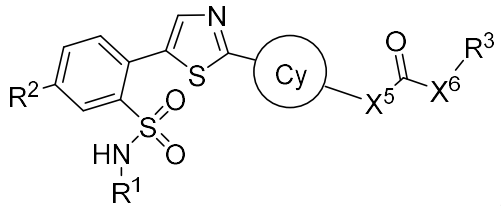
CLAIMS

What is claimed is:

1. Use of a compound in the manufacture of a medicament for the treatment of pancreatic cancer in a subject,

wherein the compound is represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

the thiazole ring is optionally substituted with –F or –Cl;

Cy is -(C_3–C_7)cycloalkyl, bridged (C_6–C_{12}) cycloalkyl, or a 4-10 membered heterocyclic ring, each of which is optionally substituted with one or more groups selected from the group consisting of halogen, -OH, (C_1-C_4)alkyl, and (C_1-C_4)alkoxy;

when X^5 is connected with a nitrogen ring atom of Cy, X^5 is absent;

when X^5 is connected with a carbon ring atom of Cy, X^5 is NR^a or O;

X^6 is NR^a or O;

R^1 is (C_1–C_5)alkyl optionally substituted with -OH;

R^3 is (C_1–C_5)alkyl, -CH_2-phenyl, -(C_3–C_7)cycloalkyl, -CH_2-(C_3–C_7)cycloalkyl, -CH_2-monocyclic 3-7 membered heterocyclic ring, or monocyclic 3-7 membered heterocyclic ring, wherein the (C_1–C_5)alkyl, -(C_3–C_7)cycloalkyl, phenyl or monocyclic 3-7 membered heterocyclic ring represented by R^3 or in the group represented by R^3 is optionally substituted with one or more groups selected from the group consisting of halogen, -OH, (C_1-C_4)alkyl, halomethyl, halomethoxy, -CN, and (C_1-C_4)alkoxy;

R^2 is -$NR^aC(O)O$(C_1-C_4)alkyl; -$NR^aC(O)NR^a$(C_1-C_4)alkyl; -$NR^aC(O)O$(C_2-C_4)alkenyl; -$NR^aC(O)NR^a$(C_2-C_4)alkenyl; -$NR^aC(O)O$-(C_3-C_6)cycloalkyl; -$NR^aC(O)NR^a$-(C_3-C_7)cycloalkyl; -$NR^aC(O)O$-phenyl; -$NR^aC(O)NR^a$-phenyl; -$NR^aC(O)O$-monocyclic 3-7 membered heterocyclic ring; -$NR^aC(O)NR^a$-monocyclic 3-7 membered heterocyclic ring; -$NR^aC(O)O$-monocyclic 5-6 membered heteroaromatic ring; -$NR^aC(O)NR^a$-monocyclic 5-6 membered heteroaromatic ring;

wherein the (C_1–C_4)alkyl and the (C_2-C_4)alkenyl in the group represented by R^2 are each optionally and independently substituted with one or more groups selected from the

group consisting of halogen, N_3, $–OR^a$, $-NR^aR^a$, $-(C_3–C_6)$cycloalkyl, phenyl, a monocyclic 3-7 membered heterocyclic ring, and a monocyclic 5-6 membered heteroaromatic ring;

wherein the $(C_3–C_7)$cycloalkyl in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of halogen, $-CH_3$, =O, $-OR^a$ and $-NR^aR^a$;

wherein the phenyl in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of halogen, $-CH_3$, halomethyl, halomethoxy, -CN, $-OR^a$, and $-N_3$;

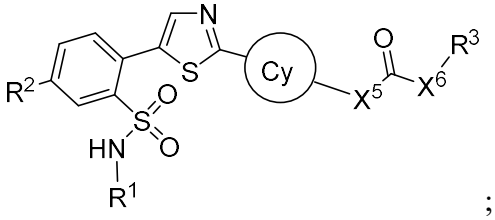
wherein the heterocyclic ring in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of =O, halogen, $–OR^a$, $-CH_3$, halomethyl, and halomethoxy;

wherein the heteroaromatic ring in the group represented by R^2 is optionally substituted with one or more groups selected from the group consisting of halogen, -CN, $-CH_3$, halomethyl, halomethoxy, $-OR^a$ and $-NR^aR^a$; and

each R^a is independently –H or $-CH_3$.

