

THIENO[2,3-C]PYRROL-4-ONE DERIVATIVES AS ERK INHIBITORS

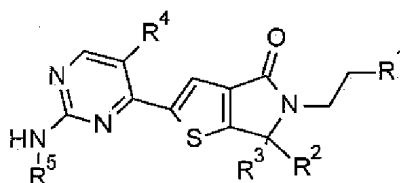
The present invention relates to thieno[2,3-c]pyrrol-4-one compounds, or pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising the compounds, that inhibit activity of extracellular-signal-regulated kinase (ERK) and may be useful for treating cancer.

The ERK/MAPK pathway is important for cell proliferation and frequently observed to be activated in many tumors. RAS genes, which are upstream of ERK1/2, are mutated in several cancers including colorectal, melanoma, non-small cell lung cancer as well as breast and pancreatic tumors. High RAS activity is accompanied by elevated ERK activity in many human tumors. Studies have also shown that ERK is a critical component of RAS signalling. These observations support the attractiveness of the ERK1/2 signaling pathway for developing anticancer therapies in a broad spectrum of human tumors.

ERK inhibitors are known in the art; see, for example, WO2013130976. Additionally, other aminopyrimidine compounds are known in the art; see, for example, WO 2010/022121. There remains a need to provide alternative ERK inhibitors, more particularly for the treatment of cancer. Accordingly, the present invention provides ERK1/2 inhibitors which may be useful for treating cancer.

Summary

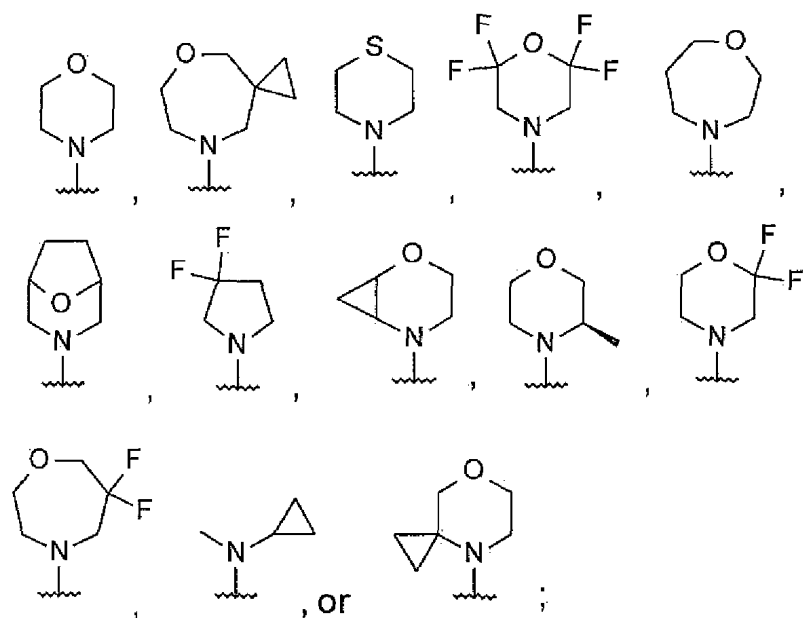
In one aspect of the present disclosure, there is provided a compound of the formula:



wherein:

1a

R¹ is



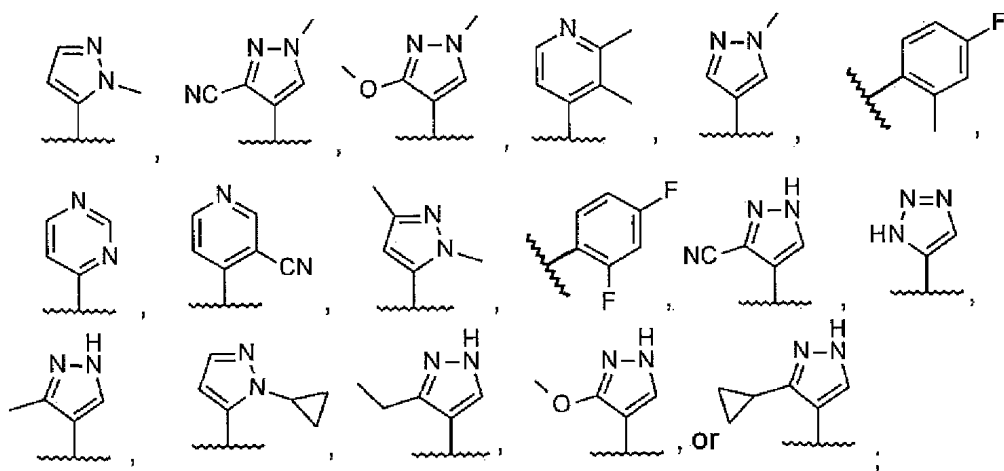
R² and R³ are methyl or R² and R³ can be taken together to form

