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(54)发明名称

4-烷氧基吡咯并[2,1-f][1,2,4]三嗪以及其制备和用途

(57)摘要

公开了用于治疗各种疾病和病变的4-烷氧基吡咯并[2,1-f][1,2,4]三嗪化合物。更特别地,本公开涉及4-烷氧基吡咯并[2,1-f][1,2,4]三嗪化合物或其类似物的用途,其用于治疗特征在于DYRK1A过表达的病症(例如癌症、唐氏综合征、阿尔茨海默病、糖尿病、病毒感染和骨关节炎)。

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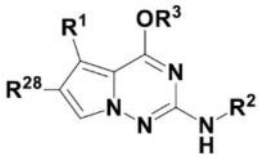
1.一种式I化合物或其药学上可接受的盐：



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其中：

R^1为任选地被1至10个R^4取代的杂芳基；

R^2选自由以下组成的组：未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^5$、-($C_{1-5}$亚烷基)CN、任选地被1至10个$R^6$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至10个$R^{26}$取代的-($C_{1-5}$亚烷基)$_p$芳基、任选地被1至10个$R^7$取代的-($C_{1-5}$亚烷基)$_p$杂芳基和任选地被1至12个$R^8$取代的-($C_{1-5}$亚烷基)$_p$碳环基，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

R^3选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和任选地被1至10个R^{18}取代的杂环基；

每个R^4独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、未被取代的-(C_{2-9}卤代烯基)、-(C_{1-5}亚烷基)$_p$$OR^9$、-($C_{1-5}$亚烷基)$_p$CN、任选地被1至10个$R^{10}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至12个$R^{11}$取代的-碳环基、任选地被1至10个$R^{20}$取代的-($C_{1-5}$亚烷基)$_p$杂芳基、-($C_{1-5}$亚烷基)$_p$C(=O)N($R^{12}$)$_2$和-C(=O)$R^{13}$，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

每个R^5独立地选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

每个R^6独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个R^{16}取代的-杂环基、任选地被1至12个R^{17}取代的-碳环基、-(C_{1-5}亚烷基)$_p$$OR^{21}$、-($C_{1-5}$亚烷基)CN、-$SO_2R^{23}$和-C(=O)$R^{24}$，其中所述-($C_{1-5}$亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

或者，连接至同一碳原子的两个R^6一起形成羰基；

每个R^7独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-OMe；

每个R^8独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-N(R^{14})$_2$、-(C_{1-5}亚烷基)$_p$$OR^{15}$、-CN、任选地被1至10个$R^{16}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、-C(=O)$R^{22}$和-$NR^{14}$C(=O)$R^{23}$，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

每个R^9独立地选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

每个R^{10}独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}

烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R11独立地选自由以下组成的组:卤素、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R12独立地选自由以下组成的组:H、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)、未被取代的-(C1-9卤代烷基)、-(C1-5亚烷基)pOR21、任选地被1至12个R17取代的-(C1-5亚烷基)p碳环基、任选地被1至10个R18取代的-杂环基和任选地被1至10个R19取代的-杂芳基,其中所述-(C1-5亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C1-3烷基)取代;

每个R13为任选地被1至10个R18取代的-杂环基;

每个R14独立地选自由以下组成的组:H、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R15独立地选自由以下组成的组:H、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)、未被取代的-(C1-9卤代烷基)和-(C1-5亚烷基)pOR21;

每个R16独立地选自由以下组成的组:卤素、-CN、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)、未被取代的-(C1-9卤代烷基)和任选地被1至12个R27取代的-碳环基;

或者,连接至同一碳原子的两个R16一起形成羰基;

每个R17独立地选自由以下组成的组:卤素、-OMe、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R18独立地选自由以下组成的组:卤素、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R19独立地选自由以下组成的组:卤素、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R20独立地选自由以下组成的组:卤素、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R21独立地选自由以下组成的组:H、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

每个R22独立地选自由以下组成的组:任选地被1至10个R18取代的-杂环基、-N(R12)2和-OR21;

每个R23独立地选自由以下组成的组:未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)、未被取代的-(C1-9卤代烷基)、-(C1-5亚烷基)pOR21和任选地被1至12个R25取代的-碳环基;

每个R24独立地选自由以下组成的组:未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)、未被取代的-(C1-9卤代烷基)、-OR21和任选地被1至12个R25取代的-碳环基;

每个R25独立地选自由以下组成的组:卤素、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)、未被取代的-(C1-9卤代烷基)和-CN;

每个R26独立地选自由以下组成的组:卤素、未被取代的-(C1-9烷基)、未被取代的-(C2-9烯基)、未被取代的-(C2-9炔基)和未被取代的-(C1-9卤代烷基);

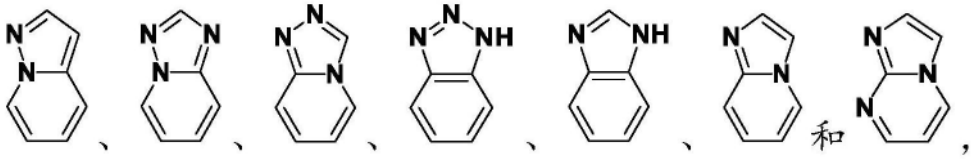
每个R^{27}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

R^{28}独立地选自由以下组成的组:H和卤素;并且

每个p独立地为0或1;

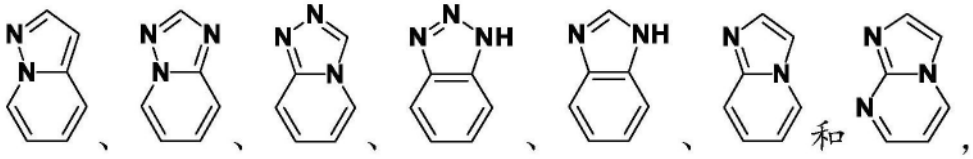
其中每个H原子任选地独立地被^{2}H(D)(氘)代替。

2.如权利要求1所述的化合物,其中R^{1}选自由以下组成的组:



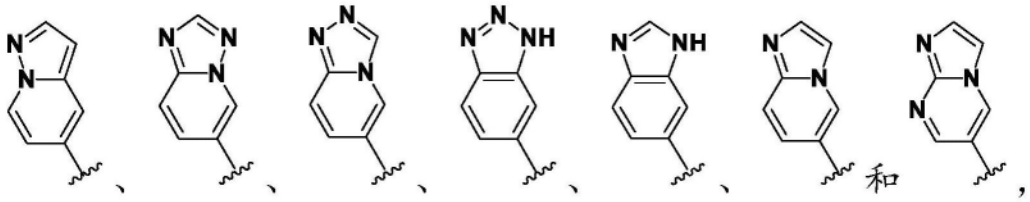
其任选地被1至10个R^{4}取代。

3.根据权利要求1-2中任一项所述的化合物,其中R^{1}选自由以下组成的组:



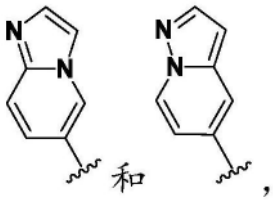
其任选地被1至3个R^{4}取代。

4.根据权利要求1-3中任一项所述的化合物,其中R^{1}选自由以下组成的组:



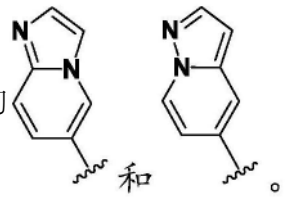
其任选地被1至3个R^{4}取代。

5.根据权利要求1-4中任一项所述的化合物,其中R^{1}选自由以下组成的组:



其任选地被1至3个R^{4}取代。

6.根据权利要求1-5中任一项所述的化合物,其中R^{1}选自由以下组成的组:

未被取代的

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7.根据权利要求1-5中任一项所述的化合物,其中R^{4}选自由以下组成的组:卤素、未被取代的-(C_{1-3}烷基)、未被取代的-(C_{1-3}卤代烷基)、-(C_{1-3}亚烷基)OH、-(C_{1-3}亚烷基)OMe、-CN和-C(=O)N(R^{12})$_2$。

8.根据权利要求1-7中任一项所述的化合物,其中R^{2}选自由以下组成的组:任选地被1至3个R^{5}取代的-杂环基、任选地被1至3个R^{8}取代的-(C_{1-2}亚烷基)$_p$碳环基和任选地被1至2个R^{7}

取代的-(C_{1-2}亚烷基)芳基,其中每个-(C_{1-2}亚烷基)独立地任选地被1至2个卤素取代。

9.根据权利要求1-8中任一项所述的化合物,其中R^3选自由以下组成的组:未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)和任选地被1至2个R^{18}取代的-杂环基。

10.根据权利要求1-9中任一项所述的化合物,其中R^3选自由以下组成的组:未被取代的-(C_{1-3}烷基)和未被取代的-(C_{1-3}卤代烷基)。

11.根据权利要求1-10中任一项所述的化合物,其中R^3为甲基。

12.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-咪唑并[4,5-b]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1];

(1r,4r)-4-((5-(3-(2,2-二氟乙基)-2-甲基-3H-咪唑并[4,5-b]吡啶-5-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[2];

(1r,4r)-4-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[3];

(1s,4s)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[4];

1-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-甲基丙-2-醇[5];

2-(顺-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[6];

(1s,3s)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[7];

(1r,3r)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[8];

4-甲氧基-N-(顺-4-甲氧基环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[9];

4-甲氧基-N-(反-4-甲氧基环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[10];

N-(顺-4-(二氟甲氧基)环己基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[11];

N-(反-4-(二氟甲氧基)环己基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[12];

2-((顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[13];

2-((反-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[14];

4-甲氧基-N-(顺-4-(2-甲氧基乙氧基)环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[15];

4-甲氧基-N-(反-4-(2-甲氧基乙氧基)环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并

[2,1-f][1,2,4]三嗪-2-胺[16];

N-(顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环已基)乙酰胺[17];

N-(反-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环已基)乙酰胺[18];

(1s,4s)-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇[19];

(1r,4r)-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇[20];

1-(3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)氮杂环丁烷-1-基)乙-1-酮[21];

N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[22];

N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[23];

N-(1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[24];

N-(1-(2,2-二氟乙基)哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[25];

4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[26];

1-(4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[27];

4-甲氧基-N-(1-(甲基磺酰基)哌啶-4-基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[28];

N-((3S,4R)-3-氟哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[29];

N-((3R,4S)-3-氟哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[30];

N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[31];

N-((3S,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[32];

N-((3R,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[33];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[34];

(S)-5-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[35];

4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[36];

1-(6-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-基)乙-1-酮[37];

4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[38];

1-(2-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮[39];

1-(7-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[40];

1-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-甲基丙-2-醇[41];

2-(顺-3-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[42];

(1s,3s)-3-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[43];

(1r,3r)-3-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[44];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(顺-4-甲氧基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[45];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(反-4-甲氧基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[46];

N-(顺-4-(二氟甲氧基)环己基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[47];

N-(反-4-(二氟甲氧基)环己基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[48];

2-((顺-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[49];

2-((反-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[50];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(顺-4-(2-甲氧基乙氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[51];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(反-4-(2-甲氧基乙氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[52];

N-(顺-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[53];

N-(反-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[54];

(1s,4s)-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-

2-基)氨基)-1-甲基环己-1-醇[55];

(1r,4r)-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[56];

1-(3-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)氮杂环丁烷-1-基)乙-1-酮[57];

N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[58];

N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[59];

N-(1-(2-氟乙基)哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[60];

N-(1-(2,2-二氟乙基)哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[61];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[62];

1-(4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[63];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(1-(甲基磺酰基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[64];

N-((3S,4R)-3-氟哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[65];

N-((3R,4S)-3-氟哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[66];

N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[67];

N-((3R,4R)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[68];

N-((3S,4S)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[69];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[70];

(S)-5-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[71];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[72];

1-(6-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-基)乙-1-酮[73];

5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[74];

1-(2-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮[75];

1-(7-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[76];

1-((1R,5S,6s)-6-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氮杂双环[3.1.0]己烷-3-基)乙-1-酮[77];

1-((1R,5S,6r)-6-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氮杂双环[3.1.0]己烷-3-基)乙-1-酮[78];

N-((1R,5S,6r)-3-氧杂双环[3.1.0]己烷-6-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[79];

N-((1R,5S,6s)-3-氧杂双环[3.1.0]己烷-6-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[80];

1-((1R,5S,6s)-6-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氮杂双环[3.1.0]己烷-3-基)乙-1-酮[81];

1-((1R,5S,6r)-6-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氮杂双环[3.1.0]己烷-3-基)乙-1-酮[82];

N-((1R,5S,6r)-3-氧杂双环[3.1.0]己烷-6-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[83];

N-((1R,5S,6s)-3-氧杂双环[3.1.0]己烷-6-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[84];

N-((1R,5S,6r)-3-氧杂双环[3.1.0]己烷-6-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-咪唑并[4,5-b]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[85];

N-((1R,5S,6s)-3-氧杂双环[3.1.0]己烷-6-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-咪唑并[4,5-b]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[86];

(1s,4s)-4-((4-(二氟甲氧基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[87];

(1r,4r)-4-((4-(二氟甲氧基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[88];

(1s,4s)-4-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]吡啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[89];

(1r,4r)-4-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]吡啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[90];

2-(顺-3-((4-乙氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[91];

6-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-甲酸叔丁酯[92];

(R)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(1-(吡啶-2-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[93];

(1r,3r)-N^1-(4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-

基)-3-甲基环丁烷-1,3-二胺[94];

(1s,3s)-N^1-(4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺[95];

N-((1r,3r)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[96];

N-((1s,3s)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[97];

((1r,3r)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)氨基甲酸叔丁酯[98];

1-(6-((4-乙氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-基)乙-1-酮[99];和

5-(2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)吡唑并[1,5-a]吡啶-3-甲酰胺[100];

或其药学上可接受的盐。

13.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

5-(2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)吡唑并[1,5-a]吡啶-3-甲酰胺[101];

5-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[102];

6-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲腈[103];

6-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲酰胺[104];

6-(2-((4,4-二氟环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[105];

6-(2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[106];

6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[107];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[108];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺[109];

氮杂环丁烷-1-基((1r,3r)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)甲酮[110];

((1r,3r)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮[111];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯

并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[112];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[113];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[114];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[115];

1-((3S,4R)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[116];

(S)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[117];

(R)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[118];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-(1-(2-氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[119];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-(1-(2,2-二氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[120];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基-N-(1-(2,2,2-三氟乙基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[121];

1-(4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[122];

N-(1-(3,3-二氟环丁基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[123];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[124];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[125];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[126];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[127];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-1-乙基-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[128];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[129];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[130];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[131];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[132];

N-((3R,4S)-1-环丙基-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[133];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[134];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[135];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[136];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[137];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[138];

(S)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[139];

(R)-N-(1-环丁基-3,3-二氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[140];

(S)-N-(1-环丁基-3,3-二氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[141];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[142];

(S)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[143];

1-((4s,6r)-6-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[144];

1-((4r,6s)-6-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[145];

1-(7-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[146];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[147];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[148];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[149];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[150];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基

吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[151];

(S)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[152];

(R)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[153];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[154];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[155];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[156];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[157];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[158];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[159];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[160];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[161];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[162];

(S)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[163];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[164];

(S)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[165];

1-((4s,6r)-6-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[166];

1-((4r,6s)-6-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[167];

(1r,4r)-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[168];

(1s,3s)-3-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[169];

(1r,3r)-3-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[170];

N-((1r,3r)-3-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[171];

(1r,4r)-4-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[172];

1-(7-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[173];

2-(6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇[174];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[175];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3R,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[176];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[177];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3S,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[178];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[179];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3R,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[180];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3S,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[181];

5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[182];

(R)-5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[183];

(S)-5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[184];

(R)-5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[185];

(S)-5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[186];

(1r,4r)-4-((5-([1,2,4]三唑并[4,3-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[187];

5-([1,2,4]三唑并[4,3-a]吡啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[188];

(1s,3s)-N^1-(5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺[189];

(1r,3r)-N^1-(5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]

三嗪-2-基)-3-甲基环丁烷-1,3-二胺[190];

N-((1s,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[191];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[192];

5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(4,4-二氟环已基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[193];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇[194];

5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基-N-(2-氮杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[195];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[196];

7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-甲酸叔丁酯[197];

5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[198];

(1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[199];和

(1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[200];

或其药学上可接受的盐。

14.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

2-(顺-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[201];

(1s,3s)-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺[202];

(1r,3r)-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺[203];

(1s,3s)-N^3-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-N^1,N^1,1-三甲基环丁烷-1,3-二胺[204];

N-((1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[205];

N-((1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[206];

N-((1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)丙酰胺[207];

2-甲氧基-N-((1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡

咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[208];

(1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[209];

(1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[210];

(1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺[211];

(1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺[212];

(1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N-(2-甲氧基乙基)-1-甲基环丁烷-1-甲酰胺[213];

(1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N-(2-甲氧基乙基)-1-甲基环丁烷-1-甲酰胺[214];

(1r,3r)-N-(2-氟乙基)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[215];

(1r,3r)-N-(2,2-二氟乙基)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[216];

(1s,3s)-N-环丙基-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[217];

(1r,3r)-N-环丙基-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[218];

(1r,3r)-N-环丁基-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[219];

(1r,3r)-N-(3,3-二氟环丁基)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[220];

(1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基-N-(氧杂环丁烷-3-基)环丁烷-1-甲酰胺[221];

((1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮[222];

1-((1r,3r)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)吡咯烷-2-酮[223];

(1s,4s)-4-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[224];

(1s,4s)-4-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环己烷-1-甲酰胺[225];

3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N-甲基双环[1.1.1]戊烷-1-甲酰胺[226];

1-(2-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮[227];

1-((3aR,5r,6aS)-5-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)六氢环戊并[c]吡咯-2(1H)-基)乙-1-酮[228];

1-(7-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[229];

4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[230];

(R)-N-(1-环丙基乙基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[231];

(S)-N-(1-环丙基乙基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[232];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-苯基乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[233];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(吡啶-2-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[234];

(S)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(吡啶-2-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[235];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-3-甲氧基环丁基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[236];

N-((1R,2S)-2-氟环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[237];

N-((1S,2R)-2-氟环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[238];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-(三氟甲基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[239];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(反-4-(三氟甲基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[240];

2-(顺-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[241];

2-(反-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[242];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-甲氧基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[243];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(反-4-甲氧基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[244];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-(甲氧基-d_3)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[245];

N-(顺-4-乙氧基环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[246];

N-(反-4-乙氧基环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,

2,4]三嗪-2-胺[247];

5-(咪唑并[1,2-a]嘧啶-6-基)-N-(顺-4-异丙氧基环己基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[248];

5-(咪唑并[1,2-a]嘧啶-6-基)-N-(反-4-异丙氧基环己基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[249];

N-(顺-4-(二氟甲氧基)环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[250];

N-(反-4-(二氟甲氧基)环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[251];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-(三氟甲氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[252];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(反-4-(三氟甲氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[253];

N-(4,4-二氟环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[254];

(R)-N-(2,2-二氟环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[255];

(S)-N-(2,2-二氟环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[256];

(1r,4r)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[257];

(1r,4r)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[258];

1-(3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)氮杂环丁烷-1-基)乙-1-酮[259];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)氮杂环丁烷-3-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[260];

2-(((3R,4S)-4-氟-1-甲基吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇[261];

N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[262];

1-((3S,4R)-3-氟-4-((4-羟基-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[263];

1-((3S,4R)-3-氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[264];

2-(((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇[265];

N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[266];

N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[267];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[268];

N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[269];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[270];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[271];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[272];

1-(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[273];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((4s,7s)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[274];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((4r,7r)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[275];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[276];

(1s,3s)-3-((4-甲氧基-5-(1H-吡咯并[3,2-b]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[277];

(1r,3r)-3-((4-甲氧基-5-(1H-吡咯并[3,2-b]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[278];

(1s,4s)-4-((4-甲氧基-5-(1H-吡咯并[3,2-b]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[279];

(1r,4r)-4-((4-甲氧基-5-(1H-吡咯并[3,2-b]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[280];

(1s,3s)-3-((4-甲氧基-5-(1H-吡咯并[3,2-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[281];

(1r,4r)-4-((4-甲氧基-5-(1H-吡咯并[3,2-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[282];

(1s,3s)-3-((4-甲氧基-5-(1H-吡咯并[2,3-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[283];

(1r,4r)-4-((4-甲氧基-5-(1H-吡咯并[2,3-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[284];

(R)-4-甲氧基-N-(1-(吡啶-2-基)乙基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[285];

2-((1s,3s)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)

环丁基)丙-2-醇[286];

2-((1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁基)丙-2-醇[287];

N-((1s,3s)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[288];

N-((1s,3s)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[289];

(1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺[290];

氮杂环丁烷-1-基((1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)甲酮[291];

((1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮[292];

(1s,4s)-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[293];

(1r,4r)-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[294];

N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[295];

N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[296];

1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[297];

1-((3S,4R)-3-氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[298];

N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[299];和

N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[300];

或其药学上可接受的盐。

15.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

(S)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[301];

(R)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[302];

N-(1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[303];

N-(1-(2,2-二氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]

三嗪-2-胺[304];

4-甲氧基-5-(喹啉-6-基)-N-(1-(2,2,2-三氟乙基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[305];

N-(1-(3,3-二氟环丁基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[306];

N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[307];

N-((3R,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[308];

N-((3S,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[309];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[310];

N-((3S,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[311];

N-((3R,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[312];

N-((3S,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[313];

N-((3R,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[314];

N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[315];

N-((3R,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[316];

N-((3S,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[317];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[318];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[319];

(S)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[320];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[321];

(S)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[322];

1-((4s,6r)-6-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[323];

1-((4r,6s)-6-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[324];

1-(7-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[325];

4-甲氧基-5-(喹啉-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[326];

2-(顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁基)丙-2-醇[327];

2-(反-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁基)丙-2-醇[328];

2-(顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[329];

(1r,3r)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[330];

(1r,3r)-3-((4-(甲氧基-d_3)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[331];

(1s,3s)-N^1-(4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺[332];

N-((1s,3s)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[333];

N-((1r,3r)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[334];

N-((1s,3s)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)丙酰胺[335];

2-甲氧基-N-((1s,3s)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[336];

((1s,3s)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)氨基甲酸叔丁酯[337];

(1r,3r)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[338];

(1r,3r)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺[339];

((1r,3r)-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮[340];

2-(顺-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[341];

2-(反-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[342];

2-((顺-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环

己基)氧基)乙-1-醇[343];

N-(反-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[344];

(1s,4s)-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[345];

2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇[346];

(1r,4r)-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[347];

(1r,4r)-4-((4-(甲氧基-d_3)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[348];

(1r,4r)-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-(三氟甲基)环己-1-醇[349];

N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[350];

N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[351];

1-((3S,4R)-3-氟-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[352];

1-((3S,4R)-3-氟-4-((4-(甲氧基-d_3)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[353];

1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[354];

N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[355];

N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[356];

(R)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[357];

(S)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[358];

(R)-N-(4,4-二氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[359];

(S)-N-(4,4-二氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[360];

N-(1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[361];

N-(1-(2,2-二氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[362];

4-甲氧基-5-(喹喔啉-6-基)-N-(1-(2,2,2-三氟乙基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[363];

N-(1-(3,3-二氟环丁基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[364];

4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[365];

4-甲氧基-5-(喹喔啉-6-基)-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[366];

N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[367];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[368];

N-((3S,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[369];

N-((3R,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[370];

N-((3S,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[371];

N-((3R,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[372];

N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[373];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[374];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[375];

(S)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[376];

(R)-N-(1-环丁基-3,3-二氟哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[377];

(S)-N-(1-环丁基-3,3-二氟哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[378];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[379];

(S)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[380];

N^1-(4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)双环[1.1.1]戊烷-1,3-二胺[381];

N-(3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环

[1.1.1]戊烷-1-基)乙酰胺[382];

1-((4s,6r)-6-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[383];

1-((4r,6s)-6-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮[384];

4-甲氧基-5-(喹喔啉-6-基)-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[385];

1-(2-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮[386];

1-((3aR,5s,6aS)-5-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)六氢环戊并[c]吡咯-2(1H)-基)乙-1-酮[387];

1-((3aR,5r,6aS)-5-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)六氢环戊并[c]吡咯-2(1H)-基)乙-1-酮[388];

1-(7-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[389];

4-甲氧基-5-(喹喔啉-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[390];

(1s,3s)-1-甲基-3-((4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁-1-醇[391];

(1r,4r)-1-甲基-4-((4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[392];

(S)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(1-(吡啶-2-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[393];

1-氰基-N-((1s,3s)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺[394];

4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[395];

(R)-5-(4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[396];

(S)-5-(4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[397];

5-(2-(环己基氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[398];

5-(4-甲氧基-2-(((1s,4s)-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[399];和

5-(2-((4,4-二甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[400];

或其药学上可接受的盐。

16.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的

组：

5-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[401]；

5-(2-(((1s,4s)-4-乙基-4-羟基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[402]；

5-(2-(((1r,4r)-4-乙基-4-羟基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[403]；

5-(4-甲氧基-2-(((1s,4s)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[404]；

5-(4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[405]；

5-(2-(((1s,4s)-4-氰基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[406]；

5-(2-(((1r,4r)-4-氰基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[407]；

5-(2-(双环[3.1.0]己烷-3-基氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[408]；

5-(2-((4-羟基双环[2.2.1]庚烷-1-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[409]；

5-(4-甲氧基-2-(螺[2.5]辛烷-6-基氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[410]；

(R)-5-(6-氟-4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[411]；

(S)-5-(6-氟-4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[412]；

5-(2-(环己基氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[413]；

5-(6-氟-4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[414]；

5-(2-((4,4-二甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[415]；

5-(6-氟-2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[416]；

5-(6-氟-2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[417]；

5-(2-(((1s,4s)-4-乙基-4-羟基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[418]；

5-(2-(((1r,4r)-4-乙基-4-羟基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[419]；

5-(6-氟-4-甲氧基-2-(((1s,4s)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[420];

5-(6-氟-4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[421];

5-(2-(((1s,4s)-4-氰基-4-甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[422];

5-(2-(((1r,4r)-4-氰基-4-甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[423];

5-(2-(双环[3.1.0]己烷-3-基氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[424];

5-(6-氟-2-((4-羟基双环[2.2.1]庚烷-1-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[425];

5-(6-氟-4-甲氧基-2-(螺[2.5]辛烷-6-基氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[426];

5-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺[427];

N-((1s,3s)-3-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[428];

N-((1r,3r)-3-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[429];

(1s,4s)-4-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[430];

(1r,4r)-4-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[431];

(1s,4s)-1-乙基-4-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[432];

(1r,4r)-1-乙基-4-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[433];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[434];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[435];

(R)-6-(4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[436];

(S)-6-(4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[437];

6-(2-(环己基氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[438];

6-(4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-

甲基咪唑并[1,2-a]吡啶-3-甲酰胺[439];

6-(2-((4,4-二甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[440];

6-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[441];

6-(2-(((1s,4s)-4-乙基-4-羟基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[442];

6-(2-(((1r,4r)-4-乙基-4-羟基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[443];

6-(4-甲氧基-2-(((1s,4s)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[444];

6-(4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[445];

6-(2-(((1s,4s)-4-氰基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[446];

6-(2-(((1r,4r)-4-氰基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[447];

6-(2-(双环[3.1.0]己烷-3-基氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[448];

6-(2-((4-羟基双环[2.2.1]庚烷-1-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[449];

6-(4-甲氧基-2-(螺[2.5]辛烷-6-基氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[450];

(R)-8-氟-6-(4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[451];

(S)-8-氟-6-(4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[452];

6-(2-(环己基氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[453];

8-氟-6-(4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[454];

6-(2-((4,4-二甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[455];

8-氟-6-(2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[456];

8-氟-6-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[457];

6-(2-(((1s,4s)-4-乙基-4-羟基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[458];

6-(2-(((1r,4r)-4-乙基-4-羟基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[459];

8-氟-6-(4-甲氧基-2-(((1s,4s)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[460];

8-氟-6-(4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[461];

6-(2-(((1s,4s)-4-氰基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[462];

6-(2-(((1r,4r)-4-氰基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[463];

6-(2-(双环[3.1.0]己烷-3-基氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[464];

8-氟-6-(2-((4-羟基双环[2.2.1]庚烷-1-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[465];

8-氟-6-(4-甲氧基-2-(螺[2.5]辛烷-6-基氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[466];

6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[467];

(R)-6-(6-氟-4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[468];

(S)-6-(6-氟-4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[469];

6-(2-(环己基氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[470];

6-(6-氟-4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[471];

6-(2-((4,4-二甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[472];

6-(6-氟-2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[473];

6-(6-氟-2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[474];

6-(2-(((1s,4s)-4-乙基-4-羟基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[475];

6-(2-(((1r,4r)-4-乙基-4-羟基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[476];

6-(6-氟-4-甲氧基-2-(((1s,4s)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[477];

6-(6-氟-4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,

2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[478];

6-(2-(((1s,4s)-4-氰基-4-甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[479];

6-(2-(((1r,4r)-4-氰基-4-甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[480];

6-(2-(双环[3.1.0]己烷-3-基氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[481];

6-(6-氟-2-((4-羟基双环[2.2.1]庚烷-1-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[482];

6-(6-氟-4-甲氧基-2-(螺[2.5]辛烷-6-基氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[483];

6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[484];

(R)-8-氟-6-(6-氟-4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[485];

(S)-8-氟-6-(6-氟-4-甲氧基-2-((1-(氧杂环丁烷-3-基)乙基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[486];

6-(2-(环己基氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[487];

8-氟-6-(6-氟-4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[488];

6-(2-((4,4-二甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[489];

8-氟-6-(6-氟-2-(((1s,4s)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[490];

8-氟-6-(6-氟-2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[491];

6-(2-(((1s,4s)-4-乙基-4-羟基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[492];

6-(2-(((1r,4r)-4-乙基-4-羟基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[493];

8-氟-6-(6-氟-4-甲氧基-2-(((1s,4s)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[494];

8-氟-6-(6-氟-4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[495];

6-(2-(((1s,4s)-4-氰基-4-甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[496];

6-(2-(((1r,4r)-4-氰基-4-甲基环己基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[497];

6-(2-(双环[3.1.0]己烷-3-基氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[498];

8-氟-6-(6-氟-2-((4-羟基双环[2.2.1]庚烷-1-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[499];和

8-氟-6-(6-氟-4-甲氧基-2-(螺[2.5]辛烷-6-基氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[500];

或其药学上可接受的盐。

17.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-8-氟-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺[501];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[502];

(1r,3r)-N-环丙基-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[503];

(1r,3r)-N-(3,3-二氟环丁基)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[504];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[505];

5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[506];

5-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[507];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-(氧杂环丁烷-3-基氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[508];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[509];

(1s,3r)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[510];

(1r,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[511];

N-((1s,4s)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[512];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[513];

1-((3S,4R)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[514];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[515];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[516];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟吡咯烷-1-基)乙-1-酮[517];

(R)-N-(4,4-二氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[518];

2-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-醇[519];

1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[520];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[521];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[522];

5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[523];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[524];

(R)-2-(4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-醇[525];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[526];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[527];

(S)-5-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[528];

N-((1s,3s)-3-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[529];

N-((1r,3r)-3-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[530];

(1s,3r)-1-乙基-3-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁-1-醇[531];

(1r,3s)-1-乙基-3-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁-1-醇[532];

N-((1s,4s)-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[533];

(1s,4s)-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[534];

1-((3S,4R)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基

吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[535];

1-((3R,4S)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[536];

N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[537];

N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[538];

(R)-1-(3,3-二氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[539];

(R)-N-(4,4-二氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[540];

5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[541];

2-((3R,4S)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-醇[542];

1-((3S,4R)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[543];

1-((3R,4S)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[544];

N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[545];

N-((3S,4R)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[546];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[547];

3-((3R,4S)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈[548];

(R)-2-(3,3-二氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-醇[549];

(R)-1-(3,3-二氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[550];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[551];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[552];

(S)-5-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[553];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[554];

5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(顺-3-乙氧基环丁基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[555];

2-(顺-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[556];

(1s,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[557];

(1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[558];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺-2,2,2-d_3[559];

N-((1s,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[560];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[561];

N-((1s,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-1-氰基环丙烷-1-甲酰胺[562];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-1-氰基环丙烷-1-甲酰胺[563];

(1s,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[564];

(1r,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[565];

2-((顺-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[566];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[567];

(1s,4s)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[568];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[569];

(R)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基吡咯烷-2-酮[570];

(S)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基吡咯烷-2-酮[571];

1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[572];

1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-羰基)环丙烷-1-甲腈[573];

1-((3R,4S)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,

2,4]三嗪-2-基)氨基)-3-氟哌啶-1-羰基)环丙烷-1-甲腈[574];

(R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(3,3-二氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[575];

(R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[576];

(R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[577];

(R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[578];

(R)-1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-羰基)环丙烷-1-甲腈[579];

(R)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[580];

(S)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[581];

4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[582];

5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(双环[3.1.0]己烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[583];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[584];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[585];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺-2,2,2-d_3[586];

(1s,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[587];

(1r,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[588];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇[589];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环已-1-醇[590];

1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[591];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[592];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[593];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁基)乙酰胺[594];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁基)乙酰胺-2,2,2-d_3[595];

(1s,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-乙基环丁-1-醇[596];

(1r,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-乙基环丁-1-醇[597];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[598];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-乙基环己-1-醇[599];和

1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)哌啶-1-基)乙-1-酮[600];

或其药学上可接受的盐。

18.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[601];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[602];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[603];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺-2,2,2-d_3[604];

(1s,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[605];

(1r,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[606];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[607];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[608];

1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[609];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[610];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[611];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[612];

N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺-2,2,2-d_3[613];

(1s,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[614];

(1r,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[615];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[616];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[617];

1-(4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[618];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[619];

1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[620];

(1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(氧杂环丁烷-3-基氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[621];

(1r,4r)-4-((4-甲氧基-5-(2-甲基-[1,2,4]三唑并[1,5-a]吡啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[622];

(S)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-N-(吗啉-2-基甲基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[623];

N-(顺-3-乙氧基环丁基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[624];

1-氰基-N-((1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺[625];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[626];

(R)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[627];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[628];

(1r,4r)-4-((6-氟-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[629];

6-氟-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[630];

(1r,4r)-1-甲基-4-((5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-4-(氧杂环丁烷-3-

基氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[631];

2-(顺-3-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[632];

N-((1s,3s)-3-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[633];

N-((1r,3r)-3-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[634];

(1s,3s)-3-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[635];

(1r,3r)-3-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[636];

2-((顺-4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[637];

(1s,4s)-4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[638];

(1r,4r)-4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[639];

1-((3R,4S)-3-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[640];

5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[641];

5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[642];

5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[643];

1-((3R,4S)-4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[644];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[645];

5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[646];

5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[647];

3-((3R,4S)-4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[648];

(R)-1-(4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[649];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[650];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[651];

2-(顺-3-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[652];

N-((1s,3s)-3-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[653];

N-((1r,3r)-3-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[654];

(1s,3s)-3-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[655];

(1r,3r)-3-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[656];

2-((顺-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[657];

(1s,4s)-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[658];

(1r,4r)-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[659];

1-((3S,4R)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[660];

5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[661];

5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[662];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[663];

1-((3R,4S)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[664];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[665];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[666];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[667];

3-((3R,4S)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈[668];

(R)-1-(3,3-二氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[669];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d]

[1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[670];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[671];

(1r,4r)-4-((5-(1-((E)-2-氟乙烯基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[672];

(E)-5-((5-(1-(2-氟乙烯基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[673];

2-(顺-3-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[674];

N-((1s,3s)-3-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[675];

N-((1r,3r)-3-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[676];

(1s,3s)-3-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[677];

(1r,3r)-3-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[678];

2-((顺-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[679];

(1s,4s)-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[680];

(1r,4r)-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[681];

1-((3S,4R)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[682];

5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[683];

5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[684];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[685];

1-((3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[686];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[687];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[688];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[689];

3-((3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈[690];

(R)-1-(3,3-二氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[691];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[692];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[693];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-(2-氟-2-甲基丙基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[694];

3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2,2-二甲基丙腈[695];

1-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-甲基丙-2-醇[696];

(R)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[697];

(S)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[698];

2-(顺-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[699];和

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[700];

或其药学上可接受的盐。

19.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[701];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[702];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[703];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[704];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[705];

1-氰基-N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺[706];

1-氰基-N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺[707];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲腈[708];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲腈[709];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[710];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[711];

(1s,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[712];

(1r,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环丁-1-醇[713];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-(三氟甲基)环丁-1-醇[714];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-(三氟甲基)环丁-1-醇[715];

2-(反-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[716];

N-(顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[717];

顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[718];

反-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[719];

2-((顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[720];

4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[721];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[722];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[723];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[724];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[725];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[726];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯

并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[727];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-(三氟甲基)环己-1-醇[728];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-(三氟甲基)环己-1-醇[729];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[730];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[731];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-1-乙基-4-氟吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[732];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-1-乙基-4-氟吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[733];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[734];

1-((3S,4R)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[735];

1-((3S,4R)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮-2,2,2-d_3[736];

1-((3S,4R)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)丙-1-酮[737];

N-((3S,4R)-1-环丙基-4-氟吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[738];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[739];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-4-氟-1-(3-甲基氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[740];

3-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)氧杂环丁烷-3-甲腈[741];

(R)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[742];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟吡咯烷-1-基)乙-1-酮[743];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟吡咯烷-1-基)乙-1-酮-2,2,2-d_3[744];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟吡咯烷-1-基)丙-1-酮[745];

(R)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基吡咯烷-2-酮[746];

(S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基吡咯烷-2-酮[747];

2-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-醇[748];

3-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2,2-二甲基丙腈[749];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[750];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[751];

3-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈[752];

1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-羰基)环丙烷-1-甲腈[753];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[754];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-1-乙基-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[755];

2-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-醇[756];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2,2-二甲基丙腈[757];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2-甲基丙-2-醇[758];

N-((3R,4S)-1-环丙基-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[759];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[760];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[761];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[762];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[763];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[764];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-1-(3-乙基氧杂环丁烷-3-基)-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[765];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-1-(3-乙炔基氧

杂环丁烷-3-基)-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[766];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-异丙基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[767];

N-((3R,4S)-1-(3-环丙基氧杂环丁烷-3-基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[768];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[769];

1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[770];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[771];

1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)丙-1-酮[772];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)丙-1-酮[773];

1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮-2,2,2-d_3[774];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮-2,2,2-d_3[775];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-羰基)环丙烷-1-甲腈[776];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[777];

(R)-N-(3,3-二氟-1-(甲基-d_2)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[778];

(R)-N-(3,3-二氟-1-(甲基-d_3)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[779];

(R)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[780];

(R)-2-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-醇[781];

(R)-3-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)-2,2-二甲基丙腈[782];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)-2-甲基丙-2-醇[783];

(R)-N-(1-环丙基-3,3-二氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[784];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[785];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[786];

(R)-3-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)氧杂环丁烷-3-甲腈[787];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[788];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮-2,2,2-d_3[789];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)丙-1-酮[790];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-羰基)环丙烷-1-甲腈[791];

(S)-1-(5-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[792];

5-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[793];

(S)-5-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[794];

(R)-5-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[795];

(R)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[796];

(S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[797];

4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[798];

1-(7-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[799];和

1-(7-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[800];

或其药学上可接受的盐。

20.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[801];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-((4r,7r)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[802];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-((4s,7s)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[803];

2-(顺-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[804];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[805];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[806];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[807];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[808];

2-((顺-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[809];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[810];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[811];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[812];

5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[813];

5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[814];

5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[815];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[816];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[817];

5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[818];

5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[819];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[820];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[821];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[822];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-

4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[823];

2-(顺-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环丁氧基)乙-1-醇[824];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁基)乙酰胺[825];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁基)乙酰胺[826];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁-1-醇[827];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁-1-醇[828];

2-((顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环己基)氧基)乙-1-醇[829];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[830];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[831];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-4-氟吡咯烷-1-基)乙-1-酮[832];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[833];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[834];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[835];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-3-氟哌啶-1-基)乙-1-酮[836];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[837];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[838];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[839];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[840];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[841];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[842];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[843];

2-(顺-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[844];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[845];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[846];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[847];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[848];

2-((顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[849];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[850];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[851];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[852];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[853];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[854];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[855];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[856];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[857];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[858];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[859];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[860];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[861];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并

[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[862];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[863];

2-(顺-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环丁氧基)乙-1-醇[864];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁基)乙酰胺[865];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁基)乙酰胺[866];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁-1-醇[867];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环丁-1-醇[868];

2-((顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环己基)氧基)乙-1-醇[869];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[870];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[871];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-4-氟吡咯烷-1-基)乙-1-酮[872];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[873];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[874];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[875];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-3-氟哌啶-1-基)乙-1-酮[876];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[877];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[878];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[879];

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[880];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[881];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[882];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[883];

2-(顺-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[884];

N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[885];

N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[886];

(1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[887];

(1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[888];

2-((顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[889];

(1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[890];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[891];

1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮[892];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[893];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[894];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[895];

1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[896];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[897];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[898];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[899];和

3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈[900];

或其药学上可接受的盐。

21.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[901];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[902];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[903];

2-(顺-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇[904];

N-((1s,3s)-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[905];

N-((1r,3r)-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[906];

(1s,3s)-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[907];

(1r,3r)-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇[908];

2-((顺-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇[909];

(1s,4s)-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[910];

(1r,4r)-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[911];

1-((3S,4R)-3-氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮[912];

4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[913];

4-甲氧基-N-(1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[914];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[915];

1-((3R,4S)-3-氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[916];

N-((3R,4S)-1-(3,3-二氟环丁基)-3-氟哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[917];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[918];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[919];

3-((3R,4S)-3-氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈[920];

(R)-1-(3,3-二氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[921];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[922];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[923];

N-(2-氟-2-甲基丙基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[924];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1,1,1-三氟丙-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[925];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(4-甲氧基丁烷-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[926];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[927];

(S)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[928];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1R,2S)-2-甲氧基环丁基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[929];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1R,2R)-2-甲氧基环丁基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[930];

N-(顺-3-乙氧基环丁基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[931];

(1s,3s)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[932];

(1r,3r)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[933];

N-((1s,3s)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[934];

N-((1r,3r)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[935];

N-((1s,3s)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[936];

N-((1r,3r)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三

嗪-2-基)氨基)-1-甲基环丁基)-N-甲基乙酰胺[937];

1-氰基-N-((1s,3s)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺[938];

1-氰基-N-((1r,3r)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺[939];

(1s,3r)-1-乙基-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁-1-醇[940];

(1r,3s)-1-乙基-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁-1-醇[941];

(1S,2R)-2-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环戊-1-醇[942];

(R)-N-(3,3-二氟环戊基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[943];

N-环己基-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[944];

2-(反-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[945];

N-(顺-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[946];

N-(4,4-二甲基环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[947];

4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[948];

(1s,4s)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[949];

(1r,4r)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈[950];

(1s,4s)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[951];

(1s,4s)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[952];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1s,4s)-4-甲氧基-4-甲基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[953];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1r,4r)-4-甲氧基-4-甲基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[954];

(R)-N-(4,4-二氟-1-甲基吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[955];

(R)-N-(1-乙基-4,4-二氟吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[956];

(R)-N-(1-环丙基-4,4-二氟吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[957];

(R)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基吡咯烷-2-酮[958];

(S)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基吡咯烷-2-酮[959];

1-(4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[960];

1-(4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-羰基)环丙烷-1-甲腈[961];

1-((3R,4S)-3-氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[962];

1-((3R,4S)-3-氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-羰基)环丙烷-1-甲腈[963];

(R)-N-(3,3-二氟哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[964];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[965];

(R)-N-(1-乙基-3,3-二氟哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[966];

(R)-N-(1-环丙基-3,3-二氟哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[967];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[968];

(R)-1-(3,3-二氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[969];

(R)-1-(3,3-二氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-羰基)环丙烷-1-甲腈[970];

(S)-5-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[971];

(R)-5-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[972];

(R)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[973];

(S)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[974];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(四氢-2H-吡喃-3-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[975];

N-(双环[3.1.0]己烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f]

[1,2,4]三嗪-2-胺[976];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(螺[2.5]辛烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[977];

4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[978];

1-(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[979];

环丙基(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)甲酮[980];

(1-氟环丙基)(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)甲酮[981];

2-(反-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环己基)丙-2-醇[982];

(1s,4s)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[983];

(1r,4r)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-1-甲基环己-1-醇[984];

(1s,4s)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环己-1-醇[985];

(1r,4r)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)环己-1-醇[986];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[987];

1-(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基-7-d)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[988];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[989];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((4r,7r)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[990];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((4s,7s)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-7-d-2-胺[991];

N-((1s,3s)-3-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[992];

N-((1r,3r)-3-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[993];

2-(反-4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[994];

(1s,4s)-4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[995];

(1r,4r)-4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[996];

(1s,4s)-1-乙基-4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[997];

(1r,4r)-1-乙基-4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[998];

6-氟-N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[999];和

1-(4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1000];或其药学上可接受的盐。

22.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

6-氟-N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1001];

6-氟-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1002];

6-氟-N-((3S,4R)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1003];

6-氟-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1004];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1005];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1006];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1007];

1-(7-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[1008];

1-(7-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮-2,2,2-d_3[1009];

2-(反-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇[1010];

(1s,4s)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1011];

(1r,4r)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1012];

(1s,4s)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1013];

(1r,4r)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f]

[1,2,4]三嗪-2-基)氨基)环己-1-醇[1014];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1015];

1-(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[1016];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1017];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)-N-((4r,7r)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1018];

5-(咪唑并[1,2-a]嘧啶-6-基)-4-(甲氧基-d_3)-N-((4s,7s)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1019];

(1s,4s)-4-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1020];

(1r,4r)-4-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1021];

(1s,4s)-4-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[1022];

(1r,4r)-4-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[1023];

1-(7-((4-(二氟甲氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[1024];

4-(二氟甲氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1025];

(1s,4s)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1026];

(1r,4r)-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1027];

(1s,4s)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1028];

(1r,4r)-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1029];

1-(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[1030];

5-(咪唑并[1,2-a]嘧啶-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1031];

(1s,4s)-4-((4-(2,2-二氟乙氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1032];

(1r,4r)-4-((4-(2,2-二氟乙氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1033];

(1s,4s)-4-((4-(2,2-二氟乙氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[1034];

(1r,4r)-4-((4-(2,2-二氟乙氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇[1035];

1-(7-((4-(2,2-二氟乙氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮[1036];

4-(2,2-二氟乙氧基)-5-(咪唑并[1,2-a]嘧啶-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1037];

(1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺[1038];

(1r,3r)-N-环丙基-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[1039];

(1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基-N-(1-甲基环丁基)环丁烷-1-甲酰胺[1040];

(1r,3r)-N-(3,3-二氟环丁基)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺[1041];

(1r,3r)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基-N-(3-甲基氧杂环丁烷-3-基)环丁烷-1-甲酰胺[1042];

(1s,3s)-N^3-(4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-N^1,N^1,1-三甲基环丁烷-1,3-二胺[1043];

N-(顺-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1044];

1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇[1045];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1046];

1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1047];

(R)-1-(3,3-二氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1048];

(R)-5-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[1049];

(R)-4-甲氧基-5-(喹啉-6-基)-N-(四氢-2H-吡喃-3-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1050];

4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1051];

N-((1s,3s)-3-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[1052];

N-((1r,3r)-3-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)

氨基)-1-甲基环丁基)乙酰胺[1053];

N-(顺-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1054];

(1s,4s)-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1055];

(1r,4r)-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1056];

6-氟-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1057];

1-((3R,4S)-3-氟-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇[1058];

6-氟-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1059];

6-氟-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1060];

1-((3R,4S)-3-氟-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1061];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1062];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1063];

(R)-1-(3,3-二氟-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1064];

N-(顺-4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1065];

(1s,4s)-4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1066];

(1r,4r)-4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1067];

1-((3R,4S)-4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2-甲基丙-2-醇[1068];

4-(二氟甲氧基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1069];

1-((3R,4S)-4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[1070];

(R)-1-(4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[1071];

4-((4-(二氟甲氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1072];

N-(顺-4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1073];

(1s,4s)-1-甲基-4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1074];

(1r,4r)-1-甲基-4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1075];

1-((3R,4S)-3-氟-4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇[1076];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1077];

1-((3R,4S)-3-氟-4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1078];

(R)-1-(3,3-二氟-4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1079];

4-((5-(喹啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1080];

N-(顺-4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1081];

(1s,4s)-4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1082];

(1r,4r)-4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1083];

1-((3R,4S)-4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2-甲基丙-2-醇[1084];

4-(2,2-二氟乙氧基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1085];

1-((3R,4S)-4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[1086];

(R)-1-(4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[1087];

4-((4-(2,2-二氟乙氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1088];

(1r,4r)-1-甲基-4-((4-(氧杂环丁烷-3-基氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1089];

N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-(氧杂环丁烷-3-基氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1090];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-(氧杂环丁烷-3-基氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1091];

N-(顺-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己

基)乙酰胺[1092];

(3S,4R)-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)四氢呋喃-3-醇[1093];

1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇[1094];

(R)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1095];

(R)-1-(3,3-二氟-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1096];

(R)-5-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮[1097];

4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1098];

N-((4s,6r)-1-(2,2-二氟乙基)-1-氮杂螺[3.3]庚烷-6-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1099];和

4-甲氧基-5-(喹喔啉-6-基)-N-(7-氧杂螺[3.5]壬烷-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1100];或其药学上可接受的盐。

23.根据权利要求1-11中任一项所述的化合物,其中所述式I化合物选自由以下组成的组:

N-((1s,3s)-3-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[1101];

N-((1r,3r)-3-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺[1102];

N-(顺-4-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1103];

(1s,4s)-4-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1104];

1-((3R,4S)-3-氟-4-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇[1105];

6-氟-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1106];

6-氟-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1107];

1-((3R,4S)-3-氟-4-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1108];

(R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1109];

(R)-N-(3,3-二氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1110];

(R)-1-(3,3-二氟-4-((6-氟-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1111];

N-(顺-4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1112];

(1s,4s)-4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1113];

(1r,4r)-4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1114];

1-((3R,4S)-4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2-甲基丙-2-醇[1115];

4-(二氟甲氧基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1116];

1-((3R,4S)-4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[1117];

(R)-1-(4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[1118];

4-((4-(二氟甲氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1119];

N-(顺-4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1120];

(1s,4s)-1-甲基-4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1121];

(1r,4r)-1-甲基-4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇[1122];

1-((3R,4S)-3-氟-4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇[1123];

N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1124];

1-((3R,4S)-3-氟-4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1125];

(R)-1-(3,3-二氟-4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮[1126];

4-((5-(喹喔啉-6-基)-4-(三氟甲氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1127];

N-(顺-4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺[1128];

(1s,4s)-4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1129];

(1r,4r)-4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-

基)氨基)-1-甲基环己-1-醇[1130];

1-((3R,4S)-4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2-甲基丙-2-醇[1131];

4-(2,2-二氟乙氧基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1132];

1-((3R,4S)-4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮[1133];

(R)-1-(4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[1134];

4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇[1135];

(R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1136];

4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)-N-(7-氧杂螺[3.5]壬烷-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1137];

4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1138];

(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇[1139];

(R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮[1140];

5-(1-(2,2-二氟乙基)-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1141];

N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1142];

1-((3R,4S)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)丙-1-酮[1143];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-((3-甲基氧杂环丁烷-3-基)甲基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1144];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(甲基磺酰基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1145];

3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2,2-二甲基丙腈[1146];

(R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(四氢-2H-吡喃-4-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1147];

N-(2,2-二甲基四氢-2H-吡喃-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1148];

N-((3S,4R)-3-氟四氢-2H-吡喃-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1149];

N-(8-氧杂双环[3.2.1]辛烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1150];

N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1151];

5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺[1152];

N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺[1153];或其药学上可接受的盐。

24.一种药物组合物,所述药物组合物包含治疗有效量的根据权利要求1-23中任一项所述的化合物或其药学上可接受的盐,和药学上可接受的赋形剂。

25.一种治疗患者的病症或疾病的方法,其中所述病症或疾病选自由以下组成的组:神经病症、糖尿病和癌症,所述方法包括向所述患者施用治疗有效量的根据权利要求1-23中任一项所述的化合物或药学上可接受的盐,或权利要求24所述的药物组合物。

26.如权利要求25所述的方法,其中所述病症或疾病为癌症。

27.如权利要求25所述的方法,其中所述病症或疾病为糖尿病。

28.如权利要求25所述的方法,其中所述病症或疾病为神经病症。

29.根据权利要求25-26中任一项所述的方法,其中所述癌症选自由以下组成的组:脑瘤、胶质母细胞瘤、卵巢癌、乳腺癌、头颈部鳞状细胞癌、肝细胞癌、胰腺癌、急性淋巴母细胞白血病、急性巨核母细胞白血病和慢性骨髓白血病。

30.根据权利要求25和28中任一项所述的方法,其中所述病症或疾病为神经病症,其中所述神经病症选自由以下组成的组:阿尔茨海默病、肌萎缩性侧索硬化、CDKL5缺乏病症、唐氏综合征、额颞叶型痴呆伴帕金森症-17(FTDP-17)、路易体痴呆、帕金森病、皮克病和伴有明显神经退行的其他疾病如自闭症、痴呆、癫痫、亨廷顿病、多发性硬化;与获得性脑损伤相关的疾病和病症如慢性创伤性脑病变、创伤性脑损伤、肿瘤、中风、皮克病、进行性核上麻痹、皮质基底节变性、嗜银颗粒病、球状神经胶质tau蛋白病变、原发性年龄相关的tau蛋白病变、神经纤维缠结痴呆、慢性创伤性脑病变(CTE)、具有tau包涵体的额颞叶变性(FTLD-tau)和老化相关的tau星形胶质细胞病变。

31.根据权利要求25、28和30中任一项所述的方法,其中所述病症或疾病为阿尔茨海默病。

32.根据权利要求25-31中任一项所述的方法,其中所述患者为人类。

4-烷氧基吡咯并[2,1-f][1,2,4]三嗪以及其制备和用途

[0001] 相关申请

[0002] 本申请要求2022年6月23日提交的美国临时申请第63/355,076号、2022年11月22日提交的美国临时申请第63/427,322号和2023年4月12日提交的美国临时申请第63/458,808号的权益,所述申请通过引用整体并入本文。

背景技术

技术领域

[0003] 本公开涉及双特异性酪氨酸磷酸化调节的1A激酶的抑制剂和包含其的组合物。更特别地,本公开涉及4-烷氧基吡咯并[2,1-f][1,2,4]三嗪化合物或其盐或类似物的用途,其用于治疗特征在于DYRK1A异常表达和/或活性的病症(例如,癌症、唐氏综合征(Down syndrome)、阿尔茨海默病(Alzheimer's disease)、糖尿病、病毒感染和骨关节炎)。

背景技术

[0005] 双特异性酪氨酸磷酸化调节的激酶(DYRK1A、1B、2-4)包含在真核激酶组的CMGC组内的蛋白激酶家族。这些蛋白激酶涉及多种细胞功能,包括细胞内信号传导、mRNA剪接、染色质转录、DNA损伤修复、细胞存活、细胞周期控制、分化、高半胱氨酸/甲硫氨酸/叶酸调节、体温调节、内饮作用、神经元发育、突触可塑性等。这些激酶中的一些,特别是DYRK1A的异常表达和/或活性可见于许多人类神经系统疾病,例如与唐氏综合征相关的认知缺陷、阿尔茨海默病和相关疾病、tau蛋白病变、痴呆、皮克病(Pick's disease)、帕金森病(Parkinson's disease)和其他神经退行性疾病、费伦-麦克德明综合征(Ph elan-McDermid syndrome)、自闭症和CDKL5缺乏症。DYRK也涉及糖尿病、异常叶酸/甲硫氨酸代谢、骨关节炎、若干实体癌(胶质母细胞瘤、乳腺癌和胰腺癌)和白血病(急性淋巴母细胞性白血病、急性巨核母细胞性白血病)、病毒感染(流感、HIV-1、HCMV、HCV、CMV、HPV)以及由单细胞寄生虫(利什曼原虫(Leishmania)、锥虫(Trypanoso ma)、疟原虫(Plasmodium))引起的感染(International Journal of Mole cular Sciences(2021),22(11),6047)。DYRK1A也已经鉴定为EGFR的关键稳定剂(Cell Death&Disease(2019),10,282),所述EGFR为在牛皮癣进展期间促成角质化、细胞过度增殖、异常分化和炎性浸润的关键因素。

发明内容

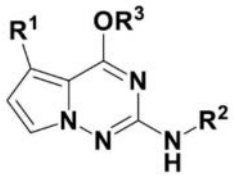
[0006] 本公开提供了方法和试剂,所述方法包括使细胞与例如4-烷氧基吡咯并[2,1-f][1,2,4]三嗪化合物的药剂接触,所述药剂的量足以拮抗DYRK1A活性,例如减少头颈部鳞状细胞癌、管腔/HER2乳腺癌(Cell(2016),164(1-2),293-309)或胰腺腺癌的扩散,以及减弱胶质母细胞瘤的自我更新能力并且破坏卵巢癌球形体细胞活力(Molecular Cancer Research(2017),15(4),371-381)。

[0007] 本公开还提供了方法和试剂,所述方法涉及使细胞与例如4-烷氧基吡咯并[2,1-f][1,2,4]三嗪化合物的药剂接触,所述药剂的量足以拮抗DYRK1A活性,例如i)使产前和产后早期脑部发育正常;ii)改善青少年和成人的认知功能;和/或iii)减弱阿尔茨海默型神

经退行。

[0008] 本文所公开的一些实施方案包括含有4-烷氧基吡咯并[2,1-f][1,2,4]三嗪核心的DYRK1A抑制剂。本文所公开的其他实施方案包括药物组合物和使用这些化合物的治疗方法。

[0009] 本文所公开的一个实施方案包括一种具有式I结构的化合物：

[0010] 

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[0011] 或其药学上可接受的盐，

[0012] 其中，

[0013] R^1为任选地被1至10个R^4取代的杂芳基；

[0014] R^2选自由以下组成的组：未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^5$、任选地被1至10个$R^6$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至10个$R^7$取代的-杂芳基和任选地被1至12个$R^8$取代的-($C_{1-5}$亚烷基)$_p$碳环基，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0015] R^3选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

[0016] 每个R^4独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^9$、-($C_{1-5}$亚烷基)CN、任选地被1至10个$R^{10}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至12个$R^{11}$取代的-碳环基、任选地被1至10个$R^{20}$取代的-($C_{1-5}$亚烷基)$_p$杂芳基、-($C_{1-5}$亚烷基)$_p$$C(=O)N(R^{12})_2$和$-C(=O)R^{13}$，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0017] 每个R^5独立地选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

[0018] 每个R^6独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个R^{16}取代的-杂环基、-(C_{1-5}亚烷基)$_p$$OR^{21}$、$-SO_2R^{23}$和$-C(=O)R^{24}$，其中所述-($C_{1-5}$亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0019] 或者，连接至同一碳原子的两个R^6一起形成羰基；

[0020] 每个R^7独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-OMe；

[0021] 每个R^8独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、$-N(R^{14})_2$、-(C_{1-5}亚烷基)$_p$$OR^{15}$、任选地被1至10个$R^{16}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、$-C(=O)R^{22}$和$-NHC(=O)R^{23}$，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0022] 每个R^9独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0023] 每个R^{10}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0024] 每个R^{11}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0025] 每个R^{12}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至12个R^{17}取代的-(C_{1-5}亚烷基)$_p$碳环基、任选地被1至10个R^{18}取代的-杂环基和任选地被1至10个R^{19}取代的-杂芳基,其中所述-(C_{1-5}亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0026] 每个R^{13}为任选地被1至10个R^{18}取代的-杂环基;

[0027] 每个R^{14}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0028] 每个R^{15}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-(C_{1-5}亚烷基)$_p$$OR^{21}$;

[0029] 每个R^{16}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0030] 每个R^{17}独立地选自由以下组成的组:卤素、-OMe、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0031] 每个R^{18}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0032] 每个R^{19}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0033] 每个R^{20}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0034] 每个R^{21}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0035] 每个R^{22}独立地选自由以下组成的组:任选地被1至10个R^{18}取代的-杂环基、-N(R^{12})$_2$和-OR^{21};

[0036] 每个R^{23}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

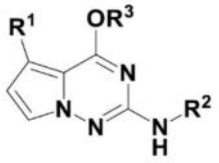
[0037] 每个R^{24}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-OR^{23}和任选地被1至12个R^{25}取代的-碳环基;

[0038] 每个R^{25}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);和

[0039] 每个p独立地为0或1;

[0040] 其中每个H原子任选地独立地被^{2}H(D)(氘)代替。

[0041] 在本文所公开的另一个实施方案中,包括一种具有式I结构的化合物:

[0042] 

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[0043] 或其药学上可接受的盐,

[0044] 其中,

[0045] R^1为任选地被1至10个R^4取代的杂芳基;

[0046] R^2选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^5$、任选地被1至10个$R^6$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至10个$R^{26}$取代的-($C_{1-5}$亚烷基)$_p$芳基、任选地被1至10个$R^7$取代的-($C_{1-5}$亚烷基)$_p$杂芳基和任选地被1至12个$R^8$取代的-($C_{1-5}$亚烷基)$_p$碳环基,其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0047] R^3选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和任选地被1至10个R^{18}取代的杂环基;

[0048] 每个R^4独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^9$、-($C_{1-5}$亚烷基)$_p$CN、任选地被1至10个$R^{10}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至12个$R^{11}$取代的-碳环基、任选地被1至10个$R^{20}$取代的-($C_{1-5}$亚烷基)$_p$杂芳基、-($C_{1-5}$亚烷基)$_p$C(=O)N($R^{12}$)$_2$和-C(=O)$R^{13}$,其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0049] 每个R^5独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0050] 每个R^6独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个R^{16}取代的-杂环基、任选地被1至12个R^{17}取代的-碳环基、-(C_{1-5}亚烷基)$_p$$OR^{21}$、-$SO_2R^{23}$和-C(=O)$R^{24}$,其中所述-($C_{1-5}$亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0051] 或者,连接至同一碳原子的两个R^6一起形成羰基;

[0052] 每个R^7独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-OMe;

[0053] 每个R^8独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-N(R^{14})$_2$、-(C_{1-5}亚烷基)$_p$$OR^{15}$、任选地被1至10个$R^{16}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、-C(=O)$R^{22}$和-NHC(=O)$R^{23}$,其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0054] 每个R^9独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0055] 每个R^{10}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0056] 每个R^{11}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0057] 每个R^{12}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^{21}$、任选地被1至12个$R^{17}$取代的-($C_{1-5}$亚烷基)$_p$碳环基、任选地被1至10个$R^{18}$取代的-杂环基和任选地被1至10个$R^{19}$取代的-杂芳基,其中所述-($C_{1-5}$亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0058] 每个R^{13}为任选地被1至10个R^{18}取代的-杂环基;

[0059] 每个R^{14}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0060] 每个R^{15}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-(C_{1-5}亚烷基)$_p$$OR^{21}$;

[0061] 每个R^{16}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0062] 或者,连接至同一碳原子的两个R^{16}一起形成羰基;

[0063] 每个R^{17}独立地选自由以下组成的组:卤素、-OMe、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0064] 每个R^{18}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0065] 每个R^{19}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0066] 每个R^{20}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0067] 每个R^{21}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0068] 每个R^{22}独立地选自由以下组成的组:任选地被1至10个R^{18}取代的-杂环基、-$N(R^{12})_2$和-OR^{21};

[0069] 每个R^{23}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-(C_{1-5}亚烷基)$_p$$OR^{21}$;

[0070] 每个R^{24}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-OR^{21}和任选地被1至12个R^{25}取代的-碳环基;

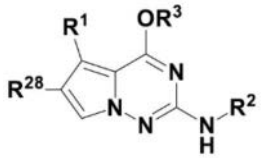
[0071] 每个R^{25}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0072] 每个R^{26}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);和

[0073] 每个p独立地为0或1;

[0074] 其中每个H原子任选地独立地被^{2}H(D)(氘)代替。

[0075] 在本文所公开的另一个实施方案中,包括一种具有式I结构的化合物:

[0076] 

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[0077] 或其药学上可接受的盐，

[0078] 其中，

[0079] R^1为任选地被1至10个R^4取代的杂芳基；

[0080] R^2选自由以下组成的组：未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^5$、-($C_{1-5}$亚烷基)CN、任选地被1至10个$R^6$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至10个$R^{26}$取代的-($C_{1-5}$亚烷基)$_p$芳基、任选地被1至10个$R^7$取代的-($C_{1-5}$亚烷基)$_p$杂芳基和任选地被1至12个$R^8$取代的-($C_{1-5}$亚烷基)$_p$碳环基，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0081] R^3选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和任选地被1至10个R^{18}取代的杂环基；

[0082] 每个R^4独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、未被取代的-(C_{2-9}卤代烯基)、-(C_{1-5}亚烷基)$_p$$OR^9$、-($C_{1-5}$亚烷基)$_p$CN、任选地被1至10个$R^{10}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至12个$R^{11}$取代的-碳环基、任选地被1至10个$R^{20}$取代的-($C_{1-5}$亚烷基)$_p$杂芳基、-($C_{1-5}$亚烷基)$_p$C(=O)N($R^{12}$)$_2$和-C(=O)$R^{13}$，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0083] 每个R^5独立地选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

[0084] 每个R^6独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个R^{16}取代的-杂环基、任选地被1至12个R^{17}取代的-碳环基、-(C_{1-5}亚烷基)$_p$$OR^{21}$、-($C_{1-5}$亚烷基)CN、-$SO_2R^{23}$和-C(=O)$R^{24}$，其中所述-($C_{1-5}$亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0085] 或者，连接至同一碳原子的两个R^6一起形成羰基；

[0086] 每个R^7独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-OMe；

[0087] 每个R^8独立地选自由以下组成的组：卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-N(R^{14})$_2$、-(C_{1-5}亚烷基)$_p$$OR^{15}$、-CN、任选地被1至10个$R^{16}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、-C(=O)$R^{22}$和-$NR^{14}$C(=O)$R^{23}$，其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0088] 每个R^9独立地选自由以下组成的组：H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

[0089] 每个R^{10}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0090] 每个R^{11}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0091] 每个R^{12}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^{21}$、任选地被1至12个$R^{17}$取代的-($C_{1-5}$亚烷基)$_p$碳环基、任选地被1至10个$R^{18}$取代的-杂环基和任选地被1至10个$R^{19}$取代的-杂芳基,其中所述-($C_{1-5}$亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0092] 每个R^{13}为任选地被1至10个R^{18}取代的-杂环基;

[0093] 每个R^{14}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0094] 每个R^{15}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-(C_{1-5}亚烷基)$_p$$OR^{21}$;

[0095] 每个R^{16}独立地选自由以下组成的组:卤素、-CN、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和任选地被1至12个R^{27}取代的-碳环基;

[0096] 或者,连接至同一碳原子的两个R^{16}一起形成羰基;

[0097] 每个R^{17}独立地选自由以下组成的组:卤素、-OMe、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0098] 每个R^{18}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0099] 每个R^{19}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0100] 每个R^{20}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0101] 每个R^{21}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0102] 每个R^{22}独立地选自由以下组成的组:任选地被1至10个R^{18}取代的-杂环基、-N(R^{12})$_2$和-OR^{21};

[0103] 每个R^{23}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^{21}$和任选地被1至12个$R^{25}$取代的-碳环基;

[0104] 每个R^{24}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-OR^{21}和任选地被1至12个R^{25}取代的-碳环基;

[0105] 每个R^{25}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-CN;

[0106] 每个R^{26}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-

(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

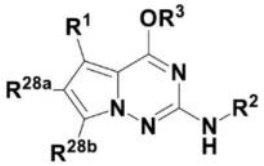
[0107] 每个R^{27}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

[0108] R^{28}独立地选自由以下组成的组:H和卤素;和

[0109] 每个p独立地为0或1；

[0110] 其中每个H原子任选地独立地被^{2}H(D)(氘)代替。

[0111] 在本文所公开的另一个实施方案中,包括一种具有式I结构的化合物:

[0112] 

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[0113] 或其药学上可接受的盐,

[0114] 其中,

[0115] R^{1}为任选地被1至10个R^{4}取代的杂芳基；

[0116] R^{2}选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_{p}OR^{5}$、-(C_{1-5}亚烷基)CN、任选地被1至10个R^{6}取代的-(C_{1-5}亚烷基)$_{p}$杂环基、任选地被1至10个R^{26}取代的-(C_{1-5}亚烷基)$_{p}$芳基、任选地被1至10个R^{7}取代的-(C_{1-5}亚烷基)$_{p}$杂芳基和任选地被1至12个R^{8}取代的-(C_{1-5}亚烷基)$_{p}$碳环基,其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0117] R^{3}选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和任选地被1至10个R^{18}取代的杂环基；

[0118] 每个R^{4}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、未被取代的-(C_{2-9}卤代烯基)、-(C_{1-5}亚烷基)$_{p}OR^{9}$、-(C_{1-5}亚烷基)$_{p}$CN、任选地被1至10个R^{10}取代的-(C_{1-5}亚烷基)$_{p}$杂环基、任选地被1至12个R^{11}取代的-碳环基、任选地被1至10个R^{20}取代的-(C_{1-5}亚烷基)$_{p}$杂芳基、-(C_{1-5}亚烷基)$_{p}C(=O)N(R^{12})_{2}$和-$C(=O)R^{13}$,其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0119] 每个R^{5}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)；

[0120] 每个R^{6}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个R^{16}取代的-杂环基、任选地被1至12个R^{17}取代的-碳环基、-(C_{1-5}亚烷基)$_{p}OR^{21}$、-(C_{1-5}亚烷基)CN、-$SO_{2}R^{23}$和-$C(=O)R^{24}$,其中所述-(C_{1-5}亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代；

[0121] 或者,连接至同一碳原子的两个R^{6}一起形成羰基；

[0122] 每个R^{7}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-OMe；

[0123] 每个R^8独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-N(R^{14})$_2$、-(C_{1-5}亚烷基)$_p$OR^{15}、-CN、任选地被1至10个R^{16}取代的-(C_{1-5}亚烷基)$_p$杂环基、-C(=O)R^{22}和-NR^{14}C(=O)R^{23},其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0124] 每个R^9独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0125] 每个R^{10}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0126] 每个R^{11}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0127] 每个R^{12}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$OR^{21}、任选地被1至12个R^{17}取代的-(C_{1-5}亚烷基)$_p$碳环基、任选地被1至10个R^{18}取代的-杂环基和任选地被1至10个R^{19}取代的-杂芳基,其中所述-(C_{1-5}亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代;

[0128] 每个R^{13}为任选地被1至10个R^{18}取代的-杂环基;

[0129] 每个R^{14}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0130] 每个R^{15}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-(C_{1-5}亚烷基)$_p$OR^{21};

[0131] 每个R^{16}独立地选自由以下组成的组:卤素、-CN、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和任选地被1至12个R^{27}取代的-碳环基;

[0132] 或者,连接至同一碳原子的两个R^{16}一起形成羰基;

[0133] 每个R^{17}独立地选自由以下组成的组:卤素、-OMe、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0134] 每个R^{18}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0135] 每个R^{19}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0136] 每个R^{20}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0137] 每个R^{21}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0138] 每个R^{22}独立地选自由以下组成的组:任选地被1至10个R^{18}取代的-杂环基、-N(R^{12})$_2$和-OR^{21};

[0139] 每个R^{23}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$OR^{21}和任选地被1

至12个R^{25}取代的-碳环基;

[0140] 每个R^{24}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-OR^{21}和任选地被1至12个R^{25}取代的-碳环基;

[0141] 每个R^{25}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-CN;

[0142] 每个R^{26}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0143] 每个R^{27}独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基);

[0144] R^{28a}独立地选自由以下组成的组:H和卤素;

[0145] R^{28b}独立地选自由以下组成的组:H和D;和

[0146] 每个p独立地为0或1;

[0147] 其中每个H原子任选地独立地被^{2}H(D)(氘)代替。

[0148] 一些实施方案包括式I化合物的立体异构体和药学上可接受的盐。一些实施方案包括式I化合物的药学上可接受的盐。

[0149] 一些实施方案包括式I化合物的前药。

[0150] 本公开的一些实施方案包括包含式I化合物和药学上可接受的载体、稀释剂或赋形剂的药物组合物。

[0151] 本文所公开的其他实施方案包括通过向受涉及DYRK1A过表达的病症或疾病影响的患者施用来抑制DYRK1A的方法,所述病症或疾病例如阿尔茨海默病、肌萎缩性侧索硬化、CDKL5缺乏病症、唐氏综合征、额颞叶型痴呆伴帕金森症-17(FTDP-17)、路易体痴呆(Lewy body dementia)、帕金森病、皮克病和伴有明显神经退行的其他疾病如自闭症、痴呆、癫痫、亨廷顿病(Huntington's disease)、多发性硬化;与获得性脑损伤相关的疾病和病症如慢性创伤性脑病变、创伤性脑损伤、肿瘤和中风。

[0152] DYRK1A的抑制剂也可用于治疗tau蛋白病变。tau蛋白病变为神经退行性病症,其特征为脑部中沉积异常tau蛋白。tau病变的范围扩展超出传统论述的疾病形式,如皮克病、进行性核上麻痹、皮质基底节变性和嗜银颗粒病。新出现的实体和病变包括球状神经胶质tau蛋白病变、原发性年龄相关的tau蛋白病变(其包括神经纤维缠结痴呆)、慢性创伤性脑病变(CTE)、具有tau包涵体的额颞叶变性(frontot emporal lobar degeneration with tau inclusions,FTLD-tau)和老化相关的tau星形胶质细胞病变。临床症状包括额颞叶型痴呆、皮质基底核综合征、理查德森综合征(Richardson syndrome)、帕金森症、纯运动不能伴步态冻结和罕见地运动神经元症状或小脑共济失调(Handbo ok of Clinical Neurology(2018),145,355-368和Aging Cell(2019),18(5),e13000)。

[0153] DYRK1A的抑制剂也可用于治疗与异常叶酸/甲硫氨酸代谢相关的病症。

[0154] 可用本文所提供的化合物和组合物治疗的疾病的非限制性实例包括多种癌症、糖尿病、牛皮癣、膝骨性关节炎、肌腱病变、人类免疫缺乏病毒1型(HIV-1)、人类巨细胞病毒(HCMV)、丙型肝炎病毒(HCV)和单纯疱疹病毒1(HSV-1)。

[0155] 本公开的一些实施方案包括制备式I化合物的方法。

[0156] 应理解,前述一般描述和以下详细描述两者都仅为示例性和解释性的,并且不限制如所要求保护的本公开。

具体实施方式

[0157] 本文提供了用于抑制DYRK1A的组合物和方法。

[0158] 本文所提供的一些实施方案涉及一种用于治疗疾病的方法,所述疾病包括(但不限于):神经疾病或病症、癌症、认知缺陷、膝骨性关节炎、肌腱病变、病毒感染、单细胞寄生虫感染和运动缺陷。

[0159] 在一些实施方案中,可用本文所提供的化合物和组合物治疗的神经疾病或病症的非限制性实例包括(但不限于)阿尔茨海默病、肌萎缩性侧索硬化、唐氏综合征、额颞叶型痴呆伴帕金森症-17(FTDP-17)、路易体痴呆、帕金森病、匹克病tau蛋白病变和伴有明显神经退行的其他疾病如自闭症、痴呆、癫痫、亨廷顿病、多发性硬化;与获得性脑损伤相关的疾病和病症如慢性创伤性脑病变、创伤性脑损伤、肿瘤和中风。

[0160] 在一些实施方案中,可用本文所提供的化合物和组合物治疗的癌症的非限制性实例包括实体癌(例如胶质母细胞瘤、卵巢癌、乳腺癌和胰腺癌)和白血病(例如急性淋巴母细胞性白血病、急性巨核母细胞性白血病和慢性骨髓性白血病)。

[0161] 在一些实施方案中,提供了对治疗动物(例如哺乳动物)的由DYRK1A过表达引起的疾病有效的药物组合物。所述组合物包括药学上可接受的载体和如本文所描述的化合物。

[0162] 定义

[0163] 除非另作定义,否则本文中所用的所有技术和科学术语都具有与本公开所属领域的普通技术人员通常所了解的含义相同的含义。所有专利、申请、公开申请和其他出版物都通过引用整体并入。除非另有说明,否则在本文术语存在多种定义的情况下,以这个部分中的定义为准。

[0164] 如本文所用,“烷基”意指仅含有碳和氢的支链或直链化学基团,例如甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、异戊基、仲戊基和新戊基。烷基可未被取代或被一个或多个取代基取代。在一些实施方案中,烷基包括1至9个碳原子(例如1至6个碳原子、1至4个碳原子或1至2个碳原子)。

[0165] 如本文所用,“烯基”意指仅含有碳和氢并且含有至少一个碳碳双键的直链或支链化学基团,例如乙烯基、1-丙烯基、2-丙烯基、2-甲基-1-丙烯基、1-丁烯基、2-丁烯基等。在各种实施方案中,烯基可未被取代或被一个或多个取代基取代。通常,烯基将包含2至9个碳原子(例如,2至6个碳原子、2至4个碳原子或2个碳原子)。

[0166] 如本文所用,“炔基”意指仅含有碳和氢并且含有至少一个碳碳三键的直链或支链化学基团,例如乙炔基、1-丙炔基、1-丁炔基、2-丁炔基等。在各种实施方案中,炔基可未被取代或被一个或多个取代基取代。通常,炔基将包含2至9个碳原子(例如,2至6个碳原子、2至4个碳原子或2个碳原子)。

[0167] 如本文所用,“亚烷基”意指仅含有碳和氢的二价支链或直链化学基团,例如亚甲基、亚乙基、亚正丙基、亚异丙基、亚正丁基、亚异丁基、亚仲丁基、亚叔丁基、亚正戊基、亚异戊基、亚仲戊基和亚新戊基。亚烷基可未被取代或被一个或多个取代基取代。在一些实施方案中,亚烷基包括1至9个碳原子(例如1至6个碳原子、1至4个碳原子或1至2个碳原子)。

[0168] 如本文所用,“亚烯基”意指仅含有碳和氢并且含有至少一个碳碳双键的二价支链或直链化学基团,例如亚乙烯基、1-亚丙烯基、2-亚丙烯基、2-甲基-1-亚丙烯基、1-亚丁烯基、2-亚丁烯基等。在各种实施方案中,亚烯基可未被取代或被一个或多个取代基取代。通常,亚烯基将包含2至9个碳原子(例如,2至6个碳原子、2至4个碳原子或2个碳原子)。

[0169] 如本文所用,“亚炔基”意指仅含有碳和氢并且含有至少一个碳碳三键的二价支链或直链化学基团,例如亚乙炔基、1-亚丙炔基、1-亚丁炔基、2-亚丁炔基等。在各种实施方案中,亚炔基可未被取代或被一个或多个取代基取代。通常,亚炔基将包含2至9个碳原子(例如,2至6个碳原子、2至4个碳原子或2个碳原子)。

[0170] 如本文所用,“烷氧基”意指其中烷基如本文中所描述的烷基-O-基团。示例性烷氧基包括甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、仲丁氧基、叔丁氧基、戊氧基、己氧基和庚氧基,并且还包括其直链或支链位置异构体。

[0171] 如本文所用,“卤代烷氧基”意指其中卤代烷基如本文中所描述的卤代烷基-O-基团。示例性卤代烷氧基包括氟甲氧基、二氟甲氧基、三氟甲氧基,并且还包括其直链或支链位置异构体。

[0172] 如本文所用,“碳环基”意指仅在环系统主链中含有碳原子的环状环系统,例如环丙基、环丁基、环戊基、环己基和环己烯基。碳环基可包括多个稠合环。碳环基可具有任何饱和度,条件是环系统中无一环是芳族的。碳环基可未被取代或被一个或多个取代基取代。在一些实施方案中,碳环基包括3至10个碳原子,例如3至6个碳原子。

[0173] 如本文所用,“芳基”意指碳原子仅存在于具有5至14个环原子、或者5、6、9或10个环原子并且具有在环状阵列中共享的6、10或14个π电子的环主链中的单环、双环、三环或多环基团;其中系统中的至少一个环为芳族。芳基可未被取代或被一个或多个取代基取代。芳基的实例包括苯基、萘基、四氢萘基、2,3-二氢-1H-茚基和其他基团。在一些实施方案中,芳基为苯基。

[0174] 如本文所用,“芳基亚烷基”意指其中芳基和亚烷基部分如先前所描述的芳基-亚烷基-基团。在一些实施方案中,芳基亚烷基含有C_{1-4}亚烷基部分。示例性芳基亚烷基包括苯甲基和2-苯乙基。

[0175] 如本文所用,术语“杂芳基”意指具有5至14个环原子、或者5、6、9或10个环原子并且具有在环状阵列中共享的6、10或14个π电子的单环、双环、三环或多环基团;其中系统中的至少一个环为芳族,并且系统中的至少一个环含有一个或多个独立地选自由N、O和S组成的组的杂原子。杂芳基可未被取代或被一个或多个取代基取代。杂芳基的实例包括噻吩基、吡啶基、呋喃基、噁唑基、噁二唑基、吡咯基、咪唑基、三唑基、噻二唑基、吡唑基、异噁唑基、噻二唑基、吡喃基、吡嗪基、嘧啶基、哒嗪基、三嗪基、噻唑基、苯并噻吩基、苯并噁二唑基、苯并呋喃基、苯并咪唑基、苯并三唑基、噌啉基、吲唑基、吲哚基、异喹啉基、异噻唑基、萘啶基、嘌呤基、噻吩并吡啶基、吡啶并[2,3-d]嘧啶基、吡咯并[2,3-b]吡啶基、喹唑啉基、喹啉基、噻吩并[2,3-c]吡啶基、吡唑并[3,4-b]吡啶基、吡唑并[3,4-c]吡啶基、吡唑并[4,3-c]吡啶、吡唑并[4,3-b]吡啶基、四唑基、色烷、2,3-二氢苯并[b][1,4]二氧杂环己烯、苯并[d][1,3]间二氧杂环戊烯、2,3-二氢苯并呋喃、四氢喹啉、2,3-二氢苯并[b][1,4]氧硫杂环己二烯、异吲哚啉和其他。在一些实施方案中,杂芳基选自噻吩基、吡啶基、呋喃基、吡唑基、咪唑基、异吲哚啉基、吡喃基、吡嗪基和嘧啶基。

[0176] 如本文所用,“卤基(halo)”、“卤素(halide)”或“卤素(halogen)”为氯、溴、氟或碘原子基团。在一些实施方案中,卤基为氯、溴或氟。例如,卤素可为氟。

[0177] 如本文所用,“卤代烷基”意指烃取代基,其为被一个或多个氯、溴、氟和/或碘原子取代的直链或支链烷基、烯基或炔基。在一些实施方案中,卤代烷基为氟烷基,其中一个或多个氢原子已被氟取代。在一些实施方案中,卤代烷基长度为1至3个碳(例如长度为1至2个碳或长度为1个碳)。术语“卤代亚烷基”意指卤代烷基的双基变体,并且此类双基可充当基团、其他原子之间或环与另一官能团之间的间隔基。

[0178] 如本文所用,“杂环基”意指在环系统主链中包含至少一个杂原子的非芳族环状环系。杂环基可包括多个稠合环,例如双环和螺环杂环基。杂环基可被一个或多个取代基取代或未被取代。在一些实施方案中,杂环具有3至11个成员。在六元单环杂环中,杂原子选自O、N和S中的一至三者,并且其中当杂环为五元时,其可具有一个或两个选自O、N和S的杂原子。杂环基的实例包括氮杂环丙烯基、氮丙啶基、氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、1,4,2-二噻唑基、二氢吡啶基、1,3-二氧杂环己烷基、1,4-二氧杂环己烷基、1,3-二氧戊环基、吗啉基、硫代吗啉基、哌嗪基、吡喃基、吡咯烷基、四氢呋喃基、四氢吡啶基、噁嗪基、噻嗪基(thiazinyl/thiinyl)、噻唑烷基、异噻唑烷基、噁唑烷基、异噁唑烷基、哌啶基、吡唑烷基、咪唑烷基、硫代吗啉基和其他基团。在一些实施方案中,杂环基选自氮杂环丁烷基、吗啉基、哌嗪基、吡咯烷基和四氢吡啶基。

[0179] 如本文所用,“单环杂环基”意指在环系主链中包含至少一个杂原子的单一非芳族环状环。杂环基可被一个或多个取代基取代或未被取代。在一些实施方案中,杂环具有3至7个成员。在六元单环杂环中,杂原子选自O、N和S中的一至三者,并且其中当杂环为五元时,其可具有一个或两个选自O、N和S的杂原子。单环杂环基的实例包括氮杂环丙烯基、氮丙啶基、氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、1,4,2-二噻唑基、二氢吡啶基、1,3-二氧杂环己烷基、1,4-二氧杂环己烷基、1,3-二氧戊环基、吗啉基、硫代吗啉基、哌嗪基、吡喃基、吡咯烷基、四氢呋喃基、四氢吡啶基、噁嗪基、噻嗪基(thiazinyl/thiinyl)、噻唑烷基、异噻唑烷基、噁唑烷基、异噁唑烷基、哌啶基、吡唑烷基、咪唑烷基、硫代吗啉基和其他基团。

[0180] 如本文所用,“双环杂环基”意指在环系主链中包含至少一个杂原子的非芳族双环系统。双环杂环基可被一个或多个取代基取代或未被取代。在一些实施方案中,双环杂环具有4至11个成员,其中杂原子选自O、N和S中的一至五者。双环杂环基的实例包括2-氮杂双环[1.1.0]丁烷、2-氮杂双环[2.1.0]戊烷、2-氮杂双环[1.1.1]戊烷、3-氮杂双环[3.1.0]己烷、5-氮杂双环[2.1.1]己烷、3-氮杂双环[3.2.0]庚烷、八氢环戊[c]吡咯、3-氮杂双环[4.1.0]庚烷、7-氮杂双环[2.2.1]庚烷、6-氮杂双环[3.1.1]庚烷、7-氮杂双环[4.2.0]辛烷、2-氮杂双环[2.2.2]辛烷等。

[0181] 如本文所用,“螺环杂环基”意指非芳族双环系统,其在环系主链中包含至少一个杂原子并且仅经由一个原子与环连接。螺环杂环基可被一个或多个取代基取代或未被取代。在一些实施方案中,螺环杂环具有5至11个成员,其中杂原子选自O、N和S中的一至五者。螺环杂环基的实例包括2-氮杂螺[2.2]戊烷、4-氮杂螺[2.5]辛烷、1-氮杂螺[3.5]壬烷、2-氮杂螺[3.5]壬烷、7-氮杂螺[3.5]壬烷、2-氮杂螺[4.4]壬烷、6-氮杂螺[2.6]壬烷、1,7-二氮杂螺[4.5]癸烷、2,5-二氮杂螺[3.6]癸烷等。

[0182] 术语“被取代”是指取代基置换分子的一个或多个非氢原子上的氢的部分。应理

解,“取代”或“被取代”包括隐含条件为此类取代是根据被取代原子和取代基的准许价态,并且取代产生稳定化合物,例如其并不自发地例如通过重排、环化、消除等进行转化。取代基可包括例如-(C_{1-9}烷基),其任选地被以下中的一者或多者取代:羟基、-NH_2、-NH(C_{1-3}烷基)和-N(C_{1-3}烷基)$_2$;-(C_{1-9}卤代烷基);卤素;羟基;羰基[例如-C(O)OR和-C(O)R];硫羰基[例如-C(S)OR、-C(O)SR和-C(S)R];-(C_{1-9}烷氧基),其任选地被以下中的一者或多者取代:卤素、羟基、-NH_2、-NH(C_{1-3}烷基)和-N(C_{1-3}烷基)$_2$;-OPO(OH)$_2$;膦酸根基[例如-PO(OH)$_2$和-PO(OR')$_2$];-OPO(OR')R″;-NRR';-C(O)NRR';-C(NR)NR'R″;-C(NR')R″;氰基;硝基;叠氮基;-SH;-S-R;-OSO_2(OR);磺酸根基[例如-SO_2(OH)和-SO_2(OR)];-SO_2NR'R″;和-SO_2R;其中R、R'和R″在每次出现时独立地选自:H;-(C_{1-9}烷基);任选地被1至3个R”'取代的C_{6-10}芳基;5元至10元杂芳基,其具有1至4个独立地选自N、O和S的杂原子并且任选地被1至3个R”'取代;任选地被1至3个R”'取代的C_{3-7}碳环基;和3元至8元杂环基,其具有1至4个独立地选自N、O和S的杂原子并且任选地被1至3个R”'取代;其中每个R”'独立地选自-(C_{1-6}烷基)、-(C_{1-6}卤代烷基)、卤素(例如F)、羟基、-C(O)OR、-C(O)R、-(C_{1-6}烷氧基)、-NRR'、-C(O)NRR'和氰基,其中R和R'在每次出现时独立地选自H和-(C_{1-6}烷基)。在一些实施方案中,所述取代基选自-(C_{1-6}烷基)、-(C_{1-6}卤代烷基)、卤素(例如F)、羟基、-C(O)OR、-C(O)R、-(C_{1-6}烷氧基)、-NRR'、-C(O)NRR'和氰基,其中R和R'在每次出现时独立地选自H和-(C_{1-6}烷基)。

[0183] 如本文所用,当两个基团指示为“连接”或“键结”形成“环”时,应理解,键形成于两个基团之间并且可涉及一个或两个基团上的氢原子被键置换,从而形成碳环基、杂环基、芳基或杂芳基环。本领域技术人员将认识到此类环可以并且容易地通过常规化学反应形成。在一些实施方案中,此类环具有3至7个成员,例如5或6个成员。

[0184] 本领域技术人员将认识到,本文所描述的一些化学结构可通过一种或多种其他共振形式展现在论文上;或可以一种或多种其他互变异构形式存在,即使在以动力学方式表示时,技术人员认识到,此类互变异构形式仅表示此类化合物的样本的极小部分。尽管本文未明确地展现此类共振形式或互变异构体,但此类化合物明显地涵盖在本公开范围内。

[0185] 本文所提供的化合物可涵盖各种立体化学形式。化合物也涵盖非对映异构体以及光学异构体,例如包括外消旋混合物的对映异构体混合物,以及由于某些化合物中的结构不对称性而产生的个别对映异构体和非对映异构体。通过应用本领域专业人员众所周知的多种方法实现个别异构体的分离或个别异构体的选择性合成。除非另外指示,否则当所公开的化合物通过未指定立体化学的结构命名或描绘并且具有一个或多个手性中心时,应理解为表示所述化合物的所有可能的立体异构体。

[0186] 本公开包括所有药学上可接受的经同位素标记的式I化合物,其中一个或多个原子被具有相同原子数但原子质量或质量数不同于在自然界中占绝大多数的原子质量或质量数的原子代替。适合于包括在本公开化合物中的同位素的实例包括(但不限于)氢的同位素,例如^{2}H(氘)和^{3}H(氚);碳的同位素,例如^{11}C、^{13}C和^{14}C;氯的同位素,例如^{36}Cl;氟的同位素,例如^{18}F;碘的同位素,例如^{123}I和^{125}I;氮的同位素,例如^{13}N和^{15}N;氧的同位素,例如^{15}O、^{17}O和^{18}O;磷的同位素,例如^{32}P;和硫的同位素,例如^{35}S。

[0187] 术语“施用(administration/administering)”是指向脊椎动物或无脊椎动物提供一个剂量的化合物或药物组合物的方法,所述脊椎动物或无脊椎动物包括哺乳动物、禽类、鱼类或两栖动物,其中施用方法是例如经口、经皮下、经静脉内、经淋巴管内、经鼻内、经

局部、透皮、经腹膜内、经肌肉内、经肺内、经阴道、经直肠、经耳(ontologically)、经耳神经(neuro-otologically)、经眼内、经结膜下、经由眼前房注射、经玻璃体内、经腹膜内、经鞘内、经囊内(intracystically)、经胸膜内、经由创口冲洗、经颊内、经腹内、经关节内、经耳内、经支气管内、经囊内(intracapsularly)、经脑膜内、经由吸入、经由气管内或支气管内滴注、经由向肺空洞中直接滴注、经脊椎内、经滑膜内、经胸内、经由胸廓造口冲洗、经硬膜外、经鼓室内、经脑池内、经血管内、经脑室内、经骨内、经由对经感染骨骼进行冲洗或经由作为与假体装置的任何掺合物的一部分施加。施用方法可以根据各种因素而变,例如药物组合物的组分、疾病部位、所涉及的疾病和疾病的严重程度。

[0188] 如本文所用的“诊断”是有助于鉴定或表征健康或疾病状态的化合物、方法、系统或装置。诊断可用于如本领域中已知的标准测定中。

[0189] 术语“哺乳动物”是以其常见生物学意义使用。因此,其具体地包括人类、牛、马、猴、犬、猫、小鼠、大鼠、牛、绵羊、猪、山羊和非人类灵长类动物,但还包括许多其他物种。

[0190] 术语“药学上可接受的载体”、“药学上可接受的稀释剂”和“药学上可接受的赋形剂”包括在生物学上或其他方面无不良作用的任何和所有溶剂、助溶剂、络合剂、分散介质、包衣、等张剂和吸收延迟剂等。此类介质和药剂用于药学活性物质的用途是本领域中众所周知的。除非任何常规介质或药剂与活性成分不相容,否则预期其在治疗组合物中的用途。补充活性成分也可并入组合物中。此外,也可包括如本领域中常用的各种佐剂。这些和其他此类化合物描述于文献中,例如Merck Index,Merck&Company,Rahway,NJ。关于将各种组分纳入药物组合物中的考虑描述于例如Gilman等人(编)(2010);Goodma n和Gilman:The Pharmacological Basis of Therapeutics,第12版,The McGraw-Hill Companies。

[0191] 术语“药学上可接受的盐”是指保留本文所提供的化合物的生物学有效性和特性并且在生物学上或其他方面无不良作用的盐。在许多情况下,本文所提供的化合物能够借助于氨基和/或羧基或其类似基团的存在形成酸盐和/或碱盐。许多此类盐在本领域中是已知的,例如,如WO 87/05297中所描述。药学上可接受的酸加成盐可由无机酸和有机酸形成。可衍生出盐的无机酸包括例如盐酸、氢溴酸、硫酸、硝酸、磷酸等。可衍生出盐的有机酸包括例如乙酸、丙酸、乙醇酸、丙酮酸、草酸、顺丁烯二酸、丙二酸、丁二酸、反丁烯二酸、酒石酸、柠檬酸、苯甲酸、肉桂酸、杏仁酸、甲磺酸、乙磺酸、对甲苯磺酸、水杨酸等。药学上可接受的碱加成盐可由无机碱和有机碱形成。可衍生出盐的无机碱包括例如钠、钾、锂、铵、钙、镁、铁、锌、铜、锰、铝等;尤其优选的是铵盐、钾盐、钠盐、钙盐和镁盐。可衍生出盐的有机碱包括例如伯胺、仲胺和叔胺、包括天然存在的被取代胺的被取代胺、环胺、碱性离子交换树脂等,具体而言,例如异丙胺、三甲胺、二乙胺、三乙胺、三丙胺和乙醇胺。

