through phosphorylation of MEK1 and 2, frequent oncogenic activating mutations are commonly found only for BRAF. In particular, substitution of V600 with glutamic acid or lysine renders the kinase highly activated with consequent hyper-stimulation of the MAPK pathway, independently from external stimulations (Cell. 2015 Jun 18; 161(7): 1681–1696.)

Mutant BRAF is a targetable oncogenic driver and three BRAF inhibitors (vemurafenib, dabrafenib and encorafenib) reached the market up to now showing efficacy in BRAFV600E-positive melanoma. However rapid acquisition of drug resistance is almost universally observed and the duration of the therapeutic benefits for the targeted therapy remains limited.

Moreover, the developed BRAF inhibitors revealed an unexpected and "paradoxical" ability to repress MAPK signalling in BRAFV600E-driven tumours while the same inhibitors presented MAPK stimulatory activities in BRAF wild type (WT) models (N Engl J Med 2012; 366:271-273; and British Journal of Cancer volume 111, pages640–645(2014)).

Mechanistic studies on the RAF paradox then clarified that oncogenic BRAFV600E phosphorylates MEK 1/2 in its monomeric cytosolic form while WT BRAF and RAF1 activation requires a complex step of events including cell membrane translocation and homo and/or heterodimerization promoted by activated RAS (KRAS, NRAS, HRAS) (Nature Reviews Cancer volume 14, pages455–467(2014)).

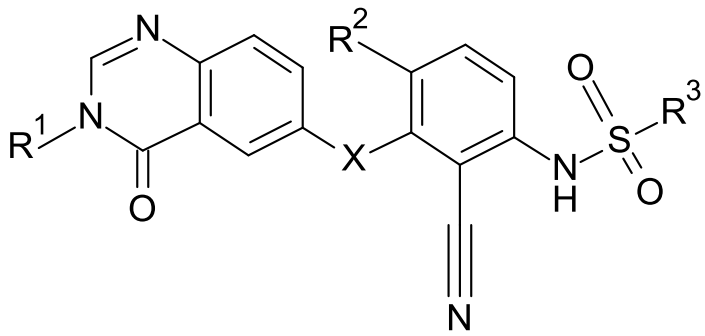
The binding of inhibitors like vemurafenib, dabrafenib or encorafenib to a WT BRAF or RAF1 protomer, quickly induces RAF homo and/or hetero dimerization and membrane association of the newly formed RAF dimer. In the dimeric conformation, one RAF protomer allosterically induces conformational changes of the second resulting in a kinase active status and, importantly, in a conformation unfavourable for the binding of the inhibitor. The dimer induced by drug treatment, as a result, promotes MEK phosphorylation by the catalysis operated by the unbound protomer with hyperactivation of the pathway.

The RAF paradox results in two clinically relevant consequences: 1) accelerated growth of secondary tumours upon BRAFi monotherapy (mainly keratochantoma and squamous-cell carcinomas) (N Engl J Med 2012; 366:271-273) and 2) the acquisition of drug resistance in the setting of BRAFi monotherapy as well as in combinations of BRAFi+MEKi presents activation of dimer-mediated RAF signalling by genetically driven events including RAS mutations, BRAF amplifications, expression of dimeric-acting BRAF splice variants (Nature Reviews Cancer volume 14, pages455–467(2014)).

The present ~~invention~~ disclosure relates to the surprising finding that the BRAF inhibitor of formula (I) shows considerably less paradoxial activation of the MAPK signalling pathway while

retaining high potency. This compound can also be referred to as a paradox breaker or RAF paradox breaker, compared to compounds inducing the RAF paradox (and which could be referred to as paradox inducers or RAF paradox inducers).

In one aspect, the present disclosure relates to a compound of formula (I)



(I)

wherein

R^1 is C_{1-6}-alkyl;

X is selected from

i) -NH-, and

ii) -O-;

R^2 is selected from

iii) H,

iv) cyano, and

v) halogen;

R^3 is selected from

vi) NR^4R^5, and

vii) CHR^6R^7;

R^4 is selected from

viii) C_{1-6}-alkyl,

ix) C_{3-8}-cycloalkyl, and

x) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

R^5 is selected from

xi) C_{1-6}-alkyl,

xii) C_{3-8}-cycloalkyl, and

xiii) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form an heterocycloalkyl optionally substituted with R^8, wherein the heterocycloalkyl is selected from pyrrolidinyl and piperidinyl;

R^6 is selected from

xiv) C_{1-6}-alkyl,

xv) C_{3-8}-cycloalkyl, and

xvi) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

R^7 is selected from

xvii) C_{1-6}-alkyl,

xviii) C_{3-8}-cycloalkyl, and

xix) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

or R^6 and R^7 together with the carbon atom to which they are attached form a C_{3-8}-cycloalkyl optionally substituted with R^8;

R^8 is halogen;

with the proviso that N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide is excluded

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound as described herein for use as therapeutically active substance.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein and a therapeutically inert carrier.