cyclopropyl;

5

R⁴ is hydrogen, methyl, chloro, fluoro, or trifluoromethyl; and

R⁵ is



or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical

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composition comprising a compound or salt disclosed herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

In a further aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in therapy.

In another aspect of the present disclosure, there is provided a compound or salt disclosed herein for use in the treatment of cancer.

5 In a further aspect of the present disclosure, there is provided a combination comprising a compound or salt thereof disclosed herein and ramucirumab for simultaneous, separate, or sequential use in the treatment of non-small cell lung cancer.

In another aspect of the present disclosure, there is provided a compound or salt thereof disclosed herein for use in simultaneous, separate or sequential combination with
10 ramucirumab in the treatment of non-small cell lung cancer.

In a further aspect of the present disclosure, there is provided a use of ramucirumab in the manufacture of a medicament for the treatment of non-small cell lung cancer, wherein the ramucirumab is to be simultaneously, separately, or sequentially combined with a compound or salt thereof disclosed herein.

15 In another aspect of the present disclosure, there is provided a combination comprising a compound or salt thereof disclosed herein and [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of non-small cell lung cancer.

20 In a further aspect of the present disclosure, there is provided a compound or salt thereof disclosed herein for use in simultaneous, separate or sequential combination with [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the treatment of non-small cell lung cancer.

25 In another aspect of the present disclosure, there is provided a use of [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of non-small cell lung cancer,

wherein the [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine is to be simultaneously, separately, or sequentially combined with a compound or salt thereof disclosed herein.

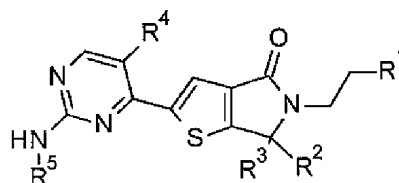
5 In a further aspect of the present disclosure, there is provided a combination comprising a compound or salt thereof disclosed herein and [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of colorectal cancer.

10 In another aspect of the present disclosure, there is provided a compound or salt thereof disclosed herein for use in simultaneous, separate or sequential combination with [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the treatment of colorectal cancer.

15 In a further aspect of the present disclosure, there is provided a use of [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer, wherein the [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine is to be simultaneously, separately, or sequentially combined with a compound or salt thereof disclosed herein.

Description

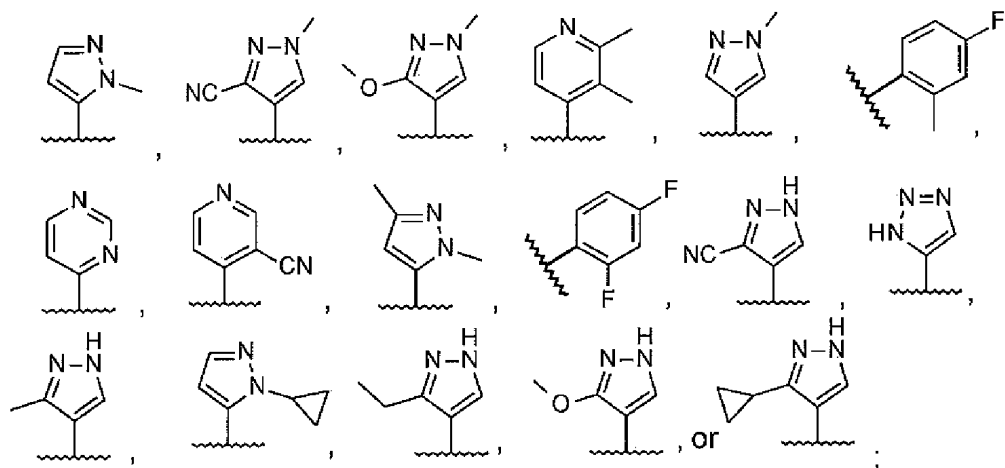
The present invention provides a compound of the following formula:



Formula I

wherein:

R¹ is

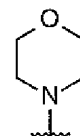


or a pharmaceutically acceptable salt thereof.

