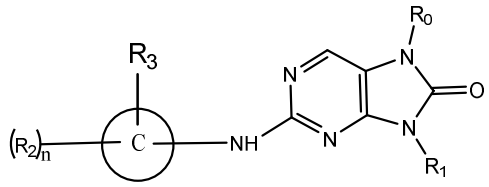
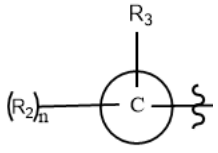
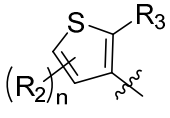
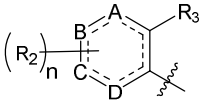
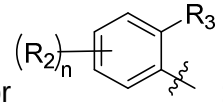
Claims

1. A pharmaceutical preparation of an imidazolinone compound, comprising an imidazolinone compound, or a stereoisomer, solvate, prodrug, metabolite, pharmaceutically acceptable salt or co-crystal thereof, wherein the pharmaceutical preparation comprises the imidazolinone compound with a specification of 1-1000 mg and one or more of a diluent, a disintegrant, and a glidant, and the imidazolinone compound is selected from a compound of formula I:

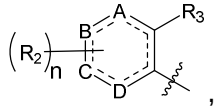


(I)

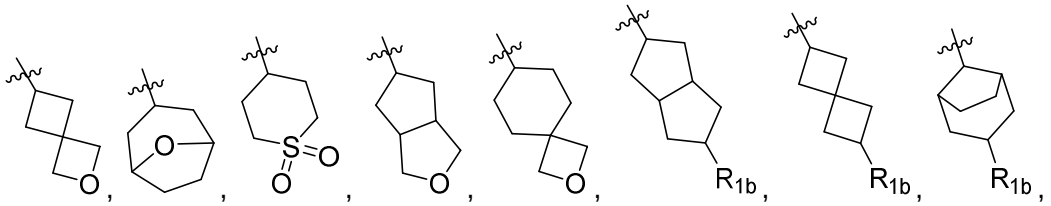
wherein

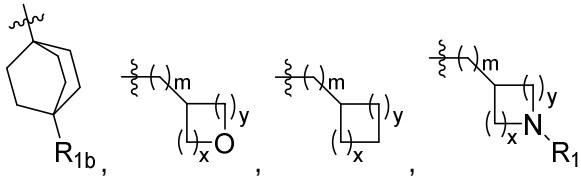
 is ,  or ;

---is a single bond or double bond;

in , A, B, C, D are each independently C or N, and at least one of A, B, C and D is N;

R_0 is H, C_{1-6} alkyl or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is 

 or pyridyl, and R_1 is optionally further substituted with 1 or 2 substituents selected from D, halogen, cyano, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy;

R_{1a} is H, C_{1-6} alkyl, or -C(=O)C_{1-6} alkyl;

R_{1b} is H, OH, cyano, or hydroxyl substituted C_{1-6} alkyl;

R_2 is H, cyano, =O, carboxyl, -C(=O)$NR_{2a}R_{2b}$, C_{1-6} alkoxy, C_{1-6} alkyl, halogen, -$S(=O)_2R_{2a}$ or -C(=O)OC_{1-6} alkyl, wherein the C_{1-6} alkyl, -C(=O)OC_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1, 2 or 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH and halogen;

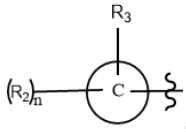
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

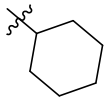
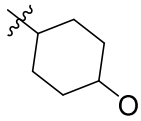
m is 0 or 1;

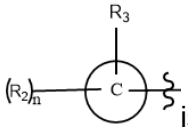
n is 0, 1 or 2; and

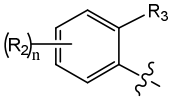
x and y are each independently 1, 2 or 3;

with the provisos that

when 

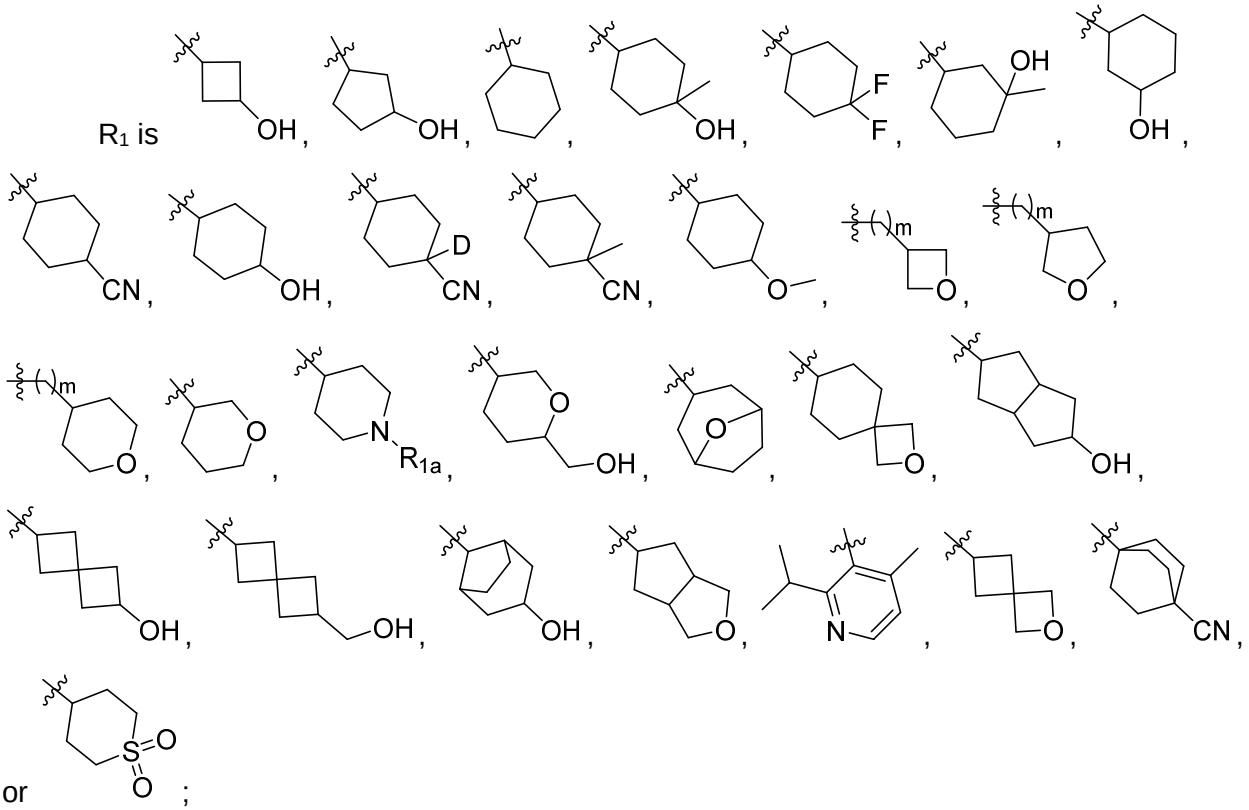
, R_0, R_2, and R_3 simultaneously satisfy the following conditions, R_1 is not ,  or 

