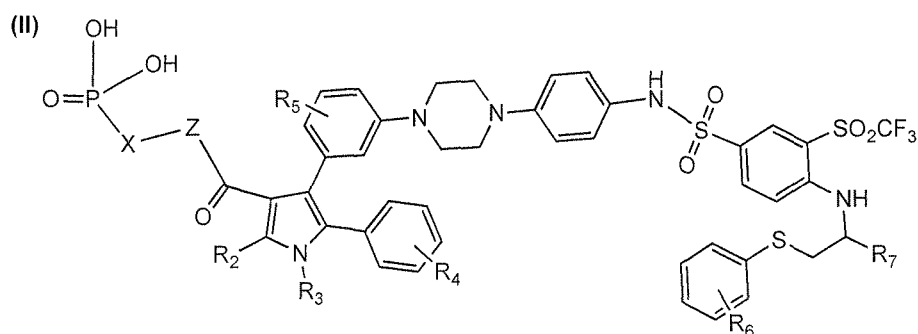
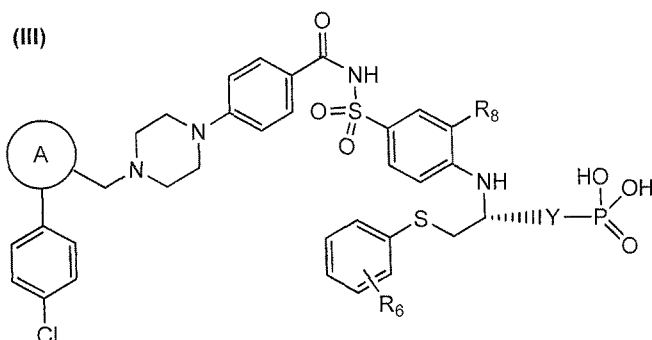
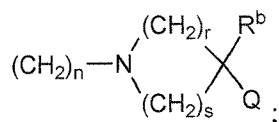


[0009] wherein the A ring is or ;

[0010] X, substituted or unsubstituted, is selected from the group consisting of alkylene, alkenylene, cycloalkylene, cycloalkenylene, and heterocycloalkylene;

[0011] Y is selected from the group consisting of $(\text{CH}_2)_n$, $\text{N}(\text{R}^a)_2$ and



[0012]

[0013] Q is selected from the group consisting of O, $\text{O}(\text{CH}_2)_{1-3}$, NR^c , $\text{NR}^c(\text{C}_{1-3}\text{alkylene})$, $\text{OC}(=\text{O})(\text{C}_{1-3}\text{alkylene})$, $\text{C}(=\text{O})\text{O}$, $\text{C}(=\text{O})\text{O}(\text{C}_{1-3}\text{alkylene})$, $\text{NHC}(=\text{O})(\text{C}_{1-3}\text{alkylene})$, $\text{C}(=\text{O})\text{NH}$, and $\text{C}(=\text{O})\text{NH}(\text{C}_{1-3}\text{alkylene})$;

[0014] Z is O or NR^c ;

[0015] R_1 and R_2 , independently, are selected from the group consisting of H, CN, NO_2 , halo, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR' , SR' , $\text{NR}'\text{R}''$, COR' , $\text{CO}_2\text{R}'$, OCOR' , $\text{CONR}'\text{R}''$, $\text{CONR}'\text{SO}_2\text{R}''$, $\text{NR}'\text{COR}''$, $\text{NR}'\text{CONR}''\text{R}'''$, $\text{NR}'\text{C}=\text{SNR}''\text{R}'''$, $\text{NR}'\text{SO}_2\text{R}''$, $\text{SO}_2\text{R}'$, and $\text{SO}_2\text{NR}'\text{R}''$;

[0016] R_3 is selected from a group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR' , $NR'R''$, $OCOR'$, CO_2R' , COR' , $CONR'R''$, $CONR'SO_2R''$, $C_{1-3}alkyleneCH(OH)CH_2OH$, SO_2R' , and $SO_2NR'R''$;

[0017] R' , R'' , and R''' , independently, are H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, $C_{1-3}alkyleneheterocycloalkyl$, or heterocycloalkyl;

[0018] R' and R'' , or R'' and R''' , can be taken together with the atom to which they are bound to form a 3 to 7 membered ring;

[0019] R_4 is hydrogen, halo, $C_{1-3}alkyl$, CF_3 , or CN ;

[0020] R_5 is hydrogen, halo, $C_{1-3}alkyl$, substituted $C_{1-3}alkyl$, hydroxyalkyl, alkoxy, or substituted alkoxy;

[0021] R_6 is selected from the group consisting of H, CN , NO_2 , halo, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR' , SR' , $NR'R''$, CO_2R' , $OCOR'$, $CONR'R''$, $CONR'SO_2R''$, $NR'COR''$, $NR'CONR''R'''$, $NR'C=SNR''R'''$, $NR'SO_2R''$, SO_2R' , and $SO_2NR'R''$;

[0022] R_7 , substituted or unsubstituted, is selected from the group consisting of hydrogen, alkyl, alkenyl, $(CH_2)_{0-3}cycloalkyl$, $(CH_2)_{0-3}cycloalkenyl$, $(CH_2)_{0-3}heterocycloalkyl$, $(CH_2)_{0-3}aryl$, and $(CH_2)_{0-3}heteroaryl$;

[0023] R_8 is selected from the group consisting of hydrogen, halo, NO_2 , CN , CF_3SO_2 , and CF_3 ;

[0024] R_a is selected from the group consisting of hydrogen, alkyl, heteroalkyl, alkenyl, hydroxyalkyl, alkoxy, substituted alkoxy, cycloalkyl, cycloalkenyl, and heterocycloalkyl;

[0025] R_b is hydrogen or alkyl;

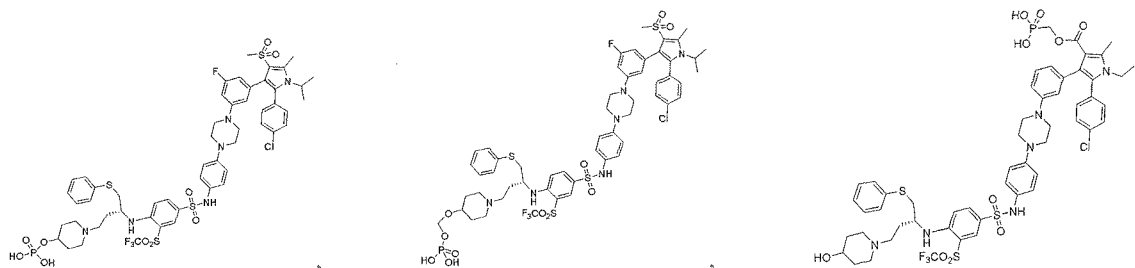
[0026] R_c is selected from the group consisting of hydrogen, alkyl, substituted alkyl, hydroxyalkyl, alkoxy, and substituted alkoxy; and

