SUBSTITUTED-INDOLE COMPOUNDS AS ESTROGEN RECEPTOR DOWN-REGULATORS

Field of invention

[0001] The present invention relates to a novel class of indole derivatives, particularly a compound represented by formula (I), a preparation method, a pharmaceutical composition and a use as estrogen receptor down-regulator in preparing a medicament for treating estrogen receptor-positive breast cancer.

Prior arts

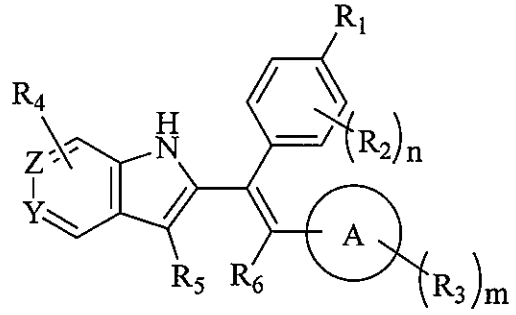
[0002] According to WHO's statistics, breast cancer has become a cancer with second highest incidence rate in the world and a cancer with the highest incidence rate among women. After years of research, the role of the estrogen-estrogen receptor signaling pathway in the progression of breast cancer has been confirmed; and the estrogen receptor (ER) has become the most important biomarker for breast cancer. According to the expression of estrogen receptor, breast cancer can be classified into estrogen receptor-positive breast cancer and estrogen receptor-negative breast cancer, wherein estrogen receptor-positive breast cancer accounts for more than 70% among the total number of breast cancer patients.

[0003] Endocrine therapy (ET) which targets the estrogen-estrogen receptor signaling pathway in breast cancer cells, has been the first choice for the treatment of estrogen receptor-positive breast cancer because of its minimal risk and remarkable efficacy. Endocrine therapy mainly includes three therapies which are ovarian suppression therapy, aromatase inhibitor (AI), and selective estrogen receptor modulator (SERM). The use of ovarian suppression therapy is less than the other two therapies because of poor efficacy and low patient satisfaction. Early aromatase inhibitors (first generation, second generation) have low target selectivity and severe side effects. After years of research, the third generation of aromatase inhibitors which have greatly improved the target selectivity and solved the problem of earlier aromatase inhibitors has been widely used. Among them, letrozole has been used as a first-line drug for the treatment of estrogen receptor-positive breast cancer. The selective estrogen receptor modulator (SERM) which targets directly at the estrogen receptor to block the signaling pathway has a significant therapeutic efficiency and a long history of application. Among them, tamoxifen is the most representative selective estrogen receptor modulator. As a first-line drug recommended for priority of use, tamoxifen has exhibited significant clinical efficacy in the prevention and treatment of estrogen receptor-positive breast cancer.

[0004] Although the aromatase inhibitor letrozole and the selective estrogen receptor modulator tamoxifen have exhibited good efficacy in the treatment of estrogen receptor-positive breast cancer, the resistance in estrogen receptor-positive breast cancer to the aromatase inhibitor and the selective estrogen receptor modulator has been becoming more prominent along with their use. A large number of studies

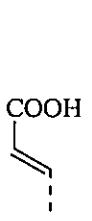
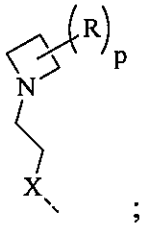
What is claimed is:

1. A compound represented by formula (I), a pharmaceutically acceptable salt, a hydrate or a prodrug thereof,



(I)

wherein,

R_1 is selected from  and  ;

X is selected from single bond, O and S;

Y and Z are each independently selected from N and CH;

ring A is selected from 5-10 membered aryl and 5-10 membered heteroaryl;

R_2 is selected from H, halogen, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R_3 is selected from H, halogen, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R_4 and R_5 are each independently selected from H, halogen, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R_6 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R is selected from H, F, Cl, Br, I, OH, CN, NH_2, COOH, C(=O)NH_2, or the group consisting of C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered

heterocycloalkyl and C_{3-6} cycloalkyl-C_{1-3} alkyl-, each of which is optionally substituted with 1, 2, or 3 R';

n is selected from 0, 1, 2, 3 and 4;

m is selected from 0, 1, 2, 3 and 4;

P is selected from 0, 1, 2 and 3;

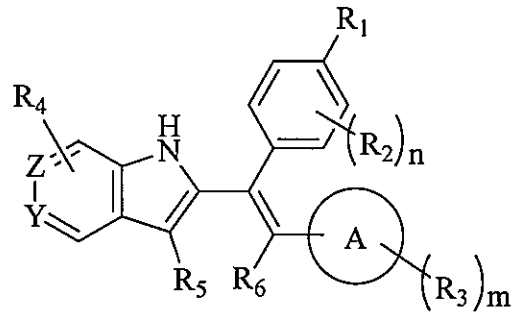
or, when m is 2, R_3 and R_3 are connected together to form a 5-6 membered ring;

R' is selected from the group consisting of F, Cl, Br, I, OH, CN, NH_2, COOH, Me, Et, CF_3, CHF_2, CH_2F, $NHCH_3$ and $N(CH_3)_2$;

"hetero" represents a heteroatom or a heteroatom group, which is selected from the group consisting of -C(=O)N(R)-, -N(R)-, -S(=O)$_2$N(R)-, -S(=O) N(R)-, -O-, -S-, =O, =S, -O-N=, -C(=O)O-, -C(=O) -, -C(=S)-, -S(=O)-, -S(=O)$_2$- and -N(R)C(=O)N(R)-;

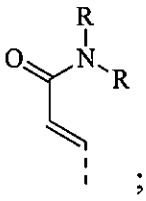
in any of the above cases, the number of the heteroatom or the heteroatom group is independently selected from 1, 2 and 3.