: 

is 

, n is 1, R_0 is H or methyl, R_2 is methoxy or -$S(=O)_2$Me, and R_3 is methyl.

2. The pharmaceutical preparation according to claim 1, wherein in the compound of formula I,

R_1 is 
or ;

R_{1a} is H or C_{1-6} alkyl;

R_2 is H, cyano, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the $-C(=O)OC_{1-6}$ alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D or halogen;

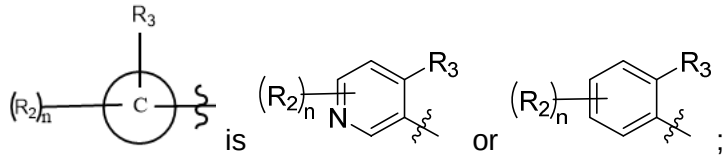
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from OH and halogen;

R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

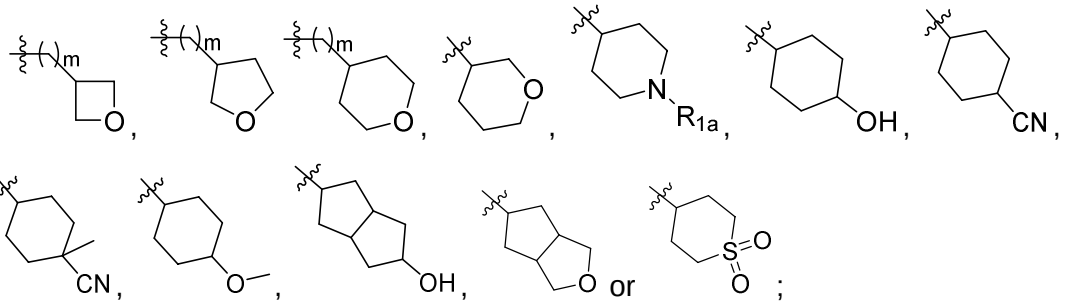
m is 0 or 1; and

n is 0, 1 or 2.

3. The pharmaceutical preparation according to claim 1, wherein in the compound of formula I,



R_0 is H, C_{1-4} alkyl or cyclopropyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and D;

R_1 is 

R_{1a} is H, C_{1-6} alkyl or -C(=O)C_{1-6} alkyl;

R_2 is H, cyano, -C(=O)N$R_{2a}R_{2b}$, C_{1-6} alkoxy, halogen, -S(=O)$_2R_{2a}$ or -C(=O)OC_{1-6} alkyl, wherein the -C(=O)OC_{1-6} alkyl or C_{1-6} alkoxy is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D and halogen;

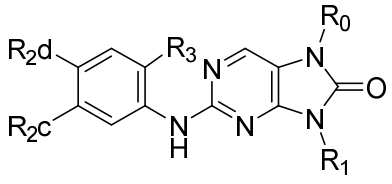
alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is also optionally further substituted with one or more substituents selected from OH and halogen;

R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1; and

n is 0, 1 or 2.

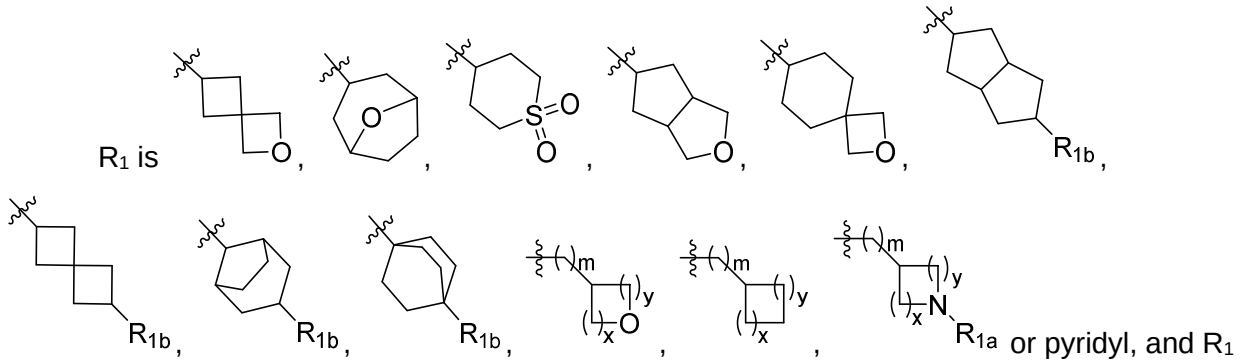
4. The pharmaceutical preparation according to claim 1, wherein the compound of formula I is selected from:



