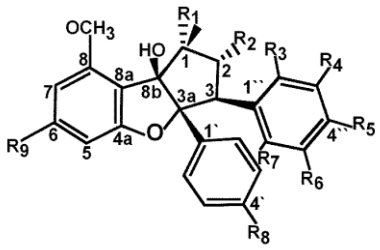
PATENT CLAIMS

1. An inhibitor of KRAS oncogene activation, which is a flavagline derivative having the general formula (I)

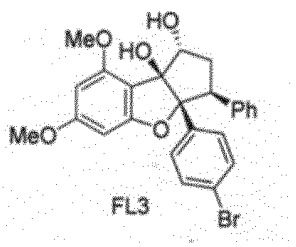


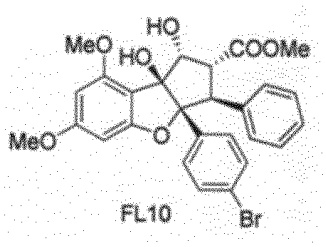
(I)

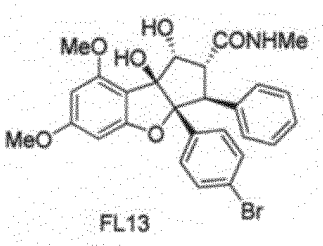
in which
R1 is -OH, -O-CH=O, - NH-CH=O, -NH-(C=O)-$N(CH_3)_2$, -NH-(C=O)-NH_2;
R2 is -H, -COO-CH_3, -CO(NH)-CH_3, -$NO(CH_3)_2$;
R3, R4, R5 are each independently -H, -OH;
R6 is -H, -OH, -F;
R7 is -H, -OH;
R8 is -H, -OCH_3, -Br, -F, -Cl;
R9 is -O-CH_3, -O-$(CH_2)_2$-HN-CH_3,

for use in the prevention or treatment of KRAS-mutated proliferative disorder or genetic disorder.

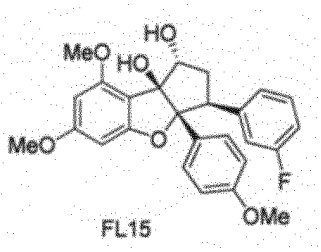
2. The inhibitor of KRAS oncogene activation according to claim 1 , wherein the flavagline derivative is FL3, FL10, FL13, FL15, FL19, FL23, FL32, FL37, FL40, FL42, or IMD-26260 having the following structure:



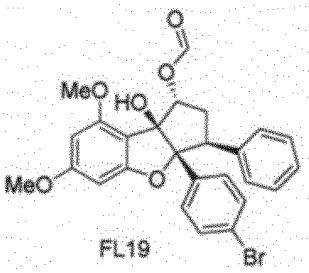




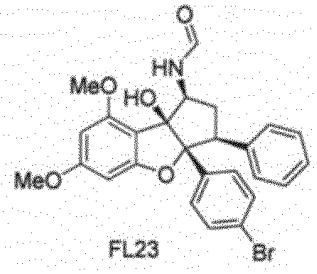
FL13



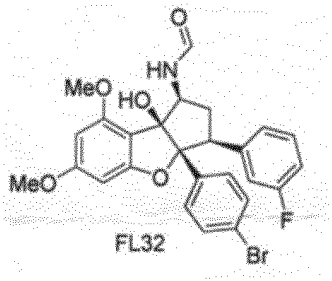
FL15



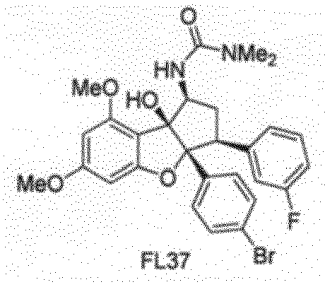
FL19



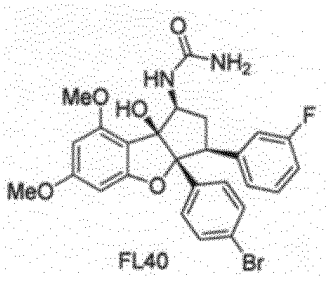
FL23



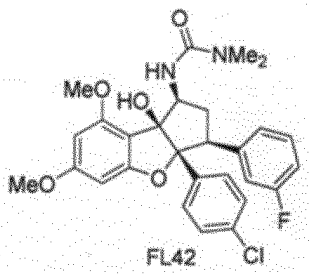
FL32



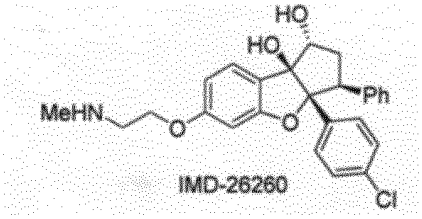
FL37



FL40



FL42



IMD-26260

3. The inhibitor of KRAS oncogene activation according to claim 1 or claim 2, wherein RAS signalling involves a mutated KRAS gene.

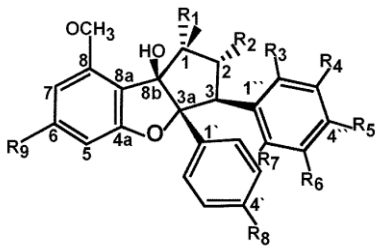
4. The inhibitor of KRAS oncogene activation according to claim 3, wherein the KRAS gene contains a G12V, G12C, G12D, G13C, G13D, G13S, Q61 H, Q61 R, and/or Q61 K mutation.

5. Use of a compound comprising anyone of the structures as defined in anyone of claims 1 to 4 in the manufacture of a medicament for inhibiting KRAS activation in cells in vitro or ex vivo in a subject having KRAS-mutated proliferative disorder or genetic disorder.