[0192] 如本文所用的“患者”意指人类或非人类哺乳动物,例如犬、猫、小鼠、大鼠、牛、绵羊、猪、山羊、非人类灵长类动物或禽类,例如鸡,以及任何其他脊椎动物或无脊椎动物。在一些实施方案中,患者为人类。

[0193] 如本文所提供的化合物的“治疗有效量”为足以达到所要生理效应并且可根据疾病状况的性质和严重程度以及化合物的效能而变化的治疗有效量。“治疗有效量”也旨在包括一种或多种式I化合物与一种或多种有效治疗本文所描述的疾病和/或疾患的其他药剂的组合。化合物组合可为协同组合。如例如Chou和Talalay,Advances in Enzyme Regulation(1984),22,27-55所描述的协同作用在化合物组合施用时的效应大于化合物作

为单一药剂单独施用时的累加效应时出现。一般而言,协同效应在化合物的次佳浓度下得到最清晰展现。应了解,与治疗活动性疾病相比,可采用不同浓度进行预防。此量可进一步根据患者的身高、体重、性别、年龄和病史而定。

[0194] 治疗效果在一定程度上减轻疾病的一种或多种症状。

[0195] 如本文所用的“治疗(treat/treatment/treating)”是指针对治疗目的施用如本文所提供的化合物或药物组合物。术语“治疗性处理(therapeutic treatment)”是指向已患有疾病的患者施用治疗剂,因此产生治疗有益的效果,例如改善现有症状;改善症状的潜在代谢诱因;推迟或预防病症的进一步发展;和/或降低将产生或预期会产生的症状的严重程度。

[0196] 如本文所用,“药物洗脱”和/或控制释放是指任何和所有机制,例如并入药物洗脱材料中的药物随时间推移从其传送至周围身体组织中的扩散、迁移、渗透和/或解吸附。

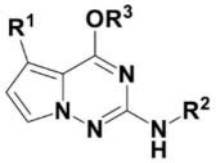
[0197] 如本文所用,“药物洗脱材料”和/或控制释放材料是指任何能够获取并保留所需形状或构型并且一种或多种药物可并入其中并且并入的药物能够随时间推移洗脱的天然、合成或半合成材料。

[0198] 如本文所用的“可洗脱药物”是指能够随时间推移从药物洗脱材料通过的任何药物或药物组合,其中所述药物洗脱材料并入周围身体区域中。

[0199] 化合物

[0200] 本文所描述的化合物和组合物可用于抑制DYRK1A以用于治疗涉及DYRK1A过表达的病症或疾病,例如神经疾病或病症、癌症、认知缺陷、膝骨性关节炎、肌腱病变、病毒感染、单细胞寄生虫感染和运动缺陷。

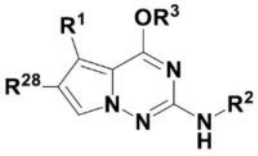
[0201] 本公开的一些实施方案包括式I化合物:

[0202] 

I

[0203] 或其盐、药学上可接受的盐或前药。

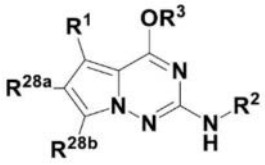
[0204] 本公开的一些实施方案包括式I化合物:

[0205] 

I

[0206] 或其盐、药学上可接受的盐或前药。

[0207] 本公开的一些实施方案包括式I化合物:

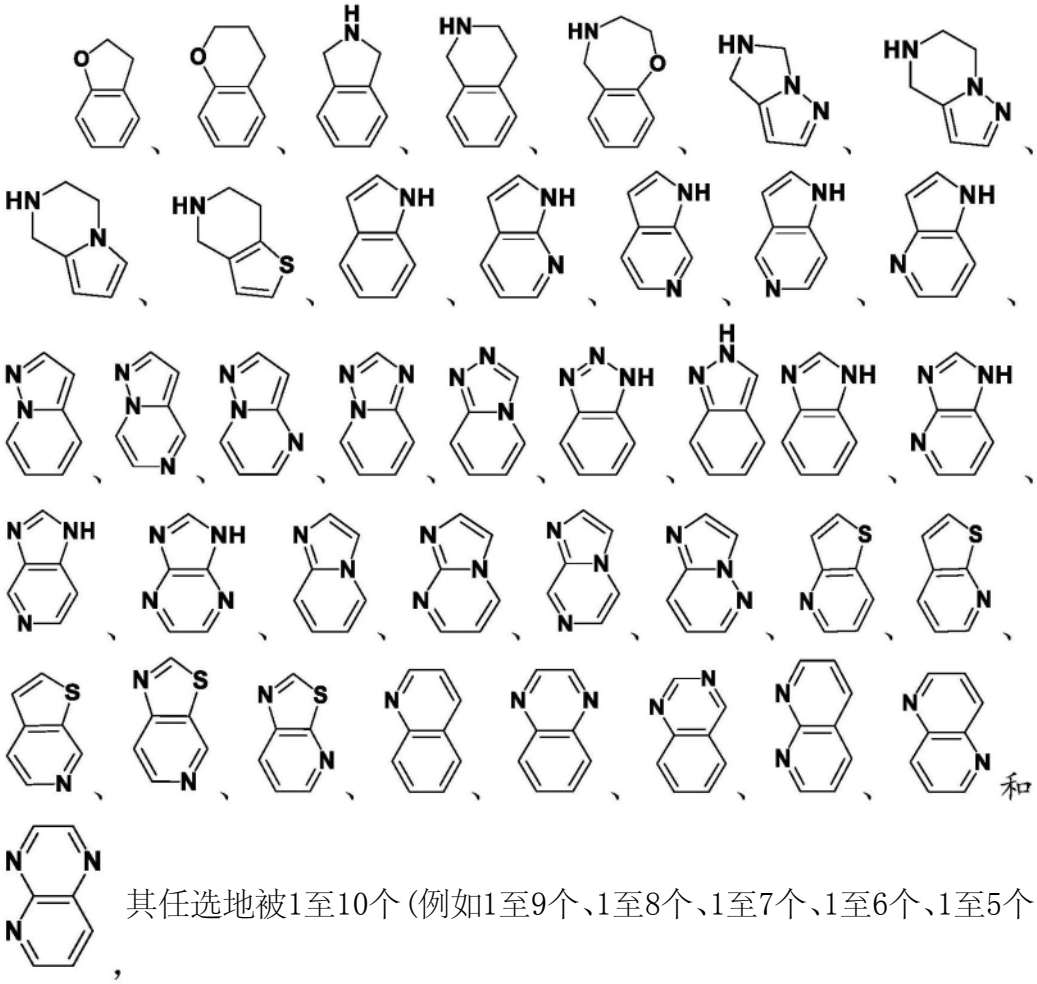
[0208] 

I

[0209] 或其盐、药学上可接受的盐或前药。

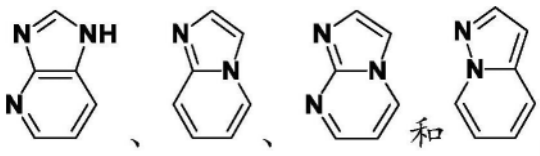
[0210] 在式I的一些实施方案中，R^1为任选地被1至10个R^4取代的杂芳基。在一些实施方案中，R^1为任选地被1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个或1个R^4取代的杂芳基。

[0211] 在式I的一些实施方案中，R^1选自由以下组成的杂芳基：

[0212] 

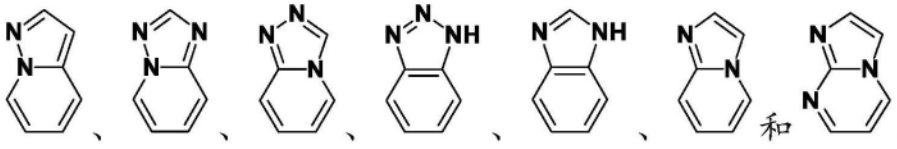
其任选地被1至10个(例如1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^4取代。

[0213] 在式I的一些实施方案中，R^1选自由以下组成的杂芳基：

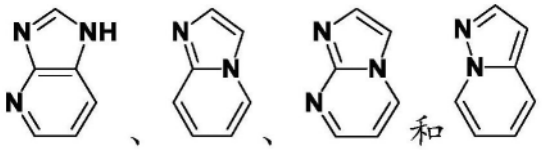
[0214] 

其任选地被1至10个(例如1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^4取代。

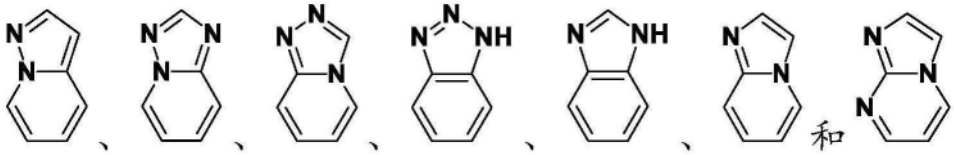
[0215] 在式I的一些实施方案中，R^1选自由以下组成的杂芳基：

[0216] 其任选地被1至10个(例如1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^4取代。

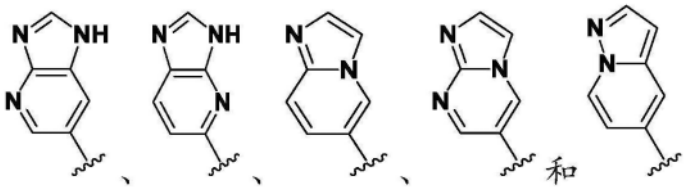
[0217] 在式I的一些实施方案中,R^1选自由以下组成的杂芳基:

[0218] 其任选地被1至3个(例如1至2个、1个)R^4取代。

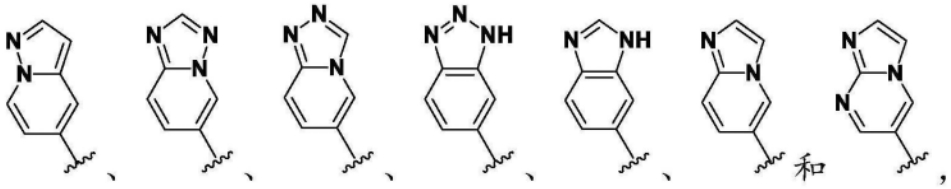
[0219] 在式I的一些实施方案中,R^1选自由以下组成的杂芳基:

[0220] 其任选地被1至3个(例如1至2个、1个)R^4取代。

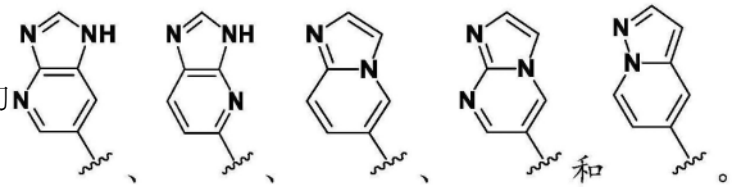
[0221] 在式I的一些实施方案中,R^1选自由以下组成的组:

[0222] 其任选地被1至3个R^4取代。

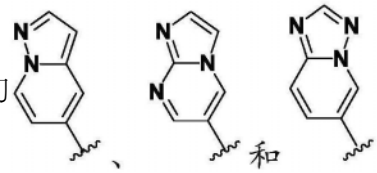
[0223] 在式I的一些实施方案中,R^1选自由以下组成的组:

[0224] 其任选地被1至3个R^4取代。

[0225] 在式I的一些实施方案中,R^1选自由以下组成的组:

[0226] 未被取代的。

[0227] 在式I的一些实施方案中,R^1选自由以下组成的组:

[0228] 未被取代的。

[0229] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$OR^5、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^6取代的-(C_{1-5}亚烷基)$_p$杂环基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^7取代的-杂芳基,和任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^8取代的-(C_{1-5}亚烷基)$_p$碳环基,其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个(例如,1至4个、1至3个、1至2个、1个)卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0230] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$OR^5、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^6取代的-(C_{1-5}亚烷基)$_p$杂环基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{26}取代的-(C_{1-5}亚烷基)$_p$芳基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^7取代的-(C_{1-5}亚烷基)$_p$杂芳基,和任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^8取代的-(C_{1-5}亚烷基)$_p$碳环基,其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0231] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$OR^5、-(C_{1-5}亚烷基)CN、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^6取代的-(C_{1-5}亚烷基)$_p$杂环基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{26}取代的-(C_{1-5}亚烷基)$_p$芳基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^7取代的-(C_{1-5}亚烷基)$_p$杂芳基,和任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^8取代的-(C_{1-5}亚烷基)$_p$碳环基,其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个卤素(例如,F、Cl、Br、I)和/或1至3个未被取代的-(C_{1-3}烷基)取代。

[0232] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)、-(C_{1-2}亚烷基)$_p$OR^5、任选地被1至3个(例如,1至2个、1个)R^6取代的-(C_{1-2}亚烷基)$_p$杂环基,和任选地被1至3个(例如,1至2个、1个)R^8取代的-(C_{1-2}亚烷基)$_p$碳环基,其中每个-(C_{1-2}亚烷基)独立地任选地被1至2个卤素取代。

[0233] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)、任选地被1至4个R^6取代的-杂环基、任选地被1至2个R^{26}取代的-(C_{1-2}亚烷基)$_p$芳基、任选地被1至2个R^7取代的-(C_{1-2}亚烷基)$_p$杂芳基,和任选地被1至4个R^8取代的-(C_{1-2}亚烷基)$_p$碳环基,其中每个-(C_{1-2}亚烷基)独立地任选地被1至2个卤素取代。

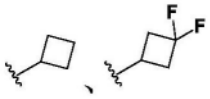
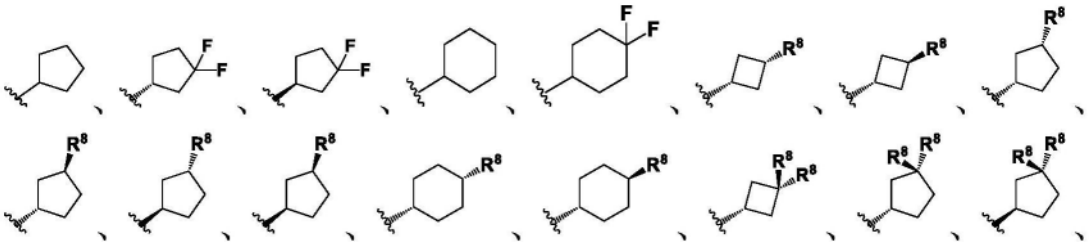
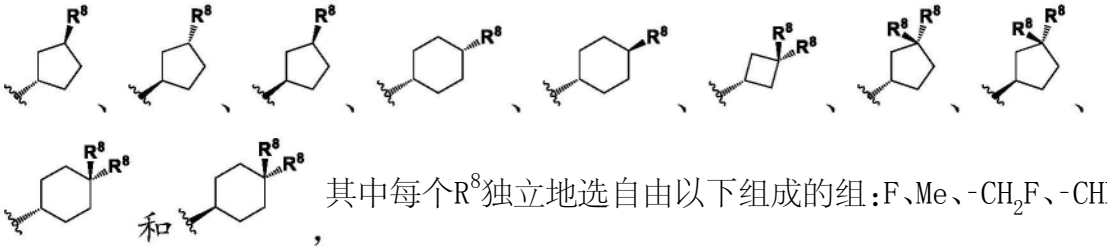
[0234] 在式I的一些实施方案中,R^2为任选地被1至3个R^8取代的-(C_{1-2}亚烷基)$_p$碳环基,其中所述-(C_{1-2}亚烷基)任选地被1至2个卤素取代,并且其中所述碳环基选自由以下组成的

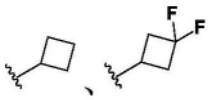
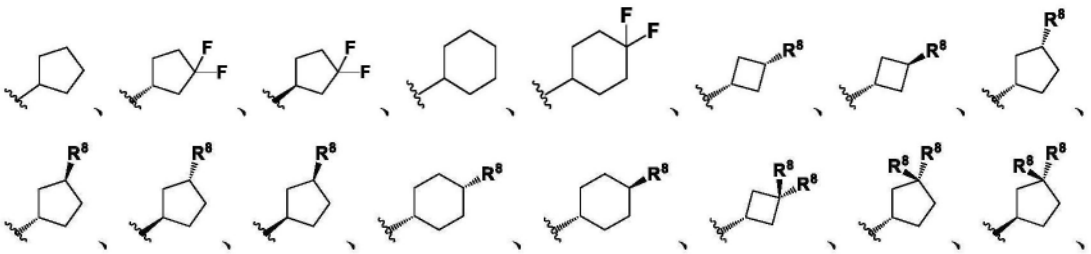
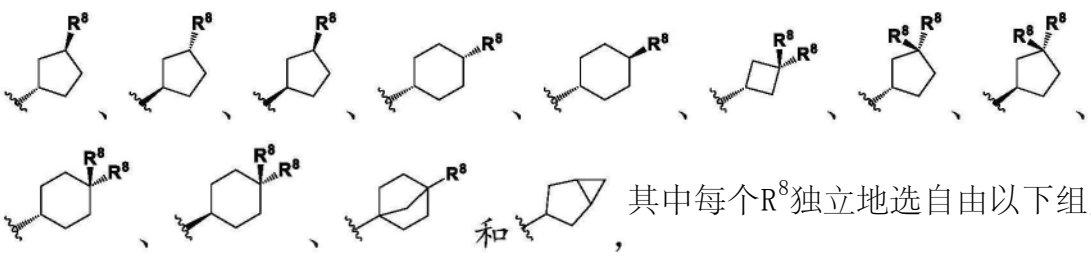
组:环丙基、环丁基、环戊基、环己基和螺[3.3]庚烷基。

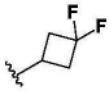
[0235] 在式I的一些实施方案中,R^2为任选地被1至3个R^8取代的-$(C_{1-2}$亚烷基$)_p$碳环基,其中所述-$(C_{1-2}$亚烷基)任选地被1至2个卤素(例如,F、Cl)取代,并且其中所述碳环基选自由以下组成的组:环丙基、环丁基、环戊基、环己基、双环[3.1.0]己烷、双环[2.2.1]庚烷和螺[3.3]庚烷基。

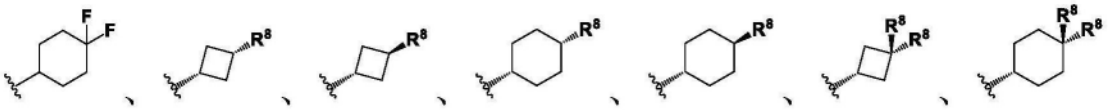
[0236] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-$(C_{1-4}$烷基)、未被取代的-$(C_{2-4}$烯基)、未被取代的-$(C_{2-4}$炔基)、未被取代的-$(C_{1-4}$卤代烷基)、-$(C_{2-4}$亚烷基)OR^5、-$(C_{2-4}$亚烷基)CN、任选地被1至3个R^6取代的-$(C_{1-2}$亚烷基$)_p$杂环基、任选地被1至2个R^{26}取代的-$(C_{1-2}$亚烷基$)_p$芳基、任选地被1至2个R^7取代的-$(C_{1-2}$亚烷基$)_p$杂芳基,和任选地被1至3个R^8取代的-$(C_{1-2}$亚烷基$)_p$碳环基,其中每个-$(C_{1-2}$亚烷基)独立地任选地被1至2个卤素(例如,F、Cl)取代。

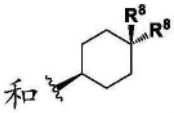
[0237] 在式I的一些实施方案中,R^2选自由以下组成的组:未被取代的-$(C_{1-5}$卤代烷基)、-$(C_{1-4}$亚烷基)OH、-$(C_{1-4}$亚烷基)OMe和-$(C_{1-4}$亚烷基)CN。

[0238] 在式I的一些实施方案中,R^2选自由以下组成的组:、、、、和,其中每个R^8独立地选自由以下组成的组:F、Me、-CH_2F、-CHF_2、-CF_3、-CH_2OH、-CH_2OMe、-OH、-OMe、-OEt、-OCD_3、-OCF_3、-OCH_2CH_2F、-OCH_2CHF_2、-OCH_2CF_3、-OCH_2CH_2OMe、-OCH_2CH_2OH、-NH_2、-NHMe和-NMe_2。

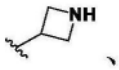
[0239] 在式I的一些实施方案中,R^2选自由以下组成的组:、、、、和,其中每个R^8独立地选自由以下组成的组:F、Me、-CH_2F、-CHF_2、-CF_3、-CH_2OH、-CH_2OMe、-OH、-OMe、-OEt、-OCD_3、-OCF_3、-OCH_2CH_2F、-OCH_2CHF_2、-OCH_2CF_3、-OCH_2CH_2OMe、-OCH_2CH_2OH、-CN、-NH_2、-NHMe和-NMe_2。

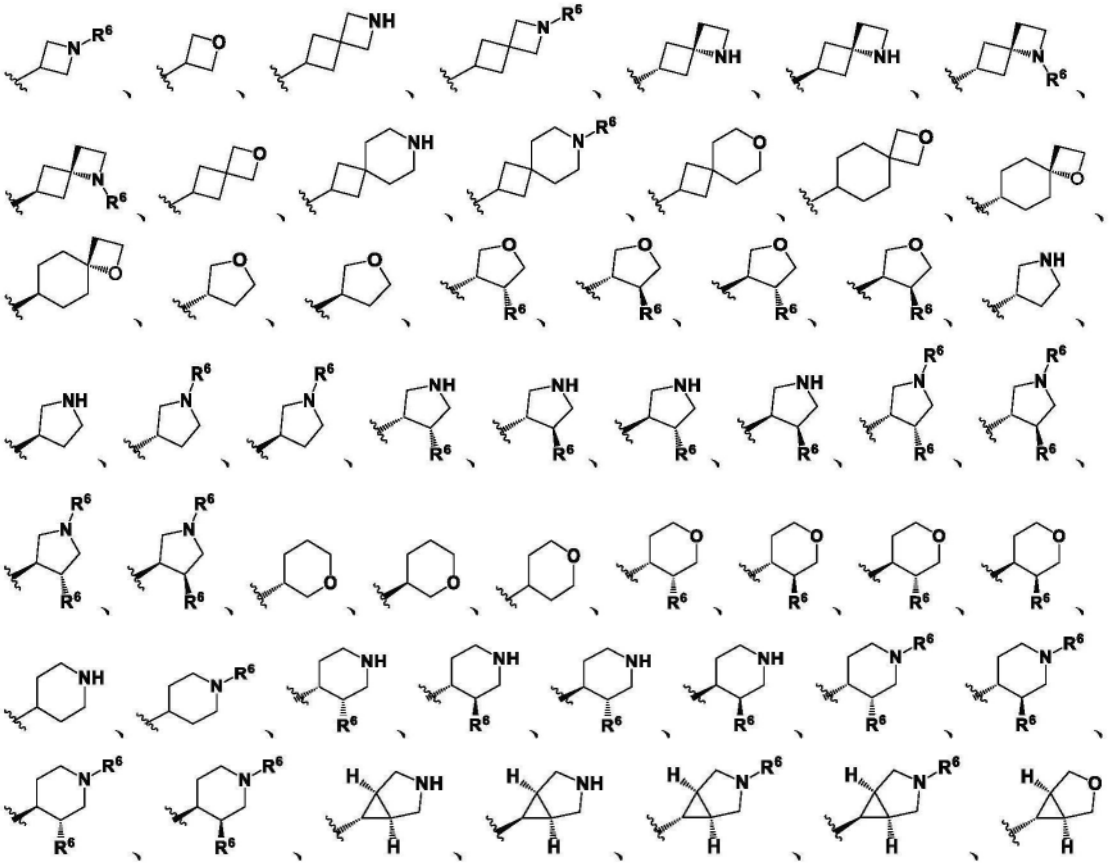
[0240] 在式I的一些实施方案中,R^2选自由以下组成的组:、

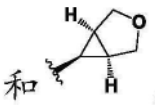


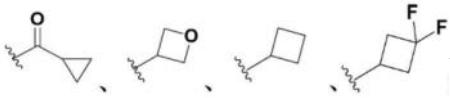
和,其中每个R^8独立地选自由以下组成的组:F、Me、-CHF_2、-CH_2OMe、-OH、-OMe、-OCD_3、-OCH_2CHF_2和-OCH_2CH_2OMe。

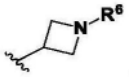
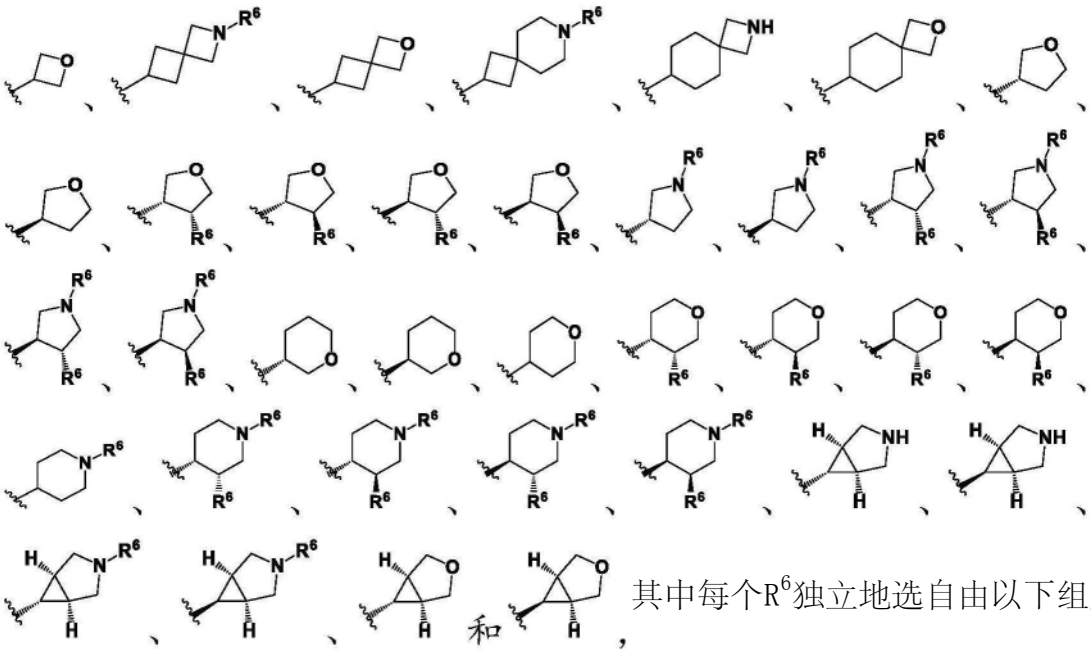
[0241] 在式I的一些实施方案中,R^2为任选地被1至3个R^6取代的-(C_{1-2}亚烷基)$_p$杂环基,其中-(C_{1-5}亚烷基)任选地被1至2个卤素取代,并且其中所述杂环基选自由以下组成的组:氧杂环丁烷基、四氢呋喃基、四氢吡喃基、氮杂环丁烷基、吡咯烷基、哌啶基、吗啉基、哌嗪基、氧杂螺[3.3]庚烷基和氧杂螺[3.3]壬烷基。

[0242] 在式I的一些实施方案中,R^2选自由以下组成的组:、



和,其中每个R^6独立地选自由以下组成的组:F、Me、Et、iPr、iBu、-CH_2F、-CHF_2、-CF_3、-CH_2OH、-CH_2OMe、-OH、-OMe、-OEt、-OCD_3、-OCF_3、-CH_2CH_2F、-CH_2CHF_2、-CH_2CF_3、-$CH_2CH_2CF_3$、-CH_2CH_2OMe、-CH_2CH_2OH、-C(=O)Me、-C(=O)Et、-C(=O)iPr、


和-SO_2Me;条件是F、-OH、-OMe、-OEt、-OCD_3和-OCF_3不连接至N。

[0243] 在式I的一些实施方案中,R^2选自由以下组成的组:、其中每个R^6独立地选自由以下组成的组:F、Me、iBu,-OH、-OMe、-CH_2CH_2F、-CH_2CHF_2、-CH_2CF_3、-$CH_2CH_2CF_3$、-CH_2CH_2OMe、-CH_2CH_2OH、-C(=O)Me、-C(=O)Et和-C(=O)iPr;条件是F、-OH、-OMe不连接至N。

[0244] 在式I的一些实施方案中,R^2为任选地被1至2个R^7取代的-杂芳基,其中所述杂芳基为吡唑基。

[0245] 在式I的一些实施方案中,R^2为任选地被1至2个R^7取代的-(C_{1-2}亚烷基)杂芳基,其中所述杂芳基为吡啶。

[0246] 在式I的一些实施方案中,R^2为任选地被1至2个R^7取代的-(C_{1-2}亚烷基)芳基,其中所述芳基为苯基。

[0247] 在式I的一些实施方案中,R^3选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0248] 在式I的一些实施方案中,R^3选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基),和任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{18}取代的-杂环基。

[0249] 在式I的一些实施方案中,R^3选自由以下组成的组:H、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{2-5}烯基)、未被取代的-(C_{2-5}炔基)和未被取代的-(C_{1-5}卤代烷基)。

[0250] 在式I的一些实施方案中,R^3选自由以下组成的组:未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)和任选地被1至2个R^{18}取代的-杂环基。

[0251] 在式I的一些实施方案中,R^3选自由以下组成的组:H、未被取代的-(C_{1-3}烷基)和未

被取代的-(C_{1-3}卤代烷基)。

[0252] 在式I的一些实施方案中,R^3为未被取代的-(C_{1-3}烷基)。

[0253] 在式I的一些实施方案中,R^3为Me。

[0254] 在式I的一些实施方案中,R^3为未被取代的-(C_{1-3}卤代烷基)。

[0255] 在式I的一些实施方案中,R^3选自由以下组成的组:-CH_2F、-CHF_2、-CF_3、-CH_2CH_2F、-CH_2CHF_2和-CH_2CF_3。

[0256] 在式I的一些实施方案中,R^3为未被取代的-杂环基。

[0257] 在式I的一些实施方案中,R^3为未被取代的-(3元至4元杂环基)。

[0258] 在式I的一些实施方案中,R^3为未被取代的-(4元杂环基)。

[0259] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_p$$OR^9$、-($C_{1-5}$亚烷基)CN、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{10}取代的-(C_{1-5}亚烷基)$_p$杂环基、任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{11}取代的-碳环基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{20}取代的-(C_{1-5}亚烷基)$_p$杂芳基、-(C_{1-5}亚烷基)$_p$C(=O)N(R^{12})$_2$和-C(=O)R^{13},其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个(例如,1至4个、1至3个、1至2个、1个)卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0260] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{2-5}烯基)、未被取代的-(C_{2-5}炔基)、未被取代的-(C_{1-5}卤代烷基)、-(C_{1-4}亚烷基)$_p$$OR^9$、-($C_{1-2}$亚烷基)$_p$$OR^9$、-($C_{1-4}$亚烷基)CN、-($C_{1-2}$亚烷基)CN、任选地被1至2个$R^{10}$取代的-($C_{1-2}$亚烷基)$_p$杂环基、任选地被1至2个$R^{11}$取代的-碳环基、任选地被1至2个$R^{20}$取代的-($C_{1-2}$亚烷基)$_p$杂芳基、-($C_{1-2}$亚烷基)$_p$C(=O)N($R^{12}$)$_2$和-C(=O)$R^{13}$,其中每个-($C_{1-2}$亚烷基)或-($C_{1-4}$亚烷基)独立地任选地被1至2个卤素取代。

[0261] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、未被取代的-(C_{2-9}卤代烯基)、-(C_{1-5}亚烷基)$_p$$OR^9$、-($C_{1-5}$亚烷基)$_p$CN、任选地被1至10个$R^{10}$取代的-($C_{1-5}$亚烷基)$_p$杂环基、任选地被1至12个$R^{11}$取代的-碳环基、任选地被1至10个$R^{20}$取代的-($C_{1-5}$亚烷基)$_p$杂芳基、-($C_{1-5}$亚烷基)$_p$C(=O)N($R^{12}$)$_2$和-C(=O)$R^{13}$,其中每个-($C_{1-5}$亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代。

[0262] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素(例如,F、Cl)、未被取代的-(C_{1-4}烷基)、未被取代的-(C_{2-4}烯基)、未被取代的-(C_{2-4}炔基)、未被取代的-(C_{1-4}卤代烷基)、未被取代的-(C_{2-4}卤代烯基)、-(C_{1-4}亚烷基)$_p$$OR^9$、-($C_{1-2}$亚烷基)$OR^9$、-($C_{1-4}$亚烷基)CN、-($C_{1-2}$亚烷基)CN、任选地被1至2个$R^{10}$取代的-($C_{1-2}$亚烷基)$_p$杂环基、任选地被1至2个$R^{11}$取代的-碳环基、任选地被1至2个$R^{20}$取代的-($C_{1-2}$亚烷基)$_p$杂芳基、-($C_{1-2}$亚烷基)$_p$C(=O)N($R^{12}$)$_2$和-C(=O)$R^{13}$,其中每个-($C_{1-2}$亚烷基)或-($C_{1-4}$亚烷基)独立地任选地被1至2个卤素(例如,F、Cl)取代。

[0263] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:F、Cl、未被取代的-

(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)、-(C_{1-4}亚烷基)$_p$OH、-(C_{1-2}亚烷基)$_p$OMe、-(C_{1-4}亚烷基)CN、-(C_{1-2}亚烷基)CN、任选地被1至2个R^{10}取代的-(CH_2)$_p$杂环基、任选地被1至2个R^{11}取代的-碳环基、任选地被1至2个R^{20}取代的-(CH_2)$_p$杂芳基、-(CH_2)C(=O)N(Me)$_2$和-C(=O)R^{13},其中每个-(C_{1-2}亚烷基)或-(C_{1-4}亚烷基)独立地任选地被1至2个卤素取代。

[0264] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-4}烷基)、未被取代的-(C_{1-4}卤代烷基)、任选地被1至3个(例如,1至2个、1个)R^{10}取代的-杂环基和任选地被1至3个(例如,1至2个、1个)R^{11}取代的-碳环基。

[0265] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素、未被取代的-(C_{1-3}烷基)、未被取代的-(C_{1-3}卤代烷基)、-(C_{1-3}亚烷基)$_p$OR^9、任选地被1至2个R^{10}取代的-杂环基、任选地被1至2个R^{11}取代的-碳环基和-C(=O)R^{13}。

[0266] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:卤素、未被取代的-(C_{1-3}烷基)、未被取代的-(C_{1-3}卤代烷基)、-(C_{1-3}亚烷基)OH、-(C_{1-3}亚烷基)OMe、-CN和-C(=O)N(R^{12})$_2$。

[0267] 在式I的一些实施方案中,每个R^4独立地选自由以下组成的组:氯、甲基、乙基、异丙基、2-氟乙基、2,2-二氟乙基、甲氧基、甲氧基甲基、四氢吡喃基、二氟环丁基和(吡咯烷-1-基)甲酮。

[0268] 在式I的一些实施方案中,每个R^5独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0269] 在式I的一些实施方案中,每个R^5独立地选自由以下组成的组:H、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{2-5}烯基)、未被取代的-(C_{2-5}炔基)和未被取代的-(C_{1-5}卤代烷基)。

[0270] 在式I的一些实施方案中,每个R^5独立地选自由以下组成的组:H、未被取代的-(C_{1-3}烷基)和未被取代的-(C_{1-3}卤代烷基)。

[0271] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{16}取代的-杂环基、-(C_{1-5}亚烷基)$_p$OR^{21}、-SO_2R^{23}和-C(=O)R^{24},其中所述-(C_{1-5}亚烷基)任选地被1至5个(例如,1至4个、1至3个、1至2个、1个)卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0272] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{16}取代的-杂环基、任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{17}取代的-碳环基、-(C_{1-5}亚烷基)$_p$OR^{21}、-SO_2R^{23}和-C(=O)R^{24},其中-(C_{1-5}亚烷基)任选地被1至5个卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0273] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、

任选地被1至10个R^{16}取代的-杂环基、任选地被1至12个R^{17}取代的-碳环基、-(C_{1-5}亚烷基)$_pOR^{21}$、-(C_{1-5}亚烷基)CN、-SO_2R^{23}和-C(=O)R^{24},其中-(C_{1-5}亚烷基)任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代。

[0274] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:F、Cl、未被取代的-(C_{1-4}烷基)、未被取代的-(C_{1-4}卤代烷基)、任选地被1至2个R^{16}取代的-杂环基、-(C_{1-2}亚烷基)$_pOR^{21}$、-(C_{1-2}亚烷基)CN、-SO_2R^{23}和-C(=O)R^{24},其中-(C_{1-2}亚烷基)任选地被1至2个卤素(例如,F、Cl)取代。

[0275] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:F、Cl、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)、任选地被1至2个R^{16}取代的-杂环基、-(C_{1-2}亚烷基)$_pOR^{21}$、-SO_2R^{23}和-C(=O)R^{24},其中-(C_{1-2}亚烷基)任选地被1至2个卤素取代。

[0276] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:F、Cl、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)、任选地被1至2个R^{16}取代的-杂环基、-OH、-OMe、-SO_2Me和-C(=O)R^{24}。

[0277] 在式I的一些实施方案中,每个R^6独立地选自由以下组成的组:F、Cl、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{1-5}卤代烷基)、任选地被1至2个R^{16}取代的-杂环基、任选地被1至4个R^{17}取代的-碳环基和-C(=O)R^{24}。

[0278] 在式I的一些实施方案中,连接至同一碳原子的两个R^6一起形成羰基。

[0279] 在式I的一些实施方案中,每个R^7独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-OMe。

[0280] 在式I的一些实施方案中,每个R^7独立地选自由以下组成的组:F、Cl、Me、CF_3和-OMe。

[0281] 在式I的一些实施方案中,每个R^8独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-N(R^{14})$_2$、-(C_{1-5}亚烷基)$_pOR^{15}$、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{16}取代的-(C_{1-5}亚烷基)$_p$杂环基、-C(=O)R^{22}和-NHC(=O)R^{23},其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个(例如,1至4个、1至3个、1至2个、1个)卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0282] 在式I的一些实施方案中,每个R^8独立地选自由以下组成的组:卤素、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-N(R^{14})$_2$、-(C_{1-5}亚烷基)$_pOR^{15}$、-CN、任选地被1至10个R^{16}取代的-(C_{1-5}亚烷基)$_p$杂环基、-C(=O)R^{22}和-NR^{14}C(=O)R^{23},其中每个-(C_{1-5}亚烷基)独立地任选地被1至5个卤素和/或1至3个未被取代的-(C_{1-3}烷基)取代。

[0283] 在式I的一些实施方案中,每个R^8独立地选自由以下组成的组:卤素(例如,F、Cl)、未被取代的-(C_{1-4}烷基)、未被取代的-(C_{2-4}烯基)、未被取代的-(C_{2-4}炔基)、未被取代的-(C_{1-4}卤代烷基)、-N(R^{14})$_2$、-(C_{1-2}亚烷基)$_pOR^{15}$、-CN、任选地被1至2个R^{16}取代的-(C_{1-2}亚烷基)$_p$杂环基、-C(=O)R^{22}和-NHC(=O)R^{23},其中每个-(C_{1-2}亚烷基)独立地任选地被1至2个卤素(例如,F、Cl)取代。

[0284] 在式I的一些实施方案中,每个R^8独立地选自由以下组成的组:卤素、未被取代的-(C_{1-5}烷基)、未被取代的-(C_{2-5}烯基)、未被取代的-(C_{2-5}炔基)、未被取代的-(C_{1-5}卤代烷基)、-$N(R^{14})_2$、-(C_{1-2}亚烷基)$_pOR^{15}$、任选地被1至2个R^{16}取代的-(C_{1-2}亚烷基)$_p$杂环基、-C(=O)R^{22}和-NHC(=O)R^{23},其中每个-(C_{1-2}亚烷基)独立地任选地被1至2个卤素取代。

[0285] 在式I的一些实施方案中,每个R^9独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0286] 在式I的一些实施方案中,每个R^{10}独立地选自由以下组成的组:卤素(例如F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0287] 在式I的一些实施方案中,每个R^{11}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0288] 在式I的一些实施方案中,每个R^{12}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)、任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{17}取代的-(C_{1-5}亚烷基)$_p$碳环基、任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{18}取代的-杂环基,和任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{19}取代的-杂芳基,其中-(C_{1-5}亚烷基)任选地被1至5个(例如,1至4个、1至3个、1至2个、1个)卤素(例如,F、Cl、Br、I)和/或1至3个(例如,1至2个、1个)未被取代的-(C_{1-3}烷基)取代。

[0289] 在式I的一些实施方案中,每个R^{13}为任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{18}取代的-杂环基。

[0290] 在式I的一些实施方案中,每个R^{14}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0291] 在式I的一些实施方案中,每个R^{15}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)和-(C_{1-5}亚烷基)$_pOR^{21}$。

[0292] 在式I的一些实施方案中,每个R^{16}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0293] 在式I的一些实施方案中,每个R^{16}独立地选自由以下组成的组:卤素、-CN、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基),和任选地被1至12个R^{27}取代的-碳环基。

[0294] 在式I的一些实施方案中,连接至同一碳原子的两个R^{16}一起形成羰基。

[0295] 在式I的一些实施方案中,每个R^{17}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、-OMe、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0296] 在式I的一些实施方案中,每个R^{18}独立地选自由以下组成的组:卤素(例如F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0297] 在式I的一些实施方案中,每个R^{19}独立地选自由以下组成的组:卤素(例如F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0298] 在式I的一些实施方案中,每个R^{20}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0299] 在式I的一些实施方案中,每个R^{21}独立地选自由以下组成的组:H、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0300] 在式I的一些实施方案中,每个R^{22}独立地选自由以下组成的组:任选地被1至10个(例如,1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{18}取代的-杂环基、-$N(R^{12})_2$和-OR^{21}。

[0301] 在式I的一些实施方案中,每个R^{23}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0302] 在式I的一些实施方案中,每个R^{23}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-(C_{1-5}亚烷基)$_pOR^{21}$和任选地被1至12个R^{25}取代的-碳环基。

[0303] 在式I的一些实施方案中,每个R^{24}独立地选自由以下组成的组:未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)、未被取代的-(C_{1-9}卤代烷基)、-OR^{23}和任选地被1至12个(例如,1至11个、1至10个、1至9个、1至8个、1至7个、1至6个、1至5个、1至4个、1至3个、1至2个、1个)R^{25}取代的-碳环基。

[0304] 在式I的一些实施方案中,每个R^{25}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0305] 在式I的一些实施方案中,每个R^{26}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0306] 在式I的一些实施方案中,每个R^{27}独立地选自由以下组成的组:卤素(例如,F、Cl、Br、I)、未被取代的-(C_{1-9}烷基)、未被取代的-(C_{2-9}烯基)、未被取代的-(C_{2-9}炔基)和未被取代的-(C_{1-9}卤代烷基)。

[0307] 在式I的一些实施方案中,R^{28}独立地选自由以下组成的组:H和卤素(例如,F、Cl、Br、I)。

[0308] 在式I的一些实施方案中,R^{28}独立地选自由以下组成的组:H和卤素(例如,F、Cl)。

[0309] 在式I的一些实施方案中,R^{28}独立地选自由以下组成的组:H和F。

[0310] 在式I的一些实施方案中,R^{28a}独立地选自由以下组成的组:H和卤素(例如,F、Cl、Br、I)。

[0311] 在式I的一些实施方案中,R^{28a}独立地选自由以下组成的组:H和卤素(例如,F、Cl)。

[0312] 在式I的一些实施方案中,R^{28a}独立地选自由以下组成的组:H和F。

[0313] 在式I的一些实施方案中,R^{28b}独立地选自由以下组成的组:H和D。

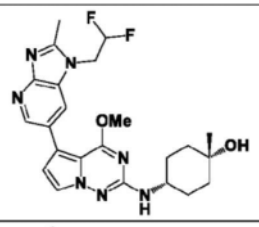
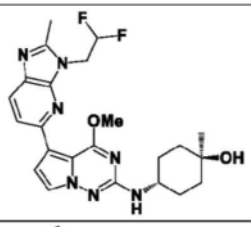
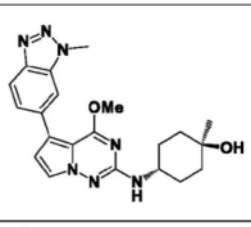
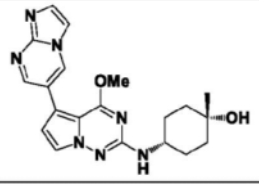
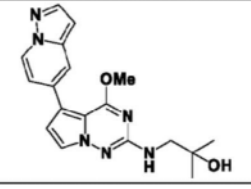
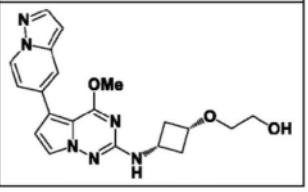
[0314] 在式I的一些实施方案中,每个p独立地为0或1。

[0315] 在式I的一些实施方案中,每个H原子任选地独立地被^{2}H(D)(氘)代替。

[0316] 说明性的式I化合物示于表1中。

[0317] 表1.

[0318]

1		2		3	
4		5		6	

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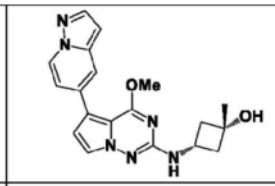
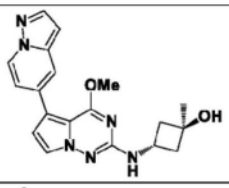
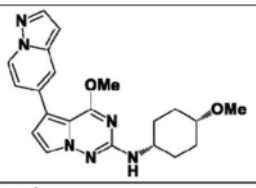
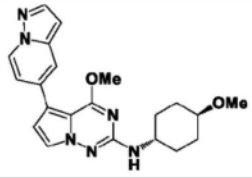
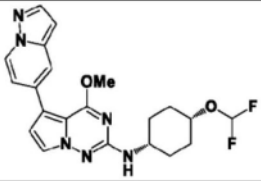
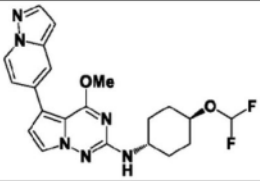
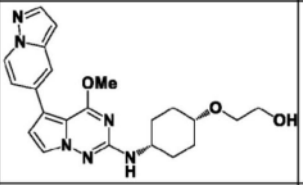
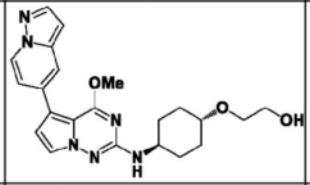
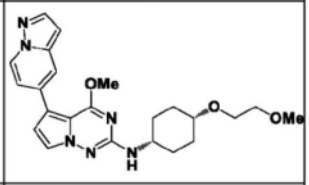
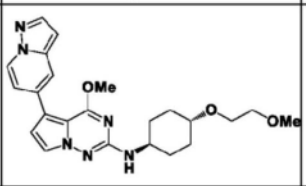
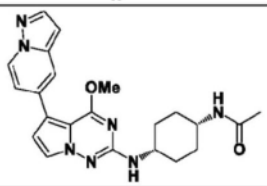
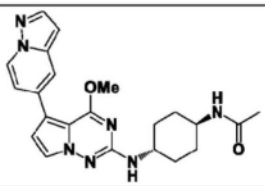
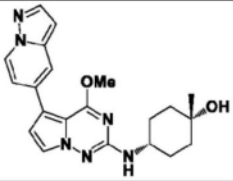
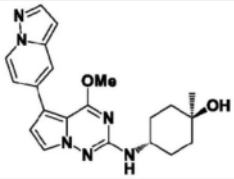
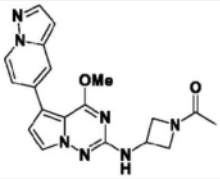
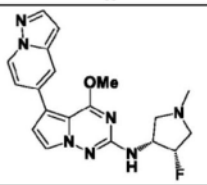
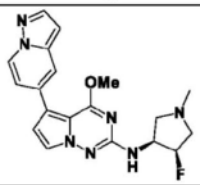
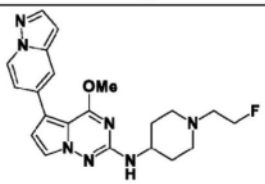
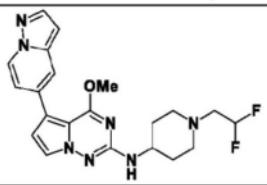
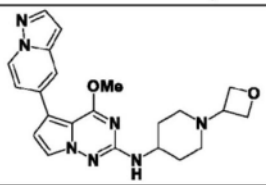
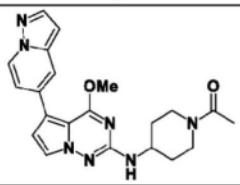
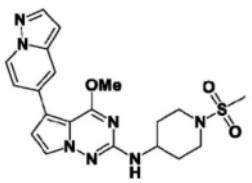
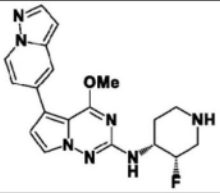
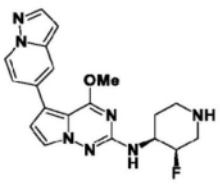
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	

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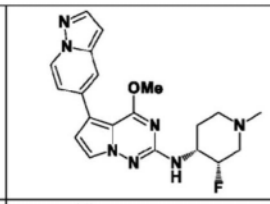
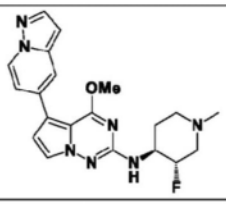
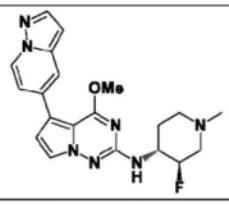
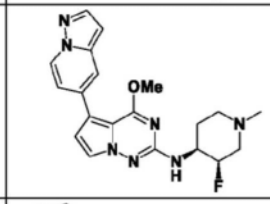
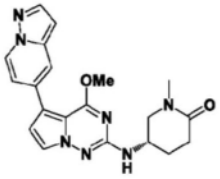
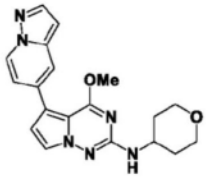
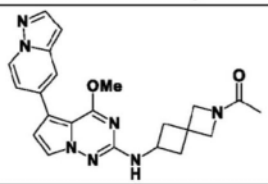
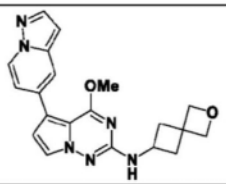
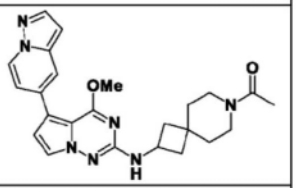
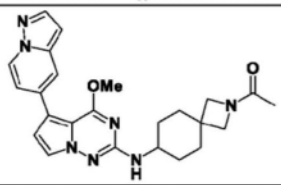
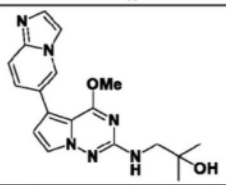
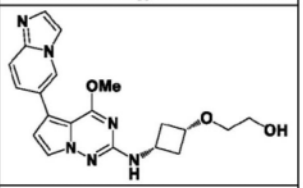
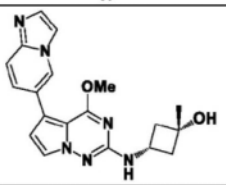
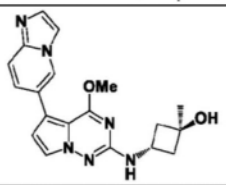
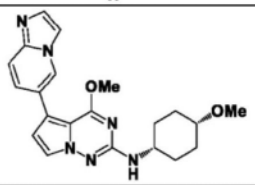
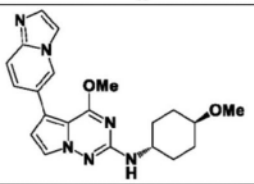
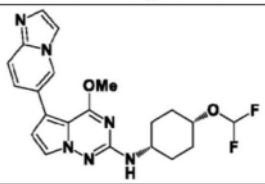
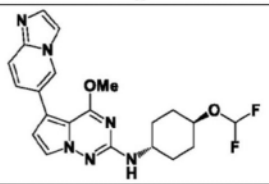
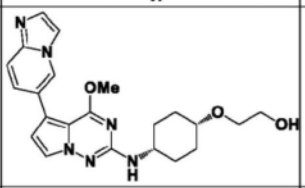
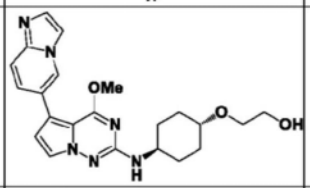
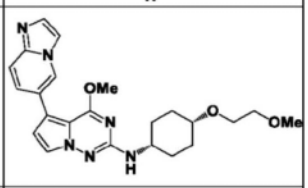
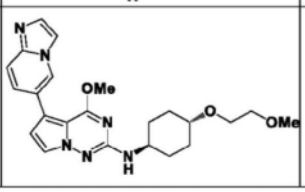
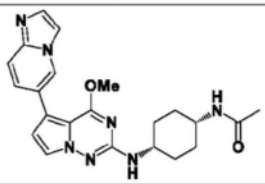
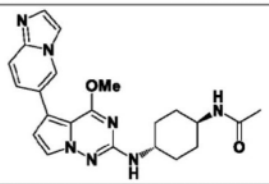
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	

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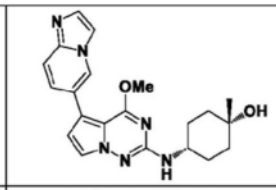
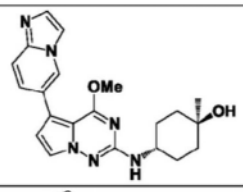
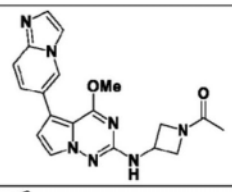
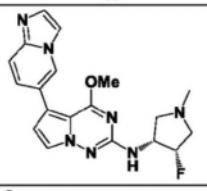
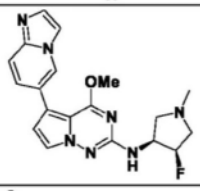
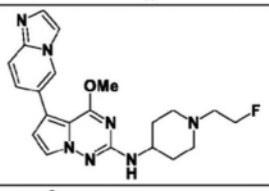
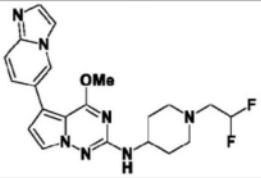
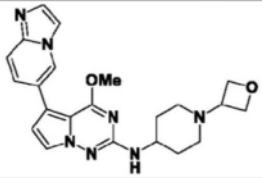
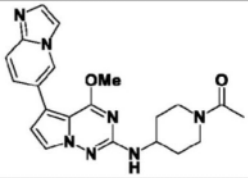
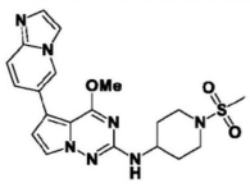
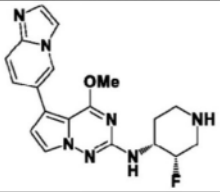
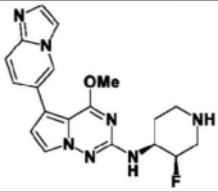
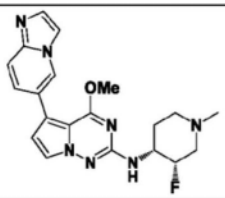
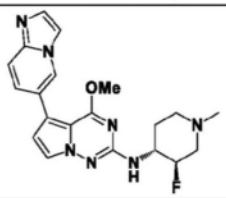
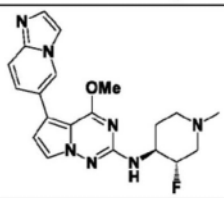
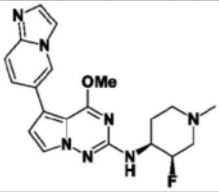
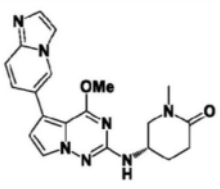
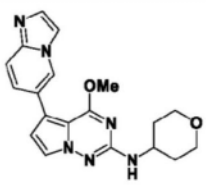
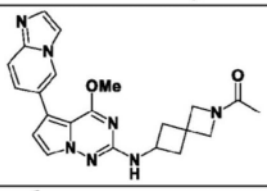
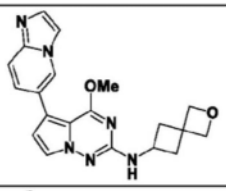
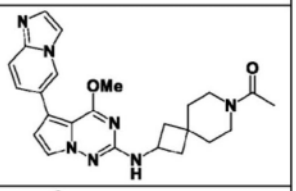
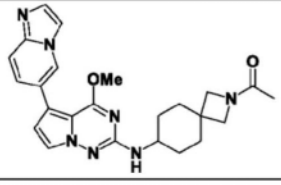
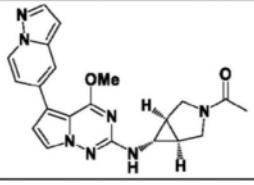
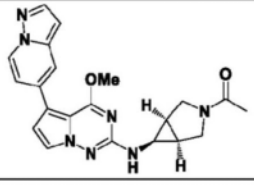
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	
76		77		78	

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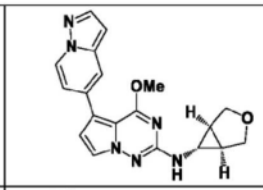
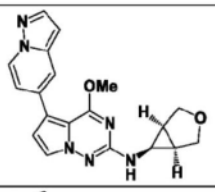
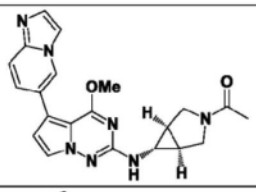
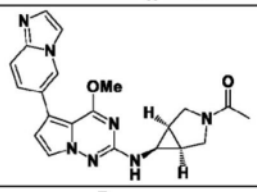
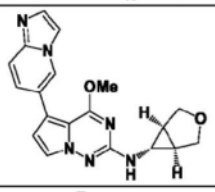
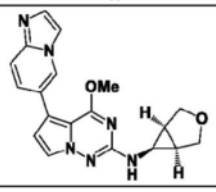
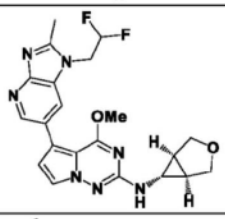
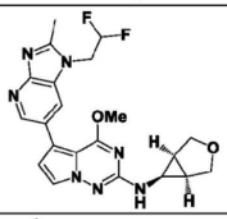
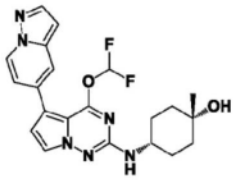
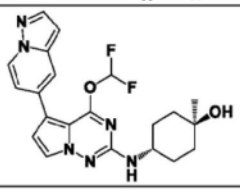
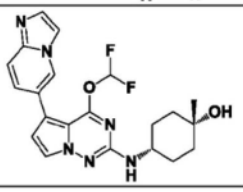
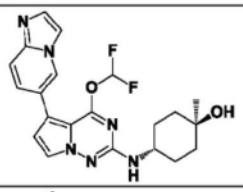
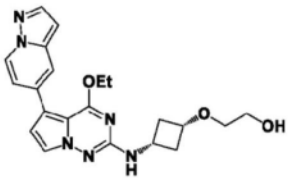
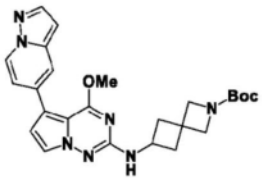
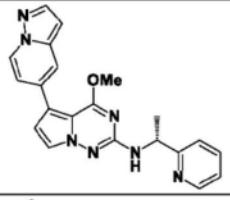
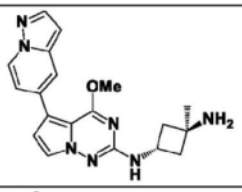
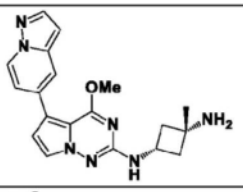
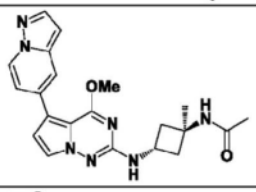
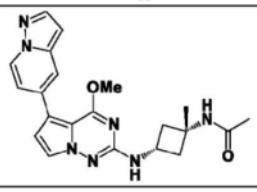
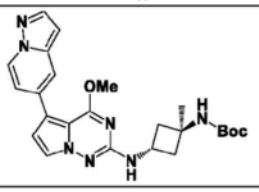
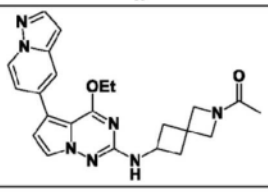
79		80		81	
82		83		84	
85		86		87	
88		89		90	
91		92		93	
94		95		96	
97		98		99	

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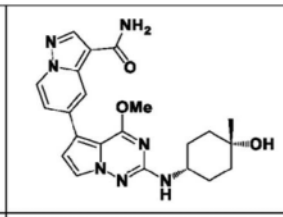
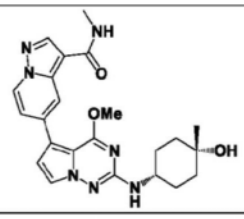
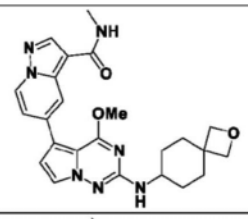
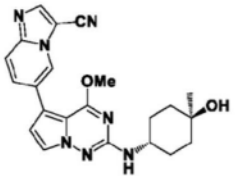
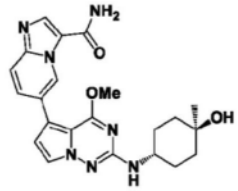
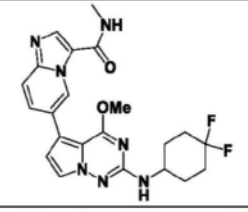
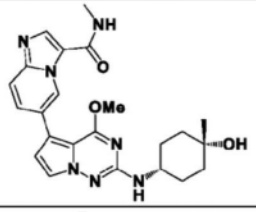
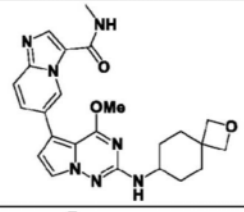
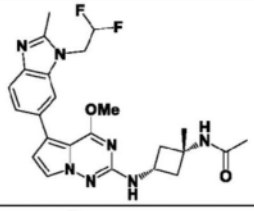
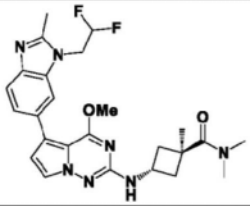
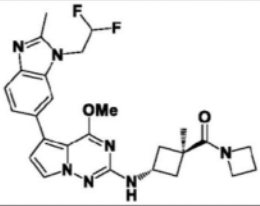
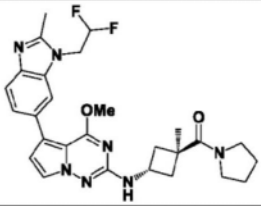
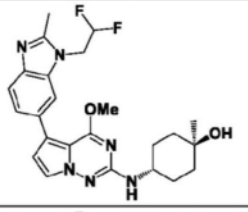
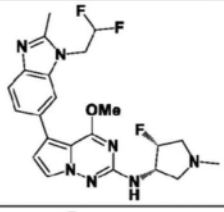
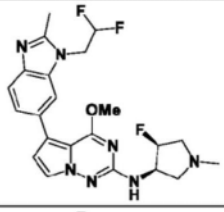
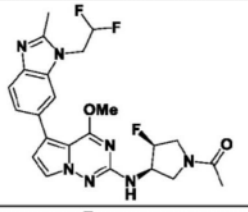
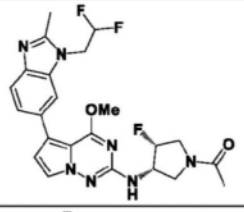
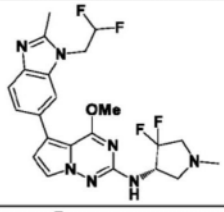
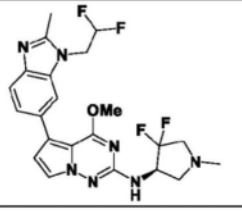
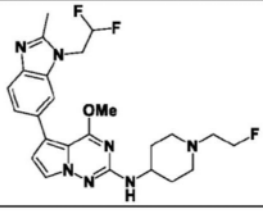
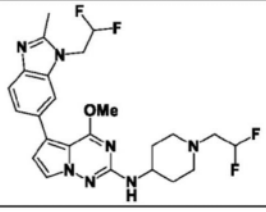
100		101		102	
103		104		105	
106		107		108	
109		110		111	
112		113		114	
115		116		117	
118		119		120	

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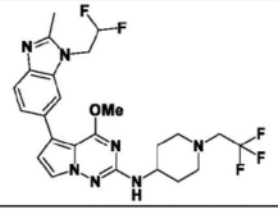
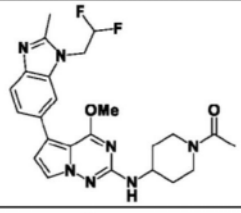
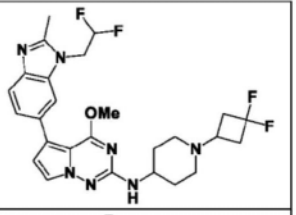
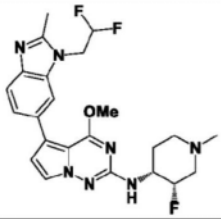
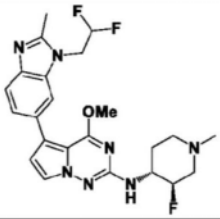
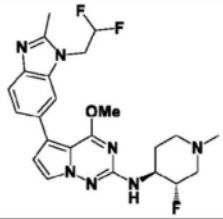
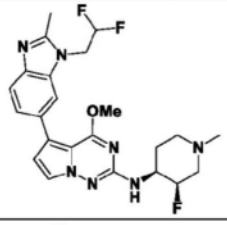
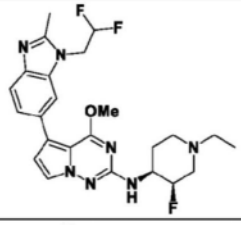
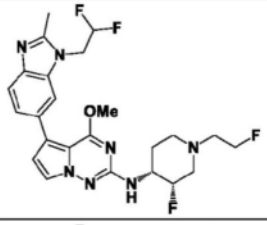
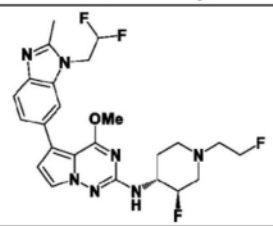
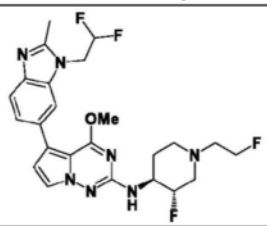
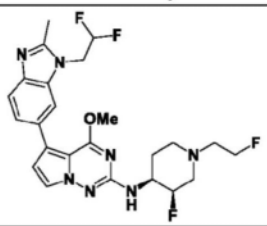
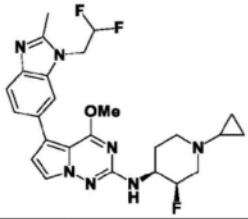
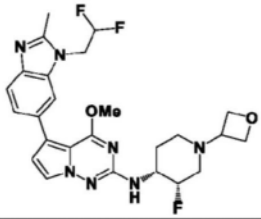
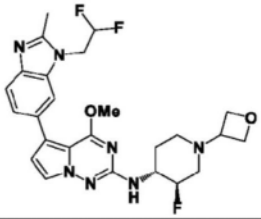
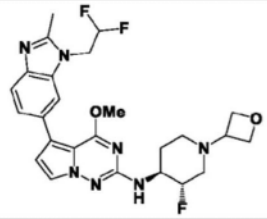
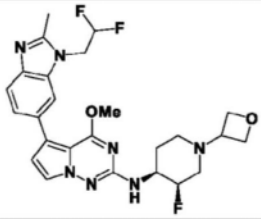
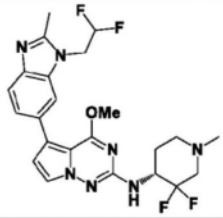
121		122		123	
124		125		126	
127		128		129	
130		131		132	
133		134		135	
136		137		138	

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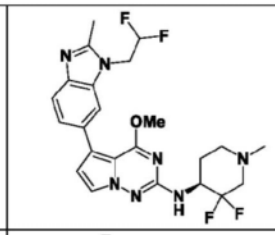
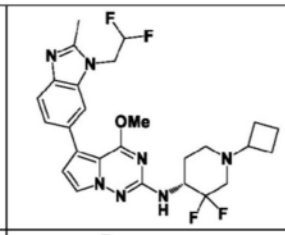
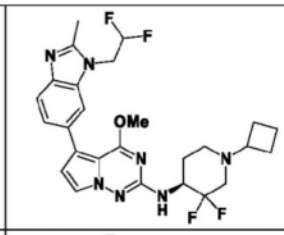
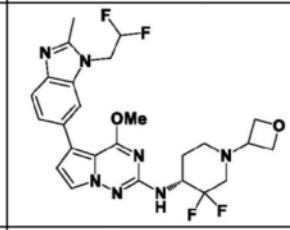
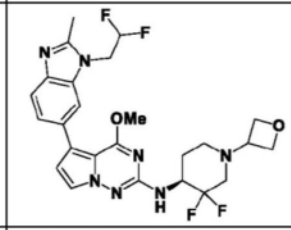
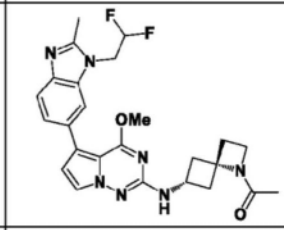
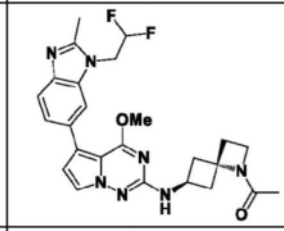
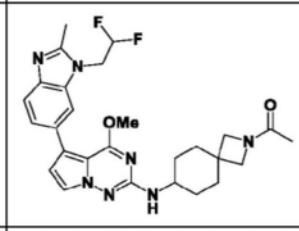
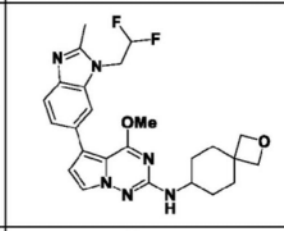
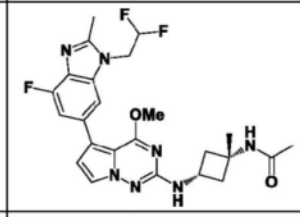
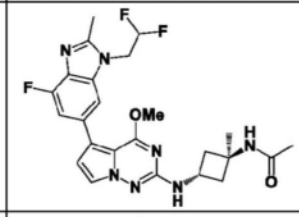
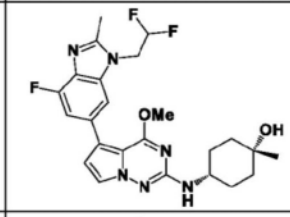
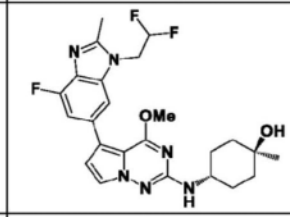
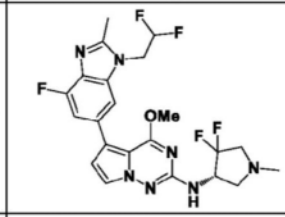
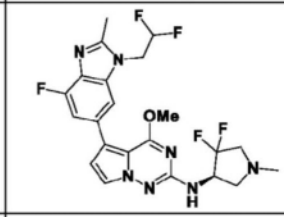
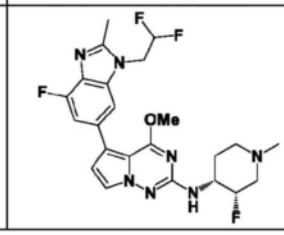
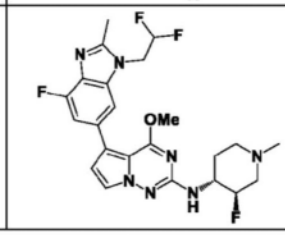
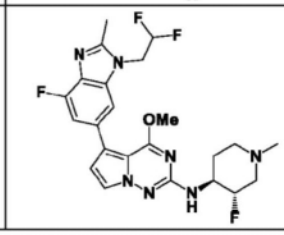
139		140		141	
142		143		144	
145		146		147	
148		149		150	
151		152		153	
154		155		156	

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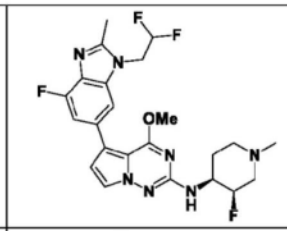
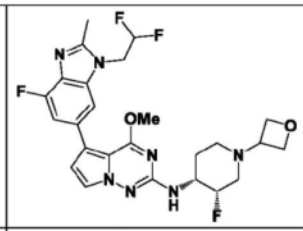
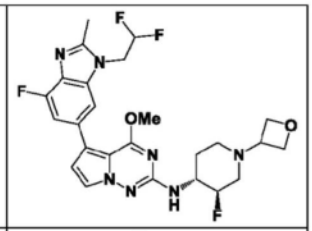
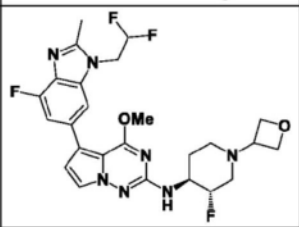
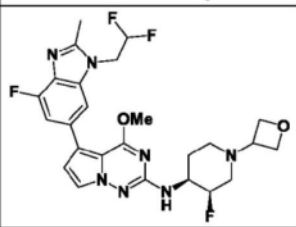
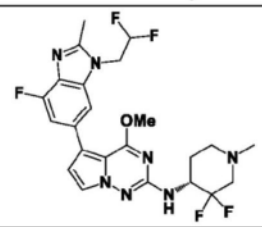
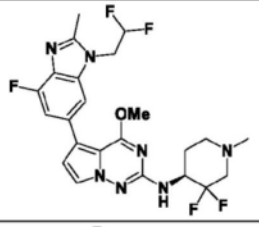
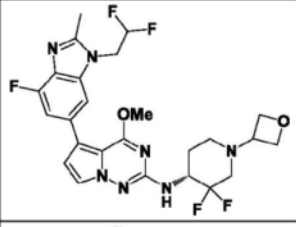
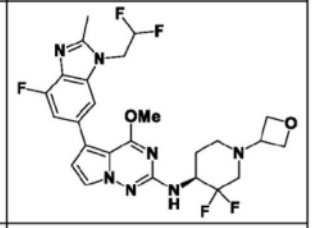
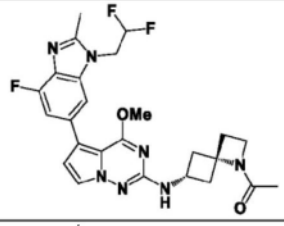
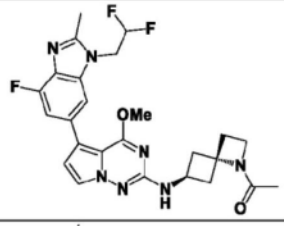
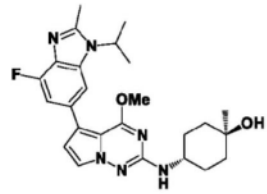
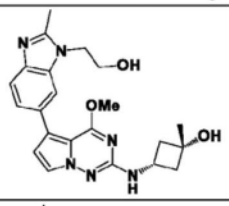
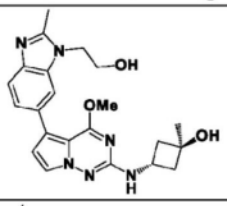
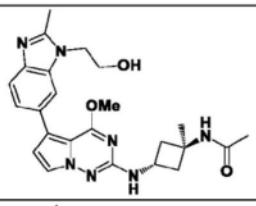
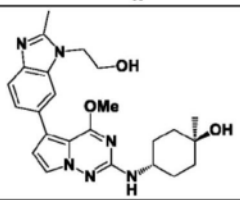
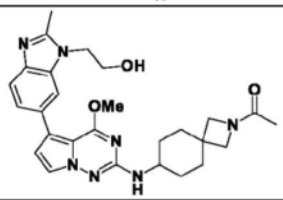
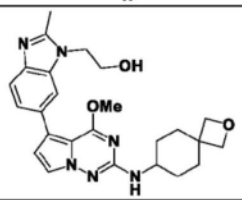
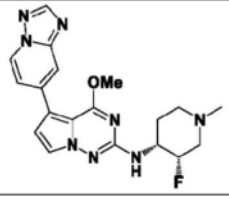
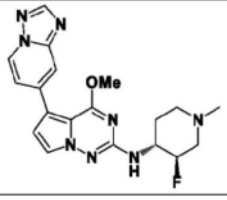
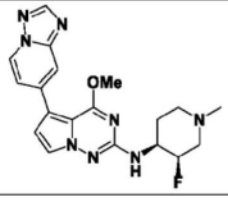
157		158		159	
160		161		162	
163		164		165	
166		167		168	
169		170		171	
172		173		174	
175		176		177	

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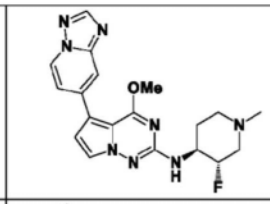
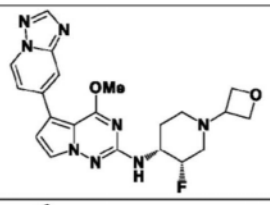
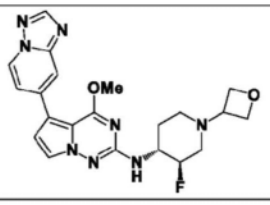
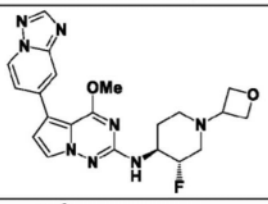
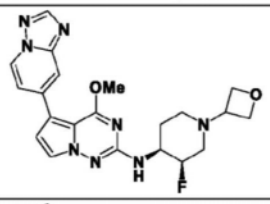
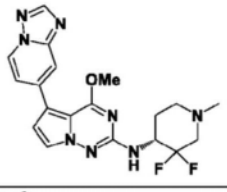
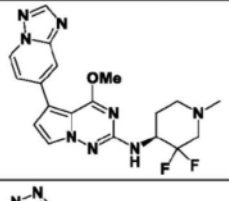
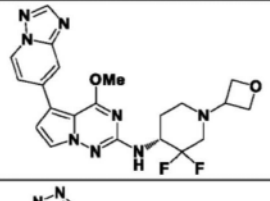
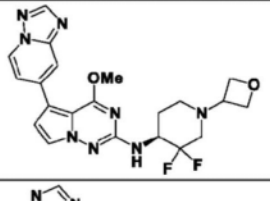
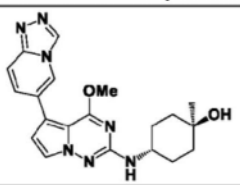
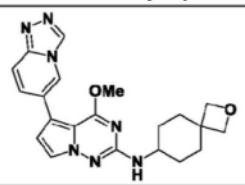
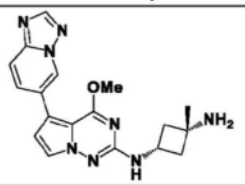
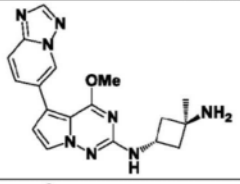
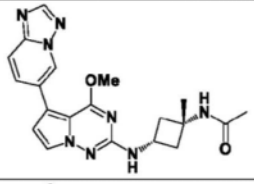
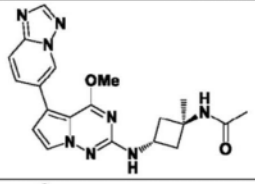
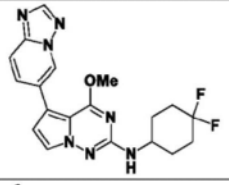
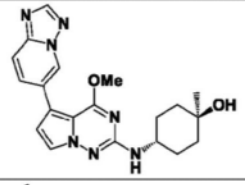
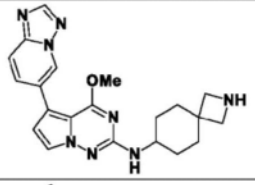
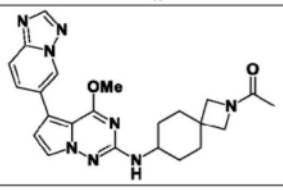
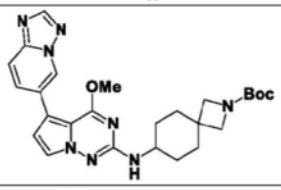
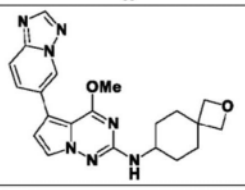
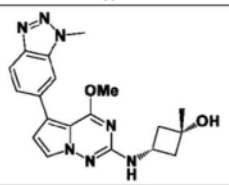
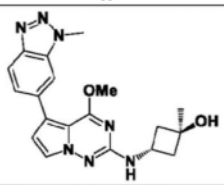
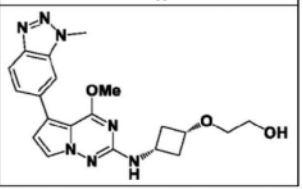
178		179		180	
181		182		183	
184		185		186	
187		188		189	
190		191		192	
193		194		195	
196		197		198	
199		200		201	

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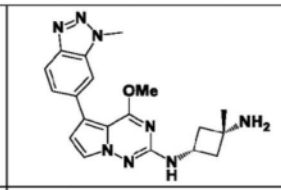
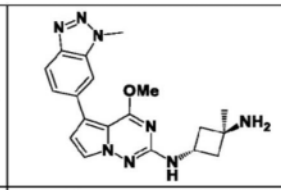
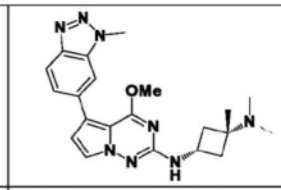
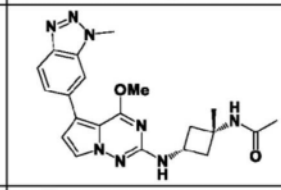
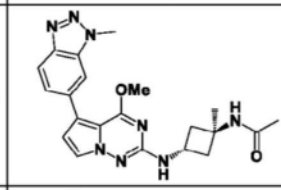
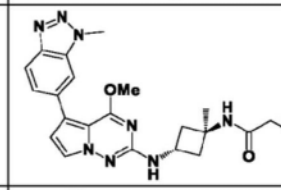
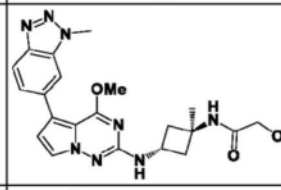
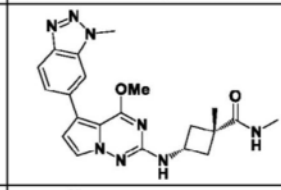
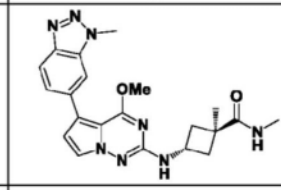
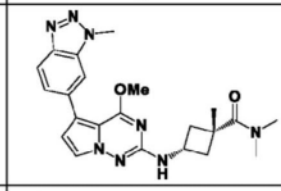
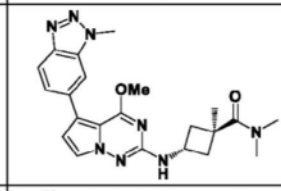
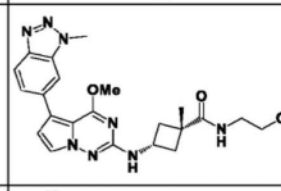
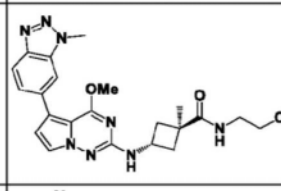
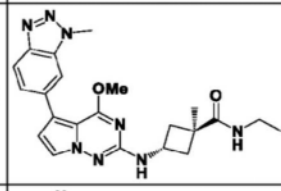
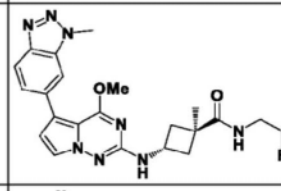
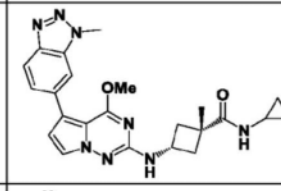
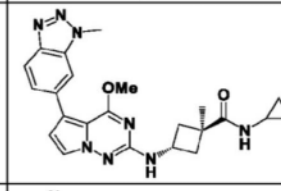
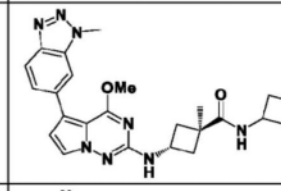
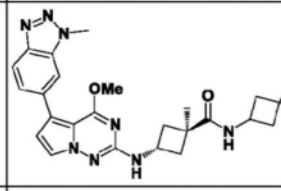
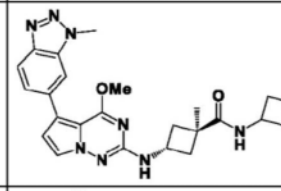
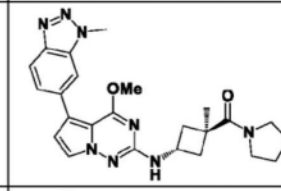
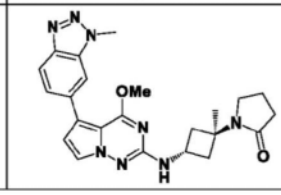
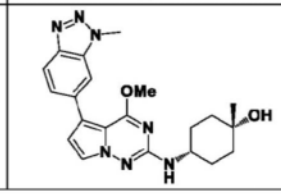
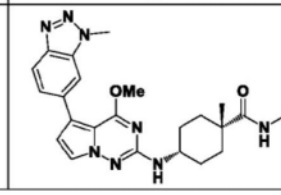
202		203		204	
205		206		207	
208		209		210	
211		212		213	
214		215		216	
217		218		219	
220		221		222	
223		224		225	

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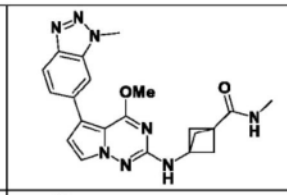
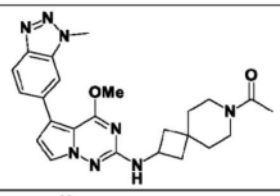
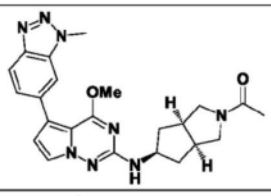
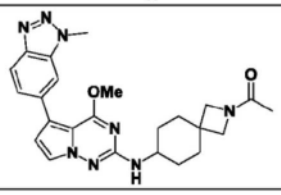
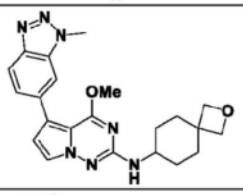
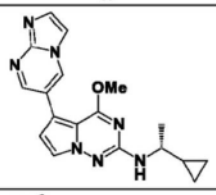
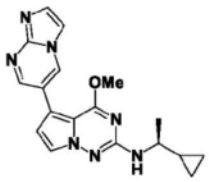
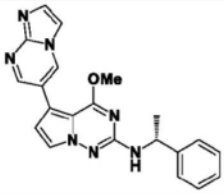
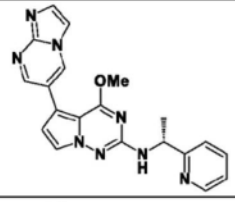
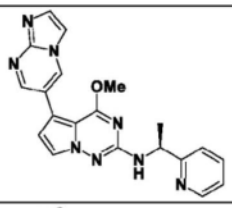
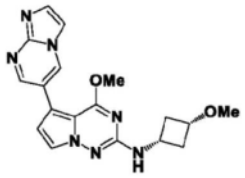
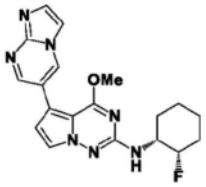
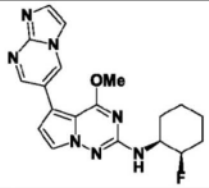
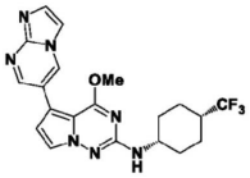
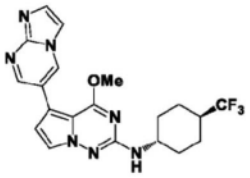
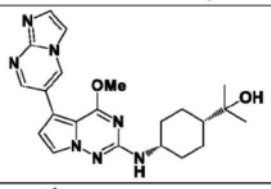
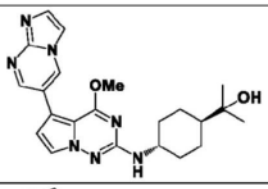
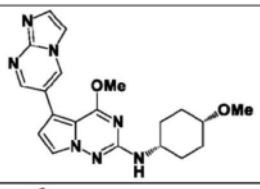
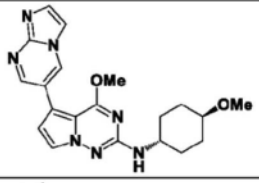
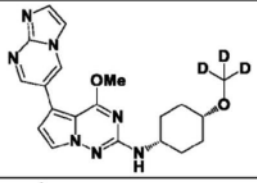
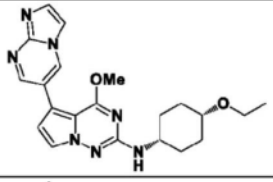
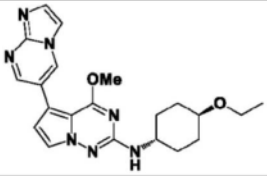
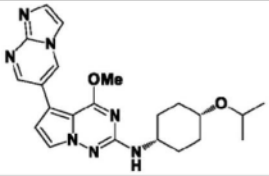
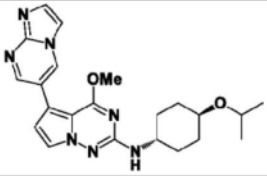
226		227		228	
229		230		231	
232		233		234	
235		236		237	
238		239		240	
241		242		243	
244		245		246	
247		248		249	

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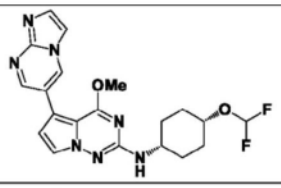
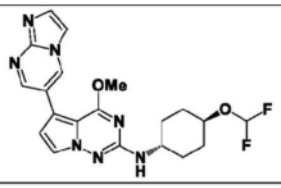
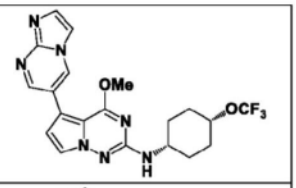
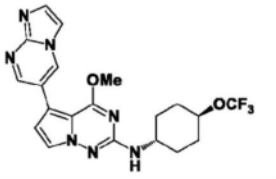
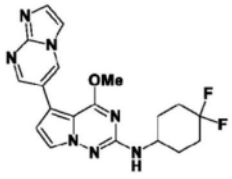
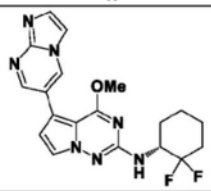
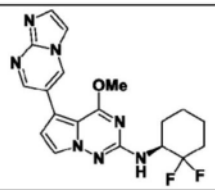
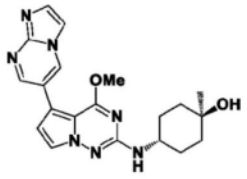
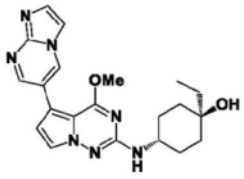
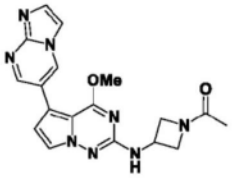
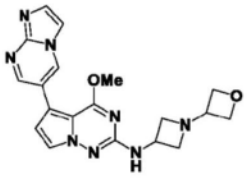
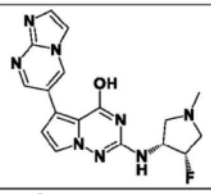
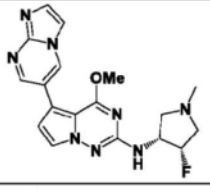
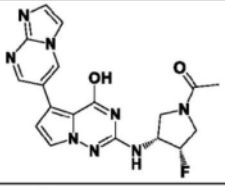
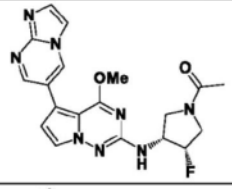
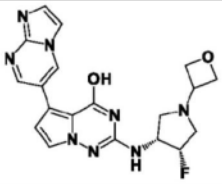
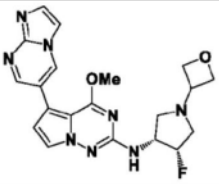
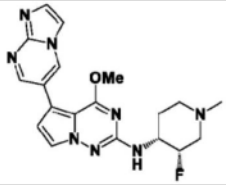
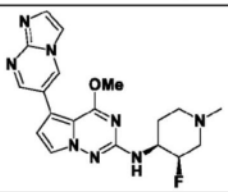
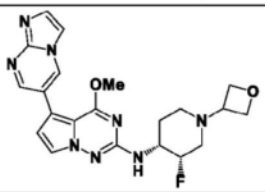
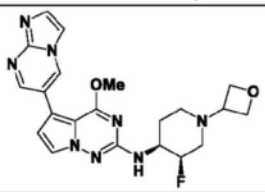
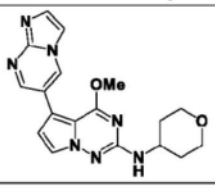
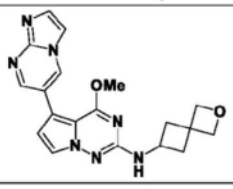
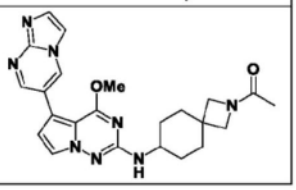
250		251		252	
253		254		255	
256		257		258	
259		260		261	
262		263		264	
265		266		267	
268		269		270	
271		272		273	