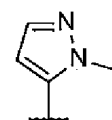
2. The compound or salt according to Claim 1 wherein R^2 and R^3 are independently methyl.

5 3. The compound or salt according to Claim 2 wherein R^4 is hydrogen.

4. The compound or salt according to Claim 3 wherein R^1 is



5. The compound or salt according to Claim 3 wherein R^5 is



6. The compound or salt according to Claim 4 which is 6,6-dimethyl-2-{2-[(1-methyl-1H-pyrazol-5-yl)amino]pyrimidin-4-yl}-5-[2-(morpholin-4-yl)ethyl]-5,6-dihydro-4H-thieno[2,3-c]pyrrol-4-one.

7. The compound according to Claim 6 which is 6,6-dimethyl-2-{2-[(1-methyl-1H-pyrazol-5-yl)amino]pyrimidin-4-yl}-5-[2-(morpholin-4-yl)ethyl]-5,6-dihydro-4H-thieno[2,3-c]pyrrol-4-one.

8. A pharmaceutical composition comprising the compound or salt according to any one of Claims 1-7, and a pharmaceutically acceptable carrier, diluent, or excipient.

9. The compound or salt according to any one of Claims 1-7 for use in therapy.

10. The compound or salt according to any one of Claims 1-7 for use in the treatment of cancer.

11. The compound or salt for use according to Claim 10 wherein the cancer is
5 selected from the group consisting of melanoma, colorectal cancer, pancreatic cancer, and non-small cell lung cancer.

12. The compound or salt for use according to Claim 11, wherein the cancer is colorectal cancer.

13. The compound or salt for use according to Claim 11, wherein the cancer is
10 pancreatic cancer.

14. The compound or salt for use according to Claim 11, wherein the cancer is non-small cell lung cancer.

15. A combination comprising a compound or salt thereof according to Claim 7 and ramucirumab for simultaneous, separate, or sequential use in the treatment of non-
15 small cell lung cancer.

16. A compound or salt thereof according to Claim 7 for use in simultaneous, separate or sequential combination with ramucirumab in the treatment of non-small cell lung cancer.

17. Use of ramucirumab in the manufacture of a medicament for the treatment
20 of non-small cell lung cancer, wherein the ramucirumab is to be simultaneously, separately, or sequentially combined with a compound or salt thereof according to Claim 7.

18. The combination, compound or salt thereof, or use according to any one of Claims 15 to 17 wherein the non-small cell lung cancer is KRAS mutant non-small cell
25 lung cancer.

19. A combination comprising a compound or salt thereof according to Claim 7 and [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of
5 non-small cell lung cancer.

20. A compound or salt thereof according to Claim 7 for use in simultaneous, separate or sequential combination with [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the treatment of non-small cell
10 lung cancer.

21. Use of [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of non-small cell lung cancer, wherein the [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine is to be simultaneously, separately, or sequentially combined with
15 a compound or salt thereof according to Claim 7.

22. The combination, compound or salt thereof, or use, according to any one of Claims 19 to 21 wherein the non-small cell lung cancer is KRAS mutant non-small cell
20 lung cancer.

23. A combination comprising a compound or salt thereof according to Claim 7 and [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, for simultaneous, separate, or sequential use in the treatment of
25 colorectal cancer.

24. A compound or salt thereof according to Claim 7 for use in simultaneous, separate or sequential combination with [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the treatment of colorectal cancer.

30 25. Use of [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the

treatment of colorectal cancer, wherein the [5-(4-Ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine is to be simultaneously, separately, or sequentially combined with a compound or salt thereof according to Claim 7.

- 5 26. The combination, compound or salt thereof, or use, according to any one of Claims 23 to 25 wherein the colorectal cancer is KRAS mutant colorectal cancer.