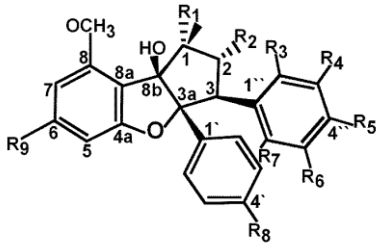
PATENT CLAIMS

~~1.~~ Use of ~~An~~an inhibitor of KRAS oncogene activation in the manufacture of a medicament for treating KRAS-mutated proliferative disorder or genetic disorder, ~~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;~~

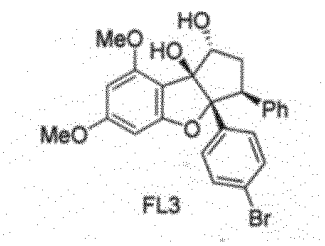
~~R7 is -H, -OH;~~

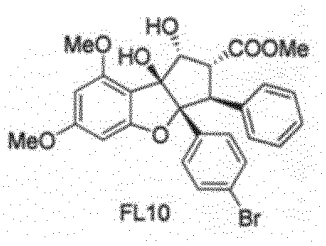
~~R8 is -H, -OCH_3, -Br, -F, -Cl;~~

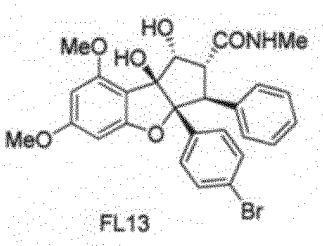
~~R9 is -O-CH_3, -O-(CH_2)$_2$-HN-CH_3,~~

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

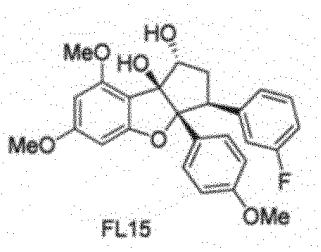
~~2.~~1. ~~The inhibitor of KRAS oncogene activation according to claim 1 ,~~ wherein the inhibitor of KRAS oncogene activation is a ~~the~~ flavagline derivative, the flavagline derivative is FL3, FL10, FL13, FL15, FL19, FL23, FL32, FL37, FL40, FL42, or IMD-26260 having the following structure:



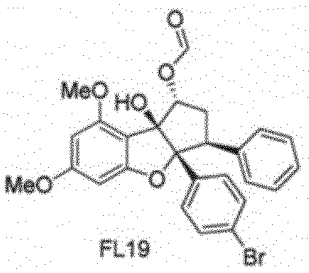




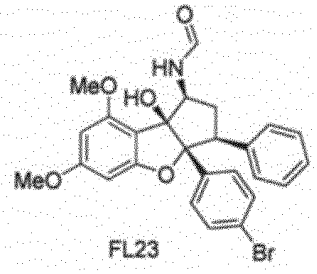
FL13



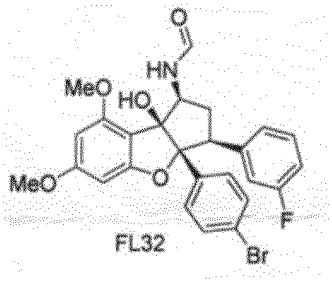
FL15



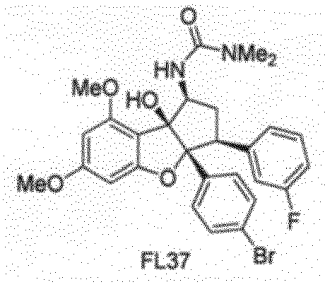
FL19



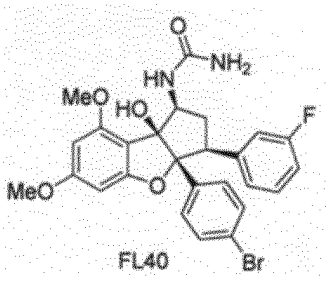
FL23



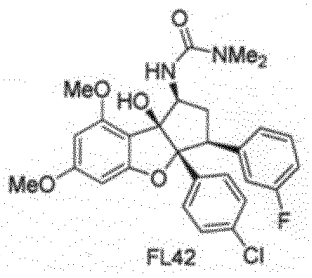
FL32



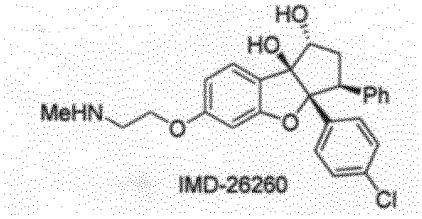
FL37



FL40



FL42



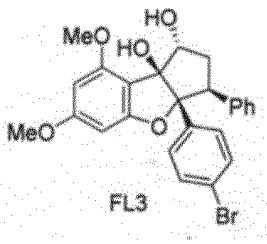
IMD-26260

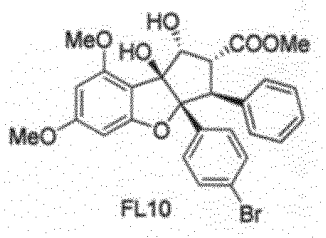
~~3.~~2. The ~~inhibitor of KRAS oncogene activation according to claim 1 or claim 2~~use according to claim 1, wherein RAS signalling involves a mutated KRAS gene.