(II)

wherein

R_0 is H, C_{1-6} alkyl or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is  or pyridyl, and R_1 is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy;

R_{1a} is H or C_{1-6} alkyl;

R_{1b} is H, OH, cyano, or hydroxyl substituted C_{1-6} alkyl;

R_{2c} is H, cyano, halogen or C_{1-6} alkoxy;

R_{2d} is H, cyano, carboxyl, $-C(=O)NR_{2a}R_{2b}$, C_{1-6} alkyl, halogen, $-S(=O)_2R_{2a}$ or $-C(=O)OC_{1-6}$ alkyl, wherein the C_{1-6} alkyl and $-C(=O)OC_{1-6}$ alkyl is optionally substituted with one or more substituents selected from halogen and deuterium;

R_{2a} and R_{2b} are H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from OH, D, halogen, C_{1-6} alkyl and C_{1-6} alkoxy;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH and halogen;

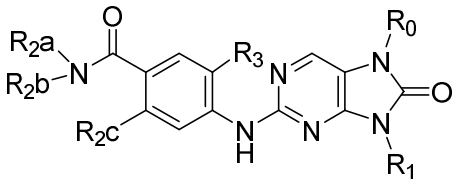
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D and halogen;

m is 0 or 1;

n is 0, 1 or 2; and

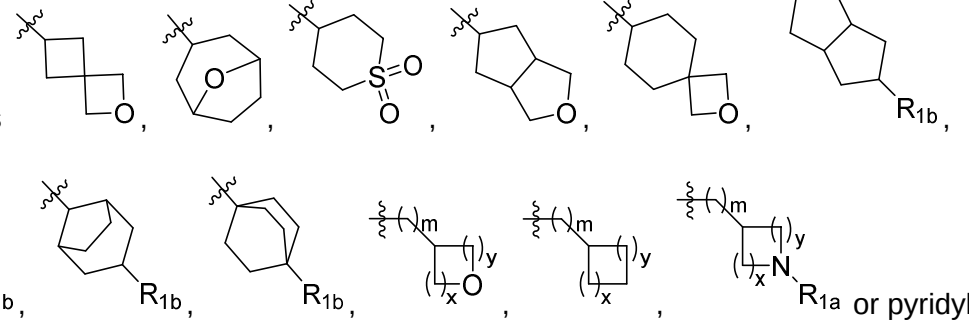
x and y are each independently 1, 2 or 3.

5. The pharmaceutical preparation according to claim 1, wherein the compound of formula I is selected from:


(III)

wherein

R_0 is H, C_{1-6} alkyl or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is  or pyridyl, and R_1 is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy;

R_{1b} is H, OH, cyano, or hydroxyl substituted C_{1-6} alkyl;

R_{2a} and R_{2b} are each independently H, C_{1-6} alkyl, or 3- to 5-membered cycloalkyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from D or halogen;

alternatively, R_{2a} and R_{2b} together with the atoms to which they are attached form a 5- to 6-membered heterocyclyl, which contains 1 to 3 heteroatoms selected from N, O and S and is optionally further substituted with one or more substituents selected from C_{1-6} alkyl, OH and halogen;

R_{2c} is H, cyano, halogen or C_{1-6} alkoxy, wherein the C_{1-6} alkoxy is optionally substituted with one or more deuterium;

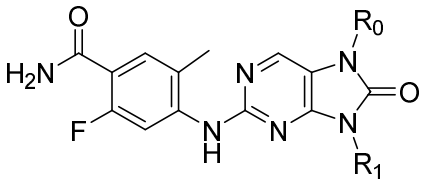
R_3 is halogen or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally further substituted with 1 to 3 substituents selected from D or halogen;

m is 0 or 1;

n is 0, 1 or 2; and

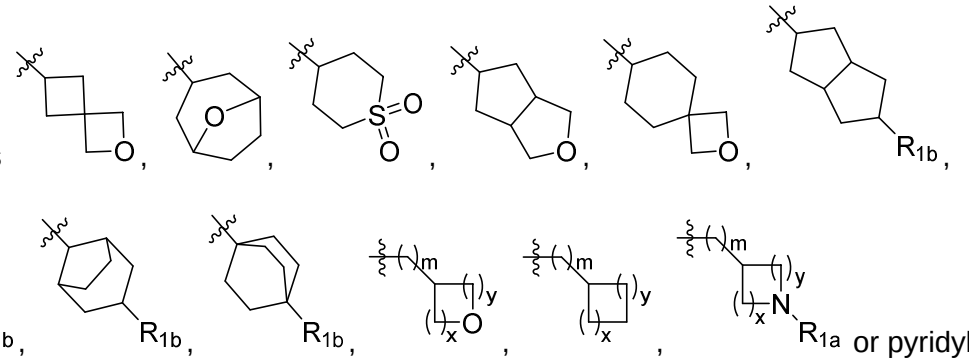
x and y are each independently 1, 2 or 3.

