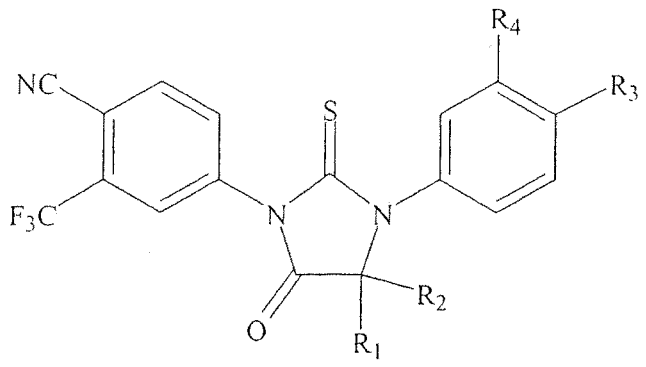
WE CLAIM:

1. A compound having the formula



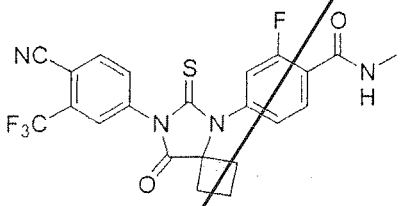
wherein R_1 and R_2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

wherein R_3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, alkylcarbamoylalkyl, cyano, and cyanoalkyl, and

wherein R_4 is hydrogen or fluorine.

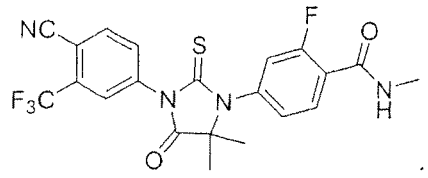
2. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

3. The compound of claim 1, having the formula



[NC'53]

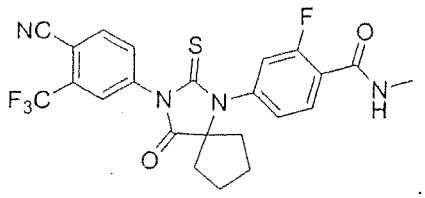
4. The compound of claim 1, having the formula



[NC54]

5. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 4 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

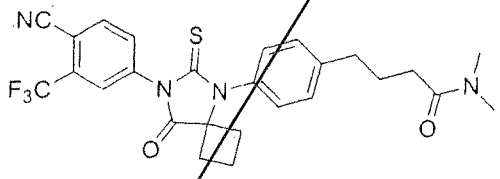
6. The compound of claim 1, having the formula



[NC55]

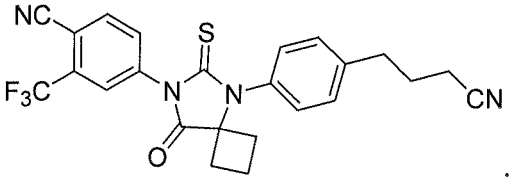
7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 6 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

8. The compound of claim 1, having the formula



[NC56]

9. The compound of claim 1, having the formula



[NC57]

10. A method for treating a hyperproliferative disorder comprising administering a pharmaceutical composition of claim 2 to a subject in need of such treatment, thereby treating the hyperproliferative disorder.

11. The method of claim 10, wherein the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release pill.

12. The method of claim 10, wherein the compound is administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally.

13. The method of claim 10, wherein the composition is administered at a dosage of the compound in the range of from about 0.001 mg per kg body weight per day to about 100 mg per kg body weight per day.

14. The method of claim 10, wherein the composition is administered at a dosage of the compound in the range of from about 0.01 mg per kg body weight per day to about 100 mg per kg body weight per day.

15. The method of claim 10, wherein the composition is administered at a dosage of the compound in the range of from about 0.1 mg per kg body weight per day to about 10 mg per kg body weight per day.

16. The method of claim 10, wherein the composition is administered at a dosage of the compound of about 1 mg per kg body weight per day.

17. A method for treating prostate cancer comprising administering a composition according to claim 2 to a subject in need of such treatment, thereby treating the prostate cancer.

18. The method of claim 10, wherein the pharmaceutical composition interferes with the transcription of prostate specific antigen mRNA.

19. The method of claim 10, wherein the pharmaceutical composition prevents nuclear translocation of an androgen receptor protein.

