

METHODS OF TREATING ABNORMAL CELL GROWTH

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/274,745 filed November 2, 2021, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Components of the RAS/RAF/MEK/ERK (MAPK) signal transduction pathway represent opportunities for the treatment of abnormal cell growth, e.g., cancer. Mutations in RAS/RAF/MEK/ERK are frequently found in human cancers. These mutants result in a constitutively active MAPK kinase cascade, leading to tumor cell proliferation, differentiation, survival, and migration. Selective inhibitors of certain components of the RAS/RAF/MEK/ERK signal transduction pathway, such as RAS, RAF, MEK and ERK, are useful in the treatment of abnormal cell growth, in particular cancer, in mammals.

[0003] Due to the severity and breadth of diseases and disorders associated with abnormal cell growth, e.g., cancer, there is a need for effective therapeutic means and methods for treatment. The compounds, compositions, and methods described herein are directed toward this end.

SUMMARY

[0003a] In a first aspect of the present disclosure, there is provided a use of dual RAF/MEK inhibitor, in combination with an antibiotic agent and a corticosteroid, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0003b] In another aspect of the present disclosure, there is provided a use of dual RAF/MEK inhibitor, in combination with an antibiotic agent and a corticosteroid, in the manufacture of a medicament for reducing the severity of or preventing toxicity or an adverse event associated with administration of the dual RAF/MEK inhibitor in a subject.

[0003c] In a further aspect of the present disclosure, there is provided a use of a FAK inhibitor or a dual RAF/MEK inhibitor, in combination with an antibiotic agent, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0004] The present disclosure provides, in part, methods and combinations of compounds (e.g., combinations of compounds as described herein, e.g., a dual RAF/MEK inhibitor and an antibiotic agent, and optionally a corticosteroid) useful for treating abnormal cell growth (e.g., cancer) in a subject in need thereof.

[0005] In some examples, provided herein is a method of administering a dual RAF/MEK inhibitor to a subject in need thereof, comprising administering to the subject an effective amount of the dual RAF/MEK inhibitor, an effective amount of an antibiotic agent, and an effective amount of a corticosteroid.

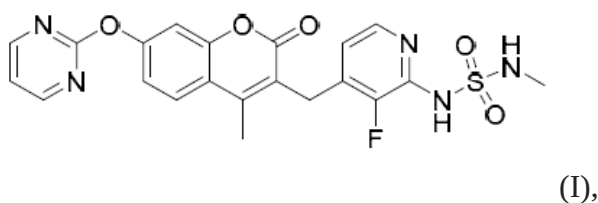
[0006] In some examples, provided herein is a method of reducing the severity of or preventing toxicity or an adverse event associated with administration of a dual RAF/MEK inhibitor in a subject, comprising administering to the subject an effective amount of the dual RAF/MEK inhibitor, an effective amount of an antibiotic agent, and an effective amount of a corticosteroid.

[0007] In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a dual RAF/MEK inhibitor and an effective amount of an antibiotic agent.

[0008] In some examples, the method further comprises administering to the subject an effective amount of a FAK inhibitor.

[0009] In some examples, provided herein is a method of treating a cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a FAK inhibitor and an effective amount of an antibiotic agent.

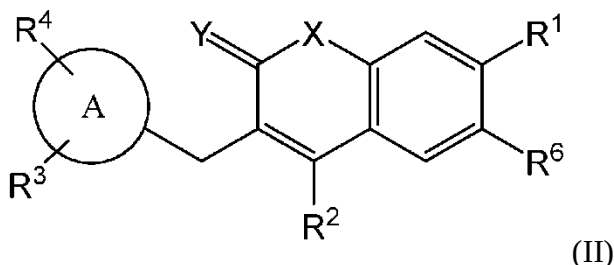
[00010] In some examples, the dual RAF/MEK inhibitor is a compound of formula (I):



or a pharmaceutically acceptable salt thereof.

[00011] In some examples, the dual RAF/MEK inhibitor is IMM-1-104, or a pharmaceutically acceptable salt thereof.

