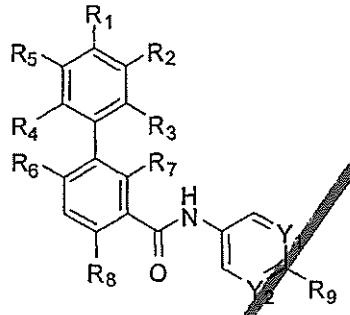
We claim:

1. A combination comprising a first agent that is a Smoothened inhibitor and a second agent that is a BCR-ABL inhibitor,

wherein the first agent is

a compound of Formula I:



I

in which

Y_1 and Y_2 are independently selected from N and CR_{10}; wherein R_{10} is selected from hydrogen, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy and -$OXNR_{10a}R_{10b}$; wherein R_{10a} and R_{10b} are independently selected from hydrogen and C_{1-6}alkyl;

R_1 is selected from cyano, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy, C_{6-10}aryl, dimethyl-amino, C_{1-6}alkyl-sulfanyl and C_{3-8}heterocycloalkyl optionally substituted with up to 2 C_{1-6}alkyl radicals;

R_2 and R_5 are independently selected from hydrogen, cyano, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy and dimethylamino;

R_3 and R_4 are independently selected from hydrogen, halo, cyano, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy and halosubstituted-C_{1-6}alkoxy; or either R_1 and R_2 or R_1 and R_5 together with the phenyl to which they are both attached form C_{5-10}heteroaryl;

R_6 and R_7 are independently selected from hydrogen, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy and halosubstituted-C_{1-6}alkoxy; with the proviso that R_6 and R_7 are not both hydrogen;

R_8 is selected from hydrogen, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy and halosubstituted-C_{1-6}alkoxy;

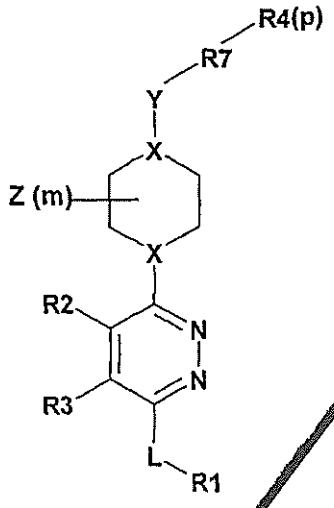
R_9 is selected from $-S(O)_2R_{11}$, $-C(O)R_{11}$, $-OR_{11}$, $-NR_{12a}R_{12b}$ and $-R_{11}$; wherein R_{11} is selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl; R_{12a} and R_{12b} are independently selected from C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl;

wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_9 can be optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy, C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl and C_{3-8}heterocycloalkyl;

wherein said aryl-alkyl substituent of R_9 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy and methyl-piperazinyl; or a pharmaceutically acceptable salt thereof

or

a compounds of the formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein

R1 is a C_{6-14} aryl group, or a 5-14 membered heteroaryl group which may be unsubstituted or substituted;

R2 and R3 are independently C_{1-8} alkyl, C_{1-8} alkylOH, or R2 and R3 form a fused C_{3-14} cycloalkyl group;

L is a bond, C_{1-8} alkylene, -C(O)O-, -C(O)NR9-, -C_{1-8} alkylOH-, -C_{1-8} haloalkyl-, -C(O)-, -NH- or -O-;

X and W are independently N or CR5, and at least one of X or W is N;

R7 is a C_{6-14} aryl group, a 5-14 membered heteroaryl group, or a 3-14 membered cycloheteroalkyl group;

R4 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-14} cycloalkyl, a C_{6-14} aryl group, a 5-14 membered heteroaryl group, a 3-14 membered cycloheteroalkyl group, C_{1-8} alkoxy, halo, NR6R8, C(O)OR6, C(O)NR6R8, C_{1-8}haloalkyl, formyl, carbalkoxy, C_{1-8}alkylOH, C(O)R6, SO_2R6, C(O)NHC$_{1-8}$alkylR6, NR6R8, SO_2NR6R8, OCF_3, NHC(O)R6, $CH_2OC(O)NR6R8$, CH_2NR6R8, NHC(O)OR6, NHC(O)NR6R8, CH_2NHSO_2R6, $CH_2NHC(O)OR6$, OC(O)R6, or NHC(O)R6, which may be substituted or unsubstituted;

Z is C_{1-8} alkyl, CN, OH, or halogen;

m and p are independently 0-3;

Y is a bond, C_{1-8} alkylene, -C(O)-, -C(O)O-,-CH(OH)-, or -C(O)NR10;

R5 is H, halogen, CN, lower alkyl, OH, OCH_3 or OCF_3;

