

By virtue of the role played by the Raf family kinases in these cancers and exploratory studies with a range of preclinical and therapeutic agents, including one selectively targeted to inhibition of B-Raf kinase activity (King A.J., et al., (2006) *Cancer Res.* 66:11100-11105), it is generally accepted that inhibitors of one or more Raf family

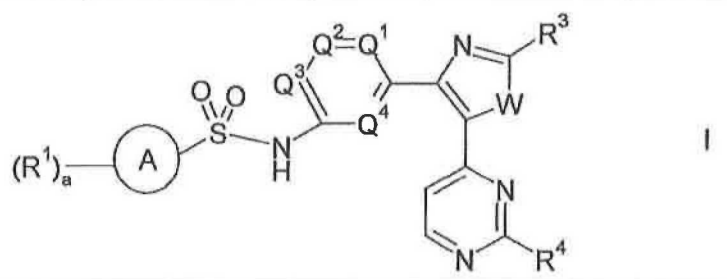
5 kinases will be useful for the treatment of such cancers or other condition associated with Raf kinase.

Mutation of B-Raf has also been implicated in other conditions, including cardio-facio cutaneous syndrome (Rodriguez-Viciano et al *Science* (2006) 311(5765) 1287-1290)

10 and polycystic kidney disease (Nagao et al *Kidney Int.* (2003) 63(2) 427-437).

SUMMARY OF THE INVENTION

In a first aspect of the present invention, there is provided a compound of formula (I)



15 wherein:

a is 0, 1, 2 or 3;

each R¹ is the same or different and is independently selected from halo, alkyl, haloalkyl, -OR⁶, -CO₂R⁶, -NR⁶R⁷, and -CN;

20 Ring A is selected from C₃₋₆cycloalkyl, phenyl, 5-6 membered heterocycle and 5-6 membered heteroaryl, said heterocycle and said heteroaryl each having 1 or 2 heteroatoms selected from N, O and S;

each of Q¹, Q², Q³ and Q⁴ is CH, C-R² or N, wherein not more than one of Q¹, Q², Q³, and Q⁴ is N;

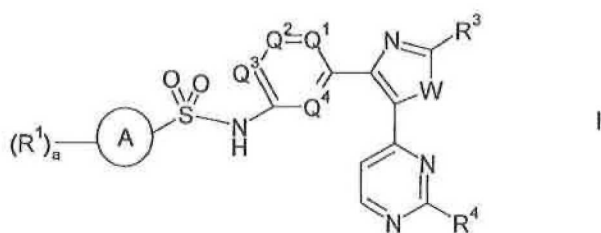
25 each R² is the same or different and is independently selected from halo, alkyl, haloalkyl, and -OR⁶;

W is selected from -O- and -S-;

R³ is selected from H, alkyl, haloalkyl-, -alkylene-OH, -NR⁶R⁷, -C₃₋₆cycloalkyl, -alkylene-C(O)-OH, -alkylene-NH₂, and Het;

wherein said R^3 C_{3-6} cycloalkyl is optionally substituted with 1 or 2 substituents
 which are the same or different and are independently selected from
 halo,
 C_{1-3} alkyl, halo C_{1-3} alkyl, OH, O- C_{1-3} alkyl, oxo, S(C_{1-3} alkyl), SO_2 , NH_2 ,
 N(H) C_{1-3} alkyl and $N(C_{1-3}alkyl)_2$;
 Het is a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N,
 O and S and optionally substituted with 1 or 2 substituents which are the
 same or different and are each independently selected from halo,
 C_{1-3} alkyl, halo C_{1-3} alkyl, O- C_{1-3} alkyl, C_{1-3} alkylene-O- C_{1-3} alkyl, OH, C_{1-3}
 alkylene-OH, oxo, $SO_2(C_{1-3}alkyl)$, $C_{1-3}alkylene-SO_2(C_{1-3}alkyl)$, NH_2 ,
 N(H) $C_{1-3}alkyl$, $N(C_{1-3}alkyl)_2$, CN, and $-CH_2CN$;
 R^4 is selected from H, alkyl, haloalkyl, alkenyl, $-OR^6$, $-R^5-OR^6$, $-R^5-CO_2R^6$, $-R^5-SO_2R^6$,
 $-R^5-Het$, $-R^5-C(O)-Het$, $-N(H)R^8$, $-N(CH_3)R^8$, and $-R^5-NR^6R^7$;
 each R^5 is the same or different and is independently C_{1-4} alkylene;
 each R^6 and each R^7 is the same or different and is independently selected from H,
 alkyl, haloalkyl, $-C(O)-alkyl$, and $-C(O)-cycloalkyl$;
 R^8 is selected from H, alkyl (optionally substituted by $-OH$), haloalkyl, C_{3-6} cycloalkyl, $-R^5-$
 C_{3-6} cycloalkyl, Het^2 , $-R^5-Het^2$, $-R^5-OR^6$, $-R^5-O-R^5-OR^6$, $-R^5-C(O)_2R^6$, $-R^5-$
 $C(O)NR^6R^7$, $-R^5-N(H)C(O)-R^6$, $-R^5-N(H)C(O)-R^5-OR^6$, $-R^5-N(H)C(O)_2R^6$, $-R^5-$
 NR^6R^7 , $-R^5-S(O)_2R^6$, $-R^5-CN$, and $-R^5-N(H)S(O)_2R^6$;
 wherein said R^8 C_{3-6} cycloalkyl is optionally substituted with 1 or 2 substituents
 which are the same or different and are independently selected from
 halo,
 C_{1-3} alkyl, halo C_{1-3} alkyl, OH, O- C_{1-3} alkyl, oxo, S(C_{1-3} alkyl), $SO_2(C_{1-3}alkyl)$,
 NH_2 , N(H) $C_{1-3}alkyl$ and $N(C_{1-3}alkyl)_2$, and N(H) $SO_2C_{1-3}alkyl$;
 and
 Het^2 is a 4-6 membered heterocycle having 1 or 2 heteroatoms selected from N,
 O and S and optionally substituted with 1, 2, 3, 4 or 5 C_{1-3} alkyl or 1 or 2
 substituents which are the same or different and are each independently
 selected from halo, C_{1-3} alkyl, halo C_{1-3} alkyl, O- C_{1-3} alkyl,
 C_{1-3} alkylene-O- C_{1-3} alkyl, OH, C_{1-3} alkylene-OH, oxo, $SO_2(C_{1-3}alkyl)$, C_{1-3}
 alkylene- $SO_2(C_{1-3}alkyl)$, NH_2 , N(H) $C_{1-3}alkyl$, $N(C_{1-3}alkyl)_2$, N(H) SO_2C_{1-3}
 alkyl, $C(O)(C_{1-3}alkyl)$, $CO_2(C_{1-4}alkyl)$, CN, and $-CH_2CN$;
 and pharmaceutically acceptable salts thereof.