[00012] In some examples, the dual RAF/MEK inhibitor is a compound of formula (II):



including pharmaceutically acceptable salts thereof, wherein the variables are as defined herein.

[00013] In some examples, the dual RAF/MEK inhibitor is a compound selected from the compound of Table I, or a pharmaceutically acceptable salt thereof.

[00014] In some examples, the corticosteroid is hydrocortisone, prednisone, triamcinolone, cortisol, corticosterone, cortisone, aldosterone, dexamethasone, prednisolone, or methylprednisolone.

[00015] In some examples, the antibiotic agent is minocycline, doxycycline, tetracycline, clindamycin, sulfadiazine, diphenhydramine, polysporin, prednisone, neomycin, bacitracin, erythromycin, or azithromycin.

[00016] In some examples, the FAK inhibitor is defactinib, or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[00017] **FIG. 1** illustrates exemplary combination effects of VS-6766 or defactinib with and without minocycline or doxycycline.

[00018] **FIG. 2** illustrates exemplary calculated synergy score plots for the combination of VS-6766 and doxycycline.

[00019] **FIG. 3** illustrates exemplary calculated synergy score plots for the combination of VS-6766 or defactinib with minocycline or doxycycline in NCI-H358 cell line.

[00020] **FIG. 4** illustrates exemplary calculated synergy score plots for the combination of VS-6766 and doxycycline across multiple cell lines.

DETAILED DESCRIPTION

[00021] As generally described herein, the present disclosure provides methods and combinations of compounds (e.g., combinations of compounds as described herein, e.g., a dual RAF/MEK inhibitor and an antibiotic agent, and optionally a corticosteroid) useful for treating abnormal cell growth (e.g., cancer) in a subject in need thereof.

Definitions

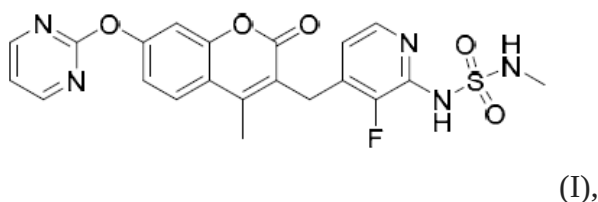
Chemical definitions

[00022] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein.

Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic*

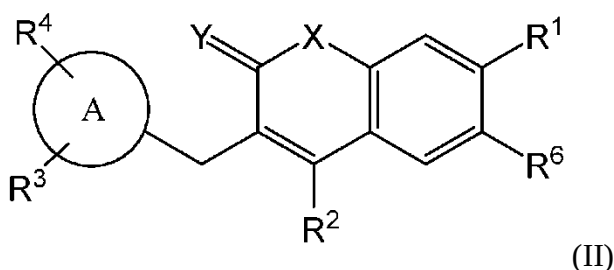
CLAIMS

1. Use of dual RAF/MEK inhibitor, in combination with an antibiotic agent and a corticosteroid, in the manufacture of a medicament for treating cancer in a subject in need thereof.
2. Use of dual RAF/MEK inhibitor, in combination with an antibiotic agent and a corticosteroid, in the manufacture of a medicament for reducing the severity of or preventing toxicity or an adverse event associated with administration of the dual RAF/MEK inhibitor in a subject.
3. The use of claim 1 or 2, wherein a FAK inhibitor is to be further administered to the subject.
4. The use of claim 3, wherein the FAK inhibitor is defactinib, or a pharmaceutically acceptable salt thereof.
5. The use of any one of claims 1-4, wherein the dual RAF/MEK inhibitor is a compound of formula (I):