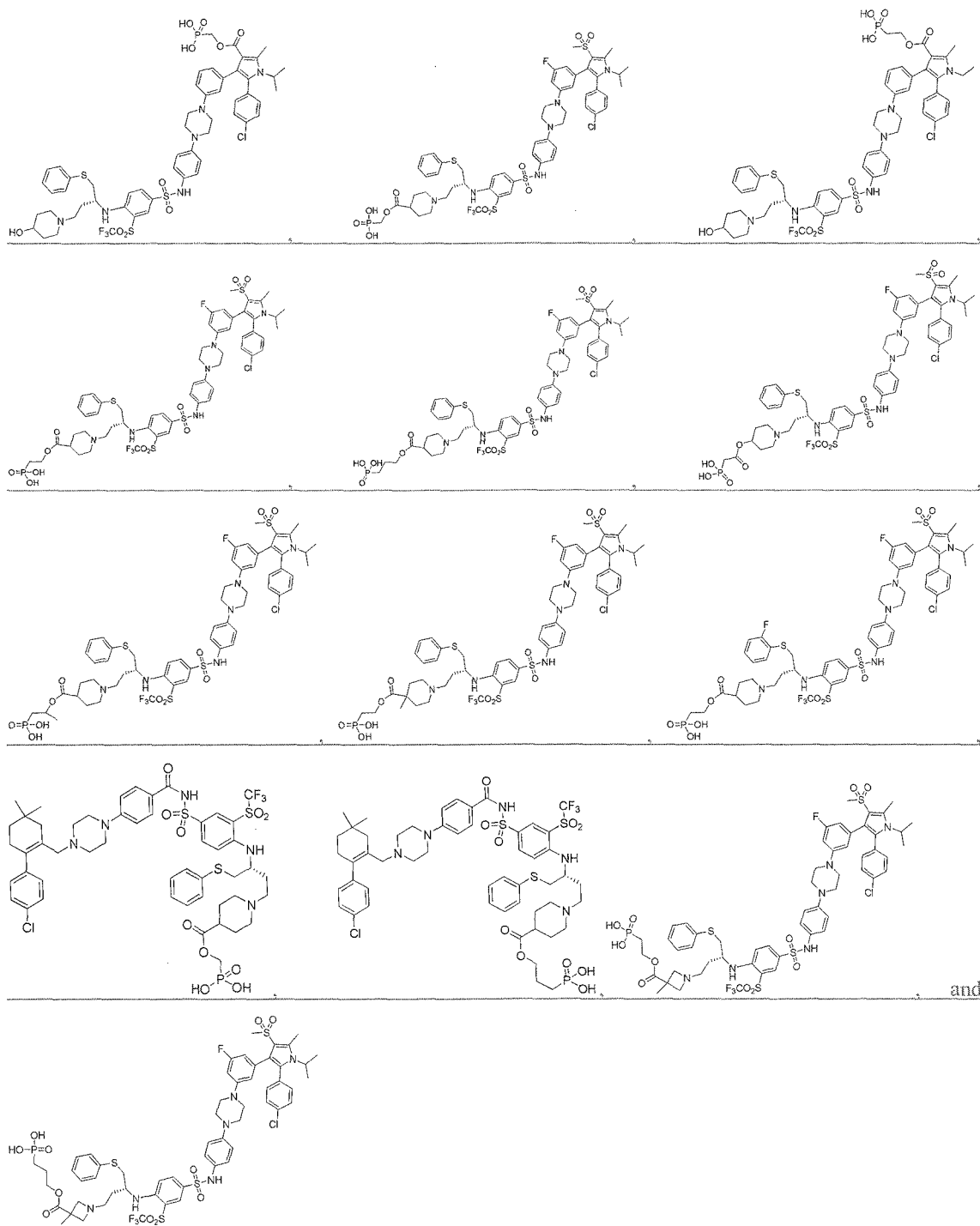
[0027] n , r , and s , independently, are 1, 2, 3, 4, 5, or 6;

[0028] or a pharmaceutically acceptable salt of (I), (II), or (III).

[0029] In some examples, R_1 and R_2 or R_2 and R_3 can be taken together to form a ring. In other embodiments, R' and R'' , or R'' and R''' , can be taken together with the atoms to which they are bound to form a 3 to 7 membered ring.

[0029a] In another aspect, the present invention provides a compound having a structure





[0029b] In another aspect, the present invention provides composition comprising (a) compound disclosed herein, (b) a second therapeutic agent useful in the treatment of a disease or condition wherein inhibition of Bcl-2 or Bcl-xL provides a benefit, and (c) an optional excipient and/or pharmaceutically acceptable carrier.

[0030] In one examples, the present disclosure provides a method of treating a condition or disease by administering a therapeutically effective amount of a compound of structural

formula (I), (II), or (III) to an individual in need thereof. The disease or condition of interest is treatable by inhibition of Bcl-2 and/or Bcl-xL, for example, a cancer.

[0031] Also disclosed is a composition comprising (a) a Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and (b) an excipient and/or pharmaceutically acceptable carrier useful in treating diseases or conditions wherein inhibition of Bcl-2/Bcl-xL provides a benefit.

[0032] Also disclosed is ~~In another aspect, the present invention provides~~ a composition comprising a compound of structural formula (I), (II), or (III) and a second therapeutically active agent in a method of treating an individual for a disease or condition wherein inhibition of Bcl-2/Bcl-xL provides a benefit.

[0032a] In another aspect, the present invention provides a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier or vehicle

[0032ab] Also disclosed is ~~In another aspect, there is provided~~ use of therapeutically effective amount of a compound as described herein to an individual in need thereof in the manufacture of a medicament for treating a disease or condition wherein inhibition of Bcl-2 or Bcl-xL provides a benefit.

[0032c] In another aspect, the present invention provides use of a therapeutically effective amount of a compound disclosed herein in the manufacture of a medicament for treating a cancer.

[0033] In a further example, the disclosure provides for use of a composition comprising a Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and an optional second therapeutic agent for the manufacture of a medicament for treating a disease or condition of interest, e.g., a cancer.

[0034] Also provided is a kit for human pharmaceutical use comprising (a) a container, (b1) a packaged composition comprising a Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III), and, optionally, (b2) a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and (c) a package insert containing directions for use of the composition or compositions, administered simultaneously or sequentially, in the treatment of the disease or condition.

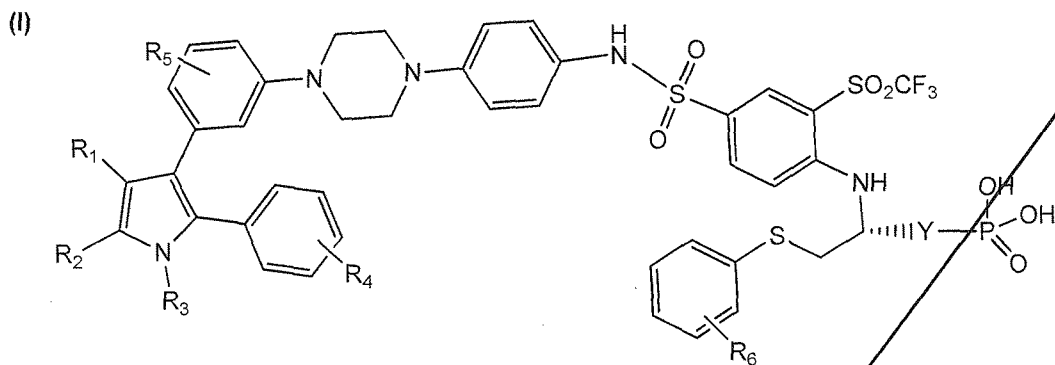
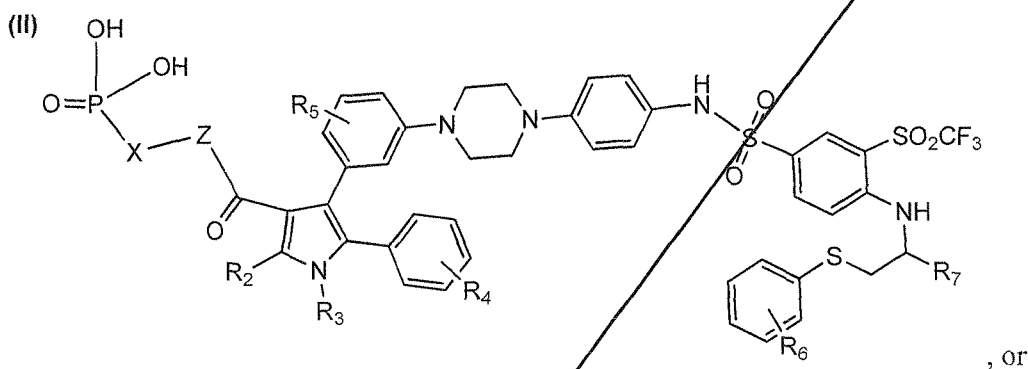
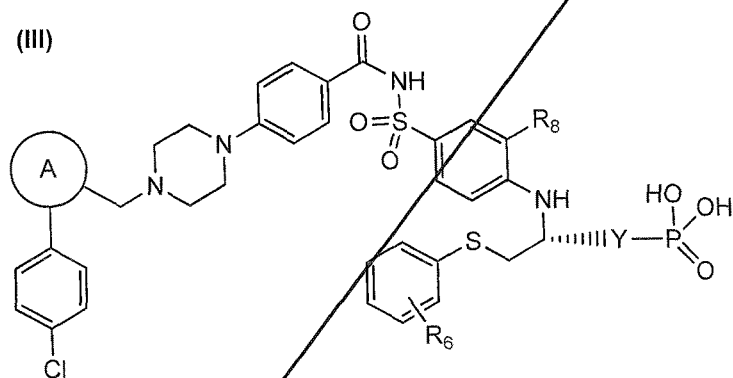
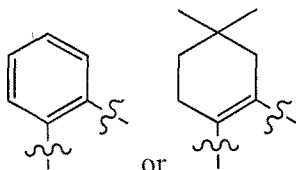
[0035] The Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and the second therapeutic agent can be administered together as a single-unit dose or separately as multi-

unit doses, wherein the Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) is administered before the second therapeutic agent or *vice versa*. It is envisioned that one or more dose of a Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and/or one or more dose of a second therapeutic agent can be administered.