In a second aspect of the present invention, there is provided a compound of formula (I):



wherein:

a is 0, 1, 2 or 3;

each R¹ is the same or different and is independently selected from halo, alkyl, haloalkyl, -OR⁶, -CO₂R⁶, -NR⁶R⁷, and -CN;

Ring A is selected from C₃-6cycloalkyl, phenyl, 5-6 membered heterocycle and 5-6 membered heteroaryl, said heterocycle and said heteroaryl each having 1 or 2 heteroatoms selected from N, O and S;

each of Q¹, Q², Q³ and Q⁴ is CH, C-R² or N, wherein not more than one of Q¹, Q², Q³, and Q⁴ is N;

each R² is the same or different and is independently halo, alkyl, haloalkyl, or -OR⁶;

W is -O- or -S-;

R³ is H, alkyl, haloalkyl, alkylene-OH, NR⁶R⁷, C₃-6cycloalkyl, or Het;

wherein said R³ C₃-6cycloalkyl is optionally substituted with 1 or 2 substituents which are the same or different and are independently selected from halo,

C₁-3alkyl, haloC₁-3alkyl, OH, O-C₁-3alkyl, oxo, S(C₁-3alkyl), SO₂, NH₂, N(H)C₁-3alkyl and N(C₁-3alkyl)₂;

Het is a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S and optionally substituted with 1 or 2 substituents which are the same or different and are each independently selected from halo, C₁-3alkyl, haloC₁-3alkyl, O-C₁-3alkyl, C₁-3alkylene-O-C₁-3alkyl, OH, C₁-3alkylene-OH, oxo, SO₂(C₁-3alkyl), C₁-3alkylene-SO₂(C₁-3alkyl), NH₂, N(H)C₁-3alkyl, N(C₁-3alkyl)₂, CN, and -CH₂CN;

R⁴ is H, alkyl, haloalkyl, alkenyl, -OR⁶, -R⁵-OR⁶, -R⁵-CO₂R⁶, -R⁵-SO₂R⁶, -R⁵-Het, -N(H)R⁸, -N(CH₃)R⁸, or -R⁵-NR⁶R⁷;

each R⁵ is the same or different and is independently C₁-4alkylene;

each R⁶ and each R⁷ is the same or different and is independently H, alkyl or haloalkyl; and

R⁸ is selected from H, alkyl, haloalkyl, C₃-6cycloalkyl, -R⁵-C₃-6cycloalkyl, Het², -R⁵-Het², -R⁵-OR⁶, -R⁵-O-R⁵-OR⁶, -R⁵-C(O)₂R⁶, -R⁵-C(O)NR⁶R⁷, -R⁵-N(H)C(O)-R⁶,

-R⁵-N(H)C(O)-R⁵-OR⁶, -R⁵-N(H)C(O)₂-R⁶, -R⁵-NR⁶R⁷, -R⁵-S(O)₂R⁶, and -R⁵-N(H)S(O)₂R⁶;

wherein said R⁸ C₃₋₆cycloalkyl is optionally substituted with 1 or 2 substituents which are the same or different and are independently selected from

halo,

C₁₋₃alkyl, haloC₁₋₃alkyl, OH, O-C₁₋₃alkyl, oxo, S(C₁₋₃alkyl), SO₂(C₁₋₃alkyl), NH₂, N(H)C₁₋₃alkyl and N(C₁₋₃alkyl)₂, and N(H)SO₂C₁₋₃alkyl;

and

Het² is a 4-6 membered heterocycle having 1 or 2 heteroatoms selected from N,

O and S and optionally substituted with 1, 2, 3, 4 or 5 C₁₋₃alkyl or 1 or 2 substituents which are the same or different and are each independently selected from halo, C₁₋₃alkyl, haloC₁₋₃alkyl, O-C₁₋₃alkyl,

