[0009] It is an aim of certain embodiments of this invention to provide new cancer treatments. In particular, it is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing treatments, optionally they should have better activity.

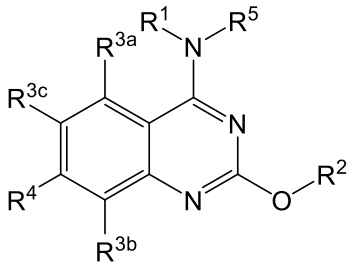
[0010] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

[0011] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0012] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0012a] In a first aspect of the present disclosure, there is provided a compound of formula (**Ia**), or a pharmaceutically acceptable salt thereof:



(**Ia**)

wherein

R^1 is C_0-C_3-alkylene-R^{1a}; wherein R^{1a} is independently selected from a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 are selected such that NR^1R^5 comprises no more than a single amine, wherein said single amine may be a primary, secondary or tertiary amine;

R^2 is independently C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_0-C_4-alkylene-R^{2a}, C_1-C_4-alkylene-R^{2b}, C_2-C_4-alkylene-R^{2c};

R^{2a} is independently selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; a 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl group; phenyl; C_3-C_7-cycloalkyl; wherein any heterocycloalkyl or cycloalkyl R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and any heteroaryl or phenyl R^{2a} group is optionally substituted with from 1 to 6 R^{11} groups;

R^{2b} is independently selected from $CONR^{12}R^{12}$ and CO_2R^{12};

R^{2c} is independently selected from $NR^{12}R^{13}$ and OR^{12};

R^{3a}, R^{3b} and R^{3c} are each independently selected from: H, halo, C_1-C_4-alkyl, O-C_1-C_4-alkyl, C_1-C_4-haloalkyl, O-C_1-C_4-haloalkyl, cyclopropyl, nitro and cyano;

R^4 is independently selected from: phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring; naphthyl; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^5, R^8 and R^{12} are each independently selected at each occurrence from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl;

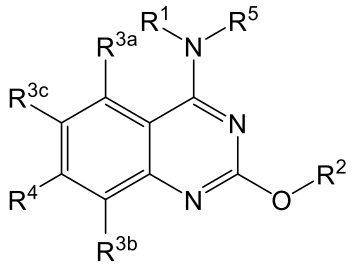
R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{11} and R^{14} are each independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

[0012b] In another aspect of the present disclosure, there is provided a compound of formula (**Ia**), or a pharmaceutically acceptable salt thereof:



(**Ia**)

wherein

R^1 and R^5 together with the nitrogen to which they are attached form a bridged bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 are selected such that NR^1R^5 comprises no more than a single amine;

R^2 is independently C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_0-C_4-alkylene-R^{2a}, C_1-C_4-alkylene-R^{2b}, C_2-C_4-alkylene-R^{2c};

R^{2a} is independently selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; a 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl group; phenyl; C_3-C_7-cycloalkyl; wherein any heterocycloalkyl or cycloalkyl R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and any heteroaryl or phenyl R^{2a} group is optionally substituted with from 1 to 6 R^{11} groups;

R^{2b} is independently selected from $CONR^{12}R^{12}$ and CO_2R^{12};

R^{2c} is independently selected from $NR^{12}R^{13}$ and OR^{12};

R^{3a}, R^{3b} and R^{3c} are each independently selected from: H, halo, C_1-C_4-alkyl, O-C_1-C_4-alkyl, C_1-C_4-haloalkyl, O-C_1-C_4-haloalkyl, cyclopropyl, nitro and cyano;

R^4 is independently selected from: phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring; naphthyl; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^8 and R^{12} are each independently selected at each occurrence from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl;

R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

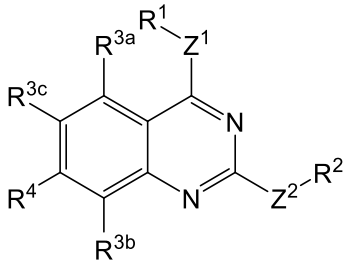
R^{11} and R^{14} are each independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl; wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, $C(O)$-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

[0012c] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0012d] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

[0012e] In another aspect of the present disclosure, there is provided a compound as disclosed herein for use in therapy.