6. An in vitro or ex vivo method of specifically inhibiting proliferation of a cell population by targeting KRAS, the method comprising the step of contacting the cell population with a compound as defined in anyone of claims 1 to 4.

7. The method according to claim 6, wherein inhibition of the proliferation of the cell population is measured as a decrease in cell viability of the cell population.

8. A pharmaceutical composition, comprising a compound, which is a flavagline derivative having the general formula (I)



(I)

in which

R1 is -OH, - O-CH=O, -NH-CH=O, -NH-(C=O)-$N(CH_3)_2$, -NH-(C=O)-NH_2;

R2 is -H, -COO-CH_3, -CO(NH)-CH_3, -$NO(CH_3)_2$;

R3, R4, R5 are each independently -H, -OH;

R6 is -H, -OH, -F;

R7 is -H, -OH;

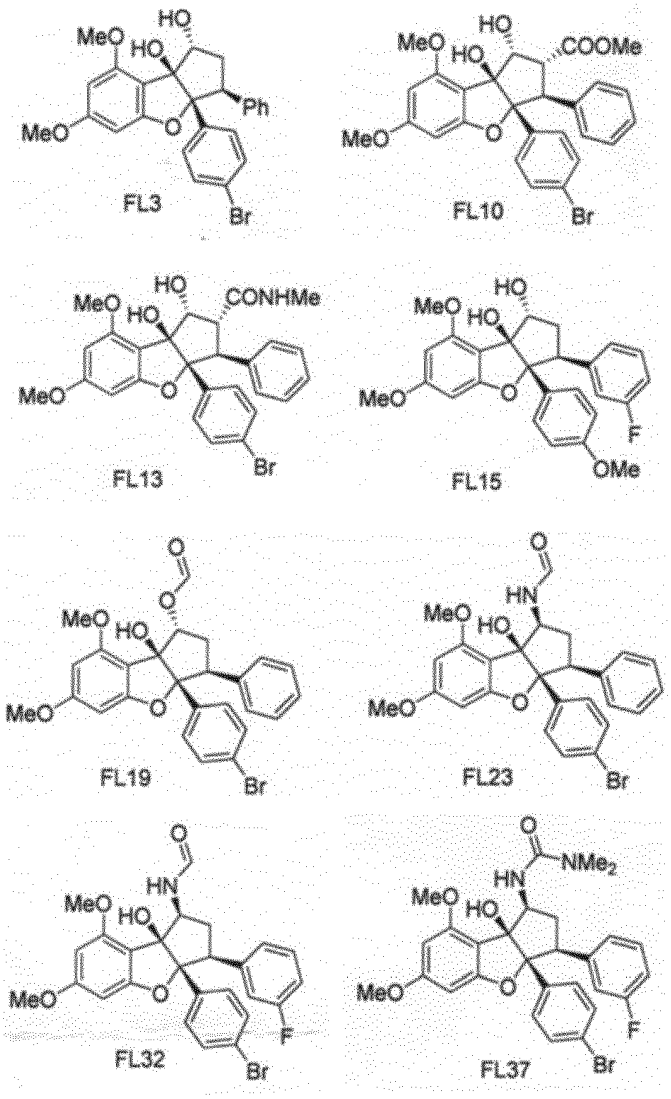
R8 is -H, -OCH3, -Br, -F, -Cl;

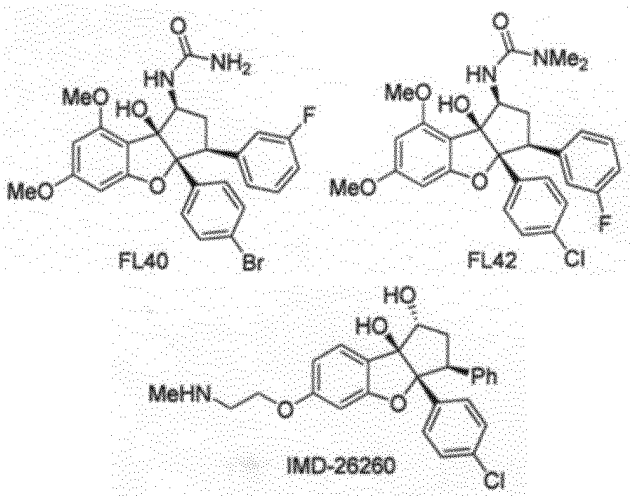
R9 is -O-CH_3, -O-$(CH_2)_2$-HN-CH_3,

and a pharmaceutically acceptable vehicle, diluent, adjuvant or excipient, for use in the prevention or treatment of a disease in which RAS signalling is pathologically involved.

9. The pharmaceutical composition according to claim 8, wherein the disease is a KRAS-mutated proliferative disorder or genetic disorder.

10. The pharmaceutical composition according to anyone of claim 8 to 9, wherein the flavagline derivative is FL3, FL10, FL13, FL15, FL19, FL23, FL32, FL37, FL40, FL42, or IMD-26260 having the following structure:





11. The pharmaceutical composition according to claim 8, wherein the disease is a neoproliferative disease, cancer, RASOpathy or craniofacial syndrome.

12. The pharmaceutical composition according to claim 11 , wherein the cancer is colorectal cancer, lung cancer, hematological cancer, MYH associated polyposis, bladder cancer, melanoma, acute myeloid leukemia (AML), or pancreatic cancer.

13. The pharmaceutical composition according to claim 8, wherein RAS signalling involves a mutated KRAS gene.

14. The pharmaceutical composition according to claim 13, wherein the mutated KRAS gene contains a G12V, G12C, G12D, G13C, G13D, G13S, Q61 H, Q61 R, and/or Q61 K mutation.

15. A Flavagline derivate, wherein the flavagline derivative is IMD-26260 having the following structure:

