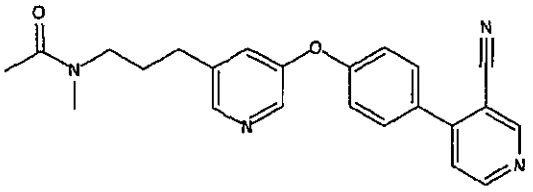
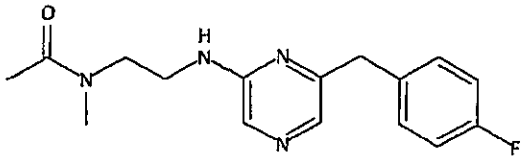
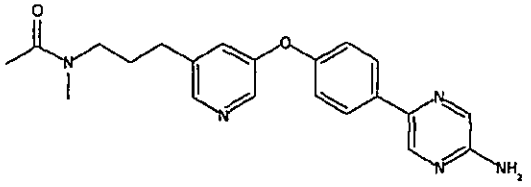
Azaheterocyclic compounds

Field of the invention

The invention relates to a series of novel substituted azaheterocyclic compounds that are useful in the treatment of hyperproliferative diseases such as cancer, as well as inflammatory or degenerative diseases, in mammals. Also encompassed by the present invention is the use of such compounds in the treatment of hyperproliferative, inflammatory or degenerative diseases in mammals, especially humans, and pharmaceutical compositions containing such compounds.

Summary of the related art

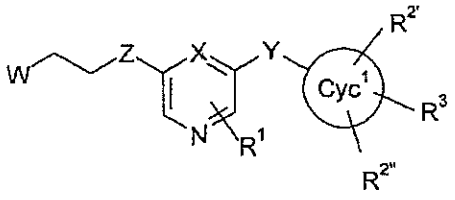
Wnt proteins comprise a large family of cysteine-rich secreted ligands that are highly conserved among species. Currently, three different pathways are believed to be activated by Wnt signaling: the canonical Wnt / β-catenin cascade, the noncanonical planar cell polarity pathway, and the Wnt/Ca2+ pathway. Of these three, the canonical pathway is best understood and has the highest incidence for cancer relevance. Therefore, this project is focusing on canonical Wnt / β-catenin signaling.
In the canonical pathway, β-catenin is the key mediator of Wnt signaling. In the absence of Wnt ligands, a protein complex, that contains Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1), functions in phosphorylating β-catenin and thereby marking it for destruction via ubiquitination and degradation by the proteasome. Following Wnt binding to a receptor complex composed of members of the Frizzled (Fz) family of seven transmembrane, serpentine receptors and low density lipoprotein receptor-related proteins 5/6 (LRP5/6), Disheveled (Dsh) and Axin are recruited to the plasma membrane. Subsequently, the Axin-APC-GSK3β complex is inhibited, non-phosphorylated β-catenin accumulates in the cytoplasm and then translocates into the nucleus where it regulates target gene expression in combination with members of the DNA-binding T cell factor / lymphoid enhancer factor (TCF/LEF) family. Many different target genes of canonical Wnt / β-catenin signaling have been described (e.g. c-Myc, Cyclin D1, VEGF, survivin) which are involved in cell

				acetamide	
321		A	1,79	N-(3-{5-[4-(3-Cyano-pyridin-4-yl)-phenoxy]-pyridin-3-yl}-propyl)-N-methyl-acetamide	
322		C	1,90	N-{2-[6-(4-Fluoro-benzyl)-pyrazin-2-ylamino]-ethyl}-N-methyl-acetamide	
323		B	1,57	N-(3-{5-[4-(5-Amino-pyrazin-2-yl)-phenoxy]-pyridin-3-yl}-propyl)-N-methyl-acetamide	1H NMR (500 MHz, DMSO-d6) δ 8.48 (s, 1H), 8.31 – 8.21 (m, 2H), 7.97 – 7.91 (m, 3H), 7.39 (dt, J = 20.3, 2.3 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.51 (s, 2H), 3.29 – 3.23 (m, 2H), 2.91, 2.76 (2xs, 3H), 2.67 – 2.53 (m, 2H), 1.95, 1.93 (2xs, 3H), 1.88 - 1.79 (m, 1H), 1.77 - 1.70 (m, 1H).

Compound numbers 1-3, 5, 6, 9-11, 13-16, 18, 20-24 and 26-28 were assigned to synthesis intermediates and, therefore, omitted from Table 1. Also omitted were compound numbers 42, 68, 297.