[0036] In one example, a Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and a second therapeutic agent are administered simultaneously. In related examples, a Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and second therapeutic agent are administered from a single composition or from separate compositions. In a further example, the Bcl-2/Bcl-xL inhibitor of structural formula (I), (II), or (III) and second therapeutic agent are administered sequentially. A Bcl-2/Bcl-xL inhibitor of structural

~~WHAT IS CLAIMED:~~

1. A compound having a structural formula:



wherein the A ring is

X, substituted or unsubstituted, is selected from the group consisting of alkylene, alkenylene, cycloalkylene, cycloalkenylene, and heterocycloalkylene;

Y is selected from the group consisting of $(\text{CH}_2)_n\text{-N}(\text{R}^a)$ and

Q is selected from the group consisting of O, O(CH₂)₁₋₃, NR^c, NR^c(C₁₋₃alkylene), OC(=O)(C₁₋₃alkylene), C(=O)O, C(=O)O(C₁₋₃alkylene), NHC(=O)(C₁₋₃alkylene), C(=O)NH, and C(=O)NH(C₁₋₃alkylene);

Z is O or NR^c .

R₁ and R₂, independently, are selected from the group consisting of H, CN, NO₂, halo, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR', SR', NR'R'', COR', CO₂R', OCOR', CONR'R'', CONR'SO₂R'', NR'COR', NR'CONR''R''', NR'C=SNR''R''', NR'SO₂R'', SO₂R', and SO₂NR'R'';

R₃ is selected from a group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR', NR'R'', OCO R', CO₂R', COR', CONR'R'', CONR'SO₂R'', C₁₋₃alkyleneCH(OH)CH₂OH, SO₂R', and SO₂NR'R'';

R', R'', and R''', independently, are H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, C₁₋₃alkyleneheterocycloalkyl, or heterocycloalkyl;

~~R' and R'', or R'' and R''', can be taken together with the atom to which they are bound to form a 3 to 7 membered ring;~~

R₄ is hydrogen, halo, C₁₋₃alkyl, CF₃, or ~~CN~~;

R₅ is hydrogen, halo, C₁₋₃alkyl, substituted C₁₋₃alkyl, hydroxyalkyl, alkoxy, or substituted alkoxy;

R₆ is selected from the group consisting of H, CN, NO₂, halo, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR', SR', NR'R'', CO₂R', OCOR', CONR'R'', CONR'SO₂R'', NR'COR'', NR'CONR''R''', NR'C=SNR''R''', NR'SO₂R'', SO₂R', and SO₂NR'R'';

~~R₇, substituted or unsubstituted, is selected from the group consisting of hydrogen, alkyl, alkenyl, (CH₂)₀₋₃cycloalkyl, (CH₂)₀₋₃cycloalkenyl, (CH₂)₀₋₃heterocycloalkyl, (CH₂)₀₋₃aryl, and (CH₂)₀₋₃heteroaryl;~~

R₈ is selected from the group consisting of hydrogen, halo, NO₂, CN, CF₃SO₂, and CF₃;

R_a is selected from the group consisting of hydrogen, alkyl, heteroalkyl, alkenyl, hydroxyalkyl, alkoxy, substituted alkoxy, cycloalkyl, cycloalkenyl, and heterocycloalkyl;

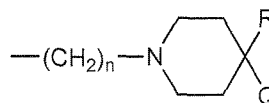
R_b is hydrogen or alkyl;

R_c is selected from the group consisting of hydrogen, alkyl, substituted alkyl, hydroxyalkyl, alkoxy, and substituted alkoxy; and

~~n, r, and s, independently, are 1, 2, 3, 4, 5, or 6;~~

~~or a pharmaceutically acceptable salt of (I), (II), or (III).~~

2. The compound of claim 1 wherein x is alkylene.



3. The compound of claim 1 or 2 wherein Y is

4. The compound of claim 3 wherein n is 1-3.

5. The compound of claim 3 wherein R_b is hydrogen or C_{1-3} alkyl.

6. The compound of any of claims 1-5 wherein Q is O, $O(CH_2)_{1-3}$, $C(=O)O(CH_2)_{1-3}$, $OC(=O)(CH_2)_{1-3}$, or $C(=O)O(C_3H_7)_{1-3}$.

7. The compound of any of claims 1-6 wherein Z is O, NH, or $N(C_{1-3}alkyl)$.

8. The compound of any of claims 1-7 wherein R_1 is SO_2R' , $SO_2NR'R''$, $NR'SOR''$, H, or alkyl.

9. The compound of any of claims 1-8 wherein R_2 is H, C_{1-3} alkyl, cycloalkyl, or halo.

10. The compound of any of claims 1-9 wherein R_3 is H, C_{1-3} alkyl, or cycloalkyl.

11. The compound of any of claims 1-10 wherein R_4 is H or halo.

12. The compound of any of claims 1-11 wherein R_5 is H, halo, or C_{1-3} alkyl.

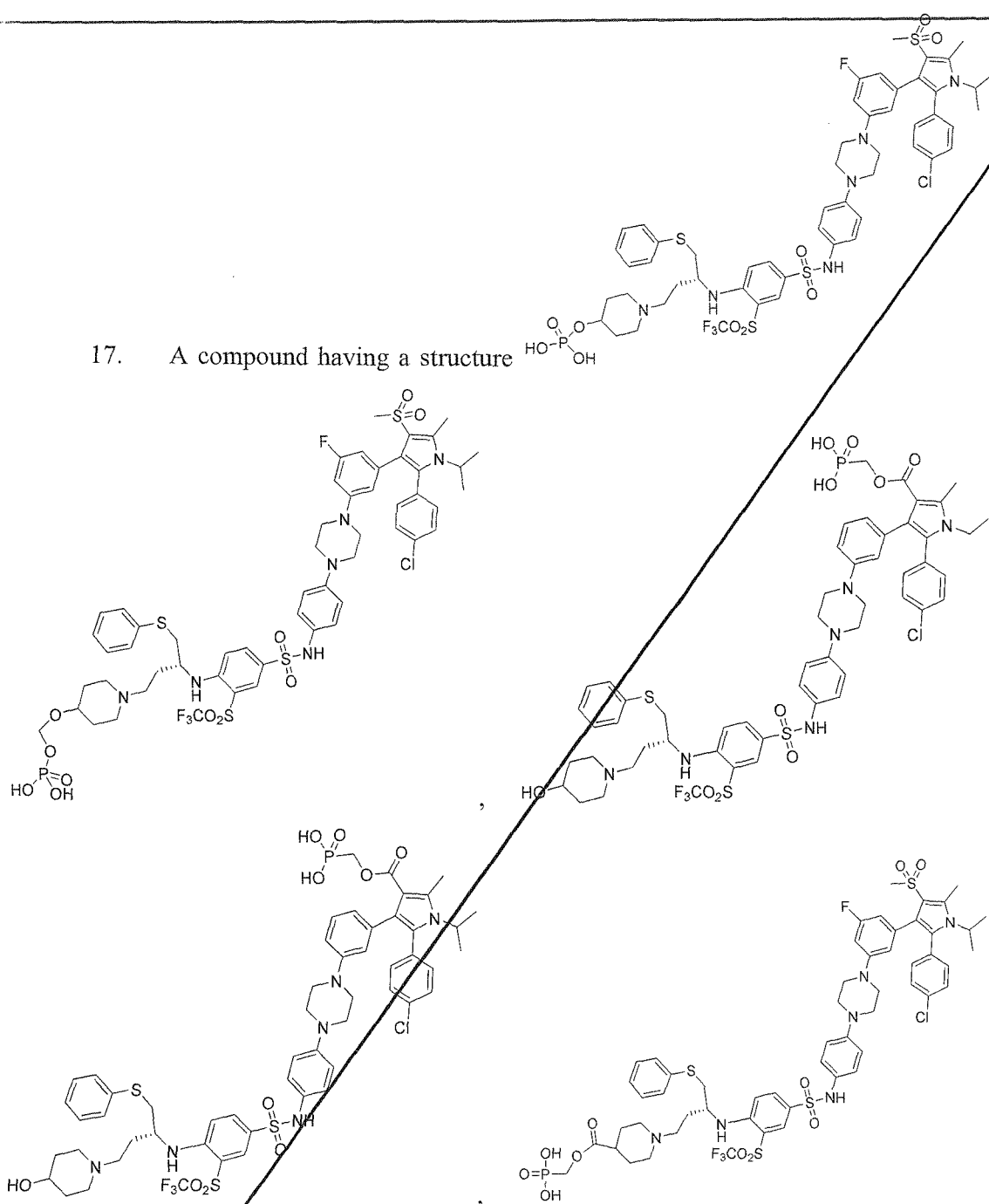
13. The compound of any of claims 1-12 wherein R_6 is H, halo, C_{1-3} alkyl, or cycloalkyl.