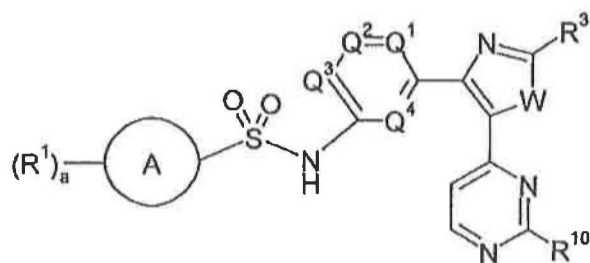
C₁₋₃alkylene-O-C₁₋₃alkyl, OH, C₁₋₃alkylene-OH, oxo, SO₂(C₁₋₃alkyl), C₁₋₃alkylene-SO₂(C₁₋₃alkyl), NH₂, N(H)C₁₋₃alkyl, N(C₁₋₃alkyl)₂, N(H)SO₂C₁₋₃alkyl, C(O)(C₁₋₃alkyl), CO₂(C₁₋₄alkyl), CN, and -CH₂CN;

or a pharmaceutically acceptable salt thereof.

In a third aspect of the present invention, there is provided a pharmaceutical composition comprising a compound as described in the first aspect and a pharmaceutically acceptable carrier, diluent or excipient.

In a fourth aspect of the present invention, there is provided a use of a therapeutically effective amount of a compound as described in the first aspect in the manufacture of a medicament for treating melanoma in a human in need thereof.

In a fifth aspect of the present invention, there is provided a process for preparing a compound as described in the first aspect, said process comprising reacting a compound of formula (VIII):

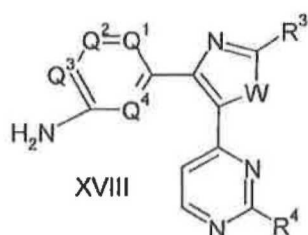


wherein R^{10} is halo or thiomethyl;

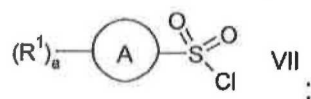
with one of:

- 5 i) molecular hydrogen
 ii) an alkyl metal reagent or alkenyl metal reagent
 iii) an alcohol, or
 iv) a compound of formula (IX): $N(R^a)-R^b$, wherein R^a is H or CH_3 , to prepare
a compound of formula (I).

- 10 In a sixth aspect of the present invention, there is provided a process for preparing a compound as described in the first aspect comprising reacting a compound of formula (XVIII):

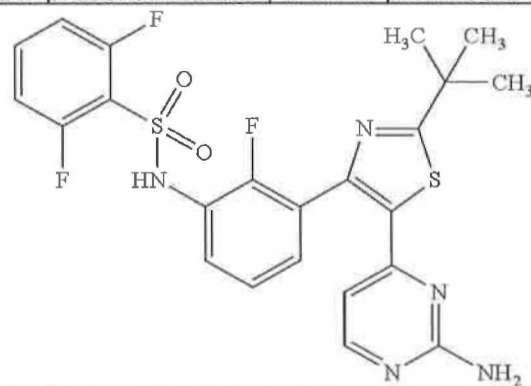


with a compound of formula (VII):



to prepare a compound of formula (I).

In a seventh aspect of the present invention, there is provided a compound of formula

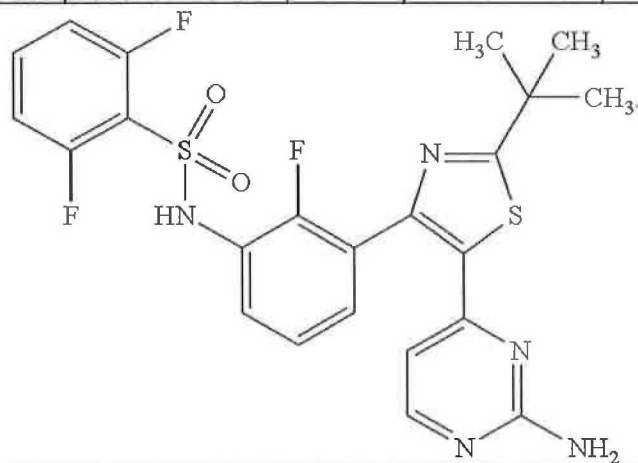


or a pharmaceutically acceptable salt thereof.

In an eighth aspect of the present invention, there is provided a pharmaceutical composition, comprising a compound as described in the seventh aspect, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

In a ninth aspect of the present invention, there is provided a use of an effective amount of a compound as described in the seventh aspect in the manufacture of a medicament for treating melanoma in a human in need thereof.

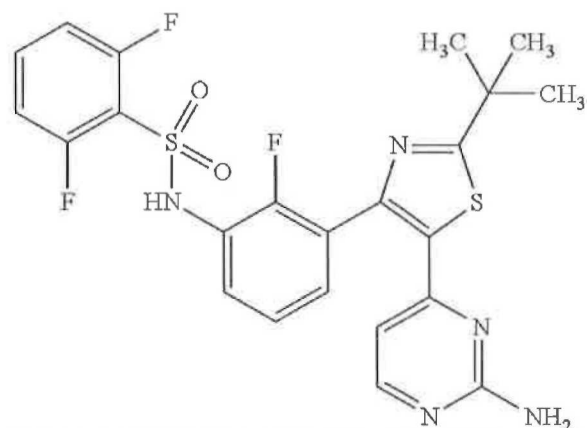
In a tenth aspect of the present invention, there is provided a compound of formula



In an eleventh aspect of the present invention, there is provided a pharmaceutical composition, comprising a compound as described in the tenth aspect, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

In a twelfth aspect of the present invention, there is provided a use of an effective amount of a compound as described in the tenth aspect in the manufacture of a medicament for treating melanoma in a human in need thereof.