2. A compound represented by formula (I), a pharmaceutically acceptable salt, a hydrate or a prodrug thereof,



(I)

wherein,

R_1 is selected from  ;

Y and Z are each independently selected from N and CH;

ring A is selected from 5-10 membered aryl and 5-10 membered heteroaryl;

R_2 is selected from H, halogen, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R_3 is selected from H, halogen, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R_4 and R_5 are each independently selected from H, halogen, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R_6 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-6} cycloalkyl and 3-6 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 R;

R is selected from H, F, Cl, Br, I, OH, CN, NH_2, COOH, $C(=O)NH_2$, or the group consisting of C_{1-8} alkyl, C_{1-8} heteroalkyl, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl and C_{3-6} cycloalkyl-C_{1-3} alkyl-, each of which is optionally substituted with 1, 2, or 3 R';

n is selected from 0, 1, 2, 3 and 4;

m is selected from 0, 1, 2, 3 and 4;

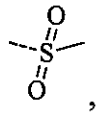
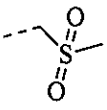
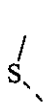
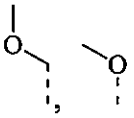
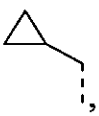
or, when m is 2, R_3 and R_3 are connected together to form a 5-6 membered ring;

R' is selected from the group consisting of F, Cl, Br, I, OH, CN, NH_2, COOH, Me, Et, CF_3, CHF_2, CH_2F, $NHCH_3$ and $N(CH_3)_2$;

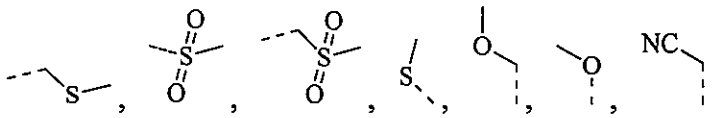
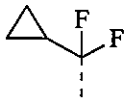
"hetero" represents a heteroatom or a heteroatom group, which is selected from the group consisting of -C(=O)N(R)-, -N(R)-, $-S(=O)_2N(R)-$, -S(=O)N(R)-, -O-, -S-, =O, =S, -O-N=, -C(=O)O-, -C(=O)-, -C(=S)-, -S(=O)-, $-S(=O)_2-$ and -N(R)C(=O)N(R)-;

in any of the above cases, the number of the heteroatom or the heteroatom group is independently selected from 1, 2 and 3.

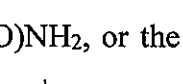
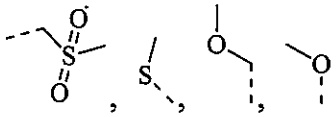
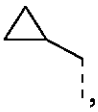
3. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 2, wherein, R is selected from H, F, Cl, Br, I, OH, CN, NH_2, COOH, or the group consisting of C_{1-5} alkyl, C_{1-5} heteroalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, each of which is optionally substituted with 1, 2, or 3 R'.

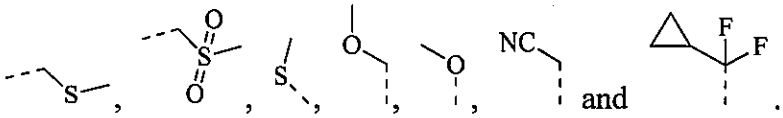
4. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 3, wherein, R is selected from H, F, Cl, Br, I, OH, CN, NH_2, COOH, $C(=O)NH_2$, or the group consisting of CH_3, CH_3CH_2, $S(=O)CH_3$,  ,  ,  ,  ,  and  , each of which is optionally substituted with 1, 2, or 3 R'.

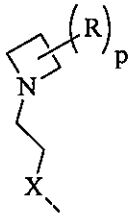
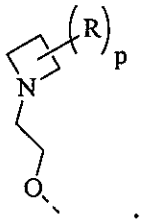
5. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 4, wherein, R is selected from the group consisting of H, F,

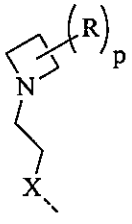
Cl, Br, I, OH, CN, NH_2, COOH, C(=O)NH_2, CH_3, CH_2Cl, CH_2F, CHF_2, CF_3, OCF_3, CH_2OH, Et, S(=O)CH_3,  , and  .

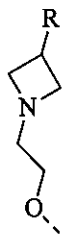
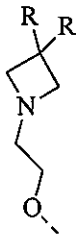
6. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 1, wherein, R is selected from H, F, Cl, Br, I, OH, CN, NH_2, COOH, or the group consisting of C_{1-5} alkyl, C_{1-5} heteroalkyl and C_{3-6} cycloalkyl-C_{1-3} alkyl-, each of which is optionally substituted with 1, 2, or 3 R'.

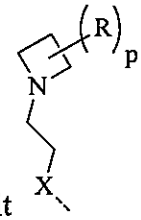
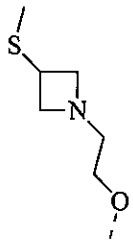
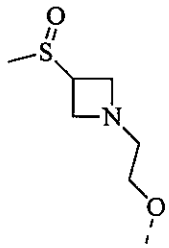
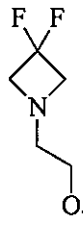
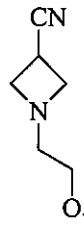
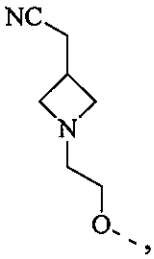
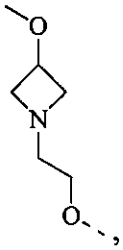
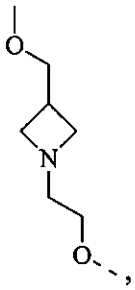
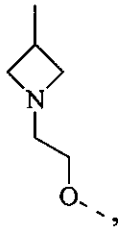
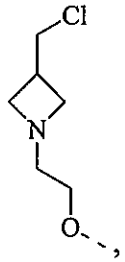
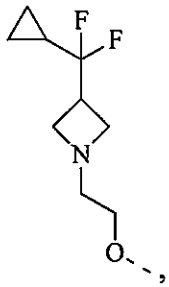
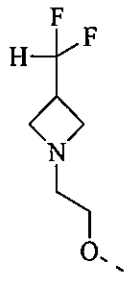
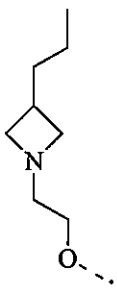
7. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 6, wherein, R is selected from H, F, Cl, Br, I, OH, CN, NH_2, COOH, C(=O)NH_2, or the group consisting of CH_3, CH_3CH_2, S(=O)CH_3,  ,  , and  , each of which is optionally substituted with 1, 2, or 3 R'.

8. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 7, wherein, R is selected from the group consisting of H, F, Cl, Br, I, OH, CN, NH_2, COOH, C(=O)NH_2, CH_3, CH_2Cl, CH_2F, CHF_2, CF_3, OCF_3, CH_2OH, Et, S(=O)CH_3,  .

9. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in any one of claim 1 and claims 6-8, wherein, the structural unit  is selected from  .

10. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 9, wherein, the structural unit  is selected from

 and  .

11. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 10, wherein, the structural unit  is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and 

12. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in any one of claims 1-8, wherein, R_2 is selected from H, F, Cl, Br, I, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, NH(C_{1-4} alkyl), *N*,*N*-di(C_{1-3} alkyl)amino and C_{3-6} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R, and/or,

R_3 is selected from H, F, Cl, Br, I, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, NH(C_{1-4} alkyl), *N*,*N*-di(C_{1-3} alkyl)amino, C_{3-6} cycloalkyl, 3-6 membered heterocycloalkyl, 5-6 membered aryl and 5-6 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 R, and/or,

R_4 and R_5 are each independently selected from H, F, Cl, Br, I, CN, NO_2, OH, COOH, NH_2, or the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, NH(C_{1-4} alkyl), *N*,*N*-di(C_{1-3} alkyl)amino and C_{3-6} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R, and/or,

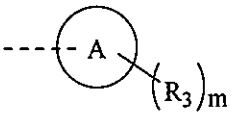
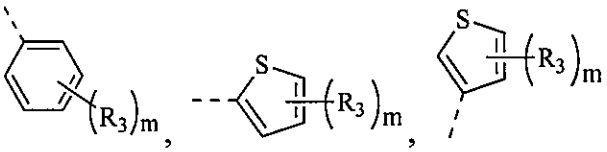
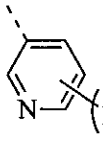
ring A is selected from the group consisting of phenyl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thienyl, benzofuranyl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, purinyl, quinolinyl and isoquinolinyl, and/or,

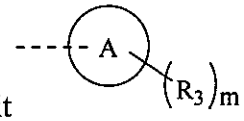
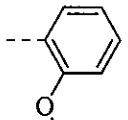
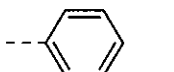
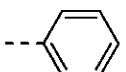
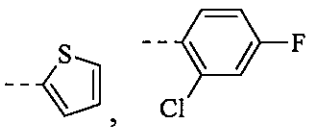
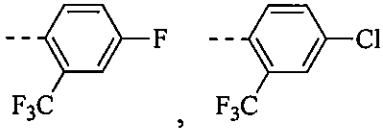
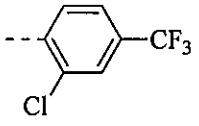
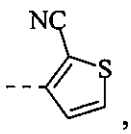
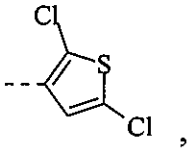
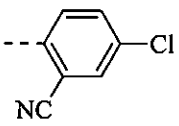
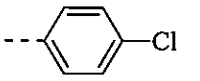
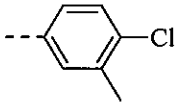
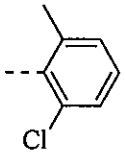
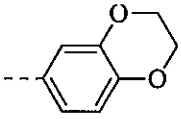
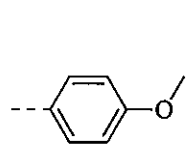
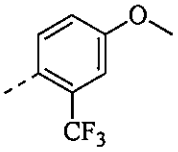
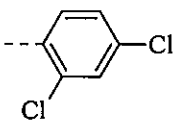
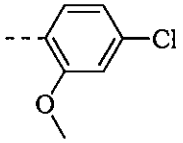
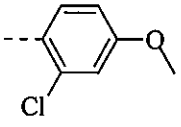
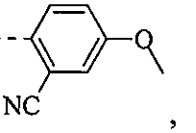
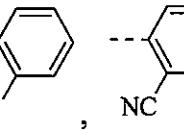
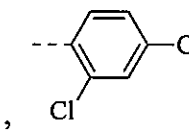
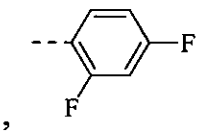
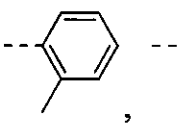
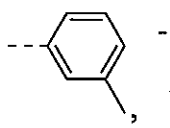
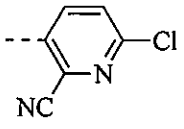
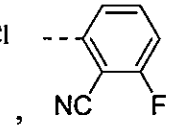
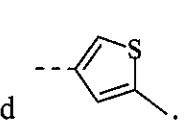
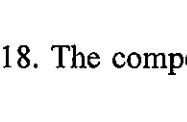
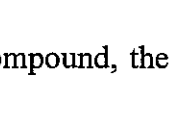
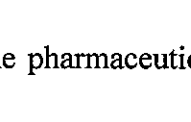
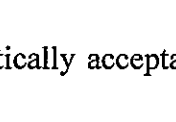
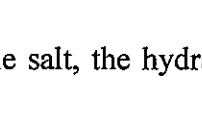
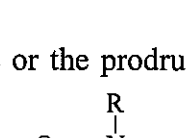
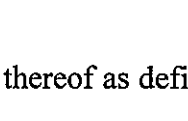
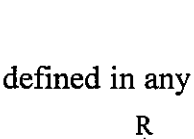
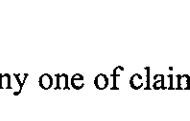
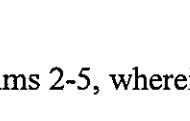
R_6 is selected from and  .

13. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 12, wherein, R_3 is selected from H, F, Cl, Br, I, CN, NO_2, OH, COOH, NH_2, or the group consisting of CH_3, CH_3CH_2, CH_3O, CH_3CH_2O and  , each of which is optionally substituted with 1, 2, or 3 R.

14. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 13, wherein, R_3 is selected from the group consisting of H, F, Cl, CN, CH_3, CF_3 and  .

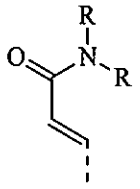
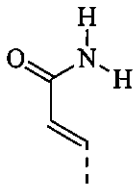
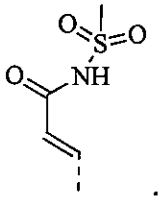
15. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 12, wherein, R_4 and R_5 are each independently selected from the group consisting of H, F, Cl, Br, CN and CH_3.

16. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 12, wherein, the structural unit  is selected from the group consisting of  ,  and .

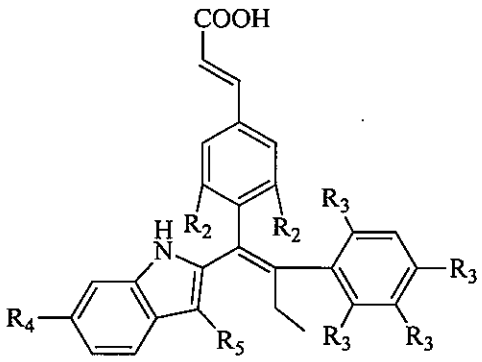
17. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in claim 16, wherein, the structural unit  is selected from the group consisting of ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and .

18. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in any one of claims 2-5, wherein, the structural unit is selected from .