In another aspect, the present disclosure relates to a compound as described herein for use in the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.

The term "pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition, these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like.

The term “protecting group” (PG) denotes a group which selectively blocks a reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Protecting groups can be removed at the appropriate point. Exemplary protecting groups are amino-protecting groups, carboxy-protecting groups or hydroxy-protecting groups. Particular protecting groups are the tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc) and benzyl (Bn) groups. Further particular protecting groups are the tert-butoxycarbonyl (Boc) and the fluorenylmethoxycarbonyl (Fmoc) groups. More particular protecting group is the tert-butoxycarbonyl (Boc) group.

The abbreviation uM means microMolar and is equivalent to the symbol µM.

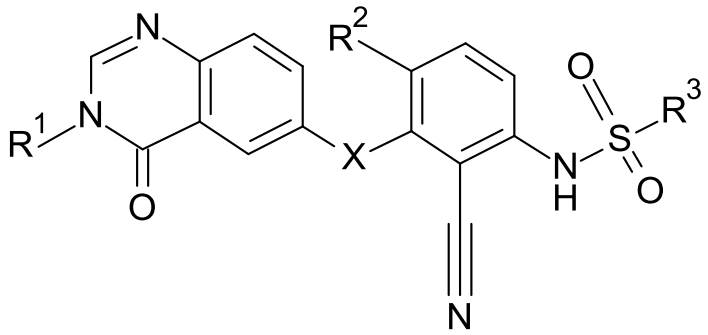
The abbreviation uL means microliter and is equivalent to the symbol µL.

The abbreviation ug means microgram and is equivalent to the symbol µg.

The compound of formula (I) can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates,

Claims

1. A compound of formula (I)



(I)

wherein

R^1 is C_{1-6}-alkyl;

X is selected from

i) -NH-, and

ii) -O-;

R^2 is selected from

iii) H,

iv) cyano, and

v) halogen;

R^3 is selected from

vi) NR^4R^5, and

vii) CHR^6R^7;

R^4 is selected from

viii) C_{1-6}-alkyl,

ix) C_{3-8}-cycloalkyl, and

x) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

R^5 is selected from

xi) C_{1-6}-alkyl,

xii) C_{3-8}-cycloalkyl, and

xiii) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form an heterocycloalkyl optionally substituted with R^8, wherein the heterocycloalkyl is selected from pyrrolidinyl and piperidinyl;

R^6 is selected from

xiv) C_{1-6}-alkyl,

xv) C_{3-8}-cycloalkyl, and

xvi) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

R^7 is selected from

xvii) C_{1-6}-alkyl,

xviii) C_{3-8}-cycloalkyl, and

xix) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

or R^6 and R^7 together with the carbon atom to which they are attached form a C_{3-8}-cycloalkyl optionally substituted with R^8;

R^8 is halogen;

with the proviso that N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide is excluded

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

R^1 is C_{1-6}-alkyl;

X is selected from

i) -NH-, and

ii) -O-;

R^2 is selected from

iii) H, and

iv) halogen;

R^3 is selected from

v) NR^4R^5, and

vi) CHR^6R^7;

R^4 is selected from

vii) C_{1-6}-alkyl,

viii) C_{3-8}-cycloalkyl, and

ix) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

R^5 is selected from

x) C_{1-6}-alkyl,

xi) C_{3-8}-cycloalkyl, and

xii) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form an heterocycloalkyl optionally substituted with R^8, wherein the heterocycloalkyl is selected from pyrrolidinyl and piperidinyl;

R^6 is selected from

xiii) C_{1-6}-alkyl,

xiv) C_{3-8}-cycloalkyl, and

xv) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

R^7 is selected from

xvi) C_{1-6}-alkyl,

xvii) C_{3-8}-cycloalkyl, and

xviii) C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

or R^6 and R^7 together with the carbon atom to which they are attached form a cyclopentyl or a cyclohexyl ring optionally substituted with R^8;

R^8 is halogen;

with the proviso that (3R)-N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide is excluded

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein

R^1 is methyl;

X is selected from

i) -NH-, and

ii) -O-;

R^2 is selected from

iii) H,

iv) chloro, and

v) fluoro;

R^3 is selected from

vi) NR^4R^5, and

vii) CHR^6R^7;

R^4 is selected from

viii) methyl,

ix) ethyl,

x) propyl,

xi) cyclopropyl, and

xii) cyclopropylmethyl;

R^5 is selected from

xiii) methyl,

xiv) ethyl,

xv) propyl,

xvi) cyclopropyl, and

xvii) cyclopropylmethyl;

or R^4 and R^5 together with the nitrogen atom to which they are attached form an heterocycloalkyl optionally substituted with R^8, wherein the heterocycloalkyl is selected from pyrrolidinyl and piperidinyl;

R^6 is selected from

xviii) methyl,

xix) ethyl,

xx) propyl,

xxi) cyclopropyl, and

xxii) cyclopropylmethyl;

R^7 is selected from

xxiii) methyl,

xxiv) ethyl,

xxv) propyl,

xxvi) cyclopropyl, and

xxvii) cyclopropylmethyl;

or R^6 and R^7 together with the carbon atom to which they are attached form a cyclopentyl or a cyclohexyl ring optionally substituted with R^8;

R^8 is fluoro;

with the proviso that (3R)-N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide is excluded

or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3, wherein R^2 is selected from

i) H,

ii) chloro, and

iii) fluoro.

