The PI3K pathway can be activated via, for example, point mutation(s) of the *PIK3CA* gene or via inactivation of the phosphatase and tensin homolog (*PTEN*) gene. Activation of this pathway occurs in approximately 30–50% human cancers and contributes to resistance to various anti-cancer therapies. *See*, Martini, M. et al., Ann. Med. 2014, 46, 372–383 and Bauer, T.M. et al., Pharmacol. Ther. 2015, 146, 53–60.

SUMMARY

Provided herein is a method for treating cancer in a subject in need thereof, the method comprising administering to the subject (a) Compound 1, or a pharmaceutically acceptable salt thereof, and (b) one or more additional therapeutic agents.

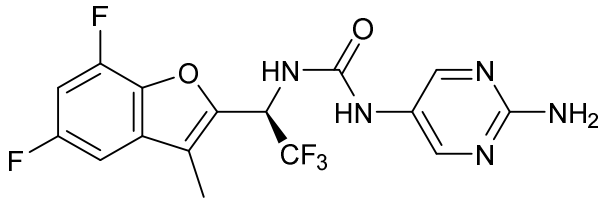
Provided herein is a method for treating cancer in a subject in need thereof, the method comprising administering to the subject (a) Compound 1, or a pharmaceutically acceptable salt thereof, and (b) one or more independently selected additional therapeutic agents selected from the group consisting of: a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, and a RAF inhibitor, a PIM (**P**rovirus **I**ntegration site for **M**oloney leukemia virus kinase, e.g., PIM1, PIM2, and PIM3) inhibitor, or a combination of any of the foregoing.

Also provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, one or more pharmaceutically acceptable excipients, and one or two independently selected additional therapeutic agents.

This disclosure also provides a method for inhibiting PI3Kα in a mammalian cell, the method comprising contacting the mammalian cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and with one or more additional therapeutic agents. In some examples, the one or more additional therapeutic agents are a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, a RAF inhibitor, a PIM (e.g., PIM1 and PIM3) inhibitor, or a combination of any of the foregoing.

In an aspect, provided herein is use of:

a compound of the formula:



, or a pharmaceutically acceptable salt thereof;

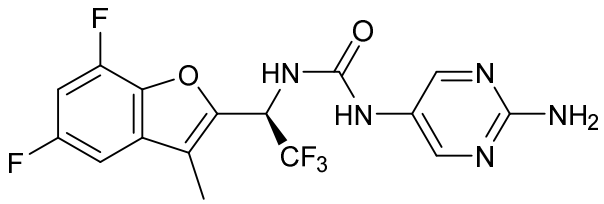
a selective estrogen receptor modulator or degrader (SERM / SERD); and

a CDK4/6 inhibitor,

in the manufacture of a medicament for treating breast cancer.

In another aspect, provided herein is use of:

a compound of the formula:



, or a pharmaceutically acceptable salt thereof;

a selective estrogen receptor modulator or degrader (SERM/SERD); and

a CDK4/6 inhibitor,

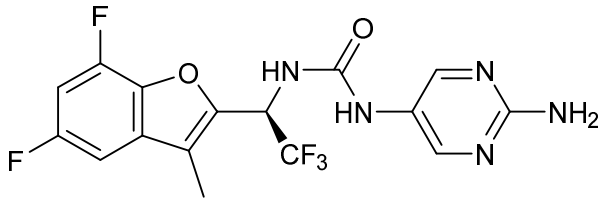
in the manufacture of a medicament for treating PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer.

Other examples include those described in the Detailed Description and/or in the claims.

WHAT IS CLAIMED IS:

1. Use of:

a compound of the formula:



, or a pharmaceutically acceptable salt thereof;

a selective estrogen receptor modulator or degrader (SERM / SERD); and

a CDK4/6 inhibitor,

in the manufacture of a medicament for treating breast cancer.

2. The use of claim 1, wherein the SERM/SERD is clomifene, cyclofenil, broparestrol, ormeloxifene, raloxifene, toremifene, lasofoxifene, bazedoxifene, ospemifene, enclomiphene, serophene, tamoxifen, fulvestrant, elacestrant, camizestrant, rintodestrant, clotrimazole, palazestrant, or fenticonazole.

3. The use of claim 1, wherein the SERM/SERD is fulvestrant.

4. The use of claim 1, wherein the SERM/SERD is imlunestrant.

5. The use of any one of claims 1-4, wherein the CDK4/6 inhibitor is palbociclib, ribociclib, abemaciclib, or trilaciclib.

6. The use of any one of claims 1-4, wherein the CDK4/6 inhibitor is ribociclib.

7. The use of any one of claims 1-4, wherein the CDK4/6 inhibitor is palbociclib.

8. The use of any one of claims 1-4, wherein the CDK4/6 inhibitor is abemaciclib.

9. The use of any one of claims 1-8, wherein the breast cancer is $HER2^+$ breast cancer.

10. The use of any one of claims 1-8, wherein the breast cancer is $HER2^-$ breast cancer.

11. The use of any one of claims 1-8, wherein the breast cancer is ER^+ breast cancer.

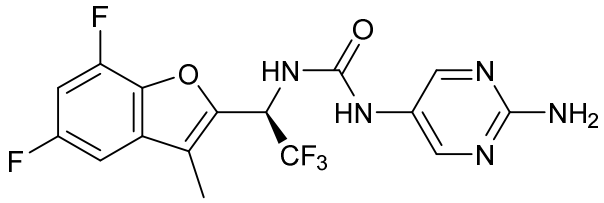
12. The use of any one of claims 1-8, wherein the breast cancer is triple negative breast cancer.

13. The use of any one of claims 1-8, wherein the breast cancer is ER+, HER2- breast cancer.

14. The use of any one of claims 1-13, wherein the breast cancer is metastatic or locally advanced.

15. Use of:

a compound of the formula:



, or a pharmaceutically acceptable salt thereof;

a selective estrogen receptor modulator or degrader (SERM/SERD); and

a CDK4/6 inhibitor,

in the manufacture of a medicament for treating PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer.

16. The use of claim 15, wherein the SERM/SERD is fulverstrant.

17. The compound for use of claim 15, wherein the SERM/SERD is imlunestrant.

18. The use of any one of claims 15-17, wherein the CDK4/6 inhibitor is palbociclib.

19. The use of any one of claims 15-17, wherein the CDK4/6 inhibitor is ribociclib.

5

20. The use of any one of claims 15-17, wherein the CDK4/6 inhibitor is abemaciclib.