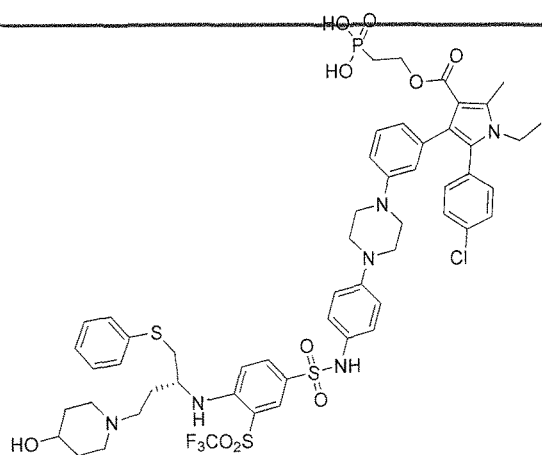
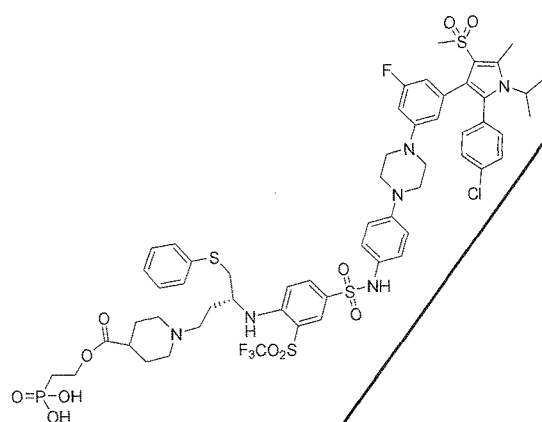
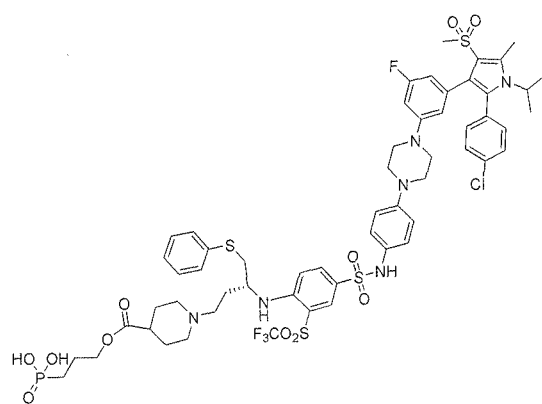
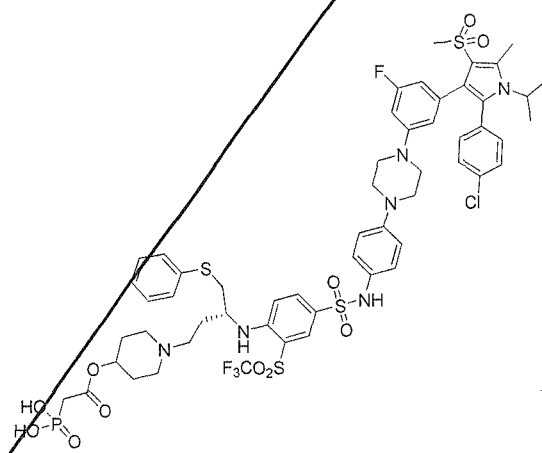
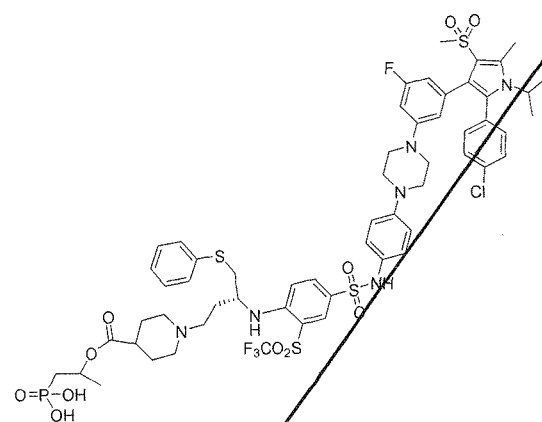
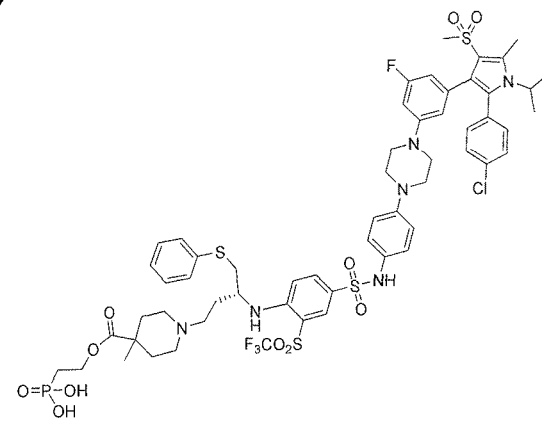
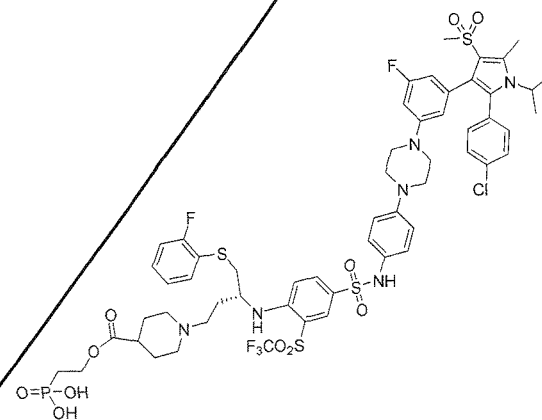
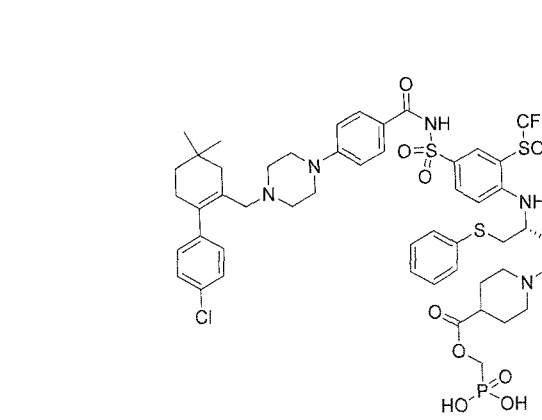
14. The compound of any of claims 1-13 wherein R_7 is $(CH_2)_{0-3}$ cycloalkyl optionally substituted with $-OH$.