20. The method of claim 10, wherein the pharmaceutical composition destabilizes an androgen receptor protein.

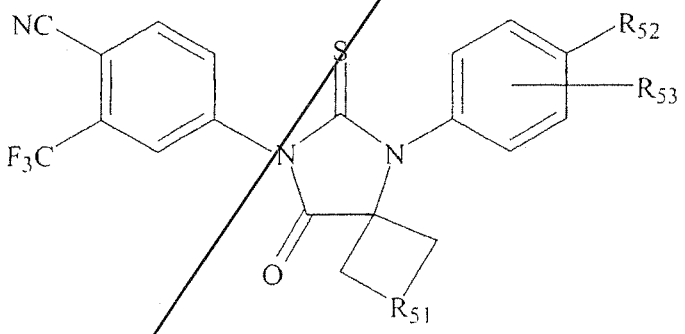
21. The method of claim 10, wherein the composition is administered orally.

22. The method of claim 10, wherein the composition has a form selected from the group consisting of a capsule, tablet, and pill.

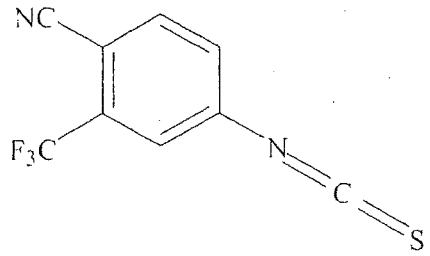
23. The method of claim 10, wherein the compound is selected from the group consisting of NC54, NC55, NC56, NC57, a pharmaceutically acceptable salt of any of these, and combinations thereof.

24. The method of claim 10, wherein the compound is NC53 or a pharmaceutically acceptable salt .

25. A method of synthesizing a diaryl compound of formula:

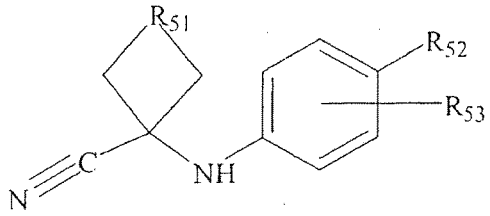


comprising mixing Compound I



Compound I

with Compound II

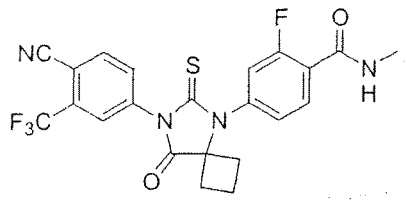


Compound II

in a first polar solvent to form a mixture,
heating the mixture,
adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture,
refluxing the mixture,
cooling the mixture and combining with water, and
separating the diaryl compound from the mixture,
wherein R51 comprises an alkyl chain of from 1 to 4 carbon atoms, R52 is selected from the group consisting of cyano, hydroxy, methylcarbamoyl, methylcarbamoyl-substituted alkyl, methylsulfonecarbamoyl-substituted alkyl, methylaminomethyl, dimethylaminomethyl, methylsulfonyloxymethyl, methoxycarbonyl, 3-cyano-4-trifluoromethylphenylcarbamoyl, carbamoyl-substituted alkyl, carboxymethyl, methoxycarbonylmethyl, methanesulfonyl, 4-cyano-3-trifluoromethylphenylcarbamoyl-substituted alkyl, carboxy-substituted alkyl, 4-methanesulfonyl-1-piperazinyl, piperazinyl, hydroxyethylcarbamoyl-substituted alkyl, and hydroxyethoxycarbonyl-substituted alkyl, and R53 is selected from the group consisting of F and H.

26. The method of claim 25, wherein R51 comprises an alkyl chain of from 1 to 2 carbon atoms, R52 is selected from the group consisting of carbamoyl and methylcarbamoyl, and R53 is F.

27. A method of synthesizing a compound of formula:



[NC53]

comprising

mixing 4-isothiocyanato-2-trifluoromethylbenzonitrile and *N*-methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide in dimethylformamide to form a first mixture,

heating the first mixture to form a second mixture,

adding alcohol and acid to the second mixture to form a third mixture,

refluxing the third mixture to form a fourth mixture,

cooling the fourth mixture,

combining the fourth mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

28. A method of synthesizing the compound of claim 4 [NC54], comprising

mixing *N*-methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide and 4-isothiocyanato-2-trifluoromethylbenzonitrile in DMF and heating to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

cooling the second mixture,

combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

29. A method of synthesizing the compound of claim 6 [NC55], comprising

mixing *N*-methyl-2-fluoro-4-(1-cyanocyclopentyl)aminobenzamide, 4-isothiocyanato-2-

trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

cooling the second mixture;

combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

30. A method of synthesizing the compound of claim 8 [NC56], comprising

mixing *N*,*N*-dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide, 4-isothiocyanato-2-trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

cooling the second mixture;

combining the second mixture with water and extracting an organic layer;

isolating the compound from the organic layer.