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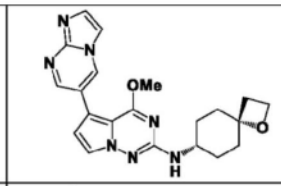
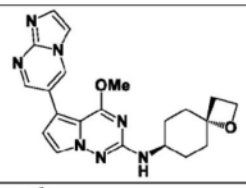
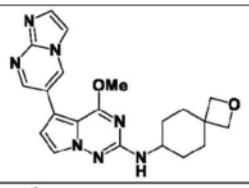
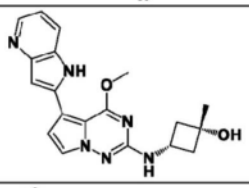
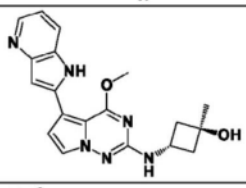
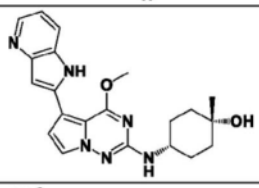
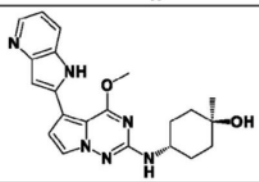
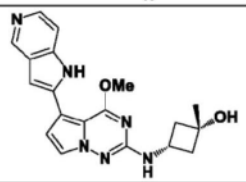
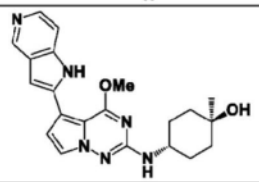
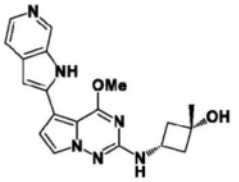
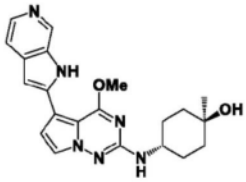
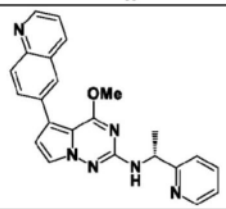
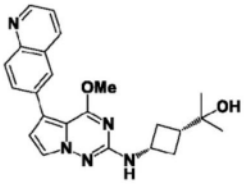
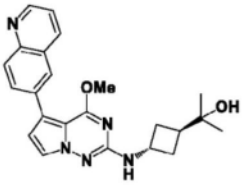
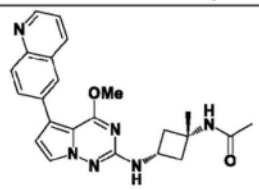
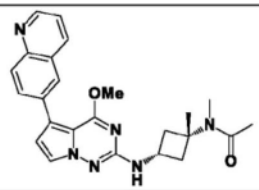
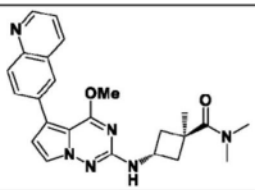
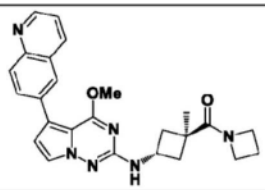
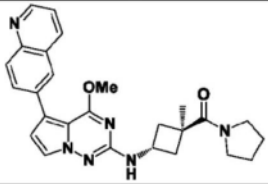
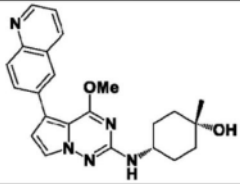
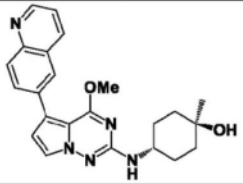
274		275		276	
277		278		279	
280		281		282	
283		284		285	
286		287		288	
289		290		291	
292		293		294	

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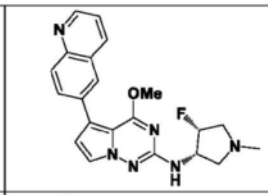
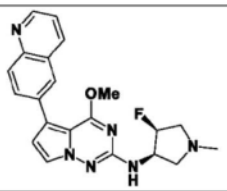
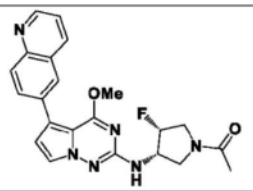
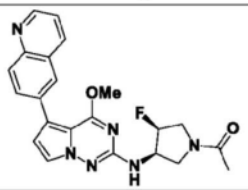
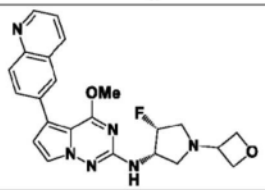
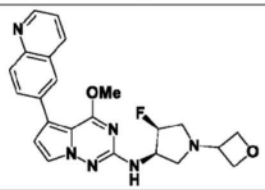
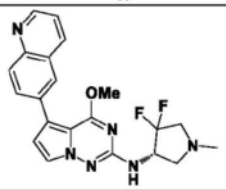
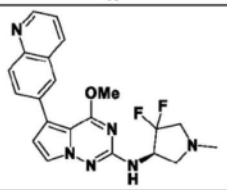
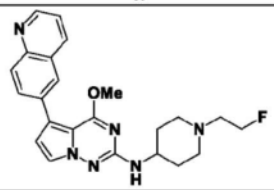
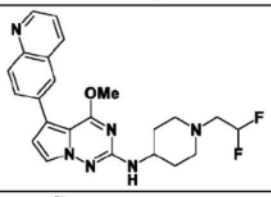
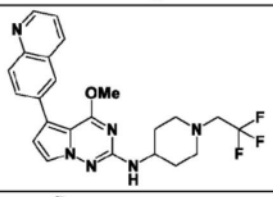
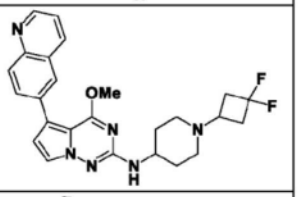
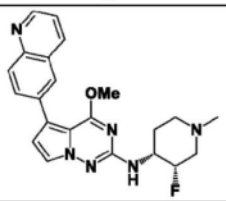
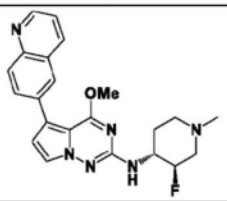
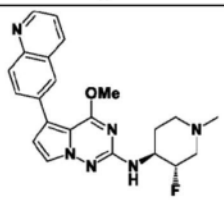
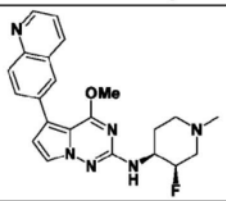
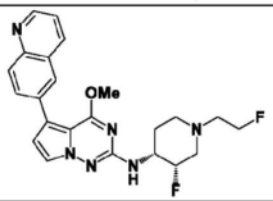
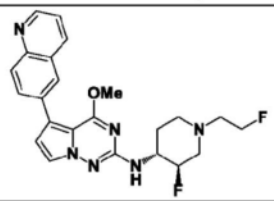
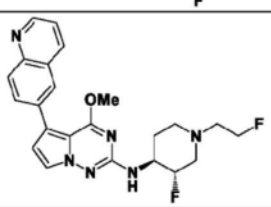
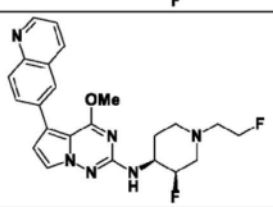
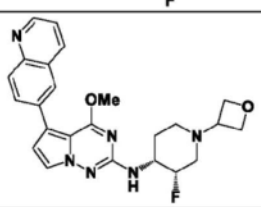
295		296		297	
298		299		300	
301		302		303	
304		305		306	
307		308		309	
310		311		312	
313		314		315	

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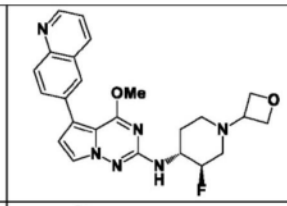
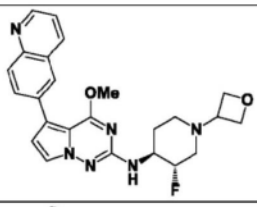
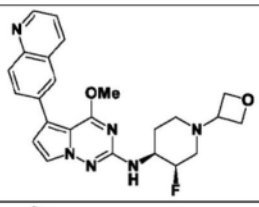
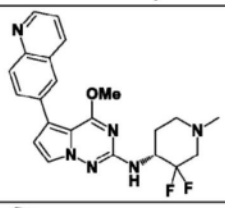
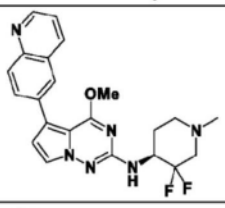
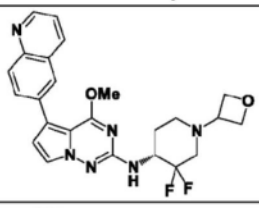
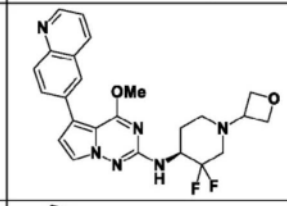
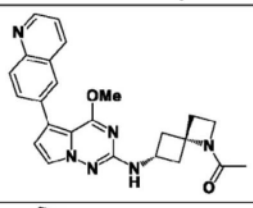
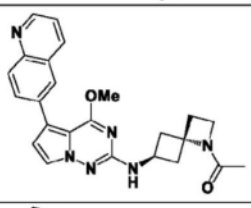
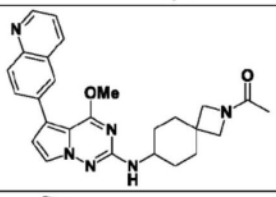
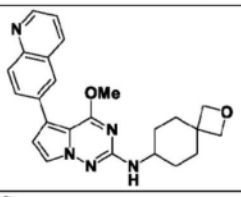
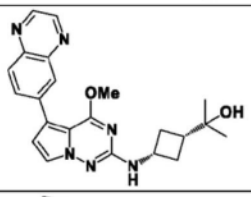
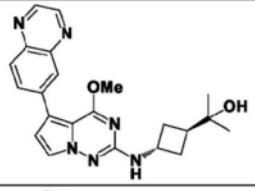
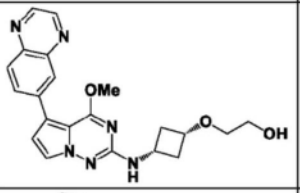
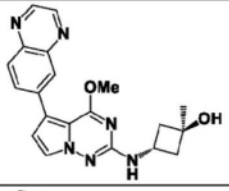
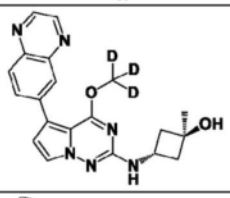
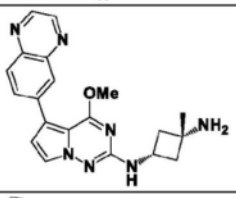
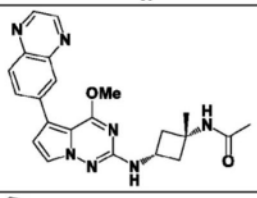
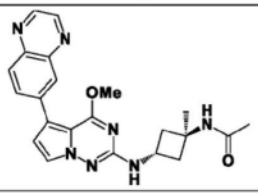
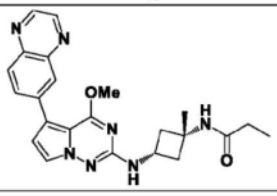
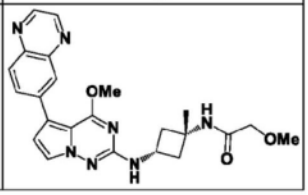
316		317		318	
319		320		321	
322		323		324	
325		326		327	
328		329		330	
331		332		333	
334		335		336	

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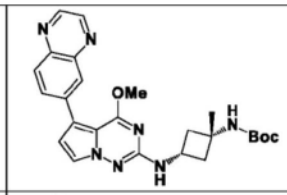
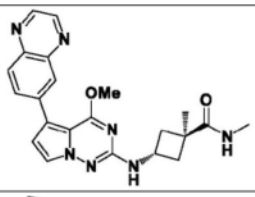
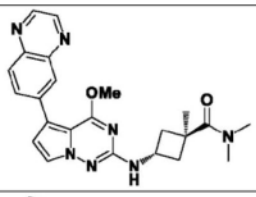
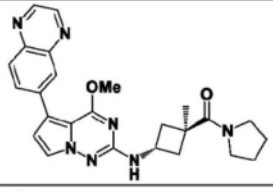
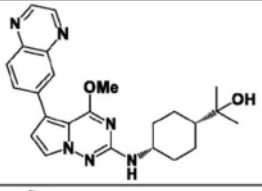
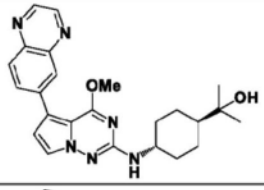
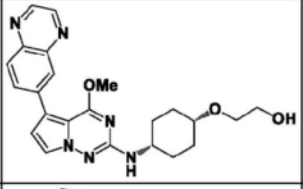
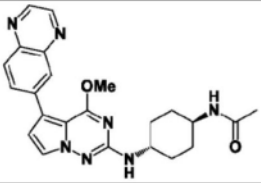
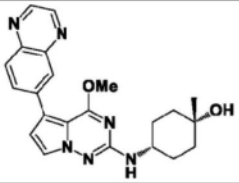
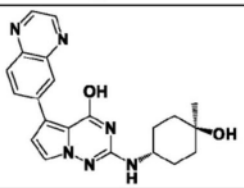
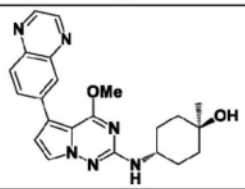
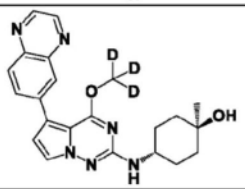
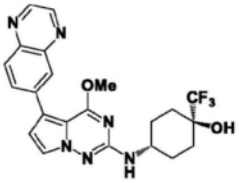
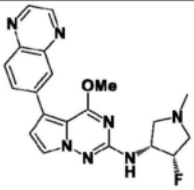
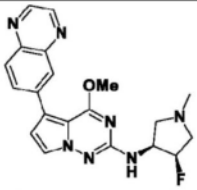
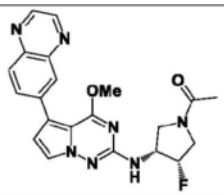
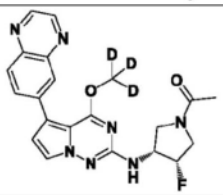
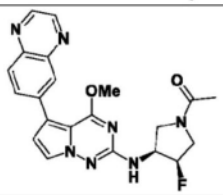
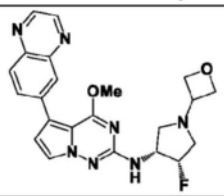
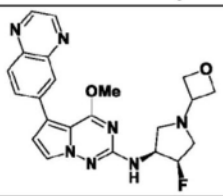
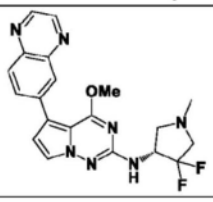
337		338		339	
340		341		342	
343		344		345	
346		347		348	
349		350		351	
352		353		354	
355		356		357	

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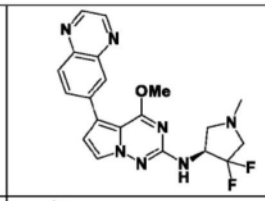
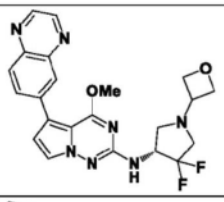
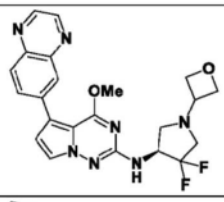
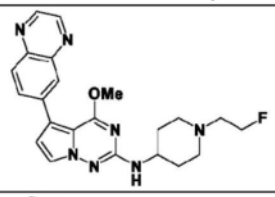
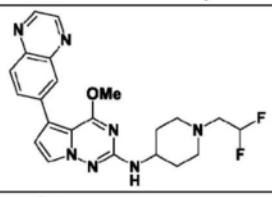
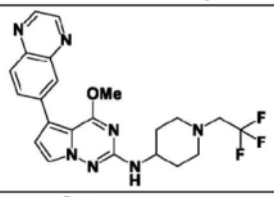
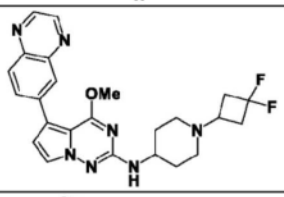
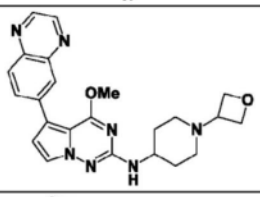
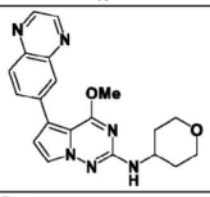
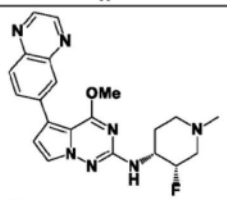
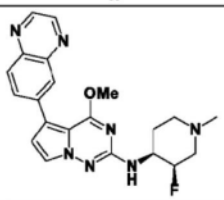
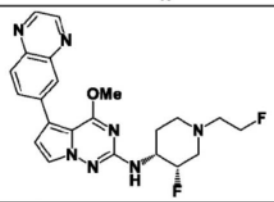
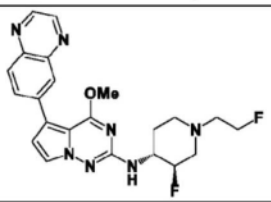
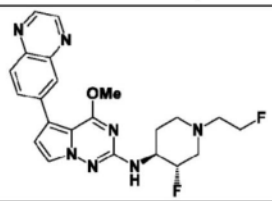
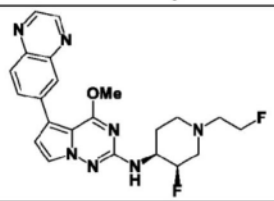
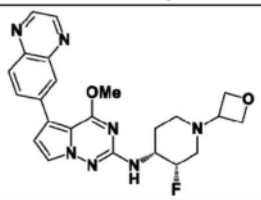
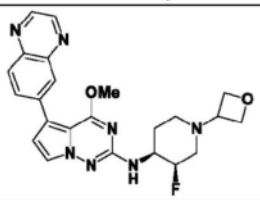
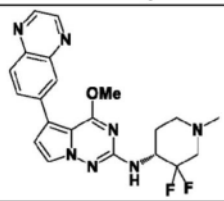
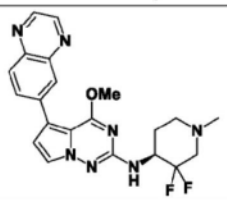
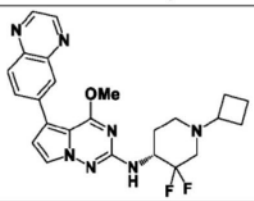
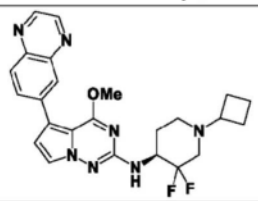
358		359		360	
361		362		363	
364		365		366	
367		368		369	
370		371		372	
373		374		375	
376		377		378	

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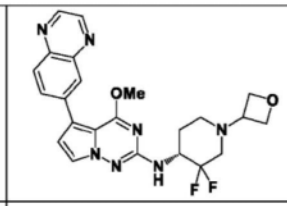
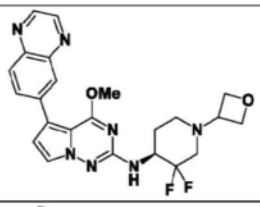
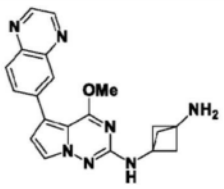
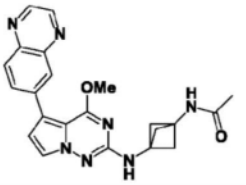
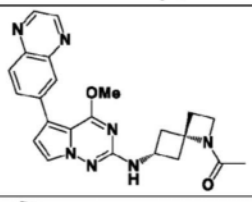
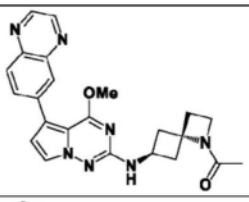
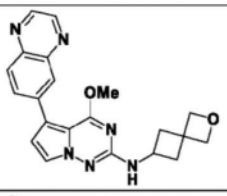
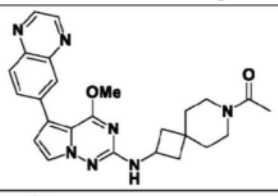
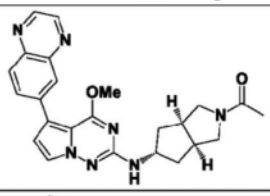
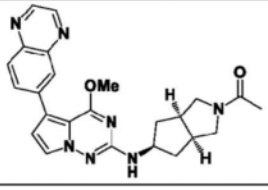
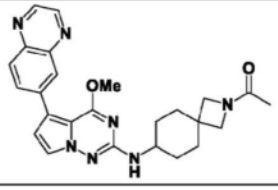
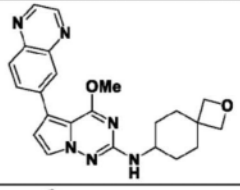
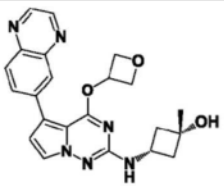
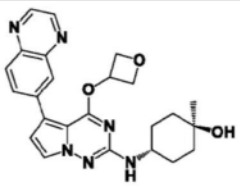
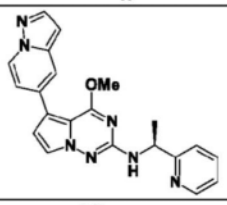
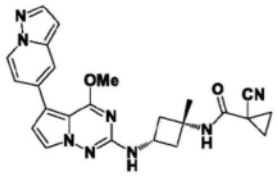
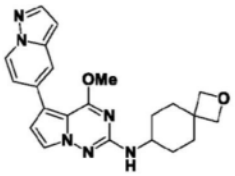
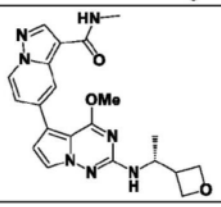
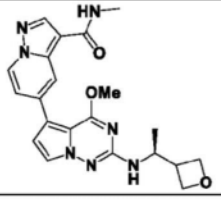
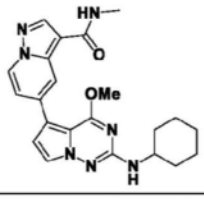
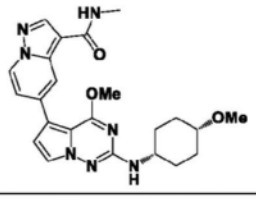
379		380		381	
382		383		384	
385		386		387	
388		389		390	
391		392		393	
394		395		396	
397		398		399	

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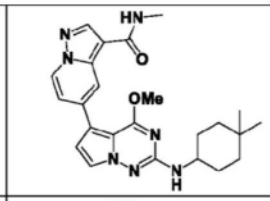
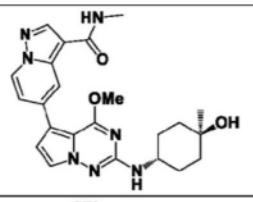
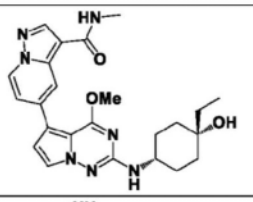
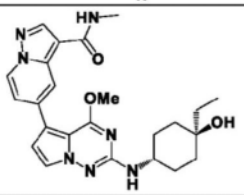
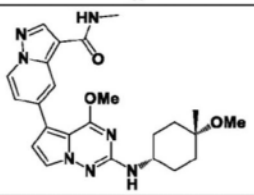
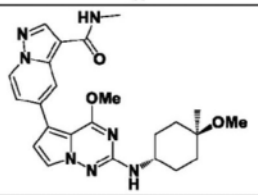
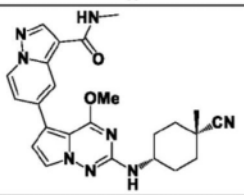
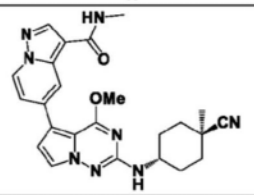
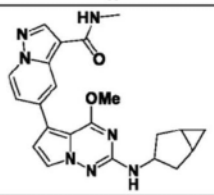
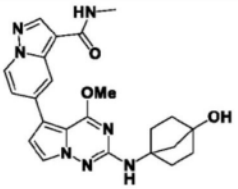
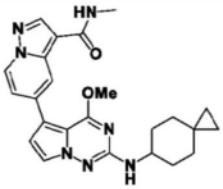
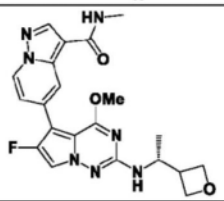
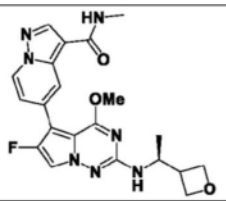
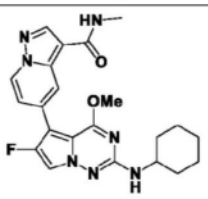
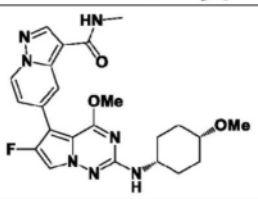
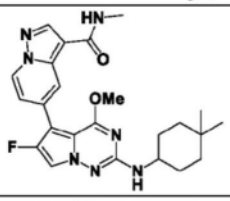
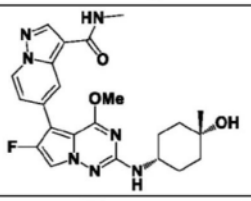
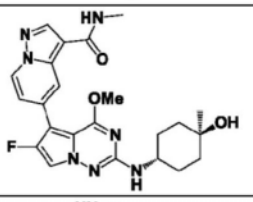
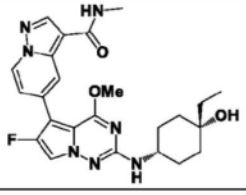
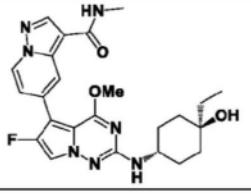
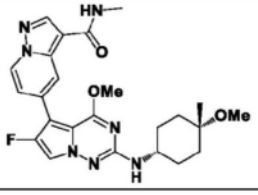
400		401		402	
403		404		405	
406		407		408	
409		410		411	
412		413		414	
415		416		417	
418		419		420	

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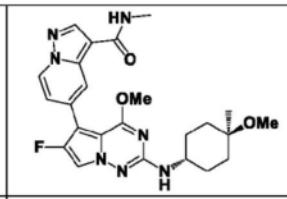
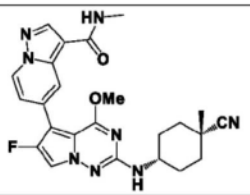
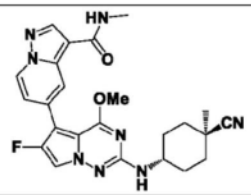
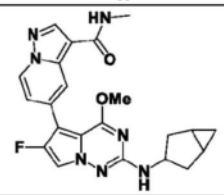
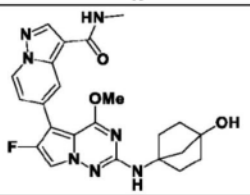
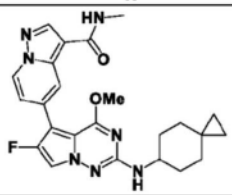
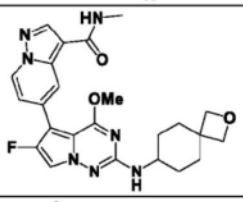
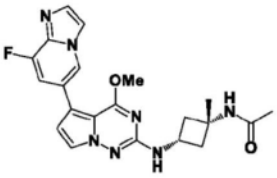
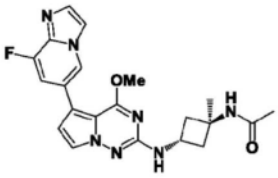
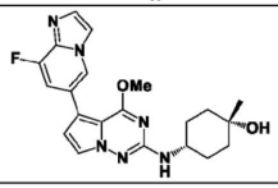
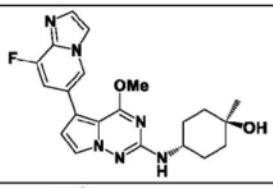
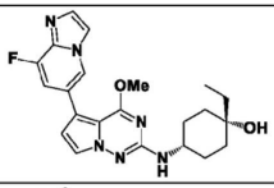
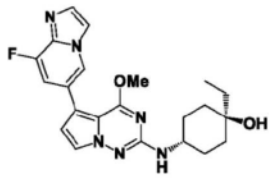
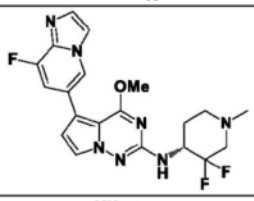
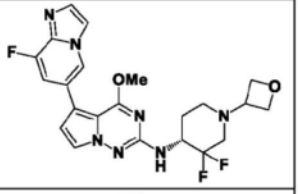
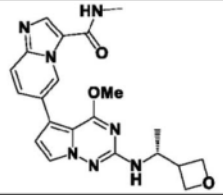
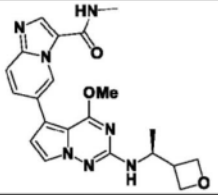
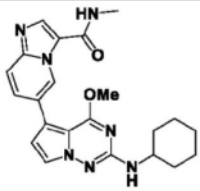
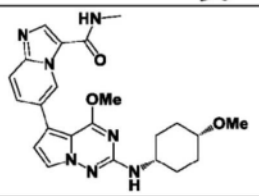
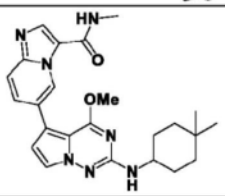
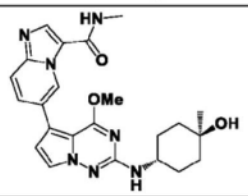
421		422		423	
424		425		426	
427		428		429	
430		431		432	
433		434		435	
436		437		438	
439		440		441	

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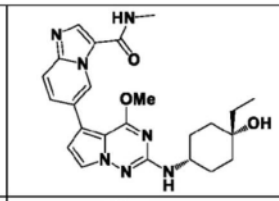
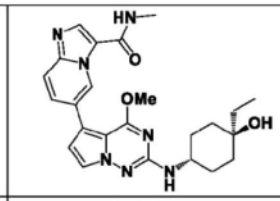
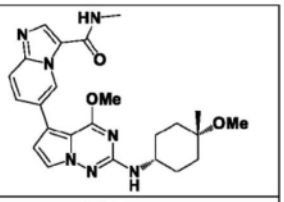
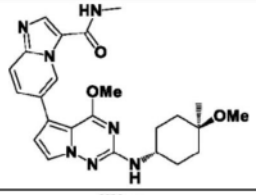
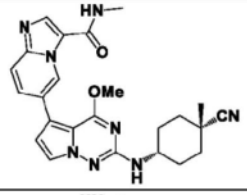
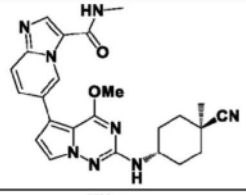
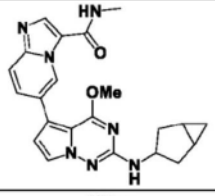
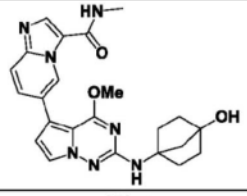
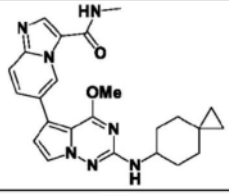
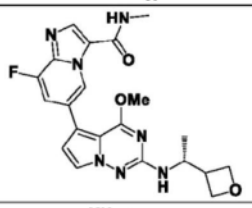
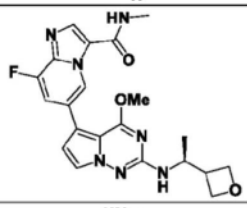
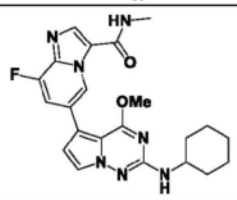
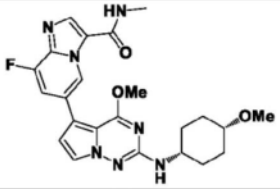
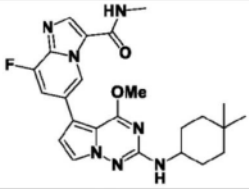
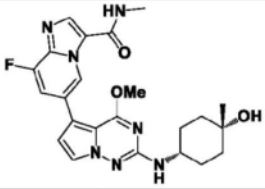
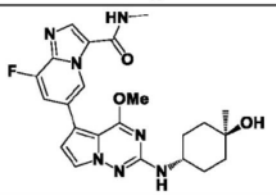
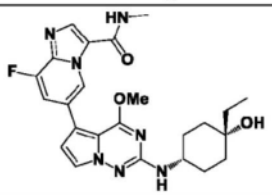
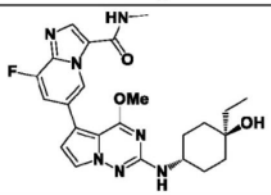
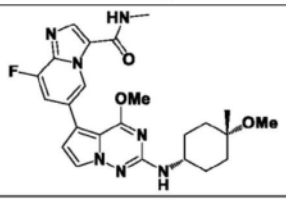
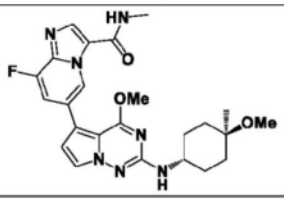
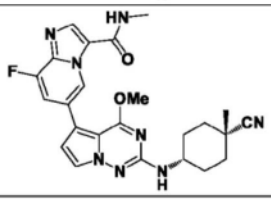
442		443		444	
445		446		447	
448		449		450	
451		452		453	
454		455		456	
457		458		459	
460		461		462	

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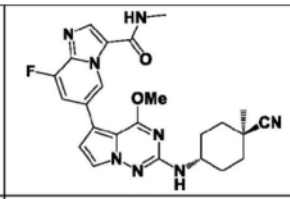
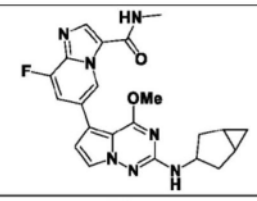
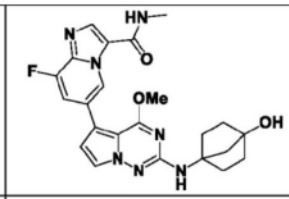
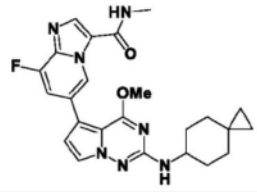
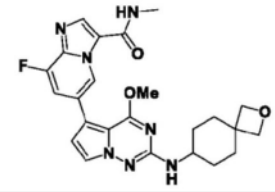
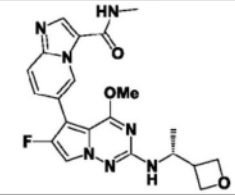
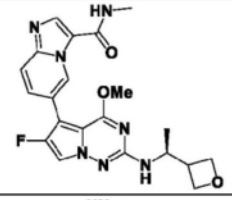
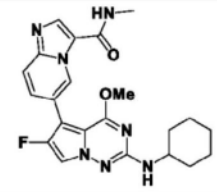
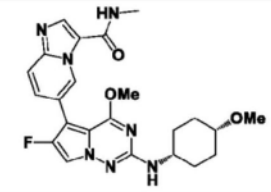
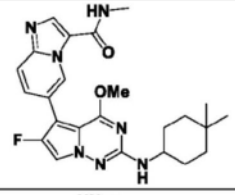
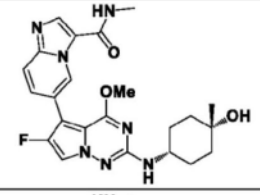
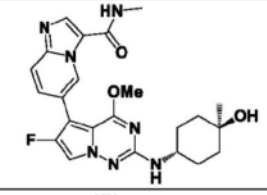
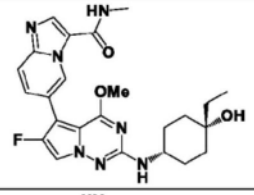
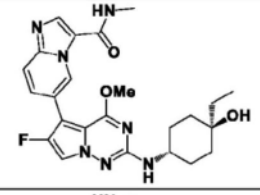
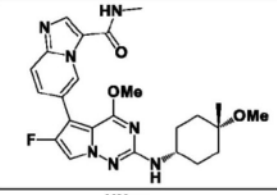
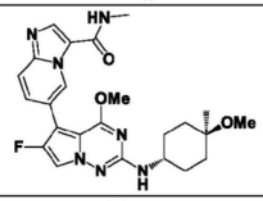
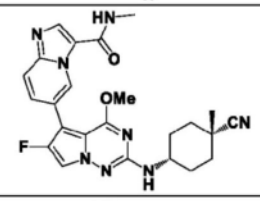
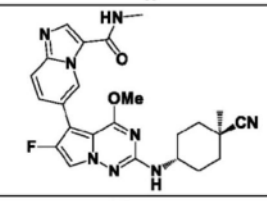
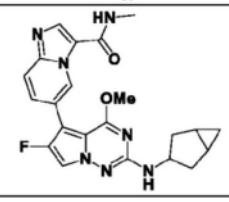
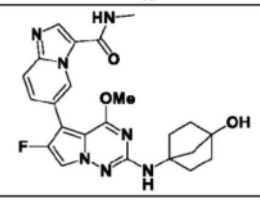
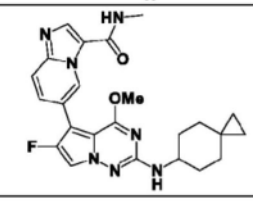
463		464		465	
466		467		468	
469		470		471	
472		473		474	
475		476		477	
478		479		480	
481		482		483	

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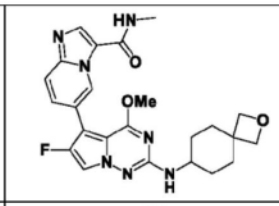
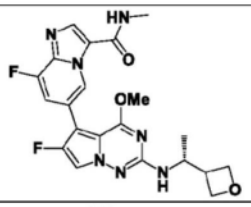
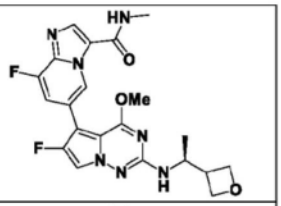
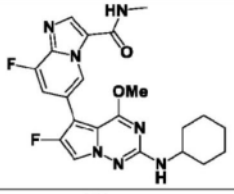
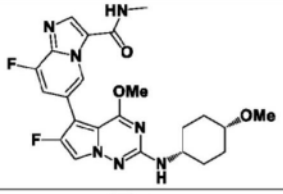
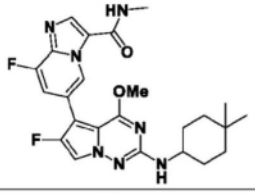
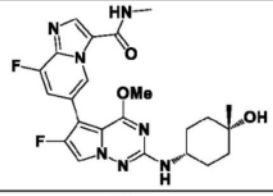
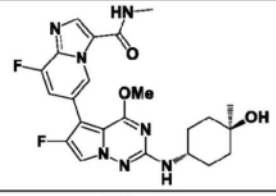
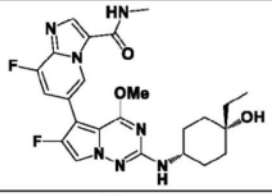
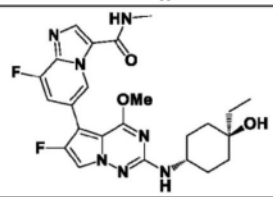
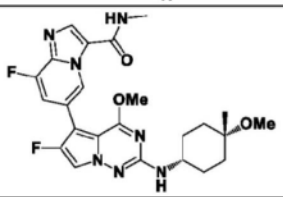
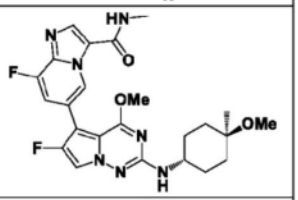
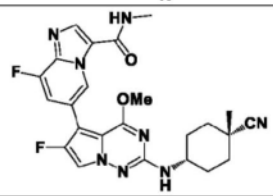
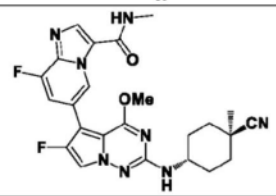
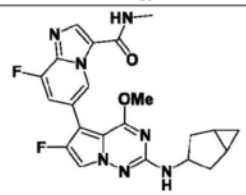
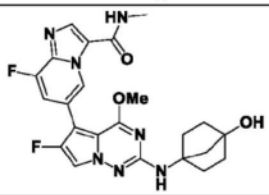
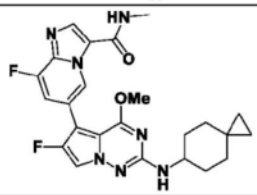
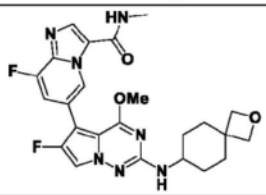
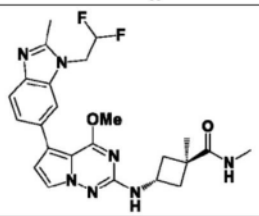
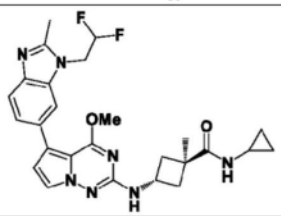
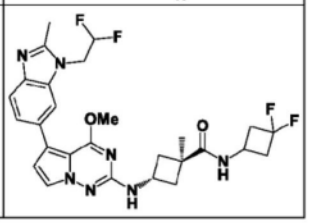
484		485		486	
487		488		489	
490		491		492	
493		494		495	
496		497		498	
499		500		501	
502		503		504	

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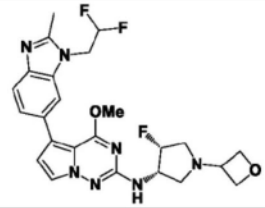
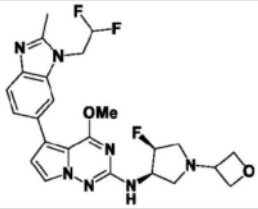
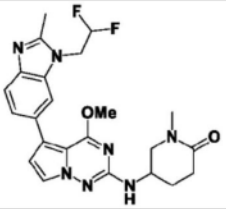
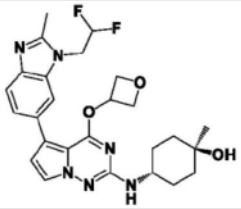
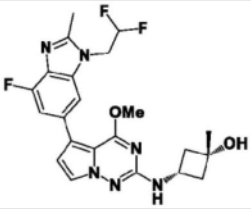
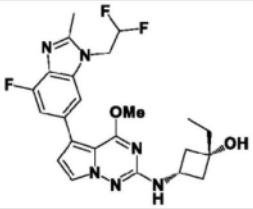
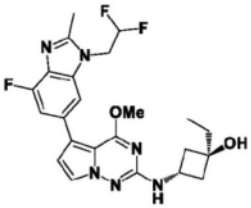
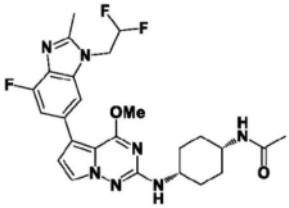
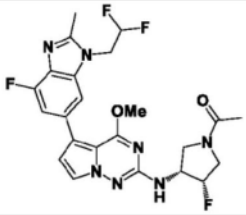
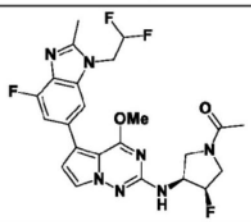
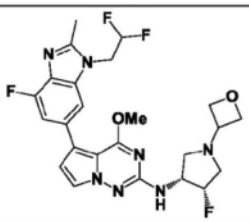
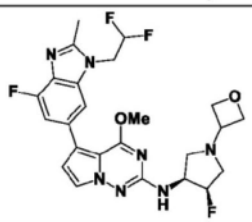
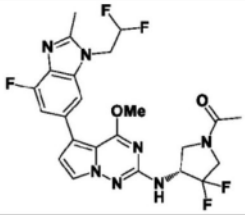
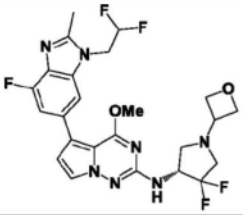
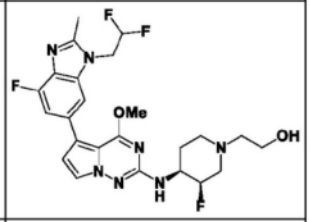
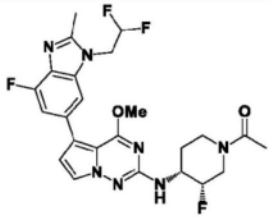
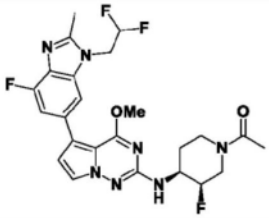
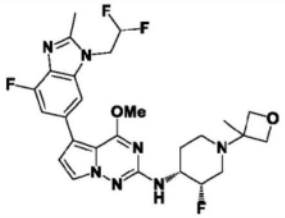
505		506		507	
508		509		510	
511		512		513	
514		515		516	
517		518		519	
520		521		522	

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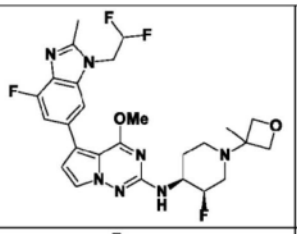
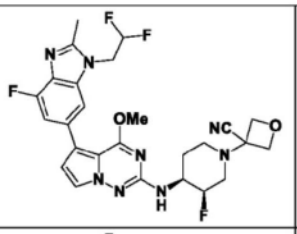
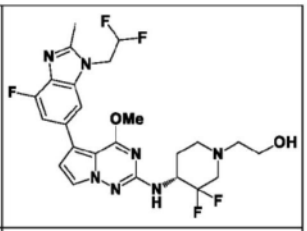
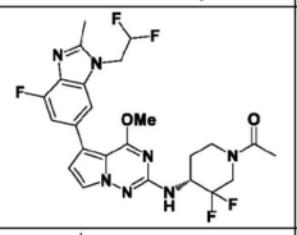
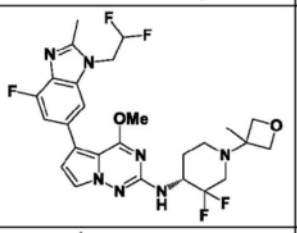
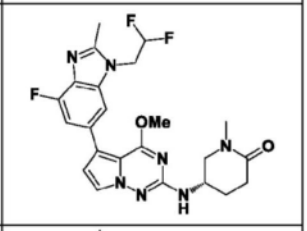
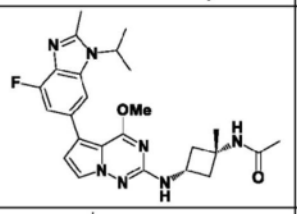
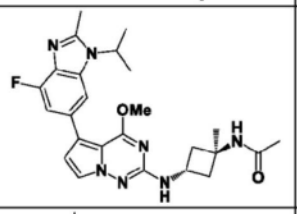
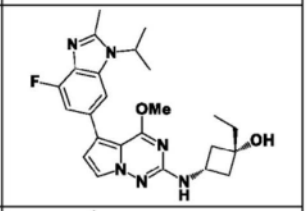
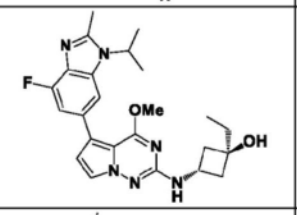
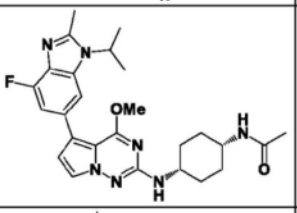
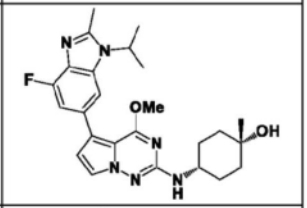
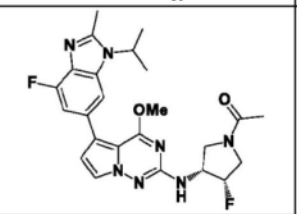
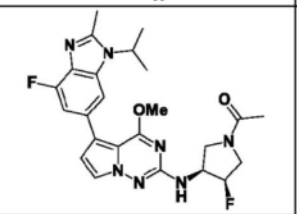
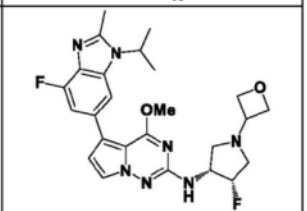
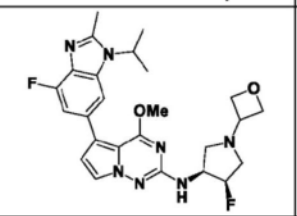
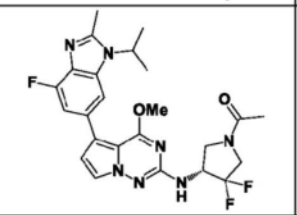
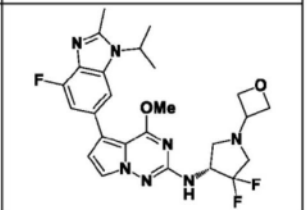
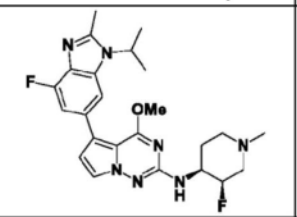
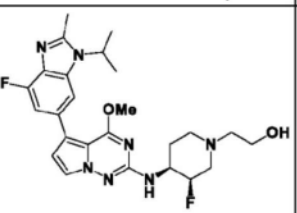
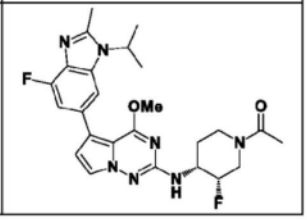
523		524		525	
526		527		528	
529		530		531	
532		533		534	
535		536		537	
538		539		540	
541		542		543	

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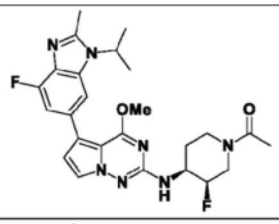
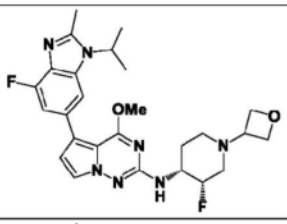
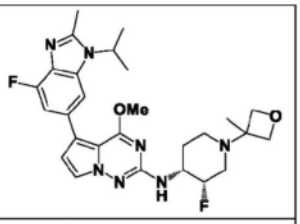
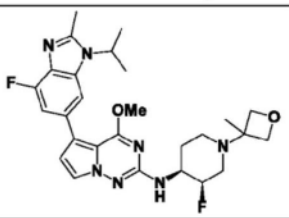
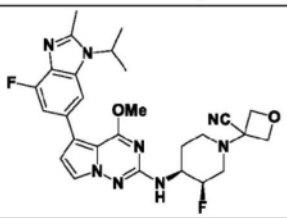
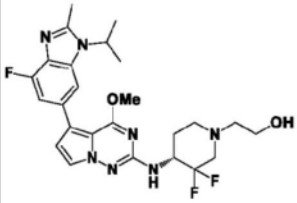
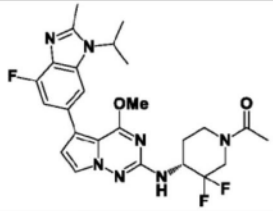
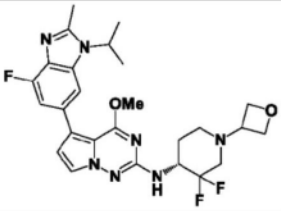
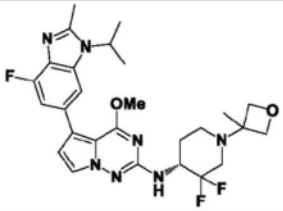
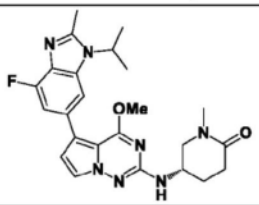
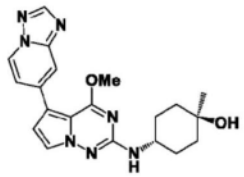
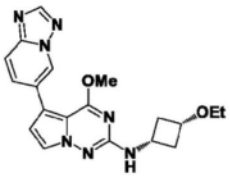
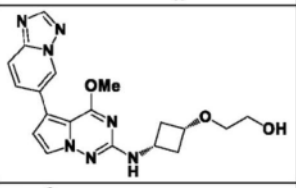
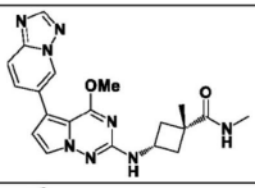
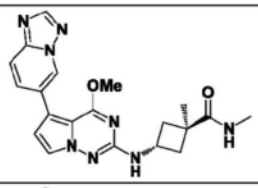
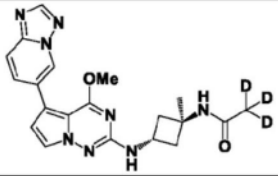
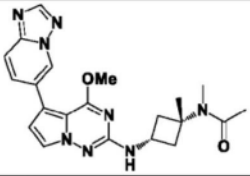
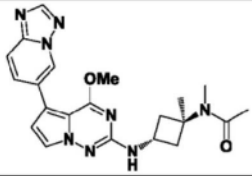
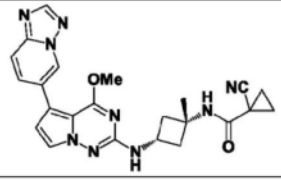
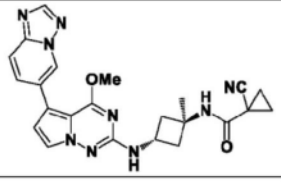
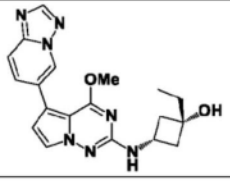
544		545		546	
547		548		549	
550		551		552	
553		554		555	
556		557		558	
559		560		561	
562		563		564	

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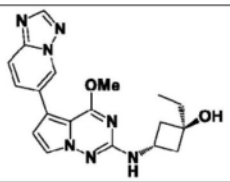
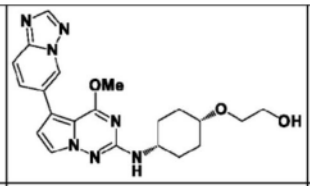
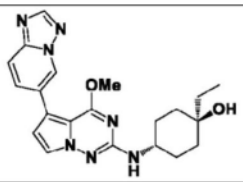
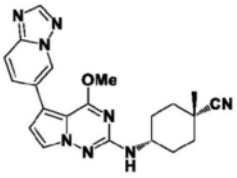
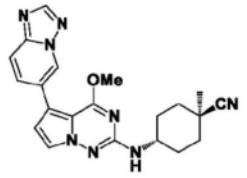
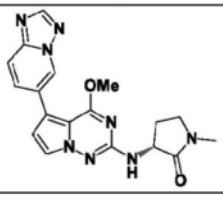
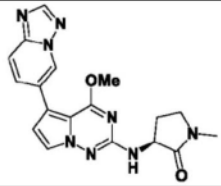
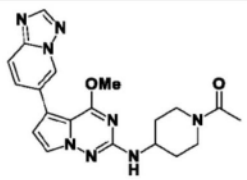
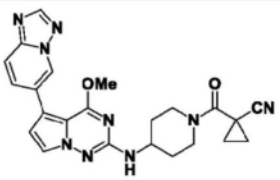
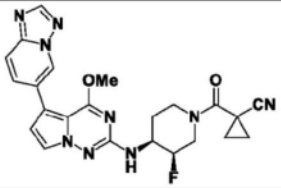
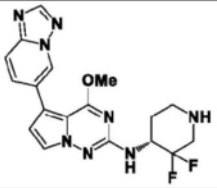
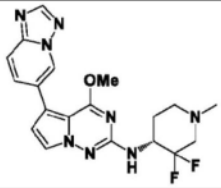
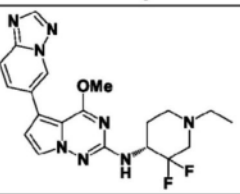
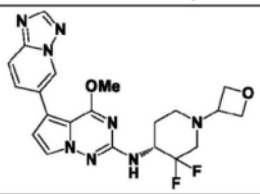
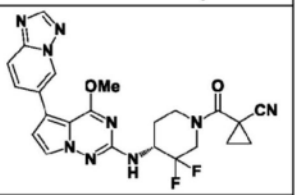
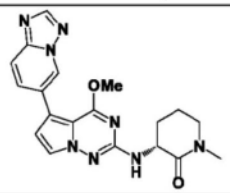
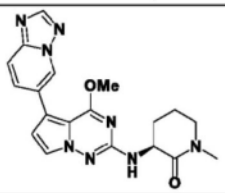
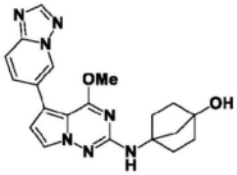
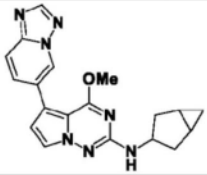
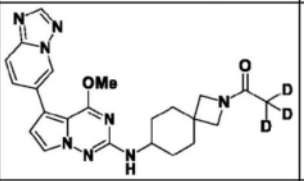
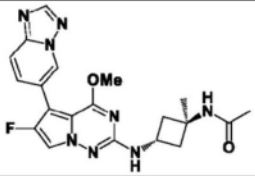
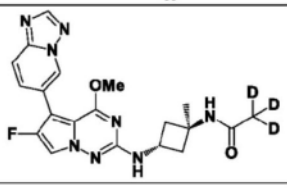
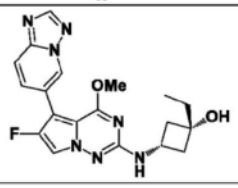
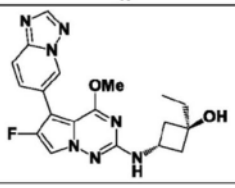
565		566		567	
568		569		570	
571		572		573	
574		575		576	
577		578		579	
580		581		582	
583		584		585	
586		587		588	

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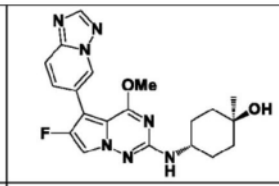
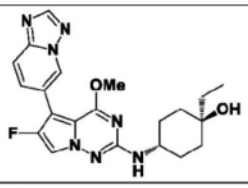
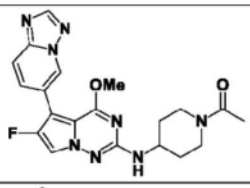
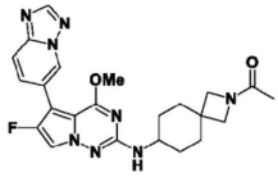
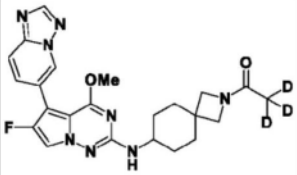
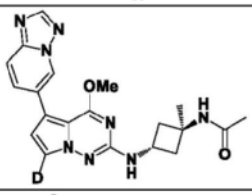
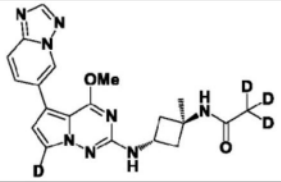
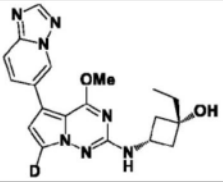
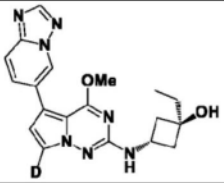
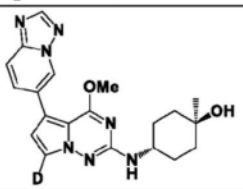
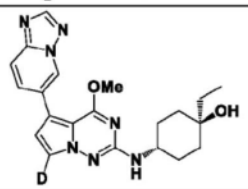
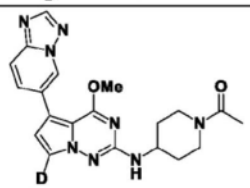
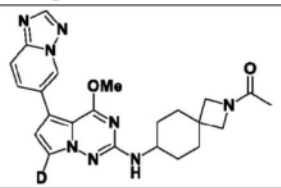
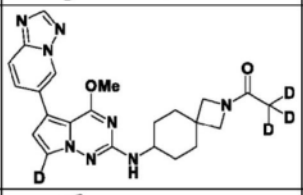
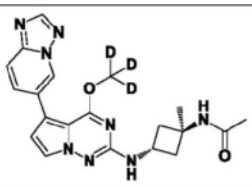
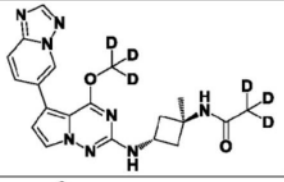
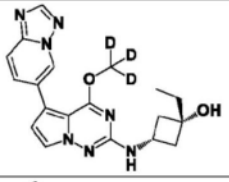
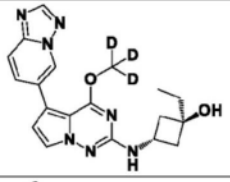
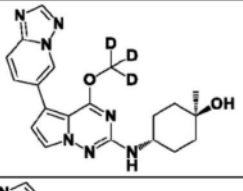
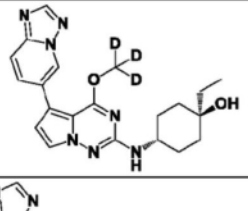
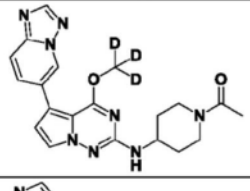
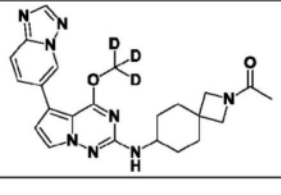
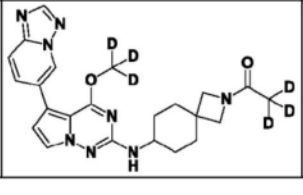
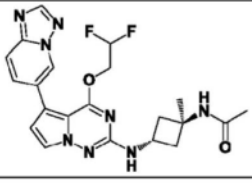
589		590		591	
592		593		594	
595		596		597	
598		599		600	
601		602		603	
604		605		606	
607		608		609	
610		611		612	

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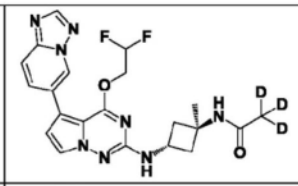
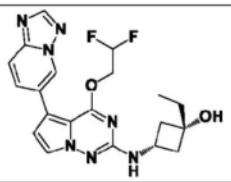
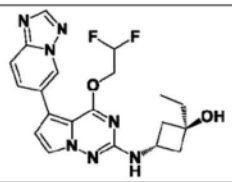
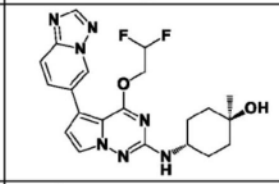
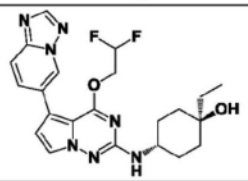
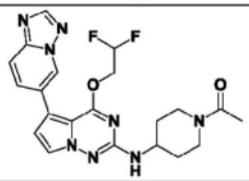
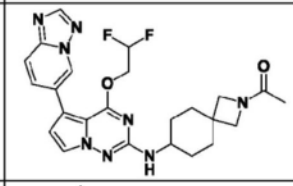
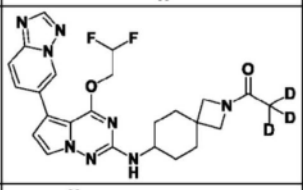
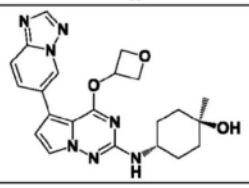
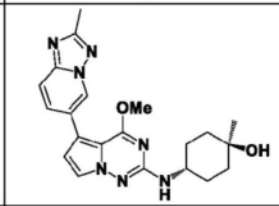
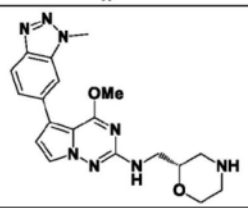
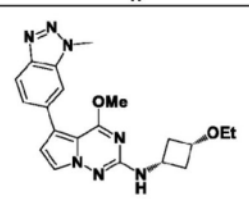
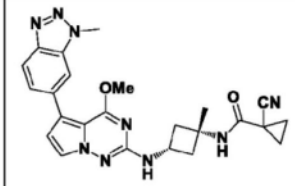
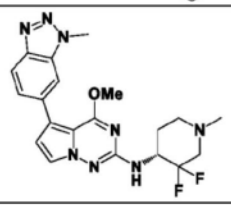
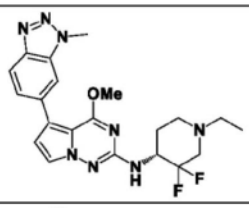
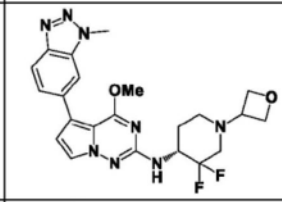
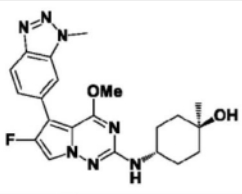
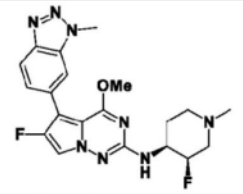
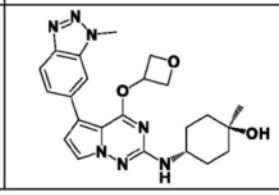
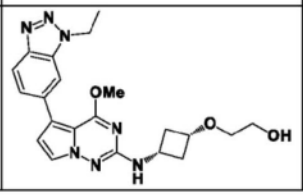
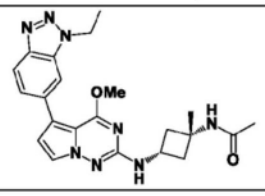
613		614		615	
616		617		618	
619		620		621	
622		623		624	
625		626		627	
628		629		630	
631		632		633	

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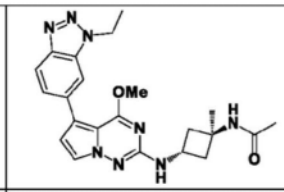
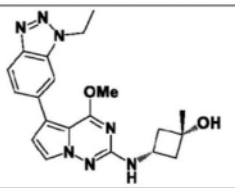
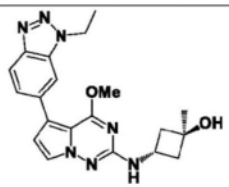
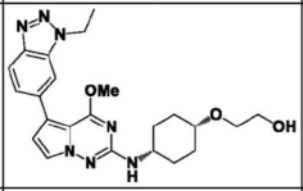
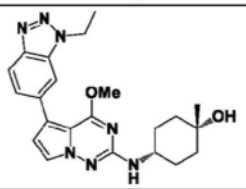
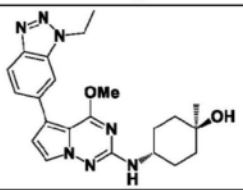
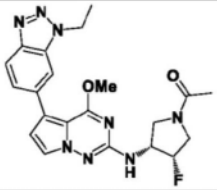
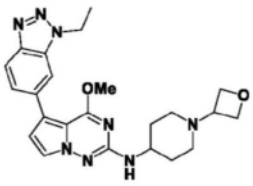
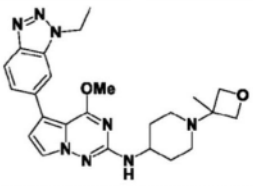
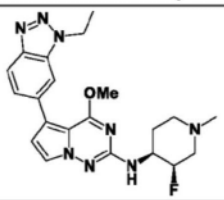
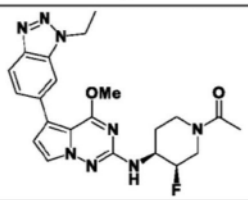
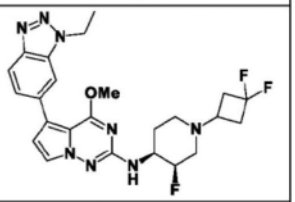
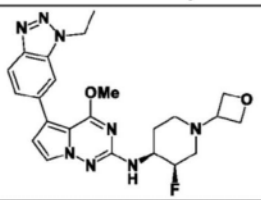
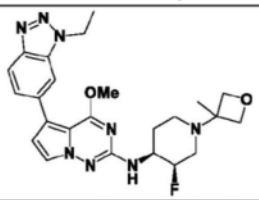
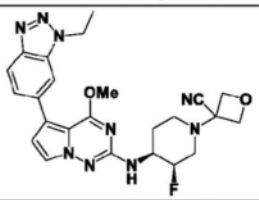
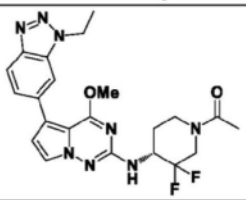
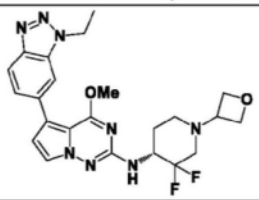
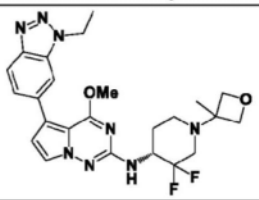
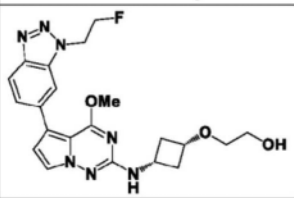
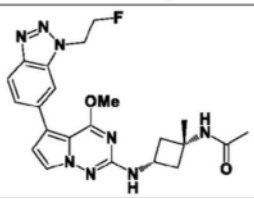
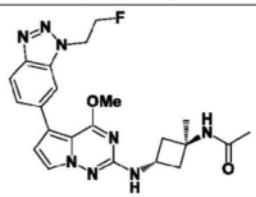
634		635		636	
637		638		639	
640		641		642	
643		644		645	
646		647		648	
649		650		651	
652		653		654	

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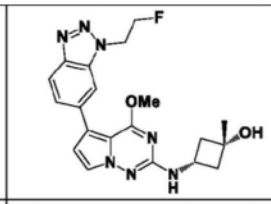
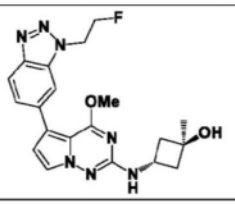
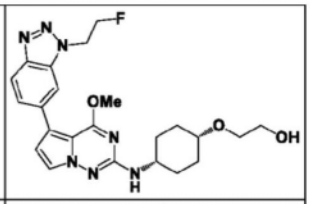
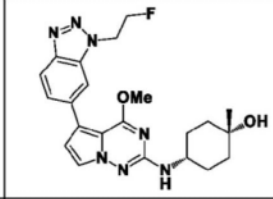
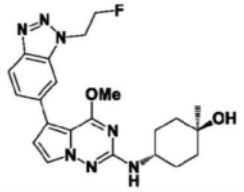
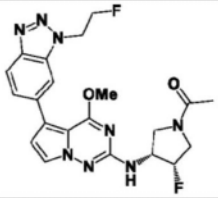
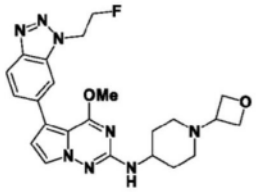
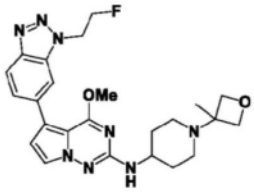
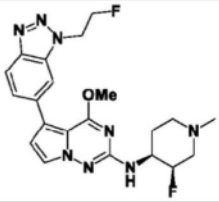
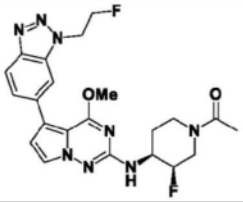
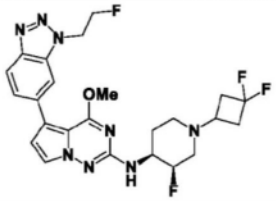
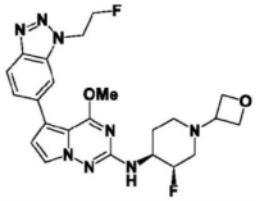
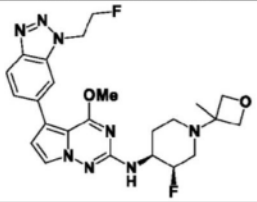
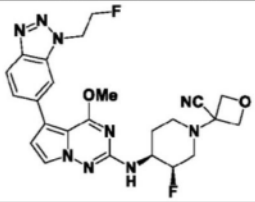
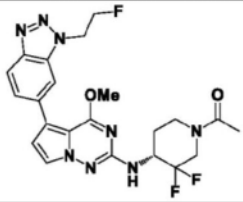
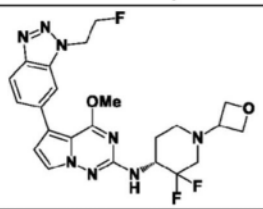
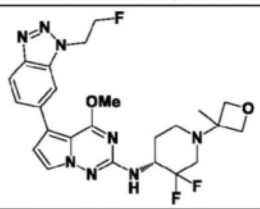
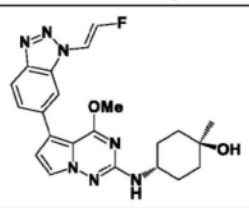
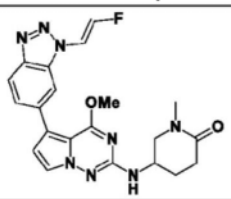
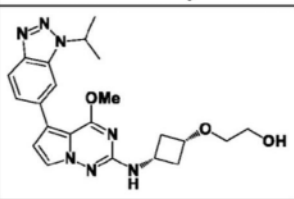
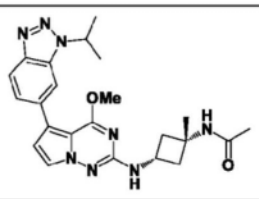
655		656		657	
658		659		660	
661		662		663	
664		665		666	
667		668		669	
670		671		672	
673		674		675	

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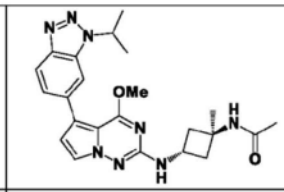
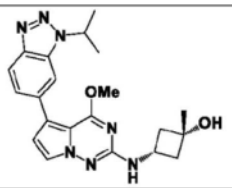
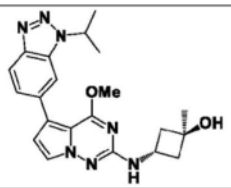
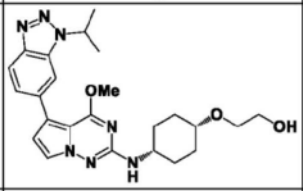
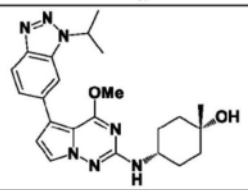
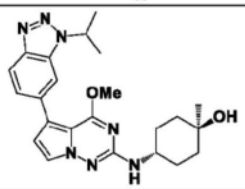
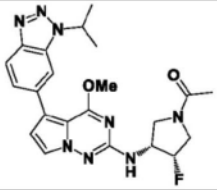
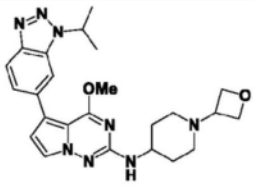
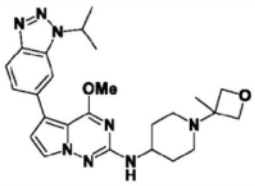
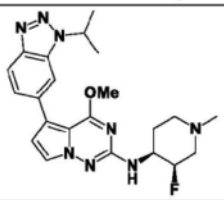
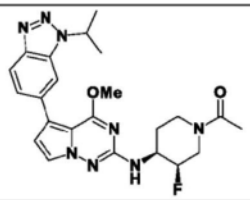
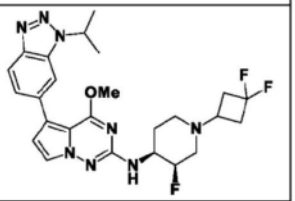
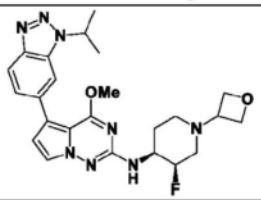
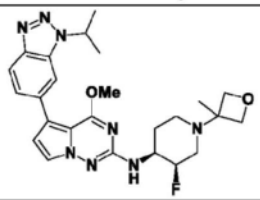
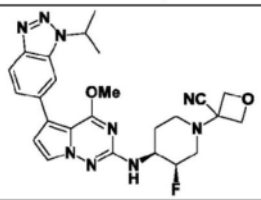
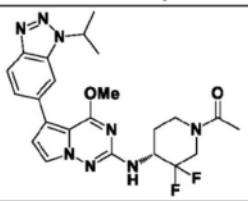
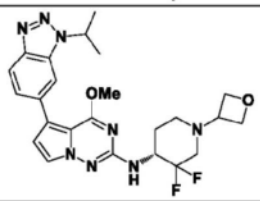
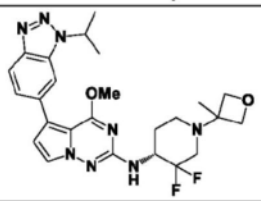
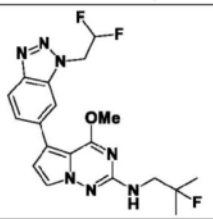
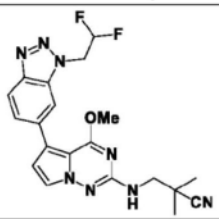
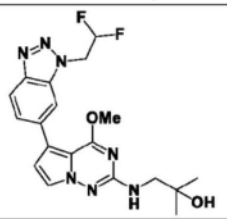
676		677		678	
679		680		681	
682		683		684	
685		686		687	
688		689		690	
691		692		693	
694		695		696	

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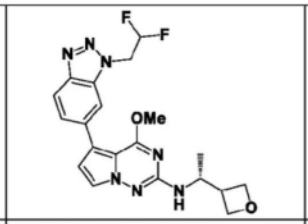
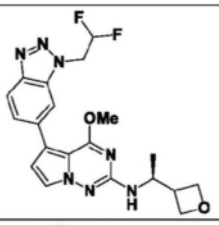
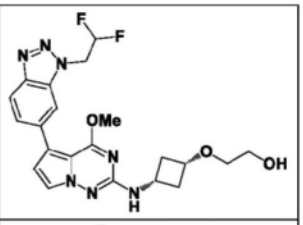
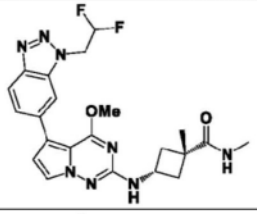
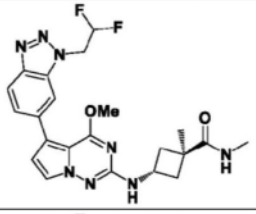
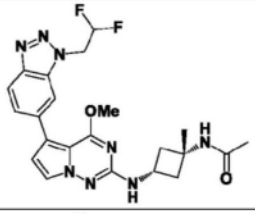
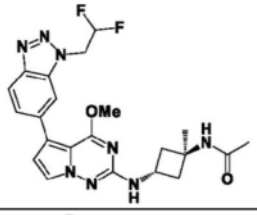
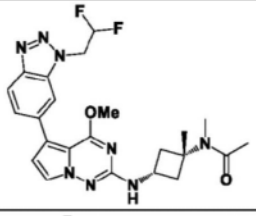
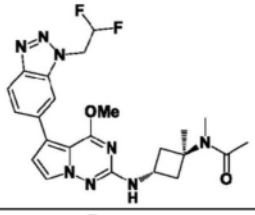
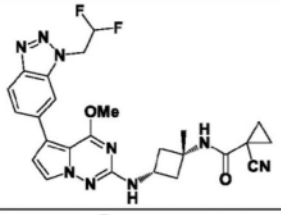
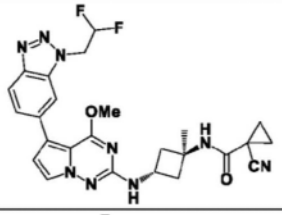
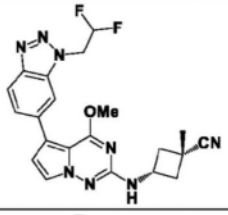
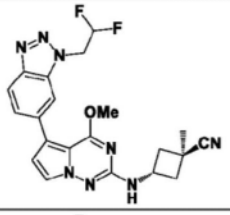
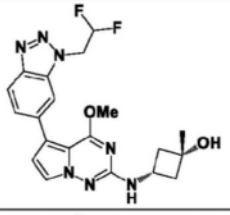
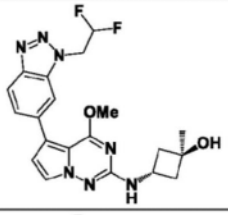
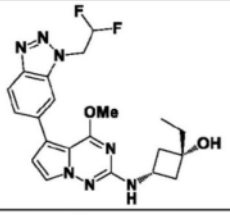
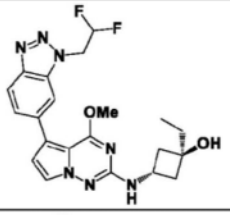
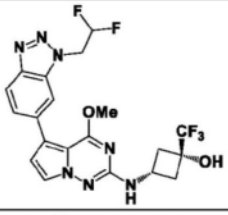
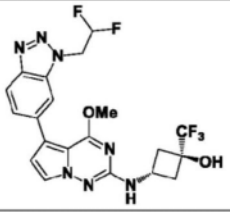
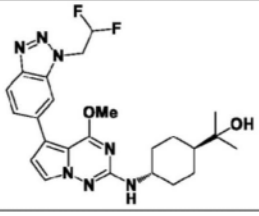
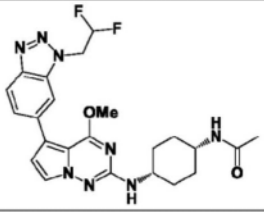
697		698		699	
700		701		702	
703		704		705	
706		707		708	
709		710		711	
712		713		714	
715		716		717	

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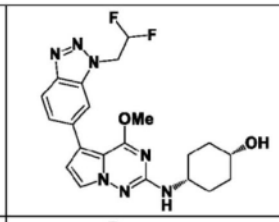
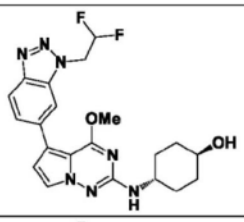
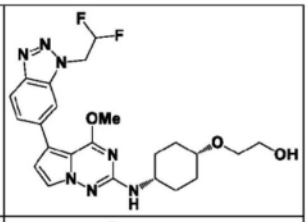
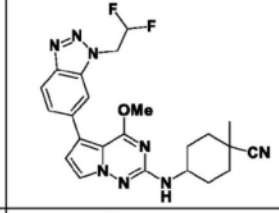
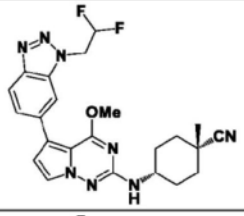
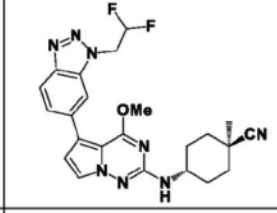
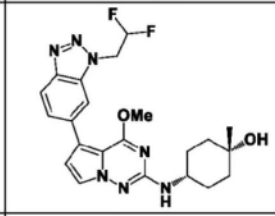
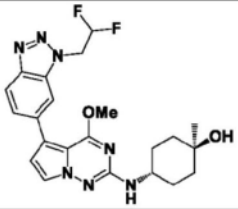
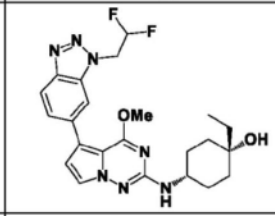
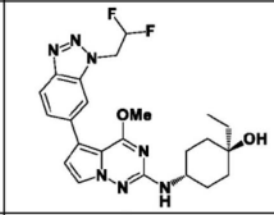
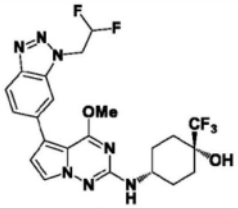
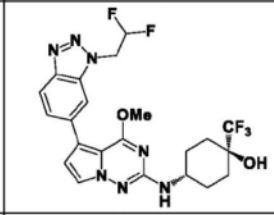
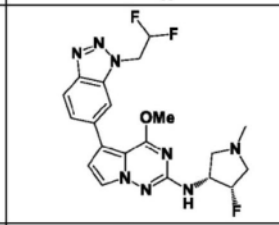
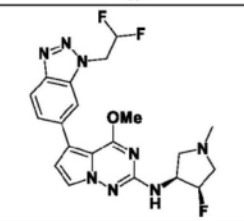
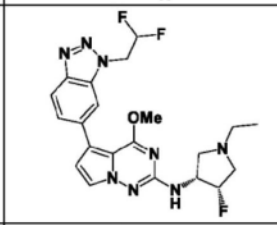
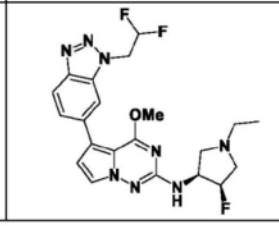
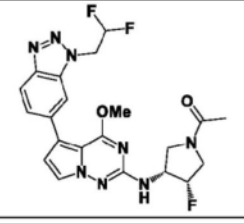
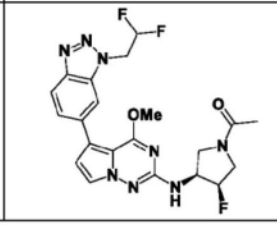
718		719		720	
721		722		723	
724		725		726	
727		728		729	
730		731		732	
733		734		735	

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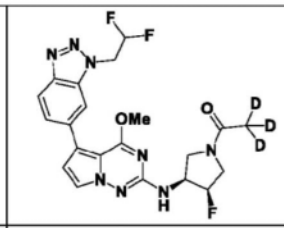
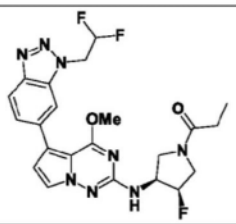
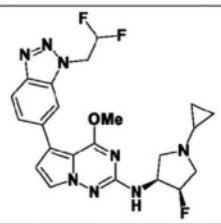
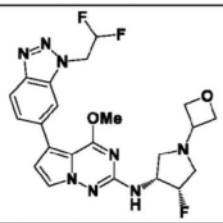
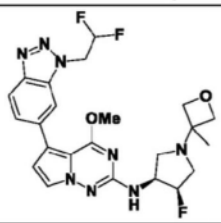
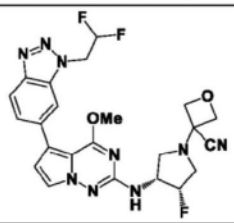
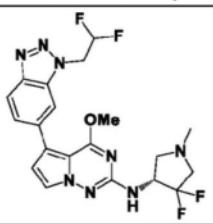
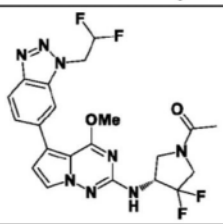
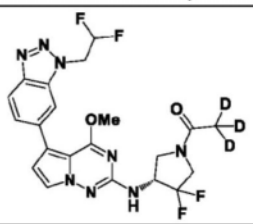
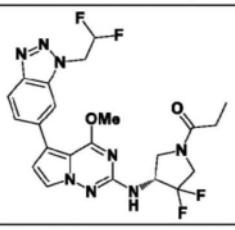
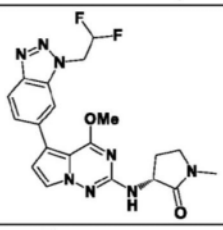
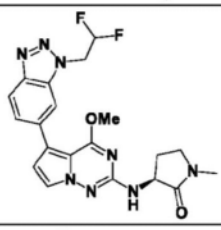
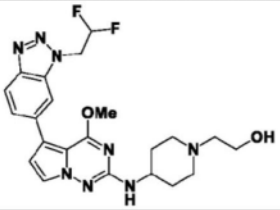
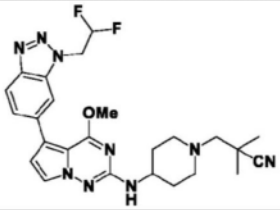
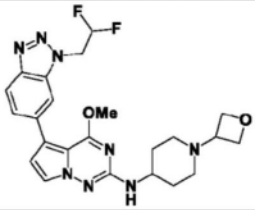
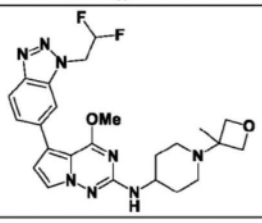
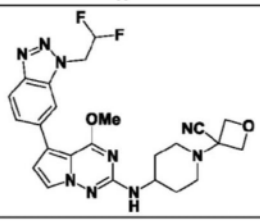
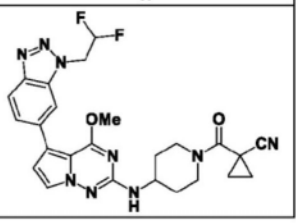
736		737		738	
739		740		741	
742		743		744	
745		746		747	
748		749		750	
751		752		753	

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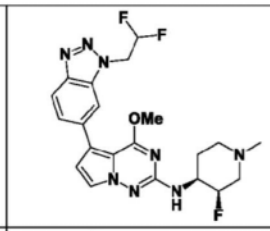
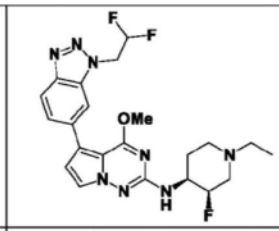
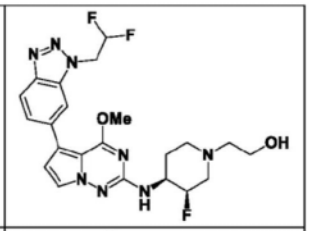
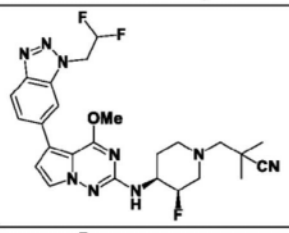
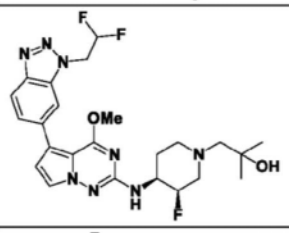
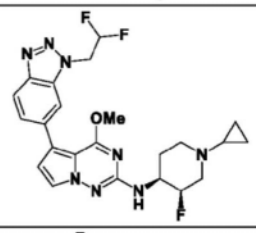
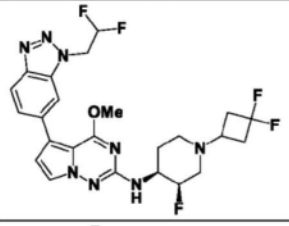
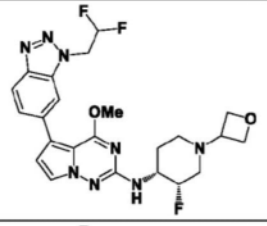
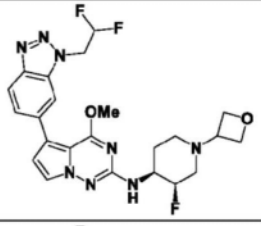
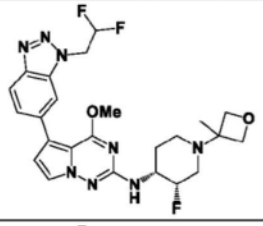
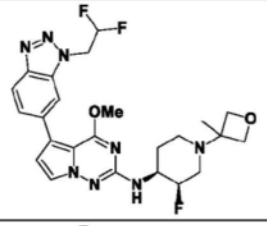
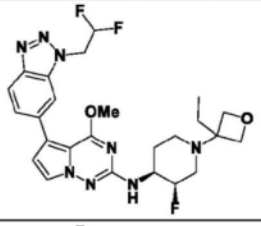
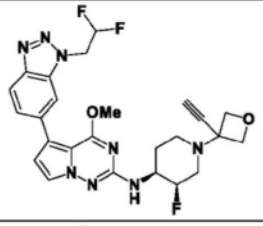
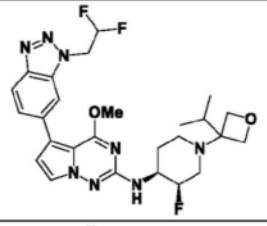
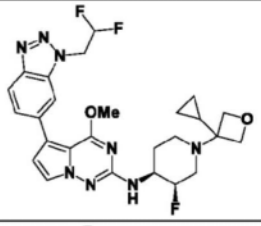
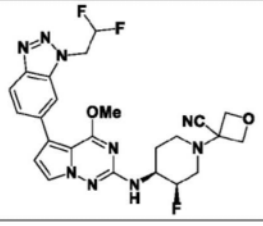
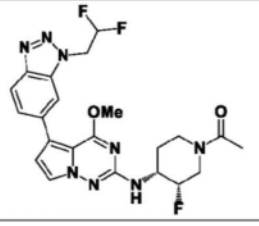
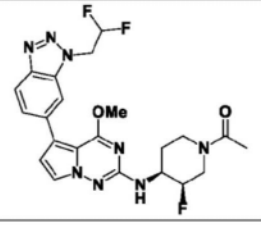
754		755		756	
757		758		759	
760		761		762	
763		764		765	
766		767		768	
769		770		771	

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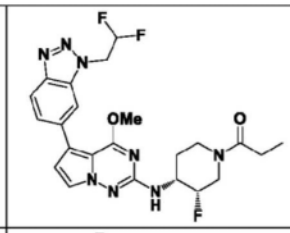
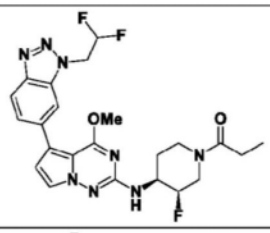
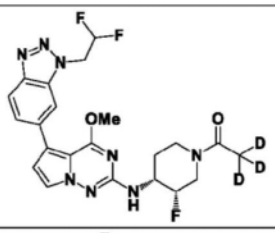
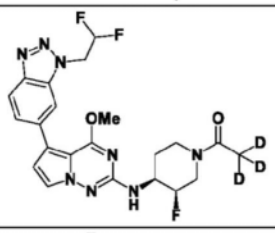
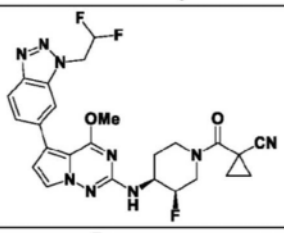
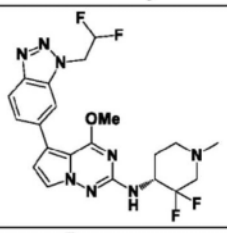
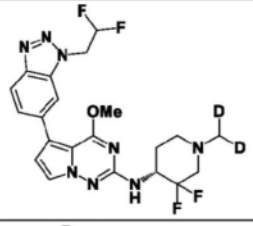
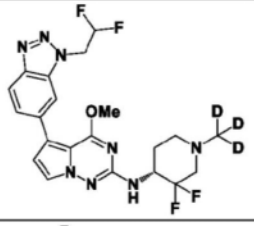
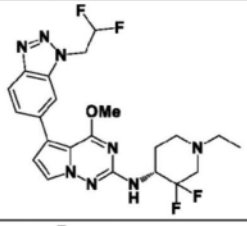
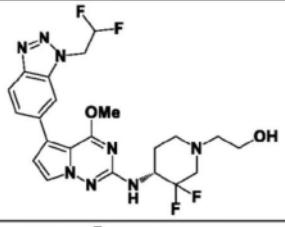
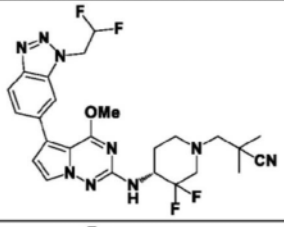
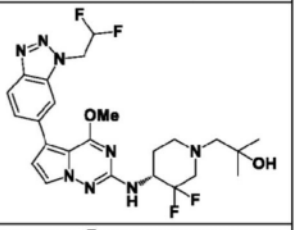
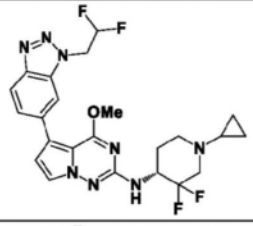
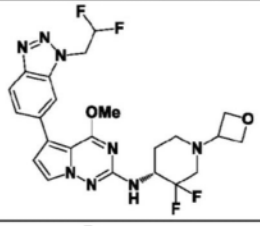
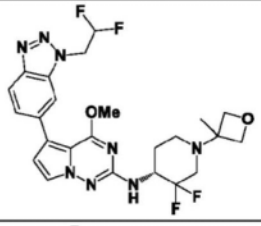
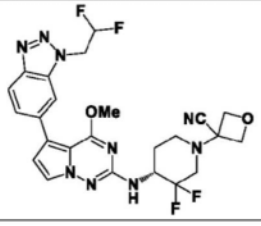
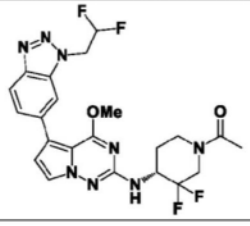
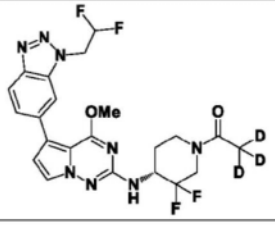
772		773		774	
775		776		777	
778		779		780	
781		782		783	
784		785		786	
787		788		789	