[0013] In accordance with the present disclosures there is provided a compound of formula (**I**), or a pharmaceutically acceptable salt thereof:



(**I**)

wherein

Z^1 is independently selected from -O- and $-NR^5$-;

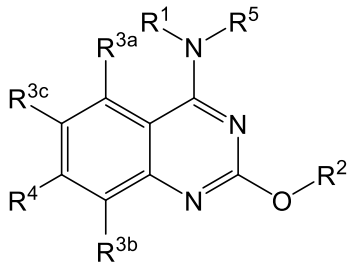
Z^2 is independently absent or is selected from -O- and $-NR^6$-;

R^1 is independently selected from C_0-C_3-alkylene-R^{1a} and C_2-C_6-alkylene-R^{1b}; wherein R^{1a} is independently selected from an oxygen containing 4- to 7- membered heterocycloalkyl ring, a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups; R^{1b} is independently selected from: NR^7R^8, OR^8, SR^8, SOR^8, SO_2R^8 and $SO(NH)R^8$;

or R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

CLAIMS

1. A compound of formula (**Ia**), or a pharmaceutically acceptable salt thereof:



(**Ia**)

wherein

R^1 is C_0-C_3-alkylene-R^{1a}; wherein R^{1a} is independently selected from a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 are selected such that NR^1R^5 comprises no more than a single amine, wherein said single amine may be a primary, secondary or tertiary amine;

R^2 is independently C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_0-C_4-alkylene-R^{2a}, C_1-C_4-alkylene-R^{2b}, C_2-C_4-alkylene-R^{2c};

R^{2a} is independently selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; a 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl group; phenyl; C_3-C_7-cycloalkyl; wherein any heterocycloalkyl or cycloalkyl R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and any heteroaryl or phenyl R^{2a} group is optionally substituted with from 1 to 6 R^{11} groups;

R^{2b} is independently selected from $CONR^{12}R^{12}$ and CO_2R^{12};

R^{2c} is independently selected from $NR^{12}R^{13}$ and OR^{12};

R^{3a}, R^{3b} and R^{3c} are each independently selected from: H, halo, C_1-C_4-alkyl, O-C_1-C_4-alkyl, C_1-C_4-haloalkyl, O-C_1-C_4-haloalkyl, cyclopropyl, nitro and cyano;

R^4 is independently selected from: phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring; naphthyl; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^5, R^8 and R^{12} are each independently selected at each occurrence from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl;

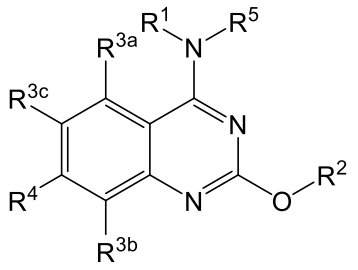
R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{11} and R^{14} are each independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

2. A compound of formula (**Ia**), or a pharmaceutically acceptable salt thereof:



(**Ia**)

wherein

R^1 and R^5 together with the nitrogen to which they are attached form a bridged bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 are selected such that NR^1R^5 comprises no more than a single amine;

R^2 is independently C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_0-C_4-alkylene-R^{2a}, C_1-C_4-alkylene-R^{2b}, C_2-C_4-alkylene-R^{2c};

R^{2a} is independently selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; a 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl group; phenyl; C_3-C_7-cycloalkyl; wherein any heterocycloalkyl or cycloalkyl R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and any heteroaryl or phenyl R^{2a} group is optionally substituted with from 1 to 6 R^{11} groups;

R^{2b} is independently selected from $CONR^{12}R^{12}$ and CO_2R^{12};