2. Use of a compound in the manufacture of a medicament for the treatment of pancreatic cancer in a subject,

wherein the compound is represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

the thiazole ring is optionally substituted with -F or –Cl;

Cy is cyclohexyl or a 6-membered monocyclic heterocyclic ring;

X^5 and X^6 are each independently NR^a or O;

R^1 is $(C_1–C_5)$alkyl;

R^3 is $(C_1–C_5)$alkyl or monocyclic 3-7-membered heterocyclic ring;

R^2 is $-NR^aC(O)O(C_1-C_4)$alkyl; $-NR^aC(O)NR^a(C_1-C_4)$alkyl; $-NR^aC(O)O(C_2-C_4)$alkenyl; $-NR^aC(O)NR^a(C_2-C_4)$alkenyl; $-NR^aC(O)-O(C_3-C_6)$cycloalkyl; $-NR^aC(O)NR^a-(C_3-C_6)$cycloalkyl; $-NR^aC(O)O$-phenyl; $-NR^aC(O)NR^a$-phenyl; $-NR^aC(O)O$-monocyclic 3-7 membered heterocyclic ring; $-NR^aC(O)NR^a$-monocyclic 3-7

membered heterocyclic ring; -$NR^aC(O)O$-monocyclic 5-6 membered heteroaromatic ring; -$NR^aC(O)NR^a$-monocyclic 5-6 membered heteroaromatic ring;

wherein the (C_1–C_4)alkyl and the (C_2-C_4)alkenyl in the group represented by R^2 are each optionally and independently substituted with one or more halogen, N_3, –OR^a, -NR^aR^a, -(C_3–C_6)cycloalkyl, phenyl, monocyclic 3–7-membered heterocyclic ring, or monocyclic 5–6-membered heteroaromatic ring;

wherein the -(C_3–C_6)cycloalkyl in the group represented by R^2 is optionally substituted with one or more halogen, -CH_3, -OR^a or -NR^aR^a;

wherein the phenyl in the group represented by R^2 is optionally substituted with one or more halogen, -CH_3, halomethyl, halomethoxy, -OR^a, or -N_3;

wherein the heterocyclic ring in the group represented by R^2 is optionally substituted with one or more =O, halogen, -CH_3, halomethyl, or halomethoxy;

wherein the heteroaromatic ring in the group represented by R^2 is optionally substituted with one or more halogen, -CH_3, halomethyl, halomethoxy, -OR^a or -NR^aR^a; and

each R^a is independently –H or -CH_3.

3. The use of claim 1, wherein Cy is

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl;

azetidinyl, azepanyl, diazaspiro[4.4]nonyl, diazaspiro[3.5]nonyl, diazepanyl, dihydroimidazole, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothienyl, dihydrothiophenyl, dihydrothiopyranyl, hexahydropyridazinyl, hexahydropyrimidinyl, hydantoinyl, indolinyl, isoindolinyl, morpholinyl, oxiranyl, oxetanyl, piperidinyl, piperazinyl, pyrrolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazole, tetrahydroindolyl, tetrahydropyranyl, tetrahydrothienyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiomorpholinyl, tropanyl, valerolactamyl;

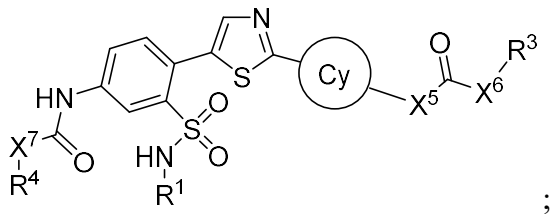
bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.3.1]decyl, bicyclo[3.3.1]nonyl, bornyl, bornenyl, norbornyl, norbornenyl, 6,6-dimethylbicyclo [3.1.1]heptyl, tricyclobutyl, adamantly;

azanorbornyl, quinuclidinyl, isoquinuclidinyl, tropanyl, azabicyclo[2.2.1]heptanyl, 2-azabicyclo[3.2.1]octanyl, azabicyclo[3.2.1]octanyl, azabicyclo[3.2.2]nonanyl, azabicyclo[3.3.0]nonanyl, azabicyclo [3.3.1]nonanyl, diazabicyclo[2.2.1]heptanyl,

diazabicyclo[3.2.1]octanyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydropyrrolo[3,4-c]pyrrolyl.