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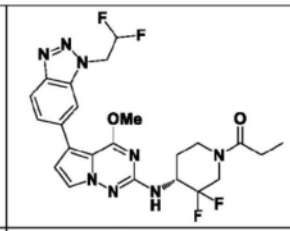
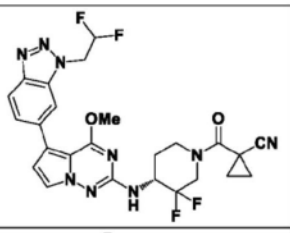
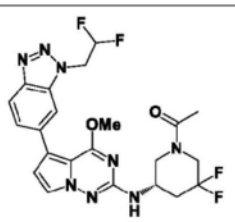
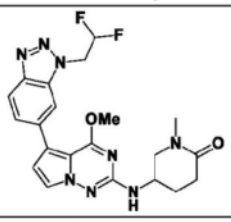
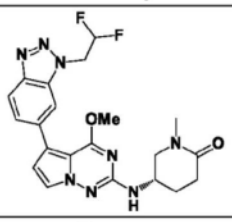
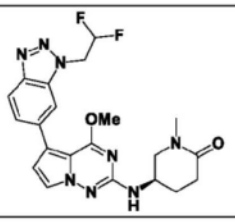
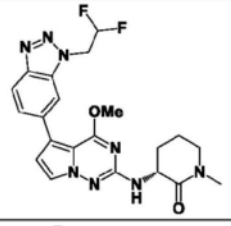
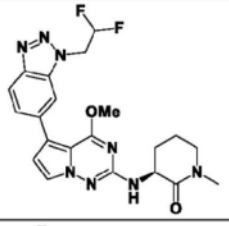
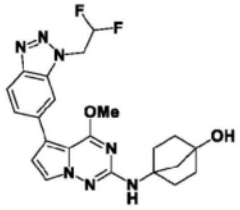
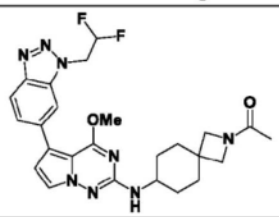
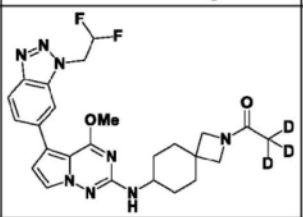
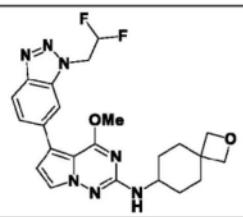
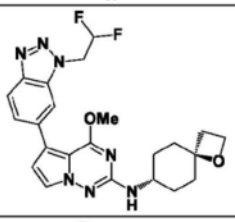
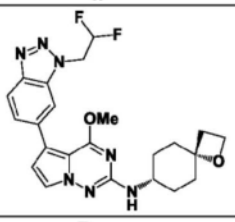
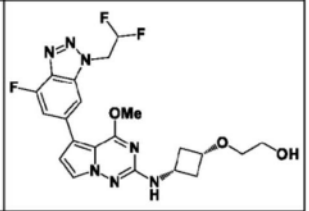
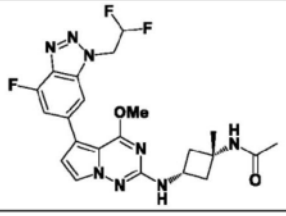
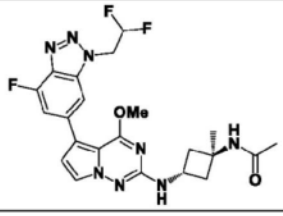
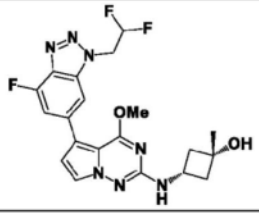
790		791		792	
793		794		795	
796		797		798	
799		800		801	
802		803		804	
805		806		807	

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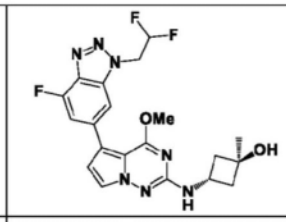
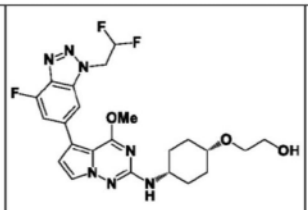
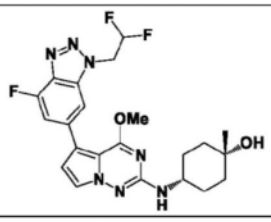
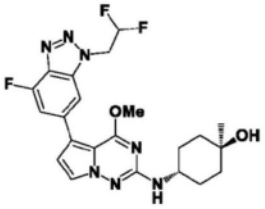
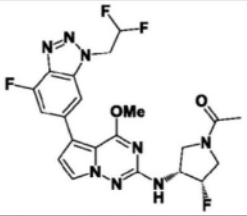
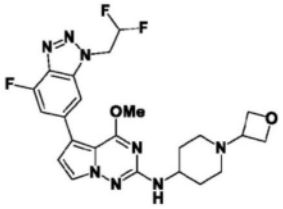
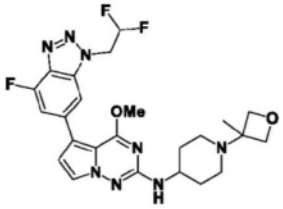
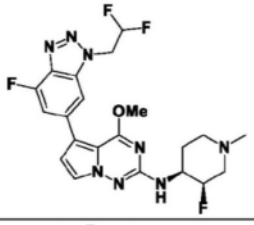
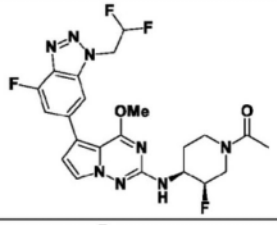
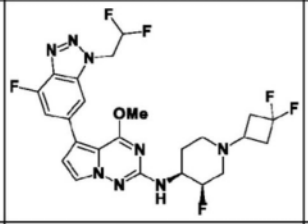
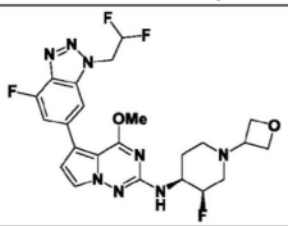
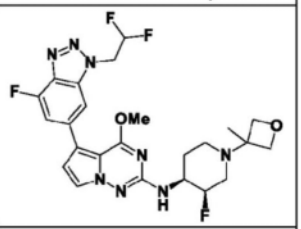
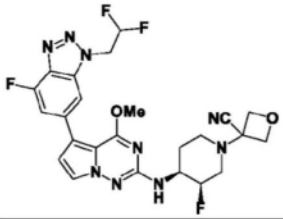
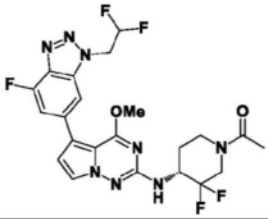
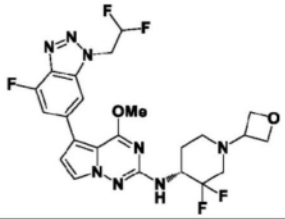
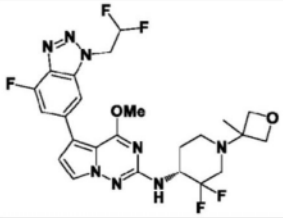
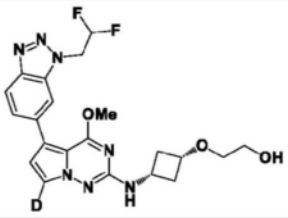
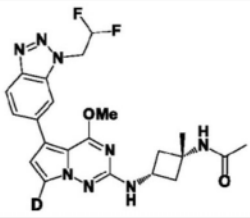
808		809		810	
811		812		813	
814		815		816	
817		818		819	
820		821		822	
823		824		825	

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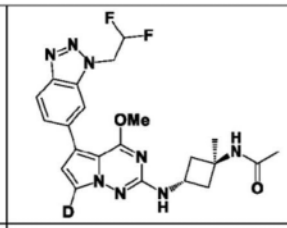
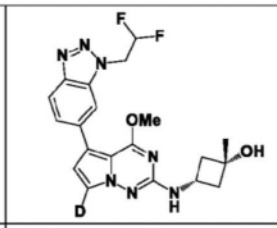
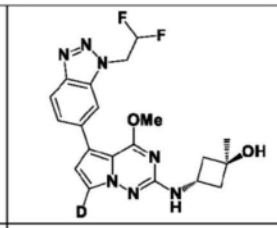
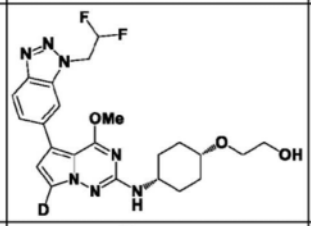
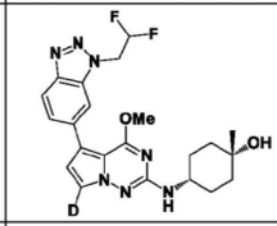
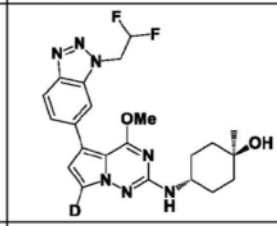
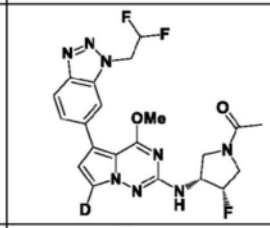
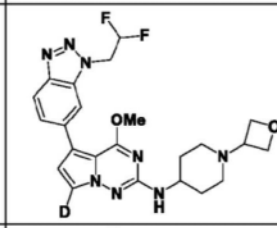
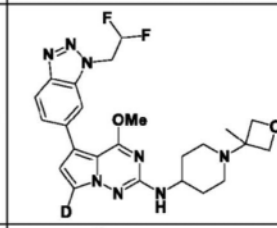
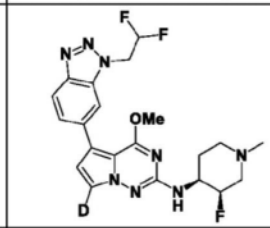
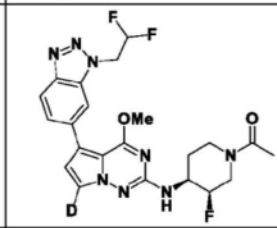
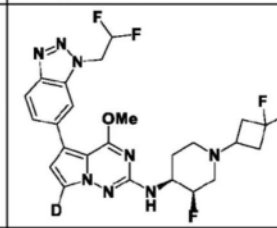
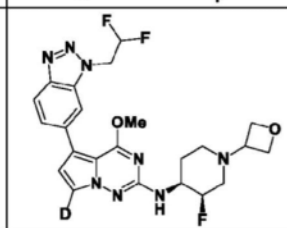
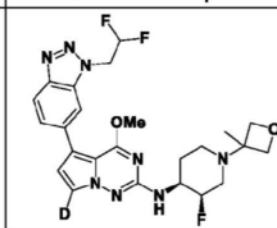
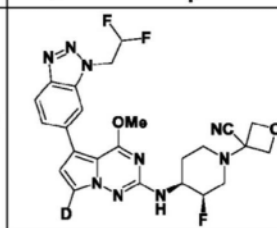
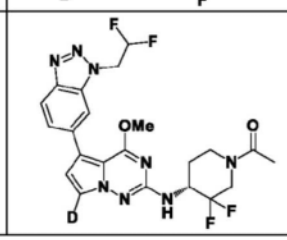
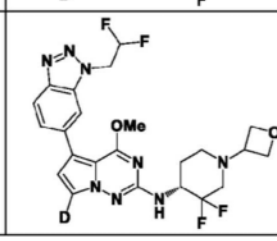
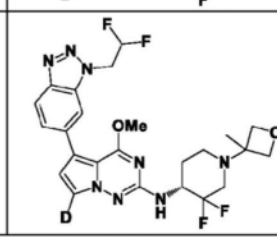
826		827		828	
829		830		831	
832		833		834	
835		836		837	
838		839		840	
841		842		843	

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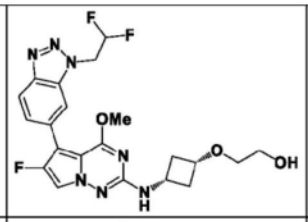
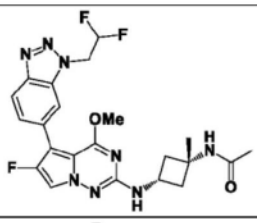
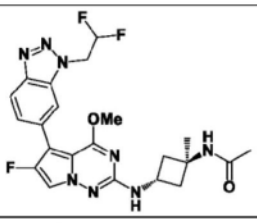
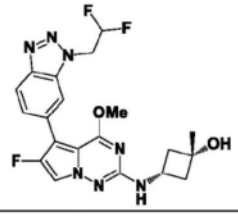
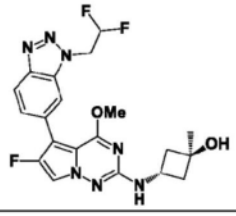
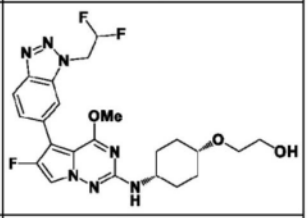
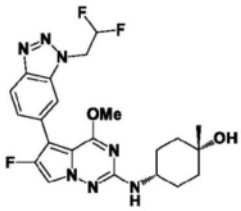
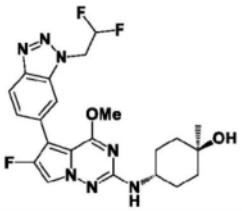
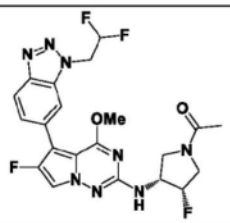
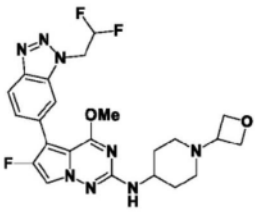
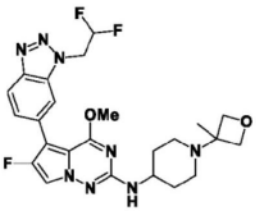
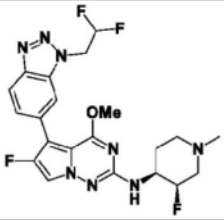
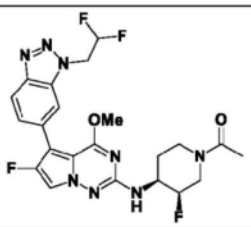
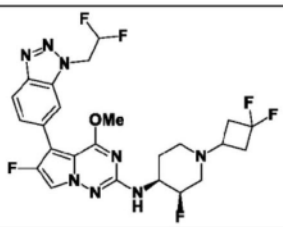
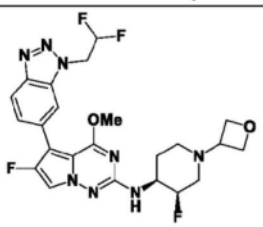
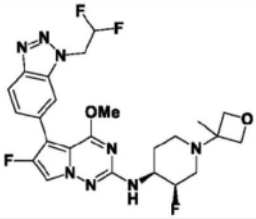
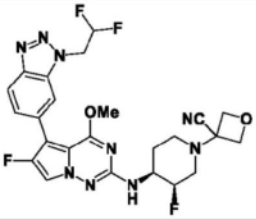
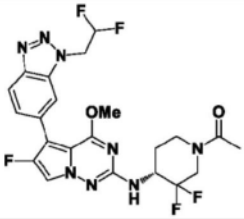
844		845		846	
847		848		849	
850		851		852	
853		854		855	
856		857		858	
859		860		861	

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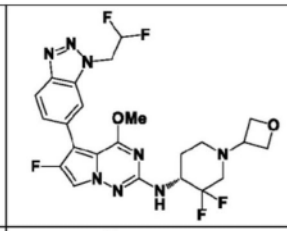
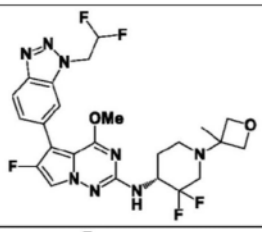
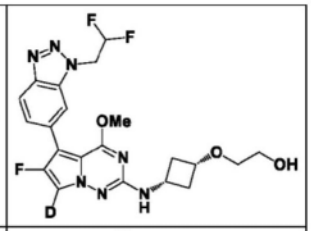
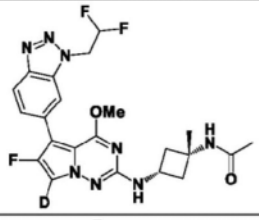
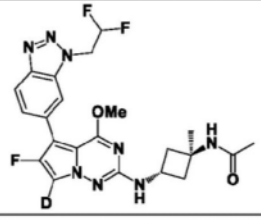
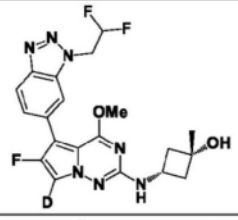
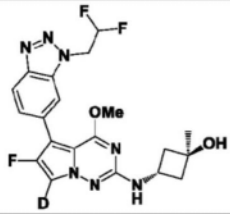
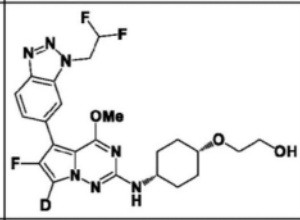
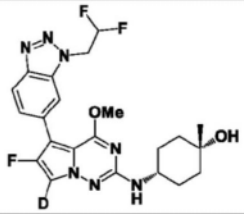
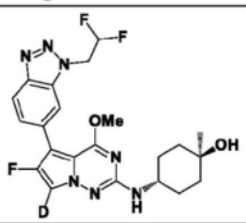
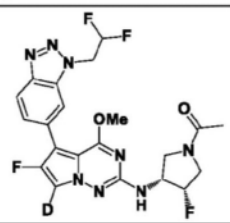
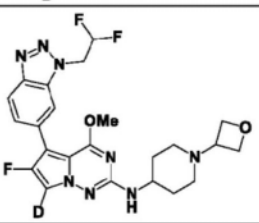
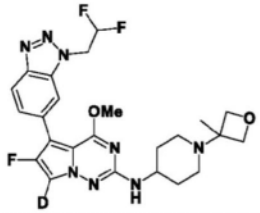
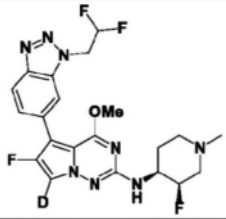
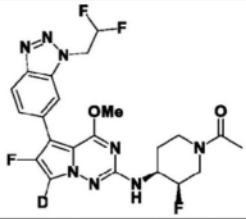
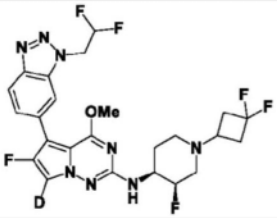
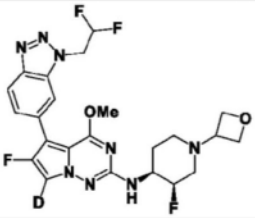
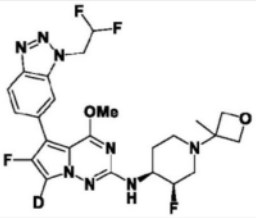
862		863		864	
865		866		867	
868		869		870	
871		872		873	
874		875		876	
877		878		879	

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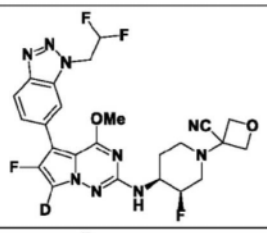
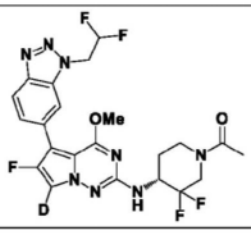
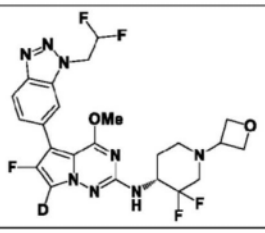
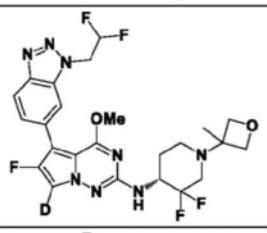
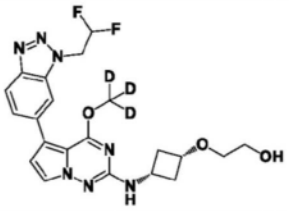
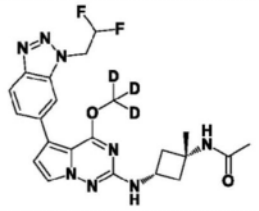
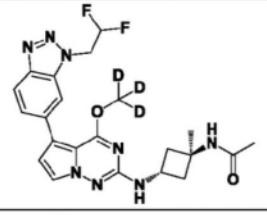
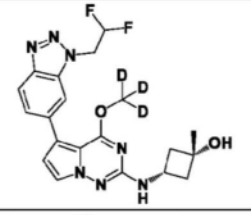
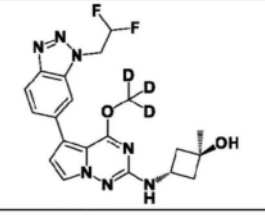
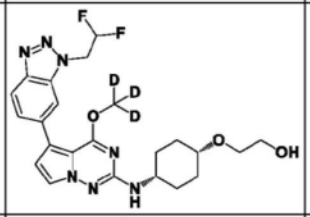
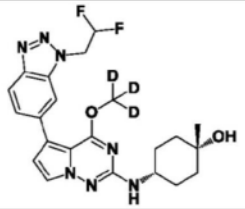
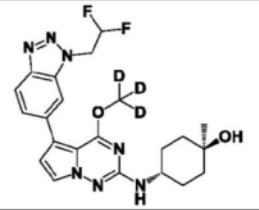
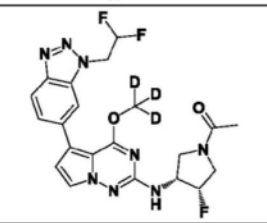
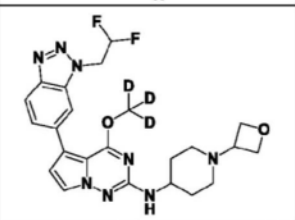
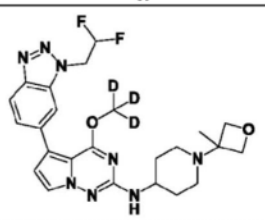
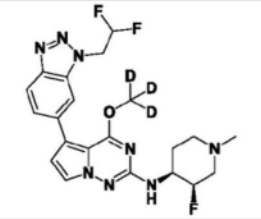
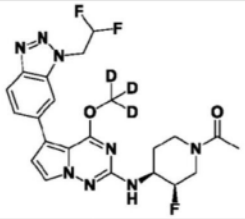
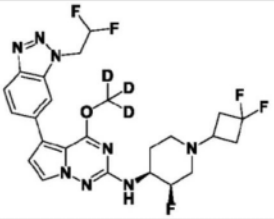
880		881		882	
883		884		885	
886		887		888	
889		890		891	
892		893		894	
895		896		897	

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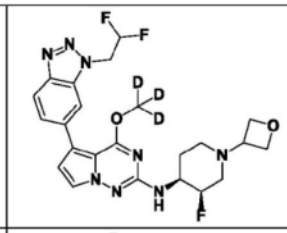
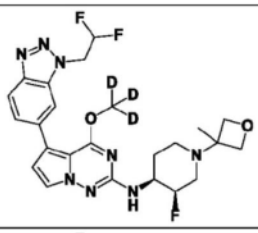
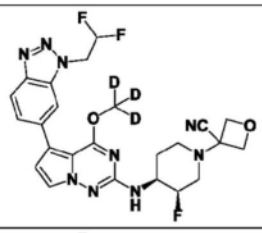
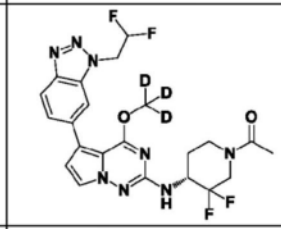
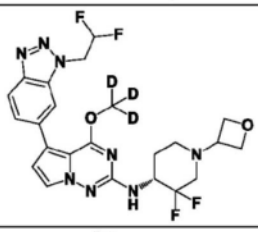
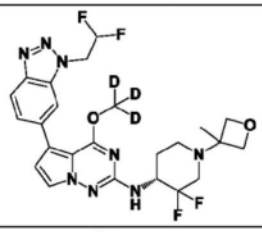
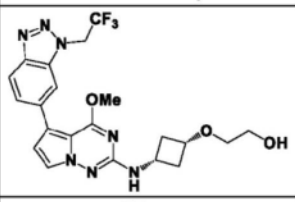
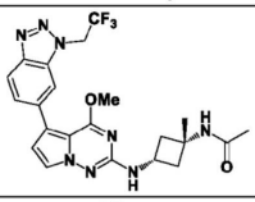
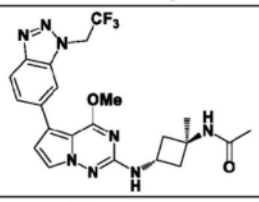
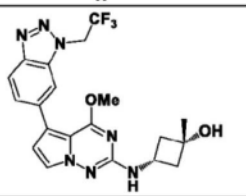
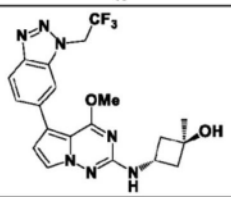
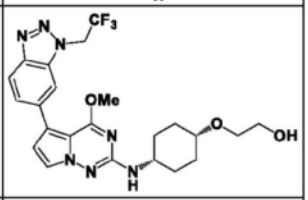
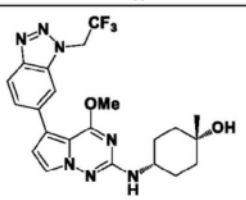
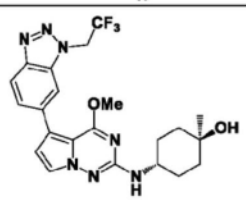
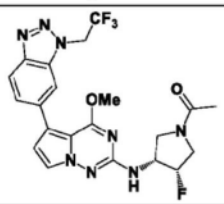
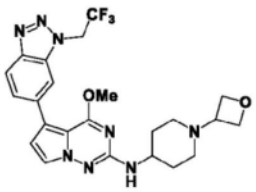
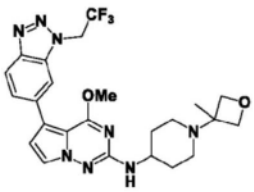
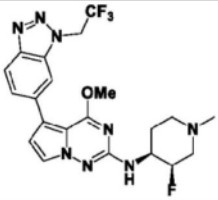
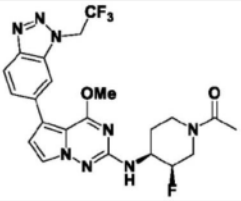
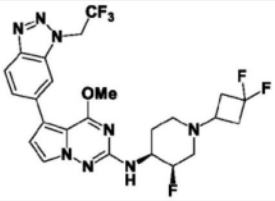
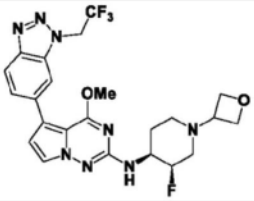
898		899		900	
901		902		903	
904		905		906	
907		908		909	
910		911		912	
913		914		915	
916		917		918	

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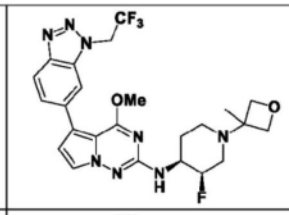
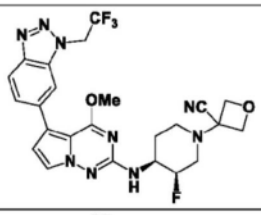
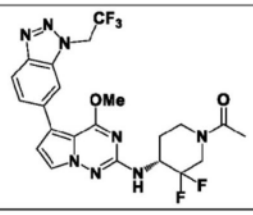
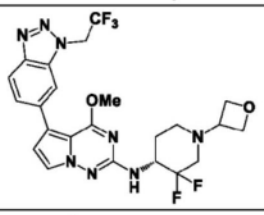
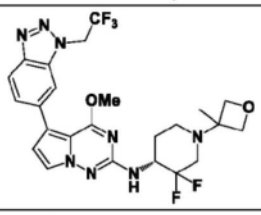
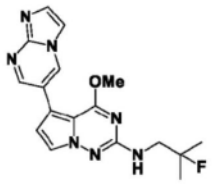
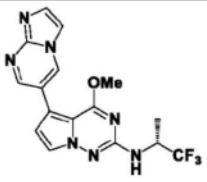
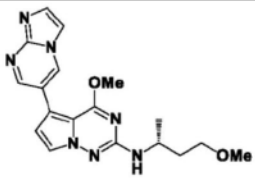
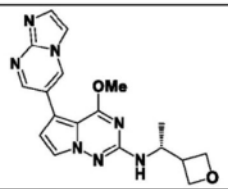
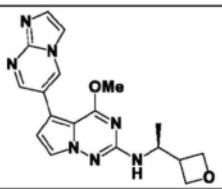
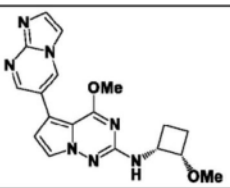
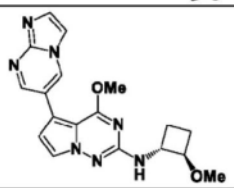
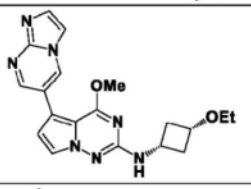
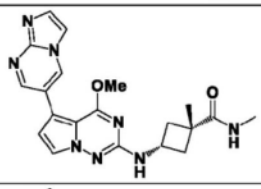
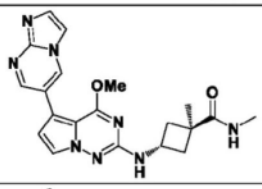
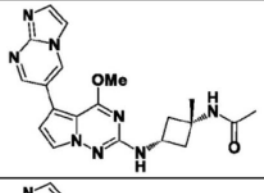
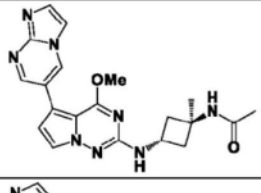
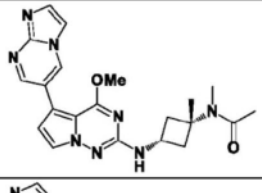
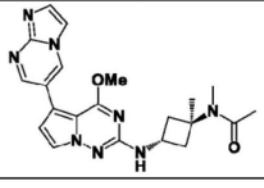
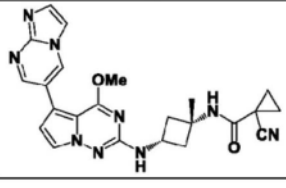
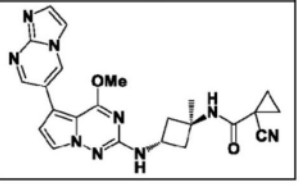
919		920		921	
922		923		924	
925		926		927	
928		929		930	
931		932		933	
934		935		936	
937		938		939	

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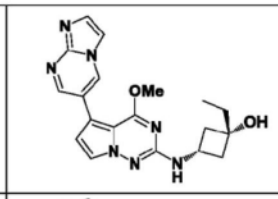
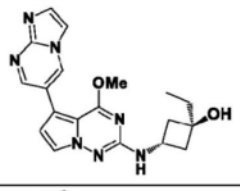
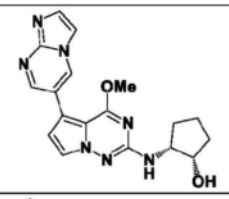
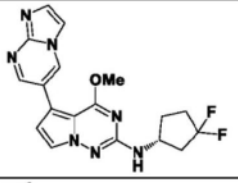
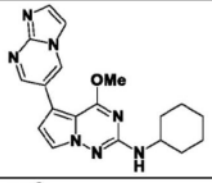
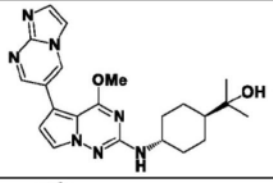
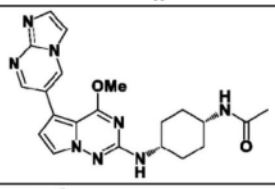
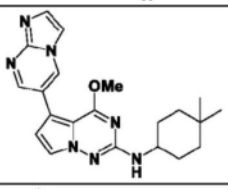
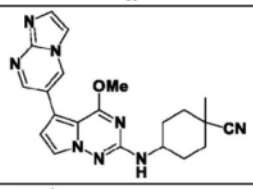
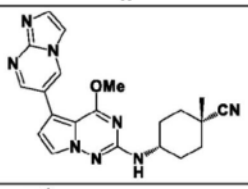
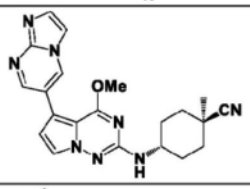
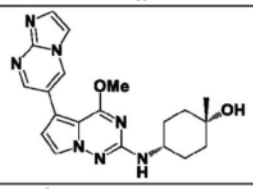
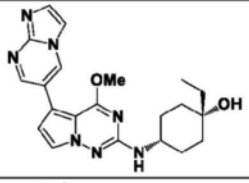
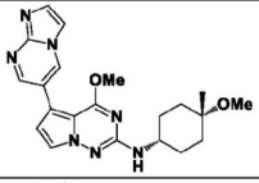
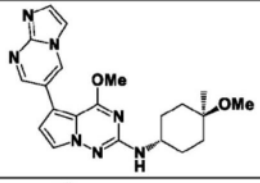
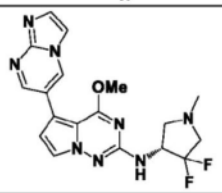
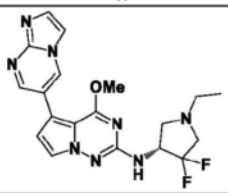
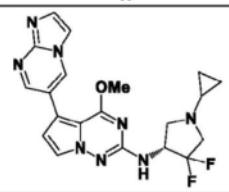
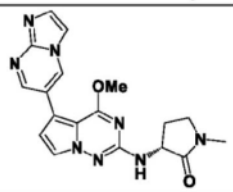
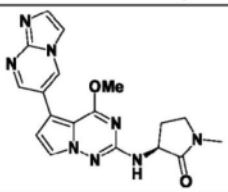
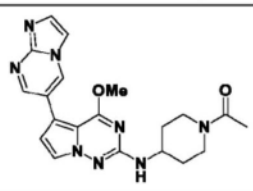
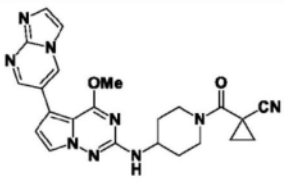
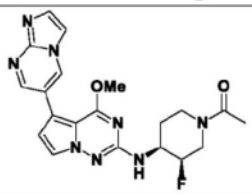
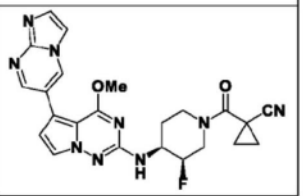
940		941		942	
943		944		945	
946		947		948	
949		950		951	
952		953		954	
955		956		957	
958		959		960	
961		962		963	

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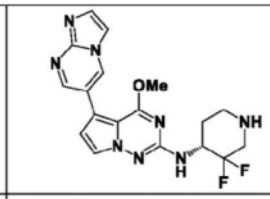
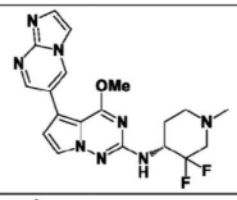
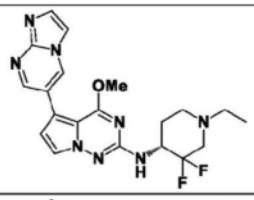
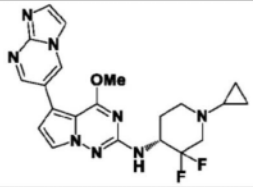
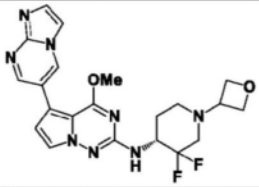
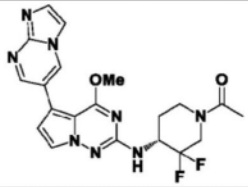
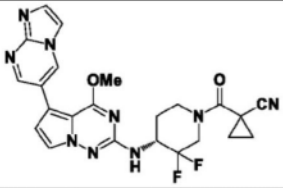
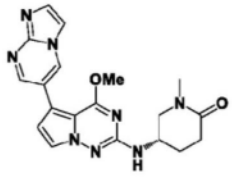
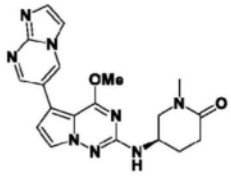
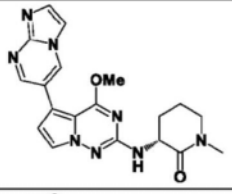
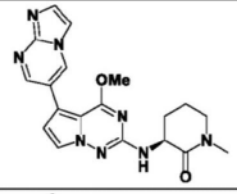
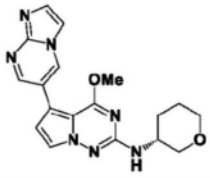
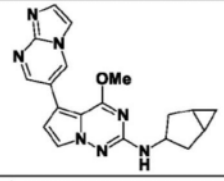
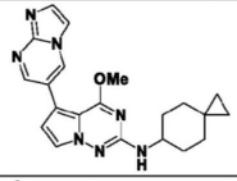
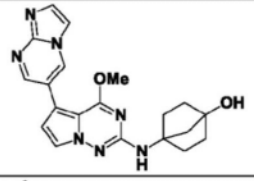
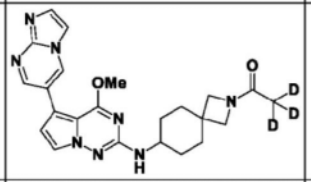
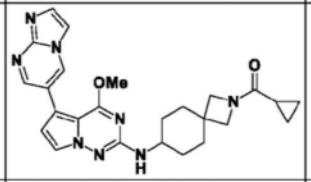
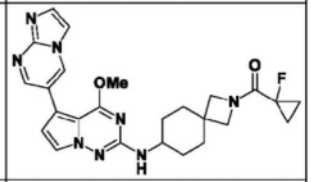
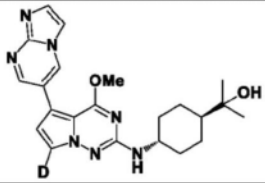
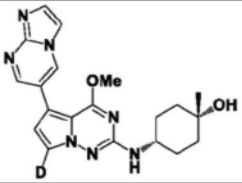
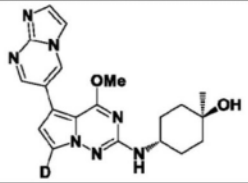
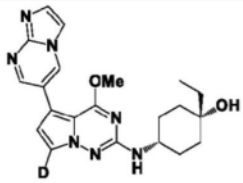
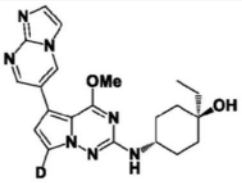
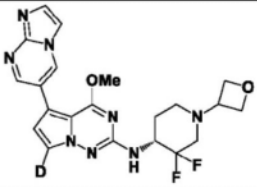
964		965		966	
967		968		969	
970		971		972	
973		974		975	
976		977		978	
979		980		981	
982		983		984	
985		986		987	

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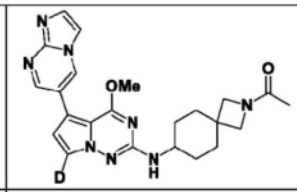
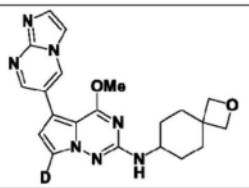
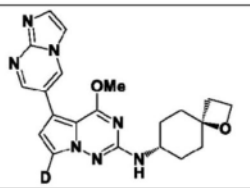
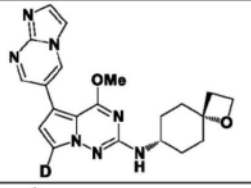
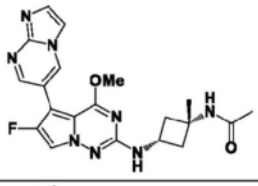
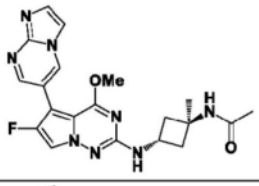
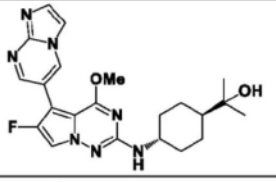
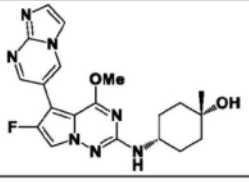
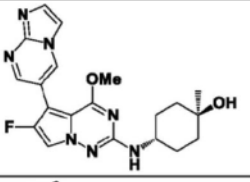
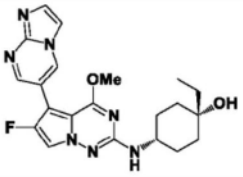
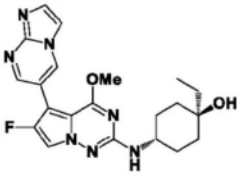
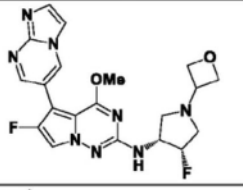
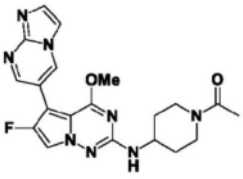
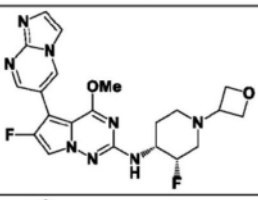
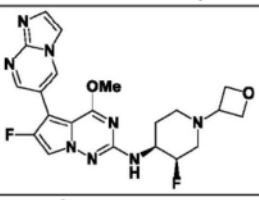
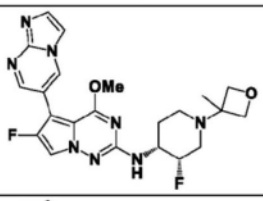
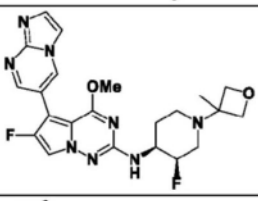
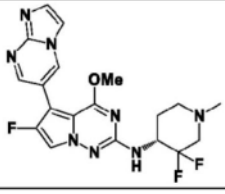
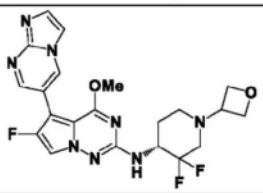
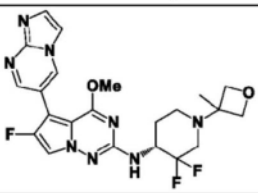
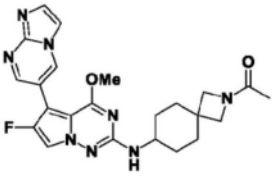
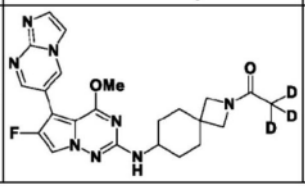
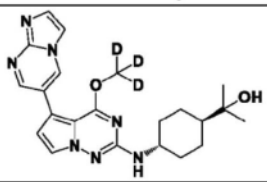
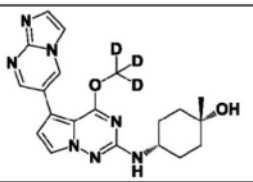
988		989		990	
991		992		993	
994		995		996	
997		998		999	
1000		1001		1002	
1003		1004		1005	
1006		1007		1008	
1009		1010		1011	

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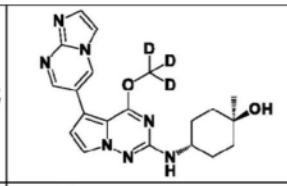
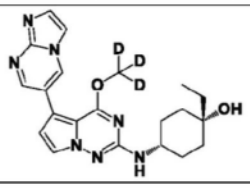
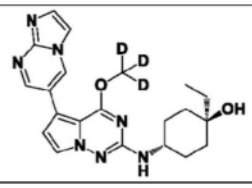
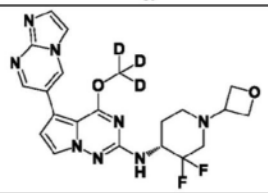
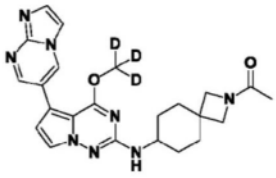
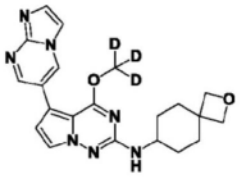
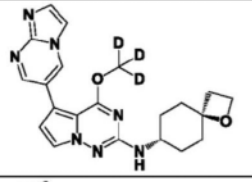
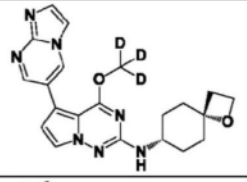
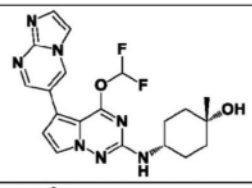
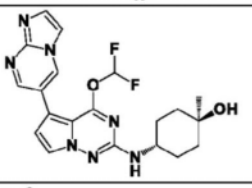
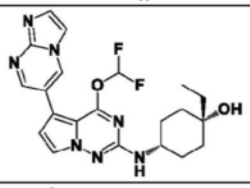
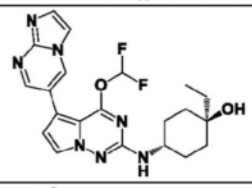
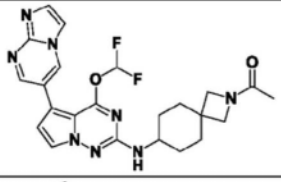
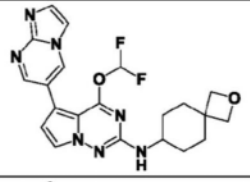
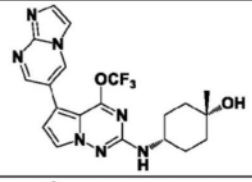
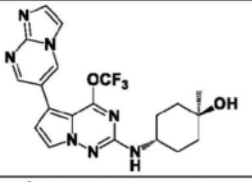
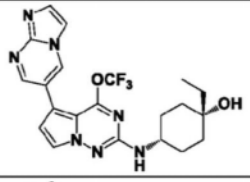
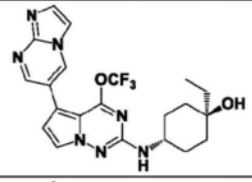
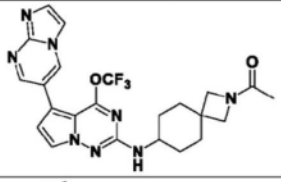
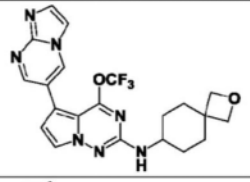
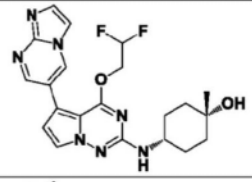
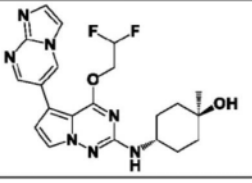
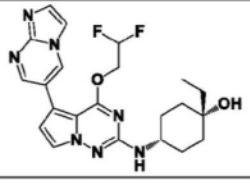
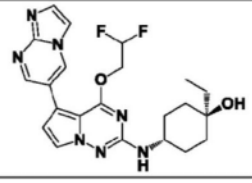
1012		1013		1014	
1015		1016		1017	
1018		1019		1020	
1021		1022		1023	
1024		1025		1026	
1027		1028		1029	
1030		1031		1032	
1033		1034		1035	

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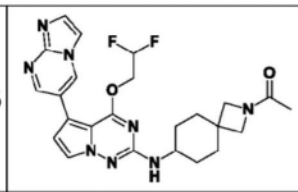
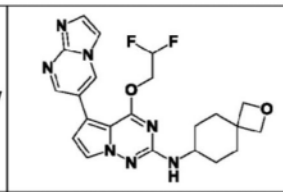
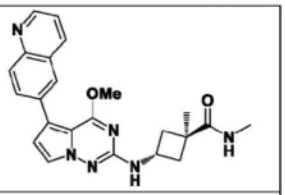
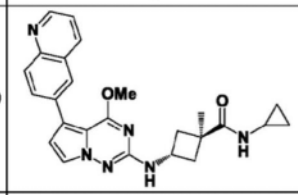
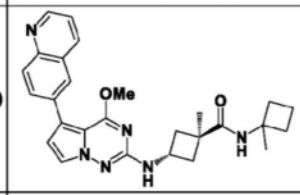
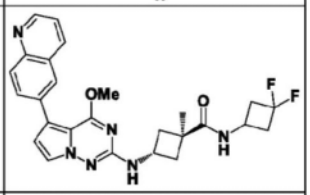
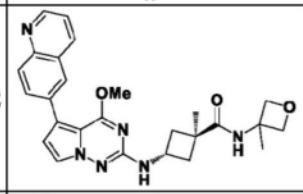
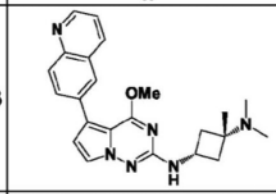
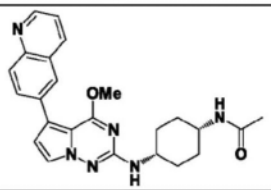
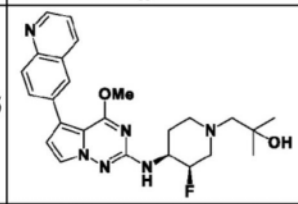
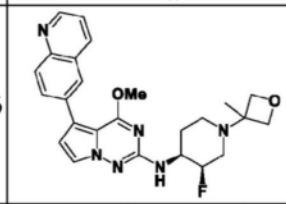
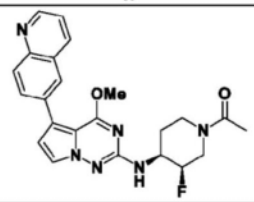
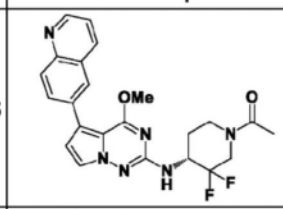
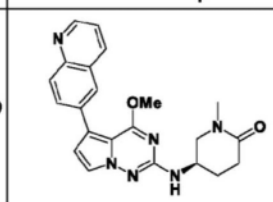
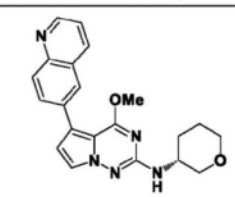
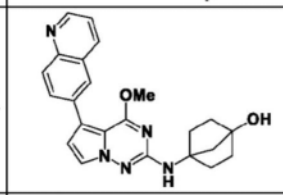
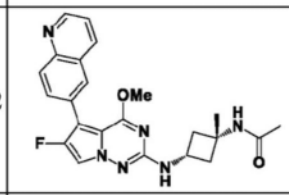
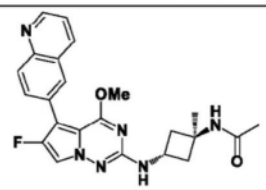
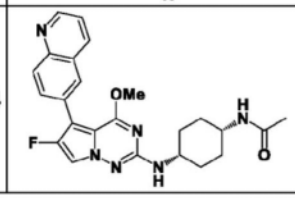
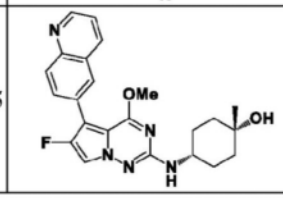
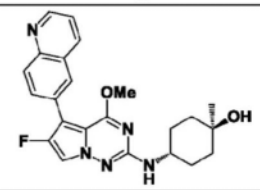
1036		1037		1038	
1039		1040		1041	
1042		1043		1044	
1045		1046		1047	
1048		1049		1050	
1051		1052		1053	
1054		1055		1056	

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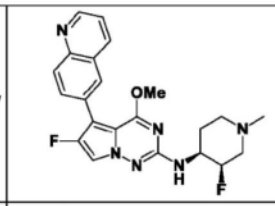
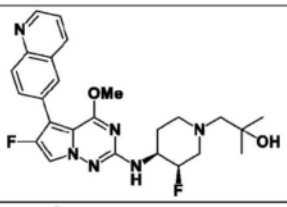
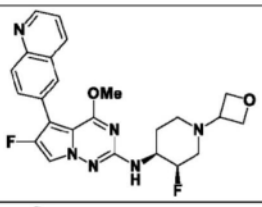
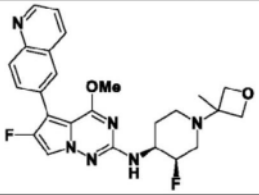
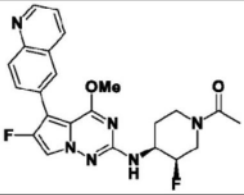
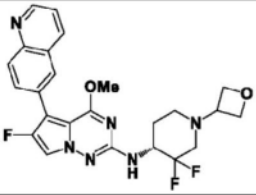
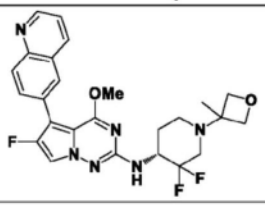
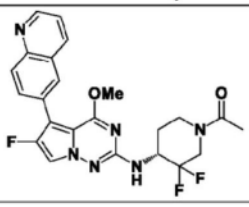
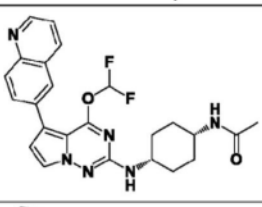
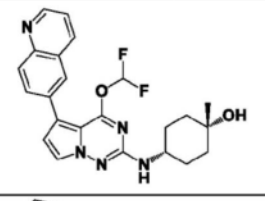
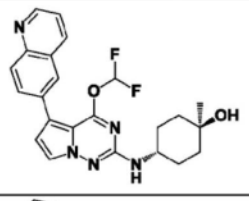
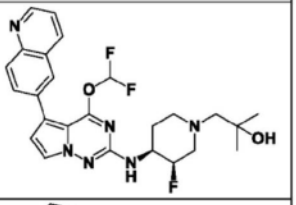
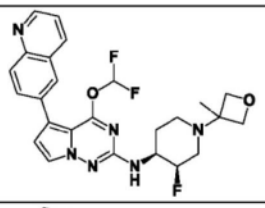
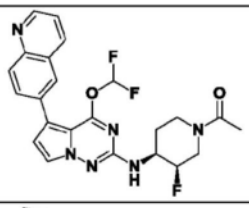
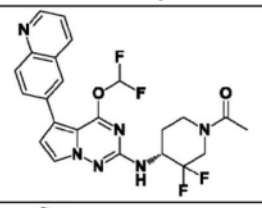
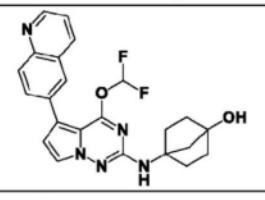
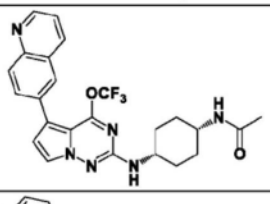
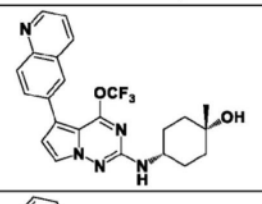
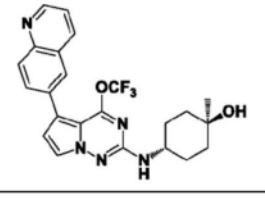
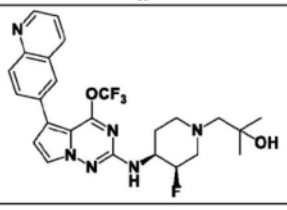
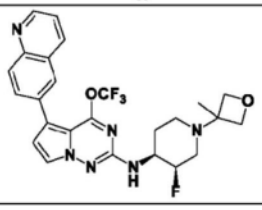
1057		1058		1059	
1060		1061		1062	
1063		1064		1065	
1066		1067		1068	
1069		1070		1071	
1072		1073		1074	
1075		1076		1077	

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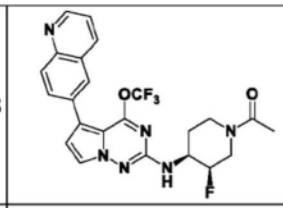
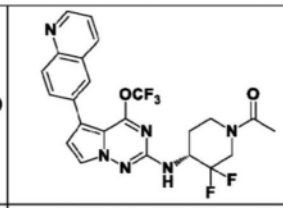
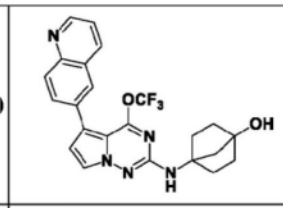
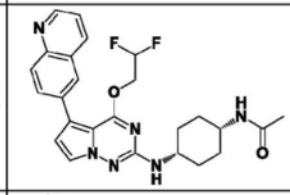
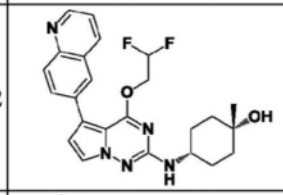
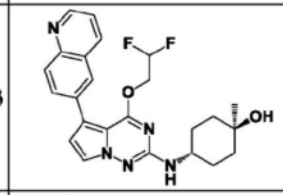
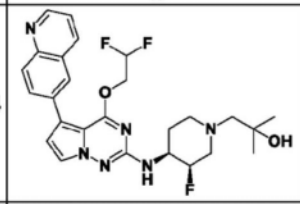
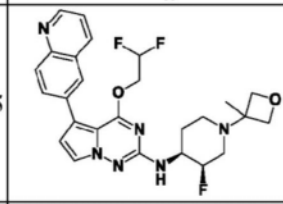
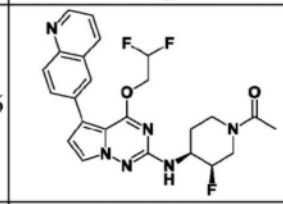
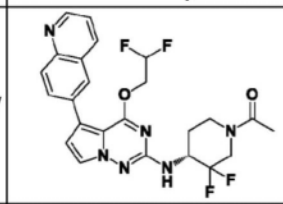
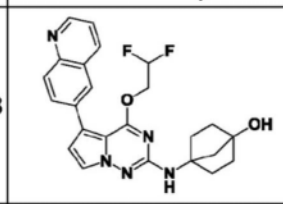
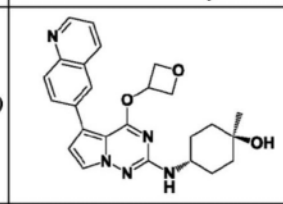
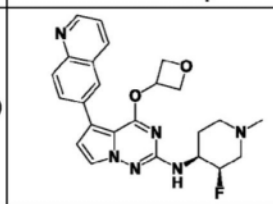
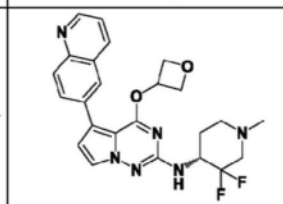
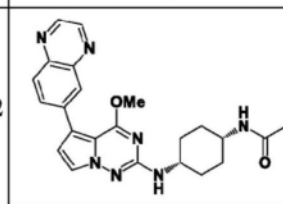
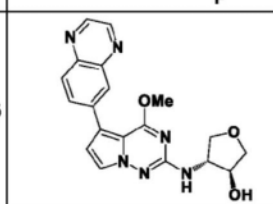
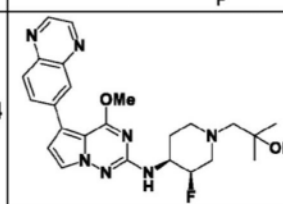
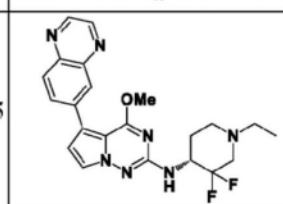
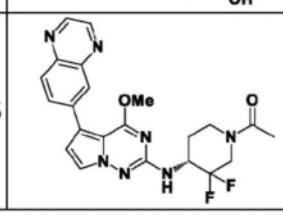
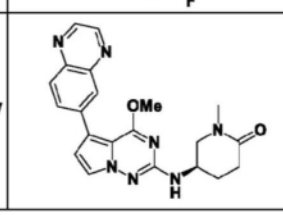
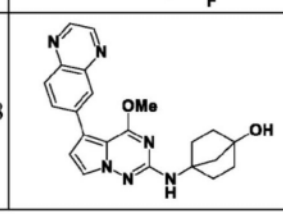
1078		1079		1080	
1081		1082		1083	
1084		1085		1086	
1087		1088		1089	
1090		1091		1092	
1093		1094		1095	
1096		1097		1098	

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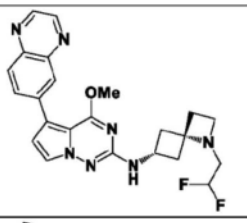
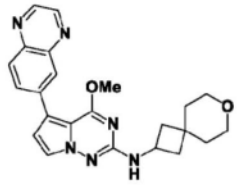
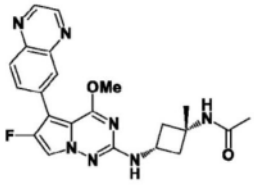
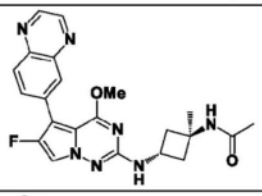
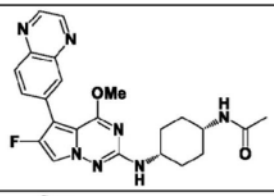
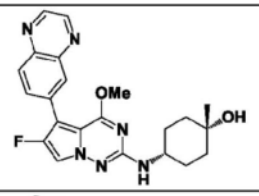
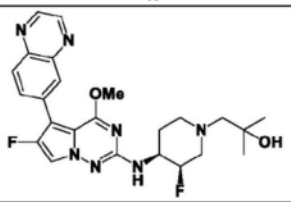
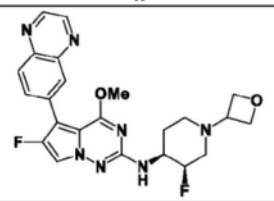
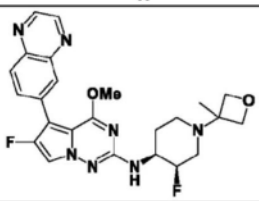
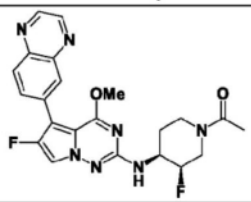
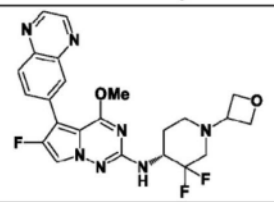
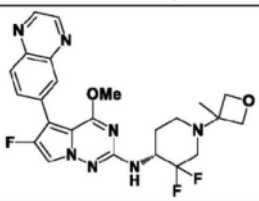
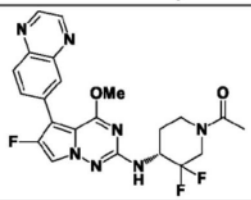
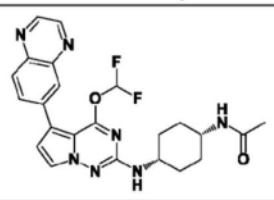
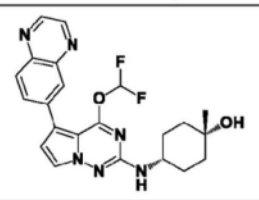
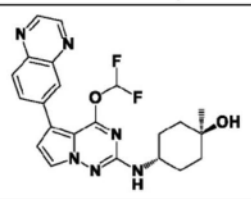
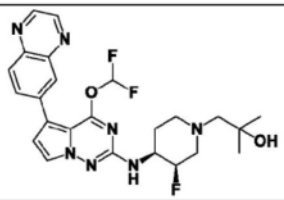
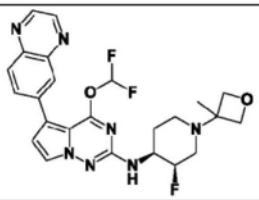
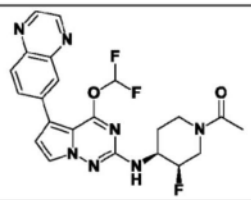
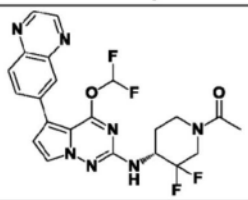
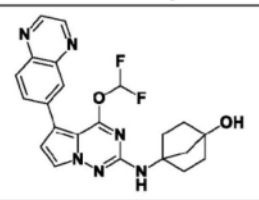
1099		1100		1101	
1102		1103		1104	
1105		1106		1107	
1108		1109		1110	
1111		1112		1113	
1114		1115		1116	
1117		1118		1119	

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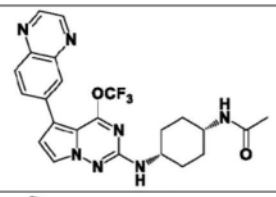
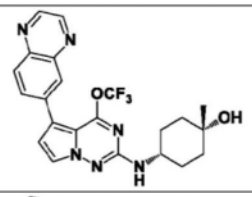
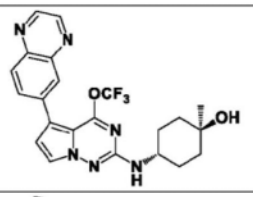
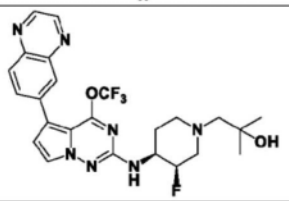
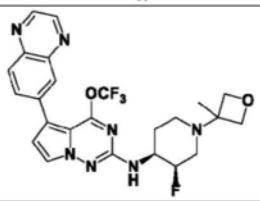
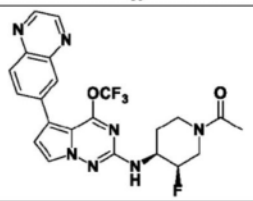
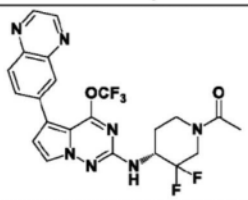
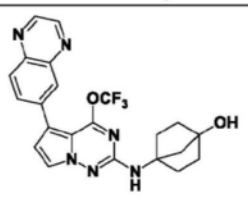
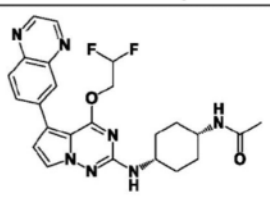
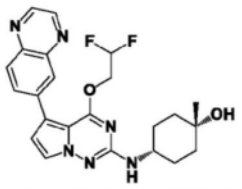
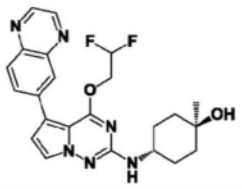
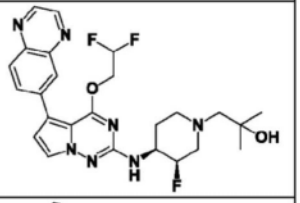
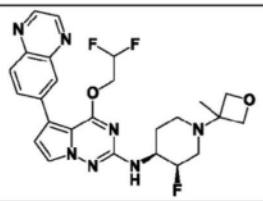
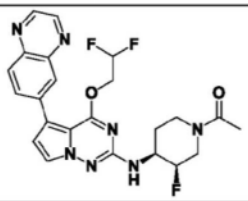
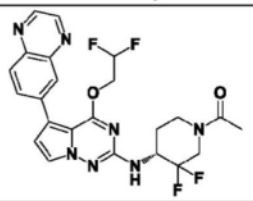
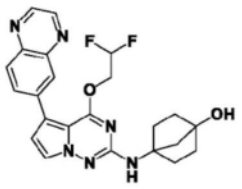
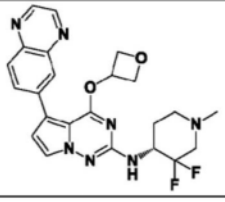
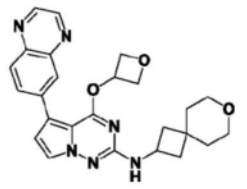
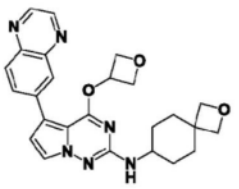
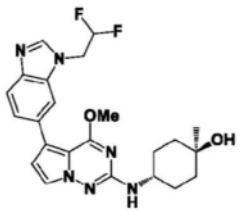
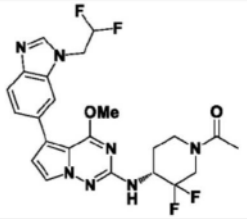
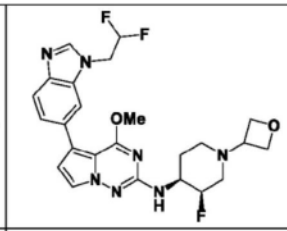
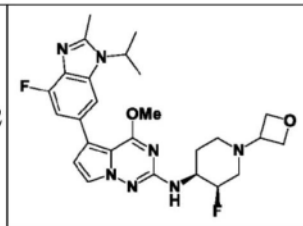
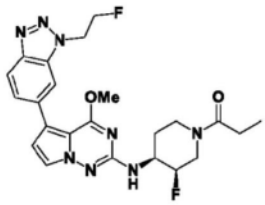
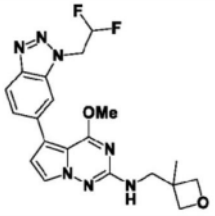
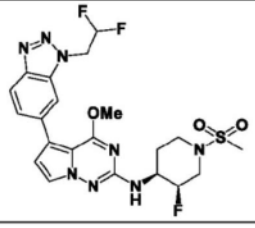
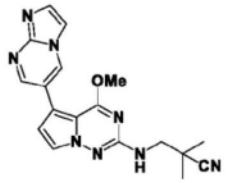
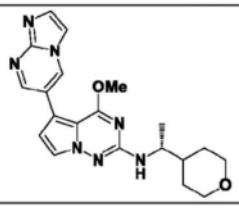
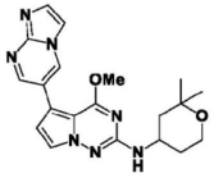
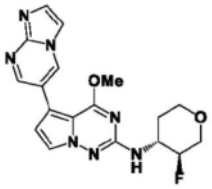
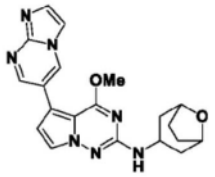
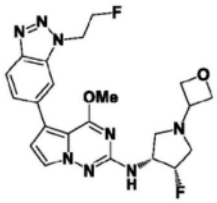
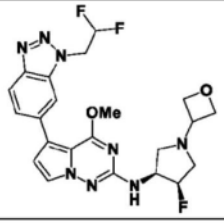
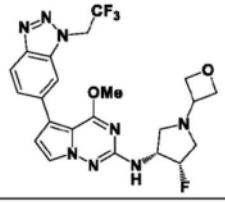
1120		1121		1122	
1123		1124		1125	
1126		1127		1128	
1129		1130		1131	
1132		1133		1134	
1135		1136		1137	
1138		1139		1140	

[0373]

1141		1142		1143	
1144		1145		1146	
1147		1148		1149	
1150		1151		1152	
1153					

[0374] 施用和药物组合物

[0375] 一些实施方案包括药物组合物,其包含:(a)治疗有效量的本文所提供的化合物或其相应对映异构体、非对映异构体或互变异构体或药学上可接受的盐;和(b)药学上可接受的载体。

[0376] 本文所提供的化合物也可适用于与其他已知药剂组合(一起或依序施用)。

[0377] 可用式I化合物与另一活性剂的组合治疗的疾病的非限制性实例为结直肠癌、卵巢癌、肝细胞癌、头颈部鳞状细胞癌、急性淋巴母细胞性白血病(ALL)、胰腺癌、脑瘤、急性巨核母细胞性白血病(AMKL)和骨关节炎。例如,式I化合物可与一种或多种化学治疗化合物组合。

[0378] 在一些实施方案中,肝细胞癌可用式I化合物与以下药物/疗法中的一者或多者的组合治疗:索拉非尼(sorafenib)(Nexavar®);瑞戈非尼(regorafenib)(Stivarga®、Regonix®)、纳武单抗(nivolumab)(Opd ivo®)、仑伐替尼(lenvatinib)(Lenvima®);派姆单抗(pembrolizumab)(Keytruda®);卡博替尼(cabozantinib)(Cometriq®、Cabometyx®);5-氟尿嘧啶(5-FU®);雷莫芦单抗(ramucirumab)

(Cyramza®);吉西他滨(gemcitabine)与奥沙利铂(oxaliplatin)的组合(GEMOX)。可与式I化合物组合进行的其他疗法为i)与阿霉素(doxorubicin)(DOXIL®)、顺铂或丝裂霉素C(Mitosol®、Mutamycin®、Jelmyto®)组合的经导管动脉化学药物栓塞治疗(transcatheter arterial chemoembolization;TACE);ii)低剂量近接疗法。

[0379] 在一些实施方案中,头颈部鳞状细胞癌可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:经口机器人手术(TransOral Robotic Surgery;TORS);使用辐射疗法的TORS;拉罗替尼(larotrectinib)(Vitrakvi®);EGFR抑制剂,例如埃罗替尼(erlotinib)(Tarceva®)、奥希替尼(osimertinib)(Tagrisso®)、来那替尼(neratinib)(Nerlynx®)、吉非替尼(gefitinib)(Iressa®)、西妥昔单抗(cetuximab)(Erbitux®)、帕尼单抗(panitumumab)(Vectibix®)、达可替尼(dacomitinib)(Vizimpro ®)、拉帕替尼(lapatinib)(Tykerb®)、耐昔妥珠单抗(necitumumab)(Por trazza)和凡德他尼(vandetanib)(Caprelsa®)。

[0380] 在一些实施方案中,急性淋巴母细胞性白血病(ALL)可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:缓解诱导疗法;巩固疗法;奈拉滨(nelarabine)(Arranon®);菊欧文菌属天冬酰胺酶(asparaginase erwinia chrysanthemi)(Erwinaze®);菊欧文菌属天冬酰胺酶(重组型)-rywn(Rylaze®);聚乙二醇化卡拉斯酶-mknl(calaspargase Pegol-mknl)(Asparlas®);伊妥珠单抗奥佐米星(inotuzumab ozogamicin)(Besponsa®);博纳吐单抗(blinatumomab)(Blincyto®);盐酸道诺霉素(daunorubicin hydrochloride)(Cerubidine®);氯法拉滨(clofarabine)(Clolar®);环磷酰胺;甲氨蝶呤钠(methotrexate sodium)(Trexall®);阿糖胞苷(Cytosar-U®);达沙替尼(dasatinib)(Sprycel®);地塞米松(dexamethasone);甲磺酸伊马替尼(imatinib mesylate)(Gleevec®);盐酸普纳替尼(ponatinib hydrochloride)(Iclusig®);巯基嘌呤(Purinethol®、Purixan®);替沙津鲁(tisagenlecleucel)(Kymriah®);硫酸长春新碱脂质体(vincristine sulfate liposome)(Marqibo®);培门冬酶(pegaspargase)(Oncaspar®);泼尼松(prednisone);盐酸道诺霉素(daunorubicin hydrochloride)(Rubidomycin®);和硫酸长春新碱。

[0381] 在一些实施方案中,胰腺癌可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:消融和栓塞处理;吉西他滨(Gemzar®);5-氟尿嘧啶(5-FU®);奥沙利铂(Eloxatin®);白蛋白结合型太平洋紫杉醇(Abraxane®);卡培他滨(capecitabine)(Xeloda®);顺铂;伊立替康(irinotecan)(Camptosar®);脂质体伊立替康(Onivyde®);太平洋紫杉醇(Taxol®)和多烯紫杉醇(docetaxel)(Taxotere®)。

[0382] 在一些实施方案中,脑瘤可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:可以格立得植入剂(Gliadel Wafer)的方式施用卡莫司汀(carmustine);对于胶质母细胞瘤和高级别神经胶质瘤,使用每日低剂量替莫唑胺(temozolomide)(Temodar®)的辐射疗法,接着在辐射疗法6个月至1年后每月给与替莫唑胺;已将洛莫司汀(lomustine)(Gleostine®)、丙卡巴肼(procarbazine)(Matulane®)和长春新碱(Vincasar®)与辐射疗法一起使用;使用贝伐珠单抗(bevacizumab)(Avastin®、Mvasi®)的抗血管生成疗法;和使用拉罗替尼(Vitrakvi®)的靶向疗法。

[0383] 在一些实施方案中,急性巨核母细胞性白血病(AMKL)可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:阿糖胞苷(Cytosar-U®)、依托泊苷(etoposide)(Vepesid®)和蒽环霉素药物。蒽环霉素包括道诺霉素(Cerubidine®)、埃达霉素(idarubicin)(Idamycin®)和米托蒽醌(mitoxantrone)(Novantrone®)。

[0384] 在一些实施方案中,急性骨髓白血病(AML)可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:维奈托克(venetoclax)和低甲基化剂(例如地西他滨(decitabine)、氮杂胞苷(azacitidine))、诱导化学疗法(阿糖胞苷(cytarabine)和蒽环霉素(例如道诺霉素或埃达霉素)、全反式视黄酸(ATRA)和三氧化二砷(ATO)单一疗法或蒽环霉素)、巩固疗法(阿糖胞苷)。

[0385] 在一些实施方案中,骨髓发育不良综合征(MDS)可用式I化合物与以下药物/疗法中的一者或多者的组合来治疗:5-氮杂胞苷(azacytidine)、地西他滨、来那度胺(lenalidomide)和地西他滨/西达尿苷(cedazuridine)(Inqovi®)。

[0386] 在一些实施方案中,结直肠癌可用式I化合物与以下药物中的一者或多者的组合来治疗:5-氟尿嘧啶(5-FU),其可与维生素类药物甲酰四氢叶酸(也称为醛叶酸)一起施用;卡培他滨(XELODA®)、伊立替康(CAMPOSTAR®)、奥沙利铂(ELOXATIN®)。可进一步与式I化合物组合的这些药物的组合实例为FOLFOX(5-FU、甲酰四氢叶酸和奥沙利铂)、FOLFIRI(5-FU、甲酰四氢叶酸和伊立替康)、FOLFOXIRI(甲酰四氢叶酸、5-FU、奥沙利铂和伊立替康)和CapeOx(卡培他滨和奥沙利铂)。对于直肠癌,可在手术之前给与使用5-FU或卡培他滨与辐射的组合的化疗(新辅助治疗(neoadjuvant treatment))。

[0387] 在一些实施方案中,卵巢癌可用式I化合物与以下药物中的一者或多者的组合来治疗:拓扑替康、脂质体阿霉素(DOXIL®)、吉西他滨(GEMZAR®)、环磷酰胺(CYTOXAN®)、长春瑞滨(NAVELBINE®)、异环磷酰胺(IFEX®)、依托泊苷(VP-16)、六甲蜜胺(altretamine)(HEXALEN®)、卡培他滨(XELODA®)、伊立替康(CPT-11,CAMPTOSAR®)、美法仑(melphalan)、培美曲塞(pemetrexed)(ALIMTA®)和白蛋白结合型太平洋紫杉醇(albumin bound paclitaxel)(白蛋白结合型太平洋紫杉醇(nab-paclitaxel),ABRAXANE®)。可进一步与式I化合物组合的这些药物的组合的实例为TIP(太平洋紫杉醇[紫杉醇]、异环磷酰胺和顺铂)、VeIP(长春碱、异环磷酰胺和顺铂)和VIP(依托泊苷[VP-16]、异环磷酰胺和顺铂)。卵巢癌也可用式I化合物与免疫检查点阻断(ICB)疗法的组合来治疗。

[0388] 在一些实施方案中,式I化合物可与以下方法中的任一者组合用于治疗癌症:(a)激素疗法,例如芳香酶抑制剂、LHRH[促黄体素释放激素]类似物和抑制剂以及其他;(b)消融或栓塞程序,例如射频消融(radiofrequency ablation;RFA)、乙醇(醇)消融、微波温热疗法和冷冻手术(冷冻疗法);(c)使用烷基化剂如顺铂和卡铂、奥沙利铂、氮芥、环磷酰胺、苯丁酸氮芥和异环磷酰胺的化学疗法;(d)使用抗代谢物如硫唑嘌呤和巯基嘌呤的化学疗法;(e)使用植物生物碱和萜类如长春花生物碱(即长春新碱、长春碱、长春瑞滨和长春地辛(vindesine))和紫杉烷的化学疗法;(f)使用鬼臼毒素(podophyllotoxin)、依托泊苷、替尼泊苷(teniposide)和多烯紫杉醇的化学疗法;(g)使用拓扑异构酶抑制剂的化学疗法,所述抑制剂例如伊立替康、拓扑替康(topotecan)、安吖啶(amsacrine)、依托泊苷、磷酸依托泊苷和替尼泊苷;(h)使用细胞毒性抗生素如放射菌素(actinomycin)、蒽环霉素、阿霉素、道诺霉素、戊柔比星(valrubicin)、埃达霉素、表柔比星(epirubicin)、博莱霉素、普卡霉素(plicamycin)和丝裂霉素的化学疗法;(i)使用酪氨酸激酶抑制剂的化学疗法,所述酪氨酸激酶抑制剂如甲磺酸伊马替尼(imatinib mes ylate)(GLEEVEC®,也称为STI-571)、吉非替尼(gefitinib)(Iressa,也称为ZD1839)、埃罗替尼(erlotinib)(以TARCEVA®出售)、硼替佐米(VELCADE®)、他莫昔芬(tamoxifen)、托法替尼(tofacitinib)、克唑替尼(crizotinib)、Bcl-2抑制剂(例如,奥巴克拉(obatoclax)、那维托克(nav itoclax)(ABT-263)、奥利默森(oblimersen)(G3139)、维奈托克(ABT-199)、棉籽酚(Gossypol))、PARP抑制剂(例如,伊尼帕尼(iniparib)、奥拉帕尼(olaparib)、卢卡帕尼(rucaparib)、尼拉帕尼(niraparib)、拉唑帕尼(talazoparib))、PI3K抑制剂(例如,III期试验中的哌立福新(perif osine))、VEGF受体2抑制剂(例如阿帕替尼(apatinib))、AN-152、(AEZS-108)、BRAF抑制剂(例如,维罗非尼(vemurafenib)、达拉非尼(dabrafenib)和LGX818)、MEK抑制剂(例如,曲美替尼(trametinib)和MEK162)、CDK抑制剂(例如PD-0332991)、盐霉素(salinomycin)和索拉非尼(sorafenib);(j)使用单克隆抗体的化学疗法,所述单克隆抗体如利妥昔单抗(rituximab)(以MABTHERA®或RITUXAN®出售)、曲妥珠单抗(trastuzumab)(赫赛汀(Herceptin),也称为ErbB2)、西妥昔单抗(ce tuximab)(以ERBITUX®出售)和贝伐珠单抗(以AVASTIN®出售);(k)使用KRAS G12C抑制剂的化学疗法,所述抑制剂如索托拉西(sotora sib)(Lumakras®和Lumykras®)、阿达格拉西布(adagrasib)(MRTX849)和ARS-3248(Wellspring Biosciences);(l)使用检查点抑制剂疗法的化学疗法,所述检查点抑制剂疗法如伊匹木单抗(ipilimumab)(Yervoy®)、纳武单抗(Opdivo®)、派姆单抗(Keytruda®)、阿替利珠单抗(atezoli zumab)(Tecentriq®)、阿维鲁单抗(avelumab)(Bavencio)、德瓦鲁单抗(durvalumab)(Imfinzi)、西米普利单抗(cemiplimab)(Libtayo®)和斯巴达珠单抗(spartalizumab)(PDR001);(m)使用抗体-药物偶联物(ADC)的化学疗法,所述抗体-药物偶联物如吉妥单抗奥佐米星(gemtuzumab ozogamicin)、本妥昔单抗维多汀(brentuximab vedotin)、曲妥珠单抗恩他新(trastuzumab emtansine)、伊妥珠单抗奥佐米星、泊洛妥珠单抗维多汀(polatuzumab vedotin)、恩弗妥单抗维多汀(enfortumab vedotin)、曲妥珠单抗德鲁特坎(trastuzumab deruxtecan)、戈沙妥珠单抗戈维特坎(sacituzumab govitecan)、贝兰妥单抗马佛多坦

(belantamab mafodo tin)、帕西妥莫单抗(moxetumomab pasudotox)和隆卡妥昔单抗特林(lo ncastuximab tesirine);(n)使用蛋白酶体抑制剂的化学疗法,所述抑制剂如卡非佐米(carfilzomib)、乳胞素(lactacystin)、双硫仑(disulfiram)、盐孢菌素A(salinosporamide A)(马瑞佐米(marizomib))、奥普洛佐米(oprozomib)、德兰佐米(delanzomib)、埃普霉素(epoxomicin)、MG132、β-羟基β-甲基丁酸(HMB)、硼替佐米(bortezomib)、伊沙佐米(ixazomi b)(单独或与来那度胺和地塞米松组合);和(o)辐射疗法。

[0389] 在一些实施方案中,式I化合物可与以下方法中的任一者组合用于治疗糖尿病:(a)胰岛素注射剂;(b)双胍,如二甲双胍(Glucophage)、苯乙双胍(DBI)和丁双胍;(c)噻唑烷二酮(TZD),如罗格列酮(rosiglitazone)(Avandia)、吡格列酮(pioglitazone)(Actos)和曲格列酮(yroglitazone)(Rezulin);(d)lyn激酶活化剂,如格列美脲(glimepiride)(Amaryl®)和托利咪酮(tolimidone)(MLR-1023);(e)促分泌物,如磺酰脲(非限制性实例为醋磺环己脲(acetohexamide)、胺磺丁脲(carbutamide)、氯磺丙脲(chlorpropamide)、格列环脲(glycyclamide)(甲苯磺环脲(tolcyclamide))、美他己脲(metahexamide)、甲磺氮卓脲(tolazamide)、甲苯磺丁脲(tolbutamide)、格列本脲(glibenclamide)(格列苯脲(glyburide))、格列波脲(glibornuride)、格列齐特(gliclazide)、格列吡嗪(glipizide)、格列喹酮(gliquidone)、格列帕特(glisoxepide)、格列吡脲(glyclopyramide)和格列美脲(glimepiride))和美格替耐(meglitinide)(非限制性实例为瑞格列奈(repaglinide)(Prandin)、那格列奈(nateglinide)(Starlix)和米格列奈(mitiglinide)(Glufast));(f)α-葡糖苷酶抑制剂,如阿卡波糖(acarbose)(Glucobay,Precose,Prandase)、米格列醇(miglitol)(Glyset)和伏格列波糖(voglibose);(g)可注射促胰岛素模拟物,如类升糖素肽-1(GLP-1)和胃抑肽(葡萄糖依赖性促胰岛素肽,GIP),可注射的类升糖素肽(GLP)类似物和激动剂的非限制性实例为艾塞那肽(exenatide)(肠促胰岛素类似物-4(Exendin-4),以Byetta出售)、利拉鲁肽(liraglutide)(Victoza,Saxenda)、他司鲁肽(taspoglutide)、利司那肽(lixisenatide)(Lyxumia)、司美鲁肽(Semaglutide)(Ozempic,Rybelsus)、度拉糖肽(dulaglutide)(Trulicity)、阿比鲁肽(albiglutide)(Tanzeum),二肽基肽酶-4(DPP-4)抑制剂的非限制性实例为西格列汀(sitagliptin)(Januvia)、维格列汀(vildagliptin)(Galvus)、沙格列汀(saxagliptin)(Onglyza)、利格列汀(linagliptin)(Tradjenta)、吉格列汀(gemigliptin)(Zemiglo)、那格列汀(anagliptin)(Suiny)、替格列汀(teneligliptin)(Tenelia)、阿格列汀(alogliptin)(Nesina、Vipidia、Kazano、Vipidomet(具有二甲双胍)、Oseni、Incresync(具有吡格列酮))、曲格列汀(trelagliptin)(Zafatek,Wedica)、奥格列汀(omarigliptin)(MK-3102)、依格列汀(evogliptin)(Suganon,Evodine)、果格列汀(gosogliptin)(Saterex)和度格列汀(dutogliptin);(h)可注射淀粉素类似物,如普兰林肽(pramlintide)(Symlin);(i)糖尿苷(glycosurics)(SGLT2抑制剂),如卡纳格列净(canagliflozin)(Invokana,Sulisent,Prominad)、达格列净(dapagliflozin)(Forxiga,Farxiga,Edistride)、恩格列净(empagliflozin)(Jardiance,Sciampa-M)、埃格列净(ertugliflozin)(Steglatro)、伊格列净(ipragliflozin)(Suglat)、鲁格列净(luseogliflozin)(Lusefi)、依碳酸瑞格列净(remogliflozin etabonate)(瑞格列净的前药)、依碳酸舍格列净(sergliflozin etabonate)(GW869682X)、

索格列净(sotagliflozin)(Zynquista)和托格列净(tofogliflozin)(CSG452)。

[0390] 在一些实施方案中,式I化合物可与以下方法中的任一者组合用于治疗骨关节炎:(d)Wnt信号通路抑制剂的注射剂(例如,洛瑞韦森(lorecivivint));(a)非类固醇抗炎药(NSAID),如布洛芬(ibuprofen)、萘普生(naproxen)、阿司匹林(aspirin)和乙酰胺苯酚;(b)物理疗法;(c)皮质类固醇药物的注射剂;(d)玻尿酸衍生物的注射剂(例如,Hyalgan、Synvisc);(e)麻醉剂,如可待因(codeine);(f)与支架和/或足垫或任何可固定或支持关节帮助避开压力的装置(例如夹板、支架、足垫或其他医疗装置)组合使用;(g)重新调整骨头(切骨术);(h)关节置换(关节造形术);和(i)与慢性疼痛类别组合。

[0391] 在一些实施方案中,式I化合物可与以下组合用于治疗阿尔茨海默病:阿杜卡努单抗(aducanumab)(Aduhelm™);乙酰胆碱酯酶抑制剂,例如他可林(tacrine)、雷斯替明(rivastigmine)(Exelon®)、加兰他敏(galantamine)(Razadyne®和GalantaMind™)和多奈哌齐(donepezil)(Aricept®);和美金刚胺(memantine)(Axura®、Ebixa®、Namenda®)。

[0392] 本文所公开的化合物或其药学上可接受的盐的施用可经由可接受的施用模式中的任一者,包括但不限于经口、经皮下、经静脉内、经鼻内、经局部、透皮、经腹膜内、经肌肉内、经肺内、经阴道、经直肠、经耳、经耳神经、经眼内、经结膜下、经由眼前房注射、经玻璃体内、经腹膜内、经鞘内、经囊内、经胸膜内、经由创口冲洗、经颊内、经腹内、经关节内、经耳内、经支气管内、经囊内、经脑膜内、经由吸入、经由气管内或支气管内滴注、经由向肺空洞中直接滴注、经脊椎内、经滑膜内、经胸内、经由胸廓造口冲洗、经硬膜外、经鼓室内、经脑池内、经血管内、经脑室内、经骨内、经由对经感染骨骼进行冲洗或经由作为与假体装置的任何掺合物的一部分施加。在一些实施方案中,施用方法包括口服或胃肠外施用。

[0393] 旨在用于医药用途的本文所提供的化合物可以结晶或非晶形产物的形式施用。药学上可接受的组合物可包括固体、半固体、液体、溶液、胶体、脂质体、乳液、悬浮液、复合物、团聚体和气雾剂。剂型,如例如片剂、胶囊、散剂、液体、悬浮液、栓剂、气雾剂、植入物、控制释放剂型等。其可例如通过例如沉淀、结晶、碾磨、研磨、超临界流体处理、凝聚、复合凝聚、包封、乳化、复合、冷冻干燥、喷雾干燥或蒸发干燥的方法以固体塞、散剂或膜形式获得。可出于此目的使用微波或射频干燥。化合物也可以持续或控制释放剂型施用,所述剂型包括储槽式注射剂、渗透泵、丸剂(片剂和或胶囊)、透皮(包括电迁移)贴剂、植入物等,以用于以预定速率长期和/或定时脉冲施用。

[0394] 化合物可单独或与常规医药载体、赋形剂等组合施用。药学上可接受的赋形剂包括(但不限于)离子交换剂;氧化铝;硬脂酸铝;卵磷脂;自乳化药物递送系统(SEDDS),如d-α-生育酚聚乙二醇1000丁二酸酯;药物剂型中所用的表面活性剂,如Tweens、泊洛沙姆(poloxamer)或其他类似聚合物递送基质;血清蛋白,如人类血清白蛋白;缓冲物质,如磷酸盐、tris、甘氨酸、山梨酸、山梨酸钾;饱和植物脂肪酸的偏甘油酯混合物;水、盐或电解质,例如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠;锌盐;胶态二氧化硅;三硅酸镁;聚乙烯吡咯烷酮;基于纤维素的物质;聚乙二醇;羧甲基纤维素钠;聚丙烯酸酯;蜡;聚乙烯-聚氧丙烯嵌段共聚物;和羊毛脂。环糊精(如α-环糊精、β-环糊精和γ-环糊精)或化学改性衍生物(如羟基烷基环糊精,包含2-羟丙基-β-环糊精和3-羟丙基-β-环糊精)或其他溶解衍生物也可用于增强本文所描述的化合物的递送。可制备含有在0.005%至100%范围内的如本文所描述的化合物而其余部分由无毒载体构成的剂型或组合物。所考虑的组合物可含有

