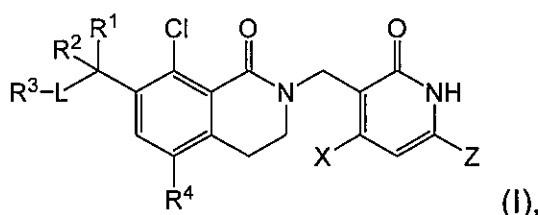


Claims

We Claim:

1. A compound of formula (I):



- 5 or a pharmaceutically acceptable salt thereof,
wherein:

R^1 is selected from the group consisting of H, F, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $C(O)R^5$, C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where each said C_1 - C_4 alkyl or C_1 - C_4 alkoxy is optionally substituted by one or more R^6 ,
10 and each said C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R^7 ;

R^2 is H, F or C_1 - C_4 alkyl;

L is a bond or a C_1 - C_4 alkylene;

- 15 R^3 is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, OH, CN, $C(O)R^8$, $COOR^9$, $NR^{10}R^{11}$, OR^{12} , C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where each said C_1 - C_4 alkyl or C_1 - C_4 alkoxy is optionally substituted by one or more R^6 , and each said C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R^7 ;

- 20 R^4 is H, halo or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^6 ;

R^5 is C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

each R^6 is independently OH, F, CN or C_1 - C_4 alkoxy;

- 25 each R^7 is independently C_1 - C_4 alkyl, OH, F, CN, C_1 - C_4 alkoxy, =O, CHO, $C(O)R^{13}$, SO_2R^{13} or 3-6 membered heterocyclyl;

R^8 is C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

R^9 is H or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

R^{10} and R^{11} are independently H or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

5 R^{12} is selected from the group consisting of C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where each said C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R^7 ;

10 each R^{13} is independently C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{15} ;

each R^{14} and R^{15} is independently OH, F, CN or C_1 - C_4 alkoxy; and

X and Z are independently C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkoxy or C_1 - C_4 fluoroalkoxy.

2. The compound or salt of claim 1, wherein R^2 is H.

15 3. The compound or salt of claim 1 or 2, wherein R^4 is Cl, F, Br or CH_3 .

4. The compound or salt of of claim 1, 2 or 3, wherein X is CH_3 , OCH_3 or $OCHF_2$ and Z is CH_3 .

5. The compound or salt any one of claims 1 to 4, wherein R^1 is C_1 - C_4 alkoxy optionally substituted by one or more R^6 .

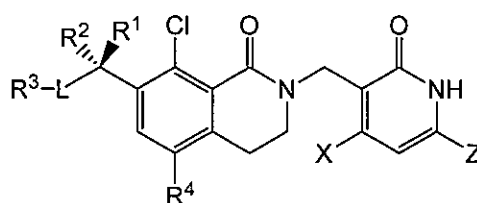
20 6. The compound or salt of claim 5 wherein said C_1 - C_4 alkoxy is OCH_3 .

7. The compound or salt of any one of claims 1 to 4, wherein R^1 is C_1 - C_4 alkyl optionally substituted by one or more R^6 .

8. The compound or salt of any one of claims 1 to 7, wherein L is a bond and R^3 is 3-12 membered heterocyclyl optionally substituted by one or more R^7 .

9. The compound or salt of claim 8, wherein said 3-12 membered heterocyclyl is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each optionally substituted by one or more R^7 .

10. A compound of Formula (I-A):



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_1 - C_4 alkoxy;

R^2 is H;

L is a bond;

R^3 is 3-12 membered heterocyclyl, optionally substituted by one or more R^7 ;

R^4 is H or Cl;

each R^7 is independently C_1 - C_4 alkyl, OH, F, CN, C_1 - C_4 alkoxy, =O, CHO, $C(O)R^{13}$, SO_2R^{13} or 3-6 membered heterocyclyl;

each R^{13} is independently C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{15} ;

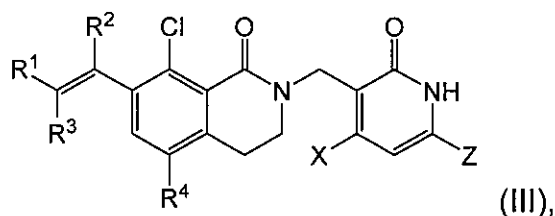
each R^{15} is independently OH, F, CN or C_1 - C_4 alkoxy; and

X and Z are independently C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkoxy or C_1 - C_4 fluoroalkoxy.

11. The compound or salt of claim 10, wherein R^3 is 3-12 membered heterocyclyl selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each optionally substituted by one or more R^7 .