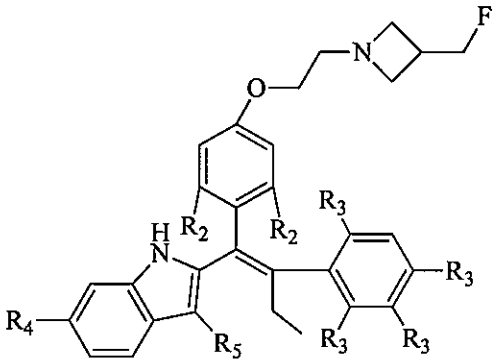
19. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug

thereof as defined in claim 18, wherein, the structural unit  is selected from  and  .

20. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in any one of claim 1 and claims 6-17, wherein, the compound is selected from the group consisting of



(II),



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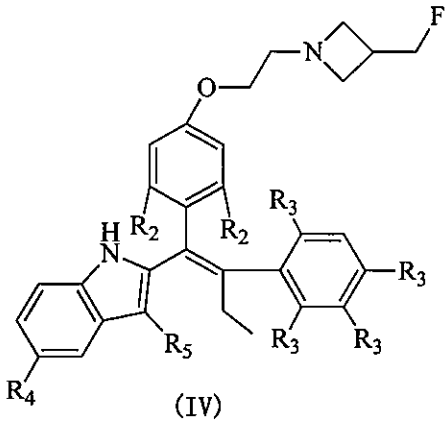
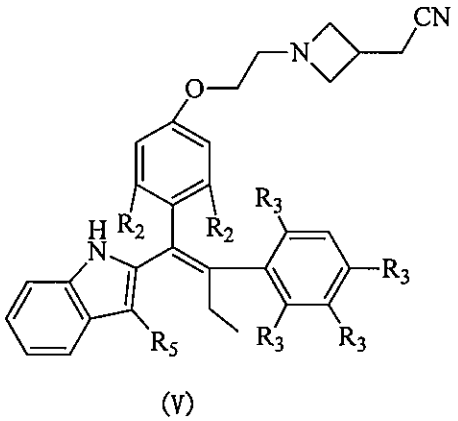


(IV),



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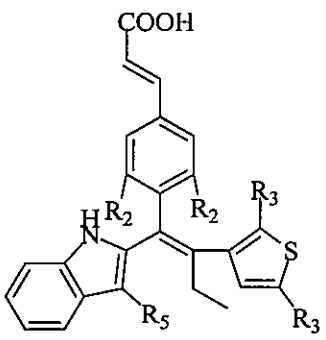
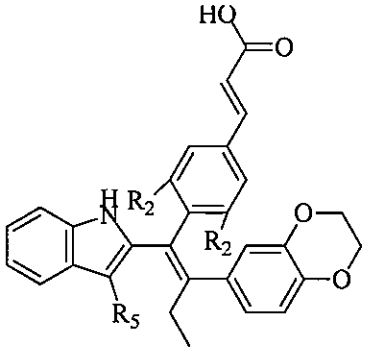


(VI)

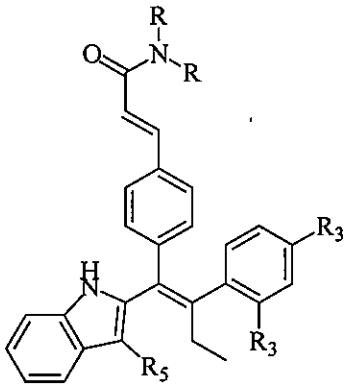
and



(VII) ,

wherein, R_2, R_3, R_4 and R_5 are defined as any one of claim 1 and claims 6-17.

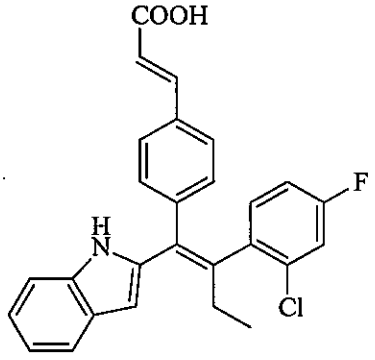
21. The compound, the pharmaceutically acceptable salt, the hydrate or the prodrug thereof as defined in any one of claims 2-5 and claims 12-19, wherein, the compound is selected from



(VIII)

wherein, R_3, R_5 and R are defined as any one of claims 2-5 and claims 12-19.

22. A compound or a pharmaceutically acceptable salt thereof, wherein, the compound is selected from the group consisting of



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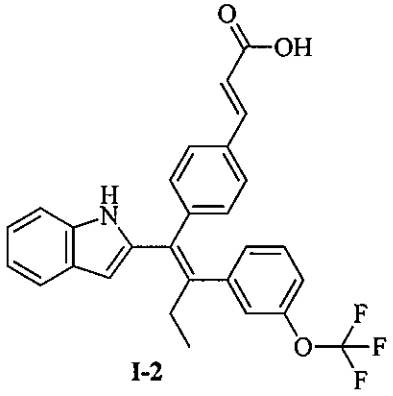

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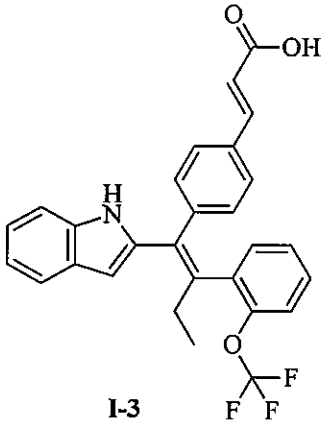

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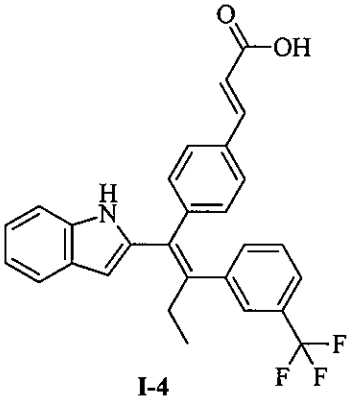

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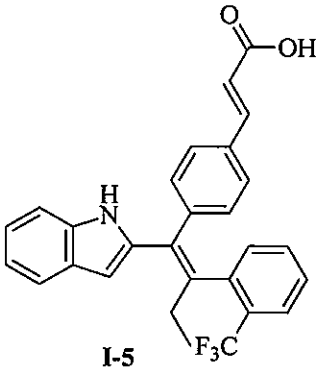