31. A method of synthesizing the compound of claim 9 [NC57], comprising

mixing DMSO, dichloromethane, and oxalyl chloride to form a first mixture,

adding 4-(4-(7-(4-cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide to the first mixture to form a second mixture;

adding triethylamine to the second mixture to form a third mixture;

warming the third mixture and quenching with aqueous NH_4Cl to form a fourth mixture;

extracting an organic layer from the fourth mixture;

isolating the compound from the organic layer.

32. A method comprising:

providing at least one diarylthiohydantoin compound;

measuring inhibition of androgen receptor activity for the compound and determining if the inhibition is above a first predetermined level,

measuring stimulation of androgen receptor activity in hormone refractory cancer cells for the compound and determining if the stimulation is below a second predetermined level,

selecting the compound if the inhibition is above the first predetermined level and the stimulation is below the second predetermined level.

33. The method of claim 32, wherein the predetermined levels are those of bicalutamide.

34. The method of claim 32, wherein the step of measuring inhibition comprises measuring inhibitory concentration (IC50) in an AR response reporter system or a prostate specific antigen secreting system.

35. The method of claim 32, wherein the step of measuring stimulation comprises measuring fold induction by increasing concentrations in an AR response reporter system or a prostate specific antigen secreting system.

36. The method of claim 32, wherein the steps of measuring inhibition and/or stimulation comprise measuring an effect of the compound on tumor growth in an animal.

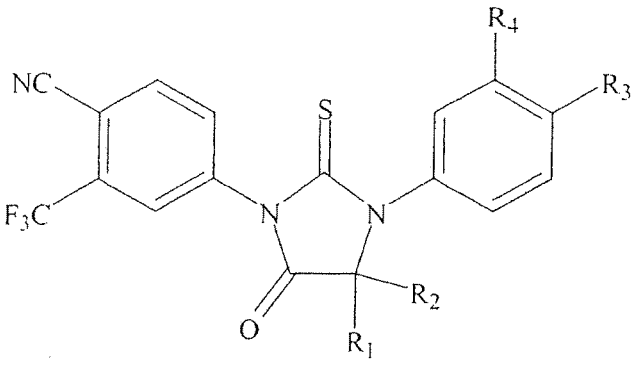
37. The method of claim 32, wherein the step of measuring inhibition and/or stimulation of androgen receptor activity comprises measuring the binding affinity of an androgen receptor to the compound.

38. The method of claim 32, wherein the step of measuring inhibition and/or stimulation of androgen receptor activity comprises measuring prevention of androgen receptor recruitment to at least one of prostate specific antigen enhancer and prostate specific antigen promoter.

39. The method of claim 32, wherein the step of measuring inhibition and/or stimulation of androgen receptor activity comprises measuring prevention of androgen receptor nuclear translocation.

40. The method of claim 32, wherein the step of measuring inhibition and/or stimulation of androgen receptor activity comprises measuring destabilization of an androgen receptor protein.

41. The method of claim 32, wherein the diarylthiohydantoin compound has the formula



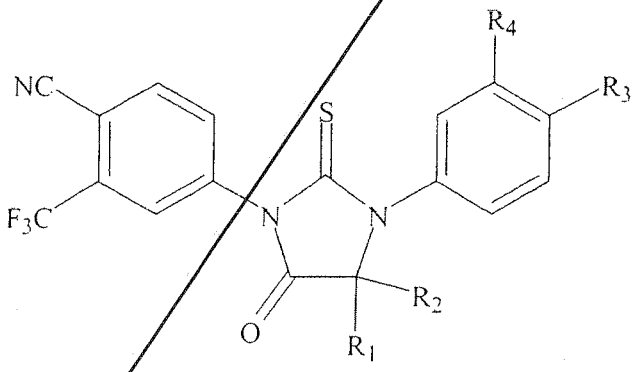
wherein R_1 and R_2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

wherein R_3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, alkylcarbamoylalkyl, cyano, and cyanoalkyl, and

wherein R_4 is hydrogen or fluorine.

