

TETRAHYDRO-PYRIDO[3,4-b]INDOLE ESTROGEN RECEPTOR MODULATORS AND USES THEREOF

5 CROSS REFERENCE TO RELATED APPLICATIONS

This non-provisional application filed under 37 CFR §1.53(b), claims the benefit under 35 USC §119(e) of US Provisional Application Serial No. 62/093,929 filed on 18 December 2014, US Provisional Application Serial No. 62/110,998 filed on 2 February 2015, and US Provisional Application Serial No. 62/142,077 filed on 2 April 2015, which are
10 incorporated by reference in their entirety.

FIELD OF THE INVENTION

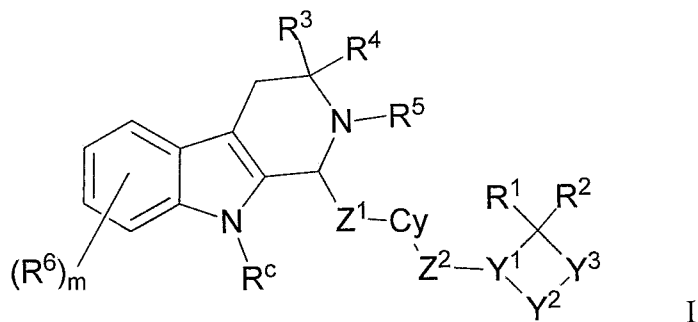
Described herein are compounds, including pharmaceutically acceptable salts, solvates, metabolites, prodrugs thereof, pharmaceutical compositions comprising such compounds, and methods of using such compounds to treat, prevent or diagnose diseases or
15 conditions that are estrogen sensitive, estrogen receptor dependent or estrogen receptor mediated in combination with other therapeutic agents.

BACKGROUND OF THE INVENTION

The estrogen receptor ("ER") is a ligand-activated transcriptional regulatory protein that mediates induction of a variety of biological effects through its interaction with
20 endogenous estrogens. Endogenous estrogens include 17 β (beta)-estradiol and estrones. ER has been found to have two isoforms, ER- α (alpha) and ER- β (beta). Estrogens and estrogen receptors are implicated in a number of diseases or conditions, such as breast cancer, lung cancer, ovarian cancer, colon cancer, prostate cancer, endometrial cancer, uterine cancer, as well as others diseases or conditions. There is a need for new ER- α targeting agents that have
25 activity in the setting of metastatic disease and acquired resistance.

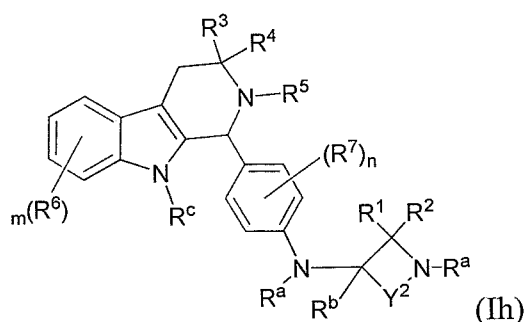
SUMMARY

The disclosure relates generally to tetrahydro-pyrido[3,4-b]indol-1-yl compounds with estrogen receptor modulation activity or function having the Formula I structure:



and stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, and with the substituents and structural features described herein.

One aspect of the disclosure is a compound having formula (Ih):



or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

Y² is -(CH₂)-;

R^a is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₈ alkenyl, propargyl, C₃-C₆ cycloalkyl, and C₃-C₆ heterocyclyl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, OH, OCH₃, and SO₂CH₃;

R^b is independently selected from the group consisting of H, -O(C₁-C₃ alkyl), C₁-C₆ alkyl, C₂-C₈ alkenyl and propargyl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH₂CH₂F, OH, OCH₃, and SO₂CH₃;

R^c is H;

R¹, R², R³ and R⁴ are independently selected from the group consisting of H, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -C(CH₃)₂OH, -CH(OH)CH(CH₃)₂, -C(CH₃)₂CH₂OH, -CH₂CH₂SO₂CH₃, -CH₂OP(O)(OH)₂, -CH₂F, -CHF₂, -CH₂NH₂, -CH₂NHSO₂CH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH(CH₃)CN, -C(CH₃)₂CN and -CH₂CN;

R⁵ is selected from the group consisting of C₁-C₉ alkyl, C₃-C₉ cycloalkyl, C₃-C₉ heterocycle, C₆-C₉ aryl, C₆-C₉ heteroaryl, -(C₁-C₆ alkylidyl)-(C₃-C₉ cycloalkyl), -(C₁-C₆

alkyldiyl)-(C₃-C₉ heterocycle), C(O)NR^a, SO₂R^a, and SO₂NR^a, each optionally substituted with one or more of halogen, CN, OR^a, N(R^a)₂, C₁-C₉ alkyl, C₃-C₉ cycloalkyl, C₃-C₉ heterocycle, C₆-C₉ aryl, C₆-C₉ heteroaryl, C(O)R^b, C(O)NR^a, SO₂R^a, and SO₂NR^a;

R⁶ is independently F or Cl;

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

R⁷ is independently halogen; and

n is 0, 1 or 2.

10 An aspect of the disclosure is the compound 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol, or a pharmaceutically acceptable salt thereof.

An aspect of the disclosure is the compound 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol, or a pharmaceutically acceptable salt thereof.

15 An aspect of the disclosure is the compound *N*-(3,5-difluoro-4-((1R,3R)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine or a pharmaceutically acceptable salt thereof.

20 An aspect of the disclosure is the compound *N*-(3,5-difluoro-4-((1R,3R)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

An aspect of the disclosure is a pharmaceutically acceptable salt of the compound *N*-(3,5-difluoro-4-((1R,3R)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

25 An aspect of the disclosure is the compound *N*-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine or a pharmaceutically acceptable salt thereof.

An aspect of the disclosure is the compound *N*-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

30 An aspect of the disclosure is a pharmaceutically acceptable salt of the compound *N*-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

An aspect of the disclosure is the compound N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine or a pharmaceutically acceptable salt thereof.

5 An aspect of the disclosure is the compound N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

An aspect of the disclosure is a pharmaceutically acceptable salt of the compound N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

10 An aspect of the disclosure is the compound 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol.

15 An aspect of the disclosure is a pharmaceutically acceptable salt of the compound 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol, or a pharmaceutically acceptable salt thereof.

An aspect of the disclosure is the compound 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol.

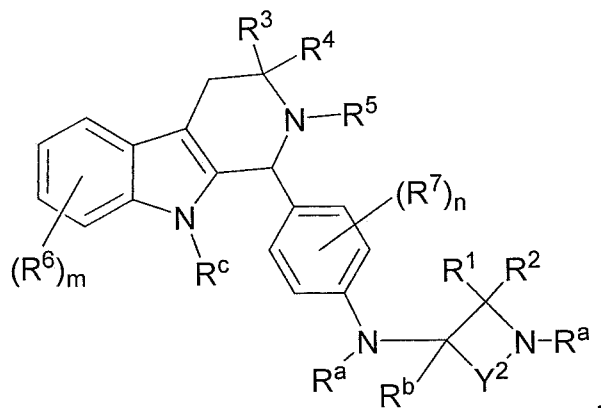
20 An aspect of the disclosure is a pharmaceutically acceptable salt of the compound 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol.

25 The disclosure also relates to a pharmaceutical composition of a Formula I compound and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. An aspect of the disclosure is a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof as defined herein and at least one pharmaceutically acceptable excipient.

The disclosure also relates to a process for making a Formula I compound or a pharmaceutical composition comprising a Formula I compound.

30 The disclosure also relates to a method of treating an ER-related disease or disorder in a patient comprising administering a therapeutically effective amount of the pharmaceutical composition to a patient with an ER-related disease or disorder.