4. The use of any one of claims 1-3, wherein Cy is cyclohexyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, hexahydropyridazinyl, hexahydropyrimidinyl, valerolactamyl, dihydropyranyl, dihydropyridinyl, dihydropyrimidinyl, dihydrothiopyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, or tetrahydrothiopyranyl.

5. The use of any one of claims 1-4, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein:

X^7 is NH or O;

R^4 is (C_1–C_4)alkyl, (C_3-C_6)cycloalkyl, or a monocyclic 3-7 membered heterocyclic ring;

wherein the (C_1–C_4)alkyl represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen, N_3, –OR^a, -NR^aR^a, -(C_3–C_6)cycloalkyl, phenyl, a monocyclic 3-7 membered heterocyclic ring, and a monocyclic 5-6 membered heteroaromatic ring,

wherein the (C_3-C_6)cycloalkyl or the monocyclic 3-7 membered heterocyclic ring represented by R^4, the (C_3-C_6)cycloalkyl or the monocyclic 3-7 membered heterocyclic ring in the group represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen, -OR^a, =O, and -CH_3,

wherein the phenyl in the group represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen, -CH_3, halomethyl, halomethoxy, -OR^a, and -N_3;

wherein the heteroaromatic ring in the group represented by R^4 is optionally substituted with one or more groups selected from the group consisting of halogen and -CH_3.

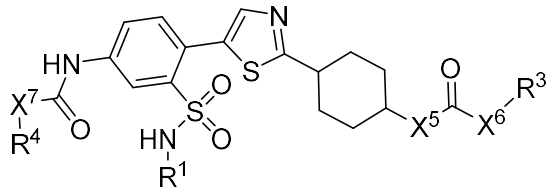
6. The use of claim 5, wherein

X^7 is NH or O;

R^3 is $(C_1–C_5)$alkyl; and

R^4 is $(C_1–C_4)$alkyl wherein the $(C_1–C_4)$alkyl represented by R^4 is optionally substituted with one or more halogen, $–OR^a$, $-NR^aR^a$, $-(C_3–C_6)$cycloalkyl, phenyl (optionally substituted by one or more halogen, $-CH_3$, halomethyl, halomethoxy, OR^a or N_3), monocyclic 3–7-membered heterocyclic ring (optionally substituted by =O, halogen or $–CH_3$), or monocyclic 5–6-membered heteroaromatic ring (optionally substituted by halogen or $–CH_3$).

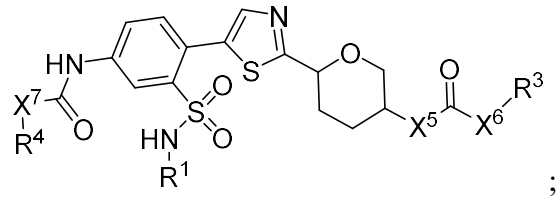
7. The use of any one of claims 1-6, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

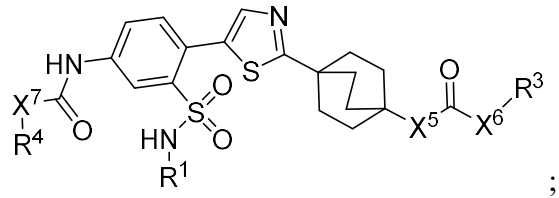
8. The use of any one of claims 1-6, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

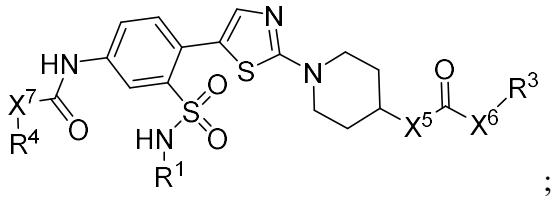
9. The use of any one of claims 1-6, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

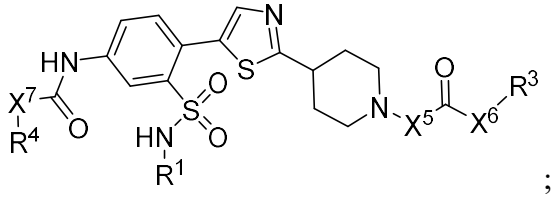
10. The use of any one of claims 1-6, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

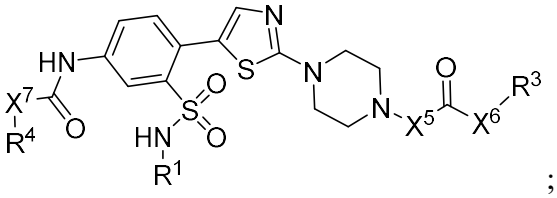
11. The use of any one of claims 1-6, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

12. The use of any one of claims 1-6, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

13. The use of any one of claims 1-6, wherein Cy is azetidinyl or pyrrolidinyl, and the nitrogen ring atom is connected with the thiazole ring.