42. A method comprising contacting a mammalian cell capable of expressing prostate specific antigen with a sufficient amount of a diarylthiohydantoin compound to interfere with the transcription of prostate specific antigen mRNA.

43. The method of claim 42, wherein the diarylthiohydantoin compound has the formula



wherein R_1 and R_2 are independently methyl or, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms.

wherein R_3 is selected from the group consisting of carbamoyl, alkylcarbamoyl, carbamoylalkyl, alkylcarbamoylalkyl, cyano, and cyanoalkyl, and

wherein R_4 is hydrogen or fluorine.

44. The method of claim 42, wherein the diarylthiohydantoin compound is selected from the group consisting of NC53, NC54, NC55, NC56, and NC57.

45. The method of claim 42, wherein the compound prevents formation of a transcription complex on a prostate specific antigen gene.

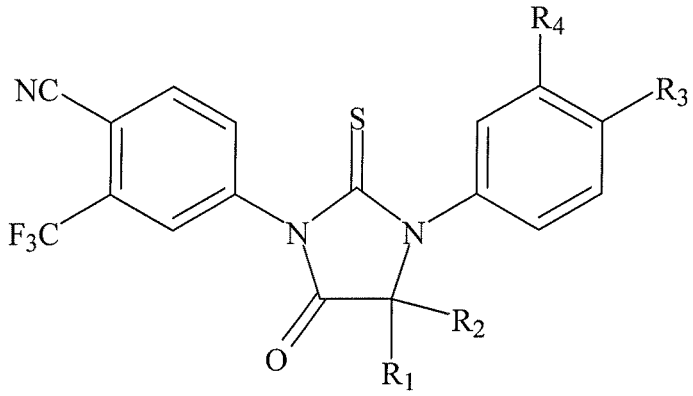
46. The method of claim 42, wherein the compound prevents an androgen receptor protein from complexing with a prostate specific antigen gene.

47. The method of claim 42, wherein the compound prevents an RNA polymerase II from complexing with a prostate specific antigen gene.

48. A method, comprising contacting a mammalian cell with a sufficient amount of a diarylthiohydantoin compound to prevent nuclear translocation of an androgen receptor protein and/or to destabilize an androgen receptor protein.

WE CLAIM:

1. A compound having the formula

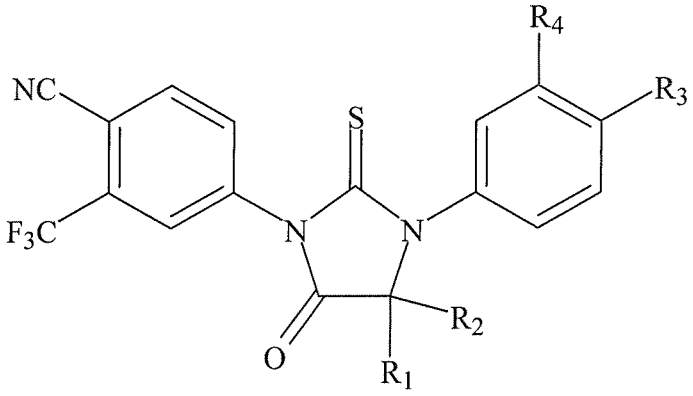


wherein R_1 and R_2 are, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

wherein R_3 is selected from the group consisting of dimethylcarbamoylalkyl and cyanoalkyl, and

wherein R_4 is hydrogen or fluorine.

2. The compound of claim 1, having the formula

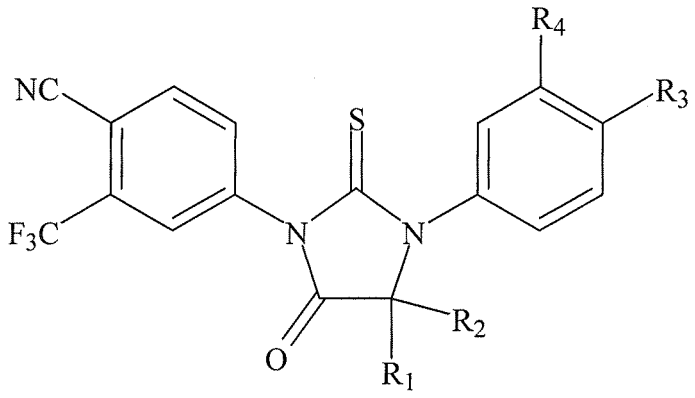


wherein R_1 and R_2 are, together with the carbon to which they are linked, cycloalkyl of 4 to 5 carbon atoms,

wherein R_3 is selected from the group consisting of dimethylbutanamide and cyanopropyl, and

wherein R_4 is hydrogen or fluorine.