In a thirteenth aspect of the present invention, there is provided a pharmaceutically acceptable salt of the compound of formula



5 In a fourteenth aspect of the present invention, there is provided a pharmaceutical composition, comprising a compound as described in the thirteenth aspect, together with one or more of pharmaceutically acceptable carriers, diluents or excipients.

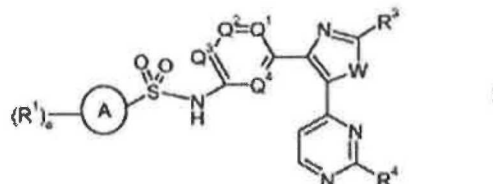
10 In a fifteenth aspect of the present invention, there is provided a use of an effective amount of a compound as described in the thirteenth aspect in the manufacture of a medicament for treating melanoma in a human in need thereof.

In a sixteenth aspect of the present invention, there is provided N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide mesylate.

15 In a seventeenth aspect of the present invention, there is provided a pharmaceutical composition, comprising a compound as described in the sixteenth aspect, together with one or more of pharmaceutically acceptable carriers, diluents or excipients.

20 In an eighteenth aspect of the present invention, there is provided a use of an effective amount of a compound as described in the sixteenth aspect in the manufacture of a medicament for treating melanoma in a human in need thereof.

In a first aspect of the present invention, there is ~~There may be~~ provided compounds of formula (I):



5 wherein:

a is 0, 1, 2 or 3;

each R¹ is the same or different and is independently selected from halo, alkyl, haloalkyl, -OR⁶, -CO₂R⁶, -NR⁶R⁷, and -CN;

10 Ring A is selected from C₃₋₆cycloalkyl, phenyl, 5-6 membered heterocycle and 5-6 membered heteroaryl, said heterocycle and said heteroaryl each having 1 or 2 heteroatoms selected from N, O and S;

each of Q¹, Q², Q³ and Q⁴ is CH, C-R² or N, wherein not more than one of Q¹, Q², Q³, and Q⁴ is N;

15 each R² is the same or different and is independently selected from halo, alkyl, haloalkyl, and -OR⁶;

W is selected from -O- and -S-;

R³ is selected from H, alkyl, haloalkyl-, -alkylene-OH, -NR⁶R⁷, -C₃₋₆cycloalkyl, -alkylene-C(O)-OH, -alkylene-NH₂, and Het;

20 wherein said R³ C₃₋₆cycloalkyl is optionally substituted with 1 or 2 substituents which are the same or different and are independently selected from halo, C₁₋₃alkyl, haloC₁₋₃alkyl, OH, O-C₁₋₃alkyl, oxo, S(C₁₋₃alkyl), SO₂, NH₂, N(H)C₁₋₃alkyl and N(C₁₋₃alkyl)₂;

25 Het is a 5-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S and optionally substituted with 1 or 2 substituents which are the same or different and are each independently selected from halo, C₁₋₃alkyl, haloC₁₋₃alkyl, O-C₁₋₃alkyl, C₁₋₃alkylene-O-C₁₋₃alkyl, OH, C₁₋₃alkylene-OH, oxo, SO₂(C₁₋₃alkyl), C₁₋₃alkylene-SO₂(C₁₋₃alkyl), NH₂, N(H)C₁₋₃alkyl, N(C₁₋₃alkyl)₂, CN, and -CH₂CN;

30 R⁴ is selected from H, alkyl, haloalkyl, alkenyl, -OR⁶, -R⁵-OR⁶, -R⁵-CO₂R⁶, -R⁵-SO₂R⁶, -R⁵-Het, -R⁵-C(O)-Het, -N(H)R⁸, -N(CH₃)R⁸, and -R⁵-NR⁶R⁷; each R⁵ is the same or different and is independently C₁₋₄alkylene;

each R⁶ and each R⁷ is the same or different and is independently selected from H, alkyl, haloalkyl, -C(O)-alkyl, and -C(O)-cycloalkyl;

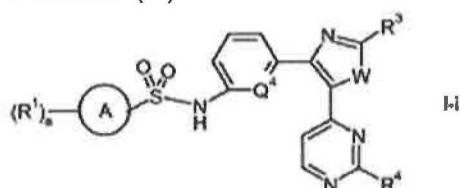
R⁸ is selected from H, alkyl (optionally substituted by -OH), haloalkyl, C₃₋₆cycloalkyl, -R⁵-C₃₋₆cycloalkyl, Het², -R⁵-Het², -R⁵-OR⁶, -R⁵-O-R⁵-OR⁶, -R⁵-C(O)₂R⁶, -R⁵-C(O)NR⁶R⁷, -R⁵-N(H)C(O)-R⁶, -R⁵-N(H)C(O)-R⁵-OR⁶, -R⁵-N(H)C(O)₂-R⁶, -R⁵-NR⁶R⁷, -R⁵-S(O)₂R⁶, -R⁵-CN, and -R⁵-N(H)S(O)₂R⁶;

wherein said R⁸ C₃₋₆cycloalkyl is optionally substituted with 1 or 2 substituents which are the same or different and are independently selected from halo, C₁₋₃alkyl, haloC₁₋₃alkyl, OH, O-C₁₋₃alkyl, oxo, S(C₁₋₃alkyl), SO₂(C₁₋₃alkyl), NH₂, N(H)C₁₋₃alkyl and N(C₁₋₃alkyl)₂, and N(H)SO₂C₁₋₃alkyl; and

