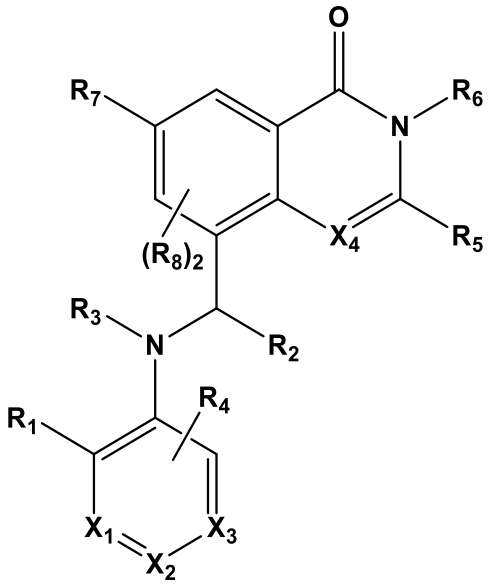
**IN THE CLAIMS**

1. A compound of Formula (1)

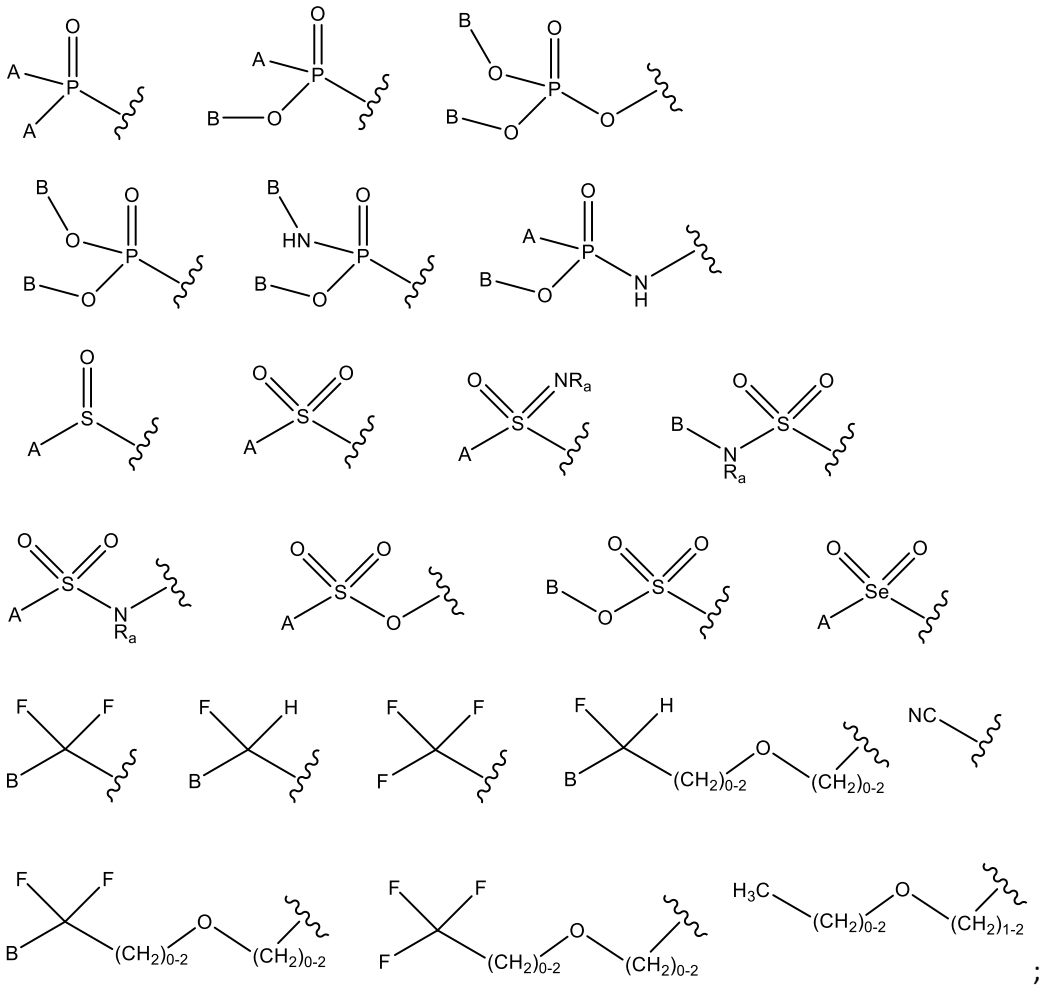



(1)

or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound thereof, or a pharmaceutically acceptable salt thereof,

wherein:

$R_1$ is selected from



each A is independently $C_1$-$C_4$ alkyl, fluoroalkyl, $C_3$-$C_7$ cycloalkyl, $N(R_a)_2$, $(CH_2)_{0-5}$-$NR_a$-C(O)-$C_3$-$C_7$ cycloalkyl, $(CH_2)_{1-5}$-O-$(CH_2)_{0-5}$-$C_1$-$C_4$ alkyl, $(CH_2)_{1-5}$-O-$C_1$-$C_3$ cycloalkyl, $(CH_2)_{1-5}$-O-$(CH_2)_{0-5}$-$CF_3$, $(CH_2)_{1-5}$-O-$(CH_2)_{1-5}$-$C_1$-$C_3$ fluoroalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{0-5}$-$NR_a$-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{0-5}$-$NR_a$-$(CH_2)_{1-5}$-N-heterocyclyl, where the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, A and A together with the attached -P(=O)- moiety may form a substituted or unsubstituted heterocyclyl ring;

each B is independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, $(CH_2)_{1-5}$-OH, $(CH_2)_{0-5}$-$N(R_a)_2$, $(CH_2)_{1-5}$-$NR_a$-C(O)-$C_3$-$C_7$ cycloalkyl, $(CH_2)_{0-5}$-aryl, $(CH_2)_{0-5}$-heteroaryl, $(CH_2)_{0-5}$-heterocyclyl, $(CH_2)_{0-5}$-C(O)-$(CH_2)_{1-5}$-O-$C_1$-$C_4$ alkyl, $(CH_2)_{1-5}$-$NR_a$-$(CH_2)_{0-5}$-heteroaryl or $(CH_2)_{1-5}$-$NR_a$-$(CH_2)_{2-5}$-N-heterocyclyl, O-$C_{1-5}$-alkyl, O-$C_{0-5}$-cycloalkyl, O-$C_{0-5}$-heterocyclyl, where the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are substituted or unsubstituted, or alternatively, B and B together with the attached -[O or NH]-P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring, or alternatively, A and B together with the attached -P(=O)-O- moiety may form a substituted or unsubstituted heterocyclyl ring;

each $R_a$ is independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, C(O)$C_1$-$C_3$ alkyl, $(CH_2)_{1-5}$-fluoroalkyl, $(CH_2)_{1-5}$-OH, $(CH_2)_{1-5}$-$NH_2$, $(CH_2)_{1-5}$-NH($C_1$-$C_4$ alkyl), $(CH_2)_{1-5}$-N($C_1$-$C_4$ alkyl)$_2$ or C(O)-$(CH_2)_{1-5}$-O-$C_1$-$C_3$ alkyl, where the alkyl and cycloalkyl are substituted or unsubstituted, or alternatively, for -S(=O)(A)(=$NR_a$) or for -S(=O)(A)($NR_a$), $R_a$ and A together with the attached atoms, may form a substituted or unsubstituted heterocyclyl ring;

$R_2$ is H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, $CF_3$, $CFH_2$ or $CF_2H$, and where $R_2$ is not H, the carbon atom attached to $R_2$ is a chiral center and exists as a (R)- and (S)-racemic mixture or as either the (R)- or (S)- enantiomer;

$R_3$ is H or $C_1$-$C_4$ alkyl;

$R_4$ is H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, halogen, CN, $CF_3$, $OCF_3$, $CFH_2$ or $CF_2H$;

$R_6$ is H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, heteroaromatic, $CF_3$, $CFH_2$ or $CF_2H$;

$R_7$ is H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, halogen, CN, $CF_3$, $OCF_3$, $CFH_2$ or $CF_2H$;

each $R_8$ is independently H, $C_1$-$C_4$ alkyl, $C_3$-$C_7$ cycloalkyl, halogen, CN, $CF_3$, $OCF_3$, $CFH_2$ or $CF_2H$;

each of $X_1$, $X_2$ and $X_3$ is independently N, CH or substituted C;

$X_4$ is CH or substituted C;

$R_5$ is

halogen;

-O-$L_1$-$L_2$-$L_3$-$L_4$-$L_5$-$L_6$-$L_7$-$R_9$;

-S-$L_1$-$L_2$-$L_3$-$L_4$-$L_5$-$L_6$-$L_7$-$R_9$;

-S(O)-$L_1$-$L_2$-$L_3$-$L_5$-$L_6$-$L_7$-$R_9$;

-S(O)$_2$-$L_1$-$L_2$-$L_3$-$L_5$-$L_6$-$L_7$-$R_9$;

-($NR_{10}$)-$L_1$-$L_2$-$L_3$-$L_4$-$L_5$-$L_6$-$L_7$-$R_9$; or

-$L_8$-$L_9$-$L_{10}$-$L_{11}$-$L_{12}$-$R_{14}$,

wherein:

each of $L_1$, $L_2$, $L_3$, $L_6$ and $L_7$ is independently ($CHR_{11}$), ($CHR_{11}$-O), ($CHR_{11}$-S), ($C_3$-$C_7$ cycloalkyl), $(CH_2)_{1-4}$ or a bond;