3. The compound of claim 1, having the formula



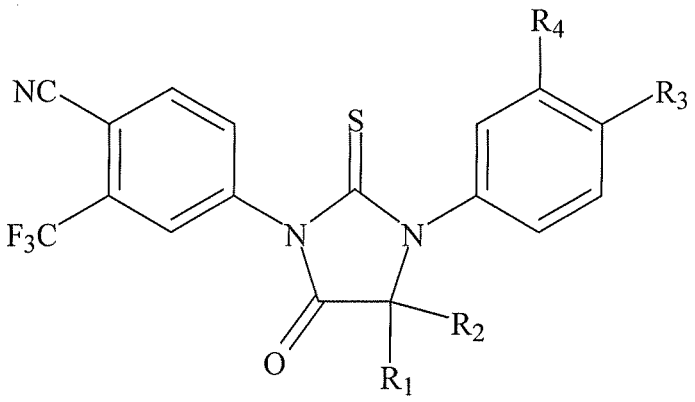
,

wherein R_1 and R_2 are, together with the carbon to which they are linked, cycloalkyl of 4 carbon atoms,

wherein R_3 is selected from the group consisting of dimethylcarbamoylalkyl and cyanoalkyl, and

wherein R_4 is hydrogen.

4. The compound of claim 1, having the formula



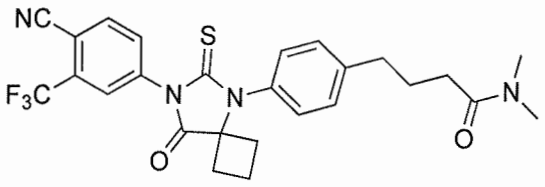
,

wherein R_1 and R_2 are, together with the carbon to which they are linked, cycloalkyl of 4 carbon atoms,

wherein R_3 is selected from the group consisting of dimethylbutanamide and cyanopropyl, and

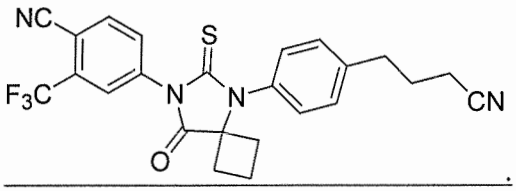
wherein R_4 is hydrogen.

5. The compound of claim 1, having the formula



[NC56]

or



.

[NC57]

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

7. A pharmaceutical composition of claim 6 for use in a method for treating a hyperproliferative disorder or a method for treating prostate cancer.

8. The pharmaceutical composition of claim 7, wherein:

(a) the composition has a form selected from the group consisting of a solution, dispersion, suspension, powder, capsule, tablet, pill, time release capsule, time release tablet, and time release

pill; or

(b) the composition has a form selected from the group consisting of a capsule, tablet and pill; or

(c) the composition is administered by intravenous injection, by injection into tissue, intraperitoneally, orally, or nasally; or

(d) the composition is administered at a dosage of the compound in the range of from 0.001 mg per kg body weight per day to 100 mg per kg body weight per day; or

(e) the composition is administered at a dosage of the compound in the range of from 0.01 mg per kg body weight per day to 100 mg per kg body weight per day; or

(f) the composition is administered at a dosage of the compound in the range of from 0.1 mg per kg body weight per day to 10 mg per kg body weight per day; or

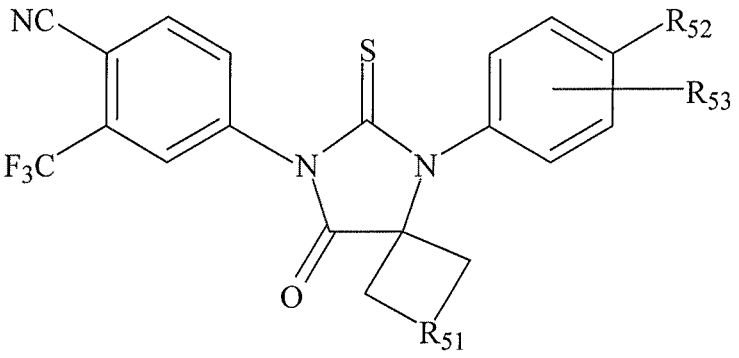
(g) the composition is administered at a dosage of the compound of 1 mg per kg body weight per day; or