Het² is a 4-6 membered heterocycle having 1 or 2 heteroatoms selected from N, O and S and optionally substituted with 1, 2, 3, 4 or 5 C₁₋₃alkyl or 1 or 2 substituents which are the same or different and are each independently selected from halo, C₁₋₃alkyl, haloC₁₋₃alkyl, O-C₁₋₃alkyl, C₁₋₃alkylene-O-C₁₋₃alkyl, OH, C₁₋₃alkylene-OH, oxo, SO₂(C₁₋₃alkyl), C₁₋₃alkylene-SO₂(C₁₋₃alkyl), NH₂, N(H)C₁₋₃alkyl, N(C₁₋₃alkyl)₂, N(H)SO₂C₁₋₃alkyl, C(O)(C₁₋₃alkyl), CO₂(C₁₋₄alkyl), CN, and -CH₂CN;

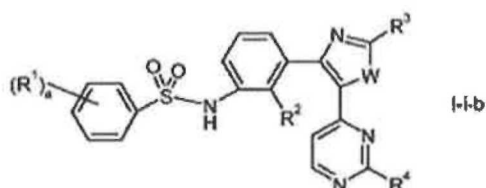
and R⁹ and R¹⁰ are independently selected from H and alkyl, and pharmaceutically acceptable salts thereof.

In a second aspect of the present invention, there is There may be provided compounds of formula (I-i)



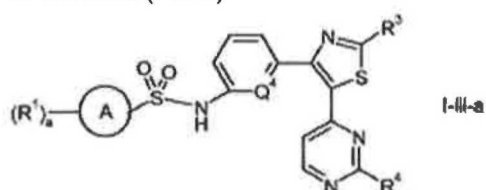
wherein Q⁴ is CH or C-R² and all other variables are as defined above, and pharmaceutically acceptable salts thereof.

In a third aspect of the present invention, there is There may be provided compounds of formula (I-i-b)



wherein all variables are as defined above, and pharmaceutically acceptable salts thereof.

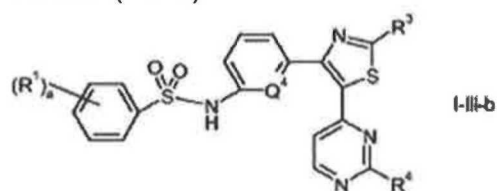
- 5 In a fourth aspect of the present invention, there is ~~There may be~~ provided compounds of formula (I-iii-a)



wherein Q⁴ is CH or C-R² and all other variables are as defined above, and pharmaceutically acceptable salts thereof.

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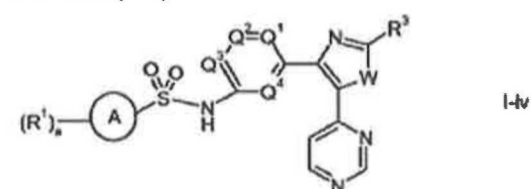
- In a fifth aspect of the present invention, there is ~~There may be~~ provided compounds of formula (I-iii- b)



wherein Q⁴ is CH or C-R² and all other variables are as defined above, and pharmaceutically acceptable salts thereof.

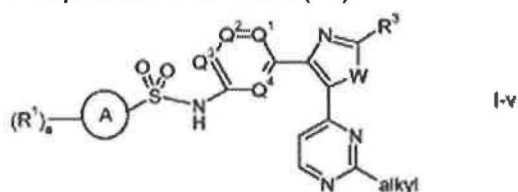
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- In a sixth aspect of the present invention, there is ~~There may be~~ provided compounds of formula (I-iv):



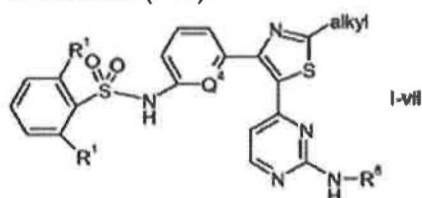
wherein Q^4 is CH or C- R^2 and all other variables are as defined above, and pharmaceutically acceptable salts thereof.

- 5 In a seventh aspect of the present invention, there is There may be provided compounds of formula (I-v):



wherein Q^4 is CH or C- R^2 and all other variables are as defined above, and pharmaceutically acceptable salts thereof.