Claims

1. A compound of Formula (I)



(I),

or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein

R^1	is H, LA , Hal, OH, CN, NO_2, NH_2, O(LA), NH(LA), $N(LA)_2$,
$R^{2'}$, $R^{2''}$	are independently H, Hal, OH, CN, LA, O(LA),
R^3	is H, LA, Hal, OH, SH, S(LA), CN, NO_2, NH_2, O(LA), (LA)OCO(LA), (LA)COO(LA),NH(LA), NHCOO(LA), $N(LA)_2$, (LA)NH_2, (LA)NH(LA), SO_2NH_2, SO_2(LA), or L-Cyc^2,
R^4	is H, LA, (LA)OH, (LA)NH(R^2), O(LA), Cyc^3,
R^5	is H, LA,
R^4, R^5	together with the atoms they are attached to, can form a 4, 5, 6 or 7 membered heterocycle, having 1 or 2 heteroatoms, which is optionally substituted by R^6,
R^6	is H, LA , Hal, OH, CN, NO_2, NH_2, O(LA), NH(LA), $N(LA)_2$,
W	is -NR^5COR^4 or -$CON(R^4)(R^5)$,
X	is N or CH,
Y	is O or CH_2,
Z	is NH, N(LA), S, CH_2, CH(LA), $C(LA)_2$,
Cyc^1	is a mono- or binuclear, aliphatic or aromatic, 4, 5, 6, 7, 8, 9 or 10 membered homo- or heterocycle, having 0, 1, 2, 3 or 4 N, O and/or S atoms, which may be substituted by one or two oxo groups, and in which one N atom may be replaced by a N^+-O^- group,
Cyc^2	is a mono- or binuclear, aliphatic or aromatic, 4, 5, 6, 7, 8, 9 or 10 membered homo- or heterocycle, having 0, 1, 2, 3 or 4 N, O and/or S atoms, which may be mono-substituted by an oxo group, S(LA), SO_2(LA), N_3, NHCOH, NHCO(LA), NHCOO(LA), $NHSO_2$(LA),

COO(LA), $CONH_2$, (LA)$CONH_2$, CONH(LA), L-Cyc^3 or A, or independently mono-, di-, tri- or tetra-substituted by LA, Hal, OH, CN, NO_2, NH_2, O(LA), NH(LA), $N(LA)_2$, CO(LA), and in which one N atom may be replaced by a N^+-O^- group,

Cyc^3 is a monocyclic, aliphatic or aromatic homo- or heterocycle having 0, 1, 2 or 3 N, N^+-O^-, O and/or S atoms and 5 or 6 skeleton atoms, which may be mono- or di-substituted by LA, Hal, OH, CN, NO_2, NH_2, O(LA), S(LA), NH(LA), $N(LA)_2$, and in which one N atom may be replaced by a N^+-O^- group,

L is a bond, or a unbranched alkyl or alkenyl linker, having 1, 2 or 3 carbon atoms, in which one CH_2 group may be replaced by a carbonyl group,

LA is unbranched or branched alkyl, alkenyl or alkynyl, having 1, 2, 3, 4 or 5 carbon atoms, wherein one, two or three H atoms may be replaced by Hal,

A is a unbranched or branched alkyl or alkenyl chain having up to 25 non-hydrogen atoms, wherein 1, 2, 3, 4, 5 or 6 CH_2 groups may be replaced by O, S, NH, CO, N(LA), SO_2, and 1-7 H atoms may be replaced by Hal, and one CH_3 group may be replaced by OH, NH_2 or Cyc^1,

Hal is F, Cl, Br or I.

2. The compound according to Claim 1, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, in which the residues not designated in greater detail have the meaning indicated for Formula (I), but in which

in Subformula 1

Z is H, NCH_3, CH_2,

in Subformula 2

W is -NR^5COR^4,

in Subformula 3

W is -$CON(R^4)(R^5)$,

in Subformula 4

Y	is O,

in Subformula 5

Z	is H, NCH_3, CH_2,
R^4, R^5	are methyl,

in Subformula 6

W	is $-NR^5COR^4$,
R^4, R^5	together with the atoms they are attached to, form piperidin-2-one or pyrrolidin-2-one,
R^6	is H,

in Subformula 7

W	is $-CON(R^4)(R^5)$,
R^4	is methyl,
R^5	is H,

in Subformula 8

X	is N,

in Subformula 9

W	is $-NR^5COR^4$,
R^4	is methyl, hydroxymethyl, tert-butyloxy, neopentyl,
R^5	is H, methyl, ethyl, isopropyl, fluoromethyl,