An aspect of the disclosure is use of a compound of formula (Ih) or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof



(Ih)

wherein:

Y² is -(CH₂);

R^a is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₈ alkenyl, propargyl, C₃-C₆ cycloalkyl, and C₃-C₆ heterocyclyl, each optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, OH, OCH₃, and SO₂CH₃;

R^b is selected from the group consisting of H, -O(C₁-C₃ alkyl), C₁-C₆ alkyl, C₂-C₈ alkenyl, and propargyl, each optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, -CH₂F, -CHF₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH₂CH₂F, OH, OCH₃, and SO₂CH₃;

R^c is H;

R¹, R², R³ and R⁴ are independently selected from the group consisting of H, -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH₂OH, -CH₂OCH₃, -CH₂CH₂OH, -C(CH₃)₂OH, -CH(OH)CH(CH₃)₂, -C(CH₃)₂CH₂OH, -CH₂CH₂SO₂CH₃, -CH₂OP(O)(OH)₂, -CH₂F, -CHF₂, -CH₂NH₂, -CH₂NHSO₂CH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CF₃, -CH₂CF₃, -CH₂CHF₂, -CH(CH₃)CN, -C(CH₃)₂CN, and -CH₂CN;

R⁵ is selected from the group consisting of C₁-C₉ alkyl, C₃-C₉ cycloalkyl, C₃-C₉ heterocycle, C₆-C₉ aryl, C₆-C₉ heteroaryl, -(C₁-C₆ alkylidyl)-(C₃-C₉ cycloalkyl), -(C₁-C₆ alkylidyl)-(C₃-C₉ heterocycle), C(O)NR^a, SO₂R^a, and SO₂NR^a, each optionally substituted with one or more of halogen, CN, OR^a, N(R^a)₂, C₁-C₉ alkyl, C₃-C₉ cycloalkyl, C₃-C₉ heterocycle, C₆-C₉ aryl, C₆-C₉ heteroaryl, C(O)R^b, C(O)NR^a, SO₂R^a, and SO₂NR^a;

R⁶ is independently F or Cl;

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

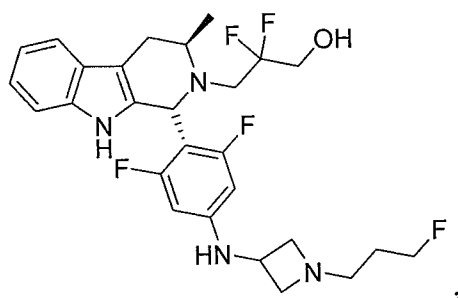
R⁷ is independently halogen; and

n is 0, 1 or 2,

in the manufacture of a medicament for the treatment of breast cancer, lung cancer,

5 ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer in a patient.

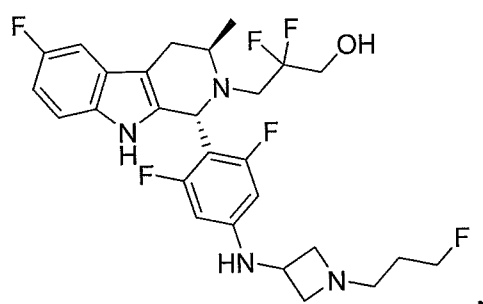
An aspect of the disclosure is use of a compound of formula:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate

10 cancer, or uterine cancer.

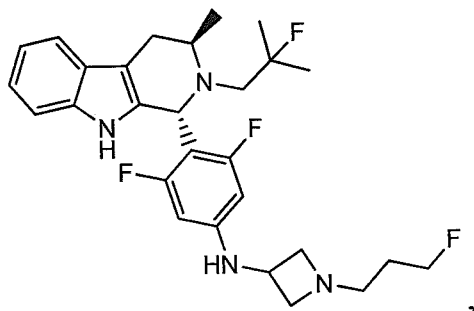
An aspect of the disclosure is use of a compound of formula:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate

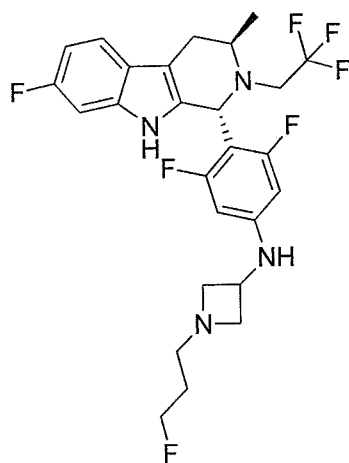
15 cancer, or uterine cancer.

An aspect of the disclosure is use of a compound of formula:



or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

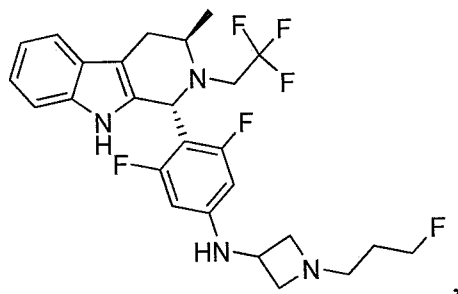
An aspect of the disclosure is use of a compound of formula:



5

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

An aspect of the disclosure is use of a compound of formula:



10

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

The disclosure also relates to a kit for treating a condition mediated by an estrogen receptor, comprising:

- a pharmaceutical composition comprising a Formula I compound; and
- instructions for use.

An aspect of the disclosure is a kit for treating breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer, comprising:

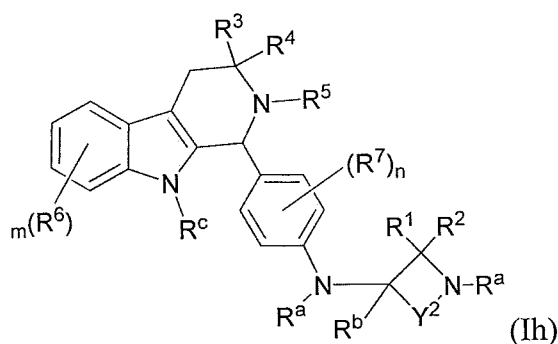
- a pharmaceutical composition as defined herein; and
- instructions for use.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of

We Claim:

1. A compound having formula (Ih):



or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein:

- 5 Y^2 is $-(CH_2)-$;

R^a is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_8 alkenyl, propargyl, C_3-C_6 cycloalkyl, and C_3-C_6 heterocyclyl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

- 10 R^b is independently selected from the group consisting of H, $-O(C_1-C_3$ alkyl), C_1-C_6 alkyl, C_2-C_8 alkenyl and propargyl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, OH, OCH_3 , and SO_2CH_3 ;

R^c is H;

- 15 R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH(CH_3)_2$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2SO_2CH_3$, $-CH_2OP(O)(OH)_2$, $-CH_2F$, $-CHF_2$, $-CH_2NH_2$, $-CH_2NHSO_2CH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CN$, $-C(CH_3)_2CN$ and $-CH_2CN$;

- 20 R^5 is selected from the group consisting of C_1-C_9 alkyl, C_3-C_9 cycloalkyl, C_3-C_9 heterocycle, C_6-C_9 aryl, C_6-C_9 heteroaryl, $-(C_1-C_6$ alkylidyl) $-(C_3-C_9$ cycloalkyl), $-(C_1-C_6$ alkylidyl) $-(C_3-C_9$ heterocycle), $C(O)NR^a$, SO_2R^a , and SO_2NR^a , each optionally substituted with one or more of halogen, CN, OR^a , $N(R^a)_2$, C_1-C_9 alkyl, C_3-C_9 cycloalkyl, C_3-C_9 heterocycle, C_6-C_9 aryl, C_6-C_9 heteroaryl, $C(O)R^b$, $C(O)NR^a$, SO_2R^a , and SO_2NR^a ;

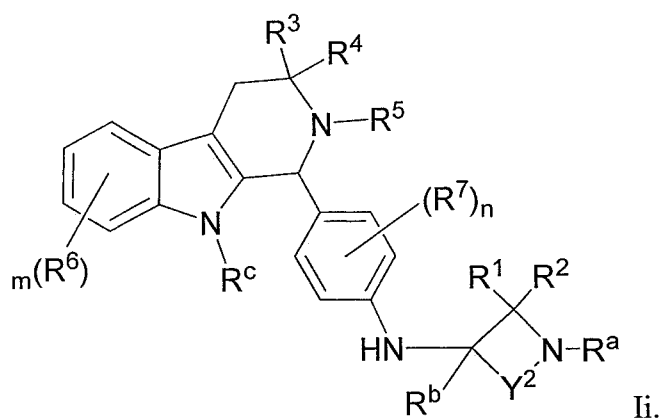
R^6 is independently F or Cl;

- 25 m is 0, 1, 2, 3, or 4;

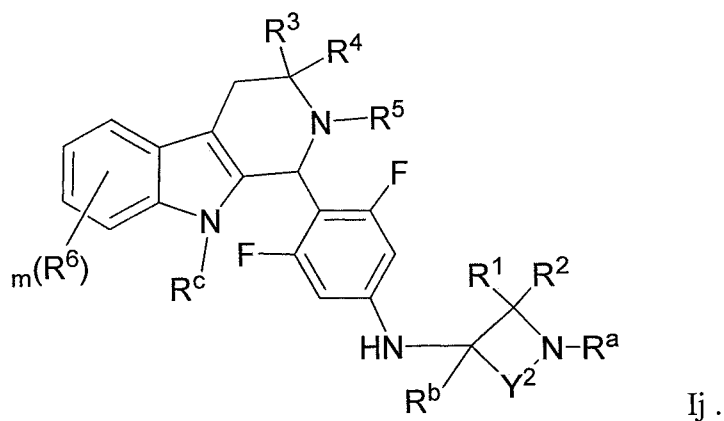
R^7 is independently halogen; and

n is 0, 1 or 2.