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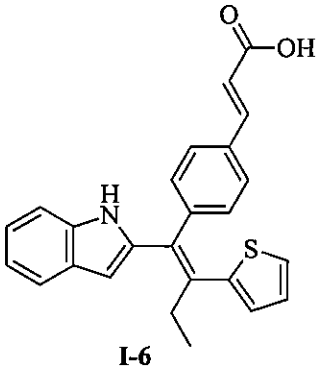

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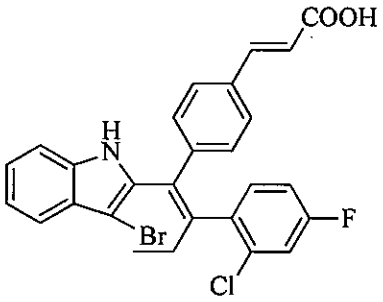

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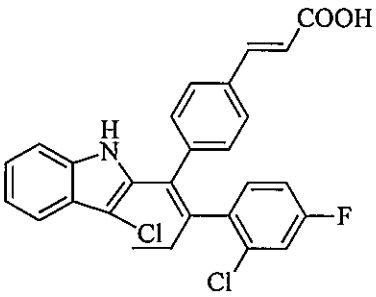

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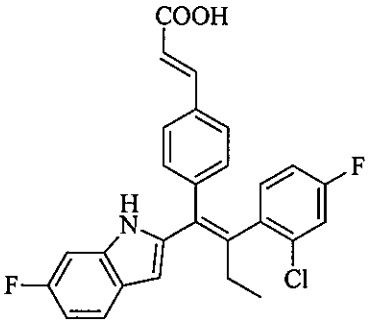

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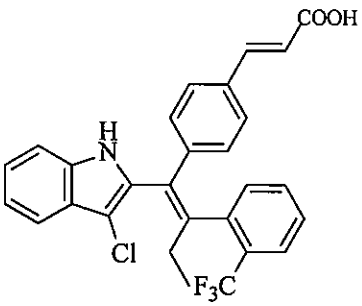

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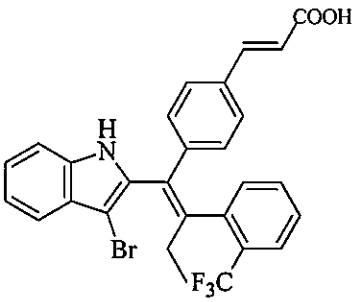

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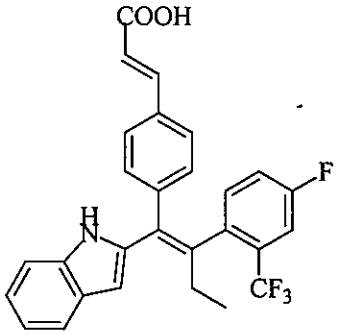

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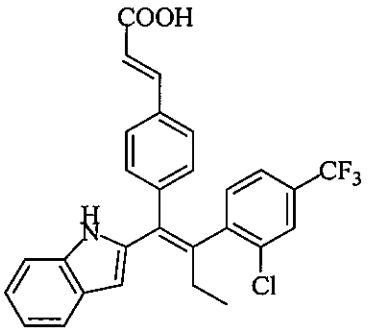

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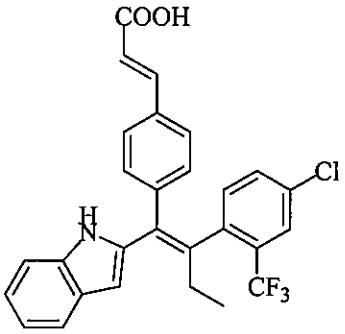

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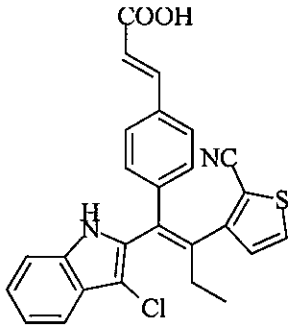

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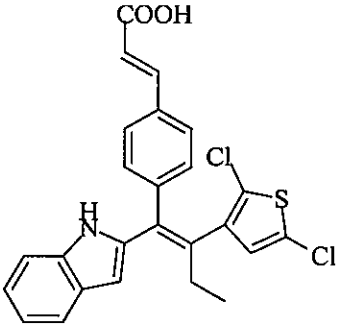

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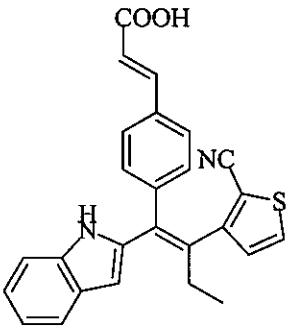

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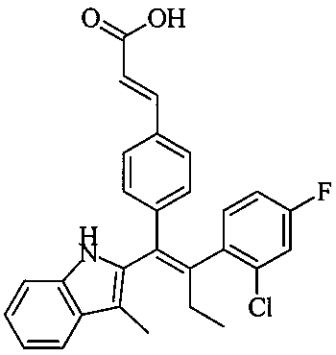

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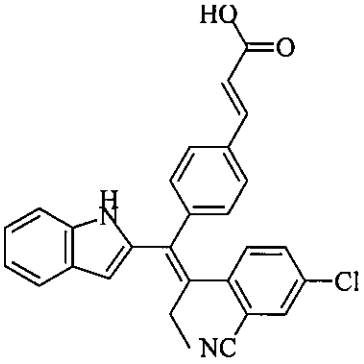

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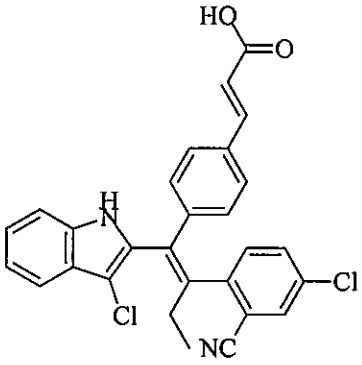

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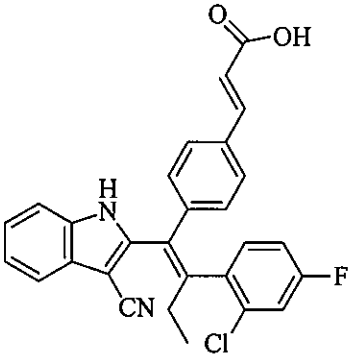

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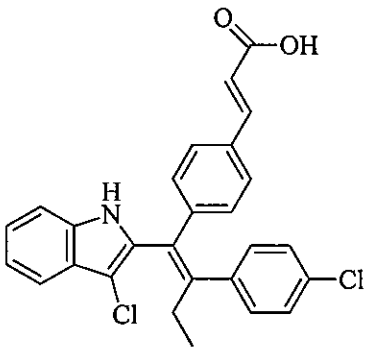