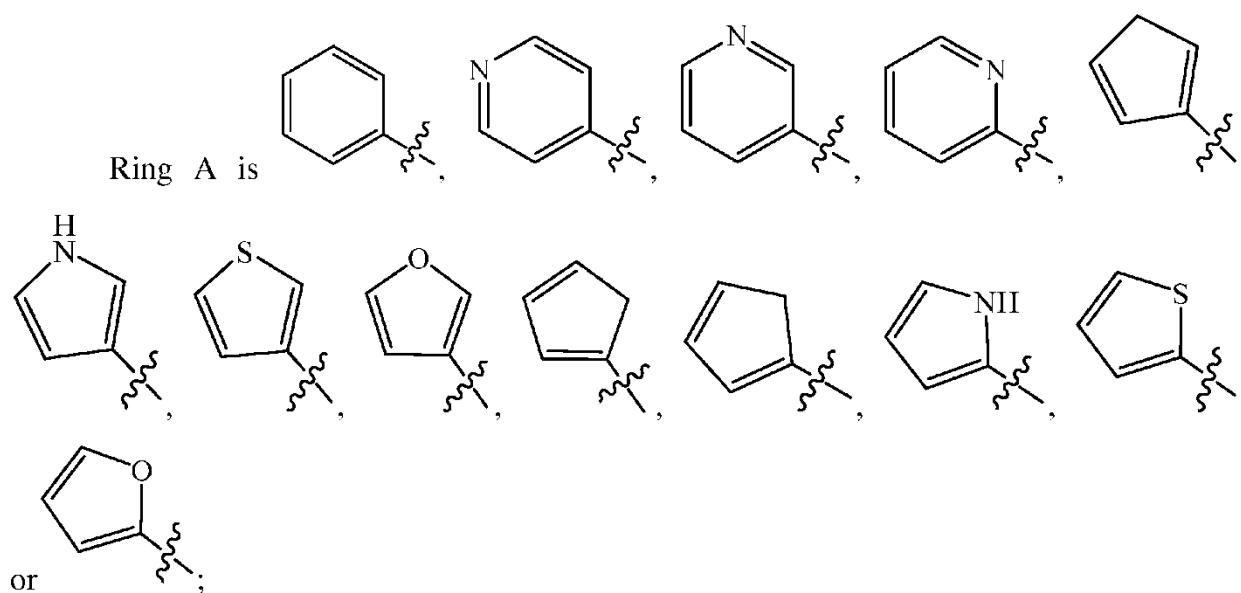


or a pharmaceutically acceptable salt thereof.

6. The use of any one of claims 1-4, wherein the dual RAF/MEK inhibitor is IMM-1-104, or a pharmaceutically acceptable salt thereof, or a compound of formula (II):



including pharmaceutically acceptable salts thereof, wherein:



R^1 , R^2 , R^3 , and R^4 are each independently selected from the group consisting of H, deuterium, hydroxyl, halogen, cyano, nitro, optionally substituted amino, optionally substituted C-amido, optionally substituted N-amido, optionally substituted ester, optionally substituted sulfonyl, optionally substituted S-sulfonamido, optionally substituted N-sulfonamido, optionally substituted sulfonate, optionally substituted O-thiocarbamyl, optionally substituted N-thiocarbamyl, optionally substituted N-carbamyl, optionally substituted O-carbamyl, optionally substituted urea, optionally substituted C1 to C6 alkoxy, optionally substituted C1 to C6 alkyl, optionally substituted C2 to C6 alkenyl, optionally substituted C2 to C6 alkynyl, optionally substituted C3 to C8 cycloalkyl, optionally substituted C6 to C10 aryl, optionally substituted C3 to C8 heterocyclyl, optionally substituted C3 to C10 heteroaryl, and L; R^6 is selected from the group consisting of H, deuterium, hydroxyl, halogen, cyano, nitro, optionally substituted amino, optionally substituted C1 to C6 alkoxy, optionally substituted C1 to C6 alkyl, optionally substituted C2 to C6 alkenyl, and optionally substituted C2 to C6 alkynyl;

X is $C(R^5)_2$, $CH(R^5)$, CH_2 , $-O-$, $>C=O$, $>C=S$, or $>N-H$;

L is $-Z_1-Z_2$ or $-Z_1-Z_2-Z_3$;