2. The compound of claim 1 having Formula Ii:

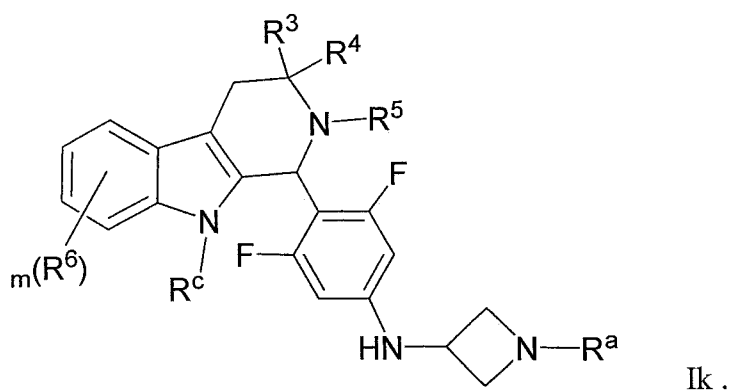


3. The compound of claim 2 having Formula Ij:



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4. The compound of claim 3 having Formula Ik:



5. The compound of claim 1 or 2, wherein R^7 is F.
6. The compound of any one of claims 1 to 3 wherein R^1 and R^2 are H.
7. The compound of any one of the preceding claims wherein R^3 is H, and R^4 is $-\text{CH}_3$.

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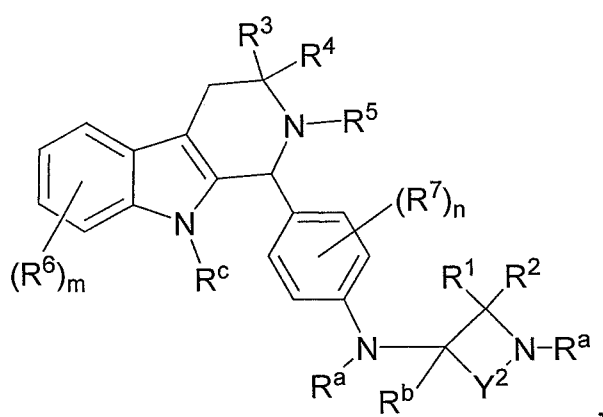
8. The compound of any one of the preceding claims wherein R^5 is C_1-C_6 fluoroalkyl.

9. The compound of any one of the preceding claims wherein m is 0.

10. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of claim 1 and at least one pharmaceutically acceptable excipient.

11. The pharmaceutical composition according to claim 10, further comprising an additional therapeutic agent.

12. Use of a compound of formula (Ih) or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof



(Ih)

wherein:

Y^2 is $-(CH_2)_2$;

R^a is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_8 alkenyl, propargyl, C_3-C_6 cycloalkyl, and C_3-C_6 heterocyclyl, each optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, OH, OCH_3 , and SO_2CH_3 ;

R^b is selected from the group consisting of H, $-O(C_1-C_3 \text{ alkyl})$, C_1-C_6 alkyl, C_2-C_8 alkenyl, and propargyl, each optionally substituted with one or more groups independently selected from the group consisting of F, Cl, Br, I, CN, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, OH, OCH_3 , and SO_2CH_3 ;

R^c is H;

R^1 , R^2 , R^3 and R^4 are independently selected from the group consisting of H, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$,

$-\text{CH}(\text{OH})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{NH}\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}(\text{CH}_3)\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$, and $-\text{CH}_2\text{CN}$;

5 R^5 is selected from the group consisting of C_1 – C_9 alkyl, C_3 – C_9 cycloalkyl, C_3 – C_9 heterocycle, C_6 – C_9 aryl, C_6 – C_9 heteroaryl, $-(\text{C}_1$ – C_6 alkylidyl)–(C_3 – C_9 cycloalkyl), $-(\text{C}_1$ – C_6 alkylidyl)–(C_3 – C_9 heterocycle), $\text{C}(\text{O})\text{NR}^a$, SO_2R^a , and SO_2NR^a , each optionally substituted with one or more of halogen, CN , OR^a , $\text{N}(\text{R}^a)_2$, C_1 – C_9 alkyl, C_3 – C_9 cycloalkyl, C_3 – C_9 heterocycle, C_6 – C_9 aryl, C_6 – C_9 heteroaryl, $\text{C}(\text{O})\text{R}^b$, $\text{C}(\text{O})\text{NR}^a$, SO_2R^a , and SO_2NR^a ;

R^6 is independently F or Cl;

10 m is 0, 1, 2, 3, or 4;

R^7 is independently halogen; and

n is 0, 1 or 2,

in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer in a patient.

15 13. The use of claim 12, wherein the cancer is breast cancer.

14. The use of claim 12 or 13, further comprising an additional therapeutic agent selected from an anti-inflammatory agent, an immunomodulatory agent, chemotherapeutic agent, an apoptosis-enhancer, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders, or a combination thereof.

25 15. The use of any one of claims 12 to 14, wherein the compound or a pharmaceutically acceptable salt thereof is to be administered in combination with a therapeutic agent selected from paclitaxel, anastrozole, exemestane, cyclophosphamide, epirubicin, fulvestrant, letrozole, gemcitabine, trastuzumab, trastuzumab emtansine, pegfilgrastim, filgrastim, tamoxifen, docetaxel, toremifene, vinorelbine, capecitabine, and ixabepilone, or a combination thereof.

30 16. The use of any one of claims 12 to 15, wherein the compound or a pharmaceutically acceptable salt thereof is to be administered in combination with a CDK 4/6 inhibitor.

17. The use of claim 16 wherein the CDK 4/6 inhibitor is selected from palbociclib, ribociclib and LY283519, or a pharmaceutically acceptable salt thereof.

18. A kit for treating breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer, comprising:

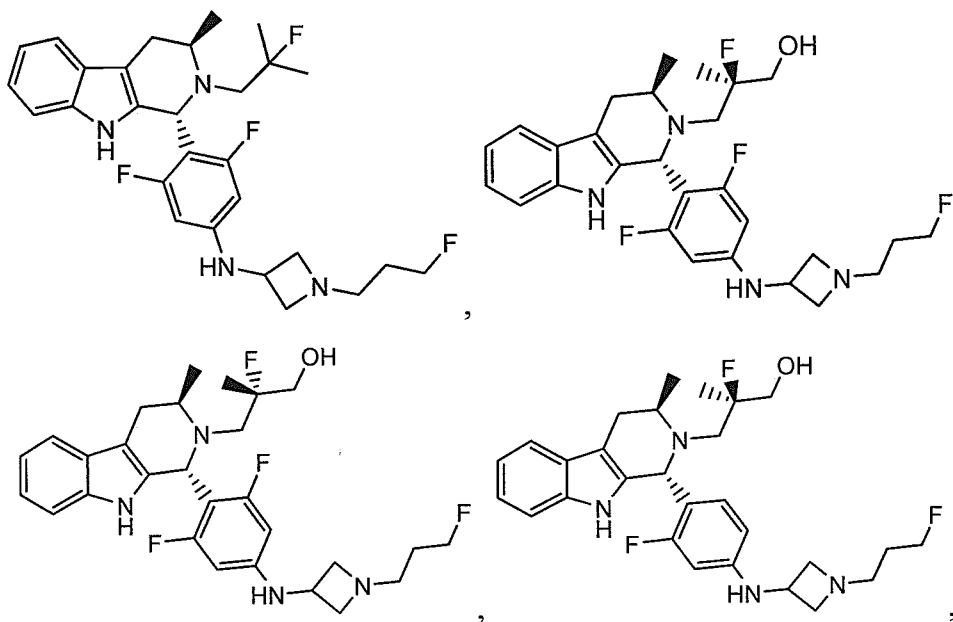
- a) a pharmaceutical composition of claim 10; and
- b) instructions for use.