14. The use of any one of claims 1-6, wherein Cy is 1,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[4.4]nonyl, 2,7-diazaspiro[3.5]nonyl, 1,4-diazepanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 3,8-diazabicyclo[3.2.1]octanyl, octahydropyrrolo[3,4-b]pyrrolyl, or octahydropyrrolo[3,4-c]pyrrolyl, and the two nitrogen ring atoms are connected with the thiazole ring and the $-X^5C(O)X^6R^3$ moiety, respectively.

15. The use of any one of claims 5 and 7-14, wherein R^4 is -(C_1–C_3)alkyl, (C_3-C_6)cycloalkyl, or a monocyclic 3-7 membered heterocyclic ring, wherein the -(C_1–C_3)alkyl is optionally substituted with (i) phenyl optionally substituted by one or more halogen or -CH_3; (ii) a monocyclic 5-6 membered heteroaromatic ring optionally substituted by one or more halogen or –CH_3; or (iii) a monocyclic 3-7 membered heterocyclic ring optionally substituted by one or more groups selected from the group consisting of halogen and –CH_3.

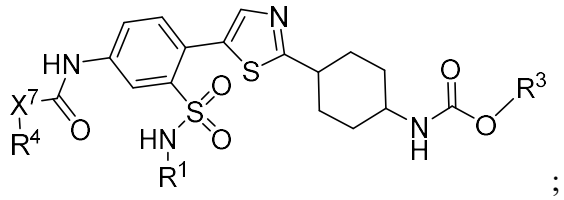
16. The use of any one of claims 5 and 7-14, wherein R^4 is -(C_1–C_3)alkyl, -CHR^a-phenyl, -CHR^a-5–6 membered heteraromatic ring, or -CHR^a-3-7 membered monocyclic heterocyclic ring, wherein the phenyl, 5–6 membered heteraromatic ring or 3-7 membered monocyclic heterocyclic ring in the group represented by R^4 is optionally substituted one or more groups selected from the group consisting of halogen and –CH_3.

17. The use of any one of claims 5-14, wherein R^4 is -(C_1–C_3)alkyl, optionally substituted with (i) phenyl optionally substituted by one or more halogen, -CH_3, halomethyl, halomethoxy, OR^a, or N_3; (ii) a monocyclic 5–6-membered heteroaromatic ring optionally substituted by one or more halogen or -CH_3; or (iii) a monocyclic 3–7-membered heterocyclic ring optionally substituted by one or more =O or –CH_3.

18. The use of claim 17, wherein R^4 is (i) -(C_1–C_3)alkyl; (ii) -CH_2-phenyl optionally substituted by halogen, -CH_3, halomethyl, halomethoxy, OR^a, or N_3; (iii) –CH(CH_3)-phenyl optionally substituted by halogen, -CH_3, halomethyl, halomethoxy, OR^a, or N_3; (iv) -CH_2-5–6-membered heteraromatic ring optionally substituted by halogen or –CH_3; or (v) -CH_2-3–7-membered monocyclic heterocyclic ring optionally substituted by =O or –CH_3.

19. The use of any one of claims 1, 3-5, and 7-18, wherein R^3 is (C_1–C_4)alkyl, -(C_4–C_6)cycloalkyl, -CH_2-phenyl, -CH_2-monocyclic 4-6 membered heterocyclic ring, or monocyclic 4-6 membered heterocyclic ring, wherein the phenyl or monocyclic 4-6 membered heterocyclic ring represented by R^3 or in the group represented by R^3 is optionally substituted with one or more groups selected from the group consisting of halogen, -OR^a, and –CH_3.