0.001％至100％的本文所提供的化合物,在一个实施方案中为0.1％至95％,在另一个实施方案中为75％至85％,在另一个实施方案中为20％至80％。制备此类剂型的实际方法对本领域技术人员为已知的或将为显而易见的;例如,参见Remington:The Science and Practice of Pharmacy,第22版(Pharmaceutical Press,London,UK.2012)。

[0395] 在一个实施方案中,组合物将呈例如丸剂或片剂的单位剂型的形式,并且因此,所述组合物除含有本文所提供的化合物以外,还可含有稀释剂如乳糖、蔗糖、磷酸二钙等;润滑剂如硬脂酸镁等;和粘合剂如淀粉、阿拉伯胶、聚乙烯吡咯烷酮、明胶、纤维素、纤维素衍生物等。在另一种固体剂型中,散剂、球形粒(marume)、溶液或悬浮液(例如,在碳酸亚丙酯、植物油、PEG、泊洛沙姆124或三酸甘油酯中)包封于胶囊(明胶或纤维素类胶囊)中。也考虑本文所提供的一种或多种化合物或其他活性剂在物理上分离的单位剂型;例如具有各药物的颗粒(或于胶囊中的片剂)的胶囊;双层片剂;双室胶囊锭等。也考虑包覆肠溶包衣或延迟释放型口服剂型。

[0396] 可例如通过将本文所提供的化合物和任选的药物佐剂于载体(例如水、生理盐水、右旋糖水溶液、甘油、二醇、乙醇等)中溶解、分散等以形成溶液、胶体、脂质体、乳液、复合物、团聚体或悬浮液来制备液体药学上可施用的组合物。必要时,药物组合物也可含有少量无毒性辅助物质,例如润湿剂、乳化剂、助溶剂、增溶剂、pH缓冲剂等(例如,乙酸钠、柠檬酸钠、环糊精衍生物、脱水山梨糖醇单月桂酸酯、三乙醇胺乙酸酯、三乙醇胺油酸脂等)。

[0397] 在一些实施方案中,式I化合物的单位剂量在人类中为约0.25mg/Kg至约50mg/Kg。

[0398] 在一些实施方案中,式I化合物的单位剂量在人类中为约0.25mg/Kg至约20mg/Kg。

[0399] 在一些实施方案中,式I化合物的单位剂量在人类中为约0.50mg/Kg至约19mg/Kg。

[0400] 在一些实施方案中,式I化合物的单位剂量在人类中为约0.75mg/Kg至约18mg/Kg。

[0401] 在一些实施方案中,式I化合物的单位剂量在人类中为约1.0mg/Kg至约17mg/Kg。

[0402] 在一些实施方案中,式I化合物的单位剂量在人类中为约1.25mg/Kg至约16mg/Kg。

[0403] 在一些实施方案中,式I化合物的单位剂量在人类中为约1.50mg/Kg至约15mg/Kg。

[0404] 在一些实施方案中,式I化合物的单位剂量在人类中为约1.75mg/Kg至约14mg/Kg。

[0405] 在一些实施方案中,式I化合物的单位剂量在人类中为约2.0mg/Kg至约13mg/Kg。

[0406] 在一些实施方案中,式I化合物的单位剂量在人类中为约3.0mg/Kg至约12mg/Kg。

[0407] 在一些实施方案中,式I化合物的单位剂量在人类中为约4.0mg/Kg至约11mg/Kg。

[0408] 在一些实施方案中,式I化合物的单位剂量在人类中为约5.0mg/Kg至约10mg/Kg。

[0409] 在一些实施方案中,组合物是以适用于单次施用的单位剂型提供。

[0410] 在一些实施方案中,组合物是以适用于一天两次施用的单位剂型提供。

[0411] 在一些实施方案中,组合物是以适用于一天三次施用的单位剂型提供。

[0412] 可注射剂可以常规形式,以液体溶液、胶体、脂质体、复合物、团聚体或悬浮液形式,以乳液形式,或以适用于在注射之前于液体中重构的固体形式中任一者制备。此类胃肠外组合物中所含的本文所提供的化合物的百分比主要取决于其特定性质,以及化合物的活性和患者的需求。然而,溶液中的0.01％至10％的活性成分百分比为可用的,并且如果组合物可随后稀释至以上百分比的固体或悬浮液,则可能将为更高。

[0413] 在一些实施方案中,组合物包含约0.1％至10％的呈溶液形式的活性剂。

[0414] 在一些实施方案中,组合物包含约0.1％至5％的呈溶液形式的活性剂。

[0415] 在一些实施方案中,组合物包含约0.1%至4%的呈溶液形式的活性剂。

[0416] 在一些实施方案中,组合物包含约0.15%至3%的呈溶液形式的活性剂。

[0417] 在一些实施方案中,组合物包含约0.2%至2%的呈溶液形式的活性剂。

[0418] 在一些实施方案中,组合物是以适合于通过静脉内输注经约1至96小时的时段连续给药的剂型提供。

[0419] 在一些实施方案中,组合物是以适合于通过静脉内输注经约1至72小时的时段连续给药的剂型提供。

[0420] 在一些实施方案中,组合物是以适合于通过静脉内输注经约1至48小时的时段连续给药的剂型提供。

[0421] 在一些实施方案中,组合物是以适合于通过静脉内输注经约1至24小时的时段连续给药的剂型提供。

[0422] 在一些实施方案中,组合物是以适合于通过静脉内输注经约1至12小时的时段连续给药的剂型提供。

[0423] 在一些实施方案中,组合物是以适合于通过静脉内输注经约1至6小时的时段连续给药的剂型提供。

[0424] 在一些实施方案中,这些组合物可通过静脉内输注以约5mg/m^2至约300mg/m^2的剂量向人类施用。

[0425] 在一些实施方案中,这些组合物可通过静脉内输注以约5mg/m^2至约200mg/m^2的剂量向人类施用。

[0426] 在一些实施方案中,这些组合物可通过静脉内输注以约5mg/m^2至约100mg/m^2的剂量向人类施用。

[0427] 在一些实施方案中,这些组合物可通过静脉内输注以约10mg/m^2至约50mg/m^2的剂量向人类施用。

[0428] 在一些实施方案中,这些组合物可通过静脉内输注以约50mg/m^2至约200mg/m^2的剂量向人类施用。

[0429] 在一些实施方案中,这些组合物可通过静脉内输注以约75mg/m^2至约175mg/m^2的剂量向人类施用。

[0430] 在一些实施方案中,这些组合物可通过静脉内输注以约100mg/m^2至约150mg/m^2的剂量向人类施用。

[0431] 应注意,浓度和剂量值也可根据特定化合物和待缓解的疾患的严重程度而变化。应进一步理解,对于任何特定患者,特定剂量方案应根据个体需要和管理或监督组合物施用的人员的专业判断而随时间调整,并且本文所阐述的浓度范围仅为示例性并且不旨在限制所要求保护的组合物的范围或实践。

[0432] 在一个实施方案中,组合物可例如经由喷雾器、定量剂量吸入器、雾化器、喷雾器、气雾剂、干粉吸入器、吹入器、液体滴注或其他适合装置或技术施用至呼吸道(包括经鼻和经肺)。

[0433] 在一些实施方案中,提供旨在递送至鼻粘膜的气雾剂以用于经由鼻吸入。为最佳递送至鼻腔,约5至约100微米的吸入粒度是适用的,其中约10至约60微米的粒度是优选的。对于经鼻递送,可能需要较大吸入粒度以使对鼻粘膜的作用达最大并且使所施用的制剂的

肺部沉积减至最小或防止其沉积。在一些实施方案中,提供旨在递送至肺部的气雾剂以用于经由鼻或嘴吸入。为递送至肺部,约小于10μm的吸入空气动力学粒度是适用的(例如约1至约10微米)。吸入粒子可定义为含有溶解药物的液滴、含有悬浮药物粒子的液滴(在药物不溶于悬浮介质中的情况下)、纯药物物质的干燥粒子、与赋形剂合并的药物物质、脂质体、乳液、胶体系统、团聚体、药物纳米粒子的聚集体或含有嵌入药物纳米粒子的稀释剂的干燥粒子。

[0434] 在一些实施方案中,本文所公开的旨在用于呼吸递送(全身或局部)的式I化合物可作为水性制剂、作为非水溶液或悬浮液、作为含或不含醇的卤化烃推进剂中的悬浮液或溶液、作为胶体系统、作为乳液团聚体或作为干燥粉末施用。水性制剂可通过液体喷雾器采用液压或超声波雾化或通过经修改的微泵系统(如软雾吸入器、Aerodose®或AERx®系统)气雾化。基于推进剂的系统可使用适合的加压定量剂量吸入器(pMDI)。干燥粉末可使用干燥粉末吸入器装置(DPI),其能够有效地分散药物物质。所需粒度和分布可通过选择适当装置获得。

[0435] 在一些实施方案中,本文所公开的式I组合物可通过各种方法施用至耳部。例如,可使用圆窗导管(例如美国专利第6,440,102号和第6,648,873号)。

[0436] 或者,制剂可并入至芯子中以在外耳与中耳之间使用(例如美国专利第6,120,484号)或吸收至胶原蛋白海绵或其他固体载体(例如美国专利第4,164,559号)。

[0437] 必要时,本公开的制剂可并入凝胶制剂中(例如美国专利第4,474,752号和第6,911,211号)。

[0438] 在一些实施方案中,本文所公开的旨在递送至耳部的式I化合物可经由植入泵和递送系统,通过针直接施用至中耳或内耳(耳蜗)中或通过耳蜗植入探针电极通道或替代制备的药物递送通道例如但不限于针经由颞骨施用至耳蜗中。

[0439] 其他选项包括经由泵递送穿过涂布在多通道电极上的薄膜或出于此目的在薄膜中刻有专门嵌入的药物递送通道(通路)的电极。在其他实施方案中,式I的酸性或碱性固体化合物可从外部或内部植入泵送系统的储集器递送。

[0440] 本公开的制剂也可通过鼓室内注射至中耳、内耳或耳蜗(例如美国专利第6,377,849号和序列号11/337,815)施用至耳部。

[0441] 治疗剂的鼓室内注射是在鼓膜后将治疗剂注射至中耳和/或内耳中的技术。在一个实施方案中,本文所描述的制剂经由经鼓膜注射直接施用至圆窗膜上。在另一个实施方案中,本文所描述的离子通道调节剂耳可接受的制剂经由通往内耳的非经鼓膜方法施用至圆窗膜上。在其他实施方案中,本文所描述的制剂经由通往包含耳蜗窗脊(crista fenestrae cochleae)的修改的圆窗膜的手术方法施用至圆窗膜上。

[0442] 在一些实施方案中,式I化合物被配制成经直肠组合物,例如灌肠剂、直肠凝胶、直肠发泡体、直肠气雾剂、栓剂、胶质栓剂或保留灌肠剂,其含有例如可可脂或其他甘油酯的常规栓剂基质以及例如聚乙烯吡咯烷酮、PEG(如PEG软膏)等的合成聚合物。

[0443] 用于经直肠施用药物的栓剂(呈溶液、胶体、悬浮液或复合物形式)可通过将本文所提供的化合物与适合的无刺激性赋形剂混合来制备,所述赋形剂在常温下为固体但在直肠温度下为液体并且因此将在直肠中熔融或腐蚀/溶解并且释放所述化合物。此类材料包括可可脂、甘油化明胶、氢化植物油、泊洛沙姆、各种分子量的聚乙二醇的混合物和聚乙二

醇的脂肪酸酯。在组合物的栓剂形式中,首先熔融低熔点蜡,例如(但不限于)脂肪酸甘油酯任选地与可可脂组合的混合物。

[0444] 取决于本文所提供的化合物的物理化学特性、所需溶解速率、成本考虑因素和其他标准,固体组合物可以各种不同类型的剂型提供。在实施方案中的一者中,固体组合物为单一单元。这暗示化合物的一个单位剂量包含在单一物理上成形的固体形式或物品中。换句话说,所述固体组合物为连贯的,其与多单元剂型形成对比,后者的单元为不连贯的。

[0445] 可用作固体组合物的剂型的单一单元的实例包括片剂(例如压缩片剂)、膜类单元、箔类单元、粉片、冻干基质单元等。在一个实施方案中,固体组合物为高度多孔冻干形式。此类冻干物(有时也称为粉片或冻干片剂)尤其适用于使其快速崩解,其也使得化合物快速溶解。

[0446] 另一方面,对于一些应用,固体组合物也可以如上文所定义的多单元剂型形成。多个单元的实例为粉末、颗粒、微粒、集结粒、微片剂、珠粒、冻干粉末等。在一个实施方案中,固体组合物为冻干粉。此类分散的冻干系统包含多个粉末粒子,并且由于用于形成粉末的冻干过程,每个粒子具有不规则多孔微结构,粉末能够经由所述微结构极快速地吸收水,从而导致快速溶解。也考虑起泡组合物以有助于化合物的快速分散和吸收。

[0447] 也能够实现快速药物溶解的另一类型的多微粒系统为由水溶性赋形剂形成的粉末、颗粒或丸粒,其涂布有本文所提供的化合物以使得化合物位于个别粒子的外表面处。在此类型的系统中,水溶性低分子量赋形剂可适用于制备此类经涂布粒子的核心,此类经涂布粒子可随后用包含所述化合物和例如一种或多种其他赋形剂(例如粘合剂、成孔剂、糖、糖醇、成膜聚合物、增塑剂或用于医药涂料组合物中的其他赋形剂)的涂料组合物涂布。

[0448] 本文还提供试剂盒。通常,试剂盒包括如本文所描述的一种或多种化合物或组合物。在某些实施方案中,试剂盒可包括一种或多种递送系统(例如用于递送或施用如本文所提供的化合物的递送系统),和使用试剂盒的说明(例如用于治疗患者的说明书)。在另一个实施方案中,试剂盒可包括如本文所描述的化合物或组合物和指示内含物待施用至患有癌症的患者的标签。在另一个实施方案中,试剂盒可包括如本文所描述的化合物或组合物和标签,所述标签指示待向患有以下中的一者或多者的患者施用内含物:胶质母细胞瘤、卵巢癌、乳腺癌、胰腺癌、急性淋巴母细胞性白血病、急性巨核母细胞性白血病、慢性骨髓性白血病、阿尔茨海默病、肌萎缩性侧索硬化、CDKL5缺乏病症、唐氏综合征、额颞叶型痴呆伴帕金森症-17(FTDP-17)、路易体痴呆、帕金森病、皮克病、自闭症、痴呆、癫痫、亨廷顿病和多发性硬化。

[0449] 治疗方法

[0450] 本文所提供的化合物和组合物可用作DYRK1A的抑制剂,并且因此可用于治疗涉及DYRK1A的过表达的各种病症和疾病,例如癌症和神经疾患/病症/疾病。可用本文所提供的化合物和组合物治疗的疾病的非限制性实例包括多种癌症、阿尔茨海默病、肌萎缩性侧索硬化、CDKL5缺乏病症、唐氏综合征、额颞叶型痴呆伴帕金森症-17(FTDP-17)、路易体痴呆、帕金森病、皮克病和伴有明显神经退行的其他疾病如自闭症、痴呆、癫痫、亨廷顿病、多发性硬化;与获得性脑损伤相关的疾病和病症如慢性创伤性脑病变、创伤性脑损伤、肿瘤、中风、tau蛋白病变(例如皮克病、进行性核上麻痹、皮质基底节变性、嗜银颗粒病、球状神经胶质tau蛋白病变、原发性年龄相关的tau蛋白病变(其包括神经纤维缠结痴呆)、慢性创伤性脑

病变(CTE)、具有tau包涵体的额颞叶变性(FTLD-tau)和老化相关的tau星形胶质细胞病变。临床症状包括额颞叶型痴呆、皮质基底核综合征、理查德森综合征、帕金森症、纯运动不能伴步态冻结和罕见地运动神经元症状或小脑共济失调、糖尿病、牛皮癣、膝骨性关节炎、肌腱病变、人类免疫缺陷病毒1型(HIV-1)、人类巨细胞病毒(HCMV)、丙型肝炎病毒(HCV)和单纯疱疹病毒1(HSV-1)。

[0451] 编码DYRK1A的基因位于第21号染色体上,位于唐氏综合征关键区(DSCR)内,其三倍体性造成大多数唐氏综合征相关缺陷(FEBS Journal(2011),278,246-256)。存在相当多的遗传和药理学证据显示,仅DYRK1A的1.5倍过表达造成唐氏综合征患者中所观测到的大部分认知缺陷。(Pharmacology&Therapeutics(2019),194,199-221和Brain Science(2018),8(10),187)。DYRK1A水平的遗传归一化或对其催化活性的药理学抑制恢复认知功能。对DYRK1A的药理学抑制剂的开发是用于治疗与唐氏综合征相关的认知缺陷的主要途径。

[0452] 在人类巨细胞病毒(HCMV)胎盘复制期间利用DYRK1A和DYRK1B。抑制DYRK阻止各种病毒的复制,所述病毒包括丙型肝炎病毒(HCV)、人类巨细胞病毒(HCMV)、人类免疫缺陷病毒1型(HIV-1)和单纯疱疹病毒1(HSV-1)(Journal of Virology(2020),94(6)和PLoS ONE(2015),10,e0144229)。

[0453] 越来越多的证据显示,DYRK1A/1B抑制剂诱导产胰岛素的胰腺β细胞的增殖,使得DYRK1A/1B激酶成为1型和2型糖尿病和妊娠期糖尿病的β细胞再生的具吸引力的治疗目标(Nature Communicatio ns(2015),6(8372);Diabetes(2016),65(6),1660-1671;JCI Insight(2020),5(1),e132594;Science Translational Medicine(2020),12(530);International Journal ofMolecular Sciences(2021),22(16),9083;和Journal of Medicinal Chemistry(2021),64(6),2901-2922)。可用DYRK抑制剂治疗的其他形式的糖尿病为年轻起病成人型糖尿病(MODY,单基因性糖尿病)、由身体的组织受体不对胰岛素起反应引起的糖尿病的病例、双重糖尿病(当1型糖尿病变得抗胰岛素时)、与胰岛素拮抗性激素过度分泌相关的糖尿病、营养不良相关的糖尿病(ICD-10编码E12)和由导致β细胞功能缺陷的任何基因突变(常染色体或线粒体)引起的糖尿病。

[0454] 存在大量文献将DYRK1A与实体癌症和白血病关联起来(Pharm acology&Therapeutics(2015),151,87-98;Cancers(2020),12(8),2106;和Cellular and Molecular Life Sciences(2021),78,603-619)。最突出的实例为胰腺癌(Gut(2019),68(8),1465-1476和Gene(2020),758,144960)、脑瘤、胶质母细胞瘤(Journal of Clinical Investiga tion(2013),123(6),2475-2487)、急性巨核母细胞性白血病(AMKL)(Journal of Clinical Investigation(2012),122(3),948-962)和急性淋巴母细胞性白血病(ALL)(Journal of Clinical Investigation(2021),131(1),e135937)。与DYRK1A有关联的其他癌症为卵巢癌(Frontier s in Oncology(2021),11,637193)、头颈部鳞状细胞癌(Scientific Re ports(2016),6,36132)、肝细胞癌(Cell Death&Disease(2021),12,125),DYRK1A调节DNA损伤反应(Scientific Reports(2019),9,6014和Scientific Reports(2019),9,6539)。在一些情况下,DYRK1A似乎充当肿瘤抑制蛋白(Molecular&Cellular Oncology(2015),2(1),e970048和Nature(2016),529,172-177)。

[0455] 其他癌症也可用本文所描述的化合物和组合物治疗。

[0456] 更特别地,可通过本文所描述的化合物、组合物和方法治疗的癌症包括(但不限于)以下:

[0457] 1)乳腺癌,包括例如ER^+乳腺癌、ER^-乳腺癌、$her2^-$乳腺癌、$her2^+$乳腺癌,基质肿瘤如纤维腺瘤、叶状肿瘤和肉瘤,以及上皮肿瘤如大导管乳头状瘤;乳房癌瘤,包括:原位(非侵入性)癌瘤,其包括乳腺管原位癌(包括佩吉特氏病(Paget's disease))和小叶原位癌,以及侵袭性(浸润性)癌瘤,其包括但不限于侵袭性乳腺管癌、侵袭性小叶癌、髓质癌、胶样(粘液性)癌瘤、管状癌和侵袭性乳头状癌;化疗抵抗性乳腺癌(TNBC)和混杂恶性赘瘤。乳腺癌的其他实例可包括管腔细胞A型、管腔细胞B型、基底细胞A型、基底细胞B型和三阴性乳腺癌,所述三阴性乳腺癌为雌激素受体阴性(ER^-)、孕酮受体阴性和her2阴性($her2^-$)。在一些实施方案中,乳腺癌可具有高风险Oncotype评分。

[0458] 2)心脏癌症,包括例如肉瘤,例如血管肉瘤、纤维肉瘤、横纹肌肉瘤和脂肪肉瘤;粘液瘤;横纹肌瘤;纤维瘤;脂瘤和畸胎瘤。

[0459] 3)肺癌,包括例如支气管癌,例如鳞状细胞、未分化小细胞、未分化大细胞和腺癌瘤;肺泡和细支气管癌瘤;支气管腺瘤;肉瘤;淋巴瘤;软骨瘤错构瘤;化疗抵抗性小细胞肺癌(SCLC)和间皮瘤。

[0460] 4)胃肠道癌,包括例如食道癌,例如鳞状细胞癌、腺癌瘤、平滑肌肉瘤和淋巴瘤;胃癌,例如癌瘤、淋巴瘤和平滑肌肉瘤;胰腺癌,例如导管腺癌瘤、胰岛素瘤、升糖素瘤、胃泌素瘤、类癌肿瘤和血管活性肠肽瘤;具有APC基因突变的结肠癌;小肠癌,例如腺癌瘤、淋巴瘤、类癌肿瘤、卡波西肉瘤(Kaposi's sarcoma)、平滑肌瘤、血管瘤、脂瘤、神经纤维瘤和纤维瘤;大肠癌,例如腺癌瘤、管状腺瘤、绒毛状腺瘤、错构瘤和平滑肌瘤。

[0461] 5)泌尿生殖道癌,包括例如肾脏癌,例如腺癌瘤、威尔姆氏肿瘤(Wilm's tumor)(肾母细胞瘤)、淋巴瘤和白血病;膀胱和尿道癌,例如鳞状细胞癌、移行细胞癌和腺癌瘤;前列腺癌,例如腺癌瘤和肉瘤;睾丸癌,例如精原细胞瘤、畸胎瘤、胚胎性癌、畸胎癌、绒毛膜癌、肉瘤、间质细胞癌瘤、纤维瘤、纤维腺瘤、腺瘤样肿瘤和脂瘤。

[0462] 6)肝部癌症,包括例如肝癌,例如肝细胞癌;胆管癌;肝母细胞瘤;血管肉瘤;肝细胞腺瘤;和血管瘤。

[0463] 7)骨癌,包括例如骨原性肉瘤(骨肉瘤)、纤维肉瘤、恶性纤维组织细胞瘤、软骨肉瘤、尤文氏肉瘤(Ewing's sarcoma)、恶性淋巴瘤(网状细胞肉瘤)、多发性骨髓瘤、恶性巨细胞瘤脊索瘤、骨软骨瘤(osteochrondroma)(骨软骨外生骨疣)、良性软骨瘤、软骨母细胞瘤、软骨粘液性纤维瘤、骨样骨瘤和巨细胞肿瘤。

[0464] 8)神经系统癌症,包括例如颅骨癌,例如骨瘤、血管瘤、肉芽肿、黄瘤和畸形性骨炎;脑膜癌,例如脑膜瘤、脑膜肉瘤和神经胶质瘤病;脑癌,例如星形细胞瘤、神经管母细胞瘤、神经胶质瘤、室管膜瘤、胚细胞瘤(松果体瘤)、多形性胶质母细胞瘤、少突胶质细胞瘤、少突细胞瘤(oligodendrocytoma)、神经鞘瘤、视网膜母细胞瘤和先天性肿瘤;和脊髓癌,例如神经纤维瘤、脑膜瘤、神经胶质瘤和肉瘤。

[0465] 9)妇科癌症,包括例如子宫癌,例如子宫内膜癌(例如癌瘤、子宫内膜样腺癌瘤、浆液性癌瘤、透明细胞癌瘤、粘液性癌瘤、混合性或未分化性癌瘤(包括混合性苗勒氏管(Müllerian)肿瘤)、子宫内膜基质肉瘤、子宫内膜鳞状细胞癌、尿道上皮癌、具有CTNNB1突变的子宫内膜癌);宫颈癌症,例如宫颈癌和肿瘤前宫颈发育不良;卵巢癌症,例如BRCA突变型卵

巢癌、表面上皮基质肿瘤(上皮卵巢癌(1型(子宫内膜样、粘液性、透明细胞、低级浆液性)或2型(分化不良、癌肉瘤和高级别浆液性)))、卵巢癌,包括浆液性囊腺癌、粘液性囊腺癌、子宫内膜样肿瘤、小细胞卵巢癌(小细胞卵巢癌高血钙型、小细胞卵巢癌肺型)未分类的癌瘤、粒膜细胞肿瘤、Sertoli Leydig细胞肿瘤、无性细胞瘤和恶性畸胎瘤;外阴癌,例如鳞状细胞癌、上皮内癌瘤、腺癌瘤、纤维肉瘤和黑素瘤;阴道癌,例如透明细胞癌瘤、鳞状细胞癌、葡萄样肉瘤和胚胎性横纹肌肉瘤;和输卵管癌,例如癌瘤、原发性输卵管癌;原发性腹膜癌(也称为浆液性表面乳头状癌、原发性腹膜癌瘤、卵巢外浆液癌、原发性浆液性乳头状癌和砂状瘤癌瘤(psammomacarcinoma))。

[0466] 10)血液癌症,包括例如血液癌,例如急性骨髓性白血病、慢性骨髓性白血病、骨髓发育不良综合征(具有单谱系发育不良的难治性细胞减少症(难治性贫血、难治性嗜中性粒细胞减少症和难治性血小板减少症)、具有环形铁粒幼红细胞的难治性贫血、具有多谱系发育不良的难治性细胞减少症、具有过量母细胞I和II的难治性贫血、儿童难治性细胞减少症)和骨髓增生性赘瘤、急性淋巴母细胞性白血病、慢性淋巴细胞性白血病、骨髓增生疾病、多发性骨髓瘤、骨髓发育不良综合征、骨髓发育不良-骨髓增生疾病、霍奇金淋巴瘤(Hodgkin’slymphoma)、非霍奇金淋巴瘤(恶性淋巴瘤)和华氏巨球蛋白血症(Waldenström's macroglobulinemia)。

[0467] 11)皮肤癌和皮肤病症,包括例如恶性黑素瘤和转移性黑素瘤、基底细胞癌、鳞状细胞癌、卡波西肉瘤、畸形痣(moles dysplastic nevi)、脂瘤、血管瘤、皮肤纤维瘤、瘢痕瘤和硬皮病。

[0468] 12)肾上腺癌,包括例如神经母细胞瘤。

[0469] 13)软组织肉瘤(STS),例如纤维肉瘤、恶性纤维组织细胞瘤、皮肤纤维肉瘤、脂肪肉瘤、横纹肌肉瘤、平滑肌肉瘤、血管内皮瘤、卡波西肉瘤、淋巴管肉瘤、滑膜肉瘤、恶性周边神经鞘肿瘤(也称为神经纤维肉瘤、恶性神经鞘瘤和神经性肉瘤)、神经纤维肉瘤、骨外软骨肉瘤、骨外骨肉瘤、骨外粘液样软骨肉瘤、骨外间叶细胞、胚胎、软组织肺泡状肉瘤(alveolar soft part sarcoma)和婴儿血管外皮细胞瘤(hemangio-pericytoma)。

[0470] 更特别地,可通过本文所描述的化合物、组合物和方法治疗的中枢神经系统肿瘤包括:

[0471] 1)星形细胞肿瘤,例如弥漫性星形细胞瘤(纤维型、原生质、饲肥星形细胞、混合性)、退行性(恶性)星形细胞瘤、多形性胶质母细胞瘤(巨细胞胶质母细胞瘤和神经胶质肉瘤)、毛状星形细胞瘤(毛细胞粘液样星形细胞瘤)、多形性黄色星形细胞瘤、室管膜下巨细胞星形细胞瘤和大脑神经胶瘤病。

[0472] 2)少突胶质细胞肿瘤,例如少突胶质细胞瘤和退行性少突胶质细胞瘤。

[0473] 3)少突星形细胞肿瘤,例如少突星形细胞瘤和退行性少突星形细胞瘤。

[0474] 4)室管膜肿瘤,例如室管膜下瘤、粘液乳头状室管膜瘤、室管膜瘤(细胞、乳头状、透明细胞、亚长细胞型)和退行性(恶性)室管膜瘤。

[0475] 5)脉络丛肿瘤,例如脉络丛乳头状瘤、非典型脉络丛乳头状瘤和脉络丛癌瘤。

[0476] 6)神经元和混合神经元-神经胶质肿瘤,例如神经节细胞瘤、神经节胶质细胞瘤、胚胎发育不良性神经上皮肿瘤(DNET)、小脑发育不良性神经节细胞瘤(Lhermitte-Duclos)、促结缔组织增生性婴儿星形细胞瘤/神经节胶质细胞瘤、中枢神经细胞瘤、退行性

神经节胶质细胞瘤、脑室外神经细胞瘤、小脑脂肪神经细胞瘤、乳头状胶质神经元肿瘤、第四脑室的菊形团形成性胶质神经元肿瘤(Rosette-forming glioneuronal tumor of the fourth ventricle)和终丝副神经节瘤。

[0477] 7)松果体肿瘤,例如松果体细胞瘤、松果体母细胞瘤、松果体区乳头状肿瘤和中分化松果体实质肿瘤。

[0478] 8)胚胎肿瘤,例如神经管母细胞瘤(广泛结节型神经管母细胞瘤、退行性神经管母细胞瘤、促结缔组织增生性、大细胞、黑色素性、髓母细胞瘤)、髓上皮瘤、幕上原始神经外胚层肿瘤和原始神经外胚层肿瘤(PNET),例如神经母细胞瘤、神经节母细胞瘤、室管膜母细胞瘤和非典型畸胎样/横纹肌瘤。

[0479] 9)神经母细胞肿瘤,例如嗅觉(敏感性神经胚细胞瘤)、嗅觉神经上皮瘤以及肾上腺和交感神经系统的神经母细胞瘤。

[0480] 10)神经胶质肿瘤,例如星形母细胞瘤、第三脑室脊索样神经胶质瘤和血管中心性神经胶质瘤。

[0481] 11)颅神经和椎旁神经肿瘤,例如神经鞘瘤、神经纤维瘤神经束膜瘤和恶性周边神经鞘肿瘤。

[0482] 12)脑膜肿瘤,例如脑膜上皮细胞肿瘤,例如脑膜瘤(非典型脑膜瘤和退行性脑膜瘤);间叶性肿瘤,例如脂肪瘤、血管脂肪瘤、蛰伏脂瘤、脂肪肉瘤、孤立性纤维性肿瘤、纤维肉瘤、恶性纤维组织细胞瘤、平滑肌瘤、平滑肌肉瘤、横纹肌瘤、横纹肌肉瘤、软骨瘤、软骨肉瘤、骨瘤、骨肉瘤、骨软骨瘤、血管瘤、上皮样血管内皮瘤、血管外皮瘤、退行性血管外皮瘤、血管肉瘤、卡波西肉瘤和尤文氏肉瘤;原发性黑色素细胞病变,例如弥漫性黑色素细胞增生症、黑色素细胞瘤、恶性黑素瘤、脑膜黑素瘤病;和血管母细胞瘤。

[0483] 13)造血系统的肿瘤,例如恶性淋巴细胞瘤、浆细胞瘤和粒细胞肉瘤。

[0484] 14)生殖细胞肿瘤,例如胚细胞瘤、胚胎性癌、卵黄囊肿瘤、绒毛膜癌、畸胎瘤和混合性生殖细胞肿瘤。

[0485] 15)蝶鞍区肿瘤,例如颅咽管瘤、颗粒细胞肿瘤、垂体细胞瘤和腺垂体梭状细胞嗜酸细胞瘤。

[0486] 癌症可为实体肿瘤,其可为或可不为转移性。如在白血病中,癌症也可作为扩散组织出现。因此,如本文中所提供的术语“肿瘤细胞”包括受以上鉴别的病症中任一者折磨的细胞。

[0487] 使用如本文所描述的化合物或组合物治疗癌症的方法可与现有的例如通过化学疗法、照射或手术(例如卵巢切除术)治疗癌症的方法组合。在一些实施方案中,化合物或组合物可在另一抗癌剂或治疗之前、期间或之后施用。

[0488] 存在越来越多的关于DYRK1A在阿尔茨海默病发作中的作用的证据(Future Medicinal Chemistry(2016),8(6),681-696和European Journal of Medicinal Chemistry(2018),158,559-592)。DYRK1A使涉及阿尔茨海默病和痴呆的以下关键底物磷酸化:Tau、septin 4、淀粉样蛋白前体蛋白(APP)、早老素1、脑啡肽酶、Munc18-1、α-突触核蛋白、RCAN1和β-微管蛋白。通过调节Tau外显子10的替代性剪接,相对于4R-Tau同工型,DYRK1A有利于产生3R-Tau剪接同工型(DS/AD/tau蛋白病变所特有)(Journal of Biological Chemistry(2015),290,15219-15237)。

[0489] 全基因组关联研究(GWAS)已揭示DYRK1A为帕金森病的风险因素(The Lancet Neurology(2019),18(12),1091-1102)。DYRK1A使帕金森病的关键因子磷酸化,所述关键因子如帕金蛋白(parkin)、septin4和α-突触核蛋白。对帕金森病具特异性的微RNA的上调靶向DYRK1A表达。存在另外的证据表明DYRK1A表达在帕金森病和皮克病中增加(Neurobiology of Disease(2005),20(2),392-400)。

[0490] 本文所提供的化合物和组合物可用作酶DYRK1A的抑制剂和/或调节剂,并且因此可用于治疗多种与tau蛋白相关的病症和疾病,包括但不限于阿尔茨海默病、肌萎缩性侧索硬化(ALS)、唐氏综合征、额颞叶型痴呆(FTD)(包括FTD伴帕金森症-17(FTDP-17))、行为变异型额颞叶型痴呆(bvFTD)、运动神经元疾病(MND)患者的FTD(通常为肌萎缩性侧索硬化,也称为FTD-ALS)、皮质基底节变性(CBD)(也称为皮质基底核神经节退化)、进行性核上麻痹、原发性渐进性失语症(PPA)、球状神经胶质tau蛋白病变(GGT)、第1型肌强直性营养不良(DM1)(也称为Steinert病)、第2型肌强直性营养不良(DM2)(也称为近端肌强直性肌病)、关岛型复合征(Guam complex)、嗜银颗粒病、拳击手型痴呆、脑炎后帕金森症、路易体痴呆、帕金森病、皮克病和伴有明显神经退行的额外疾病如自闭症、痴呆、癫痫、亨廷顿病、多发性硬化;与获得性脑损伤相关的疾病和病症如慢性创伤性脑病变、创伤性脑损伤、肿瘤和中风。

[0491] 可用本文所提供的化合物和组合物治疗的神经病症(例如神经疾患和神经疾病)的非限制性实例包括阿尔茨海默病、失语症、失用症、蜘蛛膜炎、毛细血管扩张性失调、注意力不足过动症、听觉处理障碍、自闭症、酒精中毒、贝尔氏麻痹症(Bell's palsy)、双相障碍、臂丛神经损伤、卡纳万病(Canavan disease)、腕隧道综合征、灼性神经痛、中枢性疼痛综合征、脑桥中央髓鞘溶解症、中央核肌病、头部病症、大脑动脉瘤、大脑动脉硬化、大脑萎缩、大脑巨人症、大脑性麻痹、大脑性血管炎、颈椎狭窄、恰克-马里-杜斯病(Charcot-Marie-Tooth disease)、Chiari畸形、慢性疲劳综合征、慢性炎症性脱髓鞘多发性神经病(CIDP)、慢性疼痛、Coffin-Lowry综合征、复杂区域疼痛综合征、压迫性神经病变、先天性两侧面瘫、皮质基底节变性、颅部动脉炎、颅缝早闭症、库贾病(Creutzfeldt-Jakob disease)、累积性创伤病症、库欣综合征(Cushing's syndrome)、巨细胞包涵体病(CIBD)、Dandy-Walker综合征、Dawson病、De Morsier综合征、Dejerine-Klumpke麻痹、德热里纳-索塔斯病(Dejerine-Sottas disease)、睡眠相位后移综合征、痴呆、皮肌炎、发展性运动障碍、糖尿病性神经病变、弥漫性硬化、Dravet综合征、自主神经障碍、算术障碍、书写障碍、阅读障碍、肌张力障碍、空鞍综合征、脑炎、脑膨出、大脑三叉神经性血管瘤病、排粪失禁、癫痫、欧勃氏麻痹(Erb's palsy)、红斑性肢痛、特发性震颤、法布里病(Fabry's disease)、Fahr综合征、家族性痉挛性麻痹、热痉挛、Fisher综合征、弗里德赖希共济失调(Friedreich's ataxia)、肌肉纤维疼痛、Foville综合征、戈谢病(Gaucher's disease)、格斯特曼综合征(Gerstmann'ssyndrome)、巨细胞动脉炎、巨细胞包涵体病、球状细胞脑白质营养不良、脑灰质移位脑灰质异位症、格林-巴利综合征(Guillain-Barrésyndrome)、HTLV-1相关脊髓病、霍勒沃顿-斯帕兹病(Hallervorden-Spatz disease)、半面痉挛、遗传性痉挛性下身麻痹、多神经炎型遗传性运动失调、带状疱疹病毒耳症、带状疱疹、平山综合征(Hirayama syndrome)、前脑无裂畸形、亨廷顿病、脑内积水、脑积水、皮质醇增多症、低氧症、免疫介导性脑脊髓炎、包涵体肌炎、色素失调症、婴儿植烷酸贮积病、婴儿型雷弗素姆疾病(infantile Refsum disease)、婴儿痉挛、炎症性肌病、颅内囊肿、颅内高血压、朱伯特综

合征(Joubert syndrome)、Karak综合征、卡恩斯-塞尔综合征(Kearns-Sayre syndrome)、肯尼迪病(Kennedy disease)、金斯布尔纳综合征(Kinsbourne syndrome)、Klippel Feil综合征、克拉伯病(Krabbe disease)、库格尔伯格-威兰德病(Kugelberg-Welander disease)、库鲁病(kuru)、拉福拉病(Lafora disease)、兰伯特-伊顿重肌无力综合征(Lambert-Eaton myasthenic syndrome)、兰道-克莱夫纳综合征(Landau-Kleffner syndrome)、外侧延髓(Wallenberg)综合征、莱氏病(Leigh's disease)、Lennox-Gastaut综合征、Lesch-Nyhan综合征、脑白质营养不良、路易体痴呆、平脑症、闭锁综合征、卢贾里格病(Lou Gehrig's disease)、椎间盘疾病、腰椎管狭窄症、莱姆病(Lyme disease)、Machado-Joseph病(脊髓小脑失调3型)、巨脑、视物显大症、巨脑症、Melkersson-Rosenthal综合征、梅尼尔病(Meniere'sdisease)、脑膜炎、门克斯病(Menkes disease)、异染性脑白质营养不良、小头畸形、视物显小症、Miller Fisher综合征、恐音症、线粒体肌病、Mobius综合征、单肢肌萎缩症、运动神经元疾病、运动技能障碍、烟雾病(Moyamoya disease)、粘多糖贮积症、多梗塞性痴呆、多灶性运动神经病、多发性硬化、多系统萎缩、肌肉萎缩症、肌痛性脑脊髓炎、重症肌无力、脱髓鞘弥漫性硬化、婴儿肌痉挛脑病、肌阵挛、肌病、肌微管性肌病、先天性肌强直、嗜睡症、神经纤维瘤、神经阻滞剂恶性综合征、红斑狼疮、神经肌强直、神经元蜡样脂褐质储积症、尼曼-匹克病(Niemann-Pick disease)、O'Sullivan-McLeod综合征、枕神经痛、隐性脊柱神经管闭合不全序列征(occult Spinal Dysraphism Sequence)、大田原综合征(Ohtahara syndrome)、橄榄体桥脑小脑萎缩、眼阵挛-肌阵挛综合征、视神经炎、直立性低血压、视觉重复(palinopsia)、感觉异常、帕金森病、先天性副肌强直、副肿瘤疾病、阵发性发作、Parry-Romberg综合征、Pelizaeus-Merzbacher病、周期性麻痹、周边神经病变、光敏性喷嚏反射、植烷酸贮积病、匹克病、多小脑回(PMG)、多发性肌炎、脑穿通畸形、脊髓灰质炎后综合征、带状疱疹后神经痛(PHN)、姿势性低血压、普拉德-威利综合征(Prader-Willi syndrome)、原发性侧索硬化、朊病毒病、进行性半面萎缩症、进行性多病灶脑白质病、进行性核上麻痹、大脑假性肿瘤、Ramsay Hunt综合征I型、Ramsay Hunt综合征II型、Ramsay Hunt综合征III型、Rasmussen脑炎、反射性神经血管营养不良、雷夫苏姆病(Refsum disease)、不宁腿综合征、反转录病毒相关脊髓病、雷特综合征(Rett syndrome)、雷氏综合征(Reye's syndrome)、节律性运动病症、隆伯格综合征(Romberg syndrome)、圣维特斯舞蹈症(Saint Vitus dance)、桑德霍夫病(Sandhoff disease)、精神分裂症、希尔德病(Schilder's disease)、脑裂畸形、感觉统合障碍、脑室中隔缺损合并视神经发育不全、夏伊-德尔格综合征(Shy-Drager syndrome)、Sjögren综合征、餐后喷嚏(snatiation)、索托氏综合征(Sotos syndrome)、痉挛状态、脊柱裂、脊髓肿瘤、脊髓性肌肉萎缩症、脊髓小脑失调、Steele-Richardson-Olszewski综合征、僵人综合征、中风、斯特奇-韦伯综合征(Sturge-Weber syndrome)、亚急性硬化性泛脑炎、皮质下动脉硬化性脑病、表面铁沉积症、辛登南氏舞蹈症(Sydenham's chorea)、晕厥、联觉、脊髓空洞病、踝管综合征、迟发性运动不能、迟发性神经失调、塔勒夫囊肿(Tarlov cyst)、泰-萨克斯病(Tay-Sachs disease)、颞动脉炎(temporal arteritis)、破伤风、脊髓栓系综合征、Thomsen病、胸廓出口综合征、三叉神经痛(tic douloureux)、Todd麻痹、妥瑞综合征(Tourette syndrome)、中毒性脑病、暂时性缺血性发作、传播性海绵样脑症、横贯性脊髓炎、震颤、三叉神经痛(trigeminal neuralgia)、热带强直性下身轻瘫、锥虫病、结节性硬化症、ubisiosis病(ubisiosis)、凡希

培-林道病(Von Hippel-Lindau disease)(VHL)、威流斯科脑脊髓炎(Viliuisk Encephalomyelitis)(VE)、Wallenberg综合征、Werdnig病、霍夫曼病(Hoffman disease)、韦斯特综合征(west syndrome)、威廉姆斯综合征(Williams syndrome)、威尔逊病(Wilson's disease)和Zellweger综合征。

[0492] 所述化合物和组合物也可适用于抑制侵袭性癌症、肿瘤血管生成和癌转移的发展。

[0493] 在一些实施方案中,所述药物组合物包含治疗有效量的式I化合物或其药学上可接受的盐和药学上可接受的赋形剂。

[0494] 在一些实施方案中,所述病症或疾病为癌症。

[0495] 在一些实施方案中,所述病症或疾病为转移性黑素瘤。

[0496] 在一些实施方案中,所述病症或疾病为肌腱再生。

[0497] 在一些实施方案中,所述病症或疾病为糖尿病。

[0498] 在一些实施方案中,所述病症或疾病为退化性椎间盘疾病。

[0499] 在一些实施方案中,所述病症或疾病为骨关节炎。

[0500] 在一些实施方案中,所述病症或疾病为病毒感染。

[0501] 在一些实施方案中,所述病症或疾病为神经病症。

[0502] 在一些实施方案中,所述病症或疾病为阿尔茨海默病。

[0503] 在一些实施方案中,所述病症或疾病为骨关节炎。

[0504] 在一些实施方案中,所述患者为人类。

[0505] 在一些实施方案中,所述癌症选自:肝细胞癌、结肠癌、乳腺癌、胰腺癌、慢性骨髓性白血病(CML)、慢性骨髓单核细胞性白血病、慢性淋巴细胞性白血病(CLL)、急性骨髓性白血病、急性淋巴细胞性白血病、霍奇金淋巴瘤、淋巴瘤、肉瘤和卵巢癌。

[0506] 在一些实施方案中,所述癌症选自:非小细胞肺癌、小细胞肺癌、多发性骨髓瘤、鼻咽癌、神经母细胞瘤、骨肉瘤、阴茎癌、脑垂体肿瘤、前列腺癌、视网膜母细胞瘤、滑膜肉瘤、横纹肌肉瘤、唾液腺癌、皮肤癌-基底和鳞状细胞、皮肤癌-黑素瘤、小肠癌、胃部(胃)癌、睾丸癌、胸腺癌、甲状腺癌、子宫肉瘤、阴道癌、外阴癌、喉或下咽癌、肾癌、卡波西肉瘤、妊娠滋养细胞疾病、胃肠基质瘤、胃肠类癌瘤、胆囊癌、眼部癌症(黑素瘤和淋巴瘤)、尤文氏肿瘤(Ewing tumor)、食道癌、子宫内膜癌、结直肠癌、宫颈癌、脑部或脊髓肿瘤、骨骼癌细胞转移、骨癌、膀胱癌、胆管癌、肛门癌和肾上腺皮质癌。

[0507] 在一些实施方案中,所述癌症为肝细胞癌;在一些实施方案中,所述癌症为结肠癌;在一些实施方案中,所述癌症为结直肠癌;在一些实施方案中,所述癌症为乳腺癌;在一些实施方案中,所述癌症为胰腺癌;在一些实施方案中,所述癌症为慢性骨髓性白血病(CML);在一些实施方案中,所述癌症为慢性骨髓单核细胞性白血病;在一些实施方案中,所述癌症为慢性淋巴细胞性白血病(CLL);在一些实施方案中,所述癌症为急性骨髓性白血病;在一些实施方案中,所述癌症为急性淋巴细胞性白血病;在一些实施方案中,所述癌症为霍奇金淋巴瘤;在一些实施方案中,所述癌症为淋巴瘤;在一些实施方案中,所述癌症为肉瘤;在一些实施方案中,所述癌症为卵巢癌;在一些实施方案中,所述癌症为非小细胞肺癌;在一些实施方案中,所述癌症为小细胞肺癌;在一些实施方案中,所述癌症为多发性骨髓瘤;在一些实施方案中,所述癌症为鼻咽癌;在一些实施方案中,所述癌症为神经母细胞

瘤;在一些实施方案中,所述癌症为骨肉瘤;在一些实施方案中,所述癌症为阴茎癌;在一些实施方案中,所述癌症为脑垂体肿瘤;在一些实施方案中,所述癌症为前列腺癌;在一些实施方案中,所述癌症为视网膜母细胞瘤;在一些实施方案中,所述癌症为横纹肌肉瘤;在一些实施方案中,所述癌症为唾液腺癌;在一些实施方案中,所述癌症为皮肤癌-基底和鳞状细胞;在一些实施方案中,所述癌症为皮肤癌-黑素瘤;在一些实施方案中,所述癌症为小肠癌;在一些实施方案中,所述癌症为胃部(胃)癌;在一些实施方案中,所述癌症为睾丸癌;在一些实施方案中,所述癌症为胸腺癌;在一些实施方案中,所述癌症为甲状腺癌;在一些实施方案中,所述癌症为子宫肉瘤;在一些实施方案中,所述癌症为阴道癌;在一些实施方案中,所述癌症为外阴癌;在一些实施方案中,所述癌症为威尔姆氏肿瘤(Wilms tumor);在一些实施方案中,所述癌症为喉或下咽癌;在一些实施方案中,所述癌症为肾癌;在一些实施方案中,所述癌症为卡波西肉瘤;在一些实施方案中,所述癌症为妊娠滋养细胞疾病;在一些实施方案中,所述癌症为胃肠基质瘤;在一些实施方案中,所述癌症为胃肠类癌瘤;在一些实施方案中,所述癌症为胆囊癌;在一些实施方案中,所述癌症为眼部癌症(黑素瘤和淋巴瘤);在一些实施方案中,所述癌症为尤文氏肿瘤;在一些实施方案中,所述癌症为食道癌;在一些实施方案中,所述癌症为子宫内膜癌;在一些实施方案中,所述癌症为结直肠癌;在一些实施方案中,所述癌症为宫颈癌;在一些实施方案中,所述癌症为脑部或脊髓肿瘤;在一些实施方案中,所述癌症为骨骼癌细胞转移;在一些实施方案中,所述癌症为骨癌;在一些实施方案中,所述癌症为膀胱癌;在一些实施方案中,所述癌症为胆管癌;在一些实施方案中,所述癌症为肛门癌;并且在一些实施方案中,所述癌症为肾上腺皮质癌。

[0508] 在一些实施方案中,所述病症或疾病为神经疾患、病症或疾病,其中所述神经疾病选自:阿尔茨海默病、额颞叶型痴呆、帕金森症、亨廷顿病、进行性核上麻痹、皮质基底节变性、多系统萎缩、肌萎缩性侧索硬化(ALS)、包涵体肌炎、自闭症、退化性肌病。

[0509] 在一些实施方案中,所述病症或疾病选自由以下组成的组:阿尔茨海默病、肌萎缩性侧索硬化、唐氏综合征、额颞叶型痴呆伴帕金森症-17(FTDP-17)、路易体痴呆、帕金森病、皮克病和伴有明显神经退行的额外疾病如自闭症、痴呆、癫痫、亨廷顿病、多发性硬化;与获得性脑损伤相关的疾病和病症如慢性创伤性脑病变、创伤性脑损伤、肿瘤和中风。

[0510] 在一些实施方案中,式I化合物抑制DYRK1A。

[0511] 在一些实施方案中,所述方法治疗患者的由激酶活性介导的疾病或病症,所述方法包括向所述患者施用治疗有效量的式I化合物(或多种式I化合物)或其药学上可接受的盐。

[0512] 在一些实施方案中,所述疾病或病症包含肿瘤生长、细胞增殖或血管生成。

[0513] 在一些实施方案中,所述方法抑制蛋白激酶受体的活性,所述方法包括使受体与有效量的式I化合物(或多种式I化合物)或其药学上可接受的盐接触。

[0514] 在一些实施方案中,所述方法治疗患者的与异常细胞增殖相关的疾病或病症;所述方法包括向所述患者施用治疗有效量的式I化合物(或多种式I化合物)或其药学上可接受的盐。

[0515] 在一些实施方案中,所述方法预防或减少患者的异常细胞增殖;所述方法包括向所述患者施用治疗有效量的式I化合物(或多种式I化合物)或其药学上可接受的盐。

[0516] 在一些实施方案中,所述方法治疗患者的与异常细胞增殖相关的疾病或病症,所

述方法包括向所述患者施用包含与药学上可接受的载体和一种或多种其他药剂组合的权利要求1所述的化合物中的一者或多者的药物组合物。

[0517] 生物活性的评价

[0518] 本文所描述的化合物的生物活性可使用本领域技术人员已知的任何适合的测定来测试。例如,可使用下文所概述的一种或多种测试方法测试化合物的活性。

[0519] 例如,可使用针对DYRK1A生物活性的体外测定,例如针对神经元细胞系(例如人类SH-SY5Y神经母细胞瘤细胞系)中微管相关蛋白tau(MAPT/Tau)磷酸化的调节。针对DYRK1A调节的磷酸化水平的测定可包括监测基础pSer396 Tau的水平,其可例如通过使用十微摩尔最高浓度的候选抑制剂组合物的连续稀释液来测量并且通过ELISA或蛋白质印迹(Western Blotting)检测。针对DYRK-1A调节的磷酸化的示例性测定利用以96孔板型式培养SH-SY5Y细胞持续足以使微管和Tau磷酸化稳定的时段,通常至少2天,然后用化合物的1/3连续稀释液处理过夜并裂解。细胞裂解物通过SDS PAGE解析,然后转移至硝化纤维素并用对pSer396 Tau具特异性的抗体探测。使用Carestream Image Station检测蛋白质印迹中所用的HRP连接抗体的化学发光信号,并且使用ImageJ(NIH)分析针对pSer396和β-肌动蛋白的印迹密度测定法。

[0520] 在另一实例中,候选化合物的活性可通过将上文所提及的裂解物添加至涂布有总Tau的板上并用特异性pThr212Tau抗体检测通过phosphoTau(Thr212)AlphaLISA来测量。AlphaLISA信号的比色检测通过EnVision多标签板读取器(Perkin Elmer)进行。

[0521] 为了进一步说明本公开,包括以下实施例。当然,实施例不应解释为特别限制本公开。这些实施例在权利要求的范围内的变化形式处于本领域技术人员的领域内,并且被视为属于如本文描述和要求保护的本公开范围内。读者将认识到,熟悉本公开和本领域技术的熟练技术人员不需详尽实施例就能够制备和使用本公开。

[0522] 实施例

[0523] 化合物制备

[0524] 用于制备本公开化合物的起始物质是已知的,其通过已知方法制备或为可商购的。熟练技术人员将显而易知,用于制备与本文要求保护的化合物有关的前体和官能团的方法通常描述于文献中。被给与文献和本公开的熟练技术人员充分准备好制备任何所述化合物。

[0525] 应认识到,有机化学领域的熟练技术人员可容易地在不经进一步指导的情况下进行操作,即,其完全在进行这些操作的熟练技术人员的范围和实践内。这些包括羰基化合物还原成其对应醇、氧化、酰化、亲电和亲核芳族取代、醚化、酯化和皂化等。这些操作论述于标准文本中,例如March's Advanced Organic Chemistry:Reactions,Mecha nisms,and Structure第7版,John Wiley&Sons(2013),Carey和Sundberg,Advanced Organic Chemistry第5版,Springer(2007),Com prehensive Organic Transformations:A Guide to Functional Group Transformations,第2版,John Wiley&Sons(1999)(通过引用整体并入本文)等。

[0526] 熟练技术人员将容易了解某些反应最好在分子中的其他官能团被遮蔽或保护时进行,因此避免任何非所需副反应和/或提高反应产率。熟练技术人员通常利用保护基来实现此类产率提高或避免非所需反应。这些反应见于文献中并且也完全处于熟练技术人员的

范围内。许多这些操作的实例可见于例如P.Wuts Greene's Protective Groups in Organic Synthesis,第5版,John Wiley&Sons(2014)中,其通过引用整体并入本文。

[0527] 本文所用的商标仅为实例并且反映本公开所用的说明性材料。熟练技术人员将认识到可预期批次、制造工艺等中的变化。因此,实施例和其中所用的商标为非限制性的,并且它们并不旨在为限制性的,而仅为熟练技术人员可如何选择来执行本公开的实施方案中的一者或多者的说明。

[0528] (^{1}H)核磁共振光谱(NMR)是在Bruker NMR光谱仪(Avance TM DRX300,300MHz,^{1}H,或Avance TM DRX500,500MHz,^{1}H)或Varian NMR光谱仪(Mercury 400BB,400MHz,^{1}H)上在所指示溶剂中测量。峰位置在四甲基硅烷的低场以百万分率(ppm)表示。峰多重性如下表示:s,单峰;d,二重峰;t,三重峰;q,四重峰;ABq,AB四重峰;quin,五重峰;sex,六重峰;sep,七重峰;non,九重峰;dd,双重二重峰;ddd,双重双重二重峰;d/ABq,双重AB四重峰;dt,双重三重峰;td,三重二重峰;dq,双重四重峰;m,多重峰。

[0529] 以下缩写具有指定含义:

[0530] Ac_2O=乙酸酐

[0531] Boc=叔丁氧羰基

[0532] $B(OiPr)_3$=硼酸三异丙酯

[0533] BrettPhos=二环己基(2',4',6'-三异丙基-3,6-二甲氧基-[1,1'-联苯]-2-基)膦

[0534] BrettPhos Pd G3=[(2-二环己基膦基-3,6-二甲氧基-2',4',6'-三异丙基-1,1'-联苯)-2-(2'-氨基-1,1'-联苯)]甲磺酸钯(II)甲磺酸盐

[0535] 盐水=饱和氯化钠水溶液

[0536] nBuLi=正丁基锂

[0537] $CDCl_3$=氘化氯仿

[0538] $(COCl)_2$=草酰氯

[0539] Cs_2CO_3=碳酸铯

[0540] DCE=1,2-二氯乙烷

[0541] DCM=二氯甲烷

[0542] DIPEA=N,N-二异丙基乙胺

[0543] DME=1,2-二甲氧基乙烷,或乙二醇二甲醚,或单乙二醇二甲醚

[0544] DMF=N,N-二甲基甲酰胺

[0545] DMPU=N,N'-二甲基丙烯脲

[0546] DMSO-d_6=氘化二甲亚砜

[0547] ESIMS=电喷雾质谱

[0548] EtOAc=乙酸乙酯

[0549] HATU=1-[双(二甲氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐

[0550] HCl=盐酸

[0551] HOAc=乙酸

[0552] IPA=异丙醇

[0553] ISCO＝Teledyne ISCO,Inc,品牌CombiFlash®Rf 200

[0554] KOAc＝乙酸钾

[0555] LCMS＝液相色谱-质谱法

[0556] LiHMDS＝双(三甲基甲硅烷基)氨基锂

[0557] MeCN＝乙腈

[0558] MeOH＝甲醇

[0559] MeTHF＝2-甲基四氢呋喃

[0560] $MgSO_4$＝硫酸镁

[0561] MsCl＝甲磺酰氯(methanesulfonyl chloride/mesyl chloride)

[0562] MTBE＝甲基叔丁基醚

[0563] MW＝微波照射

[0564] NaO^tBu＝叔丁醇钠

[0565] $NaHCO_3$＝碳酸氢钠

[0566] $NaBH(OAc)_3$＝三乙酰氧基硼氢化钠

[0567] Na_2SO_4＝硫酸钠

[0568] NMR＝核磁共振

[0569] ON＝过夜

[0570] Pd/C＝钯/碳

[0571] $Pd(dppf)Cl_2$＝1,1'-双(二苯基膦基)二茂铁-二氯化钯(II)

[0572] $Pd(OH)_2/C$＝氢氧化钯/碳

[0573] PE＝石油醚

[0574] PPTS＝对甲苯磺酸吡啶鎓

[0575] 制备型TLC＝制备型薄层色谱法

[0576] QPhos＝1,2,3,4,5-稠五苯基-1'-(二-叔丁基膦基)二茂铁

[0577] r.t.＝室温

[0578] TBDMSCl＝叔丁基二甲基氯硅烷

[0579] TEA＝三乙胺

[0580] TFA＝三氟乙酸

[0581] THF＝四氢呋喃

[0582] TLC＝薄层色谱法

[0583] TMSOK＝三甲基硅醇化钾

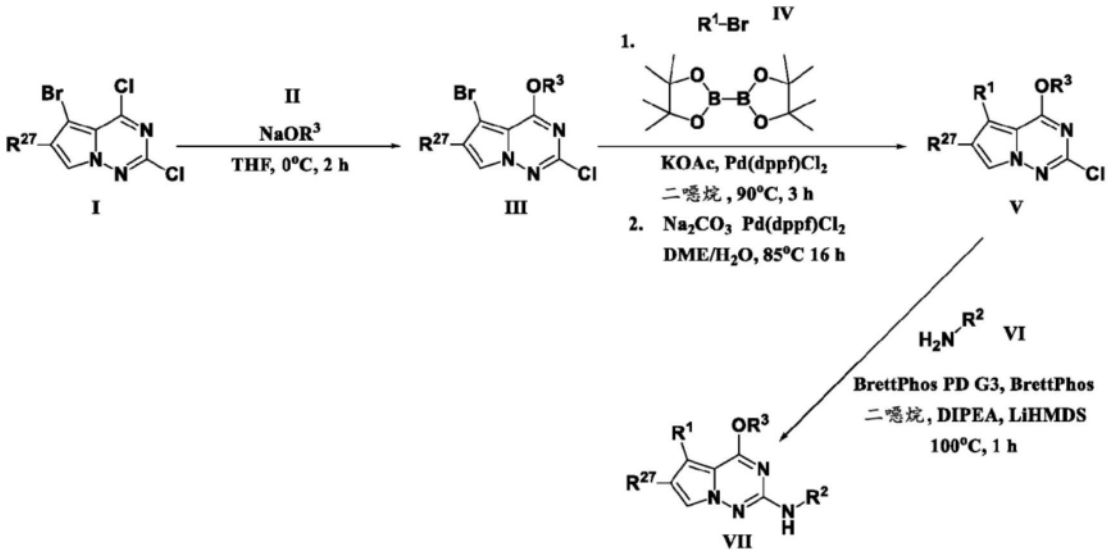
[0584] XPhos＝二环己基[2',4',6'-三(丙-2-基)[1,1'-联苯]-2-基]磷烷

[0585] 提供以下实施例方案来指导读者,并且总体而言表示用于制造本文所提供的化合物的实施例方法。此外,根据以下反应方案和实施例,用于制备本公开化合物的其他方法对于本领域普通技术人员将显而易知。熟练技术人员充分准备好通过文献和本公开的那些方法制备这些化合物。下文描绘的合成方案中所用的化合物编号仅用于那些特定方案,并且不应视为本申请的其他部分中的相同编号或与本申请的其他部分的相同编号混淆。除非另外指明,否则全部变量都如上文所定义。

[0586] 通用程序

[0587] 本公开的式I化合物可如方案1中所描绘制备。

[0588]



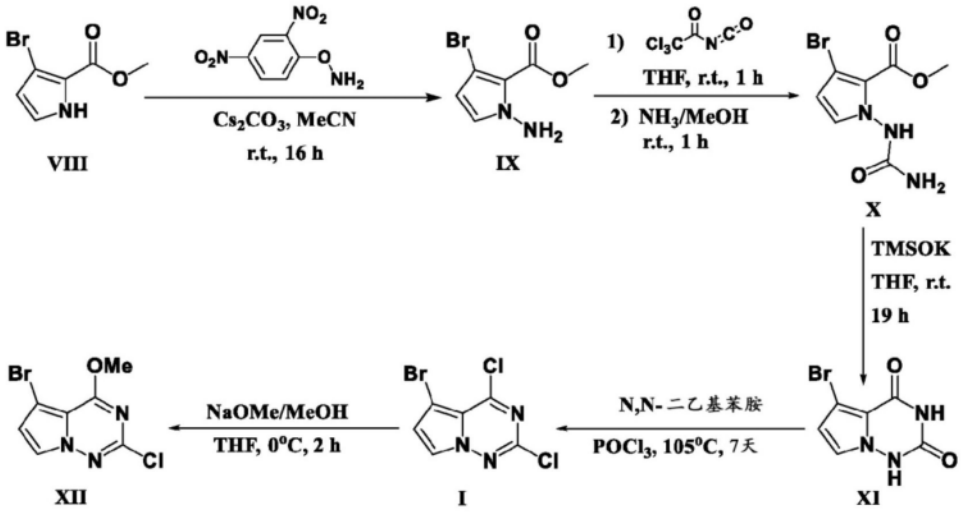
方案 1

[0589] 方案1描述了一种用于制备4-烷氧基吡咯并[2,1-f][1,2,4]三嗪衍生物(VII)的方法,其通过首先用多种烷基氧(II)置换4-氯离子(I)以产生2-氯-5-溴-4-烷氧基吡咯并[2,1-f][1,2,4]三嗪III进行。通过使各种溴离子(IV)与双(频哪醇合)二硼反应,随后与溴离子(III)进行铃木偶联以形成多种硼酸频哪醇酯,从而产生2-氯-4-烷氧基吡咯并[2,1-f][1,2,4]三嗪(V)。然后用多种胺(VI)置换氯,产生最终4-烷氧基吡咯并[2,1-f][1,2,4]三嗪(VII)。

[0590] 说明性化合物实施例

[0591] 中间体5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)的制备描绘于以下方案2中。

[0592]



方案 2

[0593] 步骤1

[0594] 在20℃向3-溴-1H-吡咯-2-甲酸甲酯(VIII)(100g,490.15mmol,1eq.)于MeCN(2L)

中的溶液中一次性添加Cs_2CO_3(255.52g,784.23mmol,1.6eq.)(不放热)。在室温搅拌反应物5h。然后在N_2下在0至5℃滴加O-(2,4-二硝基苯基)羟胺(146.40g,735.22mmol,1.5eq.)于MeCN(2L)中的溶液。添加后,使反应物升温至室温持续16h。过滤反应混合物,并用MTBE(2L)稀释滤液并用盐水(2Lx3)洗涤。以上反应进行六次。

[0595] 合并五个批次的经合并有机物,经$MgSO_4$干燥,过滤并真空浓缩,得到粗产物。通过硅胶柱色谱法(DCM/PE=0至50%,然后EtOAc/PE=20%)纯化粗产物,得到呈黄色固体的1-氨基-3-溴-1H-吡咯-2-甲酸甲酯(IX)(380g,1.62mol,55.1%产率,93.3%纯度)。^{1}H NMR(400MHz,DMSO-d_6)δppm 3.84(3H,s),6.24(1H,d,J=2.8Hz),6.38(2H,br s),7.12(1H,d,J=2.8Hz)。

[0596] 步骤2至3

[0597] 在0至5℃向1-氨基-3-溴-1H-吡咯-2-甲酸甲酯(IX)(190g,867.44mmol,1eq.)于THF(1900mL)中的溶液中滴加异氰酸2,2,2-三氯乙酰酯(179.76g,954.18mmol,113.06mL,1.1eq.),然后升温至室温持续1h。然后在室温将反应物滴加至NH_3/MeOH(7M,1.24L,10eq)中,在室温搅拌1h,得到黄色悬浮液。以上反应进行两次。

[0598] 将两种反应物合并并真空浓缩。在室温用MTBE(4L)湿磨残余物30min,过滤。将滤饼用MTBE(500mLx3)洗涤,真空干燥,得到呈灰白色固体的3-溴-1-脲基-1H-吡咯-2-甲酸甲酯(X)(402g,1.53mol,88.2%产率,99.78%纯度)。^{1}H NMR(400MHz,DMSO-d_6)δppm3.75(3H,s),6.27(2H,br s),6.28(1H,d,J=2.8Hz),7.10(1H,d,J=2.8Hz),9.27(1H,br s);$C_7H_8BrN_3O_3$的ESIMS实验值m/z 262.1(^{79}BrM+H)。

[0599] 步骤4

[0600] 在N_2下在0至5℃向3-溴-1-脲基-1H-吡咯-2-甲酸甲酯(X)(67g,255.67mmol,1eq.)于THF(4L)中的溶液中分数份添加TMSOK(65.60g,511.33mmol,2eq.)。搅拌5min后,反应物变成粘稠浆液。在室温剧烈搅拌反应混合物16h。LCMS显示剩余约25.8%起始物质。在室温再添加一份TMSOK(16.40g,127.83mmol,0.5eq.)并搅拌3h。LCMS显示反应完成。浓缩反应物。用H_2O(1.6L)稀释残余物,用冰浴冷却,滴加HCl(4M,160mL)至pH为2至3,并过滤。用H_2O(600mLx3)洗涤滤饼。以上反应进行六次。

[0601] 合并六次反应的滤饼,在室温用H_2O(6L)湿磨2h并且然后过滤。在60℃在真空干燥烘箱中干燥滤饼24h,得到呈白色固体的5-溴吡咯并[2,1-f][1,2,4]三嗪-2,4(1H,3H)-二酮(XI)(320g,1.28mol,83.4%产率,91.95%纯度)。^{1}H NMR(400MHz,DMSO-d_6)δppm 6.49(1H,d,J=2.8Hz),7.17(1H,d,J=2.8Hz),11.30(1H,br s);$C_6H_4BrN_3O_2$的ESIMS实验值m/z 232.0(^{81}BrM+H)。

[0602] 步骤5

[0603] 在室温向$POCl_3$溶液(1500mL)中分数份添加5-溴吡咯并[2,1-f][1,2,4]三嗪-2,4(1H,3H)-二酮(XI)(180g,782.55mmol,1eq.)。然后在室温(极少放热)滴加N,N-二乙基苯胺(291.95g,1.96mol,312.92mL,2.5eq.)。添加后,将反应物加热至105℃持续48h。LCMS显示起始物质耗尽,但剩余中间体,形成约4.3%所需产物。将反应物冷却至90℃,再一次性添加$POCl_3$(500mL),然后将其平缓地加热至回流持续24h。LCMS显示剩余大部分中间体,形成约11.9%所需产物。将反应物平缓地加热至回流,再持续4天。LCMS显示剩余约7.4%中间体,形成约55.5%所需产物。使反应物冷却至40℃并减压蒸馏以去除大部分$POCl_3$。将残余物用

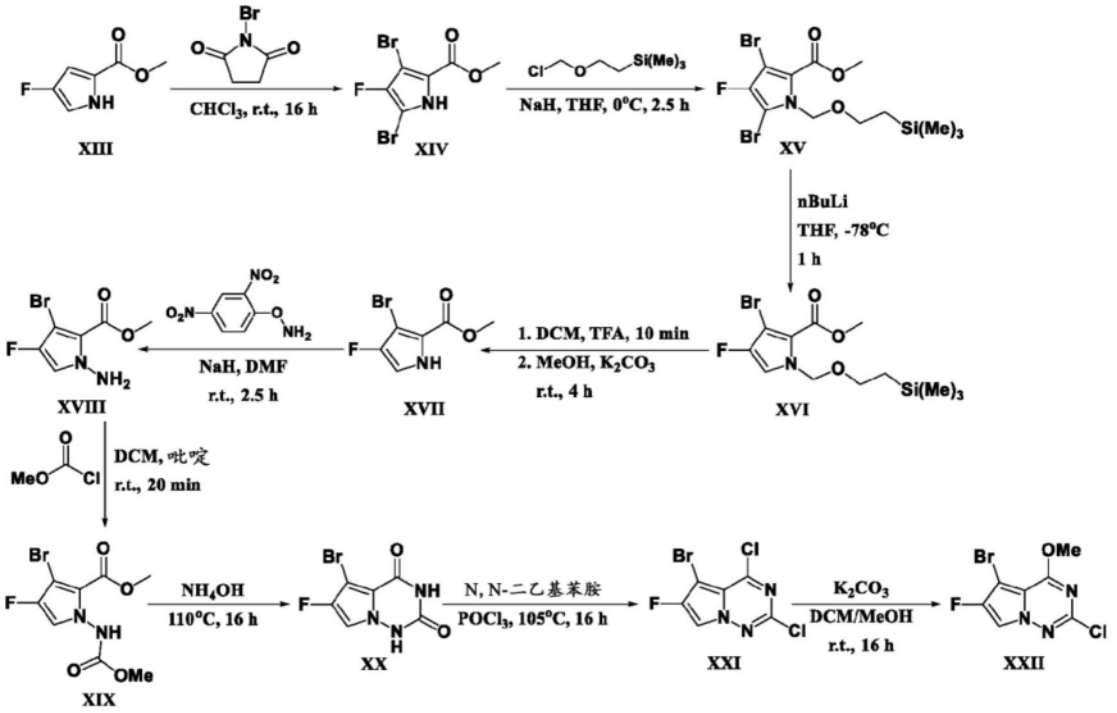
MeTHF(5L)稀释,倒入冰H_2O(2L)中,添加盐水(1L),并分离。用MeTHF(1.5Lx2)萃取水层。将合并的有机物用盐水(1.5Lx2)洗涤,经$MgSO_4$干燥,过滤并真空浓缩,得到粗产物。将粗产物通过硅胶柱色谱法(4kg,100至200目,DCM/PE=0至20%)纯化并且在室温用正庚烷(500mL)湿磨3h,然后过滤,得到呈黄色固体的5-溴-2,4-二氯吡咯并[2,1-f][1,2,4]三嗪(I)(150g,556.14mmol,71.1%产率,98.96%纯度)。^1H NMR(400MHz,$CDCl_3$)δppm 7.02(1H,d,J=2.4Hz),7.79(1H,d,J=2.4Hz);$C_6H_2BrCl_2N_3$的ESIMS实验值m/z 266.1($^{79}BrM+H$)。

[0604] 步骤6

[0605] 在0℃向5-溴-2,4-二氯吡咯并[2,1-f][1,2,4]三嗪(I)(8.0g,29.97mmol)于THF(10mL)中的经搅拌溶液中滴加含甲醇钠(66mL,33mmol)的MeOH并且搅拌混合物2h。将反应混合物用NH_4Cl饱和水溶液淬灭,溶于EtOAc中,用水和盐水洗涤。分离有机物,经无水Na_2SO_4干燥,浓缩,并在高真空下干燥,得到呈灰白色固体的5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(6g,22.86mmol,76.3%产率),其不经纯化即用于下一步骤。^1H NMR(499MHz,DMSO-d_6)δppm 4.12(3H,s),7.00(1H,d,J=3.01Hz),8.01(1H,d,J=3.01Hz);$C_7H_5BrClN_3O$的ESIMS实验值m/z 261.1($^{79}BrM+H$)。

[0606] 中间体5-溴-2-氯-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XXII)的制备描绘于以下方案3中。

[0607]



方案3

[0608] 步骤1

[0609] 在0℃向4-氟-1H-吡咯-2-甲酸甲酯(XIII)(可购自PharmaBlock(USA),Inc.)(1g,6.99mmol)于$CHCl_3$(9mL)中的溶液中添加N-溴代丁二酰亚胺(2.64g,14.68mmol)。在室温搅拌反应物16h。将反应混合物用10%硫代硫酸钠(50mL)淬灭并用CHC_3(3x30 mL)萃取。合并有机层并用NaCl饱和水溶液(50ml)洗涤并减压蒸发,产生呈米色固体的3,5-二溴-4-氟-1H-吡咯-2-甲酸甲酯(XIV)(2.1g,6.979mmol,99.9%产率)。所述产物不经进一步纯化即按

原样使用。$C_6H_4Br_2FNO_2$的ESIMS实验值m/z 299.9(M+H)。

[0610] 步骤2

[0611] 在N_2下在0℃向3,5-二溴-4-氟-1H-吡咯-2-甲酸甲酯(XIV)(2.1g,6.98mmol)于无水THF(25mL)中的溶液中分小份缓慢添加NaH(0.43g,10.63mmol)。在0℃搅拌悬浮液30min。在N_2下在0℃向悬浮液中添加(2-(氯甲氧基)乙基)三甲基硅烷(1.9mL,10.74mmol)。在0℃搅拌反应混合物2h,然后用冰水(20mL)淬灭并用EtOAc(3x30 mL)萃取。减压蒸发EtOAc层并通过硅胶柱色谱法(100%己烷)纯化,产生呈琥珀色液体的3,5-二溴-4-氟-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯-2-甲酸甲酯(XV)(2.76g,6.401mmol,91.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm-0.07(9H,s),0.81(2H,t,J=7.80Hz),3.50(2H,t,J=7.80Hz),3.82(3H,s),5.69(2H,s)。

[0612] 步骤3

[0613] 在N_2下在-78℃向3,5-二溴-4-氟-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯-2-甲酸甲酯(XV)(2.76g,6.4mmol)于无水THF(60mL)中的溶液中添加nBuLi(2.4mL,6.mmol)。在-78℃搅拌反应混合物1h。将混合物小心地用冰水(20mL)淬灭,升温至室温,并用EtOAc(3x20mL)萃取。将有机物经无水Na_2SO_4干燥,过滤并蒸发至Celite®上,并通过硅胶柱色谱法(0→6% EtOAc/己烷)纯化,产生呈澄清油状物的3-溴-4-氟-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯-2-甲酸甲酯(XVI)(760mg,2.157mmol,33.7%产率)。^{1}H NMR(500MHz,DMSO-d_6)δppm-0.06(9H,s),0.80(2H,t,J=7.96Hz),3.41-3.50(2H,m),3.80(3H,s),5.56(2H,s),7.52(1H,d,J=3.29Hz)。

[0614] 步骤4

[0615] 向3-溴-4-氟-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯-2-甲酸甲酯(XVI)(881mg,2.5mmol)于DCM(23mL)中的经搅拌溶液中添加TFA(23mL)并且在室温搅拌混合物10min。浓缩溶剂,将残余物溶于MeOH(12mL)/水(6mL)的混合物中。向此混合物中添加K_2CO_3(1.75g,12.66mmol)并在室温下搅拌4h。添加水(10mL),并且用1H HCl中和溶液并用$CHCl_3$(3x10 mL)洗涤。将有机层汽提至Celite®上,并通过硅胶柱色谱法(0→5% MeOH/$CHCl_3$(7N NH_3))纯化,产生呈灰白色固体的3-溴-4-氟-1H-吡咯-2-甲酸甲酯(XVII)(450mg,2.027mmol,81.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 3.80(3H,s),7.15(1H,d,J=3.56Hz),12.29(1H,br s);$C_6H_5BrFNO_2$的ESIMS实验值m/z 222.0(M+H)。

[0616] 步骤5

[0617] 在0℃向3-溴-4-氟-1H-吡咯-2-甲酸甲酯(XVII)(500mg,2.25mmol)于无水DMF(7mL)中的溶液中缓慢添加NaH(120mg,2.93mmol)。30min后,一次性添加O-(2,4-二硝基苯基)羟胺(490mg,2.48mmol)并且在冰浴中搅拌反应物1h并在室温搅拌1h。LC/MS显示反应不完全,因此添加O-(2,4-二硝基苯基)羟胺(490mg,2.48mmol)并在室温搅拌15min。用水(100mL)稀释反应物并用EtOAc(3x75 mL)萃取。将经合并的萃取物汽提至Celite®上,并通过硅胶柱色谱法(100%$CHCl_3$)纯化,产生呈灰白色固体的1-氨基-3-溴-4-氟-1H-吡咯-2-甲酸甲酯(XVIII)(501mg,2.114mmol,93.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 3.80(3H,s),6.36(2H,s),7.25(1H,d,J=3.29Hz);$C_6H_6BrFN_2O_2$的ESIMS实验值m/z 237.0(M+H)。

[0618] 步骤6

[0619] 向1-氨基-3-溴-4-氟-1H-吡咯-2-甲酸甲酯(XVIII)(500mg,2.11mmol)于DCM

(10mL)中的溶液中滴加吡啶(210μL,2.6mmol)和氯甲酸甲酯(180μL,2.33mmol)。在室温搅拌反应物20min。添加DCM(100mL)并用1N HCl(2x50 mL)洗涤,将其汽提至Celite®上并通过硅胶柱色谱法(0→100% EtOAc/己烷)纯化,产生呈澄清油状物的3-溴-4-氟-1-((甲氧基羰基)氨基)-1H-吡咯-2-甲酸甲酯(XIX)(560mg,1.898mmol,89.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 3.69(3H,br s),3.76(3H,s),7.48(1H,br d,J=1.92Hz),10.76(1H,br s);$C_8H_8BrFN_2O_4$的ESIMS实验值m/z 295.0(M+H)。

[0620] 步骤7

[0621] 在密封管中向NH_4OH(35mL,263.7mmol)中添加3-溴-4-氟-1-((甲氧基羰基)氨基)-1H-吡咯-2-甲酸甲酯(XIX)(560mg,1.9mmol)。将反应物密封并加热至110℃持续16h。真空去除溶剂并且使残余物溶解于MeCN中。将溶剂汽提(3次以去除水)并且置于高真空持续1h,产生呈淡棕色固体的5-溴-6-氟吡咯并[2,1-f][1,2,4]三嗪-2,4(1H,3H)-二酮(XX)(440mg,1.774mmol,93.5%产率)。所述产物不经进一步纯化即按原样使用。^{1}H NMR(499MHz,DMSO-d_6)δppm 7.04(1H,d,J=3.29Hz),7.13(1H,br s),9.58(1H,br s);$C_6H_3BrFN_3O_2$的ESIMS实验值m/z 247.9(M+H)。

[0622] 步骤8

[0623] 在室温向纯$POCl_3$(3mL,32.19mmol)溶液中分数份添加5-溴-6-氟吡咯并[2,1-f][1,2,4]三嗪-2,4(1H,3H)-二酮(XX)(440mg,1.77mmol)。然后在室温滴加N,N-二乙基苯胺(0.7mL,4.4mmol)。在105℃加热反应物16h。真空去除溶剂,然后添加水(20mL)并用EtOAc萃取。将有机层汽提至Celite®上,并通过硅胶柱色谱法(0→100% EtOAc/己烷)纯化,产生呈灰白色固体的5-溴-2,4-二氯-6-氟吡咯并[2,1-f][1,2,4]三嗪(XXI)(175mg,0.614mmol,34.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 7.92(1H,d,J=3.29Hz);$C_6HBrCl_2FN_3$的ESIMS实验值m/z 283.9(M+H)。

[0624] 步骤9

[0625] 向5-溴-2,4-二氯-6-氟吡咯并[2,1-f][1,2,4]三嗪(XXI)(175mg,0.61mmol)于MeOH(664μL)和DCM(2mL)中的溶液中添加K_2CO_3(254.1mg,1.84mmol)。盖上烧瓶并且在室温搅拌反应物16h。添加水(50mL)并用DCM(3x50 mL)萃取。分离有机层并用水(2x50 mL)和盐水(50mL)洗涤。真空去除溶剂,产生呈米色固体的5-溴-2-氯-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XXII)(163mg,0.581mmol,94.6%产率)。^{1}H NMR(500MHz,DMSO-d_6)δppm 4.12(3H,s),8.34(1H,d,J=3.29Hz);$C_7H_4BrClFN_3O$的ESIMS实验值m/z 279.95(M+H)。

[0626] 中间体2,5-二氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XXIV)的制备描绘于以下方案4中。

[0627] 

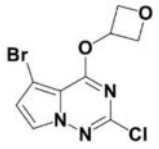
方案4

[0628] 步骤1

[0629] 在0℃向2,4,5-三氯吡咯并[2,1-f][1,2,4]三嗪(XXIII)(可购自PharmaBlock Sciences Inc.)(202mg,0.910mmol)于THF(4mL)中的经搅拌溶液中滴加含甲醇钠(2mL,

1mmol)的MeOH,并且在室温搅拌混合物过夜。将反应混合物用水淬灭,溶于EtOAc中并用盐水洗涤。分离有机物,经无水Na_2SO_4干燥,浓缩,并且经ISCO(0→100%EtOAc/己烷)纯化粗混合物。收集级分并且减压浓缩并在高真空下干燥,得到呈浅黄色固体的5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XXIV)(140mg,0.642mmol,70.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 4.12(3H,s),6.95(1H,d,J=3.01Hz),8.02(1H,d,J=3.01Hz)。

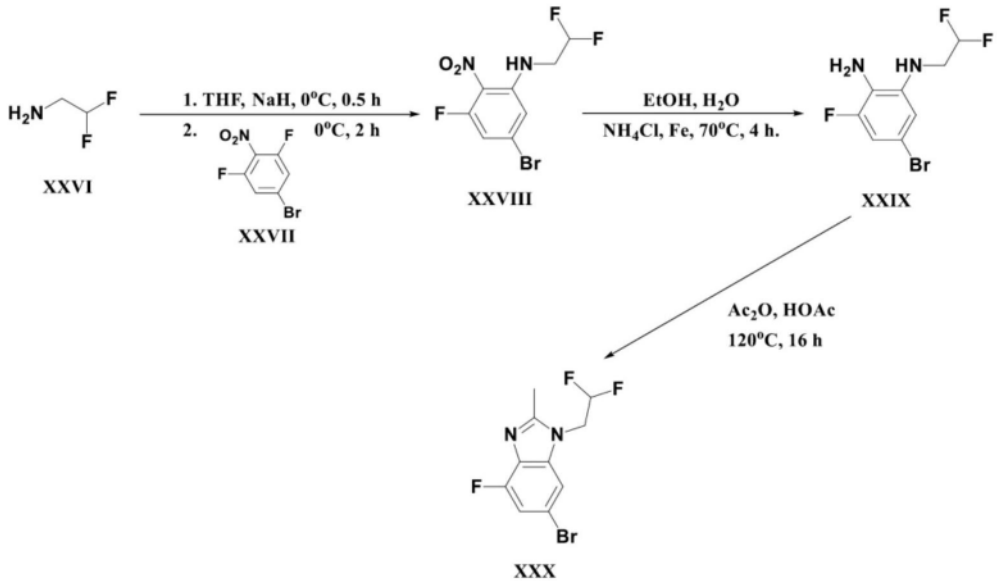
[0630] 根据以上方案4中所描述的程序制备以下中间体。

[0631] 

XXV

[0632] 5-溴-2-氯-4-(氧杂环丁烷-3-基氧基)吡咯并[2,1-f][1,2,4]三嗪(XXV):灰白色固体(558.8mg,1.84mmol,98.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 4.70(2H,ddd,J=7.94,4.65,1.10Hz),4.95(2H,ddd,J=7.73,6.37,0.96Hz),5.80(1H,tt,J=6.09,4.86Hz),7.05(1H,d,J=3.01Hz),8.05(1H,d,J=3.01Hz);$C_9H_7BrClN_3O_2$的ESIMS实验值m/z 303.95(M+H)。

[0633] 中间体6-溴-1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑(XXX)的制备描绘于以下方案5中。

[0634] 

方案5

[0635] 步骤1

[0636] 向氢化钠(222mg,9.2mmol)于THF(20mL)中的冰冷悬浮液中添加2,2-二氟乙胺(XXVI)(746mg,9.32mmol)。使反应混合物在0℃搅拌30min,然后添加5-溴-1,3-二氟-2-硝基苯(XXVII)(2.0g,8.4mmol)于THF(20mL)中的冰冷溶液。在0℃搅拌反应混合物2h。用水淬灭反应物。用EtOAc萃取水层,用盐水洗涤有机物,经无水Na_2SO_4干燥,过滤并浓缩。经由柱色谱法(40g硅胶)(0→20% EtOAc/己烷)纯化粗产物,得到呈黄色固体的5-溴-N-(2,2-二氟乙基)-3-氟-2-硝基苯胺(XXVIII)(500mg,0.836mmol,19.9%产率)。$C_8H_6BrF_3N_2O_2$的ESIMS实

验值m/z 299.0(^{79}BrM+H)。

[0637] 步骤2

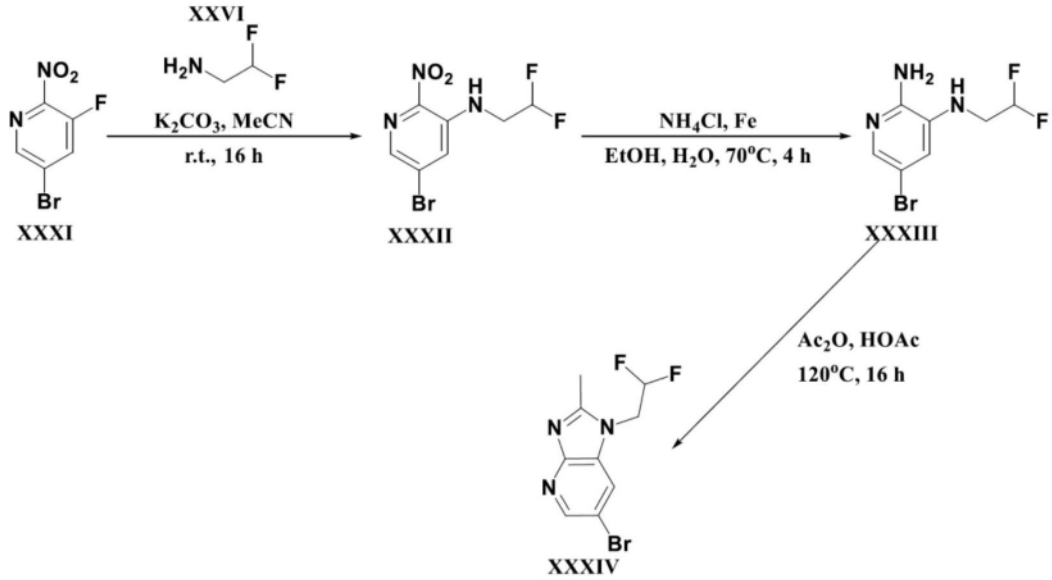
[0638] 将5-溴-N-(2,2-二氟乙基)-3-氟-2-硝基苯胺(XXVIII)(500mg,1.67mmol)、Fe(1.09g,16.72mmol)和NH_4Cl(1.34g,25.1mmol)于EtOH(6mL)和水(2.5mL)的混合物中的混合物加热至70℃持续4h。冷却反应混合物并经由Celite®过滤。将滤液溶于EtOAc中,用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并减压浓缩,得到呈棕色固体的5-溴-N^1-(2,2-二氟乙基)-3-氟苯-1,2-二胺(XXIX)(420mg,1.561mmol,93.4%产率),其不经进一步纯化即用于下一反应。$C_8H_8BrF_3N_2$的ESIMS实验值m/z 269.0(M+H)。

[0639] 步骤3

[0640] 将5-溴-N^1-(2,2-二氟乙基)-3-氟苯-1,2-二胺(XXIX)(420mg,1.56mmol)和Ac_2O(175μL,1.85mmol)于HOAc(8mL)中的溶液加热至120℃持续16h。浓缩反应混合物,将残余物分配于EtOAc/1N NaOH之间,分离有机物并用水和盐水洗涤。将有机物经无水Na_2SO_4干燥并浓缩,得到呈淡棕色固体的6-溴-1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑(XXX)(380mg,1.297mmol,83.1%产率)。$C_{10}H_{10}BrF_3N_2$的ESIMS实验值m/z 295.0(M+H)。

[0641] 中间体6-溴-1-(2,2-二氟乙基)-2-甲基-1H-咪唑并[4,5-b]吡啶(XX XIV)的制备描绘于以下方案6中。

[0642]



方案6

[0643] 步骤1

[0644] 将2,2-二氟乙-1-胺(XXVI)(410mg,5.02mmol)、5-溴-3-氟-2-硝基吡啶(XXXI)(可购自Ark Pharma Scientific Limited)(1.0g,4.53mmol)和K_2CO_3(1.38g,9.95mmol)于MeCN(20mL)中的混合物在室温搅拌16h。过滤反应物并在高真空下浓缩。将残余物溶于水中,搅拌1小时并且通过过滤收集固体并真空干燥,得到呈黄色固体的5-溴-N-(2,2-二氟乙基)-2-硝基吡啶-3-胺(XXXII)(1.066g,3.780mmol,83.5%产率),其不经纯化即用于下一步骤。$C_7H_6BrF_2N_3O_2$的ESIMS实验值m/z 282.0(^{79}BrM+H)。

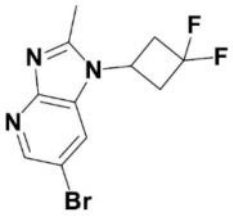
[0645] 步骤2

[0646] 将5-溴-N-(2,2-二氟乙基)-2-硝基吡啶-3-胺(XXXII)(1.32g,4.69mmol)、Fe(3.07g,46.95mmol)和NH_4Cl(3.77g,70.48mmol)的混合物溶于EtOH(18mL)与水(6mL)的混合物中并且将混合物加热至70℃持续4h。冷却反应混合物并经由Celite®过滤。将滤液溶于EtOAc中,用水和盐水洗涤,经无水Na_2SO_4干燥,过滤,并减压浓缩,得到呈灰色固体的5-溴-N^3-(2,2-二氟乙基)吡啶-2,3-二胺(XXXIII)(630mg,2.499mmol,53.2%产率),其不经进一步纯化即用于下一反应。$C_7H_8BrF_2N_3$的ESIMS实验值m/z 252.0(^{79}BrM+H)。

[0647] 步骤3

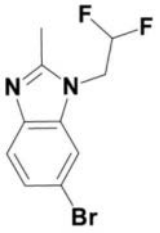
[0648] 将5-溴-N^3-(2,2-二氟乙基)吡啶-2,3-二胺(XXXIII)(630mg,2.5mmol)和乙酸酐(0.28mL,2.97mmol)于HOAc(15mL)中的溶液加热至120℃持续16h。浓缩反应混合物,将残余物分配于EtOAc/1NNaOH之间,分离有机物,并用水和盐水洗涤。经无水Na_2SO_4干燥有机物,并且在高真空下浓缩溶剂。用二乙醚湿磨残余物,经声波处理,并且通过过滤收集固体并在高真空下干燥,得到呈灰色固体的6-溴-1-(2,2-二氟乙基)-2-甲基咪唑并[4,5-b]吡啶(XXXIV)(325mg,1.177mmol,47.1%产率),其不经纯化即用于下一步骤。$C_9H_8BrF_2N_3$的ESIMS实验值m/z 276.0(^{79}BrM+H)。

[0649] 根据以上方案6中所述的程序制备以下中间体。

[0650] 

XXXV

[0651] 6-溴-1-(3,3-二氟环丁基)-2-甲基-1H-咪唑并[4,5-b]吡啶(XXXV):灰色固体(1.57g,6.178mmol,68.3%产率)。$C_{11}H_{10}BrF_2N_3$的ESIMS实验值m/z 302.1(M+H)。

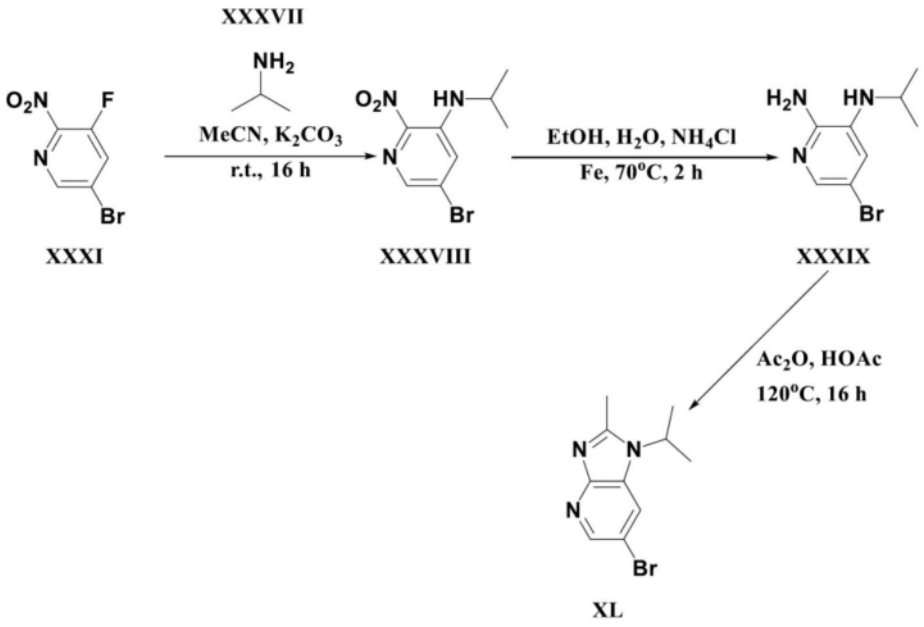
[0652] 

XXXVI

[0653] 6-溴-1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑(XXXVI):米色固体(970mg,3.526mmol,79.0%产率)。$C_{10}H_9BrF_2N_2$的ESIMS实验值m/z 275.0(M+H)。