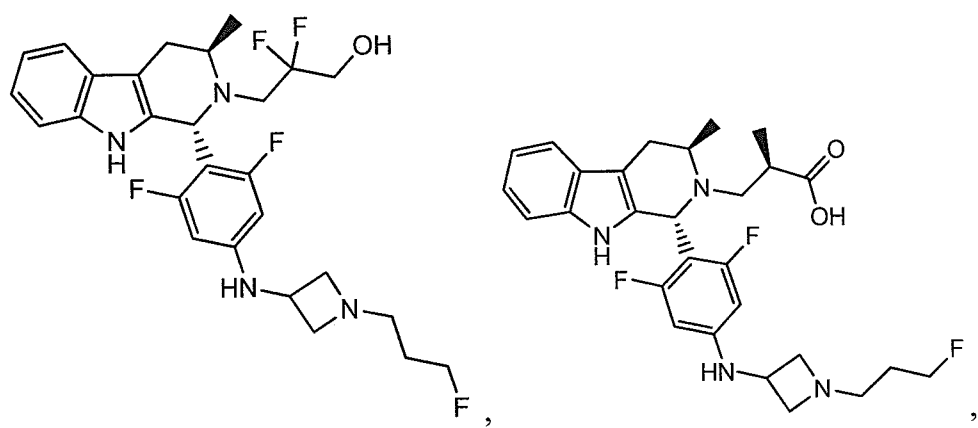
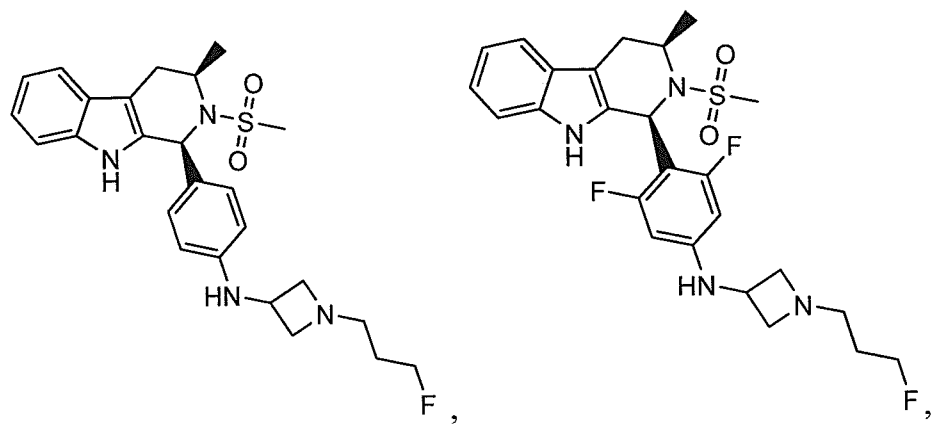
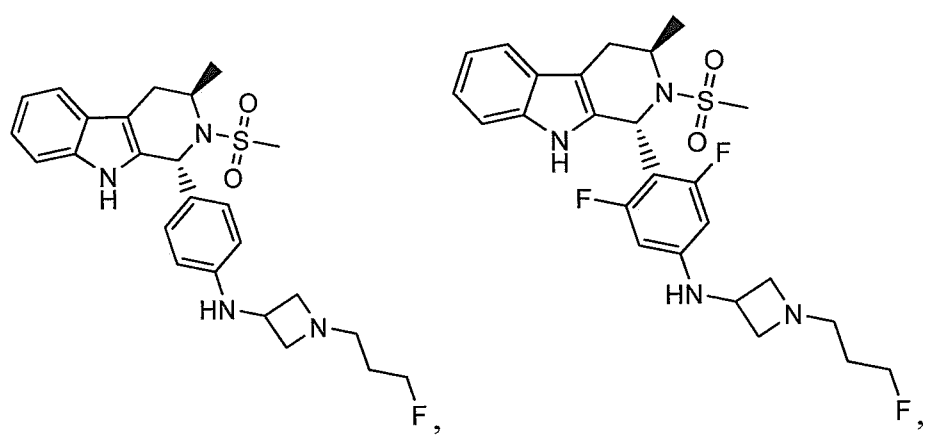
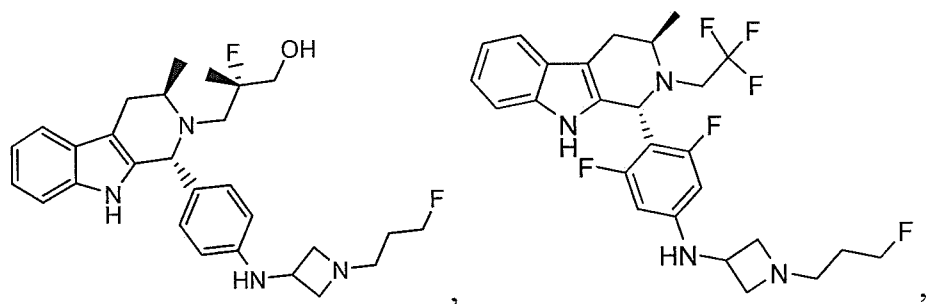
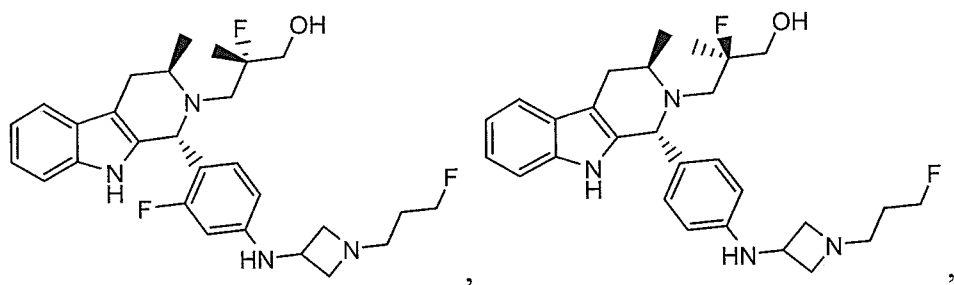
5 19. The compound of claim 1 comprising one or more deuterium.

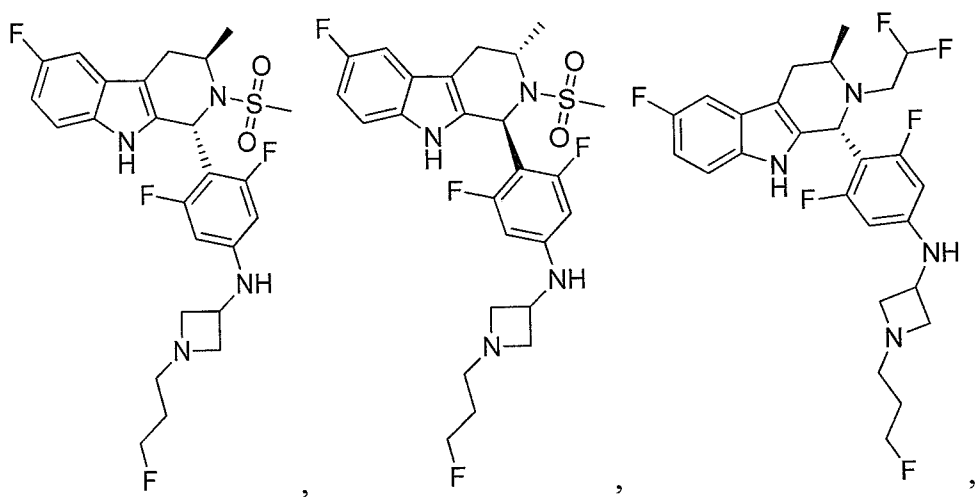
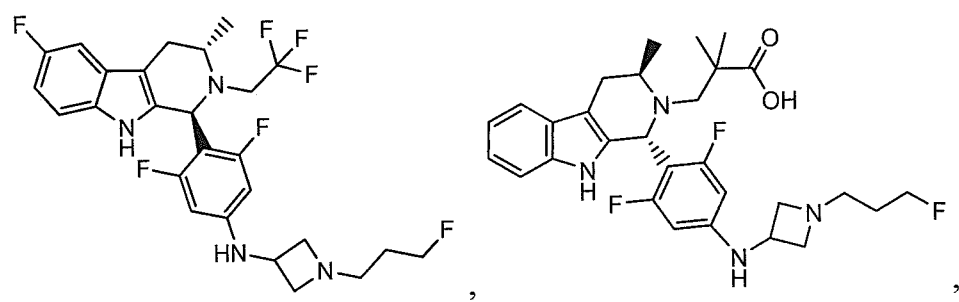
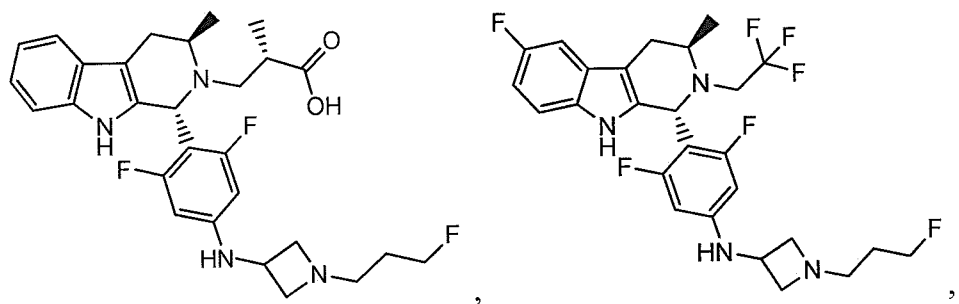
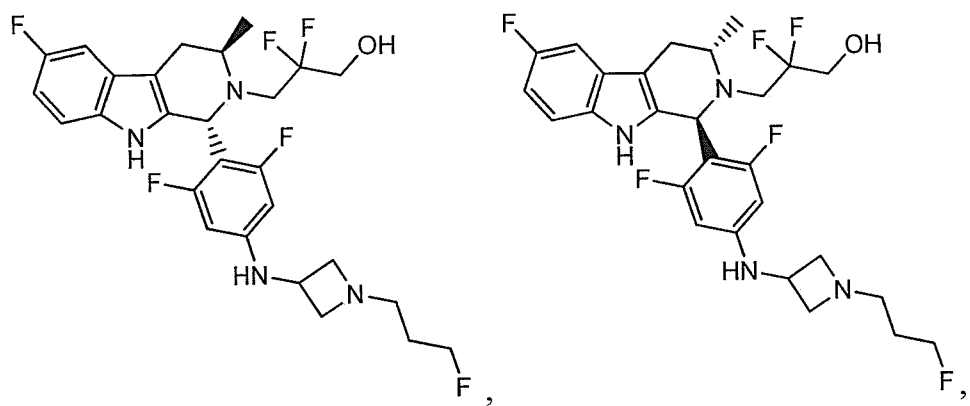
20. The compound 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol, or a pharmaceutically acceptable salt thereof.