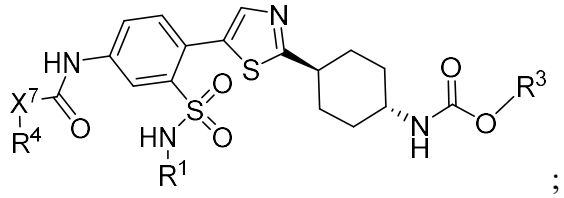
20. The use of any one of claims 1-7 and 15-19, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

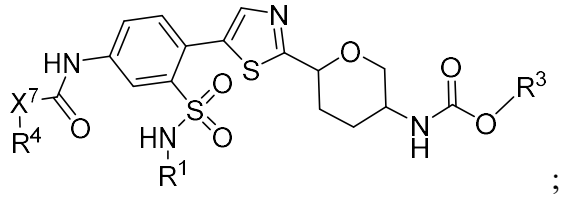
21. The use of claim 20, the medicament comprising a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof.

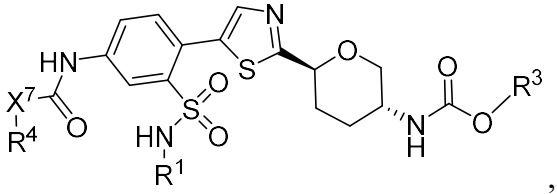
22. The use of any one of claims 1-6, 8, and 15-19, the medicament comprising a compound represented by the following structural formula:



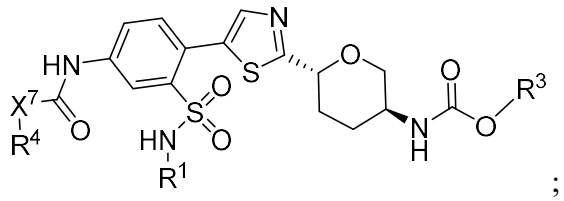
;

or a pharmaceutically acceptable salt thereof.

23. The use of claim 22, the medicament comprising a compound represented by the following structural formula:



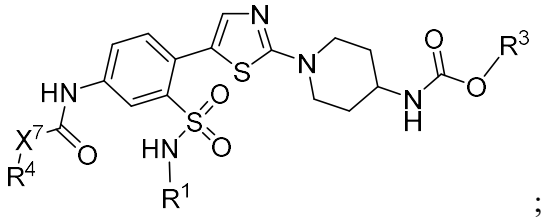
, or



;

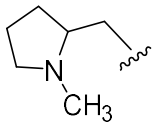
or a pharmaceutically acceptable salt thereof.

24. The use of any one of claims 1-6, 10, and 15-19, the medicament comprising a compound represented by the following structural formula:



;

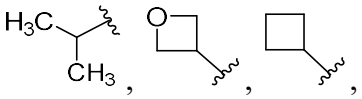
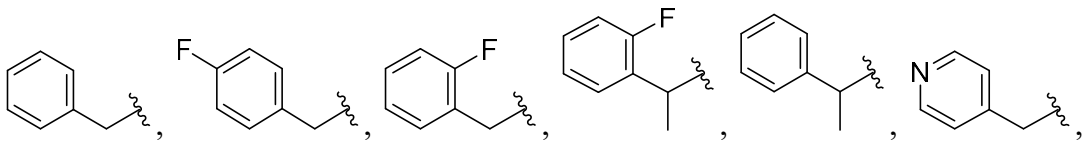
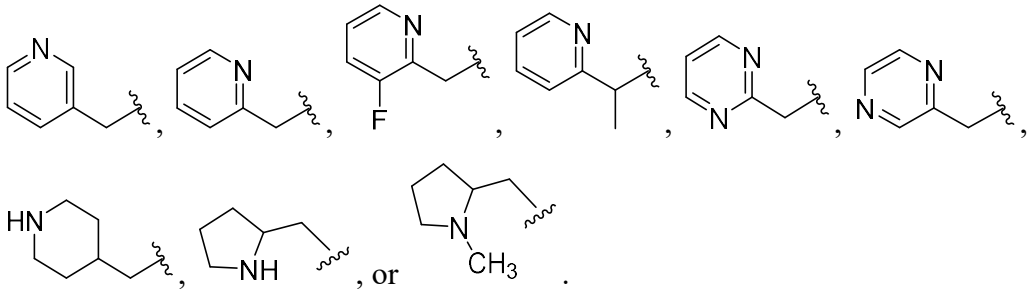
or a pharmaceutically acceptable salt thereof.