[0654] 中间体6-溴-1-异丙基-2-甲基-1H-咪唑并[4,5-b]吡啶(XL)的制备描绘于以下方案7中。

[0655]



方案7

[0656] 步骤1

[0657] 将2-氨基丙烷(XXXVII)(0.86mL,9.96mmol)、5-溴-3-氟-2-硝基吡啶(XXXI)(2g,9.05mmol)和K_2CO_3(2.5g,18.1mmol)于MeCN(40mL)中的混合物在室温搅拌16h。将反应混合物添加至水(200mL)中,搅拌1h并且通过过滤收集所得固体并在高真空下干燥,得到呈黄色固体的5-溴-N-异丙基-2-硝基吡啶-3-胺(XXXVIII)(2.36g,9.074mmol,100.3%产率),其不经纯化即用于下一步骤。$C_8H_{10}BrN_3O_2$的ESIMS实验值m/z 260.0(M+H)。

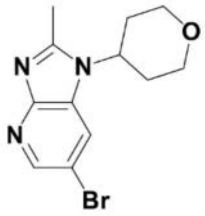
[0658] 步骤2

[0659] 将5-溴-N-异丙基-2-硝基吡啶-3-胺(XXXVIII)(2.35g,9.04mmol)Fe(5.91g,90.35mmol)和NH_4Cl(7.25g,135.53mmol)的混合物溶于EtOH(30mL)与水(10mL)的混合物中并且将混合物加热至70℃持续2h。使反应混合物冷却,经由Celite®过滤,将滤液溶于EtOAc中,用水、然后盐水洗涤,经无水Na_2SO_4脱水,过滤并减压浓缩,得到呈深棕色固体的5-溴-N^3-异丙基吡啶-2,3-二胺(XXXIX)(2.2g,9.561mmol,105.8%产率),其不经纯化即用于下一步骤。$C_8H_{12}BrN_3$的ESIMS实验值m/z 230.05(M+H)。

[0660] 步骤3

[0661] 将5-溴-N^3-异丙基吡啶-2,3-二胺(XXXIX)(2.08g,9.04mmol)和Ac_2O(1.05mL,10.84mmol)于HOAc(20mL)中的溶液加热至120℃,持续16h。浓缩反应混合物,将残余物分配于EtOAc/1N NaOH之间,分离有机物,用水和盐水洗涤。将有机物经无水Na_2SO_4干燥,浓缩并在高真空下干燥,得到呈深棕色固体的6-溴-1-异丙基-2-甲基-1H-咪唑并[4,5-b]吡啶(XL)(1.57g,6.178mmol,68.3%产率),其不经纯化即用于下一步骤。$C_{10}H_{12}BrN_3$的ESIMS实验值m/z 254.0(M+H)。

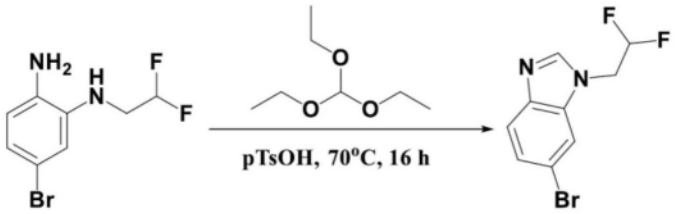
[0662] 根据以上方案7中所描述的程序制备以下中间体。

[0663] 

XLI

[0664] 6-溴-2-甲基-1-(四氢-2H-吡喃-4-基)-1H-咪唑并[4,5-b]吡啶(XLI):灰色固体(722mg,2.438mmol,66.3%产率)。$C_{12}H_{14}BrN_3O$的ESIMS实验值m/z 296.0(M+H)。

[0665] 中间体6-溴-1-(2,2-二氟乙基)-1H-苯并[d]咪唑(XLIII)的制备描绘于以下方案8中。

[0666] 

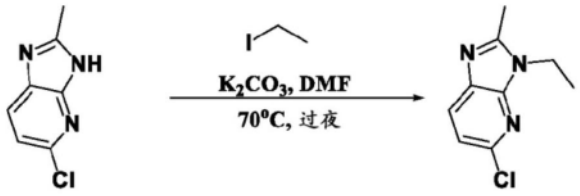
XLII XLIII

方案8

[0667] 步骤1

[0668] 在室温向5-溴-N1-(2,2-二氟乙基)苯-1,2-二胺(XLII)(3.0g,11.95mmol)于三乙氧基甲烷(60mL)中的溶液中添加对甲苯磺酸(0.23g,1.20mmol)。在70℃搅拌反应混合物16h,然后冷却至室温。浓缩反应混合物。用水(200mL)稀释反应混合物并用EtOAc(2×300mL)萃取。浓缩有机层,经Na_2SO_4干燥,过滤并浓缩。通过反相柱色谱法(Regular C18 20-4μm,乙腈/0.1% NH_4HCO_3水溶液,梯度:40%→60% MeCN)纯化混合物,得到呈黄色固体的6-溴-1-(2,2-二氟乙基)-1H-苯并[d]咪唑(XLIII)(1.5g,5.746mmol,48.1%产率)。^{1}H NMR(400MHz,DMSO-d_6)δ8.26(s 1H),7.98(d,J=1.6Hz,1H),7.64(d,J=8.4Hz,1H),7.38(dd,J=8.8,2Hz,1H),6.46(tt,J=54.3,3.0Hz,1H),5.36(td,J=16.4,3.2Hz,2H);$C_9H_7BrF_2N_2$的ESIMS实验值m/z 260.9(M+H)。

[0669] 中间体5-氯-3-乙基-2-甲基-3H-咪唑并[4,5-b]吡啶(XLV)的制备描绘于以下方案9中。

[0670] 

XLIV XLV

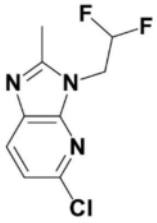
方案9

[0671] 步骤1

[0672] 将5-氯-2-甲基-3H-咪唑并[4,5-b]吡啶(XLIV)(可商购自eNovation Chemicals,

LLC)(0.5g,2.98mmol)、碘乙烷(0.56g,3.58mmol)和K_2CO_3(0.83g,5.97mmol)于DMF(10mL)中的混合物加热至70℃过夜。冷却反应混合物,浓缩溶剂,使残余物分配于EtOAc/水之间,分离有机层,用盐水洗涤,经无水$MgSO_4$干燥并且真空浓缩溶剂并干燥,得到呈深棕色固体的5-氯-3-乙基-2-甲基咪唑并[4,5-b]吡啶(XLV)(466mg,2.382mmol,79.8%产率),其不经纯化即用于下一步骤。$C_9H_{10}ClN_3$的ESIMS实验值m/z 196.05(M+H)。

[0673] 根据以上方案9中所描述的程序制备以下中间体。

[0674] 

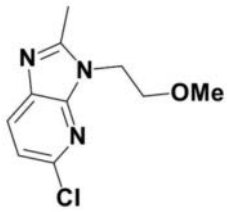
XLVI

[0675] 5-氯-3-(2,2-二氟乙基)-2-甲基-3H-咪唑并[4,5-b]吡啶(XLVI):米色固体(830mg,3.583mmol,60.1%产率)。$C_9H_8ClF_2N_3$的ESIMS实验值m/z 232.0(M+H)。

[0676] 

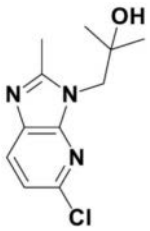
XLVII

[0677] 5-氯-3-(2-氟乙基)-2-甲基-3H-咪唑并[4,5-b]吡啶(XLVII):米色固体(220mg,1.030mmol,57.5%产率)。$C_9H_9ClFN_3$的ESIMS实验值m/z 214.05(M+H)。

[0678] 

XLVIII

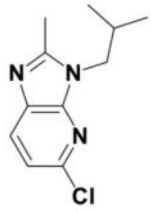
[0679] 5-氯-3-(2-甲氧基乙基)-2-甲基-3H-咪唑并[4,5-b]吡啶(XLVIII):米色固体(195mg,0.864mmol,48.3%产率)。$C_{10}H_{12}ClN_3O$的ESIMS实验值m/z 226.1(M+H)。

[0680] 

XLIX

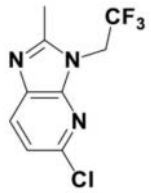
[0681] 1-(5-氯-2-甲基-3H-咪唑并[4,5-b]吡啶-3-基)-2-甲基丙-2-醇(XLIX):白色固体(229.9mg,0.959mmol,39.7%产率)。^1H NMR(499MHz,DMSO-d_6)δppm 1.13(6H,s),2.63(3H,s),4.11(2H,s),4.80(1H,s),7.25(1H,d,J=8.21Hz),7.96(1H,d,J=8.21Hz);

$C_{11}H_{14}ClN_3O$的ESIMS实验值m/z 240.1(M+H)。

[0682] 

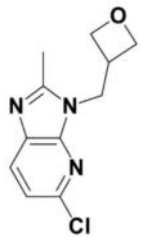
L

[0683] 5-氯-3-异丁基-2-甲基-3H-咪唑并[4,5-b]吡啶(L):白色固体(206.8mg,0.925mmol,38.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm0.87(6H,d,J=6.57Hz),2.22(1H,dquin,J=13.89,7.07,7.07,7.07,7.07Hz),2.58(3H,s),4.01(2H,d,J=7.67Hz),7.26(1H,d,J=8.21Hz),7.98(1H,d,J=8.21Hz);$C_{11}H_{14}ClN_3$的ESIMS实验值m/z 224.1(M+H)。

[0684] 

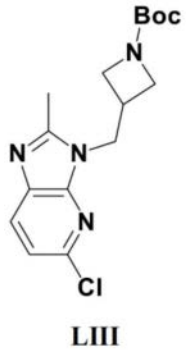
LI

[0685] 5-氯-2-甲基-3-(2,2,2-三氟乙基)-3H-咪唑并[4,5-b]吡啶(LI):米色固体(372mg,1.490mmol,50.0%产率)。$C_9H_7ClF_3N_3$的ESIMS实验值m/z 250.0(M+H)。

[0686] 

LII

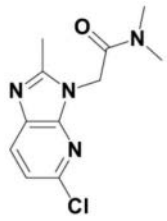
[0687] 5-氯-2-甲基-3-(氧杂环丁烷-3-基甲基)-3H-咪唑并[4,5-b]吡啶(LII):淡棕色固体(289.7mg,1.219mmol,40.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.59(3H,s),3.43-3.56(1H,m),4.47(2H,t,J=6.02Hz),4.52(2H,d,J=7.67Hz),4.62(2H,dd,J=7.67,6.02Hz),7.27(1H,d,J=8.21Hz),7.98(1H,d,J=8.21Hz);$C_{11}H_{12}ClN_3O$的ESIMS实验值m/z 238.1(M+H)。

[0688] 

LIII

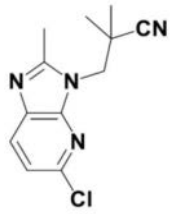
[0689] 3-((5-氯-2-甲基-3H-咪唑并[4,5-b]吡啶-3-基)甲基)氮杂环丁烷-1-甲酸叔丁酯(LIII):灰白色非晶形固体(532.6mg,1.581mmol,52.1%产率)。$C_{16}H_{21}ClN_4O_2$的ESIMS实验

值m/z 337.1(M+H)。

[0690] 

LIV

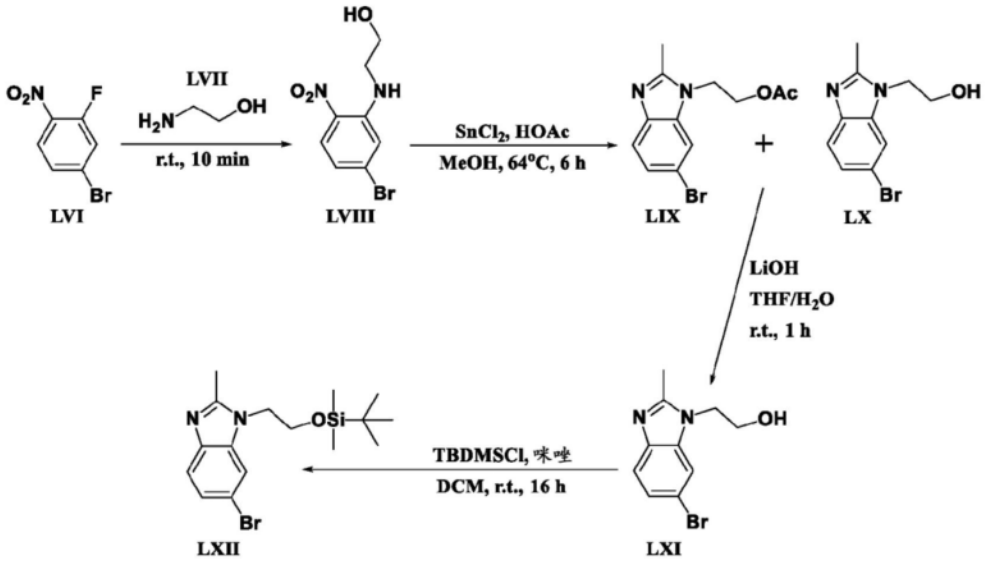
[0691] 2-(5-氯-2-甲基-3H-咪唑并[4,5-b]吡啶-3-基)-N,N-二甲基乙酰胺(LIV):灰白色固体(474.4mg,1.877mmol,62.6%产率)。$C_{11}H_{13}ClN_4O$的ESIMS实验值m/z 253.1(M+H)。

[0692] 

LV

[0693] 3-(5-氯-2-甲基-3H-咪唑并[4,5-b]吡啶-3-基)-2,2-二甲基丙腈(LV):灰白色非晶形固体(59.1mg,0.238mmol,7.9%产率)。$C_{12}H_{13}ClN_4$的ESIMS实验值m/z 249.1(M+H)。

[0694] 中间体6-溴-1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑(LXII)的制备描绘于以下方案10中。

[0695] 

方案 10

[0696] 步骤1

[0697] 将4-溴-2-氟-1-硝基苯(LVI)(2.0g,9.09mmol)溶解于2-氨基乙醇(LVII)(2.8mL,46.39mmol)中的溶液在室温搅拌10min。添加水(50mL)并用EtOAc萃取并经Celite®干燥。通过硅胶柱色谱法(0→100%EtOAc/己烷)纯化残余物,产生呈黄色固体的2-((5-溴-2-硝基苯基)氨基)乙-1-醇(LVIII)(2.349g,8.998mmol,99.0%产率)。^1H NMR(499MHz,DMSO-d_6)δ ppm 3.41(2H,q,J=5.48Hz),3.63(2H,q,J=5.48Hz),5.00(1H,t,J=5.34Hz),6.83(1H,

dd,J=9.17,2.05Hz),7.30(1H,d,J=1.92Hz),7.98(1H,d,J=9.03Hz),8.29(1H,br t,J=5.06Hz);$C_8H_9BrN_2O_3$的ESIMS实验值m/z 260.96(M+H)。

[0698] 步骤2

[0699] 在室温向2-((5-溴-2-硝基苯基)氨基)乙-1-醇(LVIII)(1.31g,5.02mmol)于MeOH(50mL)中的溶液中添加氯化锡(II)(0.96mL,20.09mmol)。将反应混合物加热至64℃持续6h,然后冷却至室温。真空去除溶剂,并且将残余物溶解于水中并通过添加Na_2CO_3碱化至pH=9。用DCM萃取混合物,并且将合并的有机相用水、盐水洗涤并经无水Na_2SO_4干燥。真空去除溶剂,然后添加HOAc(15.6mL,271.49mmol)。将溶液加热至回流持续30min。减压去除乙酸并且使用硅胶柱色谱法(0→50%7N NH_3于MeOH/$CHCl_3$中)纯化残余物,产生呈灰白色固体的80/20混合物形式的乙酸2-(6-溴-2-甲基-1H-苯并[d]咪唑-1-基)乙酯(LIX)和2-(6-溴-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇(LX)(1.45g,4.880mmol,97.2%产率)。$C_{12}H_{13}BrN_2O_2$的ESIMS实验值m/z297.0(M+H)。

[0700] 步骤3

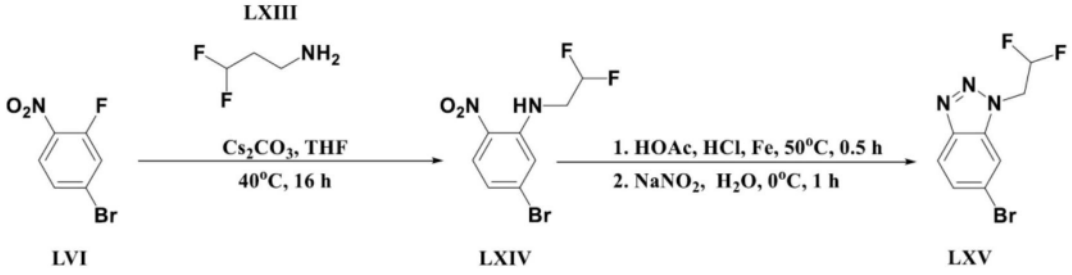
[0701] 向LiOH(3.2mL,9.6mmol)于THF(27mL)/水(6mL)中的溶液中添加乙酸2-(6-溴-2-甲基-1H-苯并[d]咪唑-1-基)乙酯(LIX)与2-(6-溴-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇(LX)(1.45g,4.88mmol)的混合物。在室温搅拌反应物1h。用1N HCl中和溶液并且将其汽提至Celite®上,然后使用硅胶柱色谱法(0→10%7N NH_3于MeOH/$CHCl_3$中)纯化,产生呈白色固体的2-(6-溴-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇(LXI)(1.02g,3.998mmol,81.9%产率)。$C_{10}H_{11}BrN_2O$的ESIMS实验值m/z 255.0(M+H)。

[0702] 步骤4

[0703] 在N_2气氛下使2-(6-溴-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇(LXI)(1.02g,4.mmol)溶解于DCM(8mL)中。然后添加咪唑(0.55g,8.1mmol)和TBDMSCl(0.9mL,4.84mmol)。在室温搅拌反应混合物16h。用EtOAc稀释溶液并用$NaHCO_3$饱和水溶液(400mL)洗涤。用EtOAc反萃取水层两次,将有机层汽提至Celite®上,然后使用硅胶柱色谱法(0→5% MeOH/$CHCl_3$)纯化,产生呈白色固体的6-溴-1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑(LXII)(1.44g,3.899mmol,97.5%产率)。$C_{16}H_{25}BrN_2OSi$的ESIMS实验值m/z369.1(M+H)。

[0704] 中间体6-溴-1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑(LXV)的制备描绘于以下方案11中。

[0705]



LVI LXIV LXV

方案11

[0706] 步骤1

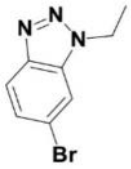
[0707] 将4-溴-2-氟-1-硝基苯(LVI)(20.0g,98.03mmol)于THF(500.0mL)中的溶液冷却

至0℃。添加Cs_2CO_3(63.9g,196.06mmol),在0℃添加2,2-二氟乙-1-胺(LXIII)(36.6g,183.81mmol)。使反应物升温至40℃持续16h。用EtOAc(500Lx3)萃取反应混合物。用盐水(500mL x3)洗涤经合并的有机物。将合并的有机层经Na_2SO_4干燥,过滤并浓缩,得到粗产物。通过硅胶柱色谱法(10% EtOAc/PE→20% EtOAc/PE)纯化粗产物,得到呈黄色固体的5-溴-N-(2,2-二氟乙基)-2-硝基苯胺(LXIV)(23g,81.83mmol,83.5%产率)。^{1}H NMR(400MHz,DMSO-d_6)δ3.99(tdd,J=15.6,6.6,3.8Hz,2H),6.29(tt,J=55.4,3.7Hz,1H),6.96(dd,J=9.2,2.0Hz,1H),7.51(d,J=1.6Hz,1H),8.05(d,J=9.2Hz,1H),8.33(t,J=6.4Hz,1H);$C_8H_7BrF_2N_2O_2$的ESIMS实验值m/z 280.9(M+H)。

[0708] 步骤2

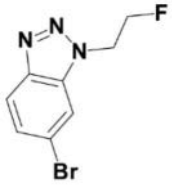
[0709] 向5-溴-N-(2,2-二氟乙基)-2-硝基苯胺(LXIV)(12.0g,42.86mmol)于HOAc/HCl(500/50mL)中的溶液中添加Fe(30.0g,428.62mmol)。在50℃搅拌反应混合物30分钟,然后冷却至室温并过滤。然后在0℃将含$NaNO_2$(3.0g,53.58mmol)的水(20mL)滴加至上述酸溶液中。在0℃搅拌反应溶液1h。将反应混合物浓缩至干燥,将反应混合物倒入EtOAc(300mL)和H_2O(300mL)中。用$NaHCO_3$将pH调节>7。用EtOAc(500mLx3)萃取反应混合物。用盐水(500mLx3)洗涤经合并的有机物。将有机层浓缩,经Na_2SO_4干燥,过滤并浓缩,得到粗产物。通过硅胶柱色谱法(10% EtOAc/PE→50% EtOAc/PE)纯化粗产物,得到呈棕色固体的6-溴-1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑(LXV)(5g,19.08mmol,44.5%)。^{1}H NMR(400MHz,DMSO-d_6)δ5.41-5.29(m,2H),6.61(tt,J=54.2,3.2Hz,1H),7.60(dd,J=8.8,1.7Hz,1H),8.08(d,J=8.8Hz,1H),8.31(d,J=1.0Hz,1H);$C_8H_6BrF_2N_3$的ESIMS实验值m/z 261.9(M+H)。

[0710] 根据以上方案11中所描述的程序制备以下中间体。

[0711] 

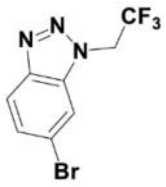
LXVI

[0712] 6-溴-1-乙基-1H-苯并[d][1,2,3]三唑(LXVI):白色固体(4.112g,18.188mmol)。^{1}H NMR(400MHz,DMSO-d_6)δ8.30(d,J=1.6Hz,1H),8.00(dd,J=8.8,3.2Hz,1H),7.54(dd,J=8.8,3.2Hz,1H),4.74(q,J=7.2Hz,2H),1.51(t,J=7.2Hz,3H);$C_8H_8BrN_3$的ESIMS实验值m/z225.9(M+H)。

[0713] 

LXVII

[0714] 6-溴-1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑(LXVII):白色固体(4.163g,17.057mmol)。^{1}H NMR(400MHz,DMSO-d_6)δ8.29(s 1H),8.05(d,J=8.4Hz,1H),7.57(dd,J=8.4,1.6Hz,1H),5.11(dt,J=28,4Hz,2H),4.92(dt,J=48,4Hz,2H);$C_8H_7BrFN_3$的ESIMS实验值m/z244.0(M+H)。

[0715] 

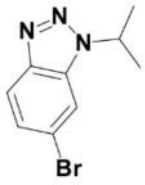
LXVIII

[0716] 6-溴-1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑(LXVIII):白色固体(5.05g,18.032mmol)。^{1}H NMR(400MHz,DMSO-d_6)δ8.38(s 1H),8.11(d,J=8.8Hz,1H),7.63(dd,J=8.4,1.6Hz,1H),5.90(q,J=9.2Hz,2H);$C_8H_5BrF_3N_3$的ESIMS实验值m/z 280.0(M+H)。

[0717] 

LXIX

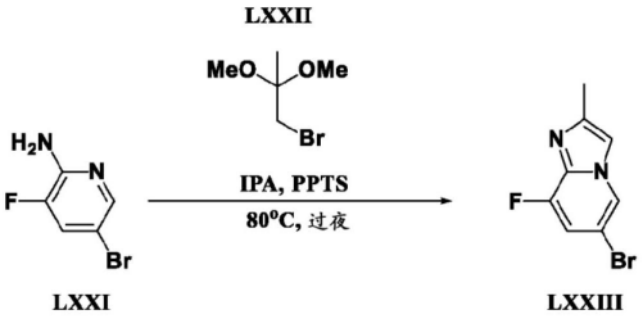
[0718] 6-溴-1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑(LXIX):白色固体(4.112g,14.683mmol)。^{1}H NMR(400MHz,DMSO-d_6)δ8.19(s1H),7.61(d,J=10.0Hz,1H),6.60(tt,J=54.3,3.0Hz,1H),5.36(td,J=15.81,2.87Hz,2H);$C_8H_5BrF_3N_3$的ESIMS实验值m/z 280.0(M+H)。

[0719] 

LXX

[0720] 6-溴-1-异丙基-1H-苯并[d][1,2,3]三唑(LXX):白色固体(10.58g,44.065mmol)。^{1}H NMR(400MHz,DMSO-d_6)δ8.32(d,J=1.2Hz,1H),8.03(d,J=9.2Hz,1H),7.54(dd,J=8.4,1.6Hz,1H),5.26(sep,J=6.8Hz,1H),5.26(d,J=6.8Hz,6H);$C_9H_{10}BrN_3$的ESIMS实验值m/z 240.1(M+H)。

[0721] 中间体6-溴-8-氟-2-甲基咪唑并[1,2-a]吡啶(LXXIII)的制备描绘于以下方案12中。

[0722] 

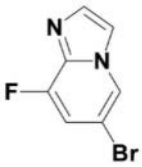
LXXI LXXIII

方案 12

[0723] 步骤1

[0724] 将5-溴-3-氟吡啶-2-胺(LXXI)(2g,10.47mmol)、1-溴-2,2-二甲氧基丙烷(LXXII)(2.11g,11.53mmol)和PPTS(260mg,1.05mmol)于IPA(25mL)中的混合物加热至80℃过夜。将反应混合物冷却至室温,添加至水(200mL)中并搅拌1h。收集所得固体并在高真空下干燥,得到呈米色固体的6-溴-8-氟-2-甲基咪唑并[1,2-a]吡啶(LXXIII)(2.61g,11.40mmol,108.8%产率),其不经进一步纯化即用于下一步骤。$C_8H_6BrFN_2$的ESIMS实验值m/z 229.0(M+H)。

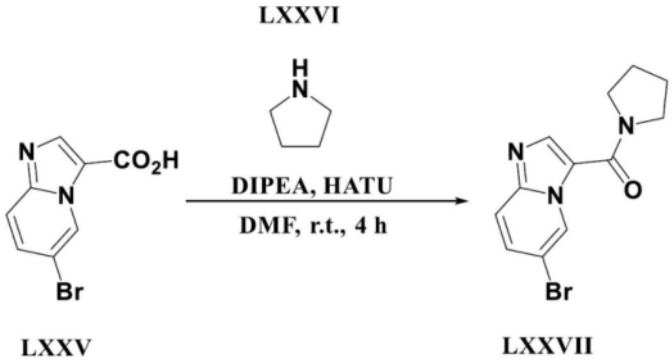
[0725] 根据以上方案12中所描述的程序制备以下中间体。

[0726] 

LXXIV

[0727] 6-溴-8-氟咪唑并[1,2-a]吡啶(LXXIV):米色固体(909.0mg,4.228mmol,80.7%产率)。$C_7H_4BrFN_2$的ESIMS实验值m/z 214.9(M+H)。

[0728] 中间体(6-溴咪唑并[1,2-a]吡啶-3-基)(吡咯烷-1-基)甲酮(LXXVII)的制备描绘于以下方案13中。

[0729] 

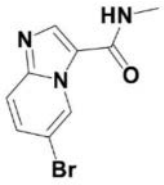
LXXV LXXVII

方案 13

[0730] 步骤1

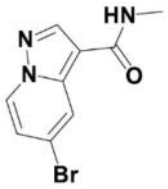
[0731] 将6-溴咪唑并[1,2-a]吡啶-3-甲酸(LXXV)(0.5g,2.07mmol)、DIPEA(0.9mL,5.17mmol)和HATU(0.79g,2.07mmol)于DMF(4mL)中的混合物搅拌5min。然后添加吡咯烷(LXXVI)(0.32mL,3.18mmol),并且将反应混合物继续在室温搅拌4h。浓缩溶剂,将残余物分配于EtOAc与$NaHCO_3$饱和水溶液之间,分离有机层,用水和盐水洗涤。将有机层经无水Na_2SO_4干燥,浓缩并在高真空下干燥,得到呈米色固体的(6-溴咪唑并[1,2-a]吡啶-3-基)-吡咯烷-1-基甲酮(LXXVII)(577mg,1.962mmol,94.6%产率)。$C_{12}H_{12}BrN_3O$的ESIMS实验值m/z 294.0(M+H)。

[0732] 根据以上方案13中所描述的程序制备以下中间体。

[0733] 

LXXVIII

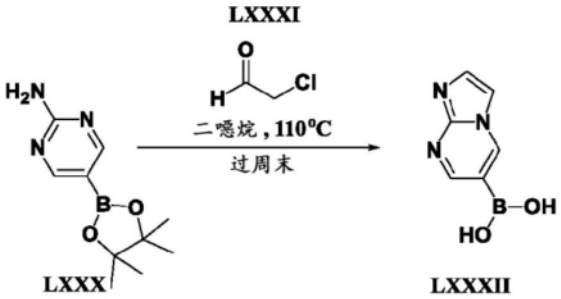
[0734] 6-溴-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺(LXXVIII):灰白色固体(530mg,2.086mmol,83.8%产率)。$C_9H_8BrN_3O$的ESIMS实验值m/z254.0(M+H)。

[0735] 

LXXIX

[0736] 5-溴-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺(LXXIX):灰白色固体(290mg,1.141mmol,91.7%产率)。$C_9H_8BrN_3O$的ESIMS实验值m/z253.95(M+H)。

[0737] 中间体咪唑并[1,2-a]嘧啶-6-基硼酸(LXXXII)的制备描绘于以下方案14中。

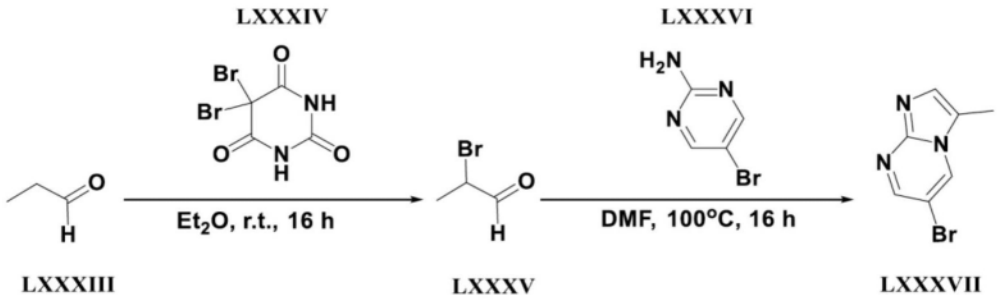
[0738] 

方案14

[0739] 步骤1

[0740] 将5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)嘧啶-2-胺(LXXX)(1g,4.52mmol)与氯乙醛(LXXXI)(0.92mL,5.39mmol)的混合物溶解于1,4-二噁烷(20mL)中并且加热至110℃过周末。冷却反应混合物,并且通过过滤收集固体并在高真空下干燥,得到呈棕色固体的咪唑并[1,2-a]嘧啶-6-基硼酸(LXXXII)(650mg,3.989mmol,88.2%产率),其不经纯化即用于下一步骤。$C_6H_6BN_3O_2$的ESIMS实验值m/z164.1(M+H)。

[0741] 中间体6-溴-3-甲基咪唑并[1,2-a]嘧啶(LXXXVII)的制备描绘于以下方案15中。

[0742] 

方案 15

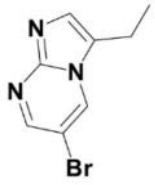
[0743] 步骤1

[0744] 向丙醛(LXXXIII)(5g,70mmol)于Et_2O(150mL)中的混合物添加5,5-二溴嘧啶-2,4,6(1H,3H,5H)-三酮(LXXXIV)(9.91g,35mmol),并且在室温搅拌所得混合物16h。完成后,通过石油醚(80mLx2)洗涤混合物。过滤有机层并浓缩,得到呈黄色油状物的2-溴丙醛(LXXXV)(2.0g,14.6mmol,20.9%产率)。

[0745] 步骤2

[0746] 在Ar下在室温向2-溴丙醛(LXXXV)(0.7g,5.11mol)于DMF(20mL)中的溶液添加5-溴嘧啶-2-胺(LXXXVI)(0.97g,5.56mmol)。在100℃搅拌混合物16h。完成后,用EtOAc稀释混合物并用盐水(20mLx3)洗涤。经无水Na_2SO_4干燥有机层,过滤并浓缩。通过硅胶柱色谱法(0%→20% EtOAc/石油醚)纯化粗残余物,得到呈白色固体的6-溴-3-甲基咪唑并[1,2-a]嘧啶(LXXXVII)(80mg,0.377mmol,7.4%产率)。$C_7H_6BrN_3$的ESIMS实验值m/z 212.1(M+H)。

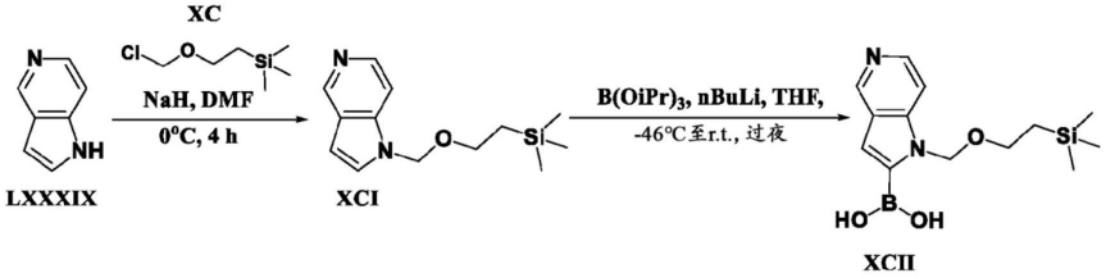
[0747] 根据以上方案15中所描述的程序制备以下中间体。

[0748] 

LXXXVIII

[0749] 6-溴-3-乙基咪唑并[1,2-a]嘧啶(LXXXVIII):白色固体(200mg,0.885mmol,19.1%产率)。$C_8H_8BrN_3$的ESIMS实验值m/z 226.0(M+H)。

[0750] 中间体(1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯并[3,2-c]吡啶-2-基)硼酸(XCII)的制备描绘于以下方案16中。

[0751] 

方案 16

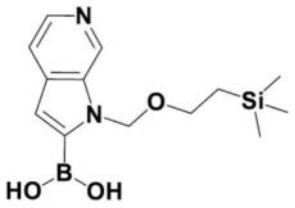
[0752] 步骤1

[0753] 在N_2下向5-氮杂吲哚(LXXXIX)(可购自Combi-Blocks Inc.)(2.0g,16.93mmol)于DMF(20mL)中的溶液中添加NaH(0.81g,20.18mmol)。在0℃搅拌混合物1h。然后添加(2-(氯甲氧基)乙基)三甲基硅烷(XC)(可购自Combi-Blocks Inc.)(3.6mL,20.34mmol)并且在0℃搅拌混合物4h。在真空浓缩以去除DMF后,添加冰冷的NH_3Cl饱和水溶液,并且用EtOAc萃取混合物。用水、盐水洗涤有机层,并且在真空下将溶剂浓缩于Celite®上。使用柱色谱法(0→100% EtOAc/己烷)纯化粗产物,产生呈琥珀色液体的1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯并[3,2-c]吡啶(XCI)(2.32g,9.340mmol,55.2%产率)。^1H NMR(499MHz,DMSO-d_6)δppm-0.11(9H,s),0.75-0.84(2H,m),3.40-3.48(2H,m),5.58(2H,s),6.64(1H,dd,J=3.29,0.82Hz),7.55-7.60(2H,m),8.23(1H,d,J=5.75Hz),8.84(1H,d,J=0.82Hz);$C_{13}H_{20}N_2OSi$的ESIMS实验值m/z 249.1(M+H)。

[0754] 步骤2

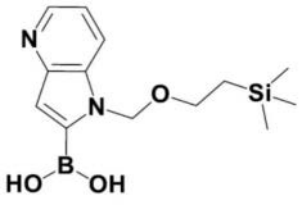
[0755] 在N_2下,在-78℃将正丁基锂(1.21mL,3.02mmol)的己烷溶液缓慢添加至1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯并[3,2-c]吡啶(XCI)(0.5g,2.01mmol)于无水THF(4.0mL)中的溶液。在-46℃搅拌混合物2h。添加硼酸三异丙酯(0.93mL,4.03mmol),并且搅拌混合物过夜,升温至室温。用1M HCl水溶液淬灭反应混合物并用4NNaOH中和至pH 8。将溶剂蒸发于Celite®上,并通过反相(C18)硅胶柱色谱法(0→40% MeCN/水(0.1%甲酸作为改性剂))纯化。LC/MS显示起始物质与[1-(2-三甲基甲硅烷基乙氧基甲基)吡咯并[3,2-c]吡啶-2-基]硼酸(XCII)(200mg,0.684mmol,34.0%产率)的呈灰白色固体的混合物(40/60)。所述混合物不经进一步纯化即按原样使用。$C_{13}H_{21}BN_2O_3Si$的ESIMS实验值m/z 293.1(M+H)。

[0756] 根据以上方案16中所描述的程序制备以下中间体。

[0757] 

XCIII

[0758] (1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯并[2,3-c]吡啶-2-基)硼酸(XCIII):棕褐色固体(796mg,2.861mmol,71.1%产率)。$C_{13}H_{21}BN_2O_3Si$的ESIMS实验值m/z 293.15(M+H)。

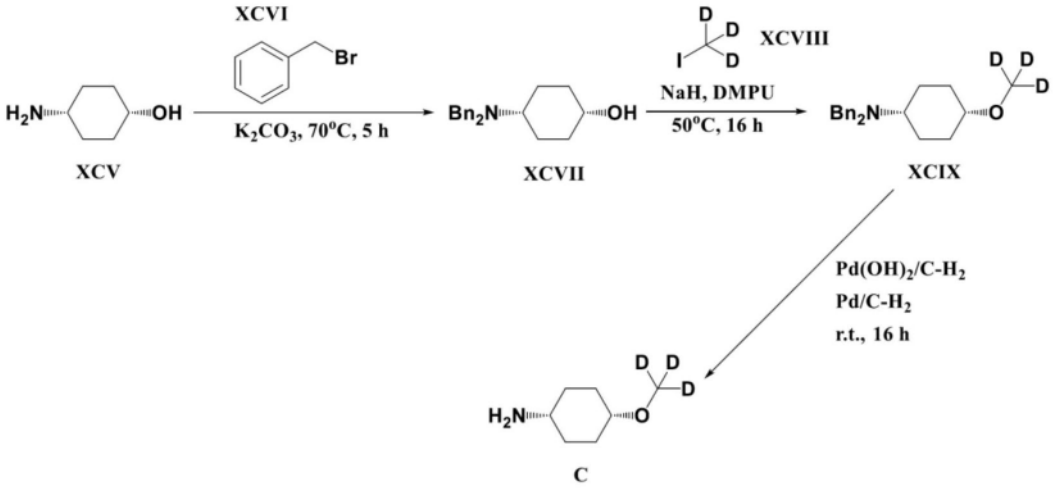
[0759] 

XCIV

[0760] (1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡咯并[3,2-b]吡啶-2-基)硼酸(XCIV):棕褐色固体(831mg,2.844mmol,70.6%产率)。$C_{13}H_{21}BN_2O_3Si$的ESIMS实验值m/z 293.1(M+H)。

[0761] 中间体顺-4-(甲氧基-d_3)环己-1-胺(C)的制备描绘于以下方案17中。

[0762]



方案 17

[0763] 步骤1

[0764] 向顺-4-氨基环己-1-醇(XCV)(5g,32.9mmol)、(溴甲基)苯(XCVI)(11.25g,65.8mmol)于MeCN(80mL)中的溶液中添加K_2CO_3(13.64g,98.7mmol)。在70℃搅拌混合物5h。减压浓缩反应混合物以去除MeCN。用EtOAc稀释混合物并且然后用EtOAc(100mLx3)和H_2O萃取。浓缩经合并的有机层,并且通过硅胶柱色谱法(0%→30%EtOAc/PE)纯化粗残余物,得到呈白色固体的顺-4-(二苯甲基氨基)环己-1-醇(XCVII)(8.0g,27.08mmol,82.3%产率)。$C_{20}H_{25}NO$的ESIMS实验值m/z 296.4(M+H)。

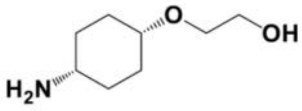
[0765] 步骤2

[0766] 在氮气气氛下在连续搅拌下向顺-4-(二苯甲基氨基)环己-1-醇(XCVII)(8.0g,27.08mmol)于DMPU(80mL)中的溶液中缓慢添加NaH(5.98g,149.7mmol)。在室温搅拌反应混合物1h。然后在室温经10min的时间段添加碘甲烷-d_3(XCVIII)(10.85g,74.86mmol)。添加完成后,在50℃搅拌反应混合物16h。然后用NH_4Cl饱和水溶液(300mL)淬灭反应混合物并搅拌10min。用EtOAc稀释混合物并且然后用EtOAc(300mLx3)和H_2O萃取。通过硅胶柱色谱法(0%→20%EtOAc/PE)纯化粗残余物,得到呈无色油状物的顺-N,N-二苯甲基-4-(甲氧基-d_3)环己-1-胺(XCIX)(6g,19.202mmol,70.9%产率)。$C_{21}H_{24}D_3NO$的ESIMS实验值m/z 313.0(M+H)。

[0767] 步骤3

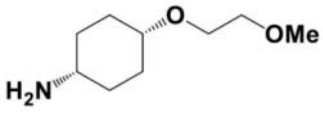
[0768] 向顺-N,N-二苯甲基-4-(甲氧基-d_3)环己-1-胺(XCIX)(200mg,0.64mmol)于EtOH(5mL)中的溶液添加$Pd(OH)_2/C$(50mg)和Pd/C(50mg)。在室温搅拌混合物16h。经由Celite®过滤混合物,并用EtOH洗涤。减压浓缩反应混合物,得到呈无色油状物的顺-4-(甲氧基-d_3)环己-1-胺(C)(76.4mg,0.578mmol,90.3%产率)。^1H NMR(400MHz,DMSO-d_6)δppm 1.51-1.40(m,4H),1.67-1.56(m,4H),1.86(td,J=9.8,4.6Hz,2H),2.71(tt,J=10.8,5.4Hz,1H),3.34(td,J=4.8,2.4Hz,1H);$C_7H_{12}D_3NO$的ESIMS实验值m/z 133.0(M+H)。

[0769] 根据以上方案17中所描述的程序制备以下中间体。

[0770] 

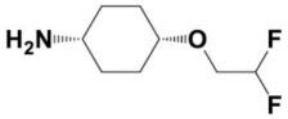
CI

[0771] 2-((顺-4-氨基环己基)氧基)乙-1-醇(CI):无色油状物(0.5g,3.14mmol,67.4%产率)。$C_8H_{17}NO_2$的ESIMS实验值m/z 160.(M+H)。

[0772] 

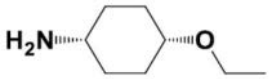
CII

[0773] 顺-4-(2-甲氧基乙氧基)环己-1-胺(CII):无色油状物(1.5g,8.65mmol,76.6%产率)。$C_9H_{19}NO_2$的ESIMS实验值m/z 174.1(M+H)。

[0774] 

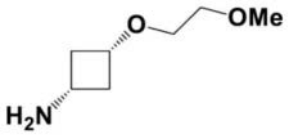
CIII

[0775] 顺-4-(2,2-二氟乙氧基)环己-1-胺(CIII):白色固体(1.352g,7.54mmol,90.3%产率)。$C_8H_{15}F_2NO$的ESIMS实验值m/z 180.1(M+H)。

[0776] 

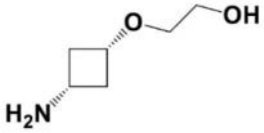
CIV

[0777] 顺-4-乙氧基环己-1-胺(CIV):无色油状物(2g,13.96mmol,64.4%产率)。^{1}H NMR(400MHz,$CDCl_3$)δ1.19(t,J=7.0Hz,3H),1.49-1.44(m,6H),1.62-1.55(m,2H),1.86-1.79(m,2H),2.4-2.723(m,1H),3.49-3.41(m,3H)。

[0778] 

CV

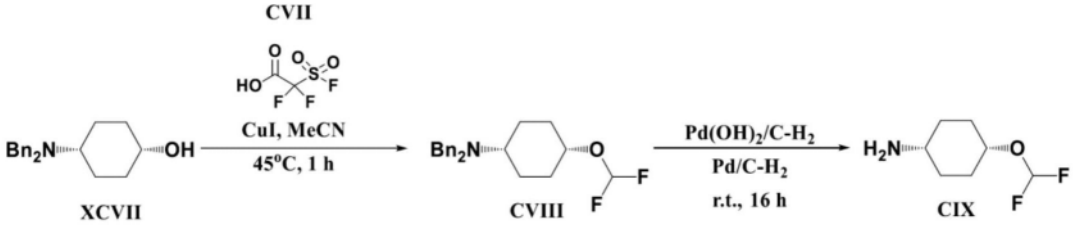
[0779] 顺-3-(2-甲氧基乙氧基)环丁-1-胺(CV):无色油状物。^{1}H NMR(400MHz,DMSO-d_6)δ1.51(dd,J=13.4,5.2Hz,2H),2.49-2.40(m,2H),2.89-2.75(m,1H),3.23(s,3H),3.37-3.35(m,3H),3.47(s,2H),3.54-3.48(m,1H)。

[0780] 

CVI

[0781] 2-(顺-3-氨基环丁氧基)乙-1-醇(CVI):无色油状物。^{1}H NMR(400MHz,DMSO-d_6)δ1.79-1.72(m,2H),2.50-2.45(m,2H),3.08-2.97(m,1H),3.29(t,J=5.4Hz,2H),3.46(t,J=5.4Hz,2H),3.73-3.57(m,1H)。

[0782] 中间体顺-4-(二氟甲氧基)环己-1-胺(CIX)的制备描绘于以下方案18中。

[0783] 

方案 18

[0784] 步骤1

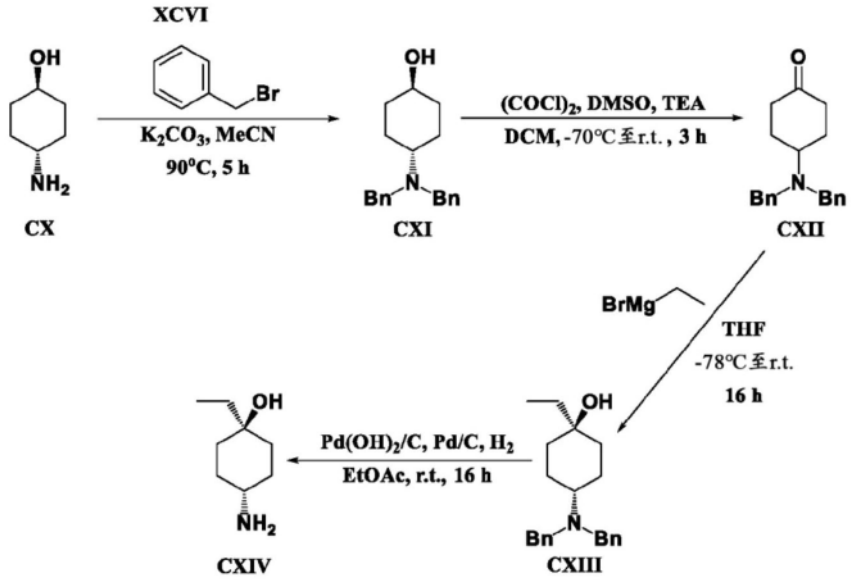
[0785] 在氮气气氛下将顺-4-(二苯甲基氨基)环己-1-醇(XCVII)(50mg,0.170mmol)、CuI(6.5mg,0.034mmol)于MeCN(5mL)中的溶液加热至45℃持续5min。经10min向此混合物中添加2,2-二氟-2-(氟磺酰基)乙酸(CVII)(60mg,0.339mmol)于(2mL)MeCN中的溶液。然后在45℃搅拌混合物1h。然后经由蒸发去除挥发性组分并用EtOAc(100mL)和水与$NaHCO_3$饱和水溶液的100mL 1:1混合物稀释残余物。经由烧结玻璃布赫纳漏斗(Buchner funnel)过滤含有固体的所得两相混合物。分离滤液层,并且用EtOAc(50mL)萃取水层。将合并的EtOAc层用盐水与水的50mL 1:1混合物洗涤,经无水$MgSO_4$干燥,过滤并浓缩成油状物。通过硅胶色谱法(100%己烷→30% EtOAc/己烷)纯化粗油状物。将含有产物的级分合并并浓缩,得到呈油状物的顺-N,N-二苯甲基-4-(二氟甲氧基)环己-1-胺(CVIII)(25mg,0.072mmol,42.3%产率),其固化成灰白色固体。$C_{21}H_{25}F_2NO$的ESIMS实验值m/z346.1(M+H)。

[0786] 步骤2

[0787] 向顺-N,N-二苯甲基-4-(二氟甲氧基)环己-1-胺(CVIII)(2.8g,8.11mmol)于THF(60mL)中的溶液添加$Pd(OH)_2/C$(1.4g)和Pd/C(1.4g)。在室温搅拌混合物16h。经由Celite®过滤混合物,并用THF洗涤。减压浓缩反应混合物,得到呈无色油状物的顺-4-(二氟甲氧基)环己-1-胺(CIX)(1.05g,6.36mmol,78.4%产率)。$C_7H_{13}F_2NO$的ESIMS实验值m/z 166.1(M+H)。

[0788] 中间体反-4-氨基-1-乙基环己-1-醇(CXIV)的制备描绘于以下方案19中。

[0789]



方案 19

[0790] 步骤1

[0791] 向反-4-氨基环己-1-醇(CX)(25g,0.217mmol)和溴甲苯(XCVI)(74.2g,0.434mmol)于MeCN(500mL)中的溶液中添加K_2CO_3(90g,0.6512mmol)。在90℃搅拌混合物5h。减压浓缩反应混合物以去除MeCN。用EtOAc稀释混合物并且然后用EtOAc(100mLx3)和H_2O萃取。将有机层经无水Na_2SO_4干燥并在高真空下蒸发,产生呈白色固体的反-4-(二苯甲基氨基)环己-1-醇(CXI)(32g,108.3mmol,49.9%产率)。所述产物不经进一步纯化即直接用于下一步骤中。$C_{20}H_{25}NO$的ESIMS实验值m/z 296.3(M+H)。

[0792] 步骤2

[0793] 在N_2下在-70℃向$(COCl)_2$(12.89g,101.55mmol)于DCM(150mL)中的溶液中缓慢添加含DMSO(10.6g,135.4mmol)的DCM(50mL)。在N_2下在-70℃添加含反-4-(二苯甲基氨基)环己-1-醇(CXI)(20.0g,67.7mmol)的DMF(50mL)并搅拌30min。然后添加TEA(21.92g,216.64mmol)并且在-70℃搅拌混合物,经3h升温至室温。用H_2O(800mL)稀释反应混合物并用DCM(800mL)萃取。将合并的有机层经无水Na_2SO_4干燥并浓缩,得到残余物。通过硅胶柱色谱法(9→25%EtOAc/PE)纯化残余物,得到呈白色固体的4-(二苯甲基氨基)环己-1-酮(CXII)(18.0g,61.3mmol,90.6%产率)。$C_{20}H_{23}NO$的ESIMS实验值m/z 294.2(M+H)。

[0794] 步骤3

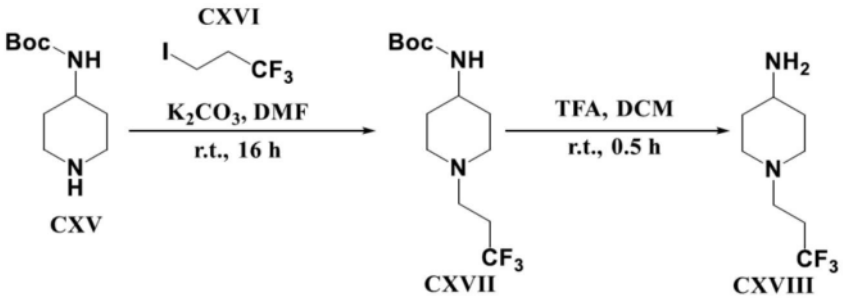
[0795] 在N_2下在-78℃将4-(二苯甲基氨基)环己-1-酮(CXII)(5.0g,17.04mmol)添加至THF(50mL)中并搅拌1h。添加溴化乙基镁(17mL,34.08mmol)并且在-78℃下搅拌反应物,经16h升温至室温。用NH_4Cl(100mL)稀释反应混合物,过滤并用EtOAc(200mLx3mL)萃取。将合并的有机层经无水Na_2SO_4干燥并在高真空下浓缩,得到残余物。LC/MS显示两种产物。通过硅胶柱色谱法(2→3% EtOAc/PE)纯化残余物,仅得到呈白色固体的反-4-(二苯甲基氨基)-1-乙基环己-1-醇(CXIII)(1.5g,4.637mmol,27.2%产率)。^1H NMR(400MHz,DMSO-d_6)δ0.80(t,J=7.4Hz,3H),1.17-1.10(m,2H),1.47-1.37(m,4H),1.65(t,J=11.4Hz,4H),2.41(s,1H),3.57(s,4H),3.91(s,1H),7.21-7.17(m,2H),7.34-7.27(m,8H);$C_{22}H_{29}NO$的ESIMS实验值m/z 324.2(M+H)。

[0796] 步骤4

[0797] 用H_2吹扫反-4-(二苯甲基氨基)-1-乙基环己-1-醇(CXIII)(1.5g,4.6mmol)于EtOAc(50.0mL)、10% Pd/C(0.4g)、20% $Pd(OH)_2/C$(0.4g)中的溶液。在H_2气氛下在室温搅拌混合物16h。经由Celite®过滤反应混合物并在高真空下浓缩,得到呈白色固体的反-4-氨基-1-乙基环己-1-醇(CXIV)(390mg,2.723mmol,58.7%产率)。^1H NMR(400MHz,DMSO-d_6)δ 0.80(t,J=7.4Hz,3H),1.14-1.03(m,2H),1.29-1.20(m,2H),1.40(q,J=7.4Hz,2H),1.59-1.49(m,2H),1.67-1.61(m,2H),2.70-2.61(m,1H),3.84(br s,1H);$C_8H_{17}NO$的ESIMS实验值m/z 144.1(M+H)。

[0798] 中间体1-(3,3,3-三氟丙基)哌啶-4-胺(CXVIII)的制备描绘于以下方案20中。

[0799]



方案 20

[0800] 步骤1

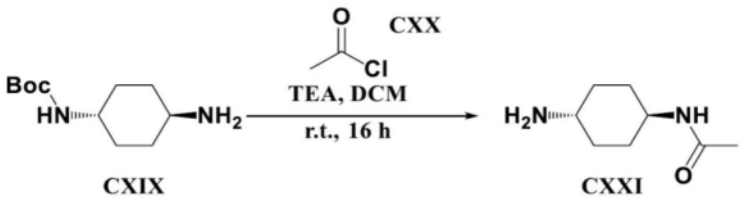
[0801] 将哌啶-4-基氨基甲酸叔丁酯(CXV)(可购自Combi-Blocks Inc.)(1g,4.99mmol)和K_2CO_3(1.73g,12.52mmol)溶解于DMF(15mL)中并且添加1-碘-3,3,3-三氟丙烷(CXVI)(878μL,7.49mmol),并且在室温搅拌反应物16h。将反应混合物倒入EtOAc中,并且分离水层。用EtOAc(×3)萃取水层,并且然后用1M柠檬酸将经合并的有机层酸化至pH 4.5。用小体积的水洗涤有机层三次以去除未反应的SM。足量产物保留在有机层中,使用无水$MgSO_4$干燥并真空缩减,得到呈白色固体的产物N-[1-(3,3,3-三氟丙基)哌啶-4-基]氨基甲酸叔丁酯(CXVII)(861mg,2.906mmol,58.2%产率)。$C_{13}H_{23}F_3N_2O_2$的ESIMS实验值m/z 297.2(M+H)。

[0802] 步骤2

[0803] 将N-[1-(3,3,3-三氟丙基)哌啶-4-基]氨基甲酸叔丁酯(CXVII)(200mg,0.670mmol)溶解于DCE(3.2mL)中并且添加TFA(800μL,10.38mmol),并且在室温下搅拌反应物30分钟。将反应混合物吹干并且通过高真空去除过量TFA,得到呈白色半固体的粗中间体1-(3,3,3-三氟丙基)哌啶-4-胺(CXVIII)(209mg,0.674mmol,99.8%产率),其不经进一步纯化即使用。$C_8H_{15}F_3N_2$的ESIMS实验值m/z 197.1(M+H)。

[0804] 中间体N-(反-4-氨基环己基)乙酰胺(CXXI)的制备描绘于以下方案21中。

[0805]

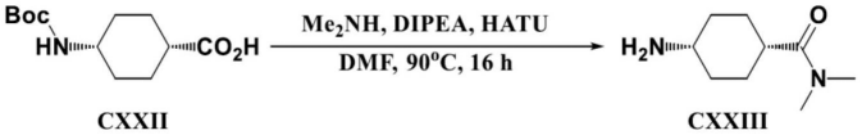


方案 21

[0806] 步骤1

[0807] 向N-(4-氨基环己基)氨基甲酸叔丁酯(CXIX)(可购自Combi-Blocks Inc.)(0.6g,2.8mmol)于DCM(6mL)中的经搅拌溶液中添加TEA(1.2mL,8.61mmol)。然后缓慢添加乙酰氯(CXX)(0.22mL,3.09mmol)并且在室温搅拌反应混合物16h。去除溶剂,并且使粗物质溶解于EtOAc中,用1M NaOH、盐水洗涤,并且经无水$MgSO_4$干燥并最后浓缩。将产物溶解于EtOH(2mL)和4M HCl(1mL)中。在室温搅拌溶液2h,然后蒸发至干燥,得到呈白色固体的N-(4-氨基环己基)乙酰胺的HCl盐(CXXI)(480mg,2.49mmol,89.0%产率)。$C_8H_{16}N_2O$的ESIMS实验值m/z 157.05(M+H)。

[0808] 中间体顺-4-氨基-N,N-二甲基环己烷-1-甲酰胺(CXXIII)的制备描绘于以下方案22中。

[0809] 

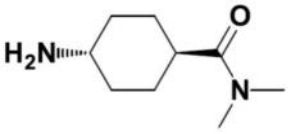
CXXII CXXIII

方案 22

[0810] 步骤1

[0811] 向4-(叔丁氧基羰氨基)环己烷甲酸(CXXII)(可购自Combi-Blocks Inc.)(0.3g,1.23mmol)于DMF(6mL)中的经搅拌溶液中添加DIPEA(0.65mL,3.73mmol)和HATU(0.7g,1.85mmol)。在室温搅拌反应物5min。添加二甲胺(0.92mL,1.84mmol),并且将反应物加热至90℃,持续16h。浓缩反应物并溶解于EtOH(2mL)和4M HCl/二噁烷(1mL)中。在室温搅拌混合物2h,真空浓缩,得到呈淡棕色粘稠固体的4-氨基-N,N-二甲基环己烷-1-甲酰胺的HCl盐(CXXIII)(280mg,1.355mmol,109.9%产率)。$C_9H_{18}N_2O$的ESIMS实验值m/z 171.15(M+H)。

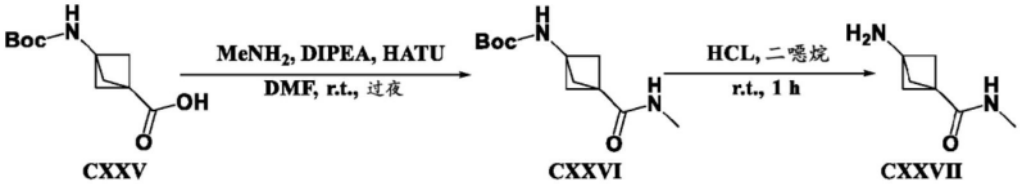
[0812] 根据以上方案22中所描述的程序制备以下中间体。

[0813] 

CXXIV

[0814] 反-4-氨基-N,N-二甲基环己烷-1-甲酰胺(CXXIV):淡棕色粘稠固体(290mg,1.403mmol,113.8%产率)。$C_9H_{18}N_2O$的ESIMS实验值m/z 171.1(M+H)。

[0815] 中间体3-氨基-N-甲基双环[1.1.1]戊烷-1-甲酰胺(CXXVII)的制备描绘于以下方案23中。

[0816] 

CXXV CXXVI CXXVII

方案 23

[0817] 步骤1

[0818] 向3-((叔丁氧羰基)氨基)双环[1.1.1]戊烷-1-甲酸(CXXV)(可购自AmBeed,Inc.)(0.5g,2.2mmol)和HATU(0.8g,2.09mmol)于DMF中的溶液中添加DIPEA(0.8mL,4.59mmol)并且搅拌混合物5min。然后在-78℃添加甲胺HCL(1.49g,22.07mmol),接着再添加DIPEA(4mL)。使反应混合物在室温搅拌过夜。浓缩溶剂,将残余物溶解于EtOAc中,用$NaHCO_3$饱和水溶液、水和盐水洗涤。将有机物经无水Na_2SO_4干燥,浓缩,并在高真空下干燥残余物,得到呈灰白色固体的(3-(甲基氨甲酰基)双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(CXXVI)(244mg,1.015mmol,46.2%产率)。$C_{12}H_{20}N_2O_3$的ESIMS实验值m/z241.1(M+H)。

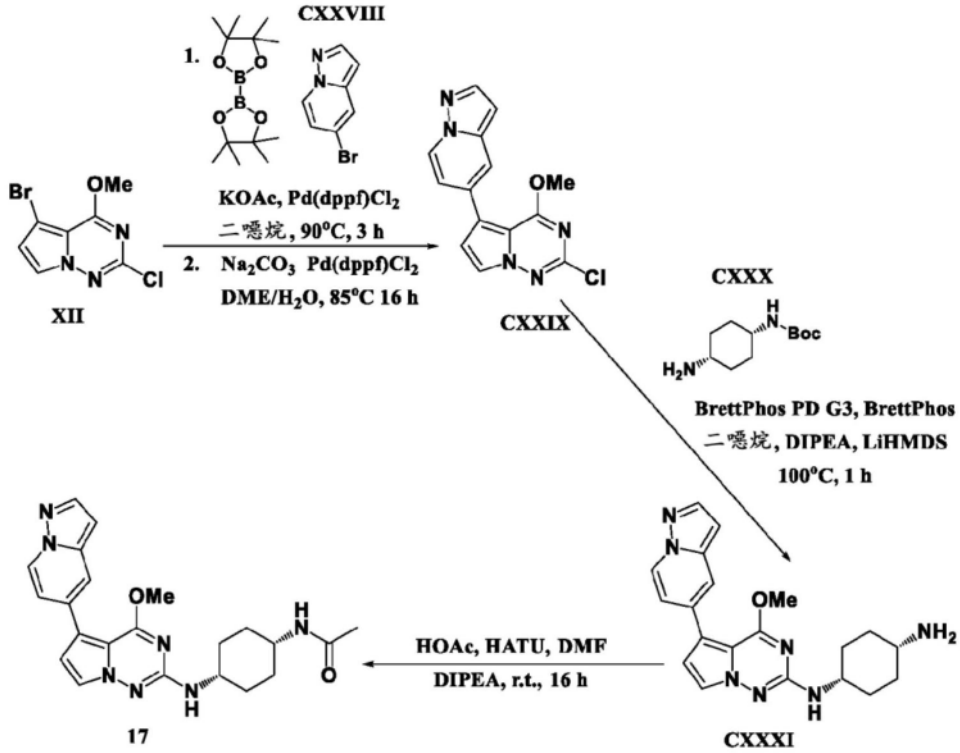
[0819] 步骤2

[0820] 将(3-(甲基氨甲酰基)双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(CXXVI)(240mg,1.0mmol)于4M HCl/二噁烷(1.25mL,5.0mmol)中的溶液在室温搅拌1h。浓缩溶剂并在高真空下干燥过夜,得到3-氨基-N-甲基双环[1.1.1]戊烷-1-甲酰胺HCL(CXXVII)(177mg,1.002mmol,100.3%产率),其不经纯化即用于下一步骤。$C_7H_{12}N_2O$的ESIMS实验值m/z141.15(M+H)。

[0821] 实施例1.

[0822] N-(顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺(17)的制备描绘于以下方案24中。

[0823]



方案 24

[0824] 步骤1至2

[0825] 在密封管中将5-溴吡唑并[1,5-a]吡啶(CXXVIII)(1.8g,9.14mmol)、Pd(dppf)Cl_2(311mg,0.380mmol)、双(频哪醇合)二硼(2.9g,11.42mmol)和KOAc(2.24g,22.82mmol)于1,4-二噁烷(15mL)中的混合物用N_2脱气并加热至90℃持续3h。将此反应物冷却至室温,向其中添加5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(2g,7.62mmol)、Pd(dppf)

Cl_2(311mg,0.380mmol)、Na_2CO_3(15mL,15mmol)和DME(15mL)。然后用N_2使反应物脱气并加热至85℃持续16h。添加水(100mL)并用EtOAc(100mLx3)萃取。将有机层蒸发至Celite®上,并通过硅胶柱(0→100% EtOAc/己烷)纯化。收集含有纯样本的试管并且真空去除溶剂。合并不纯级分并通过硅胶柱(0→100% EtOAc/己烷)再纯化。收集含有纯样本的试管并且真空去除溶剂,合并不纯级分并且通过硅胶柱(0→100% EtOAc/己烷)再纯化。合并三个纯级分并置于高真空下,产生呈米色固体的2-氯-4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基吡咯并[2,1-f][1,2,4]三嗪(CXXIX)(660mg,2.202mmol,28.9%产率)。$C_{14}H_{10}ClN_5O$的ESIMS实验值m/z 300.1(M+H)。

[0826] 步骤3

[0827] 在室温向2-氯-4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基吡咯并[2,1-f][1,2,4]三嗪(CXXIX)(100mg,0.330mmol)于1,4-二噁烷(2mL)中的经搅拌溶液中添加BrettPhos(19mg,0.040mmol)、BrettPhos PD G3(25mg,0.030mmol)、DIPEA(0.13mL,0.720mmol)、N-(4-氨基环己基)氨基甲酸叔丁酯(CXXX)(可购自Combi-Blocks Inc.)(90mg,0.420mmol)和LiHMDS(1mL,1mmol)。用N_2吹扫混合物并在100℃搅拌1h。浓缩反应混合物并通过ISCO(0→6%7N NH_3 MeOH/$CHCl_3$)纯化。收集纯级分,减压浓缩并在高真空下干燥,得到呈灰白色胶质固体的顺-N^1-(4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)环己烷-1,4-二胺(CXXXI)(70mg,0.186mmol,55.6%产率)。$C_{20}H_{23}N_7O$的ESIMS实验值m/z 378.2(M+H)。

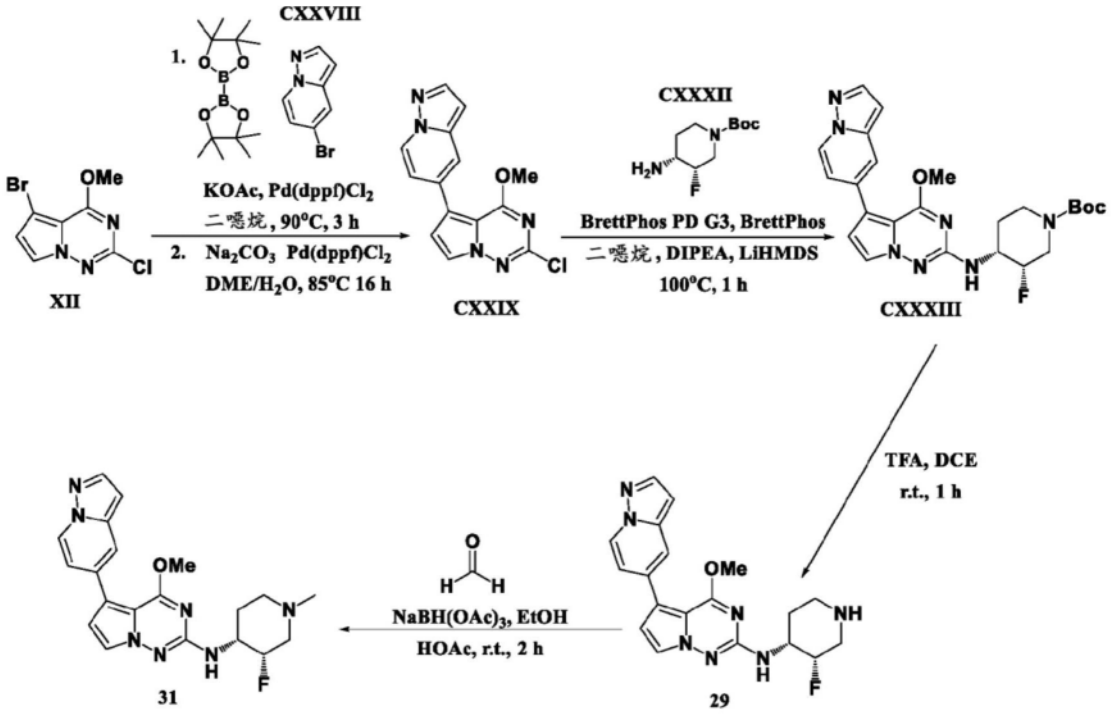
[0828] 步骤4

[0829] 向HOAc(11μL,0.190mmol)、HATU(79mg,0.210mmol)于DMF(0.2mL)中的溶液中添加DIPEA(85μL,0.490mmol)并且搅拌混合物5min。然后添加含顺-N^1-(4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)环己烷-1,4-二胺(CXXXI)(60mg,0.160mmol)的DMF(0.3mL)并且在室温搅拌反应混合物16h。添加水(10mL),并且用EtOAc萃取溶液。分离有机物,浓缩,吸收于硅胶上,并通过制备型TLC(4% MeOH/$CHCl_3$)纯化,得到呈黄色固体的N-(顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺(17)(22mg,0.052mmol,33.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.50-1.59(2H,m),1.60-1.72(4H,m),1.74-1.81(2H,m),1.81(3H,s),3.64-3.71(2H,m),3.99(3H,s),6.47(1H,d,J=6.30Hz),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),7.11(1H,dd,J=7.26,1.78Hz),7.63(1H,d,J=2.74Hz),7.70(1H,br d,J=6.84Hz),7.81(1H,s),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

[0830] 实施例2.

[0831] 4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基-N-(3R,4S)-3-氟哌啶-4-基]吡咯并[2,1-f][1,2,4]三嗪-2-胺(29)和N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺(31)的制备描绘于以下方案25中。

[0832]



方案 25

[0833] 步骤1至2

[0834] 在密封管中将5-溴吡唑并[1,5-a]吡啶(CXXVIII)(1.8g,9.14mmol)、Pd(dppf)Cl_2(311mg,0.380mmol)、双(频哪醇合)二硼(2.9g,11.42mmol)和KOAc(2.24g,22.82mmol)于1,4-二噁烷(15mL)中的混合物用N_2脱气并加热至90℃持续3h。将此反应物冷却至室温,向其中添加5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(2g,7.62mmol)、Pd(dppf)Cl_2(311mg,0.380mmol)、Na_2CO_3(15mL,15mmol)和DME(15mL)。然后用N_2使反应物脱气并加热至85℃持续16h。添加水(100mL)并用EtOAc(100mLx3)萃取。将有机层蒸发至Celite®上,并通过硅胶柱(0→100% EtOAc/己烷)纯化。收集含有纯样本的试管并且真空去除溶剂。合并不纯级分并通过硅胶柱(0→100% EtOAc/己烷)再纯化。收集含有纯样本的试管并且真空去除溶剂,合并不纯级分并通过硅胶柱(0→100% EtOAc/己烷)再纯化。合并三个纯级分并置于高真空下,产生呈米色固体的2-氯-4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基吡咯并[2,1-f][1,2,4]三嗪(CXXIX)(660mg,2.202mmol,28.9%产率)。$C_{14}H_{10}ClN_5O$的ESIMS实验值m/z 300.1(M+H)。

[0835] 步骤3

[0836] 在室温向2-氯-4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基吡咯并[2,1-f][1,2,4]三嗪(CXXIX)(100mg,0.330mmol)于1,4-二噁烷(3mL)中的经搅拌溶液中添加BrettPhos(19mg,0.040mmol)、BrettPhos PD G3(25mg,0.030mmol)、DIPEA(0.13mL,0.720mmol)、(3S,4R)-4-氨基-3-氟-1-哌啶甲酸2-甲基-2-丙烷酯(CXXXII)(100mg,0.460mmol)和LiHMDS(1mL,1mmol)。用N_2吹扫混合物并在100℃搅拌1h。浓缩反应混合物并通过ISCO(0→100% EtOAc/己烷)纯化。收集纯级分,减压浓缩并在高真空下干燥,得到呈白色固体的(3R,4S)-3-氟-4-[(4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基]哌啶-1-甲酸叔丁酯(CXXXIII)(65mg,0.135mmol,40.5%产率)。$C_{24}H_{28}FN_7O_3$的ESIMS实验值

m/z 482.25(M+H)。

[0837] 步骤4

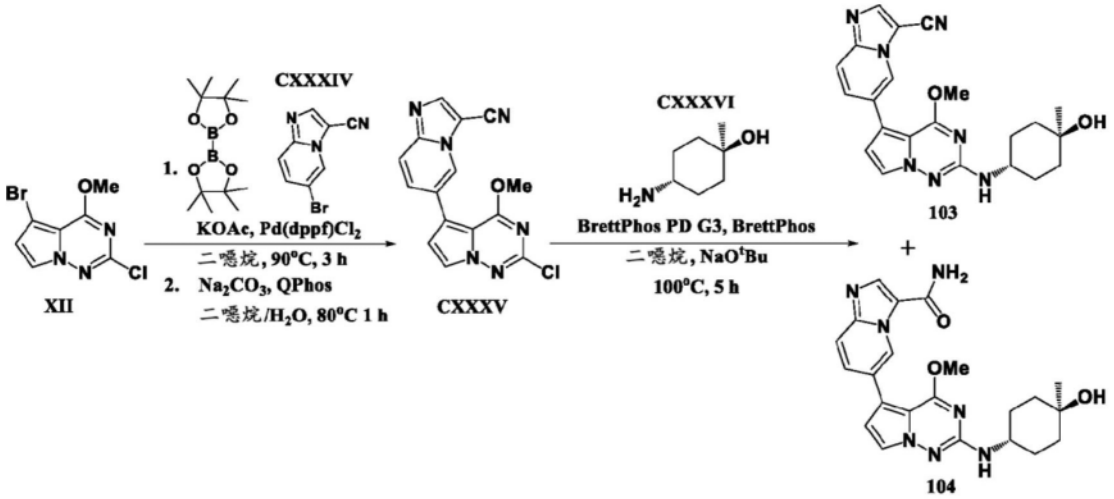
[0838] 向(3R,4S)-3-氟-4-[(4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基]哌啶-1-甲酸叔丁酯(CXXXIII)(65mg,0.130mmol)于DCM(1mL)中的经搅拌溶液中添加TFA(0.5mL,6.49mmol),并在室温搅拌1h。将反应混合物浓缩,用7N NH_3/MeOH处理,吸收于硅胶上并通过ISCO(0→100% $CHCl_3$/MeOH)纯化。收集纯级分,减压浓缩并在高真空下干燥,得到呈灰白色固体的4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基-N-(3R,4S)-3-氟哌啶-4-基]吡咯并[2,1-f][1,2,4]三嗪-2-胺(29)(45mg,0.118mmol,87.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.58-1.65(1H,m),1.73(1H,qd,J=12.37,4.24Hz),2.56(1H,br t,J=12.46Hz),2.70(1H,dd,J=38.70,14.30Hz),2.96(1H,br d,J=13.14Hz),3.13(1H,br t,J=11.50Hz),3.78-3.93(1H,m),4.00(3H,s),4.80(1H,d,J=50.75Hz),6.59(1H,d,J=1.64Hz),6.64(1H,d,J=7.94Hz),6.78(1H,d,J=2.74Hz),7.11(1H,dd,J=7.39,1.92Hz),7.63(1H,d,J=2.46Hz),7.81(1H,d,J=1.10Hz),7.97(1H,d,J=2.19Hz),8.63(1H,d,J=7.12Hz);$C_{19}H_{20}FN_7O$的ESIMS实验值m/z 382.2(M+H)。

[0839] 步骤5

[0840] 将4-甲氧基-5-吡唑并[1,5-a]吡啶-5-基-N-(3R,4S)-3-氟哌啶-4-基]吡咯并[2,1-f][1,2,4]三嗪-2-胺(29)(40mg,0.100mmol)溶解于EtOH(1mL)中并且添加HOAc(15μL,0.260mmol)和甲醛(18μL,0.320mmol),并且在室温搅拌反应物20min。添加$NaBH(OAc)_3$(56mg,0.260mmol)并且搅拌反应物2h。TLC显示起始物质完成。将反应混合物吸收于硅胶上并通过ISCO(0→8%7N NH_3 MeOH/$CHCl_3$)纯化。浓缩纯级分,并且在高真空下干燥残余物,得到呈灰白色固体的N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺(31)(30mg,0.076mmol,72.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68(1H,br dd,J=12.59,3.01Hz),1.92(1H,qd,J=12.23,3.56Hz),2.01-2.09(1H,m),2.17(1H,dd,J=37.55,13.20Hz),2.19(3H,s),2.79(1H,br d,J=11.23Hz),3.00-3.09(1H,m),3.67-3.83(1H,m),4.00(3H,s),4.91(1H,d,J=50.20Hz),6.59(1H,d,J=1.64Hz),6.64(1H,d,J=7.67Hz),6.78(1H,d,J=2.74Hz),7.11(1H,dd,J=7.12,1.92Hz),7.63(1H,d,J=2.74Hz),7.81(1H,d,J=0.82Hz),7.97(1H,d,J=2.19Hz),8.63(1H,d,J=7.39Hz);$C_{20}H_{22}FN_7O$的ESIMS实验值m/z396.2(M+1)。

[0841] 实施例3.

[0842] 6-(2-((反-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲酰胺(104)和6-(2-((反-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲腈(103)的制备描绘于以下方案26中。

[0843] 

方案 26

[0844] 步骤1至2

[0845] 将6-溴咪唑并[1,2-a]吡啶-3-甲腈(CXXXIV)(可购自Combi-Blocks Inc)(888mg,4.0mmol)、双(频哪醇合)二硼(1.016g,4.0mmol)、KOAc(1.18g,12.02mmol)和Pd(dppf)Cl_2(123mg,0.15mmol)的混合物溶解于1,4-二噁烷(12mL)中,并且用N_2吹扫反应混合物5min。密封小瓶并在95℃加热3h。向以上反应混合物中添加5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(525mg,2.0mmol)、QPhos(143mg,0.2mmol),以及Na_2CO_3(1.27g,12.mmol)于水(3mL)中的溶液。用N_2气体吹扫反应混合物5min,密封小瓶并在80℃加热1h。将有机层分离,吸收于二氧化硅上,并经ISCO(0→20% MeOH/$CHCl_3$)纯化,得到呈米色固体的6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲腈(CXXXV)(116mg,0.357mmol,17.9%产率)。$C_{15}H_9ClN_6O$的ESIMS实验值m/z 325.1(M+H)。

[0846] 步骤3

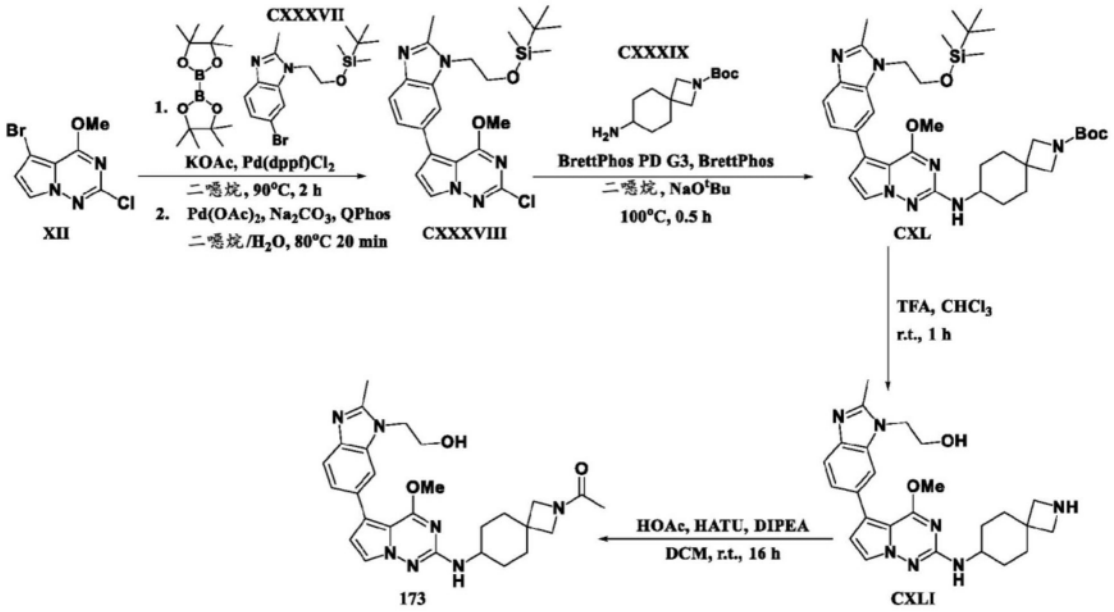
[0847] 在室温向6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲腈(CXXXV)(116.mg、0.36mmol)、反-4-氨基-1-甲基环己-1-醇(CXXXVI)(可购自PharmaBlock(USA),Inc.)(56.mg,0.43mmol)、BrettPhos Pd G3(24.mg,0.03mmol)和BrettPhos(19.mg,0.04mmol)于1,4-二噁烷(3mL)中的经搅拌溶液中添加NaO^{t}Bu(110mg,1.14mmol)。用N_2吹扫反应混合物5min,然后加热至100℃持续5h。浓缩反应混合物并通过ISCO(0→20%7N NH_3于MeOH/$CHCl_3$中)纯化,得到两种呈米色固体的产物6-(2-((反-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲腈(103)(12mg,0.029mmol,8.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.38-1.53(4H,m),1.56-1.66(3H,m),1.83-1.93(2H,m),3.60-3.71(1H,m),4.01(3H,s),4.23(1H,s),6.56(1H,d,J=7.94Hz),6.89(1H,d,J=2.74Hz),7.67(1H,d,J=2.74Hz),7.81-7.92(2H,m),8.44(1H,s),8.77-8.86(1H,m);$C_{22}H_{23}N_7O_2$的ESIMS实验值m/z 418.2(M+1)和呈米色固体的6-(2-((反-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲酰胺(104)(2.2mg,0.005mmol,1.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.39-1.48(4H,m),1.57-1.63(2H,m),1.85-1.91(2H,m),3.60-3.72(1H,m),3.99(3H,s),4.23(1H,s),6.49(1H,d,J=7.94Hz),6.75(1H,d,J

=2.46Hz),7.34(1H,br s),7.65(1H,d,J=2.74Hz),7.69(2H,s),7.95(1H,br s),8.33(1H,s),9.84(1H,s);$C_{22}H_{25}N_7O_3$的ESIMS实验值m/z 436.25(M+1)。

[0848] 实施例4.

[0849] 1-(7-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮(173)的制备描绘于以下方案27中。

[0850]



方案 27

[0851] 步骤1至2

[0852] 在密封管中将6-溴-1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑(CXXXVII)(950mg,2.57mmol)、Pd(dppf)Cl_2(99mg,0.12mmol)、双(频哪醇合)二硼(960mg,3.78mmol)和KOAc(748mg,7.62mmol)于1,4-二噁烷(10mL)中的混合物用N_2吹扫,密封,并且然后加热至90℃持续2h。LCMS显示硼酸与硼酸酯的混合物。

[0853] 将此反应物冷却至室温,然后向此混合物中添加5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(660mg,2.51mmol)、QPhos(178mg,0.25mmol)、Pd(OAc)$_2$(28mg,0.12mmol)和Na_2CO_3水溶液(5mL,5.0mmol)。用N_2吹扫反应物,密封,并且然后加热至80℃持续20min。添加水(100mL)并用EtOAc(3x100mL)萃取。将溶剂在Celite®上缩减,并通过硅胶柱色谱法(0→100% EtOAc/己烷)纯化,产生呈灰白色固体的5-(1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(CXXXVIII)(460mg,0.975mmol,38.8%产率)。$C_{23}H_{30}ClN_5O_2Si$的ESIMS实验值m/z 472.2(M+H)。

[0854] 步骤3

[0855] 向7-氨基-2-氮杂螺[3.5]壬烷-2-甲酸叔丁酯HCl(CXXXIX)(可购自J&W Pharmlab,LLC)(70mg,0.25mmol)、5-(1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(CXXXVIII)(100mg,0.21mmol)、BrettPhos(12mg,0.02mmol)和BrettPhos PD G3(10mg,0.01mmol)于二

噁烷(1.6mL)中的经搅拌溶液中添加NaO^{t}Bu(62mg,0.65mmol)。用N_2吹扫溶液,密封,并且然后在100℃加热30min。将溶剂反应物在Celite®上缩减,并通过硅胶柱色谱法(0→30%7N NH_3于MeOH/$CHCl_3$中)纯化,产生呈灰白色固体的7-((5-(1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-甲酸叔丁酯(CXL)(17mg,0.025mmol,11.9%产率)。$C_{36}H_{53}N_7O_4Si$的ESIMS实验值m/z 676.4(M+H)。

[0856] 步骤4

[0857] 向7-((5-(1-(2-((叔丁基二甲基甲硅烷基)氧基)乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-甲酸叔丁酯(CXL)(17.mg、0.03mmol)于$CHCl_3$(3mL)中的溶液中添加TFA(1mL)。在室温搅拌反应物1h。减压去除溶剂并且通过硅胶柱色谱法(0→15%7N NH_3于MeOH/$CHCl_3$中)纯化残余物,产生呈琥珀色玻璃状物的2-(6-(2-((2-氮杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇(CXLI)(11mg,0.024mmol,94.8%产率)。$C_{25}H_{31}N_7O_2$的ESIMS实验值m/z 462.3(M+H)。

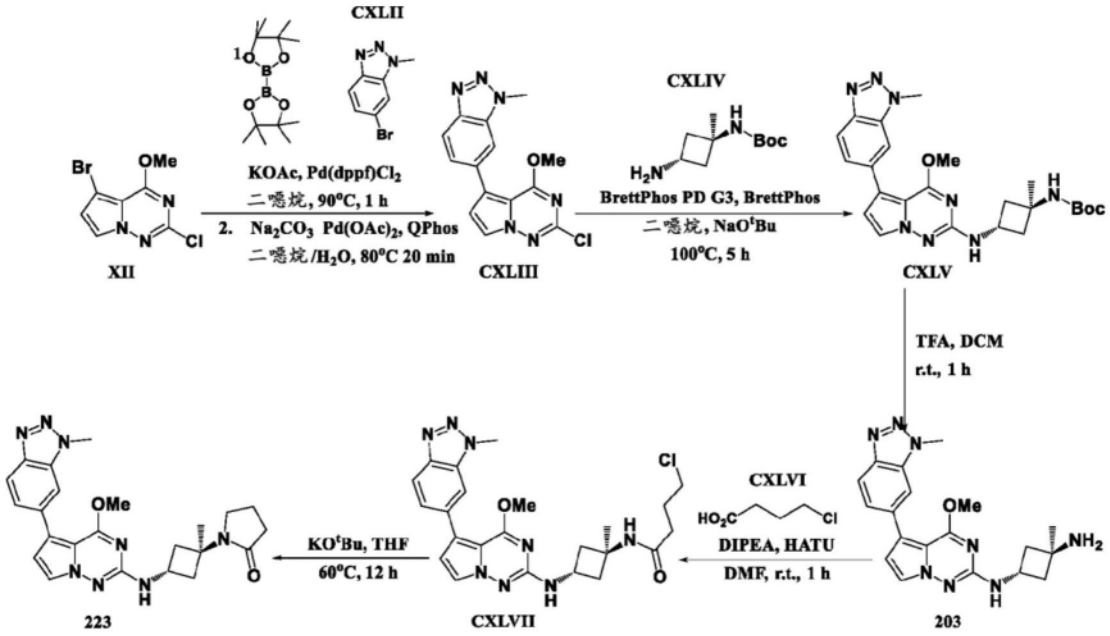
[0858] 步骤5

[0859] 将HATU(10mg,0.03mmol)、HOAc(1.5μL,0.03mmol)和DIPEA(12μL,0.07mmol)于DCM(2mL)中的溶液在室温搅拌30min,然后添加2-(6-(2-((2-氮杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇(CXLI)(11.mg,0.024mmol)并且将溶液在室温搅拌16h。将溶剂在Celite®上缩减,并通过硅胶柱色谱法(0→10%7N NH_3于MeOH/$CHCl_3$中)纯化,得到呈灰白色固体的1-(7-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮(173)(6mg,0.012mmol,50.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28-1.39(2H,m),1.48-1.60(2H,m),1.72-1.79(3H,m),1.83-1.94(4H,m),2.60(3H,s),3.47(1H,s),3.52(1H,s),3.57(1H,dt,J=10.20,6.95Hz),3.74(1H,s),3.75-3.79(2H,m),3.80(1H,s),3.93(3H,d,J=1.10Hz),4.28(2H,br t,J=5.20Hz),4.99(1H,t,J=5.48Hz),6.43(1H,dd,J=16.43,7.94Hz),6.62(1H,d,J=2.46Hz),7.37(1H,dd,J=8.21,1.37Hz),7.51(1H,d,J=8.49Hz),7.58(1H,t,J=2.74Hz),7.69(1H,s);$C_{27}H_{33}N_7O_3$的ESIMS实验值m/z 504.3(M+1)。

[0860] 实施例5.

[0861] 反-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺(203)和1-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)吡咯烷-2-酮(223)的制备描绘于以下方案28中。

[0862]



方案 28

[0863] 步骤1至2

[0864] 在密封管中将6-溴-1-甲基-1H-苯并[d][1,2,3]三唑(CXLII)(可购自Combi-Blocks Inc.)(0.93g,4.39mmol)、$Pd(dppf)Cl_2$(0.17g,0.21mmol)、双(频哪醇合)二硼(1.68g,6.62mmol)和KOAc(1.3g,13.25mmol)于1,4-二噁烷(11mL)中的混合物用N_2吹扫,密封并加热至90℃持续1h。LCMS显示硼酸与硼酸酯的混合物。

[0865] 将反应物冷却至室温并且然后向此混合物中添加5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(1.15g,4.38mmol)、$Pd(OAc)_2$(0.05g,0.22mmol)、QPhos(0.32g,0.45mmol)、Na_2CO_3(9.2mL,9.2mmol)的水溶液和1,4-二噁烷(11mL)。用N_2吹扫反应物,密封,并加热至80℃持续20min。添加水(100mL)并用EtOAc(3x100 mL)萃取。将溶剂在Celite®上缩减,并通过硅胶柱色谱法(0→100% EtOAc/己烷)纯化,产生呈灰白色固体的6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-1-甲基-1H-苯并[d][1,2,3]三唑(CXLIII)(0.763g,2.424mmol,55.3%产率)。$C_{14}H_{11}ClN_6O$的ESIMS实验值m/z 315.1(M+H)。

[0866] 步骤3

[0867] 向6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-1-甲基-1H-苯并[d][1,2,3]三唑(CXLIII)(212mg,0.67mmol)、(反-3-氨基-1-甲基环丁基)氨基甲酸叔丁酯(CXLIV)(可购自PharmaBlock(USA),Inc.)(160mg,0.8mmol)、BrettPhos PD G3(46mg,0.05mmol)和BrettPhos(37mg,0.07mmol)于1,4-二噁烷(4mL)中的经搅拌溶液中添加NaO^tBu(195mg,2.03mmol)。将反应混合物吹扫5min,然后加热至100℃持续30min。将反应混合物浓缩并经ISCO(0→10% MeOH/$CHCl_3$)纯化,得到呈无色胶状物的(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)氨基甲酸叔丁酯(CXLV)(188mg,0.393mmol,58.3%产率)。$C_{24}H_{30}N_8O_3$的ESIMS实验值m/z 479.3(M+H)。

[0868] 步骤4

[0869] 向(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)氨基甲酸叔丁酯(CXLV)(188mg,0.39mmol)于DCM(2mL)中的经搅拌溶液中添加TFA(1.2mL,15.58mmol),并在室温搅拌1h。将反应混合物浓缩,用Na_2CO_3饱和水溶液处理,用EtOAc洗涤,经无水Na_2SO_4干燥,真空浓缩,然后吸收于硅胶上,并通过ISCO(0→20%7N NH_3于MeOH/$CHCl_3$中)纯化,得到呈灰白色泡沫的反-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺(203)(110mg,0.291mmol,74.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.22(3H,s),1.80(2H,br s),1.88-1.98(2H,m),2.13-2.22(2H,m),3.95(3H,s),4.23-4.33(1H,m),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.90(1H,d,J=7.12Hz),7.60(1H,dd,J=8.76,1.37Hz),7.63(1H,d,J=2.46Hz),7.93(1H,s),7.95-8.00(1H,m);$C_{19}H_{22}N_8O$的ESIMS实验值m/z 379.2(M+1)。

[0870] 步骤5

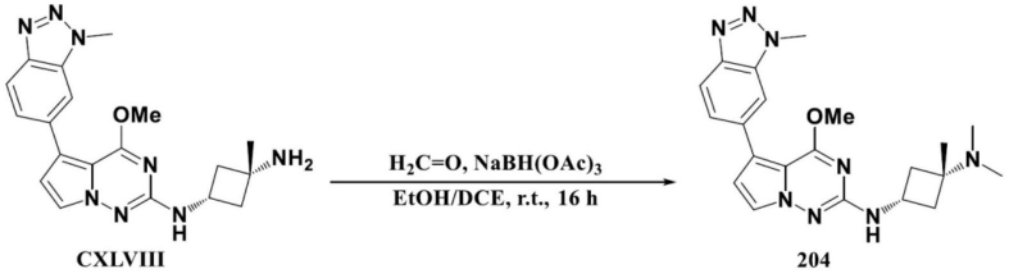
[0871] 向4-氯丁酸(CXLVI)(16μL,0.16mmol)和HATU(70mg,0.18mmol)于DMF(0.5mL)中的溶液中添加DIPEA(74μL,0.42mmol)并且搅拌混合物10min。添加含反-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺(203)(50mg,0.13mmol)的DMF(0.5mL),并且在室温搅拌反应混合物1h。用$NaHCO_3$饱和水溶液淬灭反应混合物并用EtOAc萃取。将有机层分离,浓缩,吸收于硅胶上并通过ISCO(0→10%MeOH/$CHCl_3$)纯化,得到呈灰白色固体的4-氯-N-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)丁酰胺(CXLVII)(53mg,0.110mmol,83.1%产率)。$C_{23}H_{27}ClN_8O_2$的ESIMS实验值m/z 483.2(M+H)。

[0872] 步骤6

[0873] 向4-氯-N-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)丁酰胺(CXLVII)(53mg,0.11mmol)于THF(5mL)中的溶液中添加KO^{t}Bu(37mg,0.33mmol),并且将反应混合物在60℃加热12h。用$NaHCO_3$饱和水溶液淬灭反应混合物并用EtOAc萃取。将有机层分离,浓缩,吸收于硅胶上,并通过ISCO(0→10% MeOH/$CHCl_3$)纯化,得到呈灰白色固体的1-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)吡咯烷-2-酮(223)(23mg,0.052mmol,46.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.92(2H,quin,J=7.53Hz),2.00-2.08(2H,m),2.23(2H,t,J=8.08Hz),2.82-2.92(2H,m),3.40(2H,t,J=6.84Hz),3.96(3H,s),4.04-4.12(1H,m),4.31(3H,s),6.74(1H,d,J=2.46Hz),7.06(1H,d,J=6.30Hz),7.60(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.46Hz),7.94(1H,s),7.97(1H,d,J=8.76Hz);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.3(M+1)。

[0874] 实施例6.