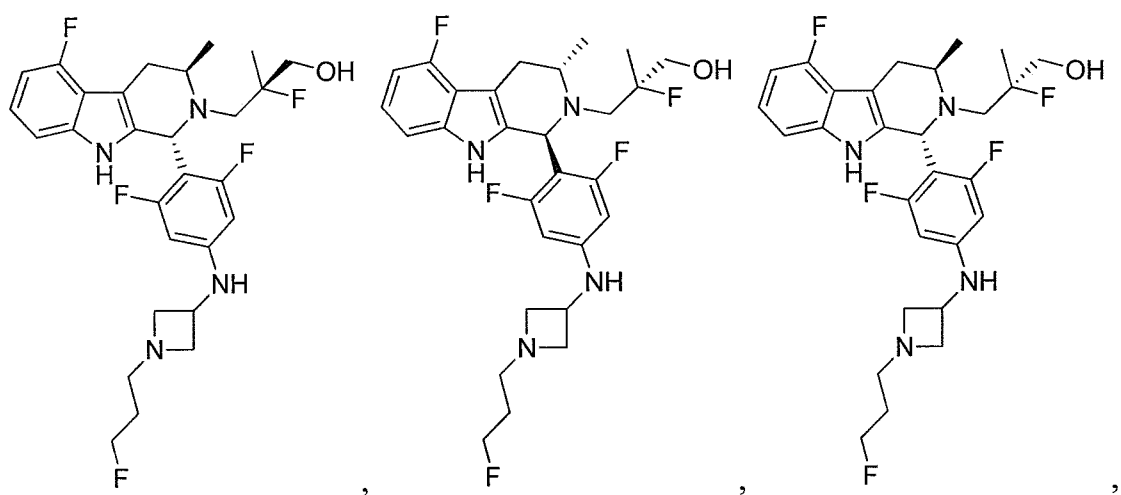
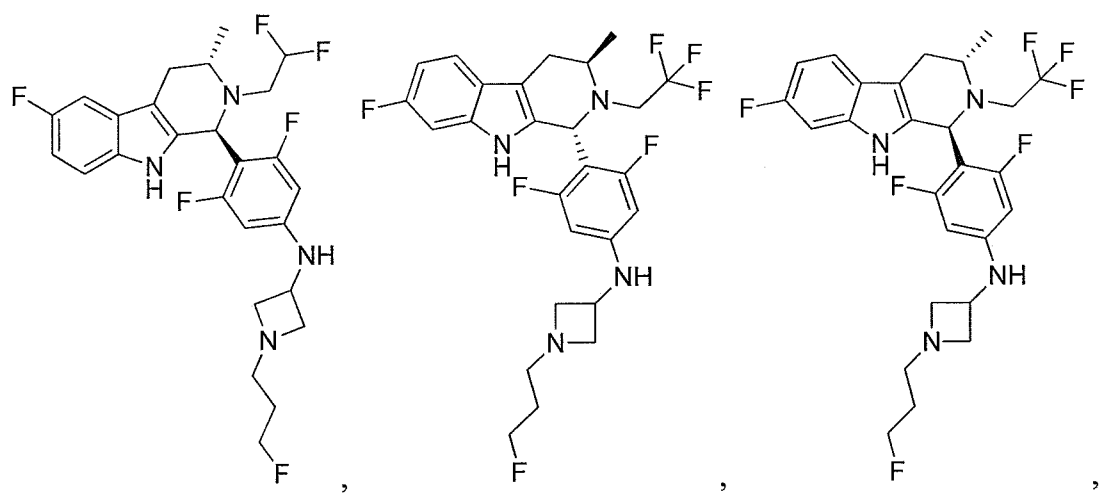
10 21. The compound 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol, or a pharmaceutically acceptable salt thereof.

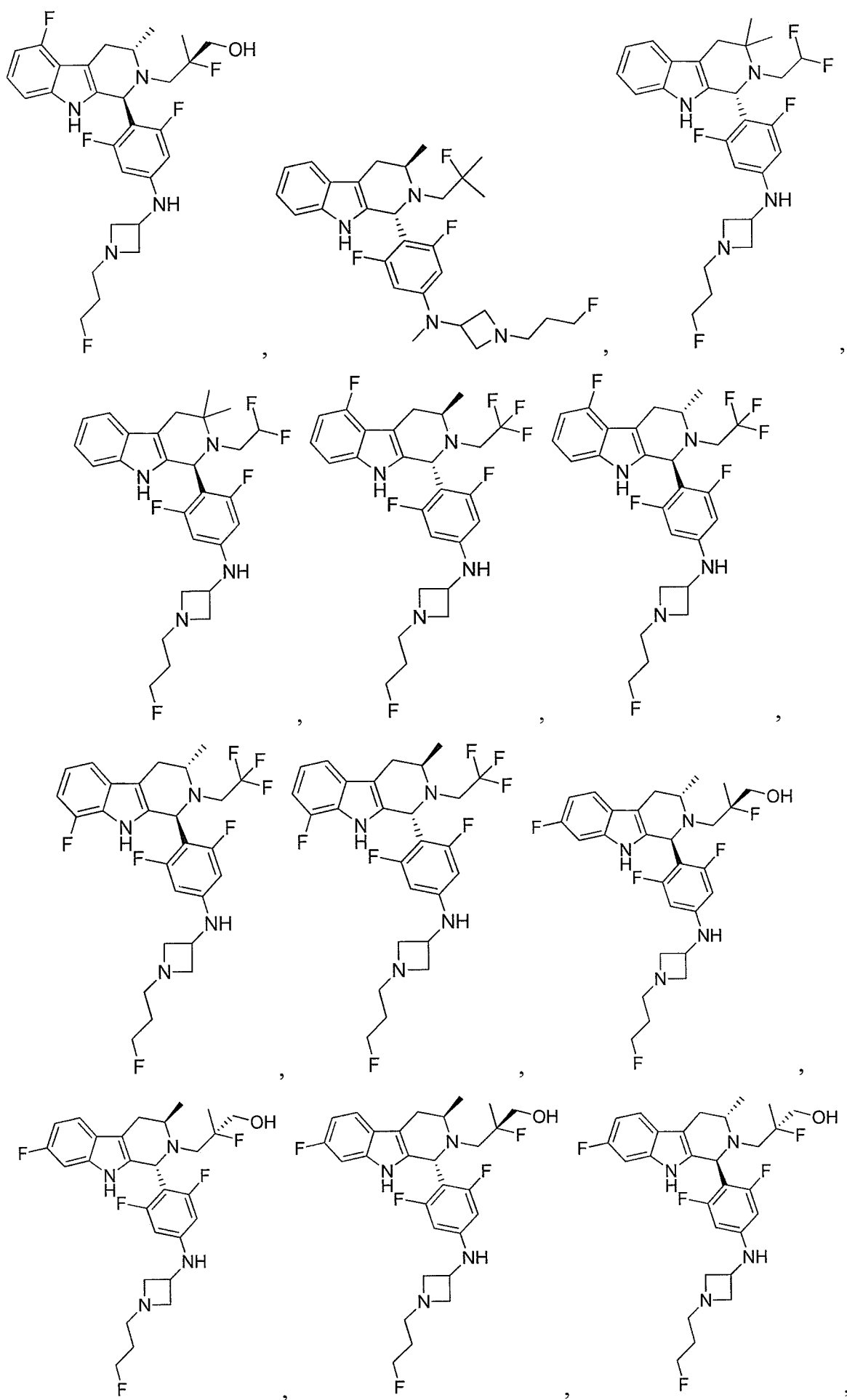
22. The compound of claim 1 having the formula:

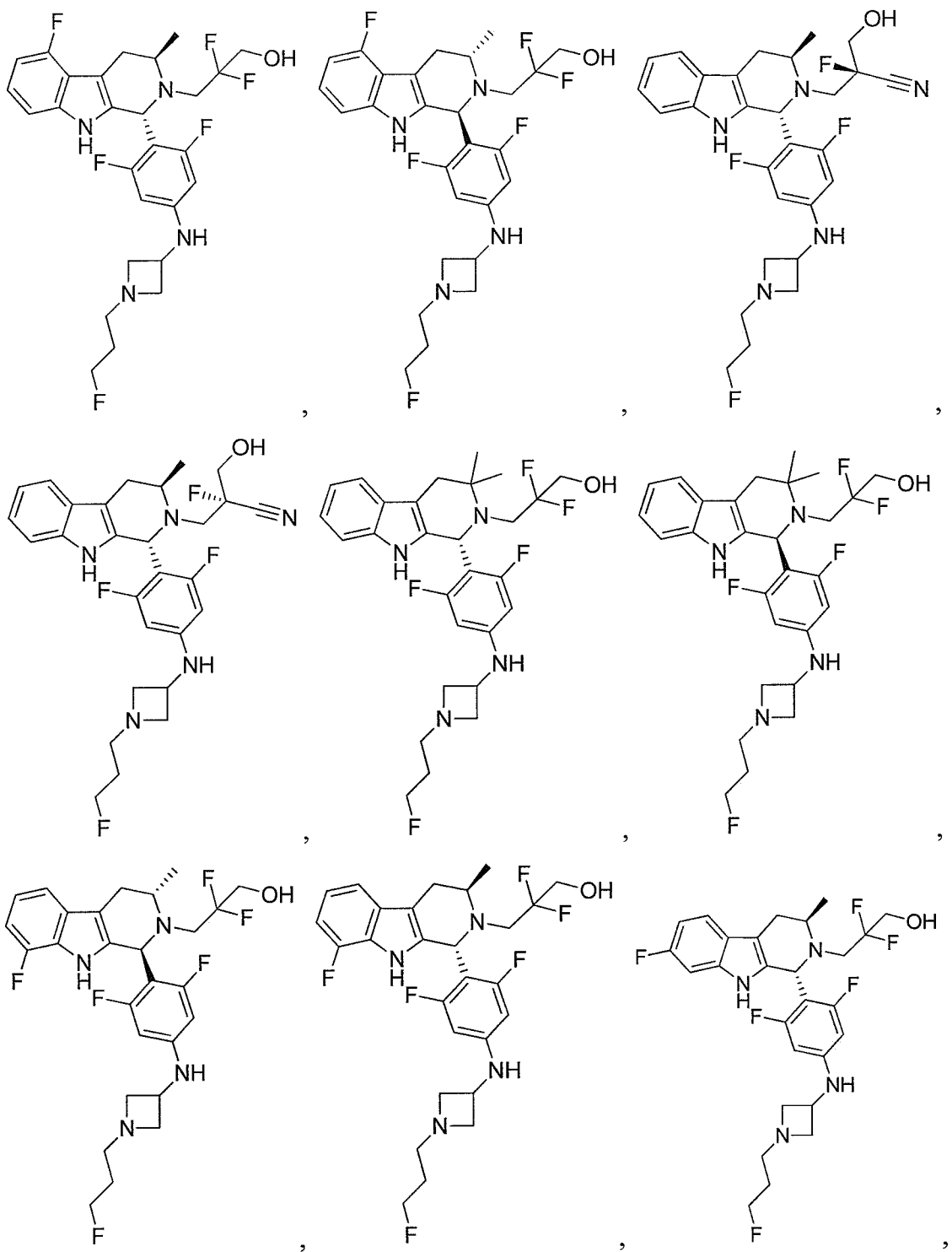


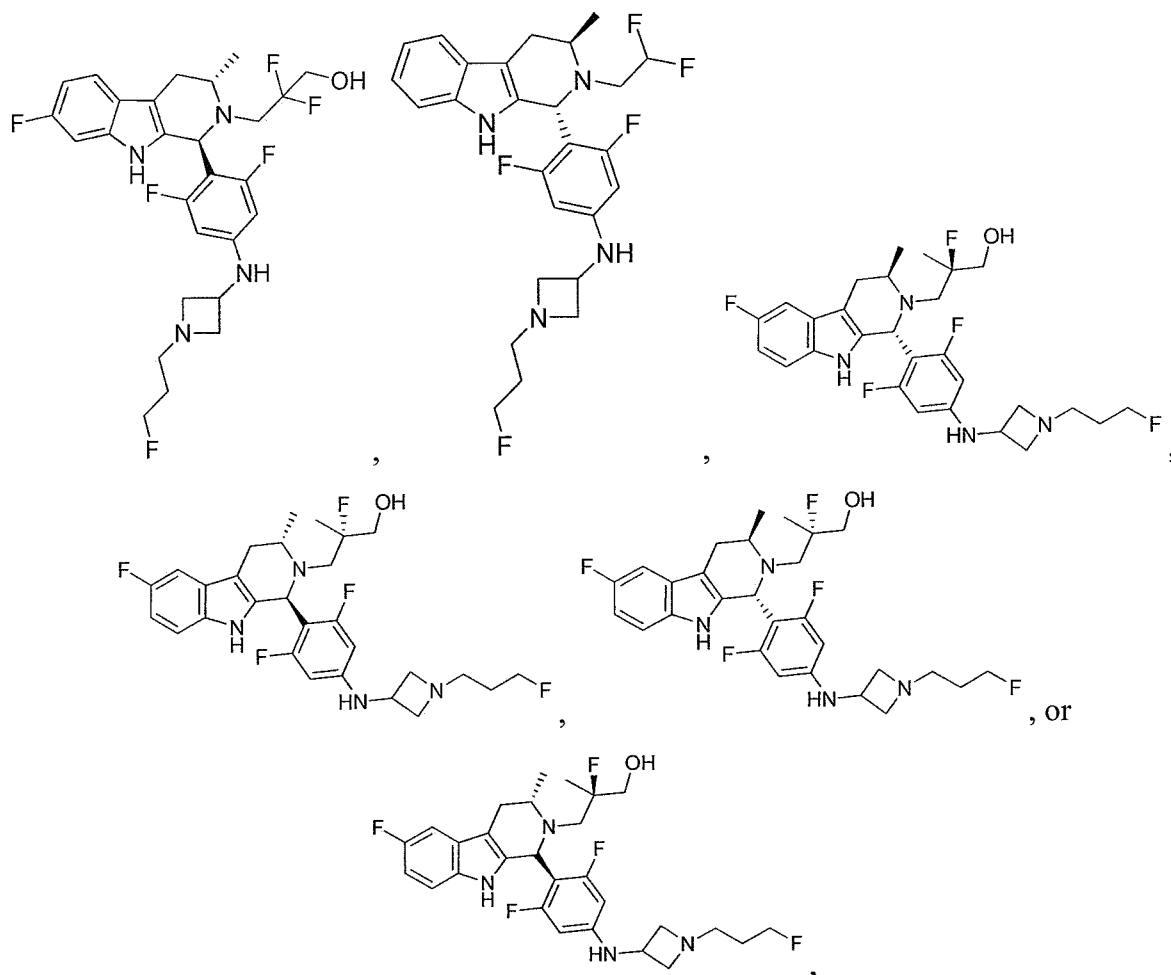












or a pharmaceutically acceptable salt thereof.

- 5 23. The use of any one of claims 12 to 17, wherein the compound or pharmaceutically acceptable salt thereof is to be administered as a pharmaceutical composition.
24. The use of any one of claims 12 to 17 or 23, wherein the breast cancer is hormone receptor positive metastatic breast cancer.
- 10 25. The use of any one of claims 12 to 17, 23 or 24, wherein the breast cancer is hormone dependent breast cancer.
26. The use of any one of claims 13 to 17, or 23 to 25, wherein the compound or pharmaceutically acceptable salt thereof is to be administered prior to the patient having received surgery.
- 15 27. The use of any one of claims 13 to 17, or 23 to 26, wherein the compound or pharmaceutically acceptable salt thereof is to be administered after the patient has received surgery.

