Processes of Preparing PI3K Inhibitors

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/532,695, filed on August 15, 2023, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

This disclosure provides processes of preparing compounds of Formula (I), such as (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (Compound 1), and salts and/or solvates thereof, that inhibit phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3Kα).

BACKGROUND

Phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha (PI3Kα), encoded by the *PIK3CA* gene is a part of the PI3K/AKT/TOR signaling network and is altered in several human cancers. Several investigators have demonstrated the role of PI3K/AKT signaling in physiological and pathophysiological functions that drive tumor progression such as metabolism, cell growth, proliferation, angiogenesis and metastasis. (*See*, Fruman, D.A. *The PI3K Pathway in Human Disease.* Cell 2017, 170, 605–635 and Janku, F. et al., *Targeting the PI3K pathway in cancer: Are we making headway?* Nat. Rev. Clin. Oncol.2018, 15, 273–291.) Suppression (e.g., pharmacological or genetic) of PI3K/AKT/TOR signaling may cause cancer cell death and regression of tumor growth.

Certain compounds of Formula (I) are described in WO 2022/265993, which is incorporated by reference herein in its entirety. There exists a need for alternative synthetic procedures for the preparation of compounds of Formula (I). Such alternative synthetic procedures are disclosed herein.

SUMMARY

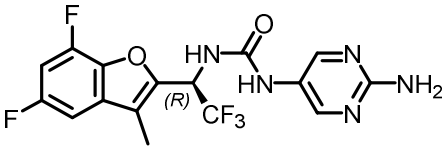
In an aspect, there is provided a process of preparing a compound of Formula (I):

hydroxyl, halogen, -C(=O)$NR^{B1}R^{C1}$, -SO_2(C1-C6 alkyl), -CO_2H, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, and C1-C6 haloalkoxy;

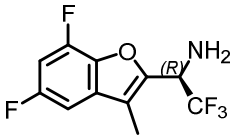
each R^{A2}, R^{B2}, and R^{C2} is independently hydrogen or C1-C6 alkyl; and

each R^G is independently selected from the group consisting of: fluoro, cyano, hydroxyl, C1-C6 alkyl optionally substituted with hydroxyl, C1-C6 alkoxy, -$NR^{A1}R^{B1}$, =NR^{A2}, -C(=O)$NR^{C1}R^{D1}$, -CO_2(C1-C6 alkyl), C1-C6 haloalkyl, C3-C6 cycloalkyl, C1-C6 haloalkoxy, -SO_2(C1-C6 alkyl), and -CO_2H.

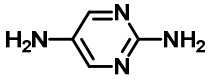
In another aspect, there is provided a process of preparing Compound 1, having the structure:



(1), or a salt and/or solvate thereof;

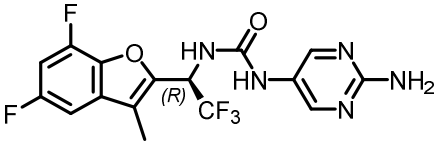
comprising contacting  with

(i) a carbonyl equivalent; and

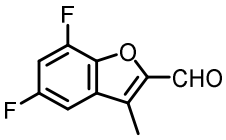
(ii) pyrimidine-2,5-diamine having the structure ;

to form Compound 1.

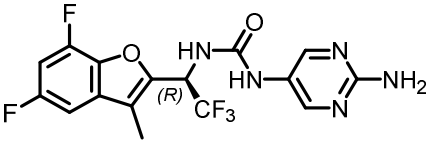
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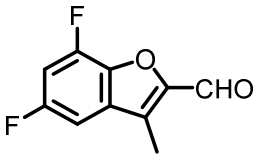
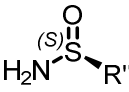
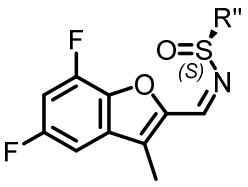
(1), or a salt and/or solvate thereof;

comprising reacting  to form Compound 1.