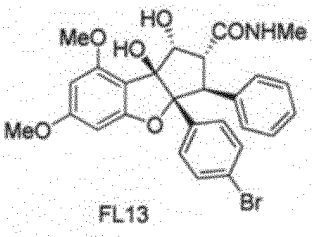
~~4.~~3. The ~~inhibitor of KRAS oncogene activation according to claim 3~~ use according to claim 2, wherein the KRAS gene contains a G12V, G12C, G12D, G13C, G13D, G13S, Q61 H, Q61 R, and/or Q61 K mutation.

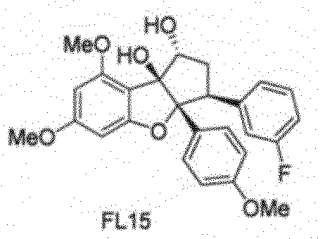
~~5. Use of a compound comprising anyone of the structures as defined in anyone of claims 1 to 4 in the manufacture of a medicament for inhibiting KRAS activation in cells in vitro or ex vivo in a subject having KRAS-mutated proliferative disorder or genetic disorder.~~

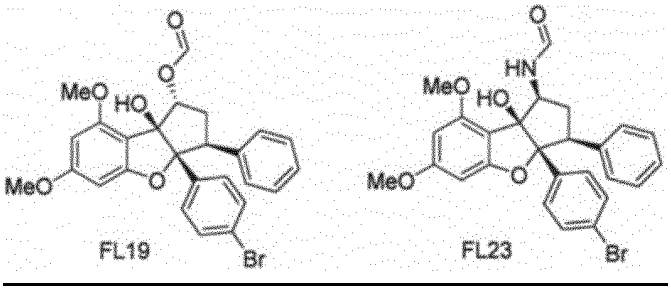
~~6.~~4. An in vitro or ex vivo method of specifically inhibiting proliferation of a cell population by targeting KRAS, the method comprising the step of contacting the cell population with ~~a compound as defined in anyone of claims 1 to 4~~ a flavagline derivative, the flavagline derivative is FL3, FL10, FL13, FL15, FL19, FL23, FL32, FL37, FL40, FL42, or IMD-26260 having the following structure:~~.~~

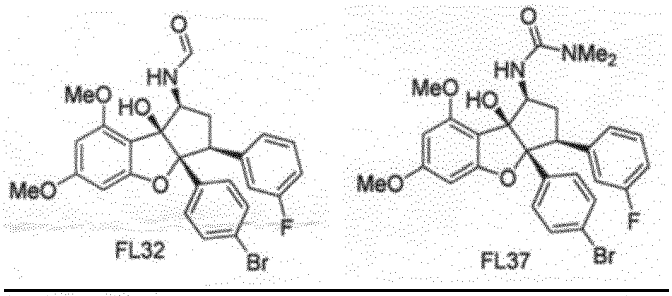


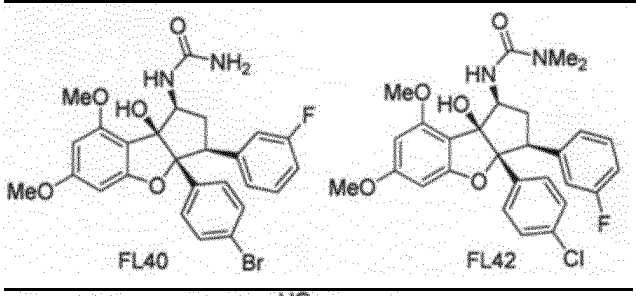


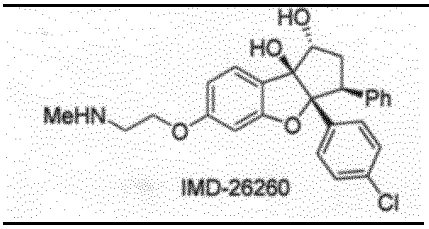






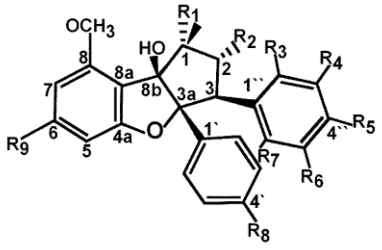






~~7.~~5. The method according to claim ~~6~~4, wherein inhibition of the proliferation of the cell population is measured as a decrease in cell viability of the cell population.