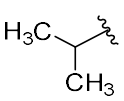
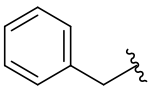
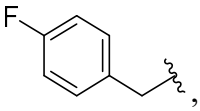
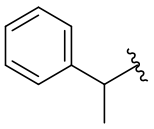
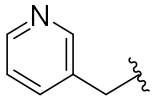
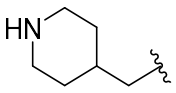
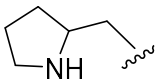
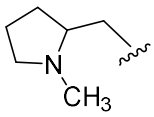
25. The use of any one of claims 1-24, wherein R^3 is isopropyl, *tert*-butyl, cyclobutyl, cyclopentyl, benzyl, oxetanyl, tetrahydro-2H-pyranyl, or .

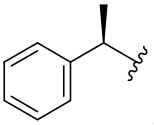
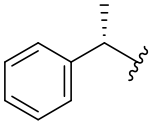
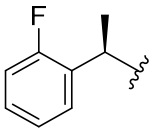
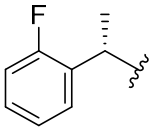
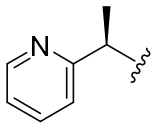
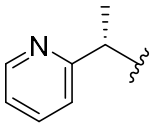
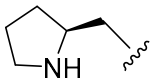
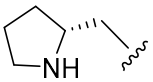
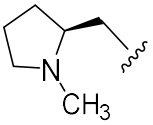
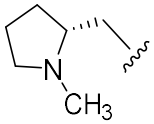
26. The use of any one of claims 1-25, wherein R^1 is *tert*-butyl.

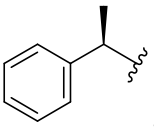
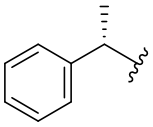
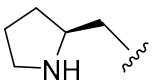
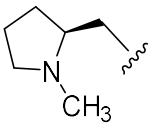
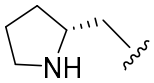
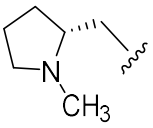
27. The use of any one of claims 1-26, wherein R^3 is isopropyl or oxetanyl.

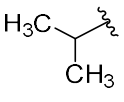
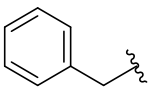
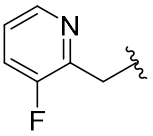
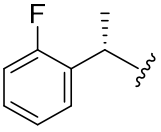
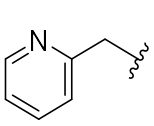
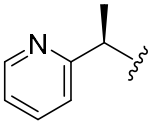
28. The use of claim 27, wherein R^3 is isopropyl.

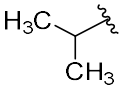
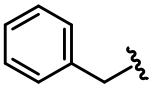
29. The use of any one of claims 5-28, wherein R^4 is , , , or .

30. The use of claim 29, wherein R^4 is , , , , , , , or .

31. The use of claim 29, wherein R^4 is , , , , , , , , , or .

32. The use of claim 29, wherein R^4 is , , , , , or .

33. The use of claim 29, wherein R^4 is , , , , , or .

34. The use of claim 29, wherein R^4 is  or .

35. The use of any one of claims 1-34, wherein the medicament further comprises a DNA repair inhibitor, a DNA damage response (DDR) inhibitor, a DNA damaging agent or an immunomodulatory agent; or

wherein the medicament is for administration with a DNA repair inhibitor, a DNA damage response (DDR) inhibitor, a DNA damaging agent or an immunomodulatory agent.

36. The use of claim 35, wherein the DNA damaging agent is selected from the group consisting of: exposure to a DNA damaging chemical; exposure to a chemotherapeutic agent; exposure to a radiochemotherapy, and exposure to ionizing or ultraviolet radiation.

37. The use of any one of claims 35-36, wherein the subject is determined to have an increased level and/or activity of a DNA damage process or DNA editing enzyme.

38. The use of claim 37, wherein the immunomodulatory agent is selected from the group consisting of immune checkpoint modulators, Toll-like receptor (TLR) agonists, cell-based therapies, cytokines and cancer vaccines.