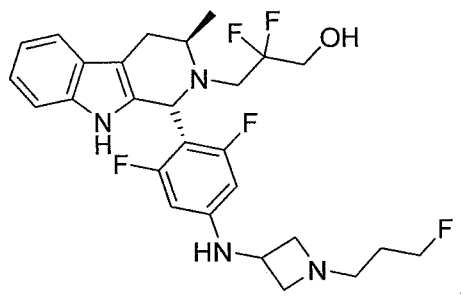
28. The use of any one of claims 12 to 17, or 23 to, wherein the patient is chemotherapy-naïve.

29. The use of any one of claims 12 to 17, or 23 to 28, wherein the breast cancer is a hormone refractory breast cancer.

5 30. The use of any one of claims 14 to 17, or 23 to 29, wherein the compound or a pharmaceutically acceptable salt thereof is to be administered prior to administration of the additional therapeutic agent to the patient.

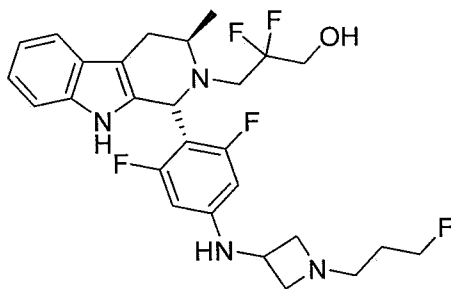
31. The use of any one of claims 14 to 17, or 23 to 30, wherein the compound or a pharmaceutically acceptable salt thereof is to be administered after the administration of the
10 additional therapeutic agent to the patient.

32. Use of a compound of formula:

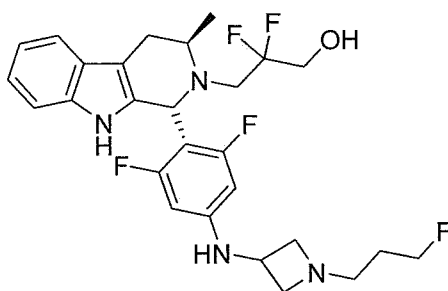


or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer,
15 or uterine cancer.

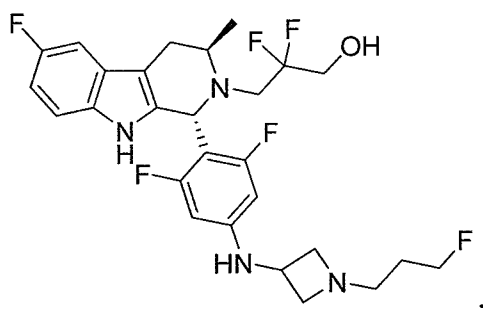
33. The use of claim 32, wherein the compound is:



34. The use of claim 32, wherein the compound is a pharmaceutically acceptable salt of the compound:

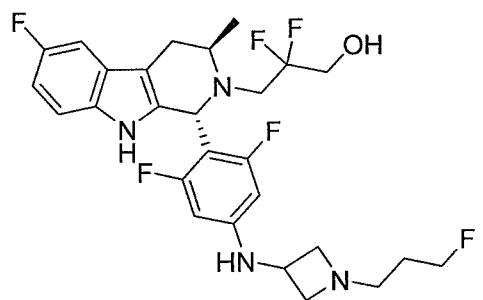


35. Use of a compound of formula:

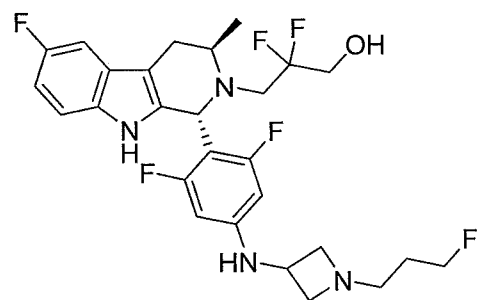


or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

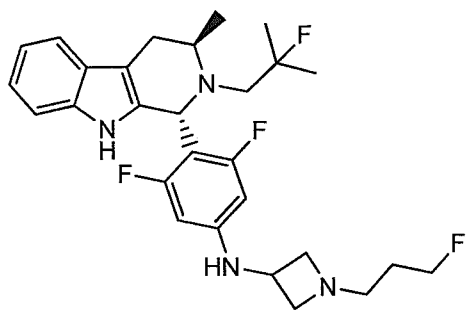
36. The use of claim 35, wherein the compound is:



37. The use of claim 35, wherein the compound is a pharmaceutically acceptable salt of the compound:

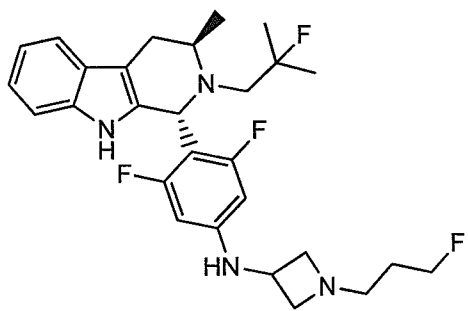


38. The use of claim 32, wherein the cancer is breast cancer.
39. The use of claim 35, wherein the cancer is breast cancer.
40. Use of a compound of formula:

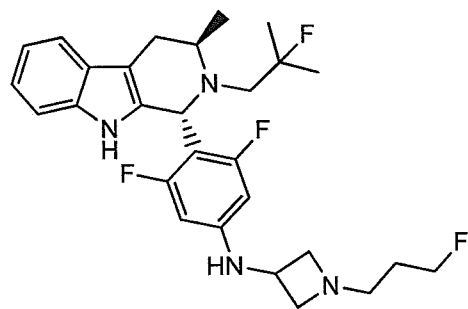


- 5 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

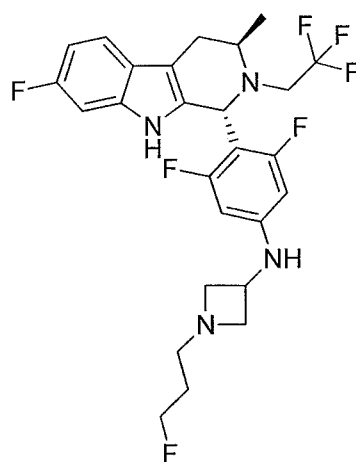
41. The use of claim 40, wherein the compound is:



42. The use of claim 40, wherein the compound is a pharmaceutically acceptable salt of:

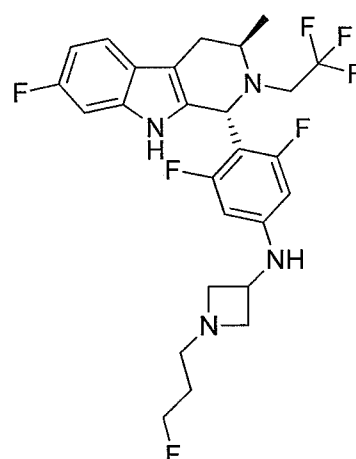


43. Use of a compound of formula:

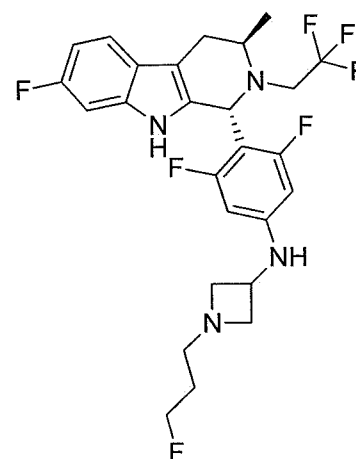


or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or uterine cancer.

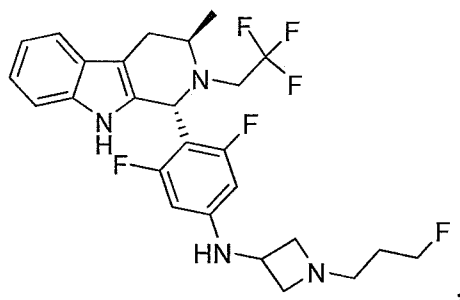
44. The use of claim 43, wherein the compound is:



45. The use of claim 43, wherein the compound is a pharmaceutically acceptable salt of:



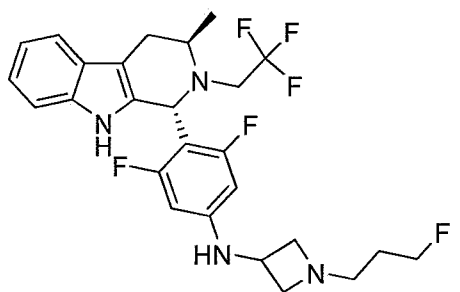
46. Use of a compound of formula:



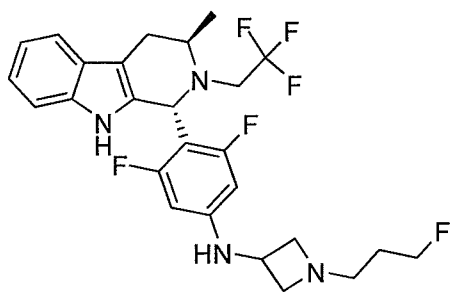
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate

5 cancer, or uterine cancer.