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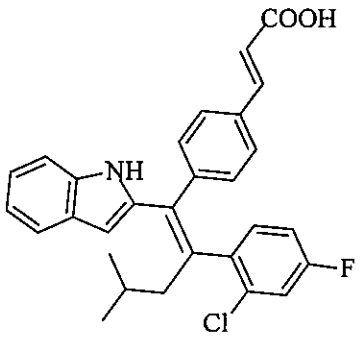

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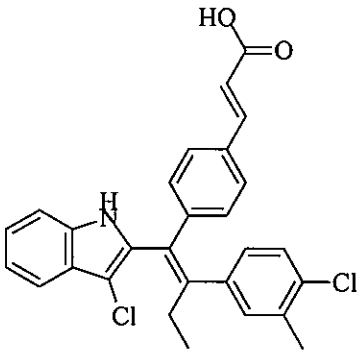

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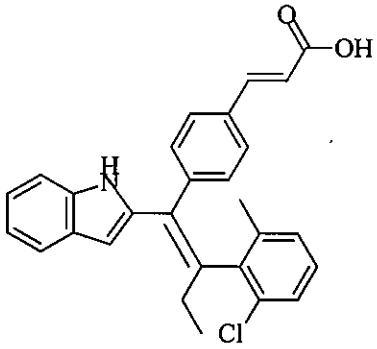

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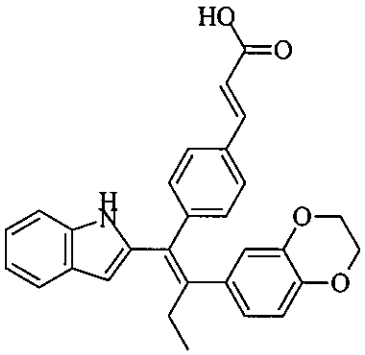

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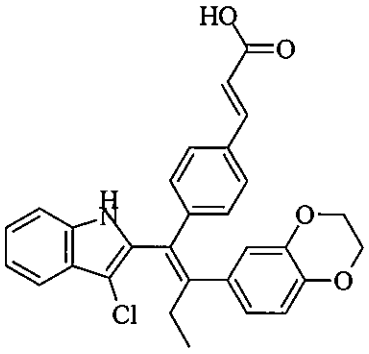

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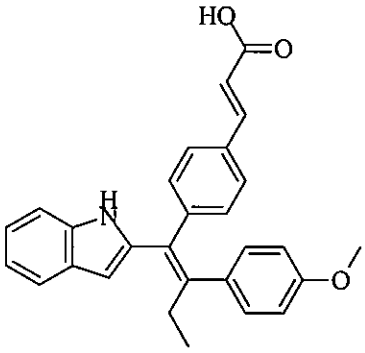

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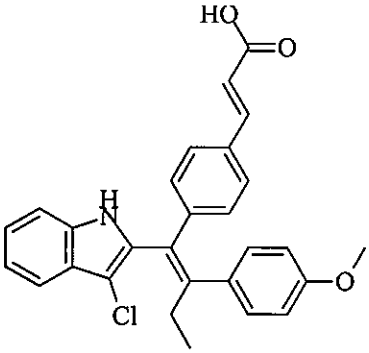

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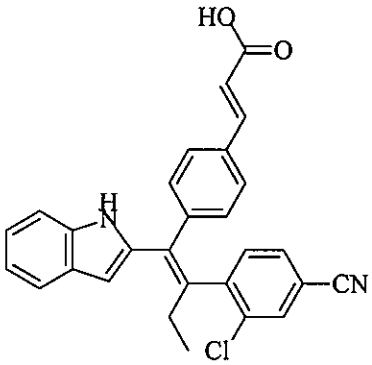

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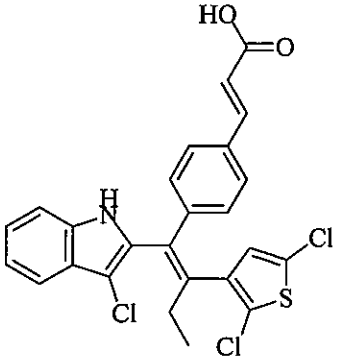

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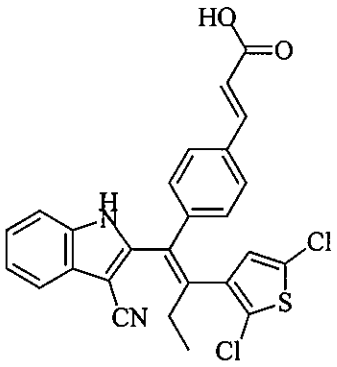

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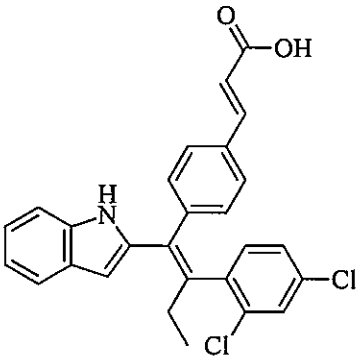

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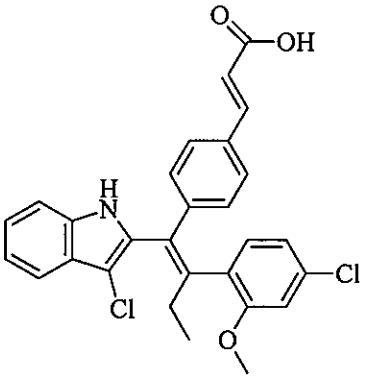

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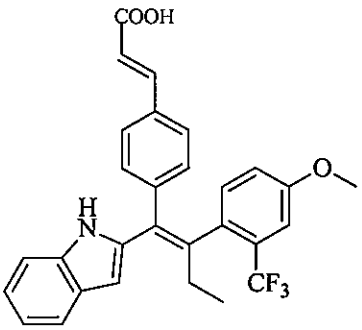

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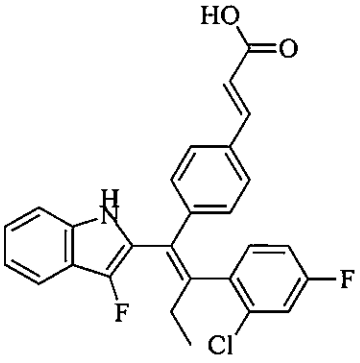