$L_4$ is C=O, C=S or a bond;

$L_5$ is $NR_{10}$, S, O or a bond;

$R_9$ is H, $C(=O)R_{12}$, $C(=O)NR_{12}R_{13}$, $NR_{12}R_{13}$, $C(=O)OR_{12}$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the $C_1$-$C_6$ alkyl, $C_1$-$C_6$ fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively when $NR_{10}$ is present, $R_9$ and $R_{10}$ together with the attached nitrogen atom may form a substituted or unsubstituted ring;

each of $R_{10}$ and $R_{11}$ is independently H or $C_1$-$C_4$ alkyl (such as $CH_3$, $CH_2CH_3$ or $CH(CH_3)_2$), where the $C_1$-$C_4$ alkyl is unsubstituted or substituted;

each of $R_{12}$ and $R_{13}$ is independently H, $C_1$-$C_6$ alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the $C_1$-$C_6$ alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively, $R_{12}$ and $R_{13}$ together with the attached nitrogen atom may form a substituted or unsubstituted ring;

$L_8$ is ($CHR_{15}$), ($CHR_{15}$-O), ($CHR_{15}$-S), ($CHR_{15}$-$NR_{16}$), C=O, C=S or a bond;

$L_9$ is $C_3$-$C_7$ cycloalkyl that is optionally part of a bridged, fused or spiro ring system, $C(R_{15})=C(R_{15})$, C≡C or a bond;

$L_{10}$ is independently ($CHR_{15}$), O, S, ($NCR_{15}$), N(C=O) or a bond;

$L_{11}$ is ($CHR_{15}$), C=O, C=S or a bond;

$L_{12}$ is H, ($C_3$-$C_7$ cycloalkyl), heterocyclyl, aryl, heteroaryl or a bond, where each of the $C_3$-$C_7$ cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted, and the $C_3$-$C_7$ cycloalkyl and/or heterocyclyl is optionally part of a bridged, fused or spiro ring system;

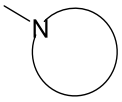
$R_{14}$ is H, $CR_{15}R_{16}R_{17}$, $OR_{17}$, $SR_{17}$, $NR_{16}R_{17}$, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the $C_1$-$C_6$ alkyl, $C_1$-$C_6$ fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted,

each of $R_{15}$ and $R_{16}$ is independently H or $C_1$-$C_3$ alkyl; and

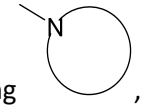
each $R_{17}$ is independently H, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ fluoroalkyl, $C_1$-$C_6$ aminoalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, where each of the $C_1$-$C_6$ alkyl, $C_1$-$C_6$ fluoroalkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is unsubstituted or substituted; or alternatively, $R_{16}$ and $R_{17}$ together with the attached nitrogen atom may form a substituted or unsubstituted ring,

with the proviso that when $R_5$ is -$L_8$-$L_9$-$L_{10}$-$L_{11}$-$L_{12}$-$R_{14}$, at least one of $L_8$, $L_9$, $L_{10}$, $L_{11}$, $L_{12}$ and $R_{14}$ is a carbon-containing moiety and $R_5$ is directly attached to the core structure by a carbon atom;

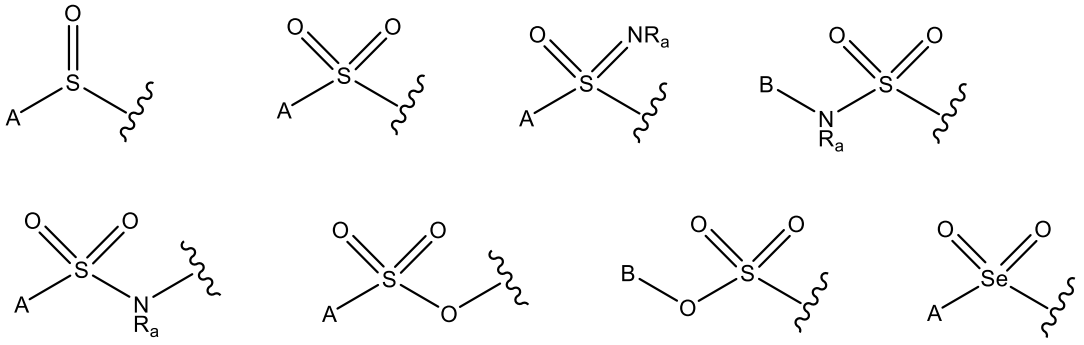
or $R_5$ is

a non-aromatic N-linked heterocyclic ring , where the heterocyclic ring is substituted or unsubstituted, optionally contains one or more additional ring atoms selected from N, O, Si and S, and is optionally part of a bridged, fused or spiro ring system.

2. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $R_5$ is $-(NR_{10})-L_1-L_2-L_3-L_4-L_5-L_6-L_7-R_9$, where $L_1$ to $L_7$, $R_9$ and $R_{10}$ are as defined.

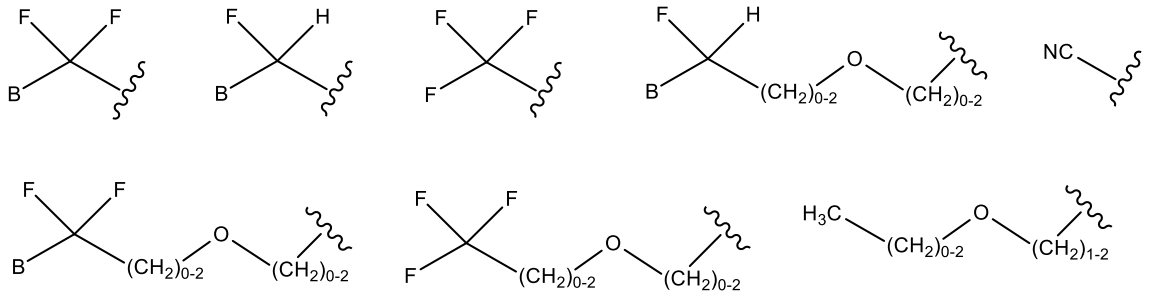
3. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $R_5$ is a non-aromatic N-linked heterocyclyl ring , where the heterocyclyl ring is substituted or unsubstituted, optionally contains one or more additional ring atoms selected from N, O, Si and S, and is optionally part of a bridged, fused or spiro ring system.

4. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $R_1$ is selected from



wherein A, B and $R_a$ are as defined in claim 1.

5. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $R_1$ is selected from



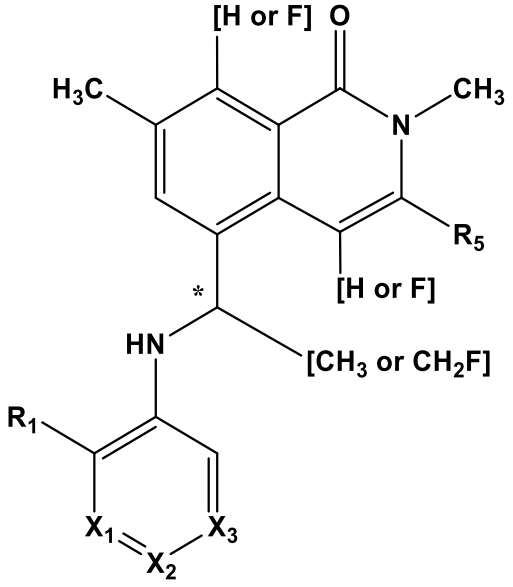
wherein B is as defined in claim 1.

6. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $X_1$ is N, and $X_2$ and $X_3$ are independently CH or substituted C.

7. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $X_1$, $X_2$ and $X_3$ are independently CH or substituted C.

8. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein $R_2$ is $CH_3$ or $CH_2F$, $R_3$ is H and $R_5$ is $-L_8-L_9-L_{10}-L_{11}-L_{12}-R_{14}$.

9. The compound according to claim 1 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (1) is a compound of Formula (2)




(2)

or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof,

wherein:

$X_1$, $X_2$, $X_3$, $R_1$ and $R_5$ are defined as in the compound of Formula (1), and

the carbon marked with * is a chiral center and exists as a (R)- and (S)-racemic mixture or as either the (R)- or (S)- enantiomer.

10. A pharmaceutical composition comprising the compound of any one of claims 1 to 29 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition according to claim 30, further comprising one or more anti-cancer agents.

12. A method of treating a disease in which PI3K activity is implicated in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 9 or a solvate, enantiomer, diastereomer, tautomer, polymorph or isotope-labeled compound, or a pharmaceutically acceptable salt thereof.

13. The method of claim 12, wherein the disease is cancer.

14. The method of claim 12, wherein the disease is congenital lipomatous overgrowth, vascular malformations, epidermal naevi, scoliosis/skeletal and spinal syndrome (CLOVES), mosaic tissue overgrowth syndromes, venous malformations and brain malformations associated with severe epilepsy or PIK3CA-related overgrowth syndrome (PROS).

15. The method of claim 12, wherein the disease is a cancer bearing a PI3Kα H1047R mutation.