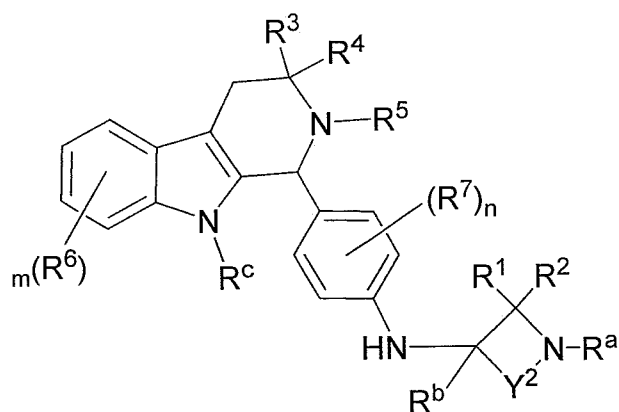
47. The use of claim 46, wherein the compound is:



48. The use of claim 46, wherein the compound is a pharmaceutically acceptable salt of:



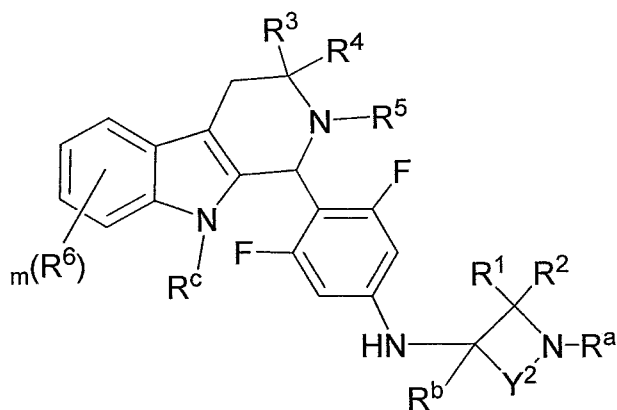
49. The use of claim 12, wherein the compound comprises a compound of Formula Ii:



(Ii)

5 or a pharmaceutically acceptable salt thereof.

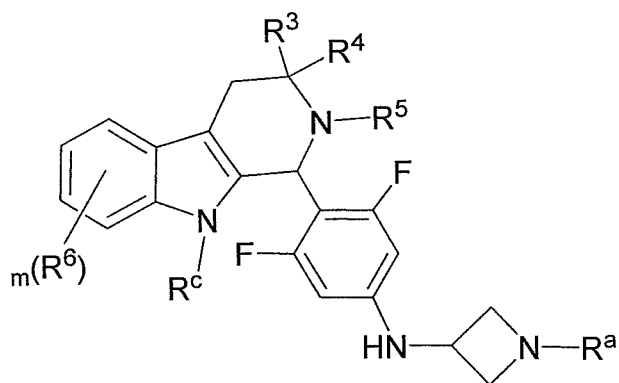
50. The use of claim 12, wherein the compound comprises a compound of Formula Ij:



(Ij)

10 or a pharmaceutically acceptable salt thereof.

51. The use of claim 12, wherein the compound comprises a compound of Formula Ik:



(Ik)

or a pharmaceutically acceptable salt thereof.

52. The use of claim 12 or 49, wherein R^7 is F.

53. The use of claim 12, 49 or 50, wherein R^1 and R^2 are H.

54. The use of claim 12 or 49 to 51, wherein R^3 is H, and R^4 is $-CH_3$.

5 55. The use of claim 12 or 49 to 51, wherein R^5 is C_1-C_6 fluoroalkyl.

56. The use of claim 12 or 49 to 51, wherein m is 0.

10 57. The use of any one of claims 12 to 31 or 49 to 56, wherein the patient has been treated at least once with one or more therapeutic agents selected from the group consisting of paclitaxel, anastrozole, exemestane, cyclophosphamide, epirubicin, fulvestrant, letrozole, gemcitabine, trastuzumab, trastuzumab emtansine, pegfilgrastim, filgrastim, tamoxifen, docetaxel, toremifene, vinorelbine, capecitabine, and ixabepilone, or a combination thereof.

58. The use of any one of claims 12 to 31 or 49 to 57, wherein the patient has been treated at least once with a hormone blocking therapy, a chemotherapeutic agent, radiation therapy, monoclonal antibody, or a combination thereof.

15 59. The use of claim 58, wherein the patient has been previously treated with at least one of chemotherapy and radiation therapy.

60. The use of claim 58, wherein the compound is to be administered in combination with a hormone blocking therapy, a chemotherapeutic agent, radiation therapy, a monoclonal antibody, or a combination thereof.

20 61. The use of any one of claims 58 to 60, wherein the chemotherapeutic agent comprises a therapeutic antibody selected from the group consisting of alemtuzumab, bevacizumab, cetuximab, panitumumab, rituximab, pertuzumab, trastuzumab, trastuzumab emtansine, and tositumomab, or a combination thereof.

25 62. The use of claim 61, wherein the chemotherapeutic agent comprises a therapeutic antibody selected from the group consisting of bevacizumab, rituximab, pertuzumab, trastuzumab, and trastuzumab emtansine, or a combination thereof.

63. The use of any one of claims 58 to 60, wherein the chemotherapeutic agent comprises one or more of: (i) anti-estrogens; (ii) selective estrogen receptor degraders; (iii)

selective estrogen receptor modulators; (iv) anti-androgens; or (v) aromatase inhibitor, or a pharmaceutically acceptable salt thereof.

64. The use of claim 63, wherein the selective estrogen receptor modulator comprises tamoxifen, raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene,
5 LY117018, onapristone, or toremifine citrate.

65. The use of claim 63, wherein the selective estrogen receptor modulator comprises fulvestrant.

66. The use of claim 63, wherein aromatase inhibitor comprises 4(5)-imidazoles, aminoglutethimide, megestrol acetate, exemestane, formestane, fadrozole, vorozole,
10 letrozole, or anastrozole.

67. The use of any one of claims 63 to 66, wherein the anti-androgen comprises ftutamide, nilutamide, bicalutamide, leuprolide, goserelin, or troxacitabine.

68. The use of any one of claims 14 to 31 or 49 to 67, wherein the compound is to be administered in combination with cobimetinib.

15 69. The use of any one of claims 14 to 31 or 49 to 68, wherein the compound is to be administered in combination with taselisib or ipatasertib.

70. The use of any one of claims 17 to 31 or 49 to 69, wherein the compound is to be administered in combination with palbociclib.

20 71. The use of any one of claims 17 to 31 or 49 to 70, wherein the compound is administered in combination with ribociclib.

72. The compound *N*-(3,5-difluoro-4-((1*R*,3*R*)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine or a pharmaceutically acceptable salt thereof.

25 73. The compound *N*-(3,5-difluoro-4-((1*R*,3*R*)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

74. A pharmaceutically acceptable salt of the compound *N*-(3,5-difluoro-4-((1*R*,3*R*)-7-fluoro-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

75. The compound N-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine or a pharmaceutically acceptable salt thereof.

76. The compound N-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

77. A pharmaceutically acceptable salt of the compound N-(3,5-difluoro-4-((1R,3R)-3-methyl-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

78. The compound N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine or a pharmaceutically acceptable salt thereof.

79. The compound N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

80. A pharmaceutically acceptable salt of the compound N-(3,5-difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)-1-(3-fluoropropyl)azetidin-3-amine.

81. The compound 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol.

82. A pharmaceutically acceptable salt of the compound 3-[(1R,3R)-1-[2,6-difluoro-4-[[1-(3-fluoropropyl)azetidin-3-yl]amino]phenyl]-3-methyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-2,2-difluoro-propan-1-ol, or a pharmaceutically acceptable salt thereof.

83. The compound 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol.

84. A pharmaceutically acceptable salt of the compound 3-((1R,3R)-1-(2,6-difluoro-4-((1-(3-fluoropropyl)azetidin-3-yl)amino)phenyl)-6-fluoro-3-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)-2,2-difluoropropan-1-ol.