Z_1 , Z_2 , and Z_3 are independently selected from the group consisting of $-CH_2-$, $-O-$, $-S-$, $S=O$, $-SO_2-$, $C=O$, $-CO_2-$, $-NO_2$, $-NH-$, $-CH_2CCH$, $-CH_2CN$, $-NR^5R^{5'}$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)NR^5R^{5'}$, $-NH-SO_2-$, $-SO_2-NH-$, $-R^5CH_2-$, $-R^5O-$, $-R^5S-$, $R^5-S=O$, $-R^5SO_2-$, $R^5-C=O$, $-R^5CO_2-$, $-R^5NH-$, $-R^5NH(CO)-$, $-R^5(CO)NH-$, $-R^5NH-SO_2-$, $-R^5SO_2-NH-$, $-NHCH_2CO-$, $-CH_2R^5-$, $-OR^5-$, $-SR^5-$, $S=O-R^5$, $-SO_2R^5-$, $C=O-R^5$, $-CO_2R^5-$, $-NHR^5-$, $-NH(CO)R^5-$, $-(CO)NHR^5-$, $-NH-SO_2R^5-$, $-SO_2-NHR^5-$, optionally substituted C1 to C6 alkyl, optionally

substituted C3 to C8 cycloalkyl, optionally substituted C6 to C10 aryl, optionally substituted C3 to C8 heterocyclyl, optionally substituted C3 to C10 heteroaryl, -CH₂-(optionally substituted aryl), -CH₂-(optionally substituted C3 to C8 cycloalkyl), and -CH₂-(optionally substituted C3 to C10 heteroaryl); each R⁵ and R⁵ are independently selected from H, deuterium, optionally substituted C1 to C6 alkyl, optionally substituted C2 to C6 alkenyl, optionally substituted C2 to C6 alkynyl, optionally substituted C3 to C8 carbocyclyl, optionally substituted C6 to C10 aryl, optionally substituted C3 to C8 heterocyclyl, and optionally substituted C3 to C10 heteroaryl; and

Y is CH₂, NH, or O, with the proviso that R¹ is not -O-pyrimidyl, or

a compound selected from the compound of Table I, or a pharmaceutically acceptable salt thereof.

7. The use of any one of claims 1-6, wherein the dual RAF/MEK inhibitor is to be administered at a dose of about 0.5 mg to about 10 mg per administration (e.g., 3.2 mg per administration, or 4 mg per administration).
8. The use of any one of claims 1-7, wherein the dual RAF/MEK inhibitor is to be administered twice a week.
9. The use of any one of claims 1-8, wherein the dual RAF/MEK inhibitor is to be dosed as a cycle, wherein, as part of the cycle, the dual RAF/MEK inhibitor is to be administered for three weeks and then the dual RAF/MEK inhibitor is not administered for one week.
10. The use of any one of claims 1-9, wherein the dual RAF/MEK inhibitor is to be orally administered to the subject.
11. The use of any one of claims 3-10, wherein the FAK inhibitor (e.g., defactinib, or a pharmaceutically acceptable salt thereof) is to be administered twice daily or once daily to the subject, optionally at about 100 mg to about 1000 mg per administration (e.g., 200 mg per administration, or 400 mg per administration).
12. The use of any one of claims 3-11, wherein the FAK inhibitor (e.g., defactinib, or a pharmaceutically acceptable salt thereof) is to be dosed as a cycle, wherein, as part of the cycle, the FAK inhibitor (e.g., defactinib, or a pharmaceutically acceptable salt thereof) is to be administered for three weeks and then the FAK inhibitor (e.g., defactinib, or a pharmaceutically acceptable salt thereof) is not administered for one week.