Wherein R1 may be substituted by one or more of C_{1-8} alkyl, a C_{6-14} aryl group, C_{1-8} haloalkyl, C_{1-8} alkoxy, halo, NH_2, CN, OCF_3, OH, C(O)NR6R8, C(O)R6, NR6R8, NHC(O)R6, SO_2R6, SO_2NR6R8;

R9 and R10 are independently C_{1-8} alkyl or H;

R6 and R8 are independently H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-14} cycloalkyl, a C_{6-14} aryl group, a 5-14 membered heteroaryl group, a 3-14 membered cycloheteroalkyl group, C_{1-8}haloalkyl, C_{1-8} alkylOH, C_{1-8}alkoxy, or two R6 on one atom can form a heteroatom containing ring; and

wherein R4, R6, and R8 can be unsubstituted or substituted by one or more of C_{1-8} alkyl, C_{3-14} cycloalkyl, a C_{6-14} aryl group, a 5-14 membered heteroaryl group, a 3-14 membered cycloheteroalkyl group, C_{1-8} alkylOH, OH, oxo, C_{1-8} haloalkyl, carboxC_{1-8} alkyl, or SO_2C_{1-8}alkyl, halo, -OCH_3, -OCF_3, -OH, -NH_2 or a salt thereof.

2. The combination of claim 1, wherein said first agent is 2-methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide or a pharmaceutically acceptable salt thereof.

3. The combination of claim 1, wherein said first agent is 2-[(*R*)-4-(6-benzyl-4,5-dimethyl-pyridazin-3-yl)-2-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

4. The combination of claim 1, wherein said second agent is an ABL inhibitor, an ABL/Scr inhibitor, an Aurora kinase inhibitor, or a non-ATP competitive inhibitor of BCR- ABL.

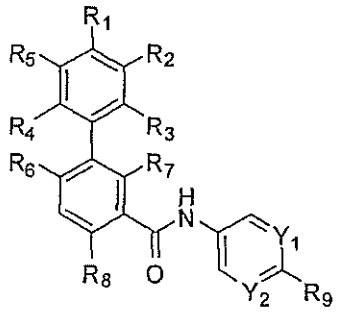
5. The combination of claim 1, wherein said second agent is selected from the group consisting of nilotinib (AMN107), imatinib (STI571), 2,6,9-trisubstituted purine analogs (e.g., AP23464), AZD-0530, bosutinib (SKI-606), CPG070603, pyrido[2,3-d]pyrimidine compounds (e.g., dasatinib (BMS-354825)), PD166326, PD173955, PD180970), ON012380, 3-substituted benzamide derivatives (e.g., INNO-406), MK-0457 (VX-680), PHA-739358, retaspimycin hydrochloride (IPI-504) and GNF-2.

6. The combination of claim 5, wherein the second agent is nilotinib.

7. The combination of claim 6, wherein the first agent is 2-methyl-4'-trifluoromethoxy-biphenyl-3-carboxylic acid [6-(cis-2,6-dimethyl-morpholin-4-yl)-pyridin-3-yl]-amide or a pharmaceutically acceptable salt thereof.

8. The combination of claim 6, wherein the first agent is 2-[(R)-4-(6-benzyl-4,5-dimethyl-pyridazin-3-yl)-2-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-yl]-propan-2-ol or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a first agent that is a Smoothened inhibitor and a second agent that is a BCR-ABL inhibitors,
wherein the first agent is
a compound of Formula I:



I

in which
Y_1 and Y_2 are independently selected from N and CR_{10}; wherein R_{10} is selected from hydrogen, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy and -OXNR$_{10a}$R$_{10b}$; wherein R_{10a} and R_{10b} are independently selected from hydrogen and C_{1-6}alkyl;

R_1 is selected from cyano, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy, C_{6-10}aryl, dimethyl-amino, C_{1-6}alkyl-sulfanyl and C_{3-8}heterocycloalkyl optionally substituted with up to 2 C_{1-6}alkyl radicals;

R_2 and R_5 are independently selected from hydrogen, cyano, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy and dimethylamino;

R_3 and R_4 are independently selected from hydrogen, halo, cyano, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy and halosubstituted-C_{1-6}alkoxy; or either R_1 and R_2 or R_4 and R_5 together with the phenyl to which they are both attached form C_{5-10}heteroaryl;

R_6 and R_7 are independently selected from hydrogen, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy and halosubstituted-C_{1-6}alkoxy; with the proviso that R_6 and R_7 are not both hydrogen;

R_8 is selected from hydrogen, halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy and halosubstituted-C_{1-6}alkoxy;