(h) the composition interferes with the transcription of prostate specific antigen mRNA; or

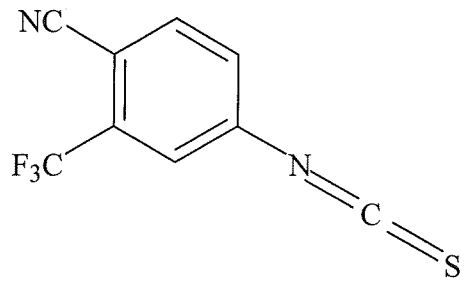
(i) the composition prevents nuclear translocation of an androgen receptor protein; or

(j) the composition destabilizes an androgen receptor protein.

9. A method of synthesizing a diaryl compound of formula:

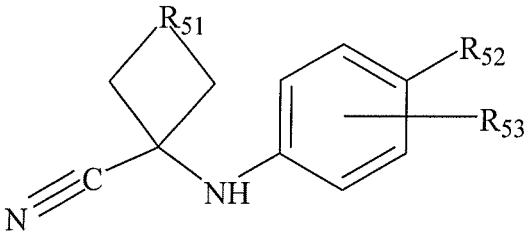


comprising mixing Compound I



Compound I

with Compound II



Compound II

in a first polar solvent to form a mixture,

heating the mixture,

adding a second polar solvent, the same as or different from the first polar solvent, and an aqueous acid to the mixture,

refluxing the mixture,

cooling the mixture and combining with water, and

separating the diaryl compound from the mixture,

wherein R51 comprises an alkyl chain of from 1 to 2 carbon atoms,

R52 is selected from the group consisting of cyanoalkyl and dimethylcarbamoyl-substituted alkyl, and

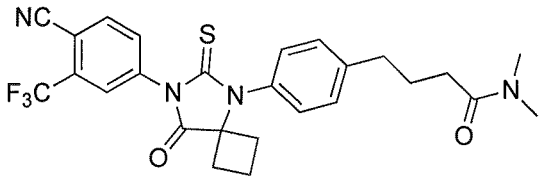
R53 is selected from the group consisting of F and H.

10. The method of claim 9, wherein R51 comprises an alkyl chain of from 1 to 2 carbon atoms, R52 is selected from the group consisting of cyanopropyl and dimethylbutanamide, and R53 is

selected from the group consisting of F and H.

11. A method of synthesizing:

the compound



[NC56],

comprising

mixing *N*,*N*-dimethyl 4-[4-(1-cyanocyclobutylamino)phenyl]butanamide, 4-isothiocyanato-2-trifluoromethyl benzonitrile, and DMF and heating under reflux to form a first mixture;

adding an alcohol and an acid to the first mixture to form a second mixture;

refluxing the second mixture;

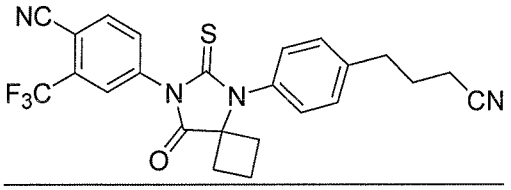
cooling the second mixture;

combining the second mixture with water and extracting an organic layer; and

isolating the compound from the organic layer.

12. A method of synthesizing

the compound



[NC57],

comprising

mixing DMSO, dichloromethane, and oxalyl chloride to form a first mixture,

adding 4-(4-(7-(4-cyano-3-(trifluoromethyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl)butanamide to the first mixture to form a second mixture;

adding triethylamine to the second mixture to form a third mixture;