6. The pharmaceutical preparation according to claim 1, wherein the compound of formula I is selected from:


(IV)

wherein

R_0 is H, C_{1-6} alkyl or cyclopropyl, wherein the C_{1-6} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium;

R_1 is  or pyridyl, and R_1 is optionally further substituted with 1 to 2 substituents selected from D, halogen, cyano, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy;

R_{1a} is H or C_{1-6} alkyl;

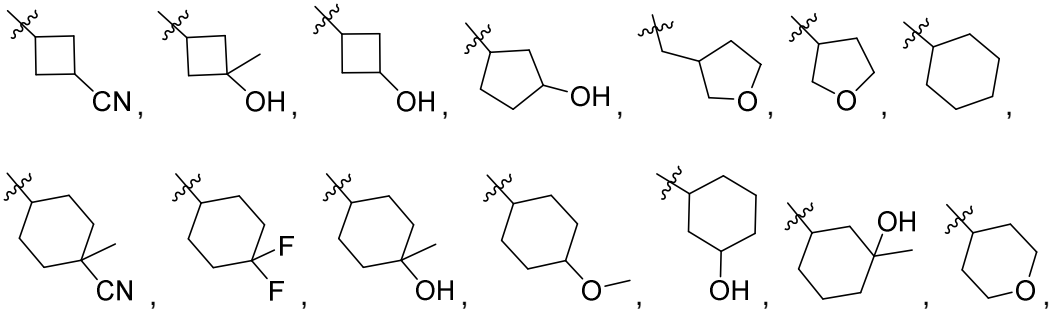
R_{1b} is H, OH, cyano, or hydroxyl substituted C_{1-6} alkyl;

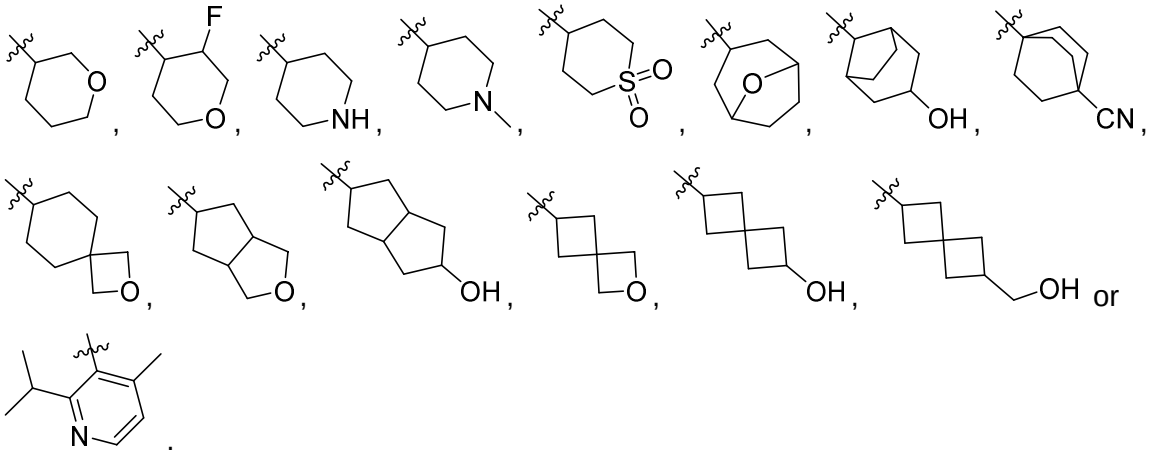
m is 0 or 1; and

x and y are each independently 1, 2 or 3.

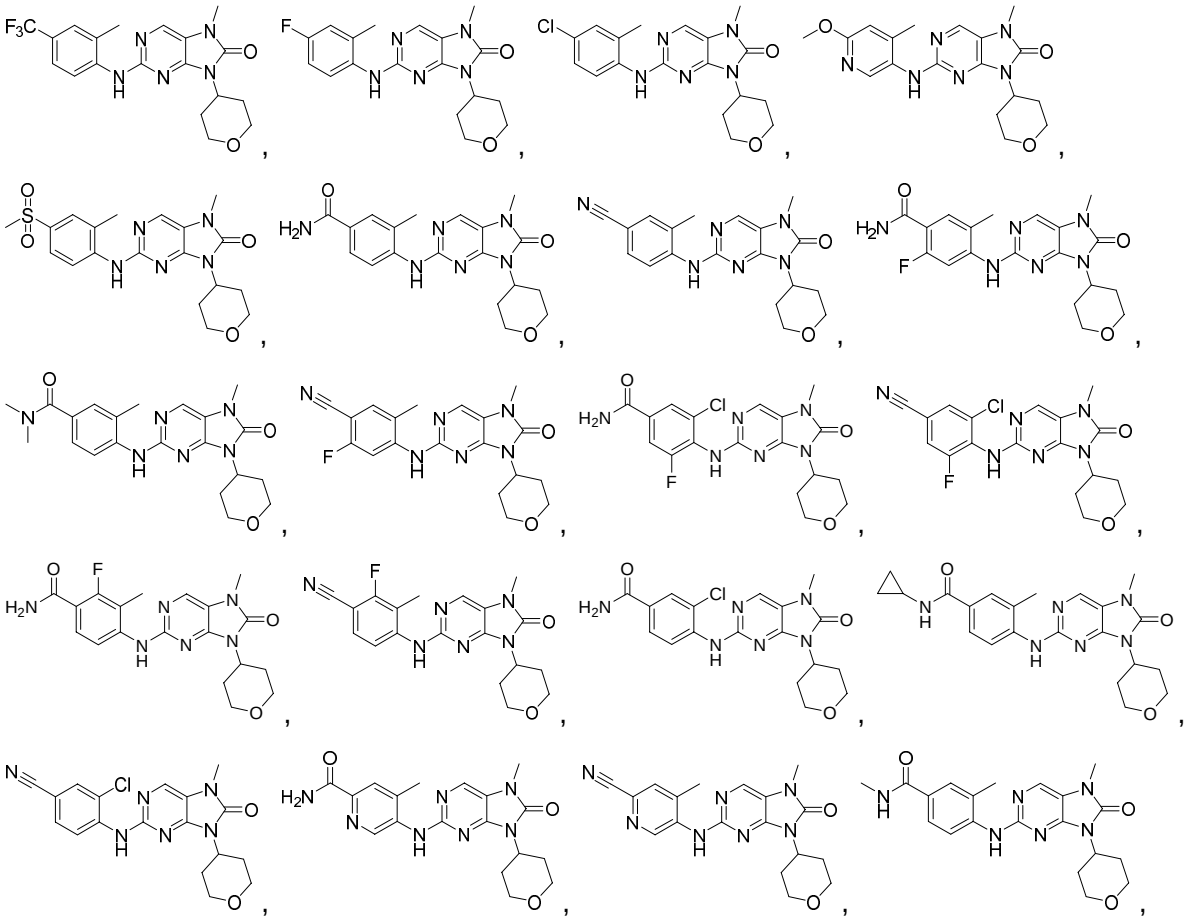
7. The pharmaceutical preparation according to claim 6, wherein in the compound of formula I,