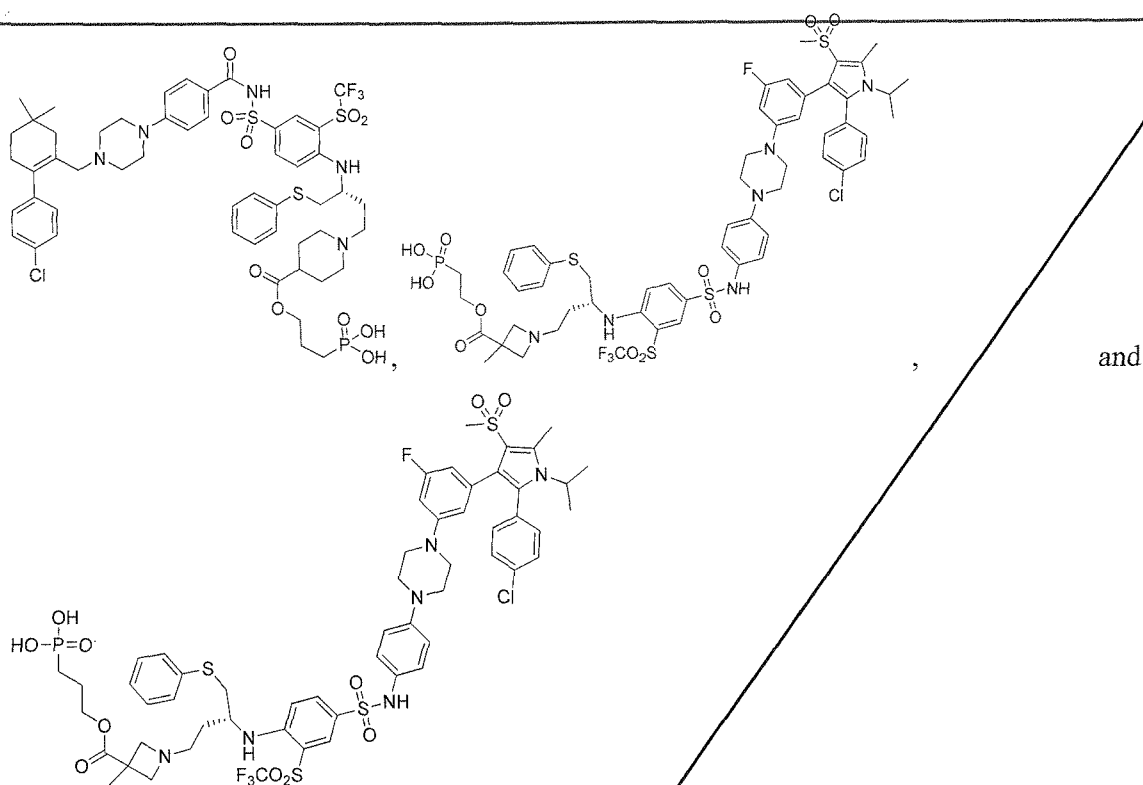
15. The compound of any of claims 1-14 wherein R_8 is CF_3SO_2 or CF_3 .

16. The compound of any of claims 1-15 wherein R_b and R_c , independently, are H or C_{1-3} alkyl.

17. A compound having a structure







18. A composition comprising (a) compound of claim 1, (b) a second therapeutic agent useful in the treatment of a disease or condition wherein inhibition of Bcl-2 or Bcl-xL provides a benefit, and (c) an optional excipient and/or pharmaceutically acceptable carrier.

19. The composition of claim 18 wherein the second therapeutic agent comprises a chemotherapeutic agent useful in the treatment of cancer.

20. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or vehicle.

21. Use of a therapeutically effective amount of a compound of claim 1 in the manufacture of a medicament for treating a disease or condition wherein inhibition of Bcl-2 or Bcl-xL provides a benefit.

22. The use of claim 21 further comprising a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

23. The use of claim 22 wherein the compound of claim 1 and the second therapeutic agent are to be administered simultaneously.

~~24. The use of claim 22 wherein the compound of claim 1 and the second therapeutic agent are to be administered separately.~~

25. The use of claim 21 wherein the disease or condition is a cancer.

26. The use of claim 22 wherein the disease is a cancer and the second therapeutic agent is one or more of a chemotherapeutic agent and radiation.

27. The use of claim 22 wherein the disease is a cancer and the second therapeutic agent is selected from the agents disclosed in paragraphs [0125] through [0131].

28. The use of claim 22 wherein the second therapeutic agent comprises radiation, and the radiation optionally is to be administered in conjunction with radiosensitizers and/or therapeutic agents disclosed in paragraphs [0122] through [0124] herein.

29. The use of claim 25 wherein the cancer is selected from a cancer disclosed in paragraphs [0110] through [0112] herein.

30. The use of claim 22 wherein the compound of claim 1 and the second therapeutic agent are to be administered from a single composition.

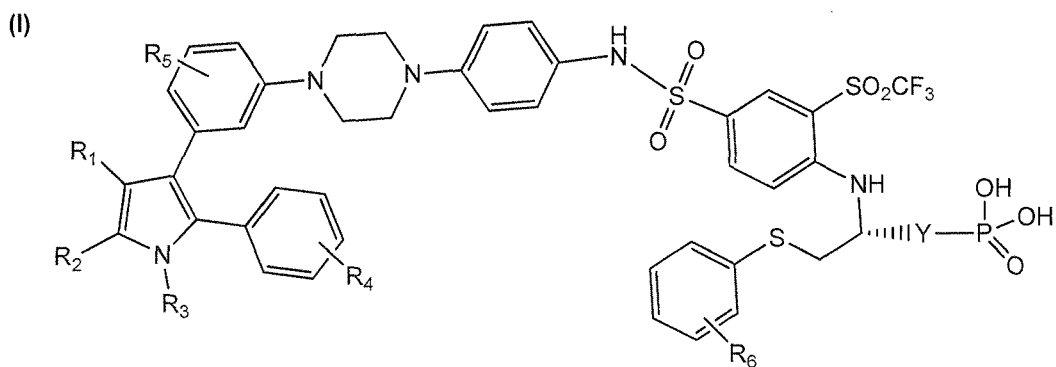
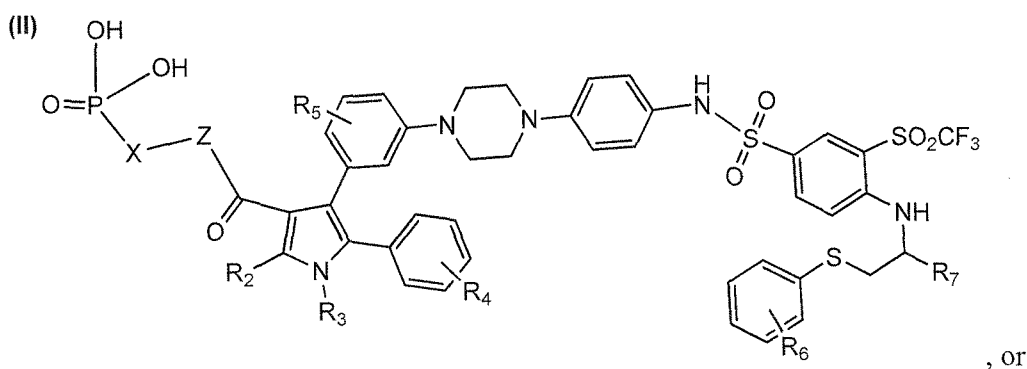
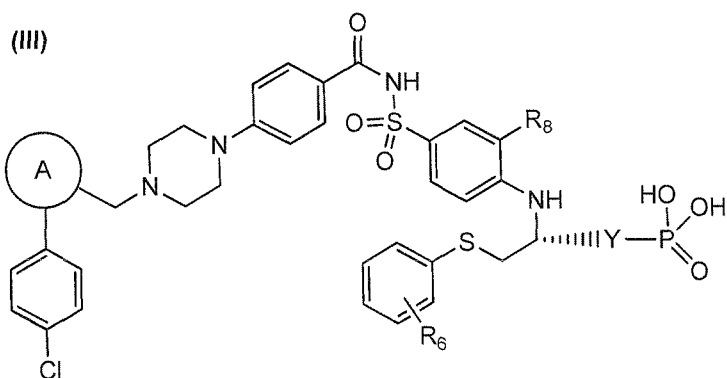
31. The use of claim 22 wherein the compound of claim 1 and the second therapeutic agent are to be administered from separate compositions.

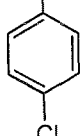
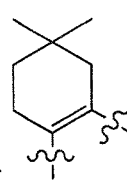
32. The use of claim 24 wherein the compound of claim 1 is to be administered prior to the second therapeutic agent.