R^{2c} is independently selected from $NR^{12}R^{13}$ and OR^{12};

R^{3a}, R^{3b} and R^{3c} are each independently selected from: H, halo, C_1-C_4-alkyl, O-C_1-C_4-alkyl, C_1-C_4-haloalkyl, O-C_1-C_4-haloalkyl, cyclopropyl, nitro and cyano;

R^4 is independently selected from: phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring; naphthyl; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^8 and R^{12} are each independently selected at each occurrence from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl;

R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

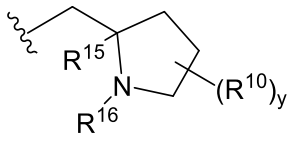
R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{11} and R^{14} are each independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

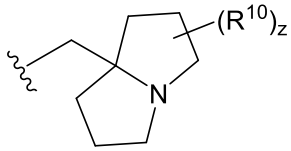
3. A compound of claim 1 or 2, wherein R^1 and R^5 are selected such that the nitrogen of NR^1R^5 is the nitrogen single amine.

4. A compound of any one of claims 1 to 3, wherein R^2 has the structure:



, wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; and y is independently selected from 0, 1, 2, 3, and 4.

5. A compound of claim 4, wherein R^2 has the structure:



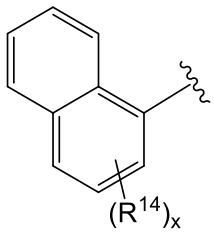
, wherein z is independently selected from 0, 1, 2, 3, and 4..

6. A compound of any one of claims 1 to 5, wherein R^{3b} is F.

7. A compound of any one of claims 1 to 6, wherein both R^{3a} and R^{3c} are H.

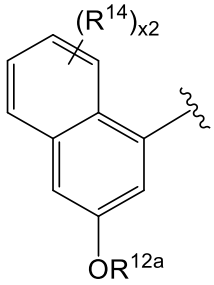
8. A compound of any one of claims 1 to 7, wherein R^4 is phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups.

9. A compound of any one of claims 1 to 7, wherein R^4 has the structure:



wherein x is independently selected from 0, 1, 2, 3, and 4.

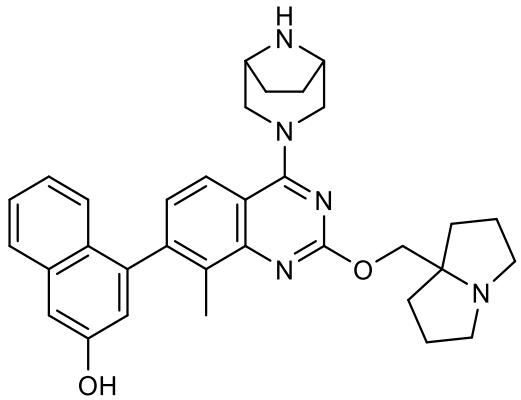
10. A compound of claim 9, wherein R^4 has the structure:



wherein R^{12a} is independently H or C_1-C_4-alkyl; x2 is independently selected from 0, 1, 2 and 3.

11. A compound of any one of claims 1 to 7, wherein R^4 is 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups.

12. A compound of claim 2, wherein the compound of formula (**I**) is:



13. Use of a compound of any one of claims 1 to 12 in the manufacture of a medicament for treating cancer in a subject in need thereof.

14. The use of claim 13, wherein the cancer is selected from: pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

15. The use of claim 13 or 14, wherein the subject being treated has a cancer having wild-type KRAS.

16. The use of claim 13 or 14, wherein the subject being treated has a cancer having a KRAS mutation selected from: KRAS G12D, KRAS G12C, KRAS G12V, KRAS G12A, KRAS G13D and KRAS Q61H.

17. A pharmaceutical composition comprising a compound of any one of claims 1 to 12 and a pharmaceutically acceptable excipient.

18. A compound of any one of claims 1 to 12 for use in therapy.