[0875] 顺-N^3-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-N^1,N^1,1-三甲基环丁烷-1,3-二胺(204)的制备描绘于以下方案29中。

[0876] 

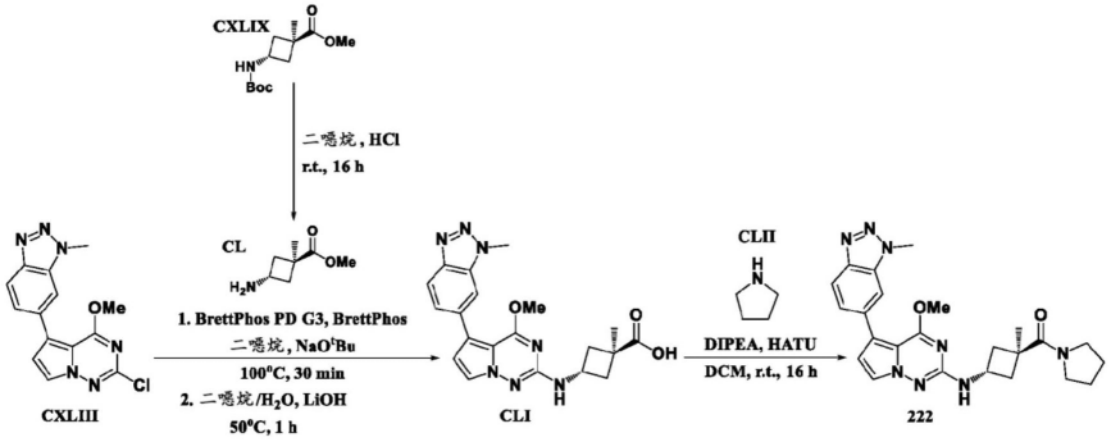
方案 29

[0877] 步骤1

[0878] 向(顺-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺(CXLVIII)(通过实施例5步骤1至4中所示的方法制备)(25mg,0.07mmol)于EtOH(1mL)和DCE(4mL)中的经搅拌溶液中添加甲醛(13μL,0.17mmol)。在室温搅拌反应物30min,然后添加$NaBH(OAc)_3$(70mg,0.33mmol)。在室温进一步搅拌反应物16h。添加Na_2CO_3饱和水溶液并用DCM萃取。分离有机层并经无水Na_2SO_4干燥。减压去除溶剂并且通过ISCO硅胶柱色谱法(0→20%7N NH_3于MeOH/$CHCl_3$中)纯化残余物,得到呈白色固体的顺-N^3-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-N^1,N^1,1-三甲基环丁烷-1,3-二胺(204)(18mg,0.044mmol,67.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.06(3H,s),1.82-1.92(2H,m),2.03(6H,s),2.19(2H,td,J=8.15,2.60Hz),3.91-4.01(1H,m),3.95(3H,s),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.95(1H,d,J=7.12Hz),7.60(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{21}H_{26}N_8O$的ESIMS实验值m/z 407.3(M+1)。

[0879] 实施例7.

[0880] (反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮(222)的制备描绘于以下方案30中。

[0881] 

方案 30

[0882] 步骤1至3

[0883] 向微波小瓶中添加反-3-{[(叔丁氧基)羰基]氨基}-1-甲基环丁烷-1-甲酸甲酯

(CXLIX)(255.1mg,1.05mmol)、MeOH(5mL)以及4MHCl于二噁烷(0.5mL,2.mmol)中的溶液。密封小瓶,并且在室温搅拌溶液16h。在加热至50℃的同时,用N_2流吹除溶剂。将残余物溶解于MeCN(5mL)中,并且在加热至50℃的同时,用N_2流吹除溶剂。将此举再重复2次,产生呈白色固体的反-3-氨基-1-甲基环丁烷-1-甲酸甲酯(CL)。

[0884] 向白色残余物中添加6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-1-甲基-1H-苯并[d][1,2,3]三唑(CXLIII)(300mg,0.95mmol)、1,4-二噁烷(4.8mL)、BrettPhos(50mg,0.09mmol)、NaO^tBu(366.4mg,3.81mmol)、BrettPhos PD G3(44mg,0.05mmol)。用N_2吹扫反应混合物,密封小瓶并加热至100℃持续30min。LC/MS显示甲酯与酸的混合物。

[0885] 向上述溶液中添加水(2mL),接着添加2M LiOH水溶液(0.48mL,0.96mmol)。在50℃加热反应物1h。将反应物倒入水(5mL)中,用1N HCl中和并用DCM(3x50 mL)萃取。将DCM层在Celite®上缩减并通过硅胶柱色谱法(0→50% EtOAc/己烷)纯化,产生呈灰白色固体的3-[[4-甲氧基-5-(3-甲基苯并三唑-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基]氨基]-1-甲基环丁烷-1-甲酸(CLI)(104mg,0.2553mmol,26.779%产率)。$C_{20}H_{21}N_7O_3$的ESIMS实验值m/z 408.2(M+H)。

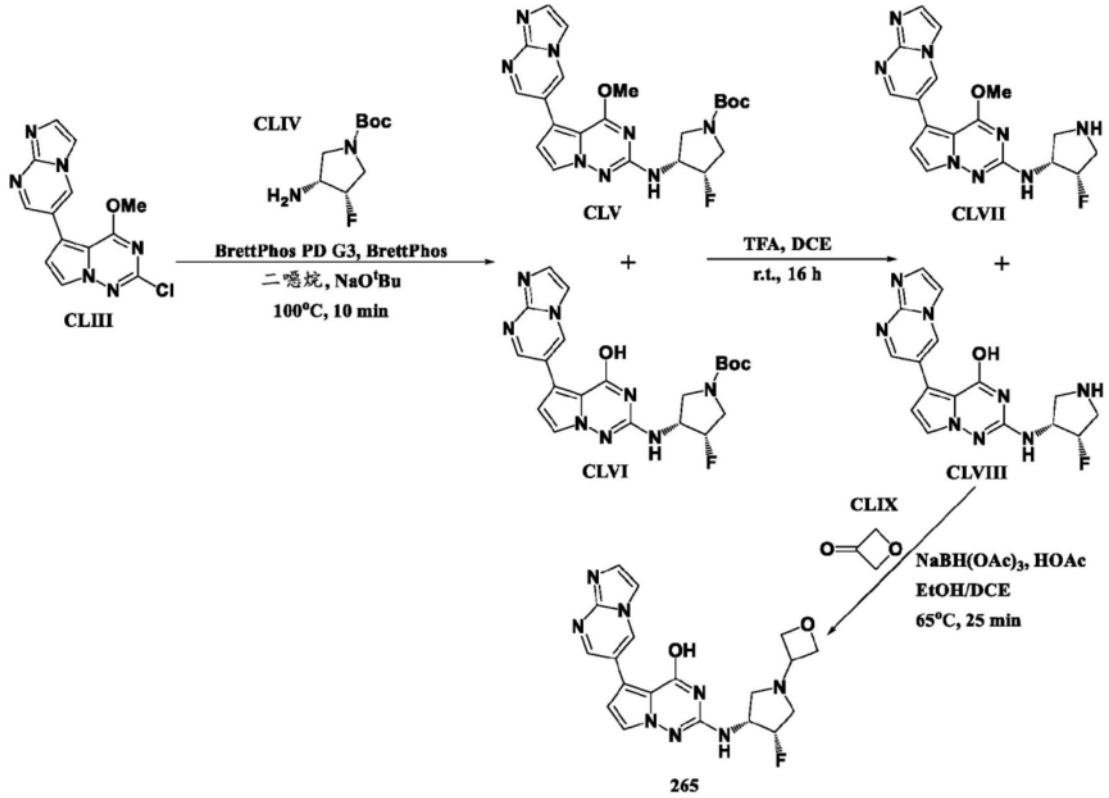
[0886] 步骤4

[0887] 将HATU(34.5mg,0.09mmol)、反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酸(CLI)(34.mg,0.08mmol)和DIPEA(30.9μL,0.18mmol)于DCM(2mL)中的溶液在室温搅拌30min,然后添加吡咯烷(CLII)(10μL,0.12mmol)。在室温搅拌反应物16h。将溶剂在Celite®上缩减,并通过硅胶柱色谱法(0→10%7N NH_3于MeOH/$CHCl_3$中)纯化,得到呈白色固体的(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮(222)(36mg,0.078mmol,93.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.73-1.80(2H,m),1.81-1.87(2H,m),1.91-1.99(2H,m),2.86-2.93(2H,m),3.30-3.34(4H,m),3.87-3.94(1H,m),3.96(3H,s),4.31(3H,s),6.74(1H,d,J=2.46Hz),7.07(1H,d,J=6.57Hz),7.60(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{24}H_{28}N_8O_2$的ESIMS实验值m/z461.3(M+1)。

[0888] 实施例8.

[0889] 2-(((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇(265)的制备描绘于以下方案31中。

[0890]



方案 31

[0891] 步骤1

[0892] 使2-氯-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(CLIII)(通过实施例3步骤1至2中所呈现的方法制备)(200mg,0.67mmol)、(3R,4S)-3-氨基-4-氟吡咯烷-1-甲酸叔丁酯(CLIV)(可购自PharmaBlock(USA),Inc.)(177mg,0.87mmol)、BrettPhos Pd G3(51mg,0.06mmol)、BrettPhos(31mg,0.06mmol)和NaO^{t}Bu(192mg,2.0mmol)悬浮于无水1,4-二噁烷(4mL)中。用Ar吹扫混合物5min,接着在100℃加热10min。将反应混合物添加至NH_4Cl饱和水溶液和DCM中,并且分离有机层。用DCM(×2)萃取水层,并且将合并的有机层干燥(无水$MgSO_4$)并真空缩减,得到呈橙色蓬松固体的产物(3S,4R)-3-氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-甲酸叔丁酯(CLV)(220mg,0.470mmol,70.6%产率)和(3S,4R)-3-氟-4-((4-羟基-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-甲酸叔丁酯(CLVI)(91mg,0.200mmol,30.1%产率)的混合物,其不经纯化即使用。通过LCMS计算量和产率。$C_{22}H_{25}FN_8O_3$的ESIMS实验值m/z 469.3(M+H)和$C_{21}H_{23}FN_8O_3$的ESIMS实验值m/z 455.2(M+H)。

[0893] 步骤2

[0894] 在0℃将(3S,4R)-3-氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-甲酸叔丁酯(CLV)(220mg,0.470mmol)和(3S,4R)-3-氟-4-((4-羟基-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-甲酸叔丁酯(CLVI)(91mg,0.200mmol)的混合物溶解于DCE(9mL)中。添加TFA(1mL)并且在室温搅拌反应物16h。蒸发反应混合物并且经由高真空去除过量TFA。通过柱色

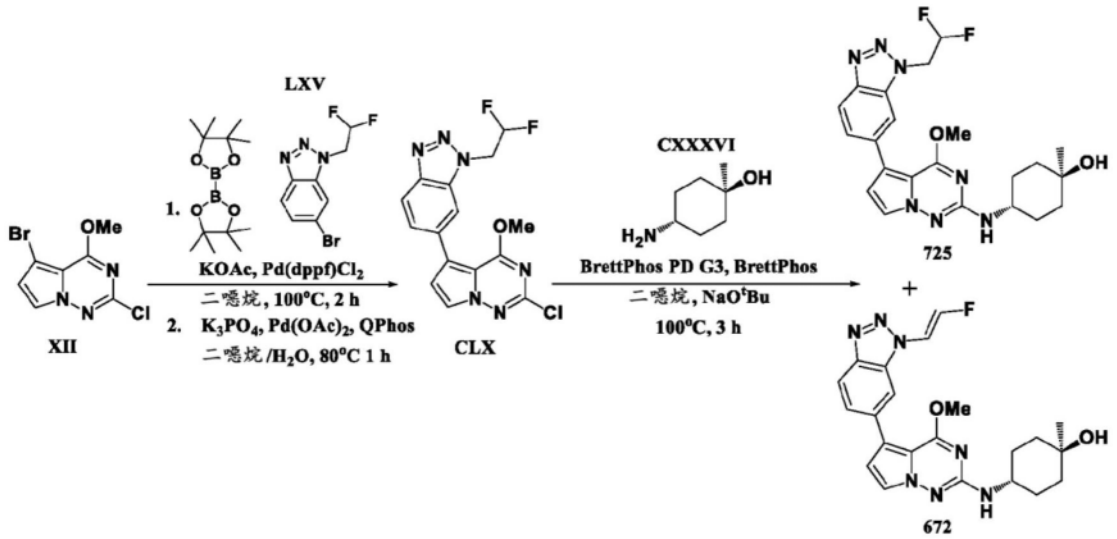
谱法(0→8%7.0NH$_3$于MeOH/CHCl$_3$中),接着通过(8→20%7.0NH$_3$于MeOH/CHCl$_3$中)纯化粗产物以分离两种化合物,收集呈浅黄色半固体的N-((3R,4S)-4-氟吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLVII)(100mg,0.272mmol,57.8%产率)。$C_{17}H_{17}FN_8O$的ESIMS实验值m/z 369.2(M+H)。收集呈黄色固体的产物2-(((3R,4S)-4-氟吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇(CLVIII)(171mg,0.483mmol,102.8%产率)。$C_{16}H_{15}FN_8O$的ESIMS实验值m/z 355.2(M+H)。在TFA Boc脱保护期间再进行去甲基化。

[0895] 步骤3

[0896] 使2-(((3R,4S)-4-氟吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇(CLVIII)(40mg,0.11mmol)悬浮于EtOH(1mL)和DCE(1mL)中。然后添加HOAc(19μL,0.33mmol)和氧杂环丁-3-酮(CLIX)(33μL,0.56mmol)并且在65℃搅拌反应物15min。添加NaBH(OAc)$_3$(48mg,0.23mmol)并且再搅拌反应物10min。LC/MS显示未反应的起始物质,因此再添加氧杂环丁-3-酮(23μL,0.36mmol)并在65℃搅拌10min,接着再添加NaBH(OAc)$_3$(48mg,0.23mmol)。在65℃搅拌反应物10min。LC/MS显示有少量起始物质并且反应停止。将反应混合物装载在Celite®上,并通过二氧化硅柱色谱法(0→9%7.0M NH$_3$于MeOH/CHCl$_3$中)纯化。通过HPLC(0→15% MeCN/H$_2$O(0.1%甲酸))进一步纯化产物,产生呈灰白色固体的2-(((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇(265)(4mg,0.010mmol,8.6%产率)。^{1}H NMR(499MHz,DMSO-d$_6$)δppm 2.56(1H,t,J=8.49Hz),2.79-2.91(1H,m),2.96-3.09(1H,m),2.98-3.03(1H,m),3.76(1H,quin,J=6.09Hz),4.22-4.37(1H,m),4.46(2H,t,J=6.02Hz),4.58(2H,t,J=6.57Hz),5.25(1H,dtd,J=55.95,4.65,4.65,1.00Hz),6.29(1H,br d,J=6.30Hz),6.81(1H,d,J=2.74Hz),7.48(1H,d,J=2.74Hz),7.71(1H,d,J=1.10Hz),7.93(1H,d,J=1.09Hz),8.90(1H,d,J=2.46Hz),9.41(1H,d,J=2.19Hz),10.78(1H,br s);$C_{19}H_{19}FN_8O_2$的ESIMS实验值m/z 411.2(M+1)。

[0897] 实施例9.

[0898] (1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇(725)和(1r,4r)-4-((5-(1-((E)-2-氟乙烯基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇(672)的制备描绘于以下方案32中。

[0899] 

方案 32

[0900] 步骤1至2

[0901] 将6-溴-1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑(LXV)(500mg,1.91mmol)、双(频哪醇合)二硼(650mg,2.56mmol)、Pd(dppf)Cl_2(75mg,0.09mmol)和KOAc(500mg,5.09mmol)悬浮于无水1,4-二噁烷(12mL)中。将反应物声波处理并脱气5min,然后在100℃加热2h。将反应混合物冷却至室温并且添加2M K_3PO_4水溶液(2.52mL,5.04mmol),并且搅拌反应物5min。添加5-溴-2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(443mg,1.69mmol)、Pd$(OAc)_2$(19mg,0.08mmol)和QPhos(84mg,0.12mmol)并用Ar吹扫反应物5min。将反应物加热至80℃持续1h。真空缩减反应混合物并且通过柱色谱法(100%$CHCl_3$)纯化粗产物。通过柱色谱法(保持0→50% EtOAc/己烷,接着是50→100% EtOAc/己烷)进一步纯化所述产物,得到固体,将其用MeOH湿磨并过滤,用MeOH洗涤,得到呈米色固体的6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑(CLX)(295mg,0.809mmol,47.9%产率)。$C_{15}H_{11}ClF_2N_6O$的ESIMS实验值m/z 365.1(M+H)。

[0902] 步骤3

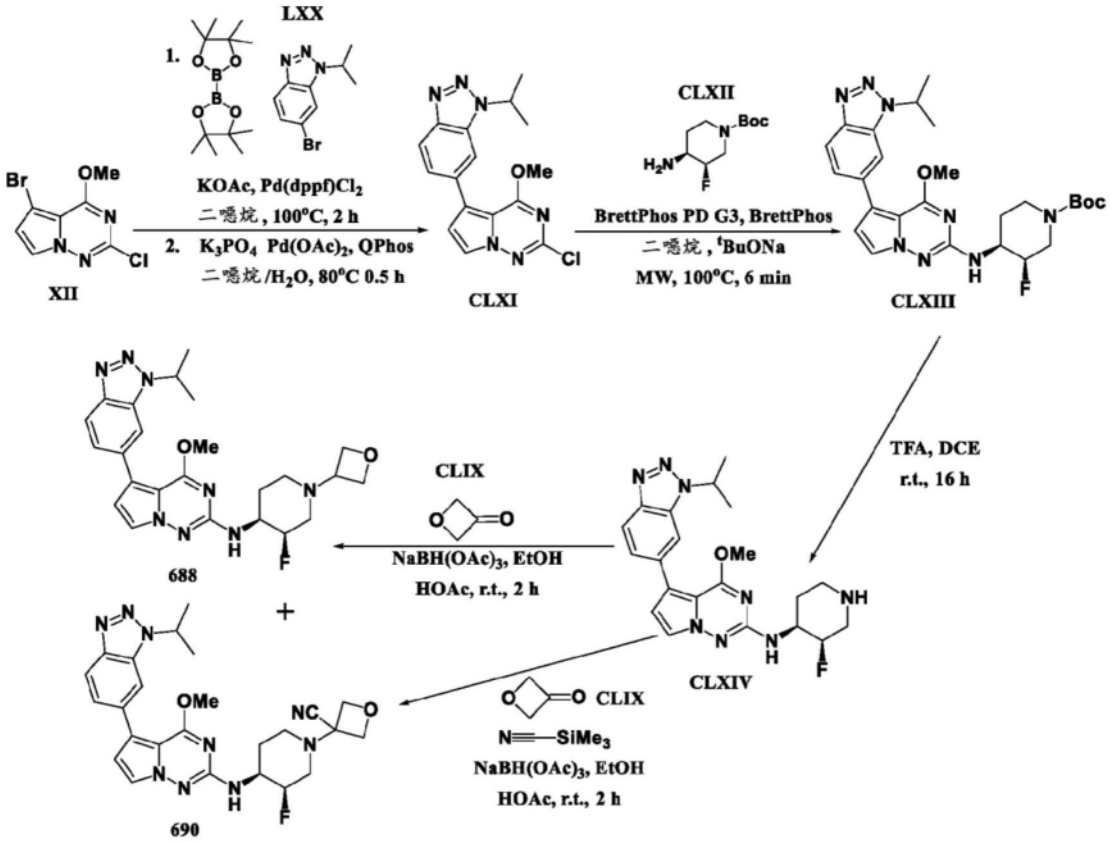
[0903] 在微波小瓶中将6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑(CLX)(25mg,0.07mmol)、反-4-氨基-1-甲基环己-1-醇(CXXXVI)(可购自PharmaBlock(USA),Inc.)(9mg,0.07mmol)、BrettPhos PD G3(5.mg,0.01mmol)、BrettPhos(4.mg,0.01mmol)和NaO^{t}Bu(21.mg,0.22mmol)溶解于无水1,4-二噁烷(0.7mL)中。用Ar吹扫悬浮液持续5min,并且然后将反应物加热至100℃持续3h。将反应物真空缩减并装载于Celite®上,并通过柱色谱法(0→90% EtOAc/己烷)纯化。通过HPLC(保持0→35%,接着5%逐步增加至80% MeOH/H_2O于0.1%甲酸中)进一步纯化经分离的产物。收集适当级分并用$NaHCO_3$饱和水溶液中和并用DCM(×2)萃取。将合并的有机层经无水$MgSO_4$干燥并真空缩减,得到呈黄色固体的(1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇(725)(3mg,0.007mmol,9.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.40-1.50(4H,m),1.57-1.65(2H,m),1.84-1.92(2H,m),3.60-3.69(1H,m),3.94(3H,s),4.23(1H,s),

5.30(2H,td,J＝15.81,2.87Hz),6.50(1H,d,J＝7.94Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.72(1H,d,J＝2.46Hz),7.62-7.65(1H,m),7.65(1H,d,J＝2.74Hz),8.00-8.05(2H,m);$C_{22}H_{25}F_2N_7O_2$的ESIMS实验值m/z 458.2(M+1)。也获得呈黄色固体的消除副产物(1r,4r)-4-((5-(1-((E)-2-氟乙烯基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇(672)(7mg,0.016mmol,23.3％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.51(4H,m),1.57-1.66(2H,m),1.82-1.93(2H,m),3.59-3.71(1H,m),3.94(3H,s),4.23(1H,s),6.51(1H,d,J＝7.94Hz),6.74(1H,d,J＝2.74Hz),7.34(1H,dd,J＝60.90,4.10Hz),7.45(1H,dd,J＝18.62,3.83Hz),7.65(1H,d,J＝2.46Hz),7.69(1H,d,J＝9.03Hz),7.92(1H,s),8.08(1H,d,J＝8.76Hz);$C_{22}H_{24}FN_7O_2$的ESIMS实验值m/z 438.2(M+1)。

[0904] 实施例10.

[0905] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(688)和3-((3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈(690)的制备描绘于以下方案33中。

[0906]



方案 33

[0907] 步骤1至2

[0908] 使用实施例9、方案32、步骤1至2中所述的程序,产生呈蓬松红色固体的6-(2-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-1-异丙基-1H-苯并[d][1,2,3]三唑(CLXI)(1.022g,2.982mmol,97.8％产率)。$C_{16}H_{15}ClN_6O$的ESIMS实验值m/z 343.1(M+H)。

[0909] 步骤3

[0910] 使用实施例9、方案32、步骤3中所述的程序,产生呈棕色半固体的(3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-甲酸叔丁酯(CLXIII)(184mg,0.351mmol,100.19%产率)。$C_{26}H_{33}FN_8O_3$的ESIMS实验值m/z 525.15(M+H)。

[0911] 步骤4

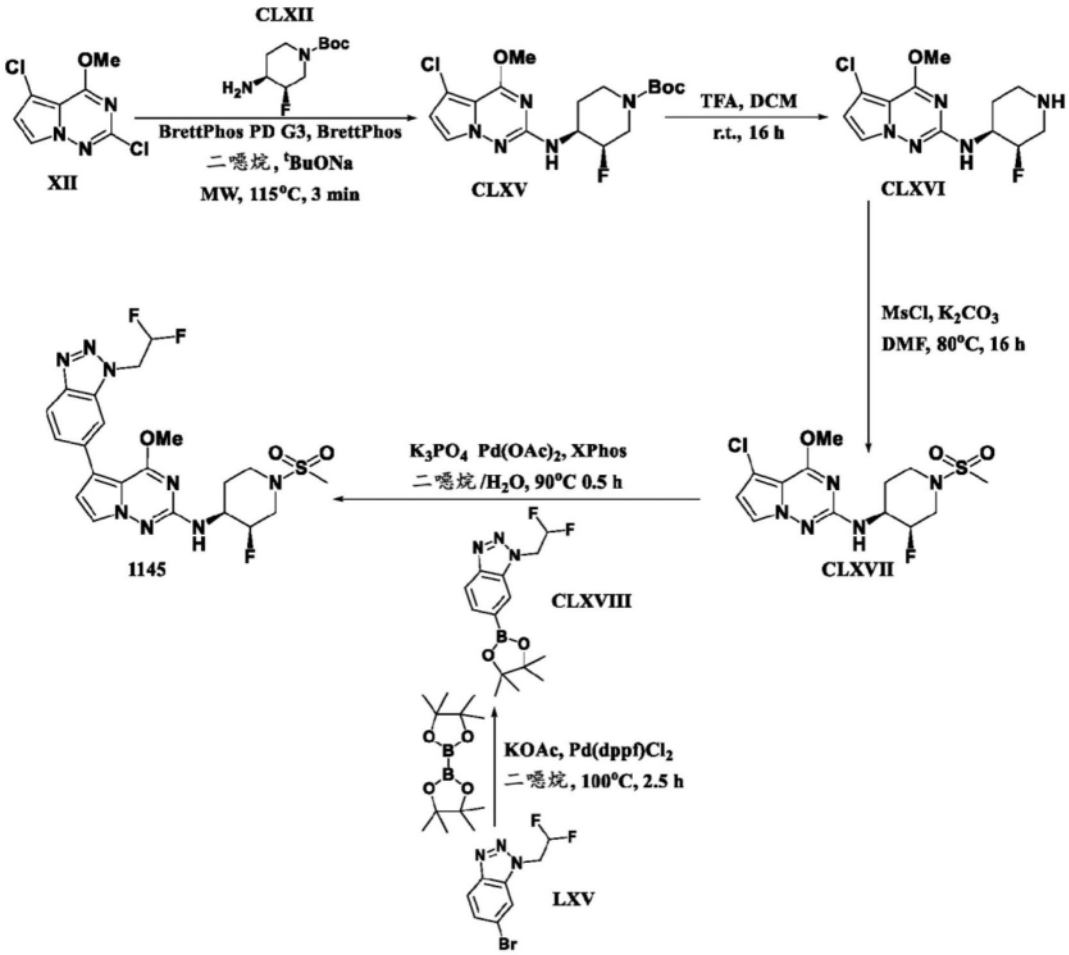
[0912] 使用实施例8、方案31、步骤2中所述的程序,产生呈棕色固体的N-((3R,4S)-3-氟哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLXIV)(148mg,0.349mmol,99.4%产率)。$C_{21}H_{25}FN_8O$的ESIMS实验值m/z 425.2(M+H)。

[0913] 步骤5a和5b

[0914] 使N-((3R,4S)-3-氟哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLXIV)(40mg,0.09mmol)悬浮于无水DCE(0.9mL)、接着EtOH(0.1mL)中以有助于溶解。添加乙酸(16μL,0.28mmol)、氧杂环丁-3-酮(CLIX)(17μL,0.29mmol)和3Å MS(5个珠粒),然后将反应物加热至65℃持续1h。将反应物冷却至室温,并且取出400μL反应混合物(留下600μL),并且添加至独立小瓶中,并将两者加热至65℃。向第一小瓶中添加$NaBH(OAc)_3$(41mg,0.19mmol)并且搅拌反应物10分钟。向第二小瓶中添加氰化三甲基硅烷(24μL,0.19mmol)并且搅拌反应物10分钟。将两个反应物分别装载于Celite®上,并通过柱色谱法(0→2%MeOH/$CHCl_3$)纯化。通过HPLC(0→50% MeCN/含0.1%甲酸的H_2O)进一步纯化化合物688。通过HPLC(0→80% MeCN/含0.1%甲酸的H_2O)进一步纯化化合物690。呈蓬松白色固体的N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(688)(11mg,0.023mmol,24.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67(6H,d,J=6.57Hz),1.70-1.77(1H,m),1.88-1.97(1H,m),1.99-2.06(1H,m),2.16(1H,dd,J=37.00,12.59Hz),2.71-2.80(1H,m),2.95-3.04(1H,m),3.49(1H,quin,J=6.37Hz),3.74-3.90(1H,m),3.96(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.43,3.01Hz),4.94(1H,d,J=49.90Hz),5.24(1H,spt,J=6.75Hz),6.69(1H,d,J=7.94Hz),6.77(1H,d,J=2.74Hz),7.59(1H,dd,J=8.76,1.37Hz),7.64(1H,d,J=2.46Hz),7.99(1H,d,J=8.76Hz),8.02(1H,s);$C_{24}H_{29}FN_8O_2$的ESIMS实验值m/z 481.25(M+1)和呈蓬松白色固体的3-((3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈(690)(10mg,0.020mmol,21.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67(6H,d,J=6.84Hz),1.82(1H,br dd,J=12.32,3.01Hz),2.00(1H,qd,J=12.37,3.70Hz),2.09-2.18(1H,m),2.26(1H,dd,J=36.20,12.32Hz),2.78-2.86(1H,m),3.00-3.11(1H,m),3.79-3.95(1H,m),3.97(3H,s),4.52(1H,d,J=6.84Hz),4.65(1H,d,J=7.12Hz),4.76(2H,t,J=6.84Hz),5.04(1H,d,J=49.35Hz),5.24(1H,spt,J=6.75Hz),6.78(1H,d,J=2.46Hz),6.81(1H,d,J=7.67Hz),7.59(1H,dd,J=8.76,1.37Hz),7.66(1H,d,J=2.46Hz),7.99(1H,d,J=8.49Hz),8.02(1H,s);$C_{25}H_{28}FN_9O_2$的ESIMS实验值m/z 506.2(M+1)。

[0915] 实施例11.

[0916] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(甲基磺酰基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(1145)的制备描绘于以下方案34中。

[0917] 

方案 34

[0918] 步骤1

[0919] 将2,5-二氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪(XII)(700mg,3.21mmol)、(3R,4S)-4-氨基-3-氟哌啶-1-甲酸叔丁酯(CLXII)(可购自Advanced ChemBlocks Inc.)(771mg,3.53mmol)、BrettPhos Pd G3(146mg,0.16mmol)、BrettPhos(86mg,0.16mmol)和^{t}BuONa(770mg,8.01mmol)装入微波小瓶中并且添加无水1,4-二噁烷(20mL)。添加3AMS(8个珠粒)并且在室温搅拌反应物1h。快速去除筛,并且密封反应物并用Ar吹扫5min,接着微波照射达到115℃持续3min。将反应混合物倒入DCM和水中并且分离有机层。用DCM(×2)萃取水层,并且将合并的有机层干燥($MgSO_4$)并真空缩减,得到呈棕色半固体的粗产物(3R,4S)-4-((5-氯-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-甲酸叔丁酯(CLXV)(1,284g,3.211mmol,100.0%产率)(假设定量产率),其不经进一步纯化即使用。$C_{17}H_{23}ClFN_5O_3$的ESIMS实验值m/z 344.10(M+H-^{t}Bu)。

[0920] 步骤2

[0921] 使用实施例8、方案31、步骤2中所述的程序,产生呈浅黄色固体的5-氯-N-((3R,4S)-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLXVI)(381mg,

1.271mmol,39.6%产率)。$C_{12}H_{15}ClFN_5O$的ESIMS实验值m/z 300.1(M+H)。

[0922] 步骤3

[0923] 使K_2CO_3(115mg,0.83mmol)和MsCl(45mg,0.39mmol)悬浮于DMF(1mL)中,并且添加5-氯-N-((3R,4S)-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLXVI)(50mg,0.17mmol),并且将反应物加热至80℃持续16h。将反应物装载于Celite®上,并通过柱色谱法(0→45% EtOAc/己烷)纯化,得到呈珠光白固体的5-氯-N-((3R,4S)-3-氟-1-(甲基磺酰基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLXVII)(13mg,0.034mmol,20.6%产率)。$C_{13}H_{17}ClFN_5O_3S$的ESIMS实验值m/z 378.1(M+H)。

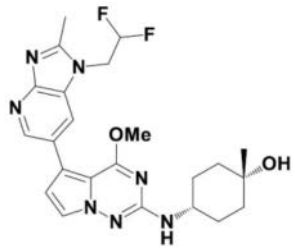
[0924] 步骤4

[0925] 使6-溴-1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑(LXV)(5.16g,19.69mmol)、双(频哪醇合)二硼(7.51g,29.57mmol)、Pd(dppf)Cl_2(803mg,0.98mmol)和KOAc(5.8g,59.1mmol)悬浮于无水1,4-二噁烷(100mL)中。将反应物声波处理并脱气5分钟,然后在100℃加热2.5h。将反应混合物装载于Celite®上,并通过柱色谱法(0→50% EtOAc/己烷)纯化,产生呈蓬松浅橙色固体的1-(2,2-二氟乙基)-6-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)-1H-苯并[d][1,2,3]三唑(CLXVIII)(5.654g,18.291mmol,92.9%产率)。$C_{14}H_{18}BF_2N_3O_2$的ESIMS实验值m/z 310.15(M+H)。

[0926] 步骤5

[0927] 使5-氯-N-((3R,4S)-3-氟-1-(甲基磺酰基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(CLXVII)(13mg,0.03mmol)、1-(2,2-二氟乙基)-6-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊-2-基)-1H-苯并[d][1,2,3]三唑(CLXVIII)(17mg,0.05mmol)、Pd(OAc)$_2$(2mg,0.01mmol)和XPhos(3mg,0.01mmol)悬浮于无水1,4-二噁烷(0.5mL)中。添加K_2PO_4(52μL,0.1mmol),并且使反应物经声波处理并用Ar鼓泡5min。然后将反应物加热至90℃持续30min。将反应混合物装载于Celite®上,并通过柱色谱法(0→1.5% MeOH/$CHCl_3$)纯化。通过HPLC(0→35% MeCN/含0.1%甲酸的H_2O)进一步纯化所述产物,得到在冻干后呈蓬松白色固体的5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(甲基磺酰基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺(1145)(6mg,0.011mmol,33.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.88(1H,m),1.96(1H,qd,J=12.50,4.38Hz),2.93(3H,s),3.02(1H,td,J=12.25,2.60Hz),3.20(1H,dd,J=37.55,12.59Hz),3.61-3.70(1H,m),3.80-3.89(1H,m),3.90-4.04(1H,m),3.96(3H,s),5.05(1H,d,J=49.10Hz),5.30(2H,td,J=15.95,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.88(1H,d,J=7.94Hz),7.63(1H,d,J=2.46Hz),7.64-7.66(1H,m),8.02-8.05(2H,m);$C_{21}H_{23}F_3N_8O_3S$的ESIMS实验值m/z 525.15(M+1)。

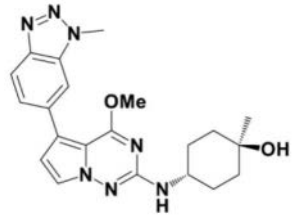
[0928] 根据以上方案1至34中所描述的程序制备以下化合物。

[0929] 

1

[0930] 顺-4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-咪唑并[4,5-b]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇1。

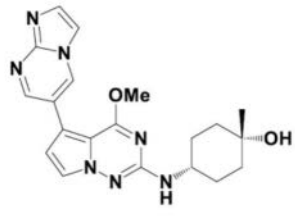
[0931] 米色固体(2.8mg,0.005mmol,2.5%产率)。^{1}H NMR(499MHz,氯仿-d)δppm 1.29(3H,s),1.58-1.68(4H,m),1.75(2H,br d,J=10.68Hz),1.99-2.06(2H,m),2.72(3H,s),3.66-3.74(1H,m),3.95(3H,s),4.50(2H,td,J=14.80,2.50Hz),6.12(1H,tt,J=54.60,3.00Hz),6.60(1H,d,J=2.46Hz),7.47(1H,d,J=2.19Hz),7.81(1H,br s),8.73(1H,br s);$C_{23}H_{27}F_2N_7O_2$的ESIMS实验值m/z 472.2(M+1)。

[0932] 

3

[0933] 反-4-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇3。

[0934] 米色固体(10mg,0.025mmol,10.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.53(4H,m),1.56-1.65(2H,m),1.84-1.93(2H,m),3.59-3.71(1H,m),3.95(3H,s),4.24(1H,s),4.31(3H,s),6.48(1H,d,J=7.94Hz),6.73(1H,d,J=2.74Hz),7.61(1H,dd,J=8.49,1.37Hz),7.64(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{21}H_{25}N_7O_2$的ESIMS实验值m/z 408.25(M+1)。

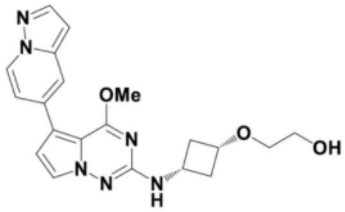
[0935] 

4

[0936] 顺-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇4。

[0937] 灰白色固体(15mg,0.038mmol,22.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.36(2H,td,J=13.00,4.11Hz),1.58(2H,br d,J=12.32Hz),1.61-1.75(4H,m),3.45-3.60(1H,m),3.97(3H,s),4.00(1H,s),6.57(1H,d,J=7.94Hz),6.76(1H,d,J=2.46Hz),7.64(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73

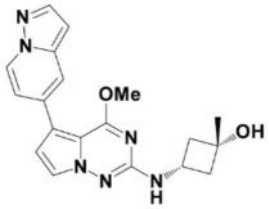
(1H,d,J＝2.46Hz),9.08(1H,d,J＝2.46Hz);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[0938] 

6

[0939] 2-(顺-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇6。

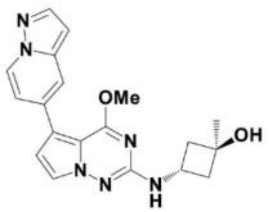
[0940] 白色固体(28mg,0.071mmol,35.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82-1.93(2H,m),2.60-2.69(2H,m),3.30-3.33(2H,m),3.48(2H,q,J＝5.48Hz),3.68-3.74(1H,m),3.74-3.81(1H,m),3.98(3H,s),4.60(1H,t,J＝5.61Hz),6.58(1H,d,J＝1.92Hz),6.77(1H,d,J＝2.46Hz),7.04(1H,d,J＝7.39Hz),7.10(1H,dd,J＝7.26,1.78Hz),7.60(1H,d,J＝2.46Hz),7.80(1H,d,J＝0.82Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.12Hz);$C_{20}H_{22}N_6O_3$的ESIMS实验值m/z 395.2(M+1)。

[0941] 

7

[0942] 顺-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇7。

[0943] 灰白色固体(53mg,0.145mmol,54.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),2.02(2H,td,J＝8.90,2.19Hz),2.31-2.41(2H,m),3.72(1H,dq,J＝15.16,7.72Hz),3.98(3H,s),4.92(1H,s),6.58(1H,d,J＝1.64Hz),6.76(1H,d,J＝2.74Hz),6.95(1H,d,J＝6.57Hz),7.10(1H,dd,J＝7.39,1.92Hz),7.63(1H,d,J＝2.74Hz),7.80(1H,d,J＝1.10Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.39Hz);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

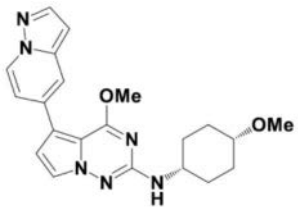
[0944] 

8

[0945] 反-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇8。

[0946] 白色固体(16mg,0.044mmol,16.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28

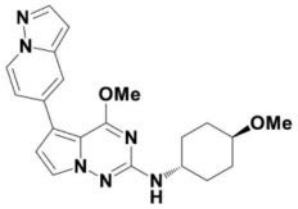
(3H,s),1.93-2.05(2H,m),2.27-2.35(2H,m),3.98(3H,s),4.25(1H,sxt,J＝7.34Hz),4.79(1H,s),6.58(1H,d,J＝1.92Hz),6.76(1H,d,J＝2.74Hz),6.95(1H,d,J＝6.57Hz),7.10(1H,dd,J＝7.12,1.92Hz),7.62(1H,d,J＝2.46Hz),7.80(1H,d,J＝0.82Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.39Hz);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

[0947] 

9

[0948] 4-甲氧基-N-(顺-4-甲氧基环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺9。

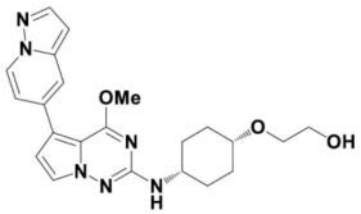
[0949] 灰白色固体(25mg,0.064mmol,31.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.54(2H,m),1.55-1.65(2H,m),1.65-1.73(2H,m),1.80-1.88(2H,m),3.22(3H,s),3.34(1H,br d,J＝2.19Hz),3.59-3.70(1H,m),3.98(3H,s),6.56-6.58(1H,m),6.58(1H,s),6.75(1H,d,J＝2.46Hz),7.10(1H,dd,J＝7.26,2.05Hz),7.61(1H,d,J＝2.74Hz),7.80(1H,d,J＝1.09Hz),7.96(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.39Hz);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[0950] 

10

[0951] 4-甲氧基-N-(反-4-甲氧基环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺10。

[0952] 灰白色固体(40mg,0.102mmol,50.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14-1.26(2H,m),1.27-1.40(2H,m),2.01(4H,br t,J＝10.81Hz),3.12(1H,tt,J＝10.23,3.73Hz),3.24(3H,s),3.51-3.63(1H,m),3.98(3H,s),6.57(1H,d,J＝7.94Hz),6.58(1H,d,J＝1.64Hz),6.75(1H,d,J＝2.46Hz),7.10(1H,dd,J＝7.39,1.92Hz),7.63(1H,d,J＝2.74Hz),7.80(1H,d,J＝0.82Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.12Hz);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

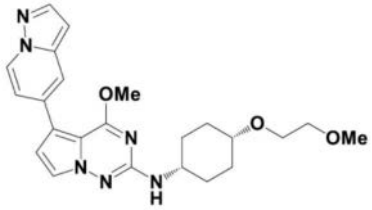
[0953] 

13

[0954] 2-((顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三

嗪-2-基)氨基)环己基)氧基)乙-1-醇13。

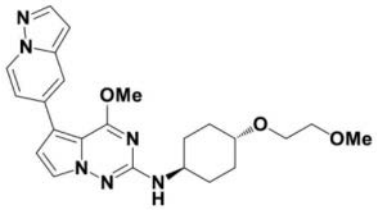
[0955] 灰白色半固体。(10mg,0.024mmol,14.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.55(2H,m),1.60-1.73(4H,m),1.78-1.88(2H,m),3.38-3.42(2H,m),3.47(1H,brs),3.50(2H,q,J=5.48Hz),3.57-3.69(1H,m),3.98(3H,s),4.51(1H,t,J=5.48Hz),6.55(1H,d,J=7.67Hz),6.58(1H,d,J=1.37Hz),6.75(1H,d,J=2.46Hz),7.10(1H,dd,J=7.39,1.64Hz),7.61(1H,d,J=2.74Hz),7.80(1H,s),7.97(1H,d,J=1.92Hz),8.62(1H,d,J=7.39Hz);$C_{22}H_{26}N_6O_3$的ESIMS实验值m/z 423.3(M+1)。

[0956] 

15

[0957] 4-甲氧基-N-(顺-4-(2-甲氧基乙氧基)环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺15。

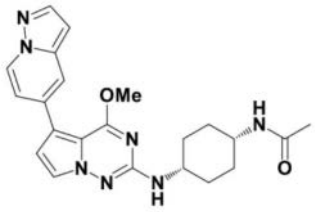
[0958] 蓬松灰白色固体(33mg,0.0756mmol,45.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.55(2H,m),1.59-1.73(4H,m),1.78-1.88(2H,m),3.27(3H,s),3.43-3.46(2H,m),3.46-3.48(1H,m),3.48-3.52(2H,m),3.57-3.69(1H,m),3.98(3H,s),6.58(1H,d,J=2.19Hz),6.59(1H,d,J=7.85Hz),6.75(1H,d,J=2.46Hz),7.10(1H,dd,J=7.39,1.92Hz),7.61(1H,d,J=2.74Hz),7.80(1H,d,J=0.82Hz),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{23}H_{28}N_6O_3$的ESIMS实验值m/z 437.25(M+1)。

[0959] 

16

[0960] 4-甲氧基-N-(反-4-(2-甲氧基乙氧基)环己基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺16。

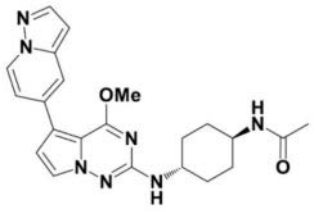
[0961] 白色固体(31mg,0.071mmol,35.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.18-1.37(4H,m),2.00(4H,br d,J=10.95Hz),3.20-3.27(1H,m),3.25(3H,s),3.40-3.45(2H,m),3.53(2H,t,J=4.93Hz),3.54-3.60(1H,m),3.97(3H,s),6.56(1H,d,J=8.21Hz),6.58(1H,d,J=1.64Hz),6.75(1H,d,J=2.46Hz),7.10(1H,dd,J=7.39,1.64Hz),7.63(1H,d,J=2.74Hz),7.80(1H,s),7.96(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{23}H_{28}N_6O_3$的ESIMS实验值m/z 437.2(M+1)。

[0962] 

17

[0963] N-(顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺17。

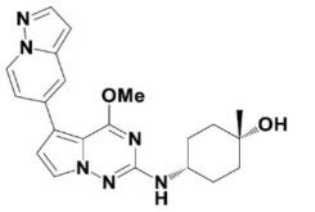
[0964] 白色固体(22mg,0.052mmol,33.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.50-1.59(2H,m),1.60-1.72(4H,m),1.74-1.81(2H,m),1.81(3H,s),3.64-3.71(2H,m),3.99(3H,s),6.47(1H,d,J=6.30Hz),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),7.11(1H,dd,J=7.26,1.78Hz),7.63(1H,d,J=2.74Hz),7.70(1H,br d,J=6.84Hz),7.81(1H,s),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

[0965] 

18

[0966] N-(反-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺18。

[0967] 白色固体(2mg,0.005mmol,2.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.19-1.29(2H,m),1.30-1.40(2H,m),1.78(3H,s),1.81(2H,br d,J=11.50Hz),1.99(2H,br d,J=10.13Hz),3.45-3.51(1H,m),3.52-3.59(1H,m),3.97(3H,s),6.56(1H,d,J=8.21Hz),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),7.10(1H,dd,J=7.26,2.05Hz),7.63(1H,d,J=2.46Hz),7.74(1H,d,J=7.67Hz),7.80(1H,d,J=1.09Hz),7.97(1H,d,J=2.46Hz),8.62(1H,d,J=7.39Hz);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

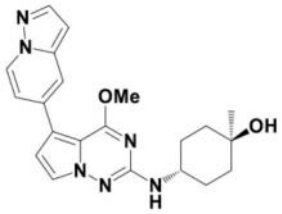
[0968] 

19

[0969] 顺-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇19。

[0970] 灰白色固体(20mg,0.051mmol,42.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.36(2H,td,J=13.00,4.38Hz),1.58(2H,br d,J=12.05Hz),1.61-1.68(2H,m),1.69-1.75(2H,m),3.45-3.59(1H,m),3.98(3H,s),3.99(1H,s),6.52(1H,d,J=7.94Hz),

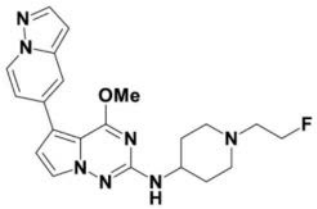
6.58(1H,d,J＝1.64Hz),6.74(1H,d,J＝2.74Hz),7.10(1H,dd,J＝7.12,1.92Hz),7.60(1H,d,J＝2.74Hz),7.80(1H,d,J＝1.09Hz),7.96(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.39Hz);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[0971] 

20

[0972] 反-4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇20。

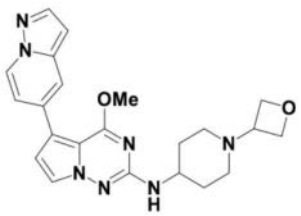
[0973] 米色固体(5mg,0.013mmol,8.3%产率)。^{1}H NMR(499MHz,氯仿-d)δppm 1.32(3H,s),1.47-1.58(2H,m),1.60-1.68(2H,m),1.71-1.79(2H,m),2.09-2.18(2H,m),3.86(1H,br d,J＝3.83Hz),4.01(3H,s),4.12(1H,s),6.53(1H,br s),6.64(1H,d,J＝2.46Hz),7.04(1H,br d,J＝5.75Hz),7.47(1H,d,J＝2.46Hz),7.71(1H,br s),7.96(1H,br s),8.50(1H,br d,J＝6.57Hz);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[0974] 

24

[0975] N-(1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺24。

[0976] 灰白色固体(17mg,0.042mmol,20.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.46-1.60(2H,m),1.85-1.96(2H,m),2.11(2H,br t,J＝11.09Hz),2.61(2H,dt,J＝28.25,4.95Hz),2.84-2.93(2H,m),3.53-3.66(1H,m),3.98(3H,s),4.53(2H,dt,J＝47.70,4.95Hz),6.58(1H,d,J＝1.64Hz),6.62(1H,d,J＝7.94Hz),6.76(1H,d,J＝2.74Hz),7.10(1H,dd,J＝7.39,1.92Hz),7.62(1H,d,J＝2.46Hz),7.81(1H,d,J＝1.10Hz),7.97(1H,d,J＝2.46Hz),8.62(1H,d,J＝7.39Hz);$C_{21}H_{24}FN_7O$的ESIMS实验值m/z 410.2(M+1)。

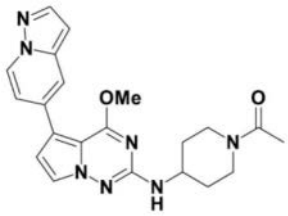
[0977] 

26

[0978] 4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺26。

[0979] 灰白色固体(2mg,0.005mmol,1.2%产率)。^{1}H NMR(499MHz,METHANOL-d_4)δppm

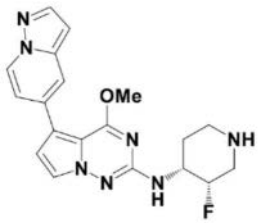
1.57-1.70(2H,m),2.06(2H,br t,J＝11.77Hz),2.09-2.15(2H,m),2.80(2H,br d,J＝11.77Hz),3.53(1H,quin,J＝6.43Hz),3.67-3.77(1H,m),4.03(3H,s),4.62(2H,t,J＝6.30Hz),4.69-4.75(2H,m),6.54-6.61(1H,m),6.70(1H,d,J＝2.46Hz),7.14(1H,dd,J＝7.39,1.92Hz),7.47(1H,d,J＝2.46Hz),7.79(1H,d,J＝1.10Hz),7.92(1H,d,J＝2.19Hz),8.46(1H,d,J＝7.12Hz);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

[0980] 

27

[0981] 1-(4-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮27。

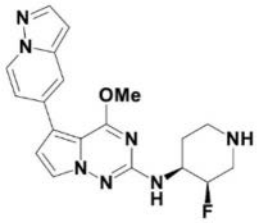
[0982] 米色固体(11mg,0.027mmol,13.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27-1.39(1H,m),1.40-1.52(1H,m),1.87-1.94(1H,m),1.94-2.00(1H,m),2.01(3H,s),2.70-2.81(1H,m),3.12-3.19(1H,m),3.78-3.87(2H,m),3.99(3H,s),4.24-4.34(1H,m),6.59(1H,dd,J＝2.19,0.82Hz),6.73(1H,d,J＝7.94Hz),6.77(1H,d,J＝2.74Hz),7.11(1H,dd,J＝7.12,1.92Hz),7.63(1H,d,J＝2.74Hz),7.81(1H,d,J＝1.10Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.12Hz);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

[0983] 

29

[0984] N-((3S,4R)-3-氟哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺29。

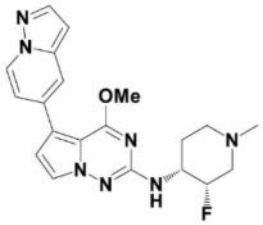
[0985] 灰白色固体(45mg,0.118mmol,87.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.57-1.65(1H,m),1.73(1H,qd,J＝12.37,4.24Hz),2.56(1H,br t,J＝12.46Hz),2.71(1H,dd,J＝39.25,14.30Hz),2.96(1H,br d,J＝13.14Hz),3.13(1H,br t,J＝11.50Hz),3.77-3.94(1H,m),4.00(3H,s),4.80(1H,d,J＝50.75Hz),6.59(1H,d,J＝1.64Hz),6.64(1H,d,J＝7.94Hz),6.78(1H,d,J＝2.74Hz),7.11(1H,dd,J＝7.39,1.92Hz),7.63(1H,d,J＝2.46Hz),7.81(1H,d,J＝1.10Hz),7.97(1H,d,J＝2.19Hz),8.63(1H,d,J＝7.12Hz);$C_{19}H_{20}FN_7O$的ESIMS实验值m/z 382.2(M+1)。

[0986] 

30

[0987] N-((3R,4S)-3-氟哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺30。

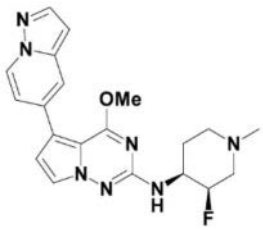
[0988] 棕色固体(109mg,0.286mmol,99.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.89-1.96(1H,m),2.07(1H,qd,J=13.23,4.11Hz),2.75(1H,s),3.11-3.18(1H,m),3.27-3.38(1H,m),3.58-3.66(1H,m),4.01(3H,s),4.05-4.18(1H,m),5.20(1H,d,J=47.45Hz),6.60(1H,d,J=1.92Hz),6.81(1H,d,J=2.46Hz),7.06(1H,d,J=7.39Hz),7.11(1H,dd,J=7.12,1.92Hz),7.59(1H,d,J=2.74Hz),7.82(1H,d,J=1.37Hz),7.98(1H,d,J=2.19Hz),8.64(1H,br d,J=7.39Hz);$C_{19}H_{20}FN_7O$的ESIMS实验值m/z 382.2(M+1)。

[0989] 

31

[0990] N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺31。

[0991] 灰白色固体(30mg,0.076mmol,72.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68(1H,br dd,J=12.59,3.01Hz),1.92(1H,qd,J=12.23,3.56Hz),2.01-2.09(1H,m),2.17(1H,dd,J=37.55,13.20Hz),2.19(3H,s),2.79(1H,br d,J=11.23Hz),3.00-3.09(1H,m),3.67-3.83(1H,m),4.00(3H,s),4.91(1H,d,J=50.20Hz),6.59(1H,d,J=1.64Hz),6.64(1H,d,J=7.67Hz),6.78(1H,d,J=2.74Hz),7.11(1H,dd,J=7.12,1.92Hz),7.63(1H,d,J=2.74Hz),7.81(1H,d,J=0.82Hz),7.97(1H,d,J=2.19Hz),8.63(1H,d,J=7.39Hz);$C_{20}H_{22}FN_7O$的ESIMS实验值m/z396.2(M+1)。

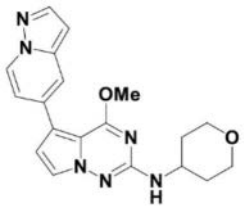
[0992] 

34

[0993] N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺34。

[0994] 灰白色固体(43mg,0.109mmol,38.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.65-

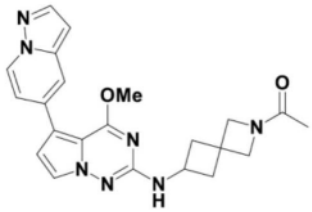
1.72(1H,m),1.92(1H,qd,J＝12.27,3.70Hz),2.01-2.09(1H,m),2.17(1H,dd,J＝37.55,13.20Hz),2.19(3H,s),2.80(1H,br d,J＝11.77Hz),3.01-3.07(1H,m),3.67-3.83(1H,m),4.00(3H,s),4.91(1H,d,J＝49.90Hz),6.59(1H,d,J＝1.37Hz),6.65(1H,d,J＝7.67Hz),6.78(1H,d,J＝2.74Hz),7.11(1H,dd,J＝7.26,2.05Hz),7.63(1H,d,J＝2.74Hz),7.81(1H,d,J＝1.10Hz),7.97(1H,d,J＝2.19Hz),8.63(1H,d,J＝7.12Hz);$C_{20}H_{22}FN_7O$的ESIMS实验值m/z 396.3(M+1)。

[0995] 

36

[0996] 4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺36。

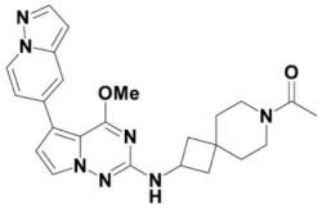
[0997] 灰白色固体(8mg,0.022mmol,6.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.47-1.60(2H,m),1.89(2H,br dd,J＝12.46,2.05Hz),3.36-3.45(2H,m),3.73-3.85(1H,m),3.85-3.92(2H,m),3.99(3H,s),6.58(1H,d,J＝1.92Hz),6.71(1H,d,J＝7.94Hz),6.76(1H,d,J＝2.46Hz),7.10(1H,dd,J＝7.26,1.78Hz),7.63(1H,d,J＝2.74Hz),7.81(1H,d,J＝0.82Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.12Hz);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

[0998] 

37

[0999] 1-(6-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-基)乙-1-酮37。

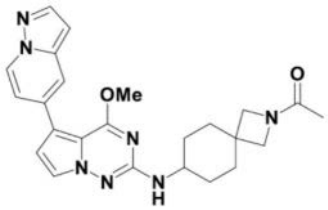
[1000] 白色固体(28mg,0.067mmol,38.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69-1.76(3H,m),2.13-2.25(2H,m),2.52-2.60(2H,m),3.77(1H,s),3.89(1H,s),3.98(3H,s),4.04-4.11(1H,m),4.05(1H,s),4.17(1H,s),6.58(1H,d,J＝1.92Hz),6.77(1H,d,J＝2.46Hz),7.03(1H,t,J＝6.98Hz),7.10(1H,dd,J＝7.39,1.92Hz),7.62(1H,dd,J＝4.79,2.60Hz),7.80(1H,d,J＝0.82Hz),7.97(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.39Hz);$C_{22}H_{23}N_7O_2$的ESIMS实验值m/z 418.2(M+1)。

[1001] 

39

[1002] 1-(2-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮39。

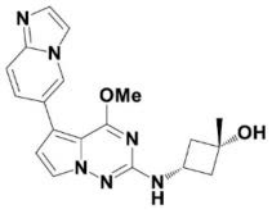
[1003] 灰白色固体(50mg,0.112mmol,79.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.40-1.46(1H,m),1.49-1.56(2H,m),1.57-1.64(1H,m),1.74-1.84(2H,m),1.95-2.01(3H,m),2.26(2H,br dd,J=9.86,8.21Hz),3.26-3.30(1H,m),3.30-3.32(1H,m),3.35-3.39(1H,m),3.39-3.44(1H,m),3.98(3H,s),4.14-4.25(1H,m),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),7.02(1H,t,J=7.12Hz),7.10(1H,dd,J=7.12,1.92Hz),7.59-7.66(1H,m),7.80(1H,d,J=1.09Hz),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.39Hz);$C_{24}H_{27}N_7O_2$的ESIMS实验值m/z 446.2(M+1)。

[1004] 

40

[1005] 1-(7-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮40。

[1006] 灰白色固体(75mg,0.168mmol,95.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.26-1.39(2H,m),1.48-1.60(2H,m),1.73-1.78(3H,m),1.83-1.93(4H,m),3.47(1H,s),3.52(1H,s),3.57(1H,br dd,J=7.53,3.15Hz),3.74(1H,s),3.80(1H,s),3.98(3H,d,J=1.10Hz),6.54(1H,dd,J=16.15,7.94Hz),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),7.10(1H,dd,J=7.39,1.92Hz),7.62(1H,t,J=2.87Hz),7.80(1H,d,J=1.09Hz),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.39Hz);$C_{24}H_{27}N_7O_2$的ESIMS实验值m/z 446.2(M+1)。

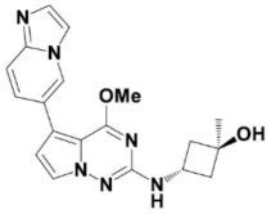
[1007] 

43

[1008] 顺-3-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇43。

[1009] 白色固体(19mg,0.052mmol,31.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27

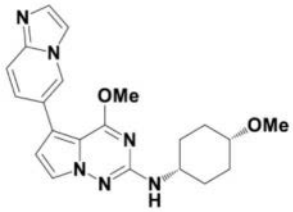
(3H,s),1.96-2.07(2H,m),2.31-2.41(2H,m),3.71(1H,dq,J＝15.16,7.72Hz),3.96(3H,s),4.91(1H,s),6.67(1H,d,J＝2.74Hz),6.92(1H,d,J＝6.84Hz),7.43(1H,dd,J＝9.31,1.64Hz),7.54(1H,d,J＝9.31Hz),7.56(1H,d,J＝0.82Hz),7.62(1H,d,J＝2.46Hz),7.95(1H,s),8.68(1H,s);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

[1010] 

44

[1011] 反-3-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇44。

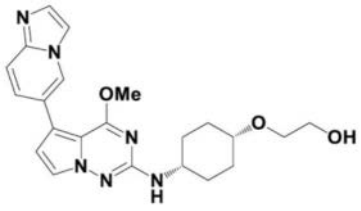
[1012] 灰白色半固体(10mg,0.027mmol,16.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28(3H,s),1.94-2.03(2H,m),2.28-2.35(2H,m),3.96(3H,s),4.25(1H,sxt,J＝7.39Hz),4.78(1H,br s),6.68(1H,d,J＝2.74Hz),6.93(1H,d,J＝6.84Hz),7.43(1H,dd,J＝9.31,1.64Hz),7.54(1H,d,J＝9.58Hz),7.56(1H,s),7.61(1H,d,J＝2.74Hz),7.95(1H,s),8.68(1H,s);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

[1013] 

45

[1014] 5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(顺-4-甲氧基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺45。

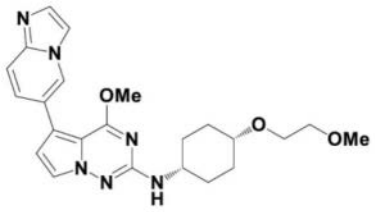
[1015] 灰白色固体(2.6mg,0.007mmol,4.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.54(2H,m),1.55-1.65(2H,m),1.69(2H,dt,J＝8.35,4.04Hz),1.80-1.88(2H,m),3.22(3H,s),3.29-3.37(1H,m),3.56-3.71(1H,m),3.96(3H,s),6.54(1H,d,J＝7.67Hz),6.67(1H,d,J＝2.46Hz),7.43(1H,dd,J＝9.31,1.37Hz),7.54(1H,d,J＝9.31Hz),7.56(1H,s),7.61(1H,d,J＝2.46Hz),7.95(1H,s),8.68(1H,s);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[1016] 

49

[1017] 2-((顺-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇49。

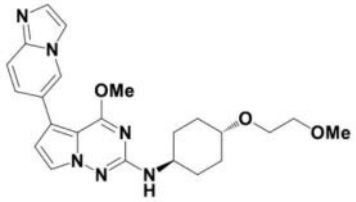
[1018] 橙色半固体。(6mg,0.014mmol,6.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.56(2H,m),1.60-1.74(4H,m),1.78-1.88(2H,m),3.38-3.42(2H,m),3.47(1H,br s),3.50(2H,q,J=5.20Hz),3.58-3.70(1H,m),3.96(3H,s),4.51(1H,br t,J=5.34Hz),6.52(1H,d,J=7.67Hz),6.67(1H,d,J=2.46Hz),7.47(1H,br d,J=9.03Hz),7.56(1H,br d,J=9.03Hz),7.58-7.60(1H,m),7.61(1H,d,J=2.46Hz),7.98(1H,br s),8.70(1H,br s);$C_{22}H_{26}N_6O_3$的ESIMS实验值m/z 423.25(M+1)。

[1019] 

51

[1020] 5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(顺-4-(2-甲氧基乙氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺51。

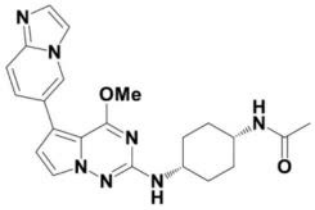
[1021] 白色固体(3mg,0.007mmol,4.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.44-1.56(2H,m),1.58-1.74(4H,m),1.77-1.88(2H,m),3.27(3H,s),3.43-3.46(2H,m),3.47(1H,br s),3.48-3.52(2H,m),3.62(1H,ddt,J=12.53,8.56,4.52,4.52Hz),3.96(3H,s),6.56(1H,d,J=7.67Hz),6.67(1H,d,J=2.46Hz),7.43(1H,dd,J=9.45,1.78Hz),7.54(1H,d,J=9.31Hz),7.56(1H,d,J=1.09Hz),7.61(1H,d,J=2.74Hz),7.95(1H,s),8.68(1H,d,J=1.64Hz);$C_{23}H_{28}N_6O_3$的ESIMS实验值m/z 437.2(M+1)。

[1022] 

52

[1023] 5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(反-4-(2-甲氧基乙氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺52。

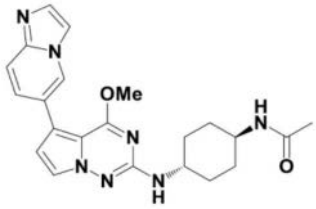
[1024] 白色固体(5mg,0.012mmol,5.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.18-1.26(2H,m),1.27-1.36(2H,m),2.00(4H,br d,J=10.95Hz),3.20-3.26(1H,m),3.25(3H,s),3.42(2H,dd,J=5.75,3.83Hz),3.53(2H,dd,J=5.75,3.83Hz),3.55-3.60(1H,m),3.95(3H,s),6.52(1H,d,J=7.94Hz),6.67(1H,d,J=2.46Hz),7.43(1H,dd,J=9.45,1.78Hz),7.54(1H,d,J=9.31Hz),7.56(1H,d,J=1.09Hz),7.63(1H,d,J=2.46Hz),7.95(1H,s),8.64-8.70(1H,m);$C_{23}H_{28}N_6O_3$的ESIMS实验值m/z 437.2(M+1)。

[1025] 

53

[1026] N-(顺-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺53。

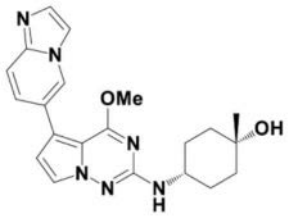
[1027] 灰白色固体(8mg,0.019mmol,37.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.50-1.59(2H,m),1.60-1.71(4H,m),1.73-1.81(2H,m),1.81(3H,s),3.67(2H,br d,J=3.56Hz),3.97(3H,s),6.43(1H,d,J=6.30Hz),6.68(1H,d,J=2.74Hz),7.44(1H,dd,J=9.31,1.64Hz),7.54(1H,d,J=9.31Hz),7.57(1H,s),7.62(1H,d,J=2.46Hz),7.70(1H,br d,J=7.12Hz),7.95(1H,s),8.68(1H,s);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

[1028] 

54

[1029] N-(反-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺54。

[1030] 灰白色固体(17mg,0.041mmol,24.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.19-1.29(2H,m),1.29-1.39(2H,m),1.78(3H,s),1.79-1.85(2H,m),1.99(2H,br d,J=10.95Hz),3.44-3.59(2H,m),3.95(3H,s),6.53(1H,d,J=8.21Hz),6.67(1H,d,J=2.46Hz),7.43(1H,dd,J=9.45,1.51Hz),7.54(1H,d,J=9.31Hz),7.56(1H,s),7.63(1H,d,J=2.46Hz),7.74(1H,d,J=7.67Hz),7.95(1H,s),8.68(1H,s);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

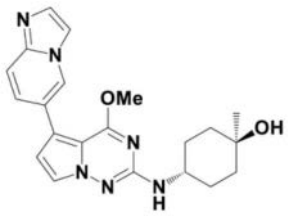
[1031] 

55

[1032] 顺-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇55。

[1033] 灰白色固体(7.9mg,0.020mmol,14.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.36(2H,td,J=13.00,4.11Hz),1.58(2H,br d,J=12.32Hz),1.60-1.68(2H,m),1.68-1.74(2H,m),3.45-3.57(1H,m),3.96(3H,s),4.00(1H,s),6.49(1H,d,J=7.94Hz),6.66(1H,d,J=2.46Hz),7.43(1H,dd,J=9.58,1.64Hz),7.54(1H,d,J=9.31Hz),7.56(1H,

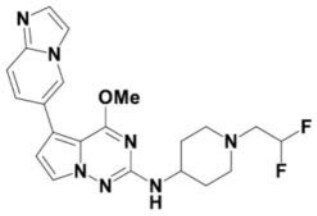
d,J＝0.82Hz),7.60(1H,d,J＝2.74Hz),7.95(1H,s),8.68(1H,s);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[1034] 

56

[1035] 反-4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇56。

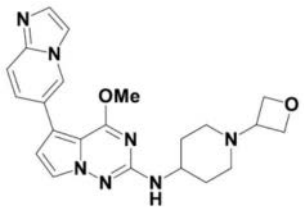
[1036] 米色固体(16mg,0.041mmol,20.4％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.37-1.52(4H,m),1.56-1.64(2H,m),1.81-1.93(2H,m),3.57-3.70(1H,m),3.96(3H,s),4.24(1H,s),6.47(1H,d,J＝7.94Hz),6.67(1H,d,J＝2.46Hz),7.43(1H,dd,J＝9.31,1.64Hz),7.54(1H,d,J＝9.31Hz),7.56(1H,s),7.62(1H,d,J＝2.46Hz),7.95(1H,s),8.68(1H,s);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[1037] 

61

[1038] N-(1-(2,2-二氟乙基)哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺61。

[1039] 白色固体(5mg,0.012mmol,5.8％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.48-1.62(2H,m),1.89(2H,br d,J＝10.95Hz),2.22-2.31(2H,m),2.72(2H,td,J＝15.74,4.38Hz),2.90(2H,br d,J＝11.77Hz),3.53-3.65(1H,m),3.96(3H,s),6.13(1H,tt,J＝55.95,4.40Hz),6.59(1H,d,J＝7.94Hz),6.68(1H,d,J＝2.74Hz),7.43(1H,dd,J＝9.45,1.78Hz),7.54(1H,d,J＝9.58Hz),7.56(1H,d,J＝0.82Hz),7.62(1H,d,J＝2.74Hz),7.95(1H,s),8.65-8.70(1H,m);$C_{21}H_{23}F_2N_7O$的ESIMS实验值m/z 428.2(M+1)。

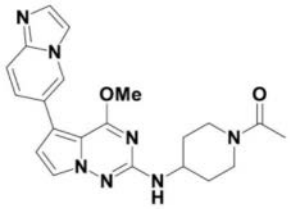
[1040] 

62

[1041] 5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺62。

[1042] 无色半固体。(10mg,0.024mmol,14.3％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.48-1.61(2H,m),1.84-1.98(4H,m),2.71(2H,br d,J＝11.22Hz),3.41(1H,br s),3.54-

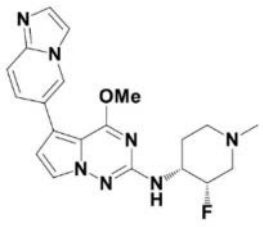
3.65(1H,m),3.96(3H,s),4.43(2H,t,J＝6.16Hz),4.54(2H,t,J＝6.57Hz),6.63(1H,d,J＝7.94Hz),6.68(1H,d,J＝2.46Hz),7.44(1H,dd,J＝9.31,1.37Hz),7.55(1H,br d,J＝9.31Hz),7.57(1H,br s),7.62(1H,d,J＝2.46Hz),7.96(1H,s),8.68(1H,s);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

[1043] 

63

[1044] 1-(4-((5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮63。

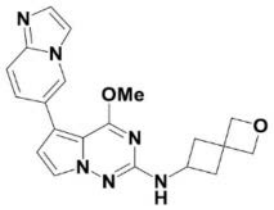
[1045] 米色固体(9mg,0.022mmol,13.3％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.29-1.38(1H,m),1.39-1.50(1H,m),1.88-1.95(1H,m),1.97(1H,br d,J＝13.14Hz),2.01(3H,s),2.69-2.82(1H,m),3.11-3.20(1H,m),3.77-3.87(2H,m),3.97(3H,s),4.28(1H,br d,J＝12.59Hz),6.68-6.72(2H,m),7.47(1H,d,J＝9.31Hz),7.56(1H,d,J＝9.31Hz),7.59(1H,s),7.63(1H,d,J＝2.46Hz),7.97(1H,s),8.70(1H,s);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

[1046] 

67

[1047] N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺67。

[1048] 白色固体(5.5mg,0.014mmol,10.6％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.63-1.74(1H,m),1.92(1H,qd,J＝12.27,3.70Hz),2.06(1H,br t,J＝11.09Hz),2.11-2.24(1H,m),2.19(3H,s),2.80(1H,br d,J＝10.95Hz),3.00-3.07(1H,m),3.66-3.83(1H,m),3.98(3H,s),4.91(1H,d,J＝49.90Hz),6.61(1H,d,J＝7.94Hz),6.70(1H,d,J＝2.74Hz),7.44(1H,dd,J＝9.45,1.78Hz),7.55(1H,d,J＝9.31Hz),7.57(1H,s),7.62(1H,d,J＝2.46Hz),7.95(1H,s),8.69(1H,s);$C_{20}H_{22}FN_7O$的ESIMS实验值m/z 396.2(M+1)。

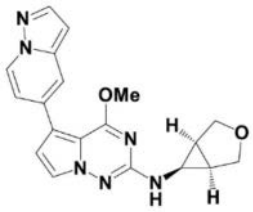
[1049] 

74

[1050] 5-(咪唑并[1,2-a]吡啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并

[2,1-f][1,2,4]三嗪-2-胺74。

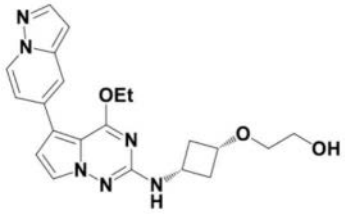
[1051] 白色固体(4.0mg,0.011mmol,4.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.12-2.23(2H,m),2.61(2H,ddd,J=9.86,7.53,2.87Hz),3.95-4.04(1H,m),3.97(3H,s),4.51(2H,s),4.63(2H,s),6.58(1H,d,J=1.92Hz),6.76(1H,d,J=2.46Hz),7.00(1H,d,J=7.12Hz),7.10(1H,dd,J=7.26,1.78Hz),7.61(1H,d,J=2.74Hz),7.80(1H,s),7.97(1H,d,J=1.92Hz),8.62(1H,d,J=7.39Hz);$C_{20}H_{20}N_6O_2$的ESIMS实验值m/z 377.2(M+1)。

[1052] 

80

[1053] N-((1R,5S,6s)-3-氧杂双环[3.1.0]己烷-6-基)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺80。

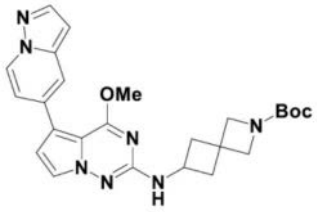
[1054] 灰白色固体(16mg,0.044mmol,13.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.95-2.04(2H,m),2.86(1H,td,J=6.78,3.15Hz),3.81-3.88(4H,m),4.00(3H,s),6.39(1H,d,J=3.01Hz),6.59(1H,d,J=1.64Hz),6.78(1H,d,J=2.74Hz),7.11(1H,dd,J=7.39,1.92Hz),7.65(1H,d,J=2.46Hz),7.82(1H,d,J=0.82Hz),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{19}H_{18}N_6O_2$的ESIMS实验值m/z 363.2(M+1)。

[1055] 

91

[1056] 2-(顺-3-((4-乙氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇91。

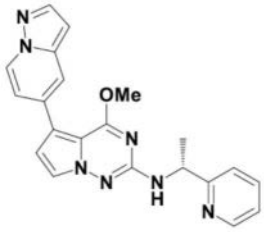
[1057] 灰白色固体(4mg,0.010mmol,4.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.33(3H,t,J=7.12Hz),1.87(2H,qd,J=8.53,2.87Hz),2.58-2.68(2H,m),3.30-3.33(2H,m),3.48(2H,q,J=5.20Hz),3.68-3.73(1H,m),3.74-3.81(1H,m),4.47(2H,q,J=7.12Hz),4.60(1H,t,J=5.48Hz),6.57(1H,d,J=1.37Hz),6.78(1H,d,J=2.46Hz),6.98(1H,d,J=7.39Hz),7.13(1H,dd,J=7.26,1.78Hz),7.59(1H,d,J=2.46Hz),7.86(1H,s),7.96(1H,d,J=2.19Hz),8.63(1H,d,J=7.39Hz);$C_{21}H_{24}N_6O_3$的ESIMS实验值m/z 409.2(M+1)。

[1058] 

92

[1059] 6-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-甲酸叔丁酯92。

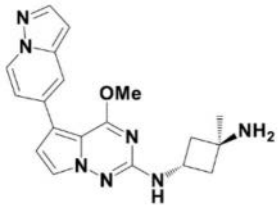
[1060] 灰白色固体(103mg,0.217mmol,64.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.37(9H,s),2.11-2.21(2H,m),2.51-2.57(2H,m),3.79(2H,br s),3.91(2H,br s),3.97(3H,s),4.01-4.09(1H,m),6.58(1H,d,J=1.64Hz),6.77(1H,d,J=2.74Hz),7.01(1H,d,J=7.12Hz),7.10(1H,dd,J=7.39,1.92Hz),7.62(1H,d,J=2.74Hz),7.80(1H,d,J=1.10Hz),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{25}H_{29}N_7O_3$的ESIMS实验值m/z 476.2(M+1)。

[1061] 

93

[1062] (R)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(1-(吡啶-2-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺93。

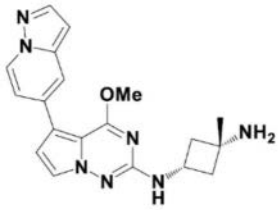
[1063] 米色固体(18mg,0.047mmol,17.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.49(3H,d,J=7.12Hz),3.98(3H,s),5.00(1H,quin,J=7.19Hz),6.58(1H,d,J=2.19Hz),6.74(1H,d,J=2.74Hz),7.09(1H,dd,J=7.12,1.92Hz),7.19(1H,d,J=7.94Hz),7.23(1H,ddd,J=7.46,4.86,0.82Hz),7.46(1H,d,J=7.94Hz),7.55(1H,d,J=2.74Hz),7.74(1H,td,J=7.67,1.64Hz),7.79(1H,d,J=1.10Hz),7.96(1H,d,J=2.19Hz),8.48-8.56(1H,m),8.61(1H,d,J=7.12Hz);$C_{21}H_{19}N_7O$的ESIMS实验值m/z 386.2(M+1)。

[1064] 

94

[1065] 反-N^1-(4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺94。

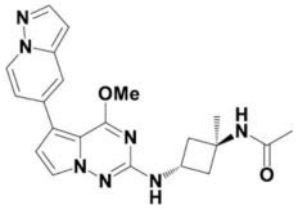
[1066] 灰白色固体(67mg,0.184mmol,85.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.22(3H,s),1.82(2H,br s),1.89-1.97(2H,m),2.12-2.22(2H,m),3.98(3H,s),4.27(1H,sxt,J=7.56Hz),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),6.92(1H,d,J=7.12Hz),7.10(1H,dd,J=7.39,1.92Hz),7.61(1H,d,J=2.74Hz),7.80(1H,d,J=1.09Hz),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.39Hz);$C_{19}H_{21}N_7O$的ESIMS实验值m/z 364.2(M+1)。

[1067] 

95

[1068] 顺-N^1-(4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺95。

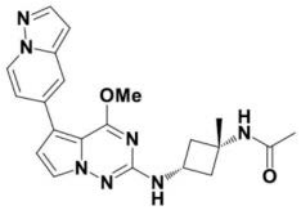
[1069] 灰白色泡沫(157mg,0.432mmol,69.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.19(3H,s),1.76(2H,br s),1.86(2H,td,J=8.90,2.46Hz),2.33(2H,ddd,J=9.03,7.53,2.60Hz),3.85(1H,dq,J=15.50,7.79Hz),3.97(3H,s),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.46Hz),6.81(1H,d,J=7.12Hz),7.10(1H,dd,J=7.12,1.92Hz),7.63(1H,d,J=2.74Hz),7.80(1H,d,J=1.10Hz),7.96(1H,d,J=2.19Hz),8.62(1H,d,J=7.12Hz);$C_{19}H_{21}N_7O$的ESIMS实验值m/z 364.2(M+1)。

[1070] 

96

[1071] N-(反-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺96。

[1072] 灰白色固体(34mg,0.084mmol,45.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.81(3H,s),1.92-1.98(2H,m),2.63(2H,ddd,J=10.27,7.80,2.74Hz),3.98(3H,s),4.19(1H,sxt,J=7.78Hz),6.58(1H,d,J=1.64Hz),6.76(1H,d,J=2.74Hz),7.01(1H,d,J=7.12Hz),7.10(1H,dd,J=7.26,2.05Hz),7.61(1H,d,J=2.74Hz),7.80(1H,d,J=1.10Hz),7.93(1H,s),7.97(1H,d,J=2.19Hz),8.62(1H,d,J=7.39Hz);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

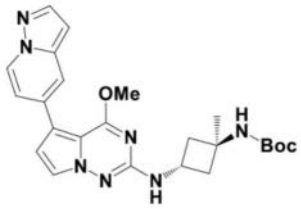
[1073] 

97

[1074] N-(顺-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺97。

[1075] 灰白色固体(27mg,0.067mmol,96.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.10-2.21(2H,m),2.42(2H,ddd,J=9.65,7.46,2.60Hz),3.98(3H,s),3.99-4.07(1H,m),6.58(1H,d,J=1.92Hz),6.76(1H,d,J=2.74Hz),7.00(1H,d,J=

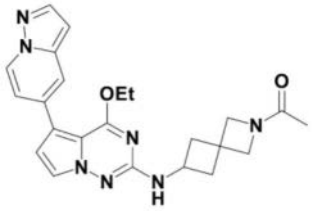
6.84Hz),7.10(1H,dd,J=7.26,2.05Hz),7.63(1H,d,J=2.46Hz),7.80(1H,d,J=1.09Hz),7.97(1H,d,J=2.19Hz),8.02(1H,s),8.62(1H,d,J=7.39Hz);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

[1076] 

98

[1077] (反-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)氨基甲酸叔丁酯98。

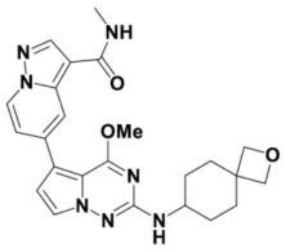
[1078] 灰白色固体(107mg,0.231mmol,46.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.33(3H,s),1.41(9H,s),1.86-1.96(2H,m),2.56-2.67(2H,m),3.97(3H,s),4.17(1H,sxt,J=7.83Hz),6.58(1H,d,J=1.37Hz),6.76(1H,d,J=2.74Hz),7.00(2H,d,J=7.39Hz),7.10(1H,dd,J=7.39,1.92Hz),7.63(1H,d,J=2.46Hz),7.80(1H,d,J=1.09Hz),7.97(1H,d,J=2.46Hz),8.62(1H,d,J=7.39Hz);$C_{24}H_{29}N_7O_3$的ESIMS实验值m/z 464.2(M+1)。

[1079] 

99

[1080] 1-(6-((4-乙氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.3]庚烷-2-基)乙-1-酮99。

[1081] 白色固体(5mg,0.012mmol,6.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.33(3H,t,J=7.12Hz),1.69-1.77(3H,m),2.13-2.25(2H,m),2.51-2.60(2H,m),3.77(1H,s),3.89(1H,s),4.05(1H,s),4.05-4.10(1H,m),4.17(1H,s),4.46(2H,q,J=7.12Hz),6.57(1H,d,J=1.92Hz),6.78(1H,d,J=2.46Hz),6.98(1H,t,J=6.57Hz),7.13(1H,dd,J=7.26,1.78Hz),7.61(1H,dd,J=4.52,2.60Hz),7.85(1H,s),7.96(1H,d,J=2.19Hz),8.63(1H,d,J=7.39Hz);$C_{23}H_{25}N_7O_2$的ESIMS实验值m/z 432.2(M+1)。

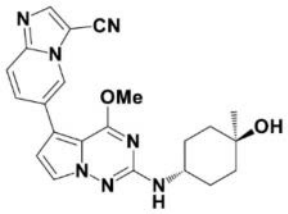
[1082] 

102

[1083] 5-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺102。

[1084] 米色固体(30mg,0.065mmol,42.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20-

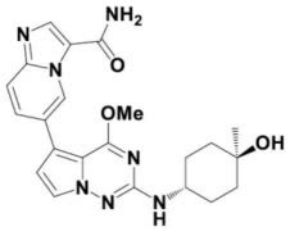
1.34(2H,m),1.52(2H,td,J＝12.94,3.42Hz),1.82-1.93(2H,m),2.07(2H,br d,J＝13.14Hz),2.79(3H,d,J＝4.65Hz),3.49-3.61(1H,m),4.01(3H,s),4.24(2H,s),4.32(2H,s),6.57(1H,d,J＝7.94Hz),6.83(1H,d,J＝2.74Hz),7.28(1H,dd,J＝7.26,2.05Hz),7.64(1H,d,J＝2.46Hz),8.10(1H,q,J＝4.56Hz),8.45(1H,s),8.52(1H,dd,J＝1.92,0.82Hz),8.64-8.73(1H,m);$C_{24}H_{27}N_7O_3$的ESIMS实验值m/z 462.2(M+1)。

[1085] 

103

[1086] 6-(2-((反-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲腈103。

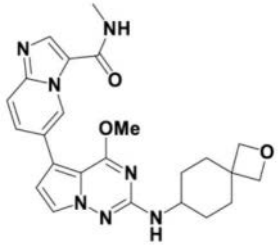
[1087] 米色固体(12mg,0.029mmol,8.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.38-1.53(4H,m),1.56-1.66(3H,m),1.83-1.93(2H,m),3.60-3.71(1H,m),4.01(3H,s),4.23(1H,s),6.56(1H,d,J＝7.94Hz),6.89(1H,d,J＝2.74Hz),7.67(1H,d,J＝2.74Hz),7.81-7.92(2H,m),8.44(1H,s),8.77-8.86(1H,m);$C_{22}H_{23}N_7O_2$的ESIMS实验值m/z 418.2(M+1)。

[1088] 

104

[1089] 6-(2-((反-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)咪唑并[1,2-a]吡啶-3-甲酰胺104。

[1090] 米色固体(2.2mg,0.005mmol,1.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.39-1.48(4H,m),1.57-1.63(2H,m),1.85-1.91(2H,m),3.60-3.72(1H,m),3.99(3H,s),4.23(1H,s),6.49(1H,d,J＝7.94Hz),6.75(1H,d,J＝2.46Hz),7.34(1H,br s),7.65(1H,d,J＝2.74Hz),7.69(2H,s),7.95(1H,br s),8.33(1H,s),9.84(1H,s);$C_{22}H_{25}N_7O_3$的ESIMS实验值m/z 436.25(M+1)。

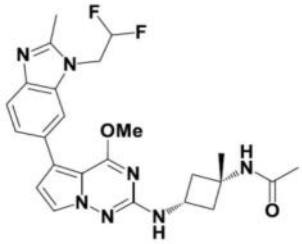
[1091] 

107

[1092] 6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-

5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺107。

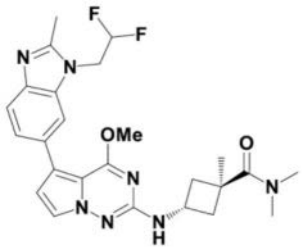
[1093] 灰白色固体(37mg,0.080mmol,32.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.17-1.37(2H,m),1.52(2H,td,J=12.87,3.29Hz),1.81-1.91(2H,m),2.07(2H,br d,J=13.14Hz),2.82(3H,d,J=4.65Hz),3.48-3.61(1H,m),4.00(3H,s),4.24(2H,s),4.32(2H,s),6.52(1H,d,J=7.94Hz),6.75(1H,d,J=2.46Hz),7.63(1H,d,J=2.46Hz),7.68(2H,d,J=1.37Hz),8.26(1H,s),8.43(1H,q,J=4.38Hz),9.80(1H,t,J=1.37Hz);$C_{24}H_{27}N_7O_3$的ESIMS实验值m/z 462.2(M+1)。

[1094] 

108

[1095] N-(顺-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺108。

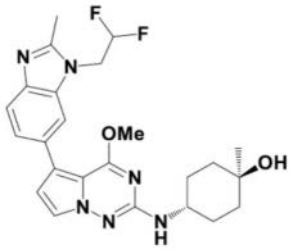
[1096] 白色固体(5mg,0.0103mmol,28.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.10-2.21(2H,m),2.42(2H,ddd,J=9.65,7.46,2.60Hz),2.56(3H,s),3.91(3H,s),3.96-4.10(1H,m),4.69-4.81(2H,m),6.47(1H,tt,J=54.40,3.00Hz),6.61(1H,d,J=2.74Hz),6.90(1H,d,J=7.12Hz),7.35(1H,dd,J=8.21,1.64Hz),7.49(1H,d,J=8.21Hz),7.59(1H,d,J=2.74Hz),7.69(1H,s),8.02(1H,s);$C_{24}H_{27}F_2N_7O_2$的ESIMS实验值m/z 484.2(M+1)。

[1097] 

109

[1098] 反-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺109。

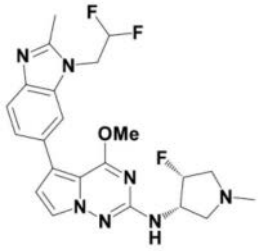
[1099] 白色固体(20mg,0.040mmol,75.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.39(3H,s),1.94-2.02(2H,m),2.56(3H,s),2.81-2.94(8H,m),3.85-3.95(1H,m),3.92(3H,s),4.68-4.80(2H,m),6.47(1H,tt,J=54.30,3.00Hz),6.60(1H,d,J=2.46Hz),6.98(1H,d,J=6.57Hz),7.35(1H,dd,J=8.35,1.51Hz),7.49(1H,d,J=8.21Hz),7.59(1H,d,J=2.46Hz),7.69(1H,s);$C_{25}H_{29}F_2N_7O_2$的ESIMS实验值m/z 498.3(M+1)。

[1100] 

112

[1101] 反-4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇112。

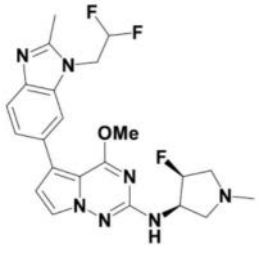
[1102] 白色固体(8mg,0.020mmol,6.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.51(4H,m),1.57-1.64(2H,m),1.83-1.92(2H,m),2.56(3H,s),3.59-3.70(1H,m),3.92(3H,s),4.23(1H,br s),4.74(2H,td,J=16.02,2.46Hz),6.47(1H,tt,J=54.50,3.00Hz),6.38(1H,d,J=7.94Hz),6.60(1H,d,J=2.46Hz),7.35(1H,dd,J=8.35,1.51Hz),7.49(1H,d,J=8.49Hz),7.59(1H,d,J=2.74Hz),7.69(1H,s);$C_{24}H_{28}F_2N_6O_2$的ESIMS实验值m/z 471.25(M+1)。

[1103] 

113

[1104] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺113。

[1105] 白色蓬松固体(13mg,0.028mmol,84.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.31(3H,s),2.56(3H,s),2.57-2.65(2H,m),2.88-2.96(1H,m),3.16(1H,ddd,J=29.35,11.64,4.79Hz),3.94(3H,s),4.19-4.35(1H,m),4.74(2H,td,J=16.08,2.60Hz),5.21(1H,dtd,J=55.95,5.07,5.07,1.92Hz),6.47(1H,tt,J=54.30,3.00Hz),6.64(1H,d,J=2.46Hz),6.65(1H,d,J=7.94Hz),7.36(1H,dd,J=8.21,1.64Hz),7.50(1H,d,J=8.21Hz),7.61(1H,d,J=2.74Hz),7.70(1H,s);$C_{22}H_{24}F_3N_7O$的ESIMS实验值m/z 460.2(M+1)。

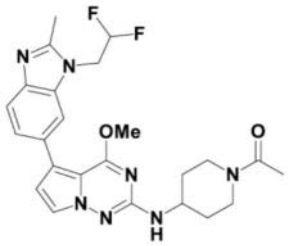
[1106] 

114

[1107] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺114。

[1108] 白色蓬松固体(13mg,0.028mmol,84.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm

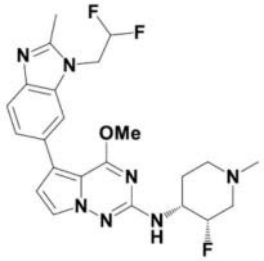
2.31(3H,s),2.56(3H,s),2.58-2.65(2H,m),2.88-2.96(1H,m),3.16(1H,ddd,J＝29.60,11.77,4.93Hz),3.94(3H,s),4.20-4.35(1H,m),4.75(2H,td,J＝16.02,2.46Hz),5.21(1H,dtd,J＝55.95,5.00,5.00,2.05Hz),6.47(1H,tt,J＝54.30,3.00Hz),6.64(1H,d,J＝2.46Hz),6.66(1H,d,J＝7.94Hz),7.36(1H,dd,J＝8.21,1.64Hz),7.50(1H,d,J＝8.21Hz),7.61(1H,d,J＝2.46Hz),7.70(1H,s);$C_{22}H_{24}F_3N_7O$的ESIMS实验值m/z 460.2(M+1)。

[1109] 

122

[1110] 1-(4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮122。

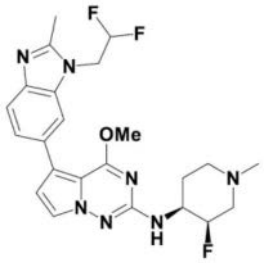
[1111] 白色固体(5mg,0.010mmol,3.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28-1.38(1H,m),1.39-1.51(1H,m),1.89-1.95(1H,m),1.95-2.00(1H,m),2.01(3H,s),2.56(3H,s),2.70-2.80(1H,m),3.09-3.21(1H,m),3.77-3.87(2H,m),3.92(3H,s),4.28(1H,br d,J＝14.51Hz),4.69-4.81(2H,m),6.47(1H,tt,J＝54.50,3.00Hz),6.60-6.63(2H,m),7.35(1H,dd,J＝8.21,1.64Hz),7.50(1H,d,J＝8.49Hz),7.59(1H,d,J＝2.46Hz),7.69(1H,s);$C_{24}H_{27}F_2N_7O_2$的ESIMS实验值m/z 484.25(M+1)。

[1112] 