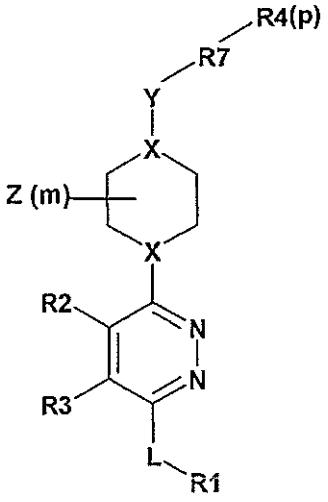
R_9 is selected from $-S(O)_2R_{11}$, $-C(O)R_{11}$, $-OR_{11}$, $-NR_{12a}R_{12b}$ and $-R_{11}$; wherein R_{11} is selected from aryl, heteroaryl, cycloalkyl and heterocycloalkyl; R_{12a} and R_{12b} are independently selected from C_{1-6}alkyl and hydroxy-substituted-C_{1-6}alkyl;

wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_9 can be optionally substituted with 1 to 3 radicals independently selected from C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy, C_{6-10}aryl-C_{0-4}alkyl, C_{5-10}heteroaryl-C_{0-4}alkyl, C_{3-12}cycloalkyl and C_{3-8}heterocycloalkyl;

wherein said aryl-alkyl substituent of R_9 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halosubstituted-C_{1-6}alkyl, C_{1-6}alkoxy, halosubstituted-C_{1-6}alkoxy and methyl-piperazinyl; or a pharmaceutically acceptable salt thereof

or

a compounds of the formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein

R1 is a C_{6-14} aryl group, or a 5-14 membered heteroaryl group which may be unsubstituted or substituted;

R2 and R3 are independently C_{1-8} alkyl, C_{1-8} alkylOH, or R2 and R3 form a fused C_{3-14} cycloalkyl group;

L is a bond, C_{1-8} alkylene, -C(O)O-, -C(O)NR9-, -C_{1-8} alkylOH-, -C_{1-8} haloalkyl-, -C(O)-, -NH- or -O-;

X and W are independently N or CR5, and at least one of X or W is N;

R7 is a C_{6-14} aryl group, a 5-14 membered heteroaryl group, or a 3-14 membered cycloheteroalkyl group;

R4 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-14} cycloalkyl, a C_{6-14} aryl group, a 5-14 membered heteroaryl group, a 3-14 membered cycloheteroalkyl group, C_{1-8} alkoxy, halo, NR6R8, C(O)OR6, C(O)NR6R8, C_{1-8}haloalkyl, formyl, carbalkoxy, C_{1-8}alkylOH, C(O)R6, SO_2R6, C(O)NHC_{1-8}alkylR6, NR6R8, SO_2NR6R8, OCF_3, NHC(O)R6, $CH_2OC(O)NR6R8$, CH_2NR6R8, NHC(O)OR6, NHC(O)NR6R8, CH_2NHSO_2R6, $CH_2NHC(O)OR6$, OC(O)R6, or NHC(O)R6, which may be substituted or unsubstituted;

Z is C_{1-8} alkyl, CN, OH, or halogen;

m and p are independently 0-3;

Y is a bond, C_{1-8} alkylene, -C(O)-, -C(O)O-,-CH(OH)-, or -C(O)NR10;

R5 is H, halogen, CN, lower alkyl, OH, OCH_3 or OCF_3;

Wherein R1 may be substituted by one or more of C_{1-8} alkyl, a C_{6-14} aryl group, C_{1-8} haloalkyl, C_{1-8} alkoxy, halo, NH_2, CN, OCF_3, OH, C(O)NR6R8, C(O)R6, NR6R8, NHC(O)R6, SO_2R6, SO_2NR6R8;

R9 and R10 are independently C_{1-8} alkyl or H;

R6 and R8 are independently H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-14} cycloalkyl, a C_{6-14} aryl group, a 5-14 membered heteroaryl group, a 3-14 membered cycloheteroalkyl group, C_{1-8}haloalkyl, C_{1-8} alkylOH, C_{1-8}alkoxy, or two R6 on one atom can form a heteroatom containing ring; and wherein R4, R6, and R8 can be unsubstituted or substituted by one or more of C_{1-8} alkyl, C_{3-14} cycloalkyl, a C_{6-14} aryl group, a 5-14 membered heteroaryl group, a 3-14 membered cycloheteroalkyl group, C_{1-8} alkylOH, OH, oxo, C_{1-8} haloalkyl, carboxC_{1-8} alkyl, or SO_2C_{1-8}alkyl, halo, $-OCH_3$, $-OCF_3$, -OH, $-NH_2$ or a salt thereof.

10. The use of the combination of claim 1, for the manufacture of a medicament for treating BCR-ABL positive leukemia.

11. The use of claim 10, wherein the BCR-ABL positive leukemia is chronic myeloid leukemia, acute myelogenous leukemia or acute lymphocyte leukemia.

12. The use of claim 11, wherein the BCR-ABL positive leukemia is chronic myeloid leukemia.

CLAIMS

1. An invention not claimed in any divisional application.