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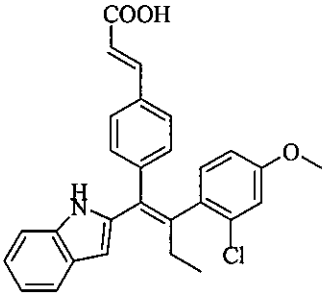

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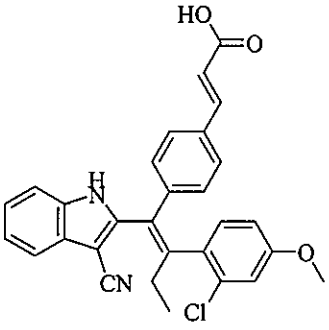

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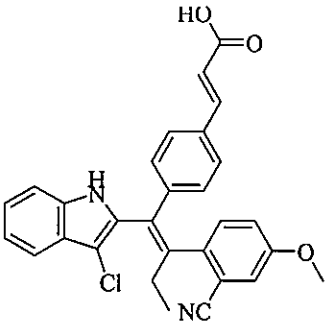

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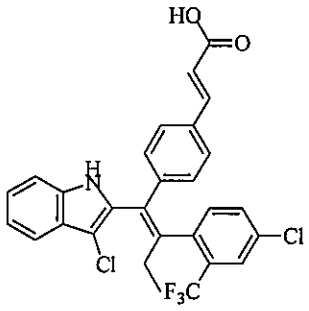

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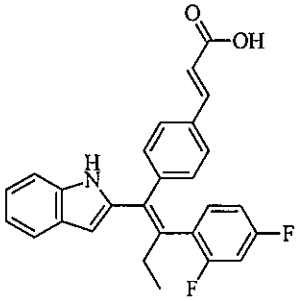

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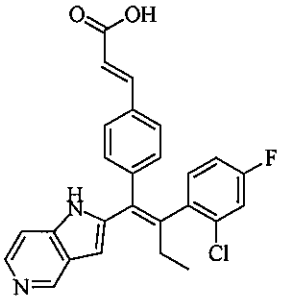

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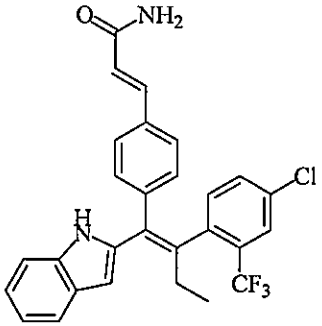

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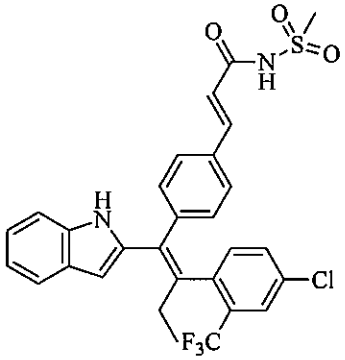

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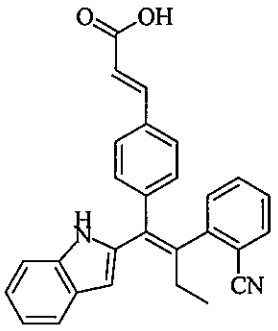

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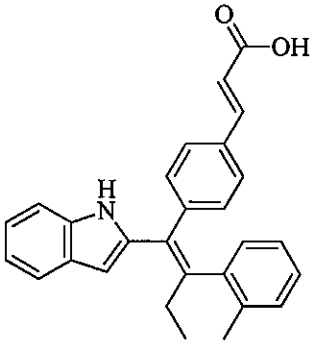

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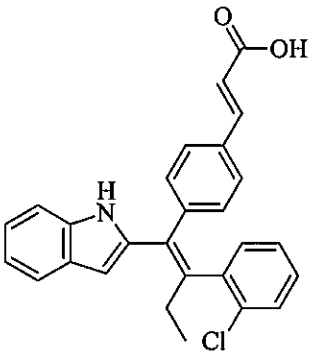

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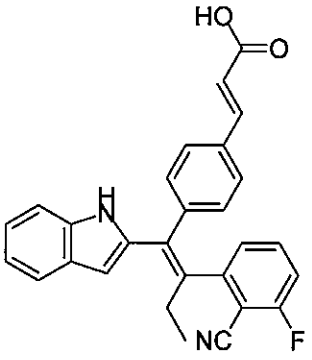

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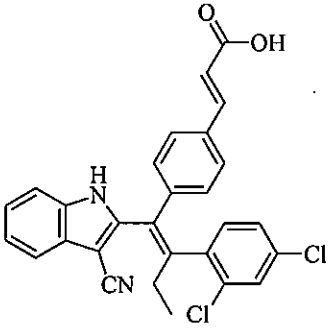

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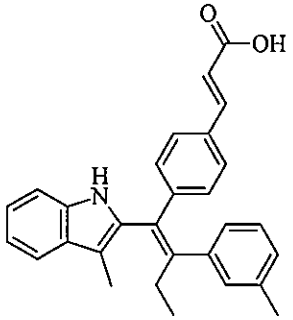

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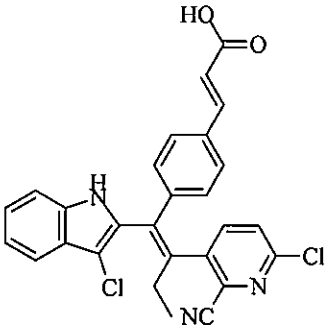

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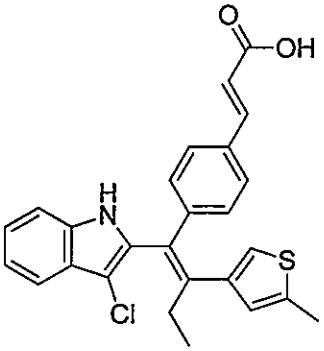

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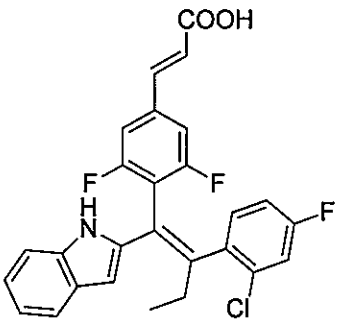

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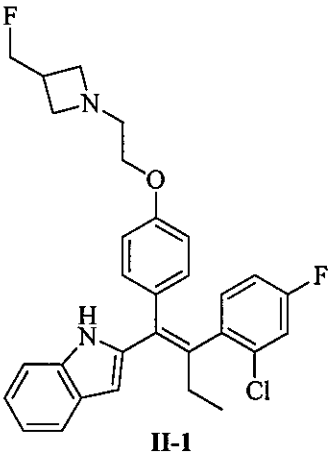