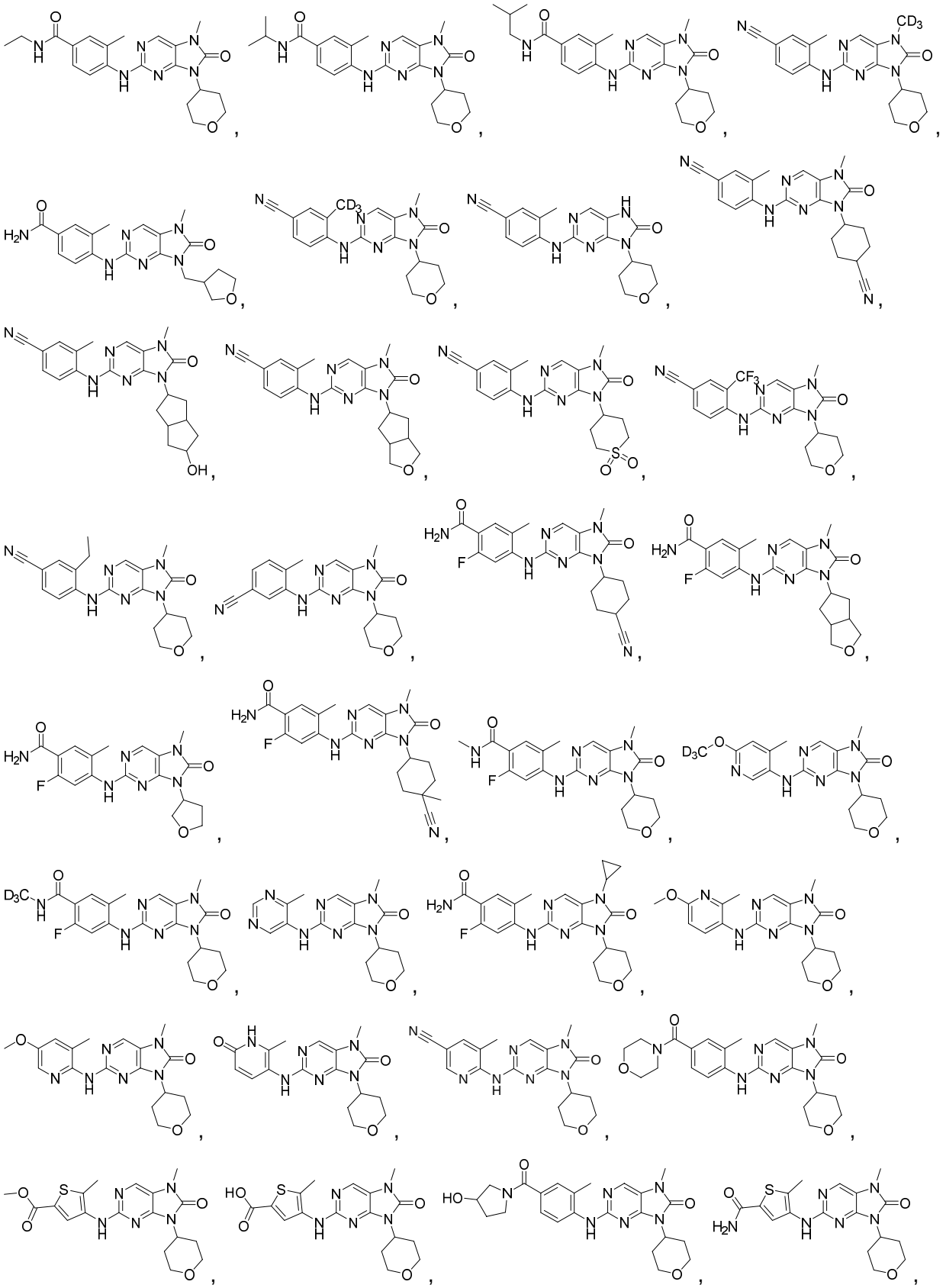
R_0 is C_{1-4} alkyl, wherein the C_{1-4} alkyl is optionally further substituted with one or more substituents selected from halogen and deuterium; and