39. The use of claim 37, wherein the DNA editing enzyme is selected from the group consisting of activation induced cytidine deaminase (AID or AICDA), APOBEC2, APOBEC3A, APOBEC3C, APOBEC3D, APOBEC3F, APOBEC3G, APOBEC3H, APOBEC4, a Type 1 Topoisomerase, a Type 2 Topoisomerase, Recombination Activating Gene 1 (RAG 1), and Recombination Activating Gene 2 (RAG2).

40. The use of any one of claims 1-39, wherein the subject is a mammal.

41. The use of any one of claims 1-40, wherein the subject is a human.

42. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage ranging from about 1 mg/m^2 to about 500 mg/m^2.

43. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage of about 3±2 mg/m^2, 3±1.8 mg/m^2, 3±1.6 mg/m^2, 3±1.5 mg/m^2, 3±1.4 mg/m^2, 3±1.3 mg/m^2, 3±1.2 mg/m^2, 3±1.1 mg/m^2, 3±1 mg/m^2, 3±0.9

mg/m^2, 3±0.8 mg/m^2, 3±0.7 mg/m^2, 3±0.6 mg/m^2, 3±0.5 mg/m^2, 3±0.4 mg/m^2, 3±0.3 mg/m^2, 3±0.2 mg/m^2, or 3±0.1 mg/m^2.

44. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage of about 3 mg/m^2.

45. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage of about 120±100 mg/m^2, 120±90 mg/m^2, 120±80 mg/m^2, 120±70 mg/m^2, 120±60 mg/m^2, 120±50 mg/m^2, 120±45 mg/m^2, 120±40 mg/m^2, 120±35 mg/m^2, 120±30 mg/m^2, 120±25 mg/m^2, 120±20 mg/m^2, 120±15 mg/m^2, 120±10 mg/m^2, 120±9 mg/m^2, 120±8 mg/m^2, 120±7 mg/m^2, 120±6 mg/m^2, 120±5 mg/m^2, 120±4 mg/m^2, 120±3 mg/m^2, 120±2 mg/m^2, or 120±1 mg/m^2.

46. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage of about 120 mg/m^2.

47. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage of about 240±100 mg/m^2, 240±90 mg/m^2, 240±80 mg/m^2, 240±70 mg/m^2, 240±60 mg/m^2, 240±50 mg/m^2, 240±45 mg/m^2, 240±40 mg/m^2, 240±35 mg/m^2, 240±30 mg/m^2, 240±25 mg/m^2, 240±20 mg/m^2, 240±15 mg/m^2, 240±10 mg/m^2, 240±9 mg/m^2, 240±8 mg/m^2, 240±7 mg/m^2, 240±6 mg/m^2, 240±5 mg/m^2, 240±4 mg/m^2, 240±3 mg/m^2, 240±2 mg/m^2, or 240±1 mg/m^2.

48. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage of about 240 mg/m^2.

49. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound followed by a 14-day dosing holiday.

50. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound followed by a 21-day dosing holiday.

51. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at about 240 mg/m^2 followed by a 14-day dosing holiday.

52. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at about 240 mg/m^2 followed by a 21-day dosing holiday.

53. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at about 120 mg/m^2 followed by a 14-day dosing holiday.

54. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at about 120 mg/m^2 followed by a 21-day dosing holiday.

55. The use of any one of claims 1-41, wherein the medicament is formulated for administration of the compound at a dosage ranging from about 50 mg/day to about 500 mg/day.

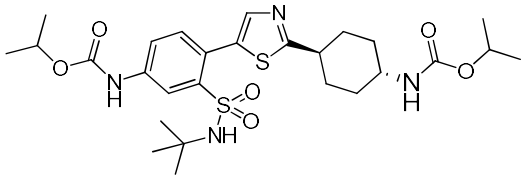
56. The use of any one of claims 1-55, wherein the medicament is formulated for administration once daily.

57. The use of any one of claims 1-55, wherein the medicament is formulated for administration once every other day.

58. The use of any one of claims 1-56, wherein the medicament is formulated for adminstration once daily for four weeks.

59. The use of any one of claims 1-56, wherein the medicament is formulated for administration once daily for four weeks followed by a dosing holiday.

60. The use of any one of claims 1-59, wherein the compound is Compound 67A:



(Compound 67A);

or a pharmaceutically acceptable salt thereof.