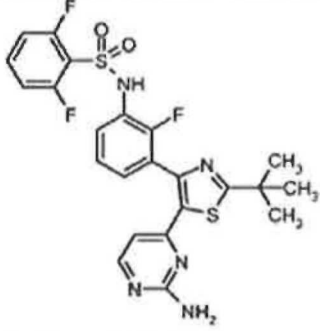
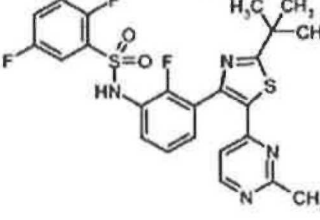
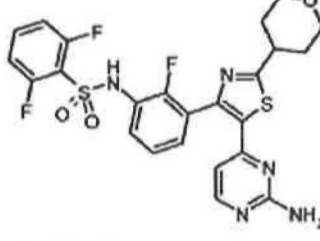
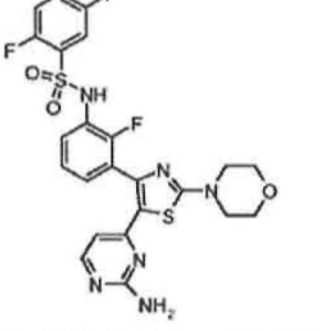
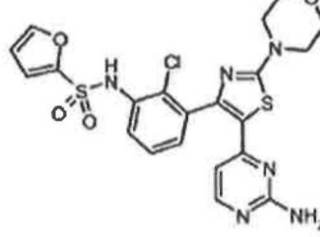
- 10 In an eighth aspect of the present invention, there is There may be provided compounds of formula (I-vii):

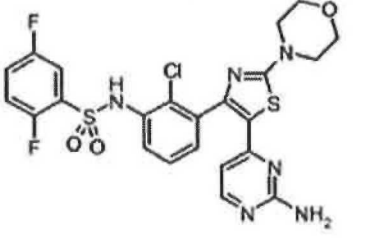
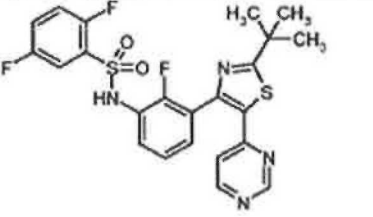
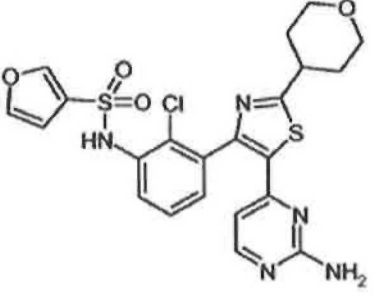
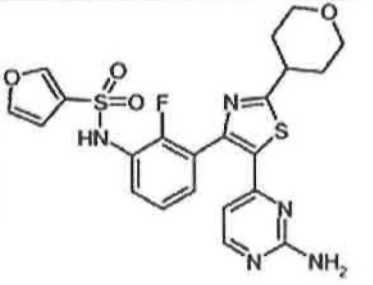


wherein Q^4 is CH or C- R^2 , and all variables are as defined above, and pharmaceutically acceptable salts thereof.

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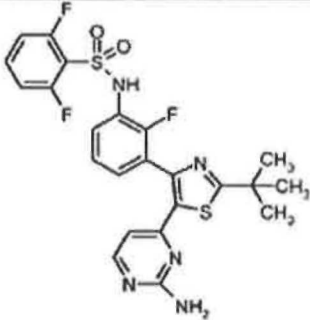
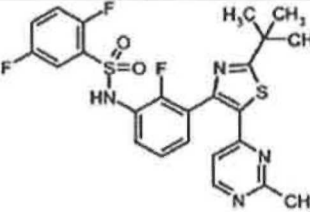
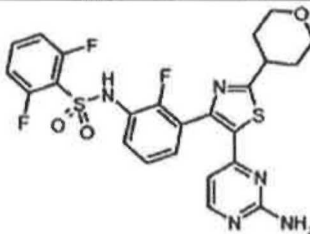
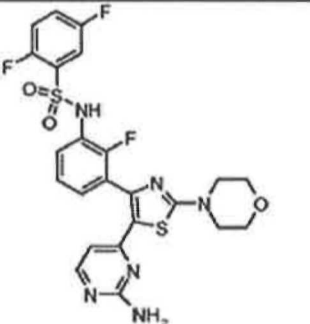
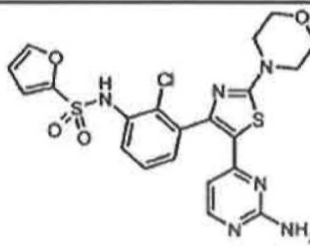
- In a ninth aspect of the present invention, there is There may be provided a compound selected from:

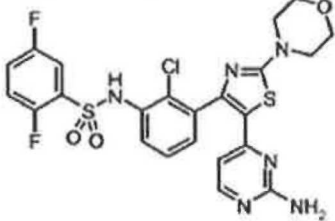
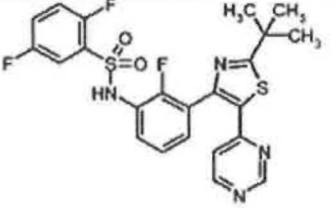
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide,	
N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide,	
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide,	
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide,	
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide,	

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide, and	
N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide	
<u>N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide</u>	
<u>N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide</u>	

and pharmaceutically acceptable salts thereof.

And more particularly, there is may be provided a compound selected from:

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide,	
N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide,	
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide,	
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide,	
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide,	

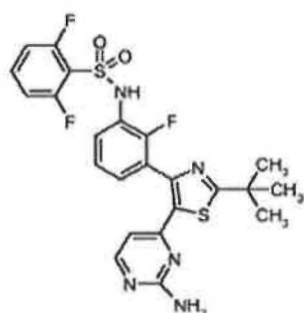
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide, and	
N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide	

and pharmaceutically acceptable salts thereof.