12. A compound that is 5,8-dichloro-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(*R*)-methoxy(oxetan-3-yl)methyl]-3,4-dihydroisoquinolin-1(2*H*)-one, or a pharmaceutically acceptable salt thereof.

13. A compound of formula (III):



or a pharmaceutically acceptable salt thereof,

wherein:

5 R^1 and R^3 are taken together to form a 3-12 membered heterocyclyl optionally substituted by one or more R^7 ;

R^2 is H, F or C_1 - C_4 alkyl;

R^4 is H, halo or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^6 ;

10 each R^6 is independently OH, F, CN or C_1 - C_4 alkoxy;

each R^7 is independently C_1 - C_4 alkyl, OH, F, CN, C_1 - C_4 alkoxy, =O, CHO, $C(O)R^{13}$, SO_2R^{13} or 3-6 membered heterocyclyl;

each R^{13} is independently C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{15} ;

15 each R^{15} is independently OH, F, CN or C_1 - C_4 alkoxy; and

X and Z are independently C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkoxy or C_1 - C_4 fluoroalkoxy.

14. The compound or salt of claim 13, wherein R^1 and R^3 are taken together to form
20 a 3-12 membered heterocyclyl selected from the group consisting of azetidiny, pyrrolidiny, piperidiny and homopiperidiny, each optionally substituted by one or more R^7 .

15. The compound or salt of claim 14, wherein R^7 is CHO, $C(O)R^{13}$ or SO_2R^{13} and
25 each R^{13} is independently C_1 - C_4 alkyl optionally substituted by one or more R^{15} .

16. A pharmaceutical composition comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

17. A method for the treatment of abnormal cell growth in a subject, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.

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18. The method of claim 17, wherein the abnormal cell growth is cancer.

19. The method of claim 17 or 18, wherein the subject is a human.

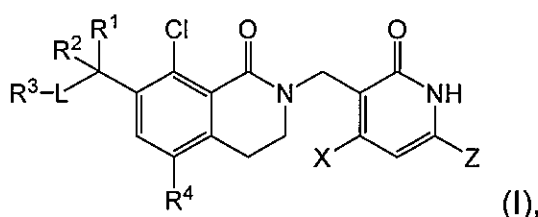
10

20. A compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for use in the treatment of abnormal cell growth in a subject.

Claims

We Claim:

1. A compound of formula (I):



- 5 or a pharmaceutically acceptable salt thereof,
wherein:

R^1 is selected from the group consisting of F, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $C(O)R^5$, C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where each said C_1 - C_4 alkyl or C_1 - C_4 alkoxy is optionally substituted by one or more R^6 , and
10 each said C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R^7 ;

R^2 is H, F or C_1 - C_4 alkyl;

L is a bond or a C_1 - C_4 alkylene;

R^3 is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, OH, CN, $C(O)R^8$, $COOR^9$, $NR^{10}R^{11}$, OR^{12} , C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where each said C_1 - C_4 alkyl or C_1 - C_4 alkoxy is optionally substituted by one or more R^6 , and each said C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R^7 ;

R^4 is H, halo or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted
20 by one or more R^6 ;

R^5 is C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

each R^6 is independently OH, F, CN or C_1 - C_4 alkoxy;

each R^7 is independently C_1 - C_4 alkyl, OH, F, CN, C_1 - C_4 alkoxy, =O, CHO, $C(O)R^{13}$, SO_2R^{13} or 3-6 membered heterocyclyl;

R^8 is C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

R^9 is H or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

R^{10} and R^{11} are independently H or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{14} ;

5 R^{12} is selected from the group consisting of C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where each said C_3 - C_8 cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R^7 ;

10 each R^{13} is independently C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{15} ;

each R^{14} and R^{15} is independently OH, F, CN or C_1 - C_4 alkoxy; and

X and Z are independently C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkoxy or C_1 - C_4 fluoroalkoxy.

2. The compound or salt of claim 1, wherein R^2 is H.

15 3. The compound or salt of claim 1 or 2, wherein R^4 is Cl, F, Br or CH_3 .

4. The compound or salt of claim 1, 2 or 3, wherein X is CH_3 , OCH_3 or $OCHF_2$ and Z is CH_3 .

5. The compound or salt any one of claims 1 to 4, wherein R^1 is C_1 - C_4 alkoxy optionally substituted by one or more R^6 .

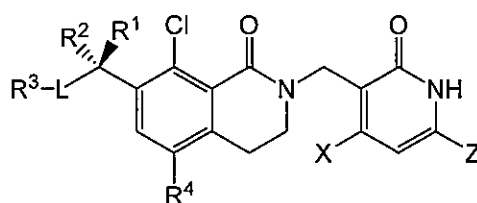
20 6. The compound or salt of claim 5 wherein said C_1 - C_4 alkoxy is OCH_3 .