33. The use of claim 24 wherein the compound of claim 1 is to be administered after the second therapeutic agent.

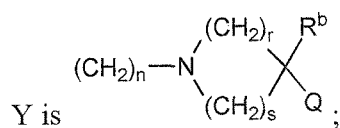
WHAT IS CLAIMED:

1. A compound having a structural formula:



wherein the A ring is  or  ;

X, substituted or unsubstituted, is selected from the group consisting of alkylene, alkenylene, cycloalkylene, cycloalkenylene, and heterocycloalkylene;



Q is selected from the group consisting of O, $O(CH_2)_{1-3}$, NR^c , $NR^c(C_{1-3}\text{alkylene})$, $OC(=O)(C_{1-3}\text{alkylene})$, $C(=O)O(C_{1-3}\text{alkylene})$, $NHC(=O)(C_{1-3}\text{alkylene})$, $C(=O)NH$, and $C(=O)NH(C_{1-3}\text{alkylene})$;

Z is O or NR^c ;

R_1 and R_2 , independently, are selected from the group consisting of H, CN, NO_2 , halo, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR' , SR' , $NR'R''$, COR' , CO_2R' , $OCOR'$, $CONR'R''$, $CONR'SO_2R''$, $NR'COR''$, $NR'CONR''R'''$, $NR'C=SNR''R'''$, $NR'SO_2R''$, SO_2R' , and $SO_2NR'R''$;

R_3 is selected from a group consisting of H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR' , $NR'R''$, $OCOR'$, CO_2R' , COR' , $CONR'R''$, $CONR'SO_2R''$, $C_{1-3}\text{alkylene}CH(OH)CH_2OH$, SO_2R' , and $SO_2NR'R''$;

R' , R'' , and R''' , independently, are H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, $C_{1-3}\text{alkyleneheterocycloalkyl}$, or heterocycloalkyl;

R' and R'' , or R'' and R''' , can be taken together with the atom to which they are bound to form a 3 to 7 membered ring;

R_4 is hydrogen, halo, $C_{1-3}\text{alkyl}$, CF_3 , or CN;

R_5 is hydrogen, halo, $C_{1-3}\text{alkyl}$, substituted $C_{1-3}\text{alkyl}$, hydroxyalkyl, alkoxy, or substituted alkoxy;

R_6 is selected from the group consisting of H, CN, NO_2 , halo, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl, heterocycloalkyl, OR' , SR' , $NR'R''$, CO_2R' , $OCOR'$, $CONR'R''$, $CONR'SO_2R''$, $NR'COR''$, $NR'CONR''R'''$, $NR'C=SNR''R'''$, $NR'SO_2R''$, SO_2R' , and $SO_2NR'R''$;

R_7 , substituted or unsubstituted, is selected from the group consisting of hydrogen, alkyl, alkenyl, $(CH_2)_{0-3}\text{cycloalkyl}$, $(CH_2)_{0-3}\text{cycloalkenyl}$, $(CH_2)_{0-3}\text{heterocycloalkyl}$, $(CH_2)_{0-3}\text{aryl}$, and $(CH_2)_{0-3}\text{heteroaryl}$;

R_8 is selected from the group consisting of hydrogen, halo, NO_2 , CN, CF_3SO_2 , and CF_3 ;

R_a is selected from the group consisting of hydrogen, alkyl, heteroalkyl, alkenyl, hydroxyalkyl, alkoxy, substituted alkoxy, cycloalkyl, cycloalkenyl, and heterocycloalkyl;

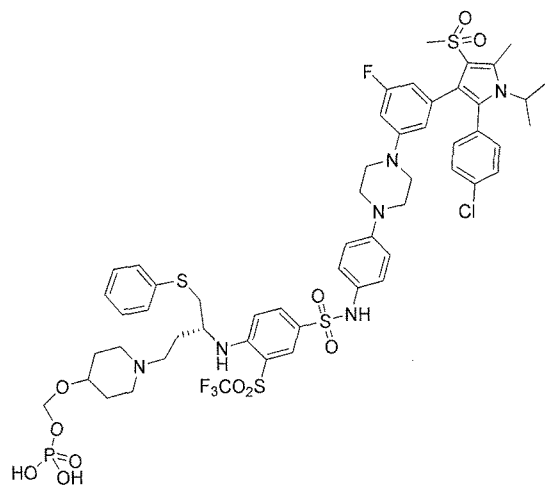
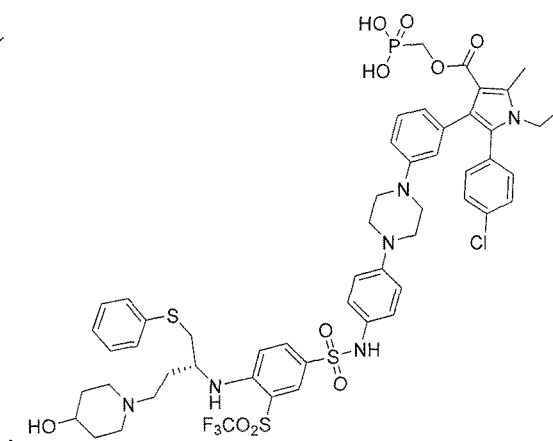
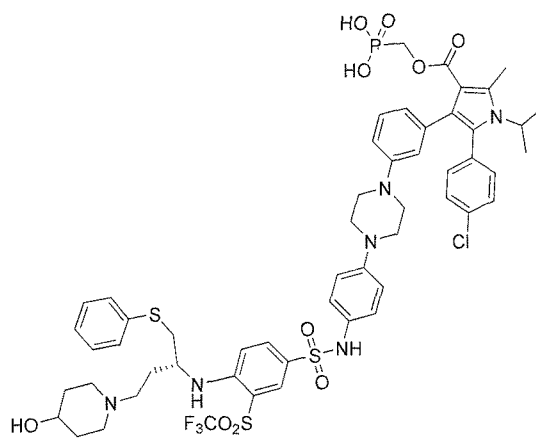
R_b is hydrogen or alkyl;

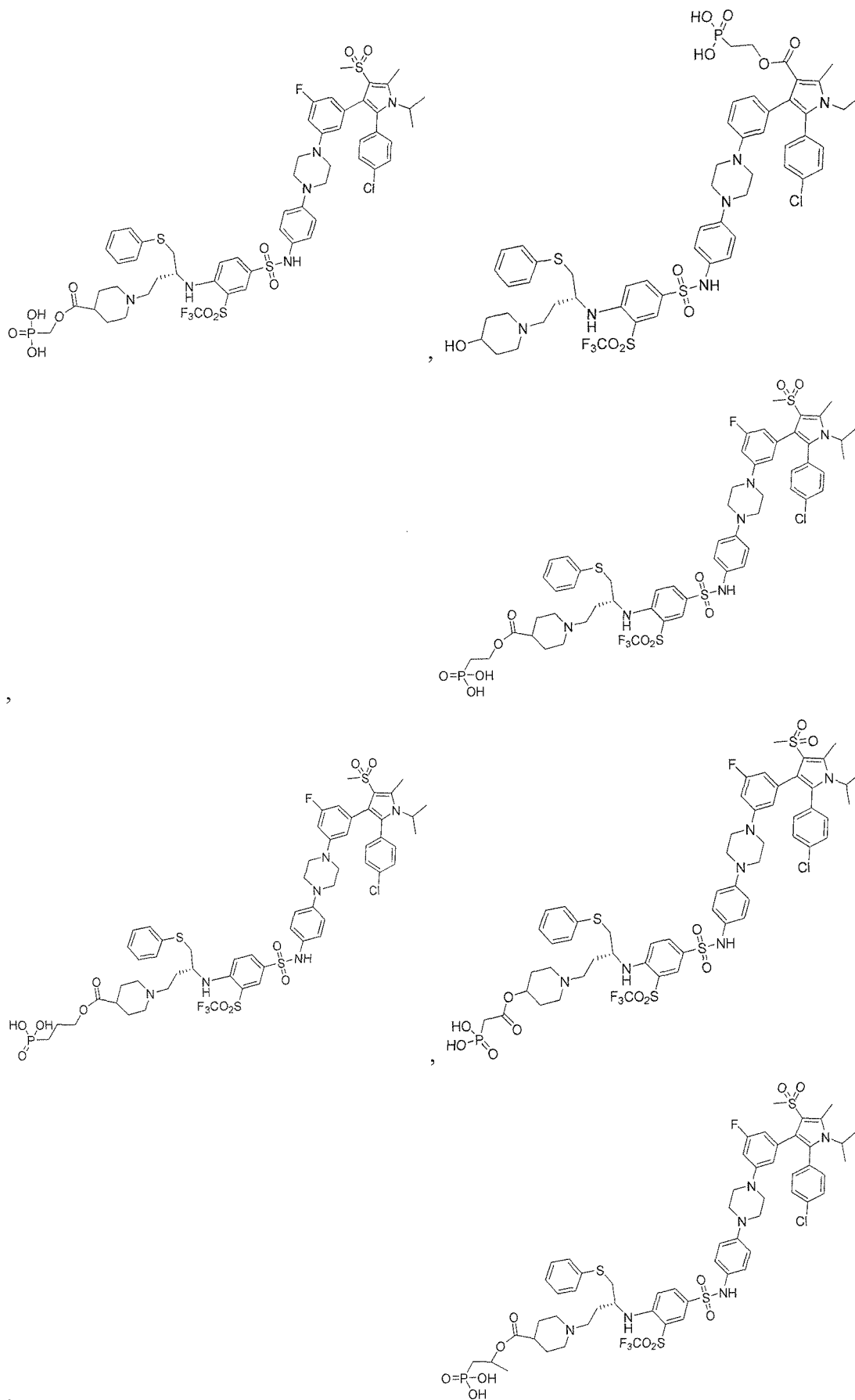
R_c is selected from the group consisting of hydrogen, alkyl, substituted alkyl, hydroxyalkyl, alkoxy, and substituted alkoxy; and

n, r, and s, independently, are 1, 2, 3, 4, 5, or 6;

or a pharmaceutically acceptable salt of (I), (II), or (III).