13. The use of any one of claims 3-12, wherein the FAK inhibitor (e.g., defactinib, or a pharmaceutically acceptable salt thereof) is to be administered orally to the subject.
14. The use of any one of claims 3-21, wherein the dual RAF/MEK inhibitor and the FAK inhibitor (e.g., defactinib, or a pharmaceutically acceptable salt thereof) are to be i) independently dosed cyclically or ii) simultaneously dosed cyclically.
15. The use of any one of claims 1-14, wherein the corticosteroid is hydrocortisone, prednisone, triamcinolone, cortisol, corticosterone, cortisone, aldosterone, dexamethasone, prednisolone, or methylprednisolone.
16. The use of any one of claims 1-15, wherein the corticosteroid is to be administered topically.
17. The use of any one of claims 1-16, wherein the corticosteroid is to be administered twice daily or once daily.
18. The use of any one of claims 1-17, wherein the corticosteroid is hydrocortisone, optionally wherein hydrocortisone is comprised in a composition comprising about 0.1 to about 10% hydrocortisone, or wherein hydrocortisone is comprised in a composition comprising 1% hydrocortisone.
19. The use of claim any one of claims 1-18, wherein the antibiotic agent is to be administered once daily or twice daily.
20. The use of claim 19, wherein the antibiotic agent is minocycline, doxycycline, tetracycline, clindamycin, sulfadiazine, diphenhydramine, polysporin, prednisone, neomycin, bacitracin, erythromycin, or azithromycin.
21. The use of any one of claims 1-20, wherein the antibiotic agent is to be administered orally.
22. The use of any one of claims 1-21, wherein the antibiotic agent is to be administered at a dose of about 50 to about 500 mg per administration.
23. The use of any one of claims 1-22, wherein the antibiotic agent is a) minocycline, optionally wherein the minocycline is to be administered once daily, optionally at a dose of

100 mg per administration, or b) doxycycline, optionally wherein the doxycycline is to be administered twice daily, optionally at a dose of 100 mg per administration.

24. The use of any one of claims 1-23, wherein the use reduces inflammation.

25. The use of any one of claims 2-24, wherein the toxicity or adverse event is a skin toxicity, optionally rash, macular edema, nausea, or diarrhea.

26. The use of any one of claims 1-25, wherein the antibiotic agent and optionally corticosteroid is to be administered for at least eight weeks (e.g., the first two cycles of administration of the dual RAF/MEK inhibitor).

27. The use of any one of claims 1-26, wherein the subject is identified as having a cancer, optionally wherein the cancer is a cancer characterized as having a RAS mutation, a RAF mutation, or a KRAS, NRAS, HRAS, and/or BRAF mutation.

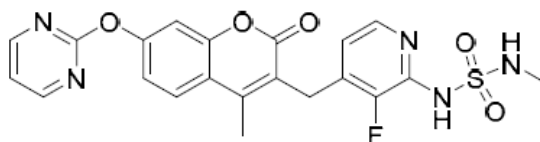
28. The use of claim 27, wherein the cancer is lung cancer (e.g., non-small cell lung cancer), colorectal cancer, pancreatic cancer, melanoma, or gynecologic cancer (e.g., cervical cancer, ovarian cancer (e.g., low grade serous ovarian cancer), uterine cancer, vaginal cancer, or vulvar cancer).

29. The use of any one of claims 1-28, wherein the medicament is to be administered to the subject and the administration is synergistic (e.g., provides a synergistic effect in the inhibition of tumor cell proliferation), and optionally is synergistic as identified by a combined synergy score of ≥ 5 .

30. Use of a FAK inhibitor or a dual RAF/MEK inhibitor, in combination with an antibiotic agent, in the manufacture of a medicament for treating cancer in a subject in need thereof.

31. The use of claim 30, wherein the FAK inhibitor is defactinib, or a pharmaceutically acceptable salt thereof.

32. The use of claim 30 or 31, wherein the dual RAF/MEK inhibitor is a compound of formula (I):



(I),

or a pharmaceutically acceptable salt thereof.

33. The use of any one of claims 30-32, wherein the antibiotic agent is minocycline, doxycycline, tetracycline, clindamycin, sulfadiazine, diphenhydramine, polysporin, prednisone, neomycin, bacitracin, erythromycin, or azithromycin.

34. The use of any one of claims 30-33, wherein the antibiotic agent is minocycline or doxycycline.

35. The use of any one of claims 30-34, wherein the medicament is to be administered to the subject and the administration is synergistic (e.g., provides a synergistic effect in the inhibition of tumor cell proliferation), and optionally is synergistic as identified by a combined synergy score of ≥ 5 .