7. The compound or salt of any one of claims 1 to 4, wherein R^1 is C_1 - C_4 alkyl optionally substituted by one or more R^6 .

8. The compound or salt of any one of claims 1 to 7, wherein L is a bond and R^3 is 3-12 membered heterocyclyl optionally substituted by one or more R^7 .

9. The compound or salt of claim 8, wherein said 3-12 membered heterocyclyl is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each optionally substituted by one or more R^7 .

10. A compound of Formula (I-A):



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_1 - C_4 alkoxy;

R^2 is H;

L is a bond;

R^3 is 3-12 membered heterocyclyl, optionally substituted by one or more R^7 ;

R^4 is H or Cl;

each R^7 is independently C_1 - C_4 alkyl, OH, F, CN, C_1 - C_4 alkoxy, =O, CHO, $C(O)R^{13}$, SO_2R^{13} or 3-6 membered heterocyclyl;

each R^{13} is independently C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{15} ;

each R^{15} is independently OH, F, CN or C_1 - C_4 alkoxy; and

X and Z are independently C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkoxy or C_1 - C_4 fluoroalkoxy.

11. The compound or salt of claim 10, wherein R^3 is 3-12 membered heterocyclyl selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each optionally substituted by one or more R^7 .

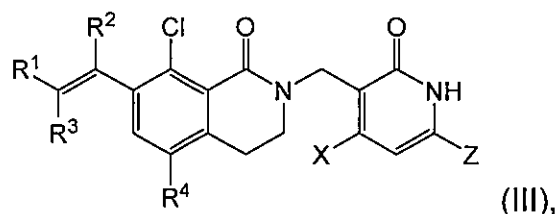
12. A compound that is 5,8-dichloro-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(*R*)-methoxy(oxetan-3-yl)methyl]-3,4-dihydroisoquinolin-1(2*H*)-one, or a pharmaceutically acceptable salt thereof.

13. A compound that is 5,8-dichloro-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)methyl]-7-[(*R*)-methoxy(oxetan-3-yl)methyl]-3,4-dihydroisoquinolin-1(2*H*)-one.

5 14. A compound that is 5,8-dichloro-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)methyl]-7-[methoxy(oxetan-3-yl)methyl]-3,4-dihydroisoquinolin-1(2*H*)-one, or a pharmaceutically acceptable salt thereof.

10 15. A compound that is 5,8-dichloro-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)methyl]-7-[(*S*)-methoxy(oxetan-3-yl)methyl]-3,4-dihydroisoquinolin-1(2*H*)-one, or a pharmaceutically acceptable salt thereof.

16. A compound of formula (III):



or a pharmaceutically acceptable salt thereof,

wherein:

R^1 and R^3 are taken together to form a 3-12 membered heterocyclyl optionally substituted by one or more R^7 ;

20 R^2 is H, F or C_1 - C_4 alkyl;

R^4 is H, halo or C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^6 ;

each R^6 is independently OH, F, CN or C_1 - C_4 alkoxy;

25 each R^7 is independently C_1 - C_4 alkyl, OH, F, CN, C_1 - C_4 alkoxy, =O, CHO, $C(O)R^{13}$, SO_2R^{13} or 3-6 membered heterocyclyl;

each R^{13} is independently C_1 - C_4 alkyl, where each said C_1 - C_4 alkyl is optionally substituted by one or more R^{15} ;

each R^{15} is independently OH, F, CN or C_1 - C_4 alkoxy; and

X and Z are independently C₁-C₄ alkyl, C₁-C₄ fluoroalkyl, C₁-C₄ alkoxy or C₁-C₄ fluoroalkoxy.

5 17. The compound or salt of claim 16, wherein R¹ and R³ are taken together to form a 3-12 membered heterocyclyl selected from the group consisting of azetidiny, pyrrolidiny, piperidiny and homopiperidiny, each optionally substituted by one or more R⁷.

10 18. The compound or salt of claim 17, wherein R⁷ is CHO, C(O)R¹³ or SO₂R¹³ and each R¹³ is independently C₁-C₄ alkyl optionally substituted by one or more R¹⁵.

15 19. A pharmaceutical composition comprising a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

20 20. A method for the treatment of abnormal cell growth in a subject, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein the abnormal cell growth is cancer.

22. The method of claim 20 or 21, wherein the subject is a human.

25 23. A compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use in the treatment of abnormal cell growth in a subject.

24. A combination of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and one or more additional anti-cancer agents.