in Subformula 10

W	is $-NR^5COR^4$,
R^4, R^5	are methyl,

in Subformula 11

X	is N,
R^1	is H,

in Subformula 12

Cyc^1	is indanyl, indolyl, isoquinolinyl, benzoisoxazolyl,

in Subformula 13

Cyc^1	is phenyl, which is independently mono-, di- or tri-substituted by F, Br, CN, O(LA), LA,

in Subformula 14

Cyc^1	is phenyl, which is substituted in 4-position by L-Cyc^2,

in Subformula 15

Cyc^1	is phenyl, which is substituted in 4-position by L-Cyc^2, and in 1- and/or 2-position by F,

in Subformula 16

X	is N,
Y	is O,
Z	is H, NCH_3, CH_2,

in Subformula 17

X	is N,
Y	is O,
Z	is NCH_3, CH_2,
R^1	is H,

in Subformula 18

W	is $-NR^5COR^4$,
X	is N,
Y	is O,
Z	is NCH_3, CH_2,
R^1	is H,
Cyc^1	is phenyl, which is independently mono-, di- or tri-substituted by F, Br, CN, O(LA), LA,

in Subformula 19

W	is $-NR^5COR^4$,

	X	is N,
	Y	is O,
	Z	is NCH_3, CH_2,
	R^1	is H,
	Cyc^1	is phenyl, which is substituted in 4-position by L-Cyc^2 and, optionally, in 1- and/or 2-position by F,
	in Subformula 20	
	W	is $-NR^5COR^4$,
	X	is N,
	Y	is O,
	Z	is NCH_3, CH_2,
	R^1	is H,
	Cyc^1	is phenyl, which is substituted in 4-position by L-Cyc^2 and, optionally, in 1- and/or 2-position by F,
	in Subformula 21	
	X	is N,
	Y	is O,
	Z	is NCH_3, CH_2, S,
	R^4	is methyl,
	R^5	is methyl, ethyl, isopropyl,
	R^1	is H,
	Cyc^1	is phenyl, which is substituted in 4-position by L-Cyc^2 and, optionally, in 1- and/or 2-position by F,
	Cyc^2	is pyridin-2, 3, or 4-yl, or pyrazin-2-yl, each of which is unsubstituted or substituted by HO(LA), LA, NH_2, CN,
	in Subformula 22	
	W	is $-NR^5COR^4$,
	X	is N,
	Y	is O,
	Z	is NCH_3, CH_2, S,
	R^4, R^5	together with the atoms they are attached to, form piperidin-2-one
	R^1	is H,

Cyc^1	is phenyl, which is substituted in 4-position by L-Cyc^2 and, optionally, in 1- and/or 2-position by F,
Cyc^2	is pyridin-2, 3, or 4-yl, or pyrazin-2-yl, each of which is unsubstituted or substituted by HO(LA), LA, NH_2, CN.

3. The compound according to Claim 1, wherein the compound is selected from the group consisting of:

1-(2-{6-[4-(5-Methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-ylamino}-ethyl)-piperidin-2-one,

1-[2-(Methyl-{6-[4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-piperidin-2-one,

5-(2-Oxo-hexahydro-thieno[3,4-d]imidazol-6-yl)-pentanoic acid [6-(4-{5-[4-(6-{[2-(acetyl-methyl-amino)-ethyl]-methyl-amino}-pyrazin-2-yloxy)-phenyl]-pyridin-2-yl}-piperazin-1-yl)-6-oxo-hexyl]-amide,

6-[5-(2-Oxo-hexahydro-thieno[3,4-d]imidazol-6-yl)-pentanoylamino]-hexanoic acid {5-[4-(6-{[2-(acetyl-methyl-amino)-ethyl]-methyl-amino}-pyrazin-2-yloxy)-phenyl]-pyridin-2-ylmethyl}-methyl-amide,

N-[2-({6-[2-Fluoro-4-(5-fluoro-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[2-Fluoro-4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[2-Fluoro-4-(6-morpholin-4-yl-pyridin-3-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(2-Amino-pyrimidin-4-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(2-Cyano-pyridin-4-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(2-Fluoro-pyridin-4-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(3-Cyano-pyridin-4-yl)-2-fluoro-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(3-Cyano-pyridin-4-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(5-Amino-pyrazin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,