2. The compound of claim 1 wherein x is alkylene.
3. The compound of claim 1 wherein n is 1-3.
4. The compound of claim 1 wherein R_b is hydrogen or C₁₋₃alkyl.
5. The compound of any of claims 1-4 wherein Q is O, O(CH₂)₁₋₃, C(=O)O(CH₂)₁₋₃, OC(=O)(CH₂)₁₋₃, or C(=O)O(C₃H₇)₁₋₃.
6. The compound of any of claims 1-5 wherein Z is O, NH, or N(C₁₋₃alkyl).
7. The compound of any of claims 1-6 wherein R₁ is SO₂R', SO₂NR'R'', NR'SOR'', H, or alkyl.
8. The compound of any of claims 1-7 wherein R₂ is H, C₁₋₃alkyl, cycloalkyl, or halo.
9. The compound of any of claims 1-8 wherein R₃ is H, C₁₋₃alkyl, or cycloalkyl.
10. The compound of any of claims 1-9 wherein R₄ is H or halo.
11. The compound of any of claims 1-10 wherein R₅ is H, halo, or C₁₋₃alkyl.
12. The compound of any of claims 1-11 wherein R₆ is H, halo, C₁₋₃alkyl, or cycloalkyl.
13. The compound of any of claims 1-12 wherein R₇ is (CH₂)₀₋₃cycloalkyl optionally substituted with -OH.
14. The compound of any of claims 1-13 wherein R₈ is CF₃SO₂ or CF₃.
15. The compound of any of claims 1-14 wherein R_b and R_c, independently, are H or C₁₋₃alkyl.

CC(C)c1nc(S(=O)(=O)c2ccccc2)c(S(=O)(=O)Nc3ccc(NC(=O)N[C@@H](Cc4ccccc4S)C(=O)Nc5ccccc5COP(=O)(O)O)cc5)c(C(F)(F)F)c1





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xL provides a benefit, and (c) an optional excipient and/or pharmaceutically acceptable carrier.

18. The composition of claim 17 wherein the second therapeutic agent comprises a chemotherapeutic agent useful in the treatment of cancer.

19. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or vehicle.

20. Use of a therapeutically effective amount of a compound of claim 1 in the manufacture of a medicament for treating a cancer.

21. The use of claim 20 further comprising a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

22. The use of claim 21 wherein the compound of claim 1 and the second therapeutic agent are to be administered simultaneously.

23. The use of claim 21 wherein the compound of claim 1 and the second therapeutic agent are to be administered separately.

24. The use of claim 21 wherein the disease is a cancer and the second therapeutic agent is one or more of a chemotherapeutic agent and radiation.

25. The use of claim 21 wherein the disease is a cancer and the second therapeutic agent is selected from the group consisting of:

- alkylating agents,
- antimetabolites,
- hormones and antagonists thereof,
- natural products and their derivatives,
- radioisotopes,
- antibodies,
- antibiotics selected from the group consisting of doxorubicin and other anthracycline analogs,
- nitrogen mustards such as cyclophosphamide,
- pyrimidine analogs selected from the group consisting of 5-fluorouracil, cis-platin, hydroxyurea, taxol and its natural and synthetic derivatives),
- leuprolide or goserelin (synthetic peptide analogs of LH-RH),

- **Alkylating agents** selected from the group consisting of
 - Nitrogen mustards selected from the group consisting of
 - mechlorethamine,
 - cyclophosphamide,
 - ifosfamide,
 - melphalan,
 - chlorambucil,
 - uracil mustard, and
 - temozolomide,
 - Nitrosoureas selected from the group consisting of
 - carmustine or BCNU,
 - lomustine or CCNU,
 - semustine or methyl CCNU,
 - chlormethine, and
 - streptozocin,
 - Ethylenimine/Methyl melamine selected from the group consisting of
 - triethylenemelamine or TEM,
 - triethylene thiophosphoramidate or thiotepa, and
 - hexamethylmelamine or HMM or altretamine,
 - Alkyl sulfonates selected from the group consisting of
 - busulfan and
 - pipobroman, and
 - Triazines or dacarbazine or DTIC,
- **Antimetabolites** selected from the group consisting of
 - Folic Acid analogs selected from the group consisting of
 - methotrexate,
 - trimetrexate, and
 - pemetrexed or Multi-targeted antifolate,
 - Pyrimidine analogs selected from the group consisting of
 - 5-fluorouracil,
 - fluorodeoxyuridine,
 - gemcitabine,
 - cytosine arabinoside or AraC or cytarabine,
 - 5-azacytidine,
 - 2,2'-difluorodeoxy-cytidine,

- floxuridine, and
- pentostatine,
- Purine analogs selected from the group consisting of
 - 6-mercaptopurine,
 - 6-thioguanine,
 - azathioprine,
 - 2'-deoxycoformycin or pentostatin,
 - erythrohydroxynonyl adenine or EHNA,
 - fludarabine phosphate, and
 - 2-chlorodeoxyadenosine or cladribine or 2-CdA,
- **Type I Topoisomerase Inhibitors** selected from the group consisting of
 - camptothecin,
 - topotecan, and
 - irinotecan,
- **Biological response modifiers** selected from the group consisting of
 - G-CSF, and
 - GM-CSF,
- **Differentiation Agents** such as retinoic acid derivatives,
- **Hormones and antagonists** selected from the group consisting of
 - Adrenocorticosteroids/antagonists selected from the group consisting of
 - prednisone and equivalents,
 - dexamethasone, and
 - ainoglutethimide,
 - Progestins selected from the group consisting of
 - hydroxyprogesterone caproate,
 - medroxyprogesterone acetate, and
 - megestrol acetate,
 - Estrogens selected from the group consisting of
 - diethylstilbestrol, and
 - ethynyl estradiol/equivalents,
 - Antiestrogen such as tamoxifen,
 - Androgens selected from the group consisting of
 - testosterone propionate, and
 - fluoxymesterone/equivalents, and
 - Antiandrogens selected from the group consisting of

- flutamide,
- gonadotropin releasing hormone analogs, and
- leuprolide, and
- **Natural products** selected from the group consisting of
 - Antimitotic drugs,
 - Taxanes selected from the group consisting of
 - paclitaxel,
 - Vinca alkaloids,
 - vinblastine or VLB,
 - vincristine,
 - vinorelbine,
 - vindesine,
 - Taxotere® or docetaxel),
 - estramustine, and
 - estramustine phosphate,
 - Epipodophylotoxins selected from the group consisting of
 - etoposide, and
 - teniposide,
 - Antibiotics selected from the group consisting of
 - actinomycin D,
 - daunomycin or rubidomycin, doxorubicin or adriamycin,
 - mitoxantroneidarubicin,
 - bleomycin,
 - splicamycin or mithramycin,
 - mitromycin-C,
 - dactinomycin,
 - aphidicolin,
 - epirubicin,
 - idarubicin,
 - daunorubicin,
 - mithramycin, and
 - deoxy co-formycin,
 - Enzymes selected from the group consisting of
 - L-asparaginase, and
 - L-arginase,

- **Radiosensitizers** selected from the group consisting of
 - metronidazole,
 - misonidazole,
 - desmethylnisonidazole,
 - pimonidazole,
 - etanidazole,
 - nimorazole,
 - RSU 1069,
 - EO9,
 - RB 6145, and
 - Nonsteroidal antiandrogens selected from the group consisting of
 - SR4233,
 - flutamide, nicotinamide,
 - 5-bromodeoxyuridine,
 - 5-iododeoxyuridine, and
 - bromodeoxycytidine,
- **Miscellaneous agents** selected from the group consisting of
 - Platinum coordination complexes selected from the group consisting of
 - cisplatin,
 - carboplatin,
 - oxaliplatin,
 - anthracenedione, and
 - mitoxantrone,
 - Substituted urea such as hydroxyurea,
 - Methylhydrazine derivatives selected from the group consisting of
 - N-methylhydrazine or MIH, and
 - procarbazine,
 - Adrenocortical suppressant selected from the group consisting of
 - mitotane or *o,p'*-DDD, and
 - ainoglutethimide,
- **Cytokines** selected from the group consisting of
 - interferon selected from the group consisting of
 - interferon α ,
 - interferon β , and
 - interferon γ , and