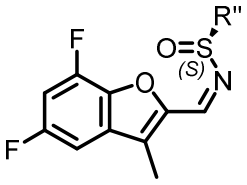
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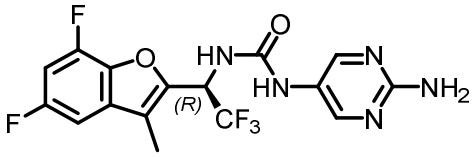
(1), or a salt and/or solvate thereof;

comprising contacting  with  to form ,

wherein R'' is C1-C6 alkyl; and

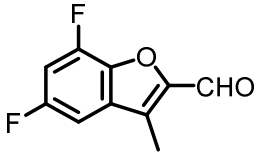
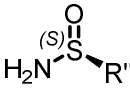
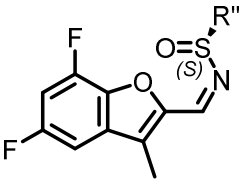
reacting  to form Compound 1.

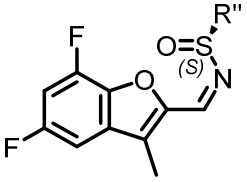
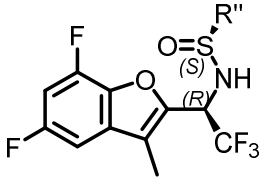
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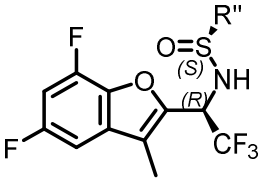
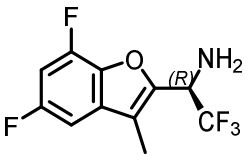


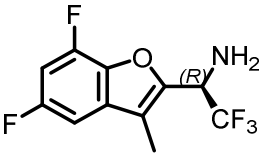
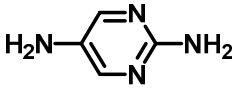
(1), or a salt and/or solvate thereof;

comprising:

(a) contacting  with  to form , wherein R'' is C1-C6 alkyl;

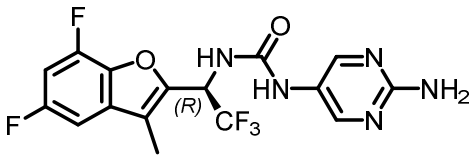
(b) contacting  with a trifluoromethylating reagent to form ;

(c) contacting  with HCl to form ; and

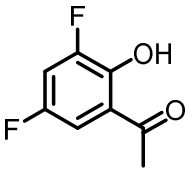
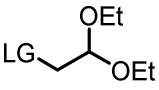
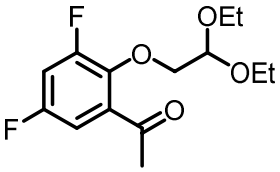
(d) contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-diamine having the structure ;

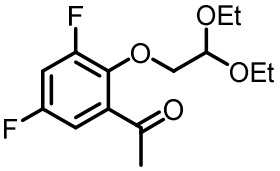
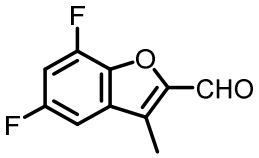
to form Compound 1.

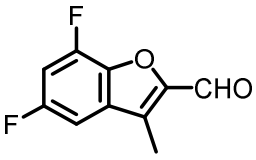
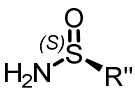
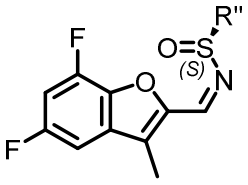
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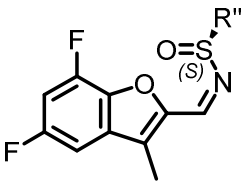
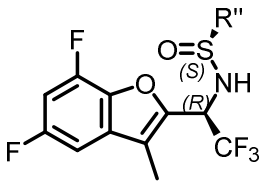
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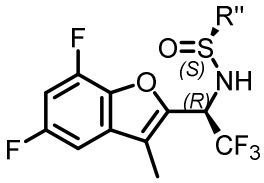
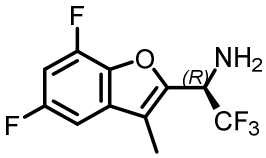
comprising:

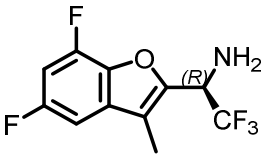
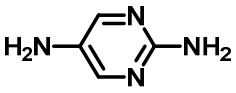
(a) contacting  with  to form , wherein LG is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

(b) contacting  with an acid to form ;

(c) contacting  with  to form , wherein R'' is C1-C6 alkyl;

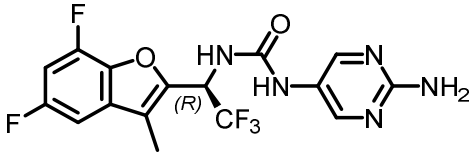
(d) contacting  with a trifluoromethylating reagent to form ;

(e) contacting  with HCl to form ; and

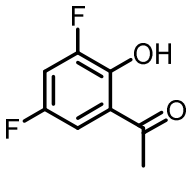
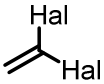
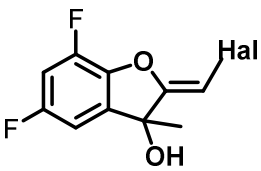
(f) contacting  with (i) a carbonyl equivalent; and (ii) pyrimidine-2,5-diamine having the structure ;

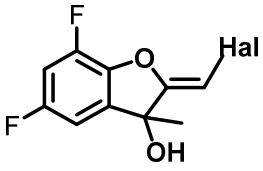
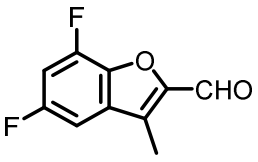
to form Compound 1.

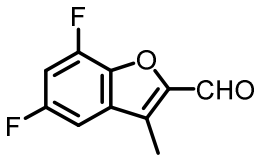
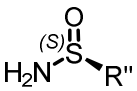
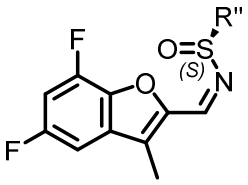
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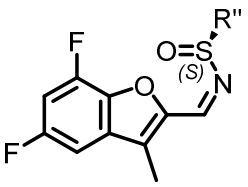
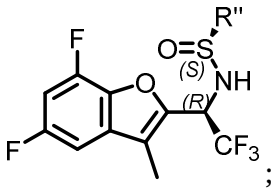
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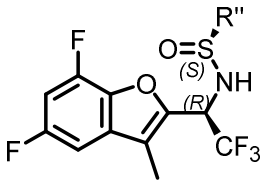
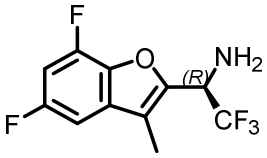
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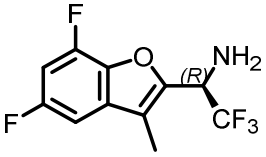
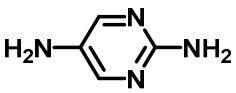
(a) contacting  with  to form , wherein Hal is selected from chloro, bromo, iodo, and trifluoromethanesulfonyl;

(b) contacting  with an acid to form  ;

(c) contacting  with  to form  , wherein R'' is C1-C6 alkyl;

(d) contacting  with a trifluoromethylating reagent to form  ;

(e) contacting  with HCl to form  ; and

(f) contacting  with (i) R'OC(O)Cl, wherein R' is selected from C1-C6 alkyl and C6-C10 aryl optionally substituted with 1-3 independently selected C1-6 alkyl or C1-6 alkoxy; and (ii) pyrimidine-2,5-diamine having the structure  ;

to form Compound 1.

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