N-[2-({6-[4-(5-Azido-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(5-Fluoro-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(5-Methoxy-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(6-Acetylamino-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(6-Acetylamino-pyridin-3-yl)-2-fluoro-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(6-Amino-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(6-Cyano-pyridin-3-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(6-Hydroxymethyl-pyridin-3-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-[2-({6-[4-(6-Methanesulfonyl-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-methyl-amino)-ethyl]-N-methyl-acetamide,
N-{5-[4-(6-{[2-(Acetyl-methyl-amino)-ethyl]-methyl-amino}-pyrazin-2-yloxy)-phenyl]-pyridin-2-yl}-acetamide,
N-Ethyl-N-(2-{6-[4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-ylsulfanyl}-ethyl)-acetamide,
N-Isopropyl-N-(2-{6-[4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-ylsulfanyl}-ethyl)-acetamide,
N-Methyl-3-(methyl-{6-[4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-amino)-propionamide,
N-Methyl-N-(2-{6-[4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-ylsulfanyl}-ethyl)-acetamide,
N-Methyl-N-(2-{methyl-[6-(4-pyridin-2-yl-phenoxy)-pyrazin-2-yl]-amino}-ethyl)-acetamide,
N-Methyl-N-(2-{methyl-[6-(4-pyridin-4-yl-phenoxy)-pyrazin-2-yl]-amino}-ethyl)-acetamide,
N-Methyl-N-(2-{methyl-[6-(4-thiazol-2-yl-phenoxy)-pyrazin-2-yl]-amino}-ethyl)-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(1H-pyrrolo[2,3-c]pyridin-5-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(5-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,

N-Methyl-N-[2-(methyl-{6-[4-(5-nitro-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(6-methylaminomethyl-pyridin-3-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(6-methyl-pyridin-2-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(6-methyl-pyridin-3-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(6-morpholin-4-yl-pyridin-3-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-[2-(methyl-{6-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-phenoxy]-pyrazin-2-yl}-amino)-ethyl]-acetamide,
N-Methyl-N-{2-[methyl-(6-{4-[6-(4-methyl-piperazin-1-yl)-pyridin-2-yl]-phenoxy}-pyrazin-2-yl)-amino]-ethyl}-acetamide,
or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios.

4. A pharmaceutical composition comprising a compound according to one or more of Claims 1 to 3, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, as active ingredient, together with a pharmaceutically acceptable carrier.

5. A compound according to one or more of Claims 1 to 3, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for use in the treatment of a hyperproliferative, inflammatory or degenerative disease.

6. The compound for use according to Claim 5, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the hyperproliferativ disease is cancer.

7. The compound for use according to Claim 6, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the cancer is selected from the group consisting of brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal,

kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer, melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogneous leukemia, myeloid cell leukemia, Kaposi's sarcoma.

8. The compound for use according to Claim 5, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the inflammatory disease is selected from multiple sclerosis, rheumatoid arthritis, systemic lupus or inflammatory bowel disease.

9. The compound for use according to Claim 5, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, wherein the degenerative disease is selected from osteoarthritis or Alzheimer's disease.

10. Use of a compound of one or more of Claims 1 to 3, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of a hyperproliferative, inflammatory or degenerative disease.

11. Use according to claim 10 wherein the disease is cancer.

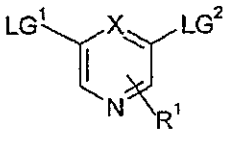
12. Use according to claim 11 wherein the cancer is selected from the group consisting of brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head & neck, renal, kidney, liver, ovarian, prostate, uterine, oesophageal, testicular, gynecological, thyroid cancer, melanoma, acute myelogenous leukemia, multiple myeloma, chronic myelogneous leukemia, myeloid cell leukemia, Kaposi's sarcoma.

13. Set (kit) consisting of separate packs of

a) an effective amount of a compound according to one or more of Claims 1 to 3, or its stereoisomers or tautomers, or pharmaceutically acceptable salts of each of the foregoing, including mixtures thereof in all ratios, and

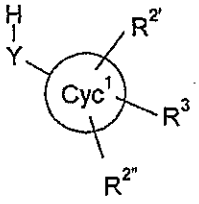
b) an effective amount of a further medicament active ingredient.

14. Process for the manufacture of compounds of Formula (I), wherein a compound of Formula (V)



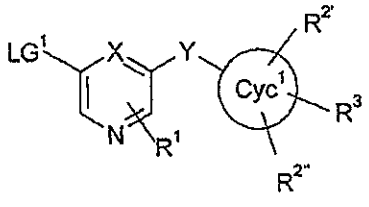
(V),

is reacted with a compound of Formula (IV)



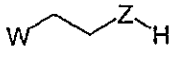
(IV),

to yield a compound of Formula (III)



(III),

which is then further reacted with a compound of Formula (II)



to yield a compound of Formula (I), wherein

LG^1, LG^2 are independently Hal.