5. A compound according to any one of claims 1 to 4, wherein R^4 is methyl.

6. A compound according to any one of claims 1 to 5, wherein R^5 is ethyl.

7. A compound according to any one of claims 1 to 6, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form an heterocycloalkyl optionally substituted with R^8, wherein the heterocycloalkyl is selected from pyrrolidinyl and piperidinyl.

8. A compound according to any one of claims 1 to 7, wherein R^4 and R^5 together with the nitrogen atom to which they are attached form an unsubstituted heterocycloalkyl, wherein the heterocycloalkyl is pyrrolidinyl.

9. A compound according to any one of claims 1 to 8, wherein R^6 and R^7 are independently selected from

i) methyl,

ii) ethyl,

iii) propyl,

iv) cyclopropyl, and

v) cyclopropylmethyl.

10. A compound according to any one of claims 1 to 9, wherein R^6 and R^7 together with the nitrogen atom to which they are attached form a cyclopentyl or a cyclohexyl ring.

11. A compound according to any one of claims 1 to 10, wherein R^8 is fluoro.

12. A compound according to any one of claims 1 to 11, wherein the compound is selected from

6-[2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]-6-fluoro-phenoxy]-3-methyl-4-oxo-quinazoline;

6-[6-chloro-2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]phenoxy]-3-methyl-4-oxo-quinazoline;

(3R)-N-[4-chloro-2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide;

N-[4-chloro-2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]pyrrolidine-1-sulfonamide;

6-[2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]phenoxy]-3-methyl-4-oxo-quinazoline;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]pyrrolidine-1-sulfonamide;

(3R)-N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-3-fluoro-pyrrolidine-1-sulfonamide;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]cyclopentanesulfonamide;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]cyclohexanesulfonamide;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]butane-2-sulfonamide;

6-[2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]anilino]-3-methyl-4-oxo-quinazoline;

(3R)-N-[2-cyano-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]-3-fluoro-pyrrolidine-1-sulfonamide;

6-[6-chloro-2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]anilino]-3-methyl-4-oxo-quinazoline;

N-[4-chloro-2-cyano-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]pyrrolidine-1-sulfonamide;

N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]pyrrolidine-1-sulfonamide;

N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]cyclopentanesulfonamide; and

6-[2-cyano-3-(dimethylsulfamoylamino)-6-fluoro-phenoxy]-3-methyl-4-oxo-quinazoline;

or a pharmaceutically acceptable salt thereof.

13. A compound according to any one of claims 1 to 12, wherein the compound is selected from

6-[2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]-6-fluoro-phenoxy]-3-methyl-4-oxo-quinazoline;

6-[6-chloro-2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]phenoxy]-3-methyl-4-oxo-quinazoline;

N-[4-chloro-2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]pyrrolidine-1-sulfonamide;

6-[2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]phenoxy]-3-methyl-4-oxo-quinazoline;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]pyrrolidine-1-sulfonamide;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]cyclopentanesulfonamide;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]cyclohexanesulfonamide;

N-[2-cyano-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]butane-2-sulfonamide;

6-[2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]anilino]-3-methyl-4-oxo-quinazoline;

6-[6-chloro-2-cyano-3-[[ethyl(methyl)sulfamoyl]amino]anilino]-3-methyl-4-oxo-quinazoline;

N-[4-chloro-2-cyano-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]pyrrolidine-1-sulfonamide;

N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]pyrrolidine-1-sulfonamide;

N-[2-cyano-4-fluoro-3-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]cyclopentanesulfonamide; and

6-[2-cyano-3-(dimethylsulfamoylamino)-6-fluoro-phenoxy]-3-methyl-4-oxo-quinazoline;

or a pharmaceutically acceptable salt thereof.

14. A compound according to any one of claims 1 to 13 for use as therapeutically active substance.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 and a therapeutically inert carrier.

16. A compound according to any one of claims 1 to 13 for use in the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.

~~17. The use of a compound according to any one of claims 1 to 13 for the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.~~

~~18.~~17. The use of a compound according to any one of claims 1 to 13 ~~for~~ in the preparation of a medicament for the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.

~~19. A method for the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 13 to a patient in need thereof.~~

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