~~8.~~6. ~~A~~Use of a pharmaceutical composition in the manufacture of a medicament for treating a disease in which RAS signaling is pathologically involved, the pharmaceutical composition comprising a compound, which is a flavagline derivative ~~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;~~

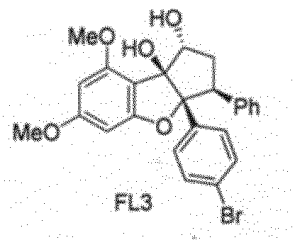
~~R8 is -H, -OCH3, -Br, -F, -Cl;~~

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

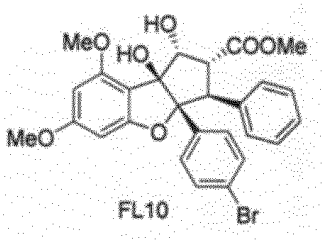
~~and a pharmaceutically acceptable vehicle, diluent, adjuvant or excipient, for use in the prevention or treatment of a disease in which RAS signalling is pathologically involved.~~

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

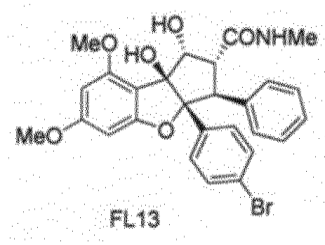
~~10.~~ ~~The pharmaceutical composition according to anyone of claim 8 to 9,~~ wherein ~~the flavagline derivative is~~<u>selected from</u> FL3, FL10, FL13, FL15, FL19, FL23, FL32, FL37, FL40, FL42, or IMD-26260 having the following structure:



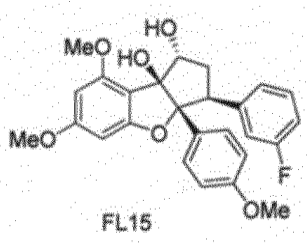
FL3



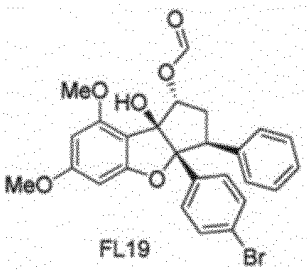
FL10



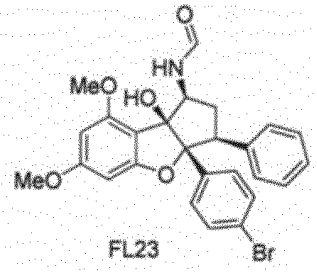
FL13



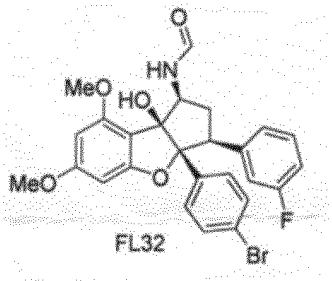
FL15



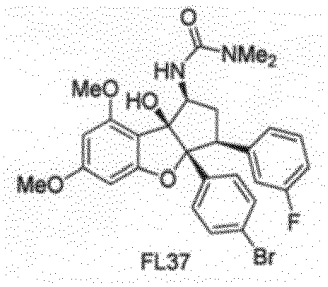
FL19



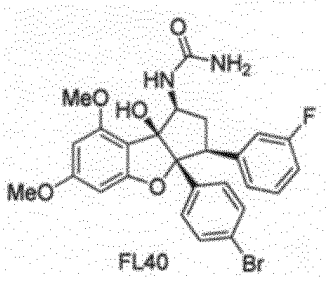
FL23



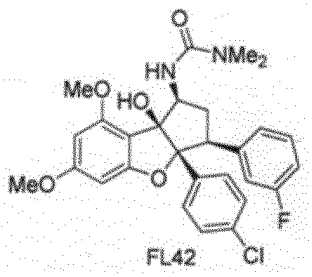
FL32



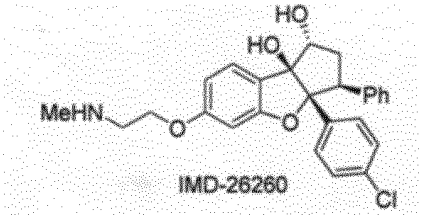
FL37



FL40



FL42



IMD-26260

and a pharmaceutically acceptable vehicle, diluent, adjuvant or excipient.

7. The use according to claim 6, wherein the disease is a KRAS-mutated proliferaive disorder or genetic disorder.

~~11.~~ 8. The ~~pharmaceutical composition according to claim 8~~ use according to claim 6, wherein the disease is a neoproliferative disease, cancer, RASOpathy or craniofacial syndrome.

~~12.~~ 9. The ~~pharmaceutical composition according to claim 11~~ use according to claim 8, wherein the cancer is colorectal cancer, lung cancer, hematological cancer, MYH associated polyposis, bladder cancer, melanoma, acute myeloid leukemia (AML), or pancreatic cancer.

~~13.~~ 10. The ~~pharmaceutical composition according to claim 8~~ use according to claim 6, wherein RAS signalling involves a mutated KRAS gene.

~~14.~~ 11. The ~~pharmaceutical composition according to claim 13~~ use according to claim 10, 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:~~

