast cancer is metastatic.

29. The use of any one of claims 22-28, wherein at least one additional anti-cancer agent is to be further administered.

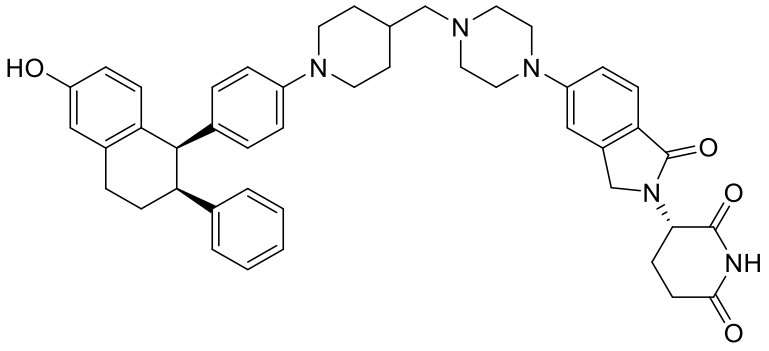
30. The use of claim 29, wherein the additional anti-cancer agent is selected from the group consisting of FLT-3 inhibitor, VEGFR inhibitor, EGFR TK inhibitor, aurora kinase inhibitor, PIK-1 modulator, Bcl-2 inhibitor, HDAC inhibitor, c-Met inhibitor, PARP inhibitor, CDK 4/6 inhibitor, anti-HGF antibody, PI3 kinase inhibitor, AKT inhibitor, mTORC1/2 inhibitor, JAK/STAT inhibitor, checkpoint 1 inhibitor, checkpoint 2 inhibitor, PD-1 inhibitor, PD-L1 inhibitor, B7-H3 inhibitor, CTLA4 inhibitor, LAG-3 inhibitor, OX40 agonist, focal adhesion kinase inhibitor, Map kinase kinase inhibitor, and VEGF trap antibody.

31. The use of claim 29 or 30, wherein the additional anti-cancer agent is a CDK 4/6 inhibitor.

32. The use of claim 29, wherein the additional anti-cancer agent is SHR6390, trilaciclib, lerociclib, AT7519M, dinaciclib, ribociclib, abemaciclib, palbociclib, everolimus, venetoclax, inavolisib, pazopanib, carboplatin, cisplatin, oxaliplatin, paclitaxel, epithilone B, fulvestrant, acolbifene, lasofoxifene, idoxifene, topotecan, pemetrexed, erlotinib, ticilimumab, ipilimumab, vorinostat, etoposide, gemcitabine, doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, capecitabine, camptothecin, PD0325901, irinotecan, tamoxifen, toremifene, anastrazole, letrozole, bevacizumab, goserelin acetate, raloxifene, alpelisib, trastuzumab, trastuzumab emtansine, pertuzumab, fam-trastuzumab deruxtecan-nxki (Enhertu), or eribulin (halaven).

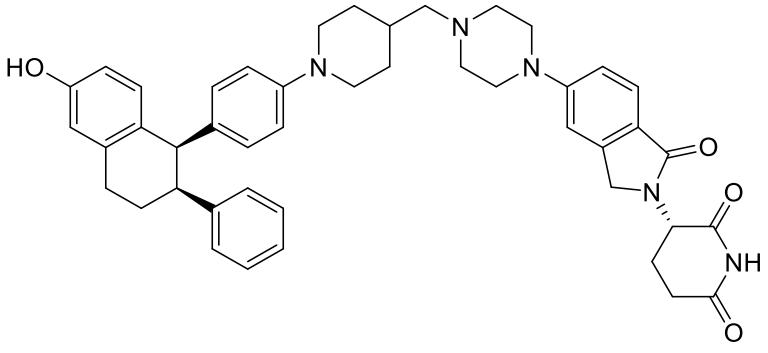
33. The use of claim 32, wherein the additional anti-cancer agent is palbociclib.

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



(I-c), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer in a subject in need thereof, wherein the breast cancer comprises at least one somatic estrogen receptor (ER) tumor mutation, and wherein about 10 mg to about 1000 mg of the compound of Formula (I-c) or a pharmaceutically acceptable salt thereof is to be administered.

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



(I-c), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer in a subpopulation of breast cancer subjects, wherein:

a breast cancer subject is selected for treatment based on the subject's somatic estrogen receptor (ER) tumor biomarker status; and

about 10 mg to about 1000 mg of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is to be administered.

36. The use of claim 35, wherein the subject's somatic ER tumor biomarker status comprises at least one somatic ER tumor mutation selected from the group consisting of Y537X, D538X, E380X, L379X, V422X, S463X, and L536X, wherein "X" refers to any amino acid residue, other than the wild-type residue at that position.

37. The use of claim 35 or 36, wherein the subject's somatic ER tumor biomarker status comprises at least one somatic ER tumor mutation selected from Y537S, Y537N, D538G, E380Q, L379I, V422del, S463P, L536P and L536_D538>P.