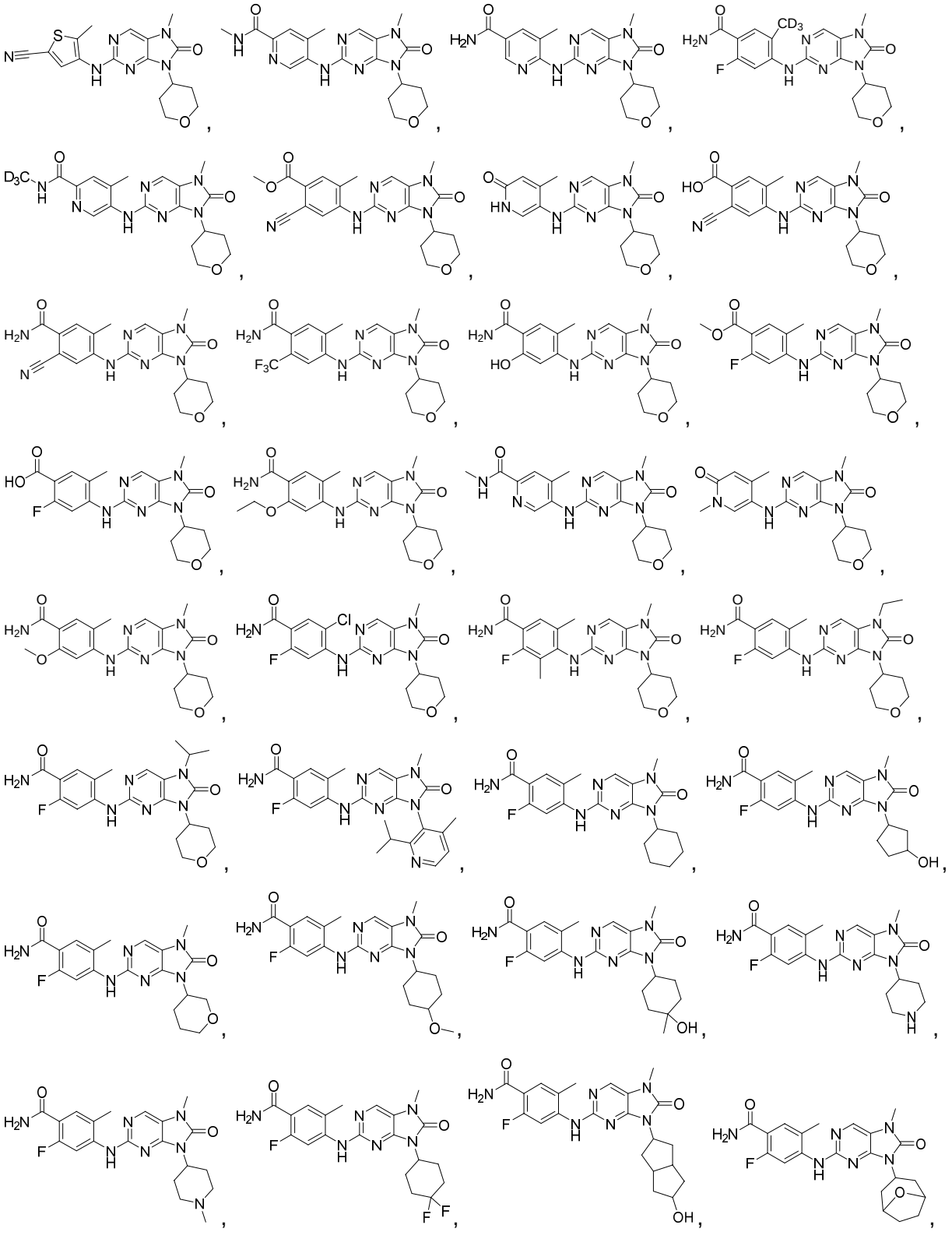
R_1 is 

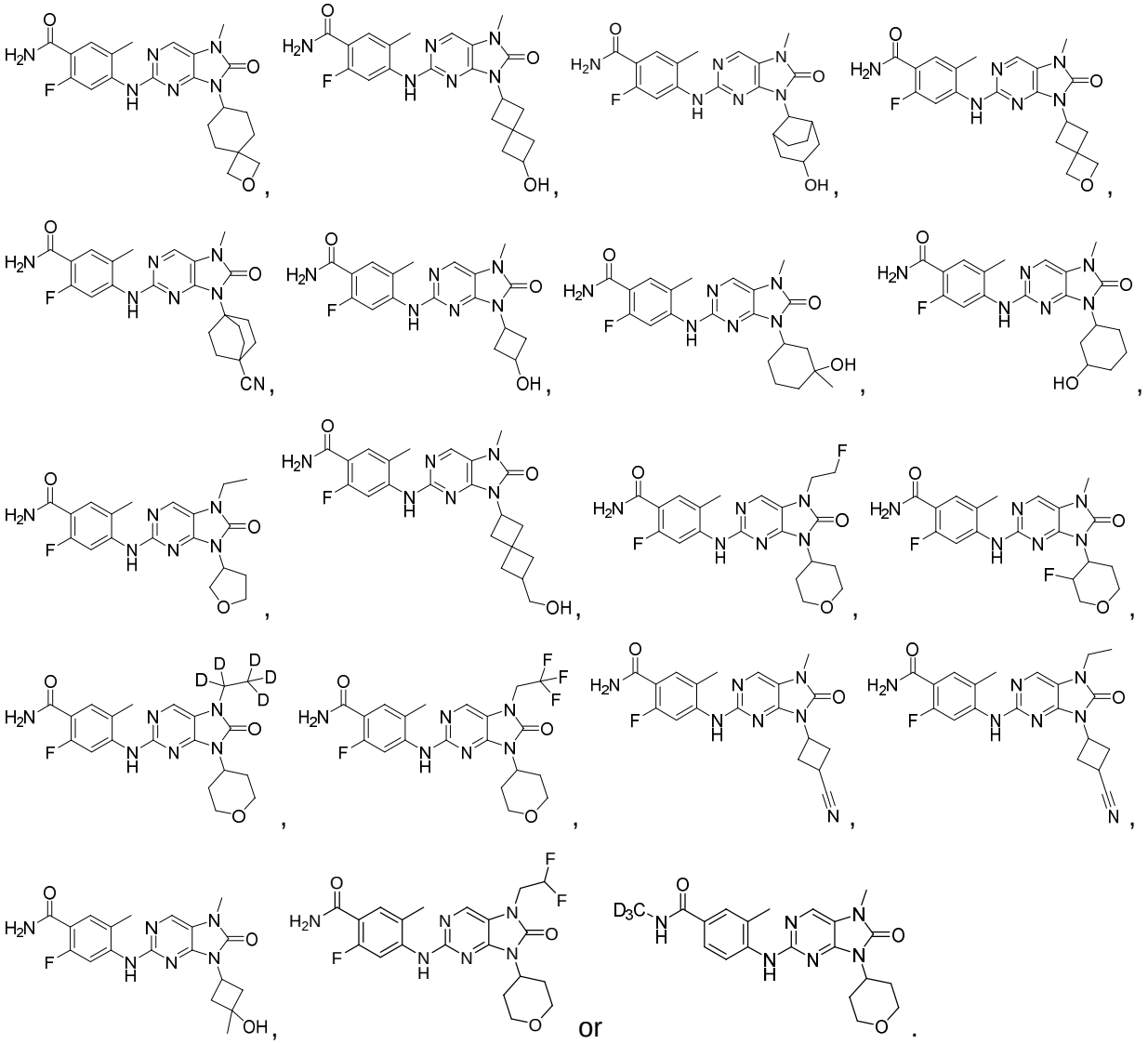


8. The pharmaceutical preparation according to claim 1, wherein the compound of formula I is selected from:

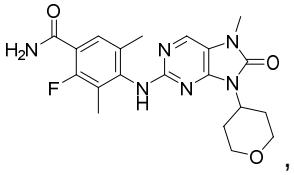






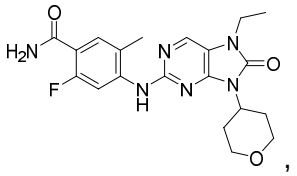


9. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



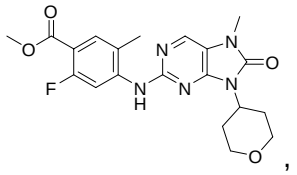
or a stereoisomer or pharmaceutically acceptable salt thereof.

10. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



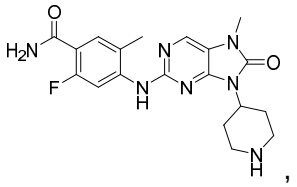
or a stereoisomer or pharmaceutically acceptable salt thereof.

11. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



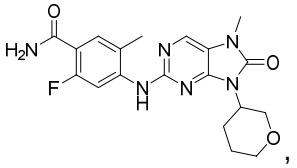
or a stereoisomer or pharmaceutically acceptable salt thereof.

12. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



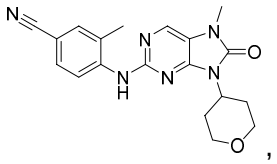
or a stereoisomer or pharmaceutically acceptable salt thereof.

13. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



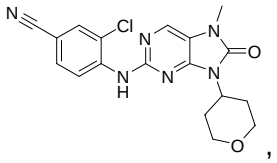
or a stereoisomer or pharmaceutically acceptable salt thereof.

14. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



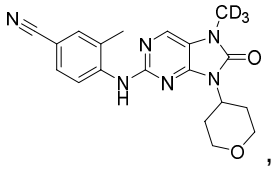
or a stereoisomer or pharmaceutically acceptable salt thereof.

15. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



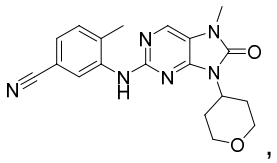
or a stereoisomer or pharmaceutically acceptable salt thereof.

16. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



or a stereoisomer or pharmaceutically acceptable salt thereof.

17. The pharmaceutical preparation according to any one of claims 1 to 8, wherein in the compound is



or a stereoisomer or pharmaceutically acceptable salt thereof.

18. The pharmaceutical preparation according to any one of claims 1-17, wherein the pharmaceutical preparation comprises the compound of formula I with a specification of 1-5 mg, 5-10 mg, 10-15 mg, 15-20 mg, 20-25 mg, 25-30 mg, 30-35 mg, 35-40 mg, 40-50 mg, 50-60 mg, 60-70 mg, 70-80 mg, 80-90 mg, 90-100 mg, 100-150 mg, 150-200 mg, 200-250 mg, 250-300 mg, 300-350 mg, 350-400 mg, 400-450 mg, 450-500 mg, 500-600 mg, 600-700 mg, 700-800 mg, 800-900 mg or 900-1000 mg.