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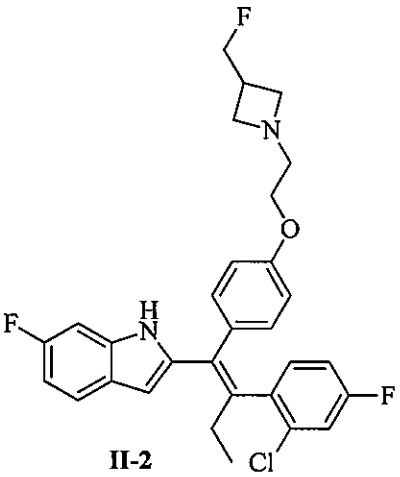

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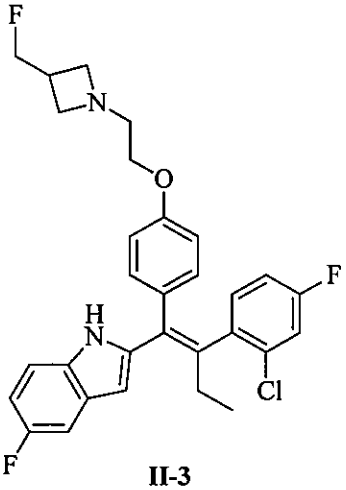

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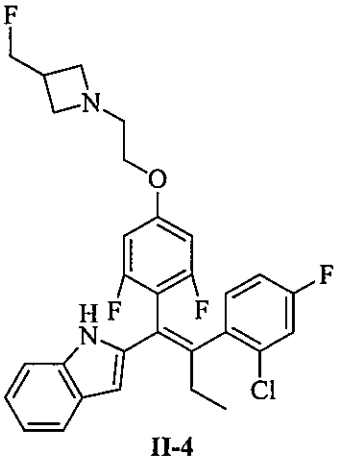

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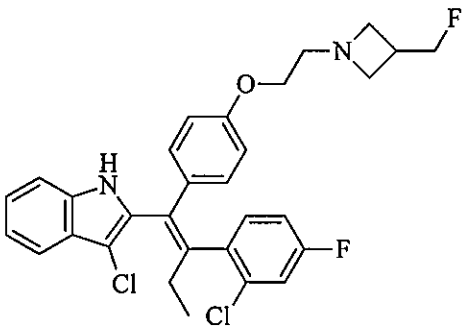

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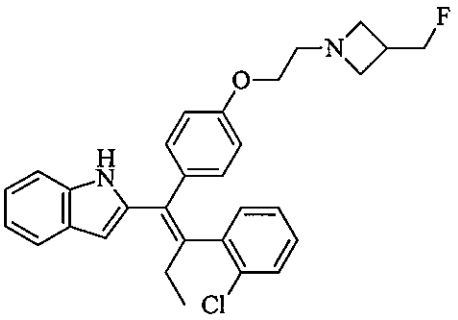

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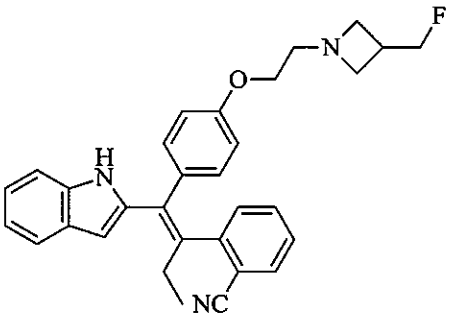

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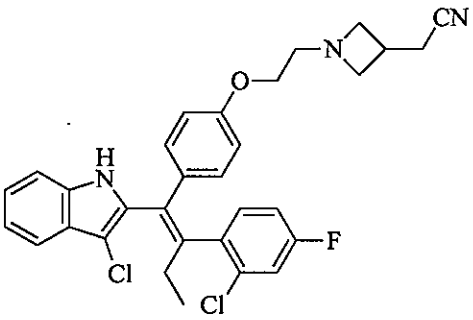

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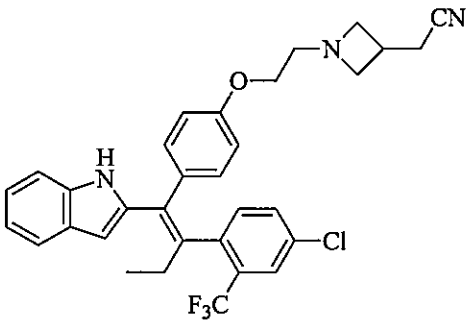

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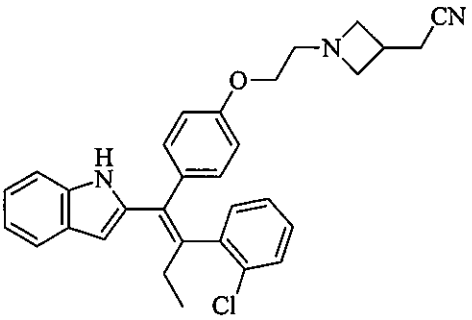

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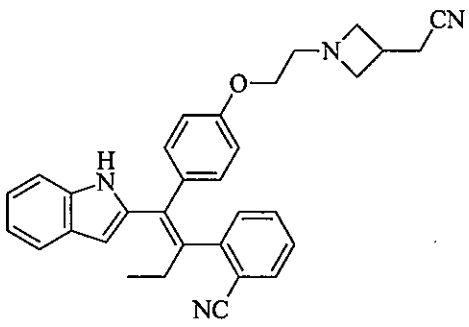

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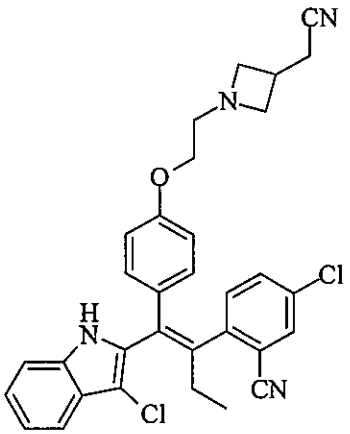

II-12

23. A pharmaceutical composition comprising a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof as defined in any one of

claims 1-22 and a pharmaceutically acceptable carrier.

24. A use of the compound or the pharmaceutically acceptable salt thereof as defined in any one of claims 1-22 or the pharmaceutical composition as defined in claim 23 in preparing a medicament for treating a disorder associated with estrogen receptor.