~~In a tenth aspect of the present invention, there is~~ There may be provided a compound selected from

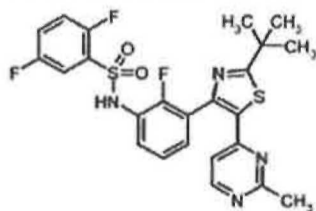
- N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;
- N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;
- N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;
- N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;
- N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;
- N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide; and
- N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide.

~~In another aspect of the present invention there is~~ There may be provided N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide



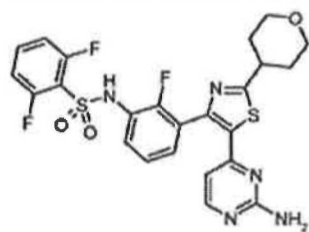
and pharmaceutically acceptable salts thereof. Particularly the free base of the compound.

- 5 ~~In another aspect of the present invention there is~~ There may be provided N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide



and pharmaceutically acceptable salts thereof. Particularly the free base of the compound.

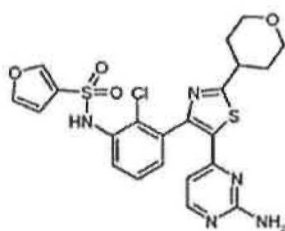
- 10 ~~In another aspect of the present invention there is~~ There may be provided N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide



and pharmaceutically acceptable salts thereof. Particularly the free base of the compound.

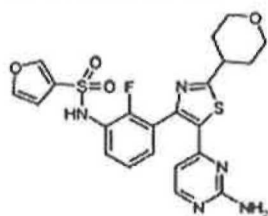
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- ~~In another aspect of the present invention there is~~ There may be provided N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide



and pharmaceutically acceptable salts thereof. Particularly the free base of the compound.

- 5 ~~In another aspect of the present invention there is~~ There may be provided N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide



and pharmaceutically acceptable salts thereof. Particularly the free base of the compound.

~~In another aspect of the present invention, there is~~ There may be provided a pharmaceutical composition comprising a compound of formula (I) (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof. In one embodiment, the pharmaceutical composition further comprises one or more of pharmaceutically acceptable carriers, diluents or excipients. ~~In one aspect, the present invention provides~~ There may be provided a pharmaceutical composition comprising any of

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide; or

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide

or a pharmaceutically acceptable salt thereof. Particularly the free base of any of the foregoing compounds.

~~In another aspect of the present invention, there is~~ There may be provided a method of treating a susceptible neoplasm in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof. Susceptible neoplasms include e.g., Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers.

~~In another aspect of the present invention, there is~~ There may be provided a method of treating breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer, in a mammal, particularly a human, in need thereof, comprising administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

~~In another aspect of the present invention, there is~~ There may be provided a method of treating a susceptible neoplasm in a mammal, particularly a human, in need thereof, comprising administering to the mammal (e.g. human) a therapeutically effective amount of a compound selected from

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;
 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;
 5 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;
 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide; and
 N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;
 10 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide;
 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide, and pharmaceutically acceptable salts thereof,
 15 and particularly selected from
 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;
 N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;
 20 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;
 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;
 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;
 25 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide; and
 N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide; and
 30 pharmaceutically acceptable salts thereof. Particularly the free base of any of the compounds.

~~In another aspect of the present invention, there is~~ There may be provided a method of treating breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell
 35 lung cancer, ovarian cancer, or thyroid cancer, in a mammal, particularly a human, in need thereof, comprising administering to the mammal (e.g. human) a therapeutically effective amount of

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide; or

5 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

or a pharmaceutically acceptable salt thereof. Particularly the free base of any of the compounds.

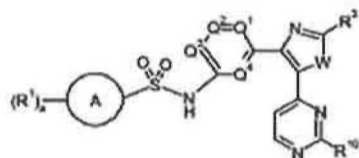
10 ~~In another aspect, there is~~ There may be provided a method for treating cholangiocarcinoma, colorectal cancer, melanoma or thyroid cancer in a human in need thereof, comprising administering to the human, a therapeutically effective amount of N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

15 N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide; or

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

20 or a pharmaceutically acceptable salt thereof. Particularly the free base of any of the compounds.

~~In another aspect of the present invention, there is~~ There may be provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof. The process comprises reacting a compound of formula (VIII):



VIII

25

wherein R^{10} is halo or thiomethyl;

with one of:

i) molecular hydrogen, or

ii) an alkyl metal reagent or alkenyl metal reagent, or

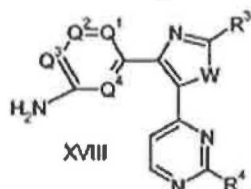
iii) an alcohol, or

iv) a compound of formula (IX): $N(R^a)-R^8$, wherein R^a is H or CH_3 and R^8 is as defined above;

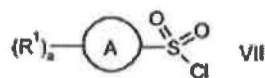
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to prepare a compound of formula (I).

In another aspect of the present invention, there is There may be provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt thereof. The process comprises reacting a compound of formula (XVIII):



with a compound of formula (VII):



In another aspect of the present invention, there is There may be provided a compound of formula (I), (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof for use in therapy.