19. The pharmaceutical preparation of any one of claims 1-17, wherein the content of the imidazolinone compound in the pharmaceutical preparation is 1-90 weight %.

20. The pharmaceutical preparation according to claim 19, wherein the content of the imidazolinone compound in the pharmaceutical preparation is 1-5 weight %, 5-10 weight %, 10-15 weight %, 15-20 weight %, 20-25 weight %, 25-30 weight %, 30-35 weight %, 35-40 weight %, 40-45 weight %, 45-50 weight %, 50-55 weight %, 55-60 weight %, 60-65 weight %, 65-70 weight %, 70-75 weight %, 75-80 weight %, 80-85 weight % or 85-90 weight %.

21. The pharmaceutical preparation according to claim 20, wherein the content of the imidazolinone compound in the pharmaceutical preparation is 27.8 weight % or 41.7 weight %.

22. The pharmaceutical preparation according to claim 19, wherein the pharmaceutical preparation is in a dosage form selected from a granule, a tablet, a capsule, a pill, or a micropellet.

23. The pharmaceutical preparation according to claim 19, wherein
the content of the diluent is 10-85 weight %;
the content of the disintegrant is 3-70 weight %; and
the content of the glidant is 0.1-30 weight %.

24. The pharmaceutical preparation according to claim 23, wherein
the content of the diluent is 10-15 weight %, 15-20 weight %, 20-25 weight %, 25-30 weight %, 30-35 weight %, 35-40 weight %, 40-45 weight %, 45-50 weight %, 50-55 weight %, 55-60 weight %, 60-65 weight %, 65-70 weight %, 70-75 weight %, 75-80 weight %, or 80-85 weight %;
the content of the disintegrant is 3-5 weight %, 5-15 weight %, 15-20 weight %, 20-25 weight %, 25-30 weight %, 30-35 weight %, 35-40 weight %, 40-45 weight %, 45-50 weight %, 50-55 weight %, 55-60 weight %, 60-65 weight %, or 65-70 weight %; and
the content of the glidant is 0.1-0.5 weight %, 0.5-1 weight %, 1-5 weight %, 5-10 weight %, 10-15 weight %, 15-20 weight %, 20-25 weight %, or 25-30 weight %.

25. The pharmaceutical preparation according to claim 24, wherein the content of the diluent is 64.1 weight %, 66.7 weight % or 50 weight %;

the content of the disintegrant is 7 weight %, 4.4 weight % or 6.7 weight %; and

the content of the glidant is 1.6 weight % or 1.1 weight %.

26. The pharmaceutical preparation according to claim 23, wherein the diluent is selected from one or more of sucrose, xylitol, maltitol, lactitol, hydroxypropyl cellulose, hypromellose, sorbitol, glucose, fructose, corn starch, inorganic salts, microcrystalline cellulose, starch, mannitol, lactose and pregelatinized starch;

the disintegrant is selected from one or more of cross-linked polyvinylpyrrolidone, sodium starch glycolate, calcium carboxymethyl cellulose, potato starch, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, croscarmellose sodium, crospovidone, sodium carboxymethyl starch and low-substituted hydroxypropyl cellulose; and

the glidant is selected from one or more of colloidal silica, silica, magnesium silicate, magnesium trisilicate, polysilicate, hydrated silica, calcium phosphate, and talc.

27. The pharmaceutical preparation according to claim 26, wherein the diluent is selected from one or more of microcrystalline cellulose, mannitol, and pregelatinized starch.

28. A preparation method for the pharmaceutical preparation of an imidazolinone compound according to any one of claims 1-27, comprising the following steps:
preparing a mixture of an imidazolinone compound, a disintegrant, and a diluent; and
mixing a glidant with the mixture and then preparing the same into a tablet, a capsule, or a granule; wherein
after mixing the glidant with the mixture, the resulting mixture is placed in a granulator for granulation and then prepared into a tablet, a capsule, or a granule;

29. The preparation method of claim 28, wherein when the mixture comprises 50-80 wt% of the prescription amount of the diluent; the mixture is placed in a mixer for mixing and then placed in a granulator for granulation to obtain mixture particles; and a glidant and the remaining prescription amount of the diluent are added to the mixture particles, and mixed in a mixer and then prepared into a tablet, a capsule, or a granule.

30. Use of the pharmaceutical preparation of an imidazolinone compound according to any one of claims 1-27 in the preparation of a drug for the treatment of a cancer.

31. The use of claim 30, wherein the drug is to be administered orally 1-4 times per day.

32. The pharmaceutical preparation according to any one of claims 1-27, wherein the compound of formula I is present in an amount to provide a daily dose of 1-1000 mg, and the daily dose is a single-dose or multi-dose.

33. The pharmaceutical preparation according to claim 32, wherein the compound of formula I is present in an amount to provide a daily dose of 1-10 mg, 10-20 mg, 20-50 mg, 50-100 mg, 100-150 mg, 150-200 mg, 200-250 mg, 250-300 mg, 300-350 mg, 350-400 mg, 400-450 mg, 450-500 mg, 500-600 mg, 600-700 mg, 700-800 mg, 800-900 mg or 900-1000 mg.

34. The pharmaceutical preparation according to any one of claims 1-27, wherein the compound of formula I is present in an amount to provide a daily dose of 1-1000 mg/60 kg.