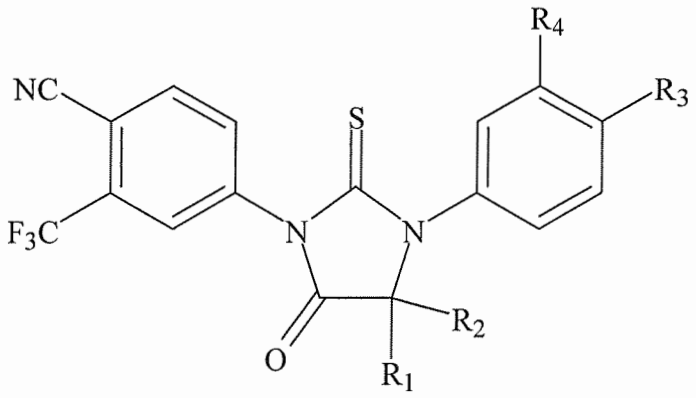
warming the third mixture and quenching with aqueous NH_4Cl to form a fourth mixture;

extracting an organic layer from the fourth mixture; and

isolating the compound from the organic layer.

13. An *in vitro* method comprising contacting a mammalian cell capable of expressing prostate specific antigen with a sufficient amount of a diarylthiohydantoin compound to interfere with the transcription of prostate specific antigen mRNA,

wherein the diarylthiohydantoin compound has the formula



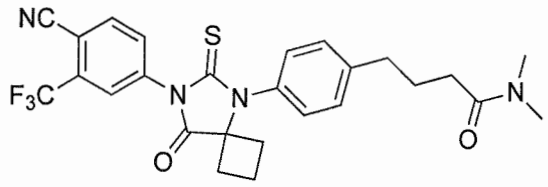
,

wherein R_1 and R_2 are, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

wherein R_3 is selected from the group consisting of dimethylcarbamoylalkyl and cyanoalkyl, and

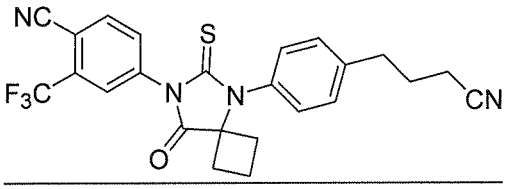
wherein R_4 is hydrogen or fluorine, or

wherein the diarylthiohydantoin compound is selected from the group consisting of the compounds



and

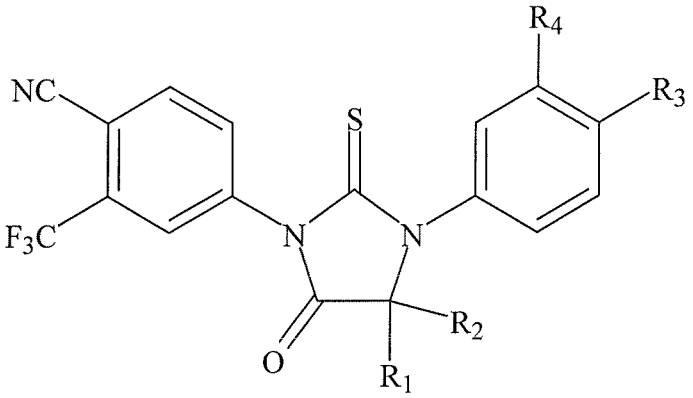
[NC56]



[NC57].

14. An *in vitro* method, comprising contacting a mammalian cell with a sufficient amount of a diarylthiohydantoin compound to prevent nuclear translocation of an androgen receptor protein and/or to destabilize an androgen receptor protein,

wherein the diarylthiohydantoin compound has the formula



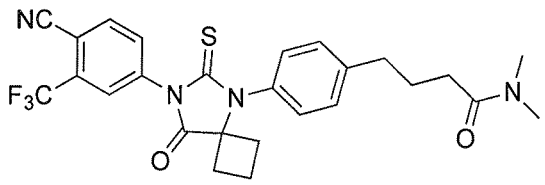
,

wherein R_1 and R_2 are, together with the carbon to which they are linked, a cycloalkyl group of 4 to 5 carbon atoms,

wherein R_3 is selected from the group consisting of dimethylcarbamoylalkyl and cyanoalkyl, and

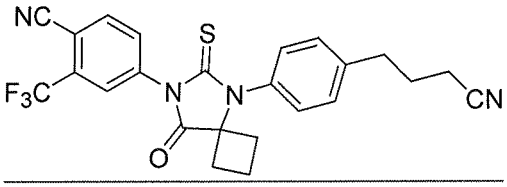
wherein R_4 is hydrogen or fluorine, or

wherein the diarylthiohydantoin compound is selected from the group consisting of the compounds



and

[NC56]



[NC57].