In another aspect, there is There may be provided a compound of formula (I) (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof for use in the treatment of a susceptible neoplasm (e.g., Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers) in a mammal (e.g., human) in need thereof.

~~In another aspect, there is~~ There may be provided a compound of formula (I) (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof for use in the treatment of breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer in a mammal (e.g., human) in need thereof.

~~In another aspect, there is~~ There may be provided a compound selected from
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-
2,6-difluorobenzenesulfonamide;
N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-
2,5-difluorobenzenesulfonamide;
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-
fluorophenyl}-2,6-difluorobenzenesulfonamide;
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-
difluorobenzenesulfonamide;
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-
furansulfonamide;
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-
difluorobenzenesulfonamide; and
N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-
difluorobenzenesulfonamide;
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-
chlorophenyl}-3-furansulfonamide;
N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-
fluorophenyl}-3-furansulfonamide; and
pharmaceutically acceptable salts thereof (particularly the free base forms)
for use in the treatment of a susceptible neoplasm (e.g., Barret's adenocarcinoma;
biliary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central
nervous system tumors including primary CNS tumors such as glioblastomas,
astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS
tumors (i.e., metastases to the central nervous system of tumors originating outside of
the central nervous system); colorectal cancer including large intestinal colon
carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell
carcinoma of the head and neck; hematologic cancers including leukemias and
lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML),
myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-

Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers) in a mammal (e.g., human) in need thereof.

~~In another aspect, there is~~ There may be provided

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide; or

N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide;

or a pharmaceutically acceptable salt thereof (particularly the free base of any of the compounds) for use in the treatment of breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer in a mammal (e.g., human) in need thereof.

~~In another aspect of the present invention, there is~~ There may be provided the use of a compound of formula (I) (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in the treatment of a susceptible neoplasm (e.g., Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e.,

metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers) in a mammal (e.g., human) in need thereof.

~~In another aspect of the present invention, there is~~ There may be provided the use of a compound of formula (I) (including any particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in the treatment of breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer in a mammal (e.g., human) in need thereof.

~~In another aspect of the present invention, there is~~ There may be provided the use of a compound selected from

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide; and

N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide; and

pharmaceutically acceptable salts thereof (particularly the free base forms)

for the preparation of a medicament for the treatment of a susceptible neoplasm (e.g.,

- 5 Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large
- 10 intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma
- 15 and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers) in a mammal (e.g., human) in need thereof.

| 20 In ~~a another aspect of the present invention, there is~~ There may be provided the use of a compound selected from

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

25 N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

30 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide;

35 N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide; and

pharmaceutically acceptable salts thereof (particularly the free base forms) for the preparation of a medicament for the treatment of breast cancer,

5 cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer in a mammal (e.g., human) in need thereof.

| ~~In another aspect of the present invention, there is~~ There may be provided a pharmaceutical composition comprising a compound of formula (I) (including any
10 particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof for use in the treatment of a susceptible neoplasm (e.g., Barret's adenocarcinoma; biliary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and
15 secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous
20 leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers
25 including melanomas; and thyroid cancers) in a mammal (e.g., human) in need thereof.

| ~~In a another aspect of the present invention, there is~~ There may be provided a pharmaceutical composition comprising a compound of formula (I) (including any
30 particular sub-generic formula described herein) or a pharmaceutically acceptable salt thereof for use in the treatment of breast cancer, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer in a mammal (e.g., human) in need thereof.

| ~~In a another aspect of the present invention, there is~~ There may be provided a pharmaceutical composition comprising a compound selected from
35 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

5 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;

10 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide;

15 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide; and

pharmaceutically acceptable salts thereof (particularly the free base forms)

for use in the treatment of a susceptible neoplasm (e.g., Barret's adenocarcinoma;

billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central

20 nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon

carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell

25 carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and

erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer

30 and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers) in a mammal (e.g., human) in need thereof.

| In a another aspect of the present invention, there is There may be provided a

35 pharmaceutical composition comprising a compound selected from

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(2-methyl-4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide;

5 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2-furansulfonamide;

10 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(4-morpholinyl)-1,3-thiazol-4-yl]-2-chlorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[2-(1,1-dimethylethyl)-5-(4-pyrimidinyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,5-difluorobenzenesulfonamide;

N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-chlorophenyl}-3-furansulfonamide;

15 N-{3-[5-(2-amino-4-pyrimidinyl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-thiazol-4-yl]-2-fluorophenyl}-3-furansulfonamide; and

pharmaceutically acceptable salts thereof (particularly the free base forms) for use in the treatment of breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer in a mammal (e.g., human) in need thereof.

These and other aspects of the invention are described further in the Detailed Description and Examples which follow.

BRIEF DESCRIPTION OF THE DRAWINGS

25 **Figure 1** is an X-Ray Powder Diffraction Pattern of a particular solid state form of N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The XRD pattern is expressed in terms of 2 theta angles and obtained with a PANalytical diffractometer equipped with a diffracted beam nickel filter using copper Ka X-radiation, according to the procedures described herein.

30 **Figure 2** is a differential scanning calorimetry (DSC) thermogram of a particular solid state form of N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The DSC was carried out on a TA