- interleukin-2,
- **Photosensitizers** selected from the group consisting of
 - hematoporphyrin derivatives,
 - PHOTOFRIN®,
 - benzoporphyrin derivatives,
 - Npe6,
 - tin etioporphyrin or SnET2,
 - pheoboride-a,
 - bacteriochlorophyll-a,
 - naphthalocyanines,
 - phthalocyanines, and
 - zinc phthalocyanines,
- **Radiation** selected from the group consisting of
 - X-ray,
 - ultraviolet light,
 - gamma radiation,
 - visible light,
 - infrared radiation, and
 - microwave radiation)
- **Microtubule affecting agents** selected from the group consisting of
 - allocolchicine or NSC 406042,
 - halichondrin B or NSC 609395,
 - colchicines or NSC 757,
 - colchicines derivatives or NSC 33410,
 - dolastatin 10 or NSC 376128,
 - maytansine or NSC 153858,
 - rhizoxin or NSC 332598,
 - paclitaxel or NSC 125973,
 - TAXOL® derivatives or NSC 608832,
 - thiocolchicine or NSC 361792,
 - trityl cysteine or NSC 83265,
 - vinblastine sulfate or NSC 49842, and
 - vincristine sulfate or NSC 67574,
- **natural and synthetic epothilones** selected from the group consisting of
 - epothilone A,

- eopthilone B,
- discodermolide,
- estramustine,
- nocodazole, and
- MAP4,
- **hormones and steroids and synthetic analogs** selected from the group consisting of
 - 17- α -ethinylestadiol,
 - diethylstilbestrol,
 - testosterone,
 - prednisone,
 - fluoxymesterone,
 - dromostanolone propionate,
 - testolactone,
 - megestrolacetate,
 - methylprednisolone,
 - methyl-testosterone,
 - prednisolone,
 - triamcinolone,
 - hlorotrianisene,
 - hydroxyprogesterone,
 - aminogluthimide,
 - estramustine,
 - medroxyprogesteroneacetate,
 - leuprolide,
 - flutamide,
 - toremifene, and
 - zoladex,
- **antiangiogenics** such as matrix metalloproteinase inhibitors,
- **VEGF inhibitors** such as anti-VEGF antibodies,
- **small molecules** selected from the group consisting of
 - ZD6474, and
 - SU668,
- **anti-Her2 antibodies**,
- **EGFR inhibitor** such as EKB-569,
- **antibody C225** immunospecific for the EGFR and Src inhibitors, and

- **cytostatic agent** selected from the group consisting of
 - CASODEX[®] or bicalutamide,
 - antiestrogen TAMOXIFEN[®],
 - Inhibitors of the transduction of cellular proliferative signals selected from the group consisting of
 - epidermal growth factor inhibitors,
 - Her-2 inhibitors,
 - MEK-1 kinase inhibitors,
 - MAPK kinase inhibitors,
 - PI3 inhibitors,
 - Src kinase inhibitors, and
 - PDGF inhibitors.

26. The use of claim 21 wherein the second therapeutic agent comprises radiation, and the radiation optionally is to be administered in conjunction with radiosensitizers and/or therapeutic agents selected from the group consisting of:

- **X-ray-activated radiosensitizers** selected from the group consisting of
 - metronidazole,
 - misonidazole,
 - desmethylmisonidazole,
 - pimonidazole,
 - etanidazole,
 - nimorazole,
 - mitomycin C,
 - RSU 1069,
 - SR 4233,
 - EO9,
 - RB 6145,
 - nicotinamide,
 - 5-bromodeoxyuridine or BUdR,
 - 5-iododeoxyuridine or IUdR,
 - bromodeoxycytidine,
 - fluorodeoxyuridine or FUdR,
 - hydroxyurea, and
 - cis-platin,

- **photodynamic radiosensitizers** selected from the group consisting of
 - o hematoporphyrin derivatives,
 - o PHOTOFRIN[®],
 - o benzoporphyrin derivatives,
 - o NPe6,
 - o tin etioporphyrin or SnET2,
 - o pheorbide-a,
 - o bacteriochlorophyll-a,
 - o naphthalocyanines,
 - o phthalocyanines, and
 - o zinc phthalocyanine. and
- **additional therapeutic agents that can be used in conjunction with radiosensitizers** selected from the group consisting of
 - o 5 -fluorouracil (5-FU),
 - o leucovorin,
 - o oxygen,
 - o carbogen,
 - o red cell transfusions,
 - o perfluorocarbons or FLUOSOLW[®]-DA,
 - o 2,3-DPG,
 - o BW12C,
 - o calcium channel blockers,
 - o pentoxifylline,
 - o antiangiogenesis compounds,
 - o hydralazine, and
 - o L-BSO.

27. The use of claim 21 wherein the cancer is selected from the group consisting of carcinomas, accelerated and metastatic bladder cancer, breast cancer, colon cancer, colorectal cancer, kidney cancer, liver cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, lung adenocarcinoma, ovary cancer, prostate cancer, testes cancer, genitourinary tract cancer, lymphatic system cancer, rectum cancer, larynx cancer, pancreas cancer, exocrine pancreatic carcinoma, esophagus cancer, stomach cancer, gall bladder cancer, cervix cancer, thyroid cancer, renal cancer, skin cancer, squamous cell carcinoma, hematopoietic tumors of lymphoid lineage, leukemia, acute lymphocytic

leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, histiocytic lymphoma, Burkett's lymphoma, hematopoietic tumors of myeloid lineage, acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, promyelocytic leukemia, tumors of the central and peripheral nervous system, astrocytoma, neuroblastoma, glioma, schwannomas, tumors of mesenchymal origin, fibrosarcoma, rhabdomyosarcoma, osteosarcoma, melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, teratocarcinoma, renal cell carcinoma (RCC), pancreatic cancer, myeloma, myeloid and lymphoblastic leukemia, neuroblastoma, glioblastoma, adult and pediatric oncology, growth of solid tumors/malignancies, myxoid and round cell carcinoma, locally advanced tumors, metastatic cancer, human soft tissue sarcomas, Ewing's sarcoma, cancer metastases, lymphatic metastases, squamous cell carcinoma, squamous cell carcinoma of the head and neck, esophageal squamous cell carcinoma, oral carcinoma, blood cell malignancies, multiple myeloma, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, hairy cell leukemia, effusion lymphomas (body cavity based lymphomas), thymic lymphoma lung cancer (including small cell carcinoma, cutaneous T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cancer of the adrenal cortex, ACTH-producing tumors, nonsmall cell cancers, breast cancer, including small cell carcinoma and ductal carcinoma), gastrointestinal cancers (including stomach cancer, colon cancer, colorectal cancer, and polyps associated with colorectal neoplasia), pancreatic cancer, liver cancer, urological cancers (including bladder cancer, such as primary superficial bladder tumors, invasive transitional cell carcinoma of the bladder, and muscle-invasive bladder cancer), prostate cancer, malignancies of the female genital tract (including ovarian carcinoma, primary peritoneal epithelial neoplasms, cervical carcinoma, uterine endometrial cancers, vaginal cancer, cancer of the vulva, uterine cancer and solid tumors in the ovarian follicle), malignancies of the male genital tract (including testicular cancer and penile cancer), kidney cancer (including renal cell carcinoma), brain cancer (including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, and metastatic tumor cell invasion in the central nervous system), bone cancers (including osteomas and osteosarcomas), skin cancers (including malignant melanoma, tumor progression of human skin keratinocytes, and squamous cell cancer), thyroid cancer, retinoblastoma, neuroblastoma, peritoneal effusion, malignant pleural effusion, mesothelioma, Wilms's tumors, gall bladder cancer, trophoblastic neoplasms, hemangiopericytoma, and Kaposi's sarcoma.

28. The use of claim 21 wherein the compound of claim 1 and the second therapeutic agent are to be administered from a single composition.

29. The use of claim 21 wherein the compound of claim 1 and the second therapeutic agent are to be administered from separate compositions.

30. The use of claim 23 wherein the compound of claim 1 is to be administered prior to the second therapeutic agent.

31. The use of claim 23 wherein the compound of claim 1 is to be administered after the second therapeutic agent.