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)).

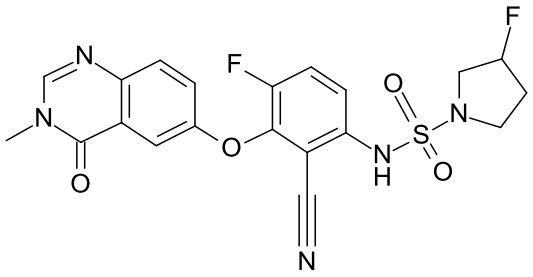
The binding of inhibitors like vemurafenib, dabrafenib or encorafenib to a WT BRAF or RAF1 protomer, quickly induces RAF homo and/or hetero dimerization and membrane association of the newly formed RAF dimer. In the dimeric conformation, one RAF protomer allosterically induces conformational changes 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, pages 455–467(2014)). There is thus the need for RAF inhibitors capable of breaking that paradox.

Furthermore, the currently approved classical BRAF inhibitors Vemurafenib (*Mol. Pharmaceutics* 2012, 9, 11, 3236–3245), Dabrafenib (J Pharmacol Ex Ther 2013, 344 (3) 655-664) and Encorafenib (Pharmacol Res. 2018;129:414-423) all have very poor brain permerability. This is major limitation for the use of those classical BRAF inhibitors for the treatment of brain cancer or brain metastases. There is thus the need for BRAF inhibitors having improved brain permeability.

Summary

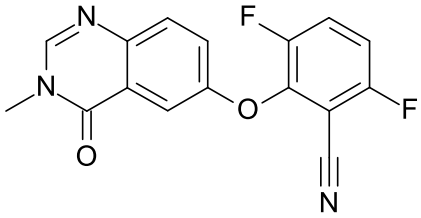
In one aspect, the present disclosure relates to the compound of formula (I)



(I)

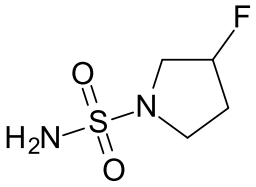
or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a process for the preparation of a compound as described herein, comprising the reaction of a compound of formula (B1)



(B1)

with a compound of formula (B2)



(B2)

in the presence of a base.

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 cancer.

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 use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of cancer.

In another aspect, the present disclosure relates to 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.

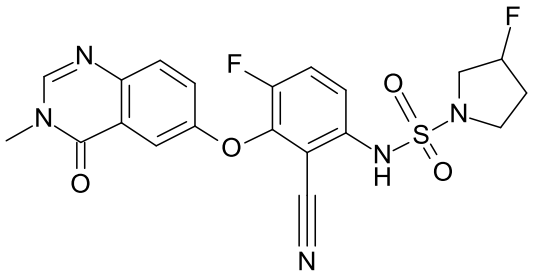
In another aspect, the present disclosure relates to use of a compound as described herein in the preparation of a medicament for the therapeutic and/or prophylactic treatment of BRAF mutant driven cancer.

In another aspect, the present disclosure relates to use of a compound as described herein in the preparation of a medicament for the therapeutic and/or prophylactic treatment of brain metastases.

The present invention relates to the surprising finding, that the BRAF inhibitor of formula (I) is a more potent and selective BRAF inhibitor showing considerably less paradoxial activation of the MAPK signaling pathway while retaining high potency. This compound can thus be referred to as a paradox breaker or RAF paradox breaker, in contrast to compounds inducing the RAF paradox (and which could be referred to as paradox inducers or RAF paradox

Claims

1. The compound of formula (I)

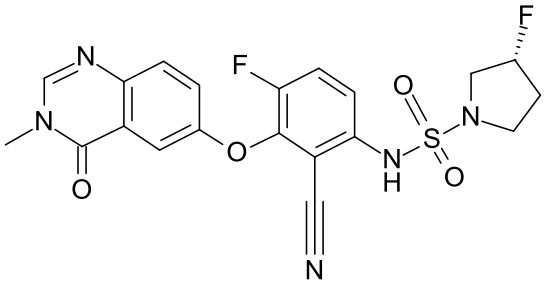


(I)

or a pharmaceutically acceptable salt thereof.

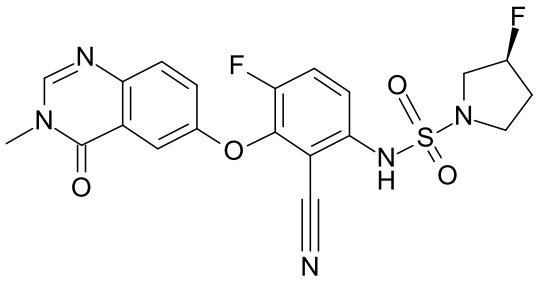
2. A compound according to claim 1, wherein the compound is the compound of formula (I).

3. A compound according to claim 1 or 2, wherein the compound is the compound of formula (Ia).



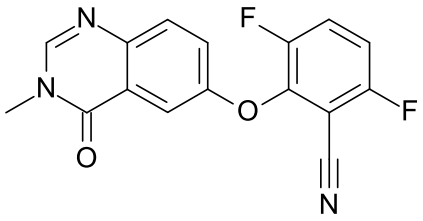
(Ia)

4. A compound according to claim 1 or 2, wherein the compound is the compound of formula (Ib).



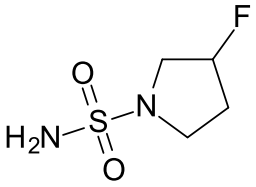
(Ib)

5. A process for the preparation of a compound according to any one of claims 1 to 4, comprising the reaction of a compound of formula (B1)



(B1)

with a compound of formula (B2)



(B2)

in the presence of a base.

6. A compound according to any one of claims 1 to 4 when manufactured according to a process of claim 5.

7. A compound according to any one of claims 1 to 4 for use as therapeutically active substance.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 and a therapeutically inert carrier.

9. A compound according to any one of claims 1 to 4 for use in the treatment or prophylaxis of cancer.

10. A compound according to any one of claims 1 to 4 for use in the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.

11. Use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the treatment or prophylaxis of cancer.

12. Use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the treatment or prophylaxis of thyroid cancer, colorectal cancer, brain cancer, melanoma or NSCLC.

13. Use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the therapeutic and/or prophylactic treatment of BRAF mutant driven cancer.

14. Use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the therapeutic and/or prophylactic treatment of brain metastases.

15. A compound according to any one of claims 1 to 4, wherein at least one substituent comprises at least one radioisotope.

16. A compound according to any one of claims 1 to 4, wherein at least one substituent comprises at least one radioisotope selected from ^{2}H, ^{3}H, ^{13}C, ^{14}C and ^{18}F.