124

[1113] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺124。

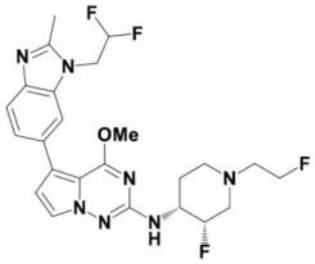
[1114] 白色固体(17mg,0.036mmol,33.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.64-1.74(1H,m),1.85-1.99(1H,m),2.06(1H,br t,J＝11.36Hz),2.18(1H,dd,J＝37.85,12.60Hz),2.19(3H,s),2.56(3H,s),2.80(1H,br d,J＝10.13Hz),3.01-3.11(1H,m),3.67-3.84(1H,m),3.93(3H,s),4.74(2H,td,J＝16.08,2.60Hz),4.91(1H,d,J＝50.20Hz),6.47(1H,tt,J＝54.30,3.00Hz),6.51(1H,d,J＝7.94Hz),6.63(1H,d,J＝2.46Hz),7.36(1H,dd,J＝8.49,1.64Hz),7.50(1H,d,J＝8.49Hz),7.59(1H,d,J＝2.46Hz),7.70(1H,s);$C_{23}H_{26}F_3N_7O$的ESIMS实验值m/z474.3(M+1)。

[1115] 

127

[1116] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺127。

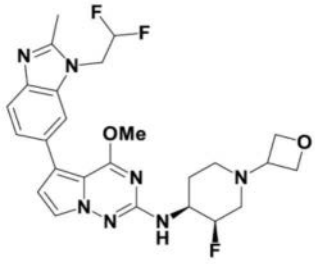
[1117] 白色固体(6mg,0.013mmol,38.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.23(3H,s),1.65-1.74(1H,m),1.92(1H,qd,J=12.23,4.11Hz),2.03-2.12(1H,m),2.13-2.29(1H,m),2.20(3H,s),2.56(3H,s),2.81(1H,br d,J=9.86Hz),3.06(1H,br t,J=10.40Hz),3.68-3.83(1H,m),3.93(3H,s),4.74(2H,td,J=16.08,2.60Hz),4.92(1H,d,J=49.65Hz),6.47(1H,tt,J=54.40,3.00Hz),6.51(1H,d,J=7.94Hz),6.63(1H,d,J=2.46Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.59(1H,d,J=2.74Hz),7.69(1H,s);$C_{23}H_{26}F_3N_7O$的ESIMS实验值m/z 474.3(M+1)。

[1118] 

129

[1119] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺129。

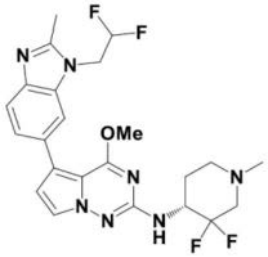
[1120] 白色蓬松固体(28mg,0.055mmol,82.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.65-1.75(1H,m),1.92(1H,qd,J=12.32,4.11Hz),2.25(1H,br t,J=11.23Hz),2.38(1H,dd,J=37.60,12.90Hz),2.56(3H,s),2.63-2.74(2H,m),2.88-2.97(1H,m),3.13-3.21(1H,m),3.71-3.87(1H,m),3.93(3H,s),4.54(2H,dt,J=48.00,4.95Hz),4.74(2H,td,J=16.02,2.19Hz),4.92(1H,d,J=49.40Hz),6.47(1H,tt,J=54.30,3.00Hz),6.53(1H,d,J=7.94Hz),6.63(1H,d,J=2.74Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.59(1H,d,J=2.46Hz),7.70(1H,s);$C_{24}H_{27}F_4N_7O$的ESIMS实验值m/z 506.3(M+1)。

[1121] 

137

[1122] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺137。

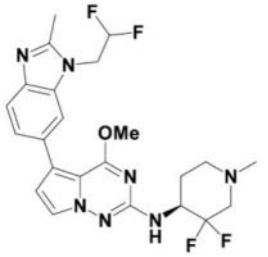
[1123] 白色固体(27mg,0.052mmol,48.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69-1.77(1H,m),1.91(1H,qd,J=12.09,3.42Hz),1.98-2.06(1H,m),2.09-2.22(1H,m),2.56(3H,s),2.76(1H,br d,J=10.40Hz),2.94-3.04(1H,m),3.49(1H,quin,J=6.43Hz),3.74-3.89(1H,m),3.94(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.43,3.01Hz),4.74(2H,td,J=16.08,2.60Hz),4.94(1H,d,J=49.65Hz),6.47(1H,tt,J=54.60,3.00Hz),6.57(1H,d,J=7.94Hz),6.63(1H,d,J=2.46Hz),7.36(1H,dd,J=8.49,1.64Hz),7.50(1H,d,J=8.21Hz),7.58(1H,d,J=2.74Hz),7.69(1H,s);$C_{25}H_{28}F_3N_7O_2$的ESIMS实验值m/z 516.3(M+1)。

[1124] 

138

[1125] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺138。

[1126] 白色蓬松固体(9mg,0.018mmol,58.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.74-1.89(2H,m),2.13-2.22(1H,m),2.26(3H,s),2.32-2.45(1H,m),2.56(3H,s),2.78(1H,br d,J=11.50Hz),3.00-3.10(1H,m),3.95(3H,s),4.16-4.32(1H,m),4.74(2H,td,J=15.88,2.46Hz),6.47(1H,tt,J=54.55,3.25Hz),6.64(1H,d,J=2.74Hz),6.72(1H,d,J=9.58Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.60(1H,d,J=2.46Hz),7.70(1H,s);$C_{23}H_{25}F_4N_7O$的ESIMS实验值m/z 492.2(M+1)。

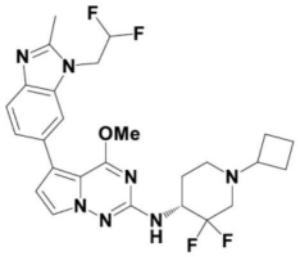
[1127] 

139

[1128] (S)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺139。

[1129] 白色蓬松固体(8mg,0.016mmol,45.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.74-1.90(2H,m),2.13-2.22(1H,m),2.26(3H,s),2.32-2.45(1H,m),2.56(3H,s),2.78(1H,br d,J=11.50Hz),3.00-3.10(1H,m),3.95(3H,s),4.16-4.32(1H,m),4.74(2H,td,J=16.02,2.46Hz),6.47(1H,tt,J=54.40,3.25Hz),6.64(1H,d,J=2.46Hz),6.72(1H,d,J=9.31Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.60(1H,d,J=

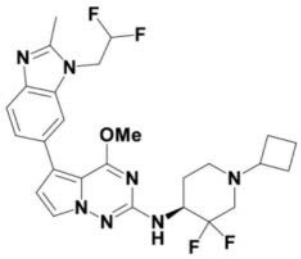
2.74Hz),7.70(1H,s);$C_{23}H_{25}F_4N_7O$的ESIMS实验值m/z 492.2(M+1)。

[1130] 

140

[1131] (R)-N-(1-环丁基-3,3-二氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺140。

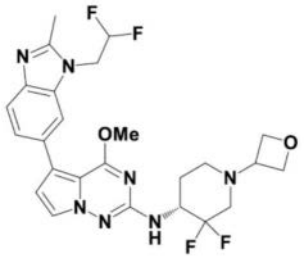
[1132] 白色蓬松固体(10mg,0.019mmol,56.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.56-1.69(2H,m),1.71-1.92(4H,m),2.00(3H,br s),2.58(3H,s),2.71-2.94(2H,m),2.95-3.09(1H,m),3.95(3H,s),4.18-4.38(1H,m),4.76(2H,td,J=15.90,2.45Hz),6.48(1H,tt,J=54.40,3.00Hz),6.65(1H,d,J=2.46Hz),6.76(1H,br s),7.38(1H,dd,J=8.35,1.51Hz),7.52(1H,d,J=8.21Hz),7.60(1H,d,J=2.46Hz),7.72(1H,s);$C_{26}H_{29}F_4N_7O$的ESIMS实验值m/z 532.3(M+1)。

[1133] 

141

[1134] (S)-N-(1-环丁基-3,3-二氟哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺141。

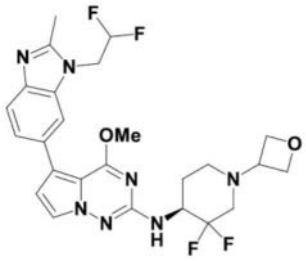
[1135] 白色蓬松固体(11mg,0.021mmol,58.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.85(1H,m),1.86-1.93(1H,m),2.16(1H,br t,J=10.27Hz),2.33-2.47(1H,m),2.58(3H,s),2.76(1H,br d,J=11.22Hz),2.96-3.07(1H,m),3.60(1H,quin,J=6.30Hz),3.95(3H,s),4.23-4.37(1H,m),4.44(2H,dt,J=15.06,6.16Hz),4.55(2H,td,J=6.57,3.56Hz),4.77(2H,td,J=15.90,2.40Hz),6.48(1H,tt,J=54.40,3.00Hz),6.65(1H,d,J=2.46Hz),6.80(1H,d,J=9.31Hz),7.39(1H,dd,J=8.35,1.51Hz),7.52(1H,d,J=8.21Hz),7.60(1H,d,J=2.46Hz),7.73(1H,s);$C_{26}H_{29}F_4N_7O$的ESIMS实验值m/z 532.3(M+1)。

[1136] 

142

[1137] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺142。

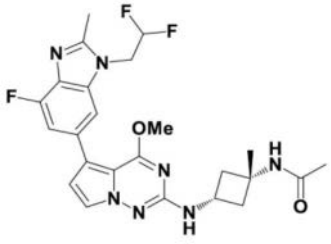
[1138] 白色蓬松固体(14mg,0.026mmol,50.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.85(1H,m),1.86-1.93(1H,m),2.16(1H,br t,J=10.27Hz),2.33-2.47(1H,m),2.58(3H,s),2.76(1H,br d,J=11.22Hz),2.96-3.07(1H,m),3.60(1H,quin,J=6.30Hz),4.23-4.37(1H,m),4.44(2H,dt,J=15.06,6.16Hz),4.55(2H,td,J=6.57,3.56Hz),4.77(2H,td,J=15.90,2.40Hz),6.48(1H,tt,J=54.40,3.00Hz),6.65(1H,d,J=2.46Hz),6.80(1H,d,J=9.31Hz),7.39(1H,dd,J=8.35,1.51Hz),7.52(1H,d,J=8.21Hz),7.60(1H,d,J=2.46Hz),7.73(1H,s);$C_{25}H_{27}F_4N_7O_2$的ESIMS实验值m/z 534.3(M+1)。

[1139] 

143

[1140] (S)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺143。

[1141] 白色蓬松固体(11mg,0.021mmol,39.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.75-1.85(1H,m),1.86-1.93(1H,m),2.12-2.22(1H,m),2.33-2.46(1H,m),2.58(3H,s),2.76(1H,br d,J=11.50Hz),2.97-3.07(1H,m),3.60(1H,quin,J=6.23Hz),3.95(3H,s),4.23-4.36(1H,m),4.44(2H,dt,J=14.92,6.23Hz),4.55(2H,td,J=6.57,3.56Hz),4.77(2H,td,J=16.00,2.45Hz),6.48(1H,tt,J=54.40,3.00Hz),6.65(1H,d,J=2.74Hz),6.80(1H,d,J=9.31Hz),7.39(1H,dd,J=8.35,1.51Hz),7.52(1H,d,J=8.21Hz),7.60(1H,d,J=2.74Hz),7.73(1H,s);$C_{25}H_{27}F_4N_7O_2$的ESIMS实验值m/z 534.3(M+1)。

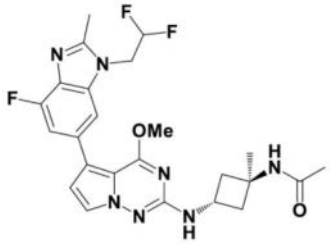
[1142] 

148

[1143] N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-

4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺148。

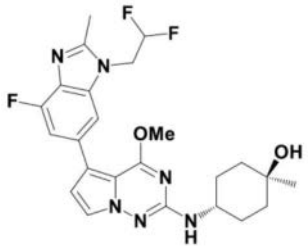
[1144] 白色固体(15mg,0.030mmol,24.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.15(2H,br dd,J=11.50,8.76Hz),2.37-2.45(2H,m),2.57(3H,s),3.93(3H,s),4.02(1H,sxt,J=7.72Hz),4.77(2H,td,J=16.02,2.46Hz),6.48(1H,tt,J=54.30,3.00Hz),6.66(1H,d,J=2.74Hz),6.94(1H,d,J=6.84Hz),7.19(1H,dd,J=12.18,1.23Hz),7.57(1H,s),7.60(1H,d,J=2.74Hz),8.02(1H,s);$C_{24}H_{26}F_3N_7O_2$的ESIMS实验值m/z 502.2(M+1)。

[1145] 

149

[1146] N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺149。

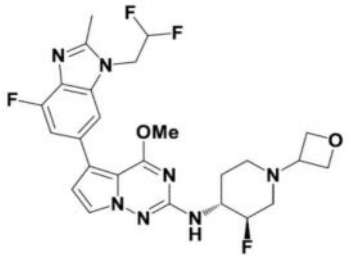
[1147] 白色固体(15mg,0.030mmol,22.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.81(3H,s),1.90-2.00(2H,m),2.58(3H,s),2.60-2.66(2H,m),3.93(3H,s),4.18(1H,sxt,J=7.72Hz),4.77(2H,td,J=16.08,2.33Hz),6.48(1H,tt,J=54.30,3.00Hz),6.66(1H,d,J=2.46Hz),6.95(1H,d,J=7.39Hz),7.19(1H,dd,J=12.18,1.23Hz),7.57(1H,s),7.58(1H,d,J=2.46Hz),7.93(1H,s);$C_{24}H_{26}F_3N_7O_2$的ESIMS实验值m/z 502.2(M+1)。

[1148] 

151

[1149] 反-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇151。

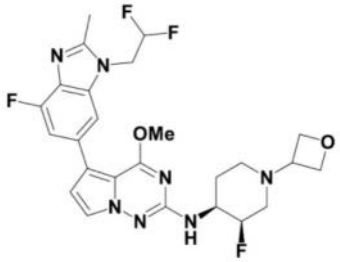
[1150] 白色固体(5mg,0.010mmol,6.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.36-1.53(4H,m),1.56-1.65(2H,m),1.83-1.92(2H,m),2.58(3H,s),3.59-3.70(1H,m),3.94(3H,s),4.23(1H,s),4.70-4.84(2H,m),6.48(1H,tt,J=54.30,3.00Hz),6.42(1H,d,J=7.94Hz),6.65(1H,d,J=2.74Hz),7.19(1H,dd,J=12.18,1.23Hz),7.57(1H,s),7.60(1H,d,J=2.74Hz);$C_{24}H_{27}F_3N_6O_2$的ESIMS实验值m/z 489.3(M+1)。

[1151] 

159

[1152] 5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺159。

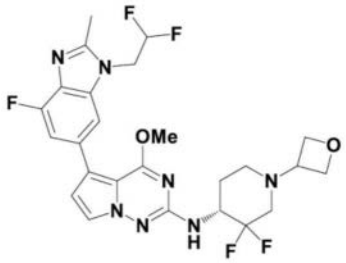
[1153] 蓬松白色固体(6mg,0.011mmol,17.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67-1.76(1H,m),1.91(1H,qd,J=12.05,3.56Hz),1.98-2.06(1H,m),2.15(1H,dd,J=36.75,12.87Hz),2.58(3H,s),2.76(1H,br d,J=11.77Hz),2.98(1H,br t,J=10.54Hz),3.49(1H,quin,J=6.37Hz),3.75-3.89(1H,m),3.96(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.77(2H,td,J=16.02,2.74Hz),4.93(1H,d,J=49.10Hz),6.48(1H,tt,J=54.30,3.00Hz),6.62(1H,d,J=7.67Hz),6.68(1H,d,J=2.46Hz),7.20(1H,dd,J=12.32,1.10Hz),7.58(1H,s),7.59(1H,d,J=2.74Hz);$C_{25}H_{27}F_4N_7O_2$的ESIMS实验值m/z 534.2(M+1)。

[1154] 

161

[1155] 5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺161。

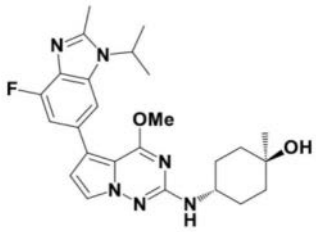
[1156] 白色固体(11mg,0.021mmol,35.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.77(1H,m),1.85-1.97(1H,m),1.98-2.06(1H,m),2.15(1H,dd,J=37.05,12.59Hz),2.58(3H,s),2.71-2.81(1H,m),2.94-3.04(1H,m),3.49(1H,quin,J=6.43Hz),3.73-3.89(1H,m),3.96(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.78(2H,td,J=16.02,2.46Hz),4.93(1H,d,J=49.90Hz),6.49(1H,tt,J=54.30,3.00Hz),6.63(1H,d,J=7.94Hz),6.68(1H,d,J=2.46Hz),7.20(1H,dd,J=12.32,1.37Hz),7.58(1H,s),7.60(1H,d,J=2.46Hz);$C_{25}H_{27}F_4N_7O_2$的ESIMS实验值m/z 534.2(M+1)。

[1157] 

164

[1158] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺164。

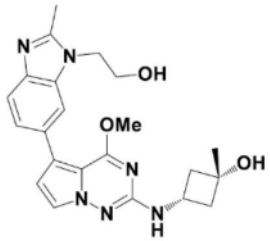
[1159] 黄白色固体(8mg,0.015mmol,14.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.85(1H,m),1.86-1.93(1H,m),2.13-2.22(1H,m),2.40(1H,dd,J=27.15,11.38Hz),2.58(3H,s),2.76(1H,br d,J=11.23Hz),2.94-3.08(1H,m),3.60(1H,quin,J=6.23Hz),3.93-4.01(3H,m),4.23-4.37(1H,m),4.44(2H,dt,J=15.06,6.16Hz),4.55(2H,td,J=6.57,3.56Hz),4.77(2H,td,J=16.08,2.33Hz),6.48(1H,tt,J=54.30,3.00Hz),6.70(1H,d,J=2.46Hz),6.83(1H,d,J=9.58Hz),7.17-7.24(1H,m),7.58(1H,s),7.60(1H,d,J=2.74Hz);$C_{25}H_{26}F_5N_7O_2$的ESIMS实验值m/z 552.2(M+1)。

[1160] 

168

[1161] 反-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇168。

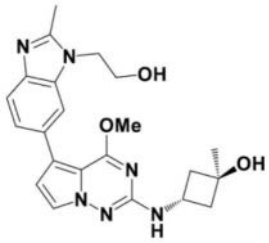
[1162] 白色固体(20mg,0.043mmol,16.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.38-1.50(4H,m),1.56-1.62(2H,m),1.59(6H,d,J=6.84Hz),1.83-1.91(2H,m),2.58(3H,s),3.59-3.70(1H,m),3.94(3H,s),4.23(1H,s),4.76(1H,spt,J=6.94Hz),6.42(1H,d,J=7.94Hz),6.66(1H,d,J=2.74Hz),7.11(1H,dd,J=12.18,1.23Hz),7.59(1H,d,J=2.46Hz),7.63(1H,d,J=1.09Hz);$C_{25}H_{31}FN_6O_2$的ESIMS实验值m/z 467.3(M+1)。

[1163] 

169

[1164] 顺-3-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇169。

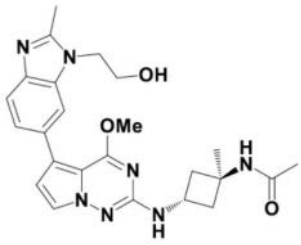
[1165] 白色固体(7mg,0.017mmol,49.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),2.01(2H,td,J=8.90,2.19Hz),2.35(2H,ddd,J=8.90,7.26,2.74Hz),2.55(3H,s),3.67-3.73(1H,m),3.75(2H,q,J=5.38Hz),3.93(3H,s),4.24(2H,t,J=5.34Hz),4.91(1H,s),4.96(1H,t,J=5.48Hz),6.60(1H,d,J=2.74Hz),6.81(1H,d,J=6.57Hz),7.30(1H,dd,J=8.35,1.51Hz),7.47(1H,d,J=8.21Hz),7.58(1H,d,J=2.46Hz),7.62(1H,d,J=1.37Hz);$C_{22}H_{26}N_6O_3$的ESIMS实验值m/z 423.2(M+1)。

[1166] 

170

[1167] 反-3-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇170。

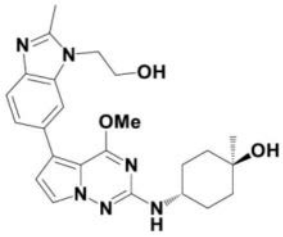
[1168] 白色固体(3mg,0.007mmol,127.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28(3H,s),1.96-2.01(2H,m),2.27-2.34(2H,m),2.61(3H,s),3.76(2H,q,J=5.20Hz),3.93(3H,s),4.20-4.27(1H,m),4.29(2H,br t,J=5.06Hz),4.78(1H,s),4.99(1H,t,J=5.34Hz),6.62(1H,d,J=2.46Hz),6.85(1H,d,J=6.84Hz),7.38(1H,br d,J=8.49Hz),7.52(1H,d,J=8.21Hz),7.58(1H,d,J=2.74Hz),7.70(1H,s);$C_{22}H_{26}N_6O_3$的ESIMS实验值m/z 423.2(M+1)。

[1169] 

171

[1170] N-(反-3-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺171。

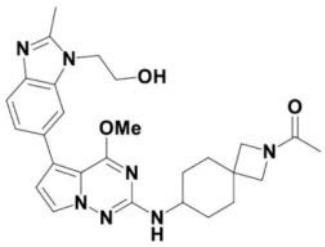
[1171] 白色固体(6mg,0.0130mmol,62.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.81(3H,s),1.91-1.99(2H,m),2.55(3H,s),2.59-2.67(2H,m),3.75(2H,br d,J=3.83Hz),3.93(3H,s),4.14-4.21(1H,m),4.24(2H,br t,J=5.34Hz),4.96(1H,br s),6.60(1H,d,J=2.46Hz),6.89(1H,d,J=7.12Hz),7.30(1H,dd,J=8.08,1.23Hz),7.47(1H,br d,J=7.94Hz),7.56(1H,d,J=2.46Hz),7.61(1H,s),7.93(1H,s);$C_{24}H_{29}N_7O_3$的ESIMS实验值m/z 464.3(M+1)。

[1172] 

172

[1173] 反-4-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇172。

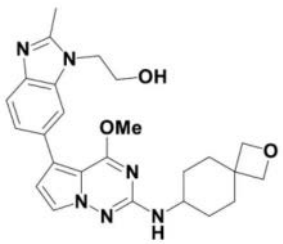
[1174] 白色固体(14mg,0.031mmol,54.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.37-1.51(4H,m),1.59(2H,br d,J=10.95Hz),1.83-1.93(2H,m),2.55(3H,s),3.60-3.69(1H,m),3.75(2H,q,J=5.48Hz),3.93(3H,s),4.20-4.27(3H,m),4.95(1H,t,J=5.34Hz),6.36(1H,d,J=7.94Hz),6.59(1H,d,J=2.46Hz),7.30(1H,dd,J=8.35,1.51Hz),7.46(1H,d,J=8.21Hz),7.58(1H,d,J=2.74Hz),7.61(1H,s);$C_{24}H_{30}N_6O_3$的ESIMS实验值m/z 451.3(M+1)。

[1175] 

173

[1176] 1-(7-((5-(1-(2-羟基乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮173。

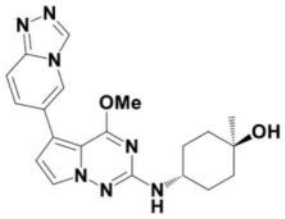
[1177] 灰白色固体(6mg,0.012mmol,50.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28-1.39(2H,m),1.48-1.60(2H,m),1.72-1.79(3H,m),1.83-1.94(4H,m),2.60(3H,s),3.47(1H,s),3.52(1H,s),3.57(1H,dt,J=10.20,6.95Hz),3.74(1H,s),3.75-3.79(2H,m),3.80(1H,s),3.93(3H,d,J=1.10Hz),4.28(2H,br t,J=5.20Hz),4.99(1H,t,J=5.48Hz),6.43(1H,dd,J=16.43,7.94Hz),6.62(1H,d,J=2.46Hz),7.37(1H,dd,J=8.21,1.37Hz),7.51(1H,d,J=8.49Hz),7.58(1H,t,J=2.74Hz),7.69(1H,s);$C_{27}H_{33}N_7O_3$的ESIMS实验值m/z 504.3(M+1)。

[1178] 

174

[1179] 2-(6-(2-((2-氧杂螺[3.5]壬烷-7-基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-2-甲基-1H-苯并[d]咪唑-1-基)乙-1-醇174。

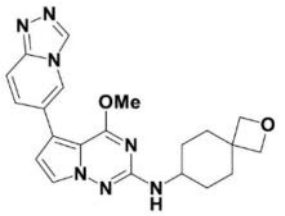
[1180] 白色固体(6mg,0.013mmol,57.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20-1.33(2H,m),1.52(2H,td,J=12.87,3.29Hz),1.83-1.93(2H,m),2.06(2H,br d,J=12.87Hz),2.55(3H,s),3.48-3.60(1H,m),3.74(2H,q,J=5.38Hz),3.92(3H,s),4.21-4.25(2H,m),4.24(2H,s),4.32(2H,s),4.95(1H,t,J=5.34Hz),6.38(1H,d,J=7.94Hz),6.59(1H,d,J=2.74Hz),7.30(1H,dd,J=8.21,1.64Hz),7.46(1H,d,J=8.21Hz),7.57(1H,d,J=2.46Hz),7.61(1H,d,J=1.37Hz);$C_{25}H_{30}N_6O_3$的ESIMS实验值m/z 463.3(M+1)。

[1181] 

187

[1182] 反-4-((5-([1,2,4]三唑并[4,3-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇187。

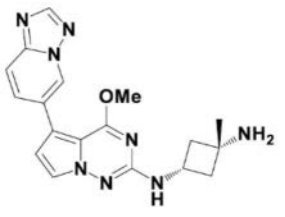
[1183] 灰白色固体(9mg,0.023mmol,13.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.37-1.53(4H,m),1.56-1.64(2H,m),1.83-1.92(2H,m),3.64(1H,br dd,J=8.08,3.70Hz),3.97(3H,s),4.23(1H,s),6.52(1H,d,J=7.67Hz),6.72(1H,d,J=2.74Hz),7.61(1H,dd,J=9.45,1.51Hz),7.65(1H,d,J=2.46Hz),7.76(1H,d,J=9.58Hz),8.69(1H,s),9.26(1H,s);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[1184] 

188

[1185] 5-([1,2,4]三唑并[4,3-a]吡啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺188。

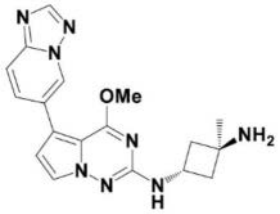
[1186] 米色固体(17mg,0.042mmol,21.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20-1.32(2H,m),1.52(2H,td,J=12.94,3.42Hz),1.82-1.92(2H,m),2.06(2H,br d,J=13.14Hz),3.48-3.63(1H,m),3.97(3H,s),4.23(2H,s),4.31(2H,s),6.54(1H,d,J=7.94Hz),6.72(1H,d,J=2.74Hz),7.60(1H,dd,J=9.58,1.64Hz),7.64(1H,d,J=2.74Hz),7.76(1H,d,J=9.58Hz),8.69(1H,t,J=1.23Hz),9.26(1H,s);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

[1187] 

189

[1188] 顺-N^1-(5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺189。

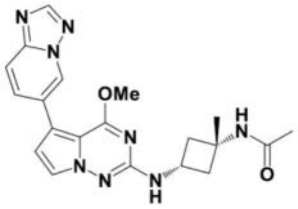
[1189] 白色泡沫(108mg,0.296mmol,62.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.19(3H,s),1.76(2H,br s),1.86(2H,td,J=8.76,2.46Hz),2.27-2.38(2H,m),3.85(1H,sxt,J=7.78Hz),3.96(3H,s),6.80(1H,d,J=2.46Hz),6.84(1H,d,J=7.12Hz),7.66(1H,d,J=2.74Hz),7.81-7.86(1H,m),7.87-7.92(1H,m),8.49(1H,s),9.06(1H,dd,J=1.64,0.82Hz);$C_{18}H_{20}N_8O$的ESIMS实验值m/z 365.2(M+1)。

[1190] 

190

[1191] 反-N^1-(5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺190。

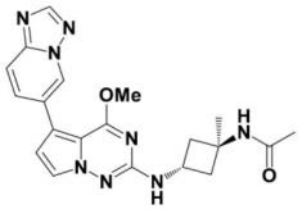
[1192] 白色泡沫(83mg,0.228mmol,65.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.22(3H,s),1.74(2H,br s),1.88-1.98(2H,m),2.12-2.22(2H,m),3.96(3H,s),4.27(1H,sxt,J=7.50Hz),6.80(1H,d,J=2.46Hz),6.93(1H,d,J=7.12Hz),7.64(1H,d,J=2.46Hz),7.82-7.86(1H,m),7.87-7.91(1H,m),8.49(1H,s),9.03-9.10(1H,m);$C_{18}H_{20}N_8O$的ESIMS实验值m/z 365.2(M+1)。

[1193] 

191

[1194] N-(顺-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺191。

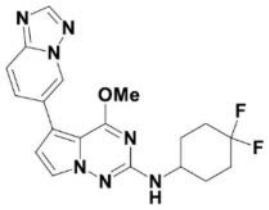
[1195] 灰白色固体(27mg,0.066mmol,96.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.10-2.22(2H,m),2.42(2H,ddd,J=9.65,7.46,2.60Hz),3.96(3H,s),4.02(1H,sxt,J=7.83Hz),6.80(1H,d,J=2.74Hz),7.03(1H,d,J=6.84Hz),7.66(1H,d,J=2.46Hz),7.82-7.85(1H,m),7.87-7.91(1H,m),8.02(1H,s),8.49(1H,s),9.06(1H,d,J=1.10Hz);$C_{20}H_{22}N_8O_2$的ESIMS实验值m/z 407.2(M+1)。

[1196] 

192

[1197] N-(反-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺192。

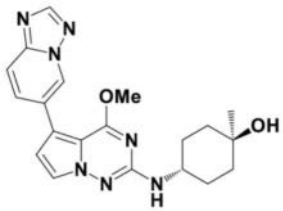
[1198] 灰白色固体(27mg,0.066mmol,96.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.81(3H,s),1.89-2.01(2H,m),2.64(2H,ddd,J=10.13,7.94,2.74Hz),3.96(3H,s),4.13-4.27(1H,m),6.80(1H,d,J=2.74Hz),7.03(1H,d,J=7.12Hz),7.64(1H,d,J=2.74Hz),7.81-7.86(1H,m),7.87-7.91(1H,m),7.93(1H,s),8.49(1H,s),9.06(1H,s);$C_{20}H_{22}N_8O_2$的ESIMS实验值m/z 407.2(M+1)。

[1199] 

193

[1200] 5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(4,4-二氟环己基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺193。

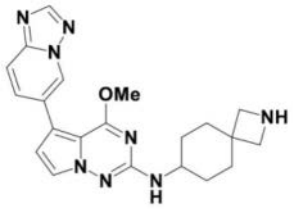
[1201] 灰白色固体(15mg,0.038mmol,18.8%产率)。^{1}H NMR(499MHz,氯仿-d)δppm 1.62-1.75(2H,m),1.88-2.06(2H,m),2.11-2.27(4H,m),3.87(1H,br dd,J=5.07,1.78Hz),4.02(3H,s),6.64(1H,d,J=2.74Hz),7.50(1H,d,J=2.74Hz),7.82(2H,s),8.09(1H,d,J=7.67Hz),8.40(1H,s),8.82(1H,s);$C_{19}H_{19}F_2N_7O$的ESIMS实验值m/z 400.2(M+1)。

[1202] 

194

[1203] 反-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇194。

[1204] 灰白色固体(41mg,0.104mmol,44.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.37-1.52(4H,m),1.55-1.65(2H,m),1.82-1.93(2H,m),3.64(1H,br dd,J=8.08,3.70Hz),3.96(3H,s),4.24(1H,s),6.52(1H,d,J=7.94Hz),6.79(1H,d,J=2.46Hz),7.66(1H,d,J=2.46Hz),7.80-7.86(1H,m),7.87-7.94(1H,m),8.49(1H,s),9.02-9.10(1H,m);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

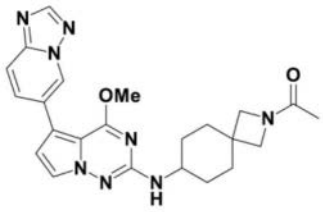
[1205] 

195

[1206] 5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基-N-(2-氮杂螺[3.5]壬烷-7-基)

吡咯并[2,1-f][1,2,4]三嗪-2-胺195。

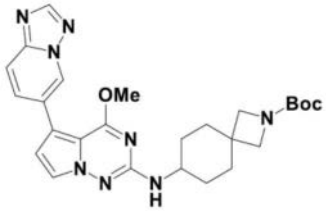
[1207] 灰白色泡沫(55mg,0.136mmol,71.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.25-1.34(2H,m),1.37-1.49(2H,m),1.84(3H,br d,J=10.13Hz),1.96(2H,br d,J=12.87Hz),3.14(2H,br s),3.20(2H,br s),3.46-3.62(2H,m),3.95(3H,s),6.51(1H,d,J=7.94Hz),6.79(1H,d,J=2.74Hz),7.64(1H,d,J=2.74Hz),7.81-7.85(1H,m),7.87-7.91(1H,m),8.49(1H,s),9.06(1H,s);$C_{21}H_{24}N_8O$的ESIMS实验值m/z405.3(M+1)。

[1208] 

196

[1209] 1-(7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮196。

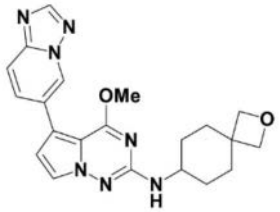
[1210] 灰白色固体(46mg,0.103mmol,83.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.26-1.41(2H,m),1.48-1.60(2H,m),1.72-1.80(3H,m),1.83-1.93(4H,m),3.47(1H,s),3.52(1H,s),3.57(1H,br dd,J=6.98,2.87Hz),3.74(1H,s),3.80(1H,s),3.96(3H,d,J=1.10Hz),6.56(1H,dd,J=16.02,7.80Hz),6.80(1H,d,J=2.74Hz),7.65(1H,t,J=2.87Hz),7.80-7.86(1H,m),7.86-7.93(1H,m),8.49(1H,s),9.04-9.10(1H,m);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.3(M+1)。

[1211] 

197

[1212] 7-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-甲酸叔丁酯197。

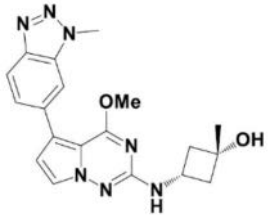
[1213] 灰白色泡沫(98mg,0.194mmol,58.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27-1.36(2H,m),1.38(9H,s),1.46-1.58(2H,m),1.86(4H,br d,J=10.40Hz),3.55(5H,br s),3.96(3H,s),6.52(1H,br d,J=7.39Hz),6.80(1H,d,J=2.46Hz),7.64(1H,d,J=2.74Hz),7.82-7.85(1H,m),7.87-7.91(1H,m),8.49(1H,s),9.06(1H,s);$C_{26}H_{32}N_8O_3$的ESIMS实验值m/z 505.3(M+1)。

[1214] 

198

[1215] 5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺198。

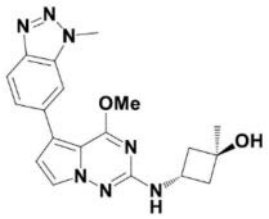
[1216] 灰白色固体(46mg,0.114mmol,56.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.19-1.31(2H,m),1.52(2H,td,J=12.87,3.29Hz),1.87(2H,br dd,J=13.14,3.29Hz),2.06(2H,br d,J=13.14Hz),3.48-3.60(1H,m),3.95(3H,s),4.23(2H,s),4.32(2H,s),6.54(1H,d,J=7.94Hz),6.79(1H,d,J=2.74Hz),7.64(1H,d,J=2.74Hz),7.80-7.85(1H,m),7.87-7.92(1H,m),8.49(1H,s),9.06(1H,s);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

[1217] 

199

[1218] 顺-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇199。

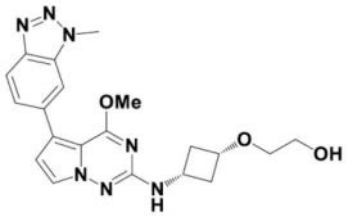
[1219] 灰白色固体(12mg,0.032mmol,16.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),2.02(2H,td,J=8.83,2.33Hz),2.31-2.40(2H,m),3.72(1H,dq,J=15.09,7.75Hz),3.95(3H,s),4.31(3H,s),4.92(1H,s),6.74(1H,d,J=2.46Hz),6.93(1H,d,J=6.57Hz),7.60(1H,dd,J=8.76,1.37Hz),7.64(1H,d,J=2.46Hz),7.93(1H,s),7.97(1H,d,J=8.49Hz);$C_{19}H_{21}N_7O_2$的ESIMS实验值m/z 380.2(M+1)。

[1220] 

200

[1221] 反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇200。

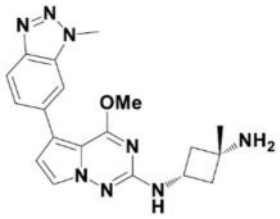
[1222] 白色固体(5mg,0.013mmol,8.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28(3H,s),1.95-2.03(2H,m),2.28-2.35(2H,m),3.95(3H,s),4.21-4.29(1H,m),4.31(3H,s),4.79(1H,s),6.74(1H,d,J=2.74Hz),6.94(1H,d,J=6.84Hz),7.60(1H,dd,J=8.62,1.51Hz),7.63(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{19}H_{21}N_7O_2$的ESIMS实验值m/z 380.2(M+1)。

[1223] 

201

[1224] 2-(顺-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇201。

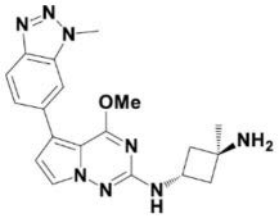
[1225] 灰白色固体(27mg,0.066mmol,25.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82-1.94(2H,m),2.60-2.71(2H,m),3.29-3.34(2H,m),3.48(2H,q,J=5.48Hz),3.68-3.75(1H,m),3.75-3.83(1H,m),3.95(3H,s),4.31(3H,s),4.60(1H,t,J=5.61Hz),6.75(1H,d,J=2.74Hz),7.02(1H,d,J=7.39Hz),7.60(1H,dd,J=8.76,1.37Hz),7.62(1H,d,J=2.46Hz),7.94(1H,s),7.97(1H,d,J=8.76Hz);$C_{20}H_{23}N_7O_3$的ESIMS实验值m/z 410.2(M+1)。

[1226] 

202

[1227] 顺-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺202。

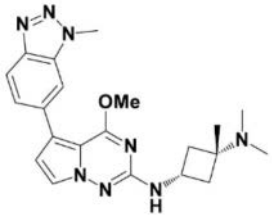
[1228] 灰白色固体(155mg,0.410mmol,70.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.19(3H,s),1.77(2H,br s),1.86(2H,td,J=8.83,2.33Hz),2.33(2H,ddd,J=8.97,7.46,2.74Hz),3.86(1H,dq,J=15.50,7.79Hz),3.95(3H,s),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.80(1H,d,J=7.12Hz),7.60(1H,dd,J=8.76,1.64Hz),7.64(1H,d,J=2.74Hz),7.93(1H,d,J=1.37Hz),7.97(1H,d,J=8.76Hz);$C_{19}H_{22}N_8O$的ESIMS实验值m/z 379.25(M+1)。

[1229] 

203

[1230] 反-N^1-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺203。

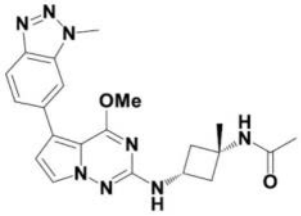
[1231] 灰白色泡沫(110mg,0.291mmol,74.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.22(3H,s),1.80(2H,br s),1.88-1.98(2H,m),2.13-2.22(2H,m),3.95(3H,s),4.23-4.33(1H,m),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.90(1H,d,J=7.12Hz),7.60(1H,dd,J=8.76,1.37Hz),7.63(1H,d,J=2.46Hz),7.93(1H,s),7.95-8.00(1H,m);$C_{19}H_{22}N_8O$的ESIMS实验值m/z 379.2(M+1)。

[1232] 

204

[1233] 顺-N^3-(4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-N^1,N^1,1-三甲基环丁烷-1,3-二胺204。

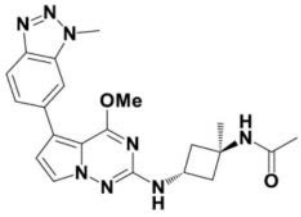
[1234] 白色固体(18mg,0.044mmol,67.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.06(3H,s),1.82-1.92(2H,m),2.03(6H,s),2.19(2H,td,J=8.15,2.60Hz),3.91-4.01(1H,m),3.95(3H,s),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.95(1H,d,J=7.12Hz),7.60(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{21}H_{26}N_8O$的ESIMS实验值m/z 407.3(M+1)。

[1235] 

205

[1236] N-(顺-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺205。

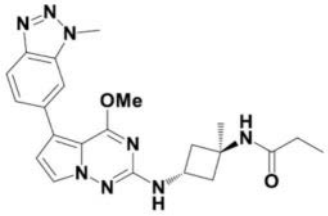
[1237] 灰白色固体(25mg,0.060mmol,90.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.11-2.21(2H,m),2.42(2H,ddd,J=9.58,7.39,2.46Hz),3.95(3H,s),3.99-4.08(1H,m),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.99(1H,d,J=6.84Hz),7.60(1H,dd,J=8.76,1.64Hz),7.65(1H,d,J=2.46Hz),7.93(1H,s),7.97(1H,d,J=9.03Hz),8.02(1H,s);$C_{21}H_{24}N_8O_2$的ESIMS实验值m/z 421.2(M+1)。

[1238] 

206

[1239] N-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺206。

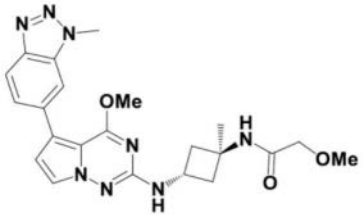
[1240] 灰白色固体(84mg,0.200mmol,92.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.82(3H,s),1.90-2.00(2H,m),2.64(2H,ddd,J=10.20,7.87,2.46Hz),3.95(3H,s),4.19(1H,sxt,J=7.78Hz),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.99(1H,d,J=7.39Hz),7.60(1H,dd,J=8.62,1.51Hz),7.62(1H,d,J=2.74Hz),7.93(2H,s),7.97(1H,d,J=8.49Hz);$C_{21}H_{24}N_8O_2$的ESIMS实验值m/z 421.2(M+1)。

[1241] 

207

[1242] N-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)丙酰胺207。

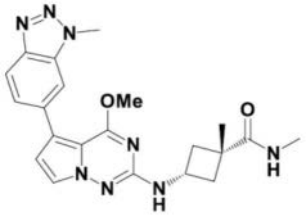
[1243] 灰白色固体(30mg,0.069mmol,96.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.00(3H,t,J=7.53Hz),1.36(3H,s),1.92-2.00(2H,m),2.08(2H,q,J=7.57Hz),2.64(2H,ddd,J=10.27,7.94,2.60Hz),3.95(3H,s),4.19(1H,sxt,J=7.78Hz),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.99(1H,d,J=7.12Hz),7.60(1H,dd,J=8.62,1.51Hz),7.62(1H,d,J=2.46Hz),7.83(1H,s),7.93(1H,s),7.97(1H,d,J=8.76Hz),8.31(1H,s);$C_{22}H_{26}N_8O_2$的ESIMS实验值m/z 435.3(M+1)。

[1244] 

208

[1245] 2-甲氧基-N-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺208。

[1246] 灰白色固体(15mg,0.033mmol,63.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.39(3H,s),1.95-2.05(2H,m),2.69-2.78(2H,m),3.78(2H,s),3.95(3H,s),4.13-4.24(1H,m),4.31(3H,s),6.74(1H,d,J=2.74Hz),7.01(1H,d,J=7.39Hz),7.60(1H,dd,J=8.76,1.37Hz),7.63(1H,d,J=2.74Hz),7.72(1H,s),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{22}H_{26}N_8O_3$的ESIMS实验值m/z 451.3(M+1)。

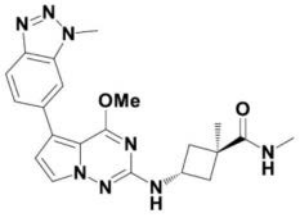
[1247] 

209

[1248] 顺-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺209。

[1249] 灰白色固体(7.3mg,0.017mmol,9.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34(3H,s),2.14-2.22(2H,m),2.22-2.31(2H,m),2.58(3H,d,J=4.38Hz),3.94(3H,s),4.20(1H,sxt,J=7.88Hz),4.31(3H,s),6.75(1H,d,J=2.74Hz),6.93(1H,d,J=7.12Hz),7.47(1H,q,J=4.29Hz),7.60(1H,dd,J=8.76,1.37Hz),7.65(1H,d,J=2.46Hz),7.93(1H,s),

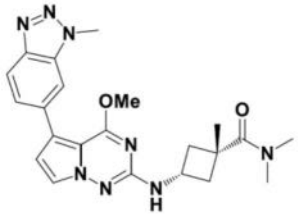
7.96-8.00(1H,m);$C_{21}H_{24}N_8O_2$的ESIMS实验值m/z 421.2(M+1)。

[1250] 

210

[1251] 反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺210。

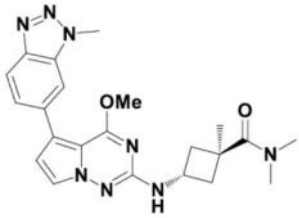
[1252] 白色固体(35mg,0.083mmol,99.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.32(3H,s),1.86-1.94(2H,m),2.62(3H,d,J=4.38Hz),2.70-2.79(2H,m),3.95(3H,s),4.04(1H,sxt,J=7.99Hz),4.31(3H,s),6.74(1H,d,J=2.74Hz),6.98(1H,d,J=7.39Hz),7.60(1H,dd,J=8.62,1.51Hz),7.60-7.64(1H,m),7.66(1H,d,J=2.46Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{21}H_{24}N_8O_2$的ESIMS实验值m/z 421.2(M+1)。

[1253] 

211

[1254] 顺-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺211。

[1255] 白色固体(4.4mg,0.010mmol,5.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),2.27-2.40(4H,m),2.80(3H,s),2.87(3H,s),3.94(3H,s),4.18(1H,dq,J=15.74,7.89Hz),4.31(3H,s),6.75(1H,d,J=2.74Hz),6.94(1H,d,J=7.12Hz),7.60(1H,dd,J=8.76,1.64Hz),7.65(1H,d,J=2.46Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{22}H_{26}N_8O_2$的ESIMS实验值m/z 435.3(M+1)。

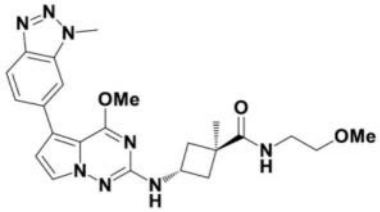
[1256] 

212

[1257] 反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺212。

[1258] 白色固体(35mg,0.081mmol,96.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.40(3H,s),1.94-2.03(2H,m),2.84(3H,br s),2.89(3H,s),2.89-2.94(2H,m),3.86-3.94(1H,m),3.96(3H,s),4.31(3H,s),6.74(1H,d,J=2.74Hz),7.08(1H,d,J=6.30Hz),7.60(1H,dd,J=8.76,1.37Hz),7.64(1H,d,J=2.74Hz),7.93(1H,d,J=1.10Hz),7.97(1H,d,J=

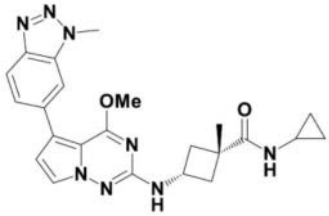
8.76Hz);$C_{22}H_{26}N_8O_2$的ESIMS实验值m/z 435.3(M+1)。

[1259] 

214

[1260] 反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N-(2-甲氧基乙基)-1-甲基环丁烷-1-甲酰胺214。

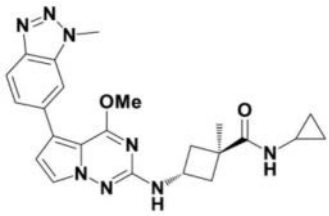
[1261] 白色固体(39mg,0.084mmol,45.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.32(3H,s),1.84-1.94(2H,m),2.70-2.80(2H,m),3.22-3.28(2H,m),3.26(3H,s),3.35-3.39(2H,m),3.95(3H,s),4.03(1H,sxt,J=7.94Hz),4.31(3H,s),6.74(1H,d,J=2.74Hz),6.98(1H,d,J=7.39Hz),7.60(1H,dd,J=8.76,1.37Hz),7.65(1H,d,J=2.46Hz),7.69(1H,t,J=5.61Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{23}H_{28}N_8O_3$的ESIMS实验值m/z 465.3(M+1)。

[1262] 

217

[1263] 顺-N-环丙基-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺217。

[1264] 灰白色固体(7mg,0.016mmol,8.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.39-0.46(2H,m),0.56-0.64(2H,m),1.32(3H,s),2.13-2.20(2H,m),2.20-2.29(2H,m),2.58-2.67(1H,m),3.94(3H,s),4.17(1H,sxt,J=7.88Hz),4.31(3H,s),6.74(1H,d,J=2.46Hz),6.92(1H,d,J=7.12Hz),7.49(1H,d,J=4.11Hz),7.60(1H,dd,J=8.62,1.51Hz),7.65(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.2(M+1)。

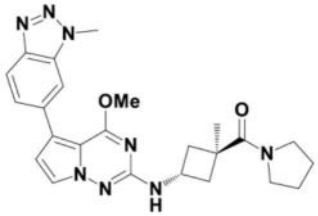
[1265] 

218

[1266] 反-N-环丙基-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺218。

[1267] 白色固体(44mg,0.099mmol,53.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.42-0.49(2H,m),0.58-0.65(2H,m),1.30(3H,s),1.82-1.92(2H,m),2.67(1H,tq,J=7.46,

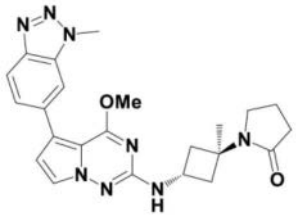
3.88Hz),2.74(2H,ddd,J=9.92,7.87,2.46Hz),3.95(3H,s),3.97-4.04(1H,m),4.31(3H,s),6.74(1H,d,J=2.74Hz),6.98(1H,d,J=7.39Hz),7.60(1H,dd,J=8.62,1.51Hz),7.62(1H,d,J=4.38Hz),7.66(1H,d,J=2.46Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.25(M+1)。

[1268] 

222

[1269] (反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)(吡咯烷-1-基)甲酮222。

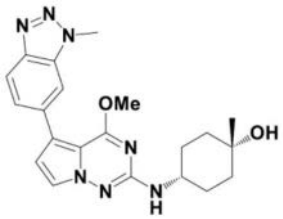
[1270] 白色固体(36mg,0.078mmol,93.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.73-1.80(2H,m),1.81-1.87(2H,m),1.91-1.99(2H,m),2.86-2.93(2H,m),3.30-3.34(4H,m),3.87-3.94(1H,m),3.96(3H,s),4.31(3H,s),6.74(1H,d,J=2.46Hz),7.07(1H,d,J=6.57Hz),7.60(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.74Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{24}H_{28}N_8O_2$的ESIMS实验值m/z461.3(M+1)。

[1271] 

223

[1272] 1-(反-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)吡咯烷-2-酮223。

[1273] 灰白色固体(23mg,0.052mmol,46.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.92(2H,quin,J=7.53Hz),2.00-2.08(2H,m),2.23(2H,t,J=8.08Hz),2.82-2.92(2H,m),3.40(2H,t,J=6.84Hz),3.96(3H,s),4.04-4.12(1H,m),4.31(3H,s),6.74(1H,d,J=2.46Hz),7.06(1H,d,J=6.30Hz),7.60(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.46Hz),7.94(1H,s),7.97(1H,d,J=8.76Hz);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.3(M+1)。

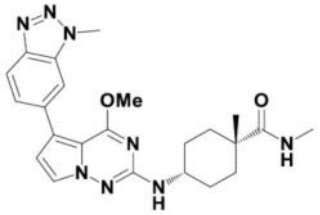
[1274] 

224

[1275] 顺-4-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇224。

[1276] 灰白色固体(36mg,0.088mmol,34.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12

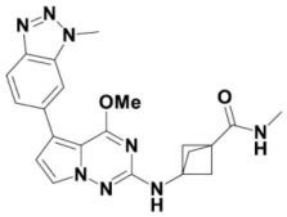
(3H,s),1.37(2H,td,J＝13.00,4.38Hz),1.58(2H,br d,J＝12.32Hz),1.61-1.69(2H,m),1.69-1.75(2H,m),3.47-3.58(1H,m),3.95(3H,s),4.00(1H,s),4.31(3H,s),6.50(1H,d,J＝7.94Hz),6.72(1H,d,J＝2.46Hz),7.59-7.63(2H,m),7.93(1H,s),7.97(1H,d,J＝8.49Hz);$C_{21}H_{25}N_7O_2$的ESIMS实验值m/z 408.2(M+1)。

[1277] 

225

[1278] 顺-4-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环己烷-1-甲酰胺225。

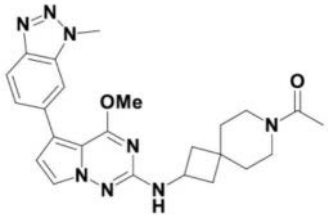
[1279] 灰白色固体(10mg,0.022mmol,31.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.03(3H,s),1.15-1.27(2H,m),1.27-1.37(2H,m),1.77-1.87(2H,m),2.18(2H,br d,J＝12.32Hz),2.61(3H,d,J＝4.38Hz),3.49-3.61(1H,m),3.93(3H,s),4.31(3H,s),6.51(1H,d,J＝7.94Hz),6.73(1H,d,J＝2.46Hz),7.53(1H,q,J＝4.38Hz),7.59-7.61(1H,m),7.62(1H,d,J＝2.46Hz),7.93(1H,d,J＝0.82Hz),7.97(1H,d,J＝8.76Hz);$C_{23}H_{28}N_8O_2$的ESIMS实验值m/z 449.3(M+1)。

[1280] 

226

[1281] 3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N-甲基双环[1.1.1]戊烷-1-甲酰胺226。

[1282] 灰白色固体(5mg,0.012mmol,5.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.23(6H,s),2.55-2.59(3H,m),3.96(3H,s),4.31(3H,s),6.79(1H,d,J＝2.46Hz),7.47(1H,s),7.61(1H,dd,J＝8.76,1.37Hz),7.64(1H,d,J＝2.46Hz),7.73(1H,q,J＝4.47Hz),7.95(1H,s),7.98(1H,d,J＝8.76Hz);$C_{21}H_{22}N_8O_2$的ESIMS实验值m/z 419.2(M+1)。

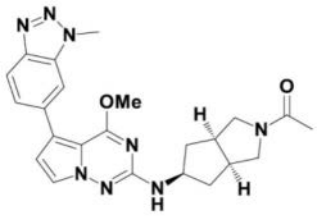
[1283] 

227

[1284] 1-(2-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮227。

[1285] 灰白色固体(23mg,0.050mmol,69.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.41-

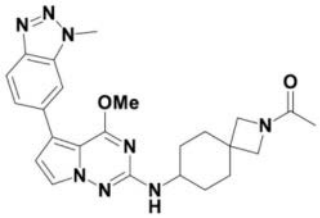
1.46(1H,m),1.52(2H,br t,J＝10.27Hz),1.57-1.63(1H,m),1.76-1.85(2H,m),1.95-2.00(3H,m),2.23-2.32(2H,m),3.26-3.30(1H,m),3.31-3.35(1H,m),3.35-3.39(1H,m),3.40-3.44(1H,m),3.95(3H,s),4.15-4.26(1H,m),4.31(3H,s),6.74(1H,d,J＝2.46Hz),7.00(1H,t,J＝7.12Hz),7.60(1H,dd,J＝8.76,1.37Hz),7.63-7.65(1H,m),7.93(1H,s),7.97(1H,d,J＝8.76Hz);$C_{24}H_{28}N_8O_2$的ESIMS实验值m/z 461.3(M+1)。

[1286] 

228

[1287] 1-((3aR,5r,6aS)-5-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)六氢环戊并[c]吡咯-2(1H)-基)乙-1-酮228。

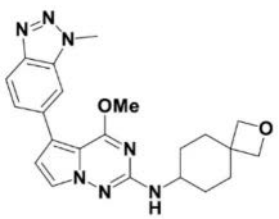
[1288] 灰白色固体(74mg,0.166mmol,89.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34-1.49(2H,m),1.94(3H,s),2.24-2.36(2H,m),2.57(1H,quind,J＝8.01,8.01,8.01,8.01,4.65Hz),2.62-2.72(1H,m),3.35-3.46(3H,m),3.59(1H,dd,J＝10.68,7.94Hz),3.95(3H,s),4.07-4.20(1H,m),4.31(3H,s),6.74(1H,d,J＝2.74Hz),6.82(1H,d,J＝7.39Hz),7.60(1H,dd,J＝8.76,1.37Hz),7.63(1H,d,J＝2.46Hz),7.93(1H,s),7.97(1H,d,J＝9.03Hz);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.2(M+1)。

[1289] 

229

[1290] 1-(7-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮229。

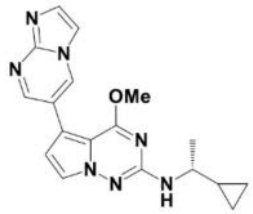
[1291] 灰白色固体(12mg,0.026mmol,72.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27-1.39(2H,m),1.49-1.61(2H,m),1.72-1.78(3H,m),1.82-1.94(4H,m),3.47(1H,s),3.52(1H,s),3.54-3.65(1H,m),3.75(1H,s),3.80(1H,s),3.95(3H,d,J＝1.10Hz),4.31(3H,s),6.52(1H,dd,J＝16.43,7.94Hz),6.74(1H,d,J＝2.74Hz),7.61(1H,dd,J＝8.62,1.51Hz),7.63(1H,t,J＝2.87Hz),7.93(1H,s),7.97(1H,d,J＝8.76Hz);$C_{24}H_{28}N_8O_2$的ESIMS实验值m/z 461.3(M+1)。

[1292] 

230

[1293] 4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺230。

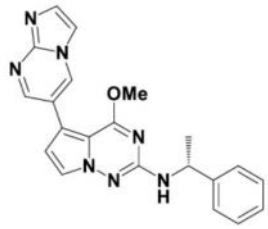
[1294] 米色固体(28mg,0.067mmol,35.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.21-1.33(2H,m),1.53(2H,td,J=12.87,3.29Hz),1.82-1.93(2H,m),2.07(2H,br d,J=13.14Hz),3.51-3.61(1H,m),3.94(3H,s),4.24(2H,s),4.31(3H,s),4.32(2H,s),6.50(1H,d,J=7.94Hz),6.73(1H,d,J=2.74Hz),7.60(1H,dd,J=8.76,1.37Hz),7.63(1H,d,J=2.46Hz),7.93(1H,s),7.97(1H,d,J=8.76Hz);$C_{22}H_{25}N_7O_2$的ESIMS实验值m/z 420.2(M+1)。

[1295] 

231

[1296] (R)-N-(1-环丙基乙基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺231。

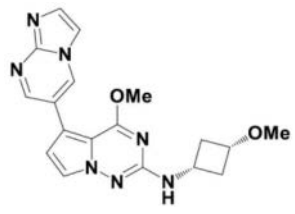
[1297] 米色固体(4mg,0.011mmol,6.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.16-0.24(1H,m),0.33-0.40(2H,m),0.47(1H,s),0.97-1.07(1H,m),1.23(3H,d,J=6.57Hz),3.33-3.38(1H,m),3.97(3H,s),6.66(1H,d,J=8.49Hz),6.76(1H,d,J=2.46Hz),7.63(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O$的ESIMS实验值m/z350.2(M+1)。

[1298] 

233

[1299] (R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-苯基乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺233。

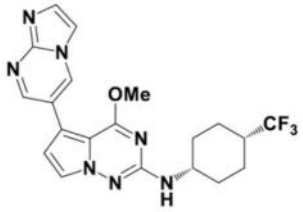
[1300] 灰白色固体(10mg,0.026mmol,15.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.46(3H,d,J=7.12Hz),3.98(3H,s),4.95(1H,quin,J=7.39Hz),6.74(1H,d,J=2.46Hz),7.17-7.22(1H,m),7.28-7.33(3H,m),7.43(2H,d,J=7.39Hz),7.58(1H,d,J=2.74Hz),7.71(1H,d,J=1.10Hz),7.91(1H,d,J=1.09Hz),8.71(1H,d,J=2.46Hz),9.06(1H,d,J=2.46Hz);$C_{21}H_{19}N_7O$的ESIMS实验值m/z 386.2(M+1)。

[1301] 

236

[1302] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-3-甲氧基环丁基)吡咯并[2,1-f][1,2,4]三嗪-2-胺236。

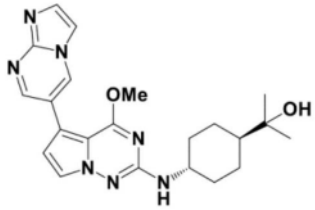
[1303] 白色固体(65mg,0.178mmol,53.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.78-1.91(2H,m),2.59-2.70(2H,m),3.14(3H,s),3.61(1H,quin,J=7.12Hz),3.73-3.87(1H,m),3.97(3H,s),6.78(1H,d,J=2.46Hz),7.07(1H,d,J=7.39Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.09Hz),7.92(1H,d,J=1.09Hz),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[1304] 

239

[1305] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-(三氟甲基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺239。

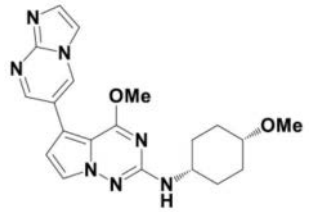
[1306] 灰白色固体(31mg,0.072mmol,36.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.59-1.69(4H,m),1.69-1.80(2H,m),1.95-2.06(2H,m),2.23-2.35(1H,m),3.87-3.95(1H,m),4.00(3H,s),6.78(1H,d,J=2.46Hz),6.80(1H,d,J=6.30Hz),7.66(1H,d,J=2.46Hz),7.72(1H,d,J=1.10Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{20}H_{20}F_3N_7O$的ESIMS实验值m/z 432.2(M+1)。

[1307] 

242

[1308] 2-(反-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇242。

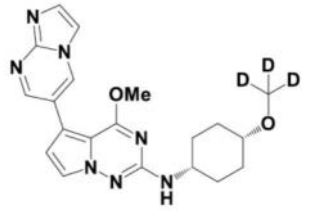
[1309] 白色固体(1mg,0.002mmol,1.4%产率)。^{1}H NMR(499MHz,氯仿-d)δppm 1.22(6H,s),1.24-1.30(3H,m),1.31-1.41(2H,m),1.95(2H,br d,J=12.05Hz),2.30(2H,br d,J=10.95Hz),3.66(1H,tdt,J=11.21,11.21,7.63,3.87,3.87Hz),4.00(3H,s),4.37(1H,d,J=7.94Hz),6.59(1H,d,J=2.46Hz),7.49(1H,d,J=2.46Hz),7.57(1H,br s),7.85(1H,br s),8.42-8.66(2H,m),8.79(1H,br s);$C_{22}H_{27}N_7O_2$的ESIMS实验值m/z 422.2(M+1)。

[1310] 

243

[1311] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-甲氧基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺243。

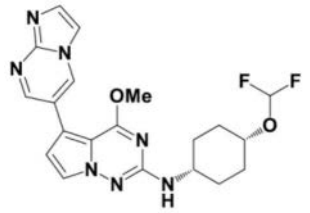
[1312] 白色固体(71mg,0.181mmol,54.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.54(2H,m),1.56-1.65(2H,m),1.66-1.73(2H,m),1.80-1.89(2H,m),3.22(3H,s),3.34-3.37(1H,m),3.55-3.70(1H,m),3.97(3H,s),6.62(1H,d,J=7.67Hz),6.76(1H,d,J=2.46Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.10Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[1313] 

245

[1314] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-(甲氧基-d_3)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺245。

[1315] 灰白色固体(49mg,0.124mmol,41.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.44-1.54(2H,m),1.55-1.65(2H,m),1.65-1.73(2H,m),1.80-1.88(2H,m),3.33-3.38(1H,m),3.58-3.71(1H,m),3.97(3H,s),6.62(1H,d,J=7.67Hz),6.76(1H,d,J=2.46Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz)$C_{20}H_{20}[^2H_3]N_7O_2$的ESIMS实验值m/z 397.2(M+1)。

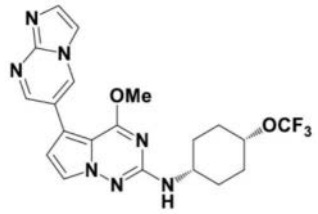
[1316] 

250

[1317] N-(顺-4-(二氟甲氧基)环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺250。

[1318] 米色固体(21mg,0.049mmol,21.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.61-1.72(4H,m),1.74-1.82(2H,m),1.87(2H,dt,J=9.58,4.79Hz),3.68(1H,br dd,J=8.08,3.97Hz),3.98(3H,s),4.29(1H,br s),6.72(1H,t,J=77.05Hz),6.73(1H,d,J=7.67Hz),6.77(1H,d,J=2.46Hz),7.65(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{21}F_2N_7O_2$的ESIMS实验值m/z

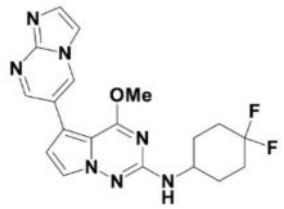
430.2(M+1)。

[1319] 

252

[1320] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(顺-4-(三氟甲氧基)环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺252。

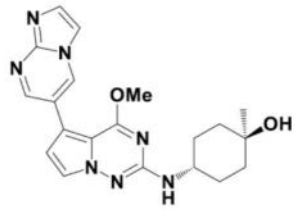
[1321] 灰白色固体(31mg,0.069mmol,34.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.61-1.71(2H,m),1.71-1.79(2H,m),1.83(2H,td,J=8.42,3.97Hz),1.91-1.99(2H,m),3.65-3.77(1H,m),3.98(3H,s),4.60(1H,dt,J=5.00,2.29Hz),6.76(1H,d,J=7.67Hz),6.77(1H,d,J=2.74Hz),7.66(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.74Hz);$C_{20}H_{20}F_3N_7O_2$的ESIMS实验值m/z 448.2(M+1)。

[1322] 

254

[1323] N-(4,4-二氟环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺254。

[1324] 灰白色固体(68mg,0.170mmol,56.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.54-1.69(2H,m),1.85-2.02(4H,m),2.03-2.16(2H,m),3.74-3.86(1H,m),3.98(3H,s),6.78(1H,d,J=2.46Hz),6.80(1H,d,J=7.67Hz),7.67(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.09Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{19}H_{19}F_2N_7O$的ESIMS实验值m/z 400.2(M+1)。

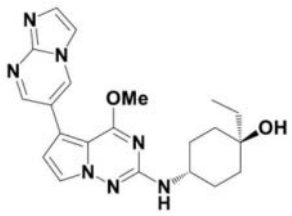
[1325] 

257

[1326] 反-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇257。

[1327] 灰白色固体(25mg,0.064mmol,29.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.36-1.52(4H,m),1.55-1.68(2H,m),1.82-1.93(2H,m),3.58-3.72(1H,m),3.97(3H,s),4.24(1H,s),6.54(1H,d,J=7.94Hz),6.76(1H,d,J=2.46Hz),7.67(1H,d,J=

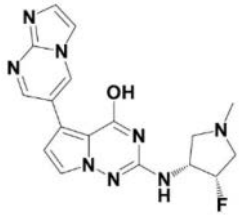
2.74Hz),7.72(1H,d,J=1.37Hz),7.92(1H,d,J=1.10Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[1328] 

258

[1329] 反-1-乙基-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇258。

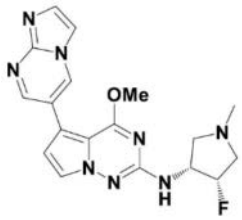
[1330] 灰白色固体(13mg,0.032mmol,24.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.83(3H,t,J=7.39Hz),1.31-1.39(2H,m),1.40-1.49(4H,m),1.64(2H,br d,J=10.68Hz),1.85(2H,br dd,J=12.05,6.30Hz),3.68(1H,dt,J=8.01,3.80Hz),3.97(3H,s),3.98(1H,br s),6.53(1H,d,J=7.67Hz),6.76(1H,d,J=2.46Hz),7.67(1H,d,J=2.46Hz),7.72(1H,s),7.92(1H,s),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{21}H_{25}N_7O_2$的ESIMS实验值m/z 408.2(M+1)。

[1331] 

261

[1332] 2-(((3R,4S)-4-氟-1-甲基吡咯烷-3-基)氨基)-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇261。

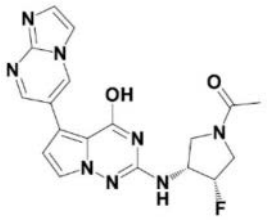
[1333] 浅黄色半固体(11mg,0.030mmol,26.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.29(3H,s),2.47-2.52(16H,m),2.71(1H,ddd,J=30.45,12.05,1.10Hz),2.88(1H,dd,J=9.17,7.26Hz),2.96(1H,ddd,J=31.85,12.10,4.70Hz),4.19-4.34(1H,m),5.22(1H,dtd,J=55.95,5.20,5.20,1.35Hz),6.17(1H,br d,J=7.39Hz),6.81(1H,d,J=2.74Hz),7.48(1H,d,J=2.74Hz),7.71(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.90(1H,d,J=2.46Hz),9.41(1H,d,J=2.46Hz),10.69(1H,br s);$C_{17}H_{17}FN_8O$的ESIMS实验值m/z 369.2(M+1)。

[1334] 

262

[1335] N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺262。

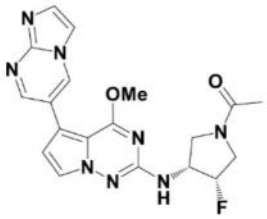
[1336] 浅黄色半固体(12mg,0.031mmol,39.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.31(3H,s),2.55-2.66(2H,m),2.92(1H,t,J=8.08Hz),3.17(1H,ddd,J=29.35,11.80,4.95Hz),4.00(3H,s),4.20-4.35(1H,m),5.21(1H,dtd,J=55.95,5.20,5.20,1.95Hz),6.81(1H,d,J=2.46Hz),6.84(1H,d,J=7.67Hz),7.69(1H,d,J=2.74Hz),7.73(1H,d,J=1.09Hz),7.93(1H,d,J=1.09Hz),8.74(1H,d,J=2.46Hz),9.10(1H,d,J=2.46Hz);$C_{18}H_{19}FN_8O$的ESIMS实验值m/z 383.2(M+1)。

[1337] 

263

[1338] 1-((3S,4R)-3-氟-4-((4-羟基-5-(咪唑并[1,2-a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮263。

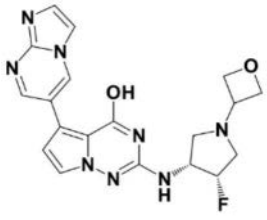
[1339] 浅黄色固体(7mg,0.018mmol,15.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.91-2.03(3H,m),3.48-3.76(2H,m),3.79-3.93(1H,m),3.99-4.09(1H,m),4.28-4.61(1H,m),5.22-5.49(1H,m),6.30-6.43(1H,m),6.83(1H,br s),7.48(1H,d,J=2.19Hz),7.71(1H,s),7.94(1H,s),8.91(1H,d,J=1.64Hz),9.41(1H,s),10.77(1H,br s);$C_{18}H_{17}FN_8O_2$的ESIMS实验值m/z 397.2(M+1)。

[1340] 

264

[1341] 1-((3S,4R)-3-氟-4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮264。

[1342] 黄色固体(24mg,0.059mmol,74.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.93-2.01(3H,m),3.47-3.57(1H,m),3.58-3.76(1H,m),3.78-3.97(2H,m),4.01(3H,d,J=1.37Hz),4.28-4.59(1H,m),5.24-5.50(1H,m),6.83(1H,t,J=2.33Hz),7.15(1H,dd,J=7.12,4.65Hz),7.70(1H,dd,J=3.83,2.74Hz),7.73(1H,s),7.94(1H,d,J=0.82Hz),8.75(1H,d,J=2.46Hz),9.11(1H,d,J=2.46Hz);$C_{19}H_{19}FN_8O_2$的ESIMS实验值m/z 411.2(M+1)。

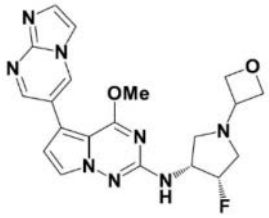
[1343] 

265

[1344] 2-(((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-5-(咪唑并[1,2-

a]嘧啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-4-醇265。

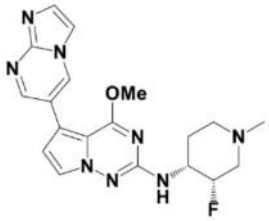
[1345] 灰白色固体(4mg,0.010mmol,8.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.56(1H,t,J=8.49Hz),2.79-2.91(1H,m),2.96-3.09(1H,m),2.98-3.03(1H,m),3.76(1H,quin,J=6.09Hz),4.22-4.37(1H,m),4.46(2H,t,J=6.02Hz),4.58(2H,t,J=6.57Hz),5.25(1H,dtd,J=55.95,4.65,4.65,1.00Hz),6.29(1H,br d,J=6.30Hz),6.81(1H,d,J=2.74Hz),7.48(1H,d,J=2.74Hz),7.71(1H,d,J=1.10Hz),7.93(1H,d,J=1.09Hz),8.90(1H,d,J=2.46Hz),9.41(1H,d,J=2.19Hz),10.78(1H,br s);$C_{19}H_{19}FN_8O_2$的ESIMS实验值m/z 411.2(M+1)。

[1346] 

266

[1347] N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺266。

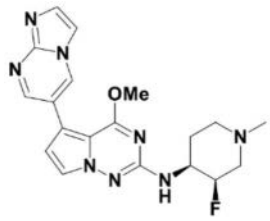
[1348] 灰白色固体(15mg,0.035mmol,33.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.69(1H,t,J=9.17Hz),2.77(1H,ddd,J=29.65,12.10,1.10Hz),3.01(1H,t,J=8.35Hz),3.18(1H,ddd,J=32.95,12.05,4.40Hz),3.74-3.84(1H,m),4.00(3H,s),4.23-4.38(1H,m),4.47(2H,t,J=6.02Hz),4.60(2H,t,J=6.57Hz),5.25(1H,dtd,J=55.65,4.65,4.65,1.65Hz),6.82(1H,d,J=2.46Hz),6.90(1H,d,J=7.67Hz),7.69(1H,d,J=2.74Hz),7.73(1H,d,J=1.10Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.10(1H,d,J=2.46Hz);$C_{20}H_{21}FN_8O_2$的ESIMS实验值m/z 425.2(M+1)。

[1349] 

267

[1350] N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺267。

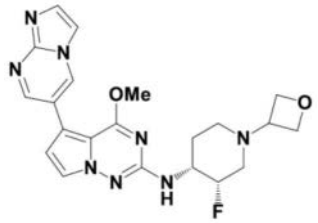
[1351] 白色固体(14mg,0.035mmol,67.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.65-1.72(1H,m),1.92(1H,qd,J=12.18,3.70Hz),2.02-2.10(1H,m),2.11-2.25(1H,m),2.19(3H,s),2.80(1H,br d,J=12.32Hz),3.00-3.12(1H,m),3.67-3.84(1H,m),3.99(3H,s),4.55(4H,s),4.91(1H,d,J=50.20Hz),6.70(1H,d,J=7.94Hz),6.79(1H,d,J=2.74Hz),7.67(1H,d,J=2.74Hz),7.73(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{19}H_{21}FN_8O$的ESIMS实验值m/z 397.2(M+1)。

[1352] 

268

[1353] N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺268。

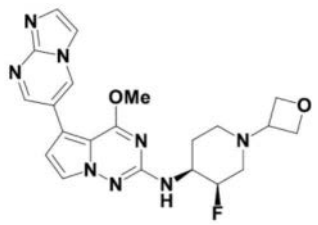
[1354] 白色固体(15mg,0.038mmol,72.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.62-1.74(1H,m),1.92(1H,qd,J=12.09,3.70Hz),2.01-2.10(1H,m),2.11-2.24(1H,m),2.18(3H,s),2.79(1H,br d,J=11.23Hz),3.00-3.11(1H,m),3.68-3.83(1H,m),3.99(3H,s),4.91(1H,d,J=50.20Hz),6.69(1H,d,J=7.94Hz),6.79(1H,d,J=2.46Hz),7.67(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{19}H_{21}FN_8O$的ESIMS实验值m/z 397.2(M+1)。

[1355] 

269

[1356] N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺269。

[1357] 白色固体(13mg,0.030mmol,36.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.78(1H,m),1.92(1H,qd,J=12.14,3.56Hz),1.98-2.06(1H,m),2.10-2.25(1H,m),2.76(1H,br d,J=10.13Hz),2.93-3.06(1H,m),3.49(1H,quin,J=6.30Hz),3.74-3.90(1H,m),3.99(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.94(1H,d,J=49.35Hz),6.76(1H,d,J=7.67Hz),6.79(1H,d,J=2.46Hz),7.67(1H,d,J=2.74Hz),7.73(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{21}H_{23}FN_8O_2$的ESIMS实验值m/z 439.2(M+1)。

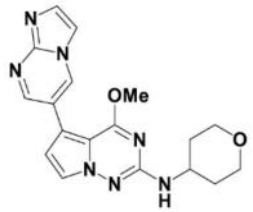
[1358] 

270

[1359] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺270。

[1360] 白色固体(23mg,0.053mmol,37.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69-1.76(1H,m),1.92(1H,qd,J=12.14,3.29Hz),1.98-2.06(1H,m),2.08-2.24(1H,m),2.71-

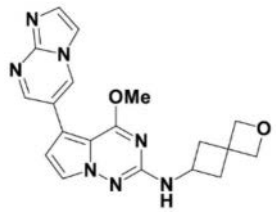
2.80(1H,m),2.94-3.05(1H,m),3.49(1H,quin,J=6.50Hz),3.74-3.91(1H,m),3.99(3H,s),4.40(1H,t,J=6.02Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.50,3.15Hz),4.93(1H,d,J=49.35Hz),6.76(1H,d,J=7.94Hz),6.79(1H,d,J=2.74Hz),7.67(1H,d,J=2.46Hz),7.73(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{21}H_{23}FN_8O_2$的ESIMS实验值m/z 439.2(M+1)。

[1361] 

271

[1362] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺271。

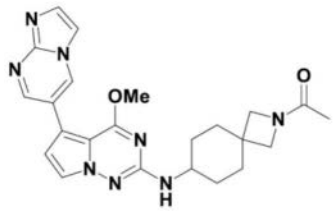
[1363] 米色固体(4mg,0.011mmol,6.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.48-1.61(2H,m),1.90(2H,br dd,J=12.59,2.19Hz),3.40(2H,td,J=11.64,1.92Hz),3.76-3.84(1H,m),3.85-3.91(2H,m),3.98(3H,s),6.74(1H,d,J=7.94Hz),6.77(1H,d,J=2.46Hz),7.67(1H,d,J=2.46Hz),7.72(1H,d,J=1.09Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz)$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[1364] 

272

[1365] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺272。

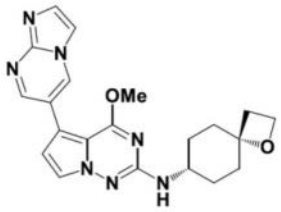
[1366] 灰白色固体(6mg,0.016mmol,6.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.12-2.23(2H,m),2.61(2H,ddd,J=9.99,7.53,2.74Hz),3.92-4.05(1H,m),3.96(3H,s),4.51(2H,s),4.63(2H,s),6.78(1H,d,J=2.74Hz),7.03(1H,d,J=7.12Hz),7.66(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.92(1H,d,J=1.37Hz),8.72(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{19}H_{19}N_7O_2$的ESIMS实验值m/z 378.2(M+1)。

[1367] 

273

[1368] 1-(7-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮273。

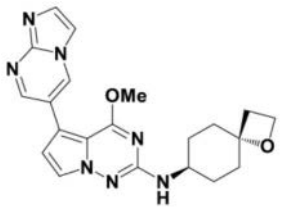
[1369] 无色胶状物(10mg,0.022mmol,21.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.26-1.40(2H,m),1.49-1.61(2H,m),1.74-1.77(3H,m),1.83-1.93(4H,m),3.47(1H,s),3.52(1H,s),3.53-3.63(1H,m),3.75(1H,s),3.80(1H,s),3.97(3H,s),6.59(1H,dd,J=16.70,7.94Hz),6.77(1H,d,J=2.74Hz),7.67(1H,t,J=2.87Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{23}H_{26}N_8O_2$的ESIMS实验值m/z 447.3(M+1)。

[1370] 

274

[1371] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((4s,7s)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺274。

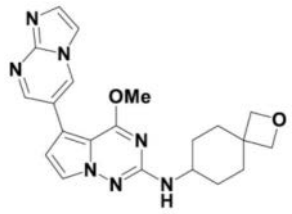
[1372] 白色固体(4.2mg,0.0104mmol)。^{1}H NMR(400MHz,DMSO-d_6)δppm 1.28-1.41(2H,m),1.52(2H,td,J=12.38,3.38Hz),1.85-1.98(2H,m),2.05(2H,br d,J=12.88Hz),2.34(2H,t,J=7.69Hz),3.50-3.64(1H,m),3.97(3H,s),4.37(2H,t,J=7.69Hz),6.58(1H,d,J=7.75Hz),6.76(1H,d,J=2.63Hz),7.67(1H,d,J=2.63Hz),7.72(1H,s),7.92(1H,d,J=1.00Hz),8.73(1H,d,J=2.38Hz),9.08(1H,d,J=2.38Hz);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.0(M+1)。

[1373] 

275

[1374] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((4r,7r)-1-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺275。

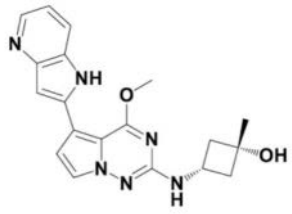
[1375] 白色固体(4.20mg,0.010mmol)。^{1}H NMR(400MHz,DMSO-d_6)δppm 1.29-1.43(2H,m),1.47-1.60(2H,m),1.86-1.97(2H,m),2.05(2H,br d,J=12.88Hz),2.34(2H,t,J=7.69Hz),3.51-3.63(1H,m),3.97(3H,s),4.37(2H,t,J=7.69Hz),6.58(1H,d,J=7.75Hz),6.76(1H,d,J=2.63Hz),7.67(1H,d,J=2.63Hz),7.72(1H,s),7.92(1H,d,J=1.00Hz),8.73(1H,d,J=2.38Hz),9.08(1H,d,J=2.38Hz);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.0(M+1)。

[1376] 

276

[1377] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺276。

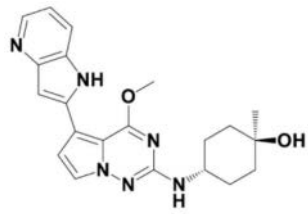
[1378] 米色固体(32mg,0.079mmol,29.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20-1.32(2H,m),1.52(2H,td,J=12.87,3.29Hz),1.87(2H,br dd,J=13.14,3.29Hz),2.07(2H,br d,J=13.14Hz),3.48-3.62(1H,m),3.96(3H,s),4.24(2H,s),4.32(2H,s),6.55(1H,d,J=7.94Hz),6.76(1H,d,J=2.46Hz),7.66(1H,d,J=2.46Hz),7.73(1H,s),7.93(1H,s),8.73(1H,d,J=2.19Hz),9.08(1H,d,J=2.46Hz);$C_{21}H_{23}N_7O_2$的ESIMS实验值m/z 406.2(M+1)。

[1379] 

277

[1380] 顺-3-((4-甲氧基-5-(1H-吡咯并[3,2-b]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇277。

[1381] 米色固体(39mg,0.107mmol,46.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),1.99-2.07(2H,m),2.31-2.40(2H,m),3.72(1H,dq,J=15.09,7.75Hz),4.11(3H,s),4.92(1H,s),6.94(1H,dd,J=2.19,0.82Hz),6.99(1H,d,J=2.74Hz),7.00(1H,d,J=6.57Hz),7.03(1H,dd,J=7.95,4.65Hz),7.65(1H,d,J=2.74Hz),7.70(1H,dt,J=8.01,1.20Hz),8.25(1H,dd,J=4.65,1.37Hz),11.18(1H,d,J=1.92Hz);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

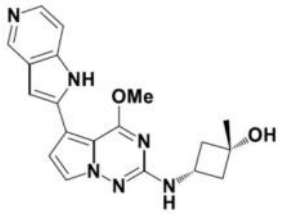
[1382] 

280

[1383] 反-4-((4-甲氧基-5-(1H-吡咯并[3,2-b]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇280。

[1384] 黄色固体(37mg,0.094mmol,39.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.33-1.52(4H,m),1.54-1.63(2H,m),1.82-1.91(2H,m),3.64(1H,dt,J=8.08,4.18Hz),4.12(3H,s),4.23(1H,s),6.55(1H,d,J=7.94Hz),6.93(1H,d,J=1.37Hz),6.98

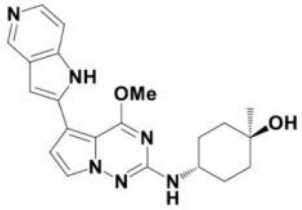
(1H,d,J＝2.74Hz),7.03(1H,dd,J＝7.95,4.65Hz),7.65(1H,d,J＝2.74Hz),7.69-7.72(1H,m),8.25(1H,dd,J＝4.65,1.37Hz),11.18(1H,d,J＝1.92Hz);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[1385] 

281

[1386] 顺-3-((4-甲氧基-5-(1H-吡咯并[3,2-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇281。

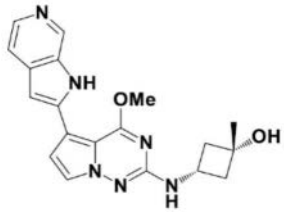
[1387] 灰白色固体(2mg,0.006mmol,9.1％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),1.97-2.07(2H,m),2.30-2.41(2H,m),3.71(1H,dq,J＝15.09,7.65Hz),4.10(3H,s),4.93(1H,s),6.93(1H,d,J＝1.10Hz),6.95(1H,d,J＝2.74Hz),6.98(1H,d,J＝6.57Hz),7.34(1H,d,J＝5.48Hz),7.64(1H,d,J＝2.74Hz),8.11(1H,d,J＝5.48Hz),8.76(1H,s),11.41(1H,s);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

[1388] 

282

[1389] 反-4-((4-甲氧基-5-(1H-吡咯并[3,2-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇282。

[1390] 白色固体(7mg,0.018mmol,31.7％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.36-1.52(4H,m),1.57-1.65(2H,m),1.83-1.92(2H,m),3.63(1H,br dd,J＝7.80,3.70Hz),4.11(3H,s),4.24(1H,s),6.53(1H,d,J＝7.94Hz),6.93(1H,d,J＝1.10Hz),6.95(1H,d,J＝2.74Hz),7.34(1H,d,J＝5.75Hz),7.64(1H,d,J＝2.46Hz),8.12(1H,br d,J＝5.48Hz),8.76(1H,s),11.41(1H,d,J＝0.82Hz);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

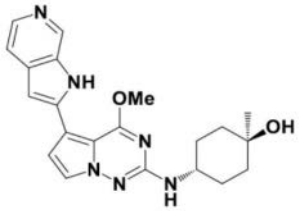
[1391] 

283

[1392] 顺-3-((4-甲氧基-5-(1H-吡咯并[2,3-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇283。

[1393] 棕褐色固体(6mg,0.017mmol,40.7％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),1.96-2.07(2H,m),2.30-2.41(2H,m),3.66-3.78(1H,m),4.11(3H,s),4.93(1H,s),

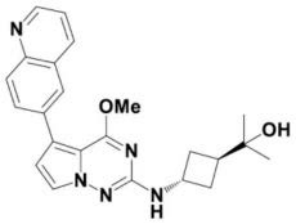
6.86(1H,d,J＝1.64Hz),6.99(1H,d,J＝2.74Hz),7.02(1H,d,J＝6.57Hz),7.45(1H,br d,J＝5.20Hz),7.65(1H,d,J＝2.74Hz),8.04(1H,br d,J＝4.93Hz),8.70(1H,br s),11.42(1H,s);$C_{19}H_{20}N_6O_2$的ESIMS实验值m/z 365.2(M+1)。

[1394] 

284

[1395] 反-4-((4-甲氧基-5-(1H-吡咯并[2,3-c]吡啶-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇284。

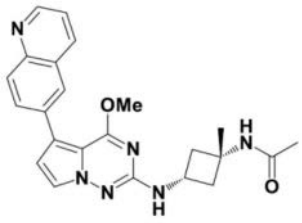
[1396] 米色固体(12mg,0.031mmol,66.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.30-1.53(4H,m),1.54-1.63(2H,m),1.63-1.77(2H,m),3.47-3.70(1H,m),4.11(3H,d,J＝1.64Hz),6.58(1H,dd,J＝14.51,7.94Hz),6.86(1H,d,J＝1.64Hz),6.98(1H,t,J＝2.87Hz),7.45(1H,br d,J＝5.48Hz),7.64(1H,dd,J＝14.78,2.46Hz),8.04(1H,br d,J＝4.93Hz),8.70(1H,s),11.41(1H,br s);$C_{21}H_{24}N_6O_2$的ESIMS实验值m/z 393.2(M+1)。

[1397] 

287

[1398] 2-(反-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁基)丙-2-醇287。

[1399] 黄色固体(36mg,0.089mmol,46.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.05(6H,s),1.98(2H,ddd,J＝12.39,9.65,5.89Hz),2.16-2.27(1H,m),2.27-2.36(2H,m),3.96(3H,s),4.09(1H,dq,J＝13.62,6.96Hz),4.19(1H,s),6.76(1H,d,J＝2.74Hz),6.96(1H,d,J＝6.84Hz),7.52(1H,dd,J＝8.21,4.11Hz),7.64(1H,d,J＝2.46Hz),7.94-8.01(2H,m),8.10(1H,s),8.36(1H,dd,J＝8.35,1.51Hz),8.86(1H,dd,J＝4.24,1.78Hz);$C_{23}H_{25}N_5O_2$的ESIMS实验值m/z 404.2(M+1)。

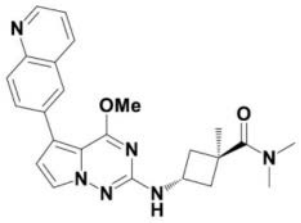
[1400] 

288

[1401] N-(顺-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺288。

[1402] 灰白色固体(39mg,0.094mmol,97.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38

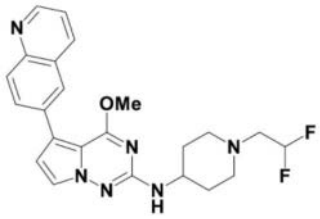
(3H,s),1.76(3H,s),2.10-2.21(2H,m),2.43(2H,ddd,J＝9.58,7.39,2.46Hz),3.96(3H,s),4.04(1H,sxt,J＝7.72Hz),6.77(1H,d,J＝2.46Hz),7.00(1H,d,J＝6.84Hz),7.52(1H,dd,J＝8.35,4.24Hz),7.66(1H,d,J＝2.74Hz),7.95-8.01(2H,m),8.03(1H,s),8.11(1H,s),8.36(1H,dd,J＝8.35,1.51Hz),8.86(1H,dd,J＝4.11,1.64Hz);$C_{23}H_{24}N_6O_2$的ESIMS实验值m/z 417.2(M+1)。

[1403] 

290

[1404] 反-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺290。

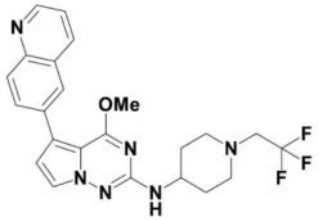
[1405] 淡黄色固体(32mg,0.074mmol,60.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.40(3H,s),1.95-2.05(2H,m),2.80-2.95(8H,m),3.91(1H,dq,J＝14.78,7.30Hz),3.97(3H,s),6.78(1H,d,J＝2.74Hz),7.08(1H,d,J＝6.57Hz),7.56(1H,dd,J＝8.35,4.24Hz),7.66(1H,d,J＝2.46Hz),8.00(2H,s),8.13(1H,s),8.40(1H,d,J＝7.39Hz),8.88(1H,br d,J＝3.01Hz);$C_{24}H_{26}N_6O_2$的ESIMS实验值m/z 431.2(M+1)。

[1406] 

304

[1407] N-(1-(2,2-二氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺304。

[1408] 黄色固体(42mg,0.096mmol,37.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.47-1.62(2H,m),1.85-1.95(2H,m),2.21-2.32(2H,m),2.72(2H,td,J＝15.61,4.38Hz),2.91(2H,br d,J＝11.77Hz),3.54-3.66(1H,m),3.96(3H,s),6.14(1H,tt,J＝55.95,4.38Hz),6.61(1H,d,J＝7.94Hz),6.77(1H,d,J＝2.46Hz),7.47-7.57(1H,m),7.65(1H,d,J＝2.74Hz),7.94-8.03(2H,m),8.11(1H,s),8.36(1H,dd,J＝8.35,1.51Hz),8.86(1H,dd,J＝4.11,1.64Hz);$C_{23}H_{24}F_2N_6O$的ESIMS实验值m/z439.2(M+1)。

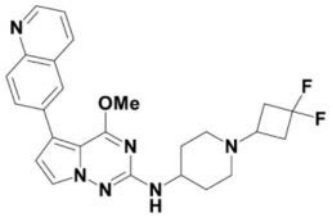
[1409] 

305

[1410] 4-甲氧基-5-(喹啉-6-基)-N-(1-(2,2,2-三氟乙基)哌啶-4-基)吡咯并[2,1-f]

[1,2,4]三嗪-2-胺305。

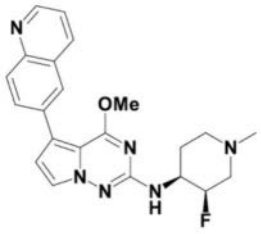
[1411] 灰白色固体(30mg,0.066mmol,26.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.49-1.61(2H,m),1.91(2H,br d,J=9.86Hz),2.39-2.48(2H,m),2.93(2H,br d,J=11.77Hz),3.17(2H,q,J=10.40Hz),3.55-3.66(1H,m),3.96(3H,s),6.62(1H,d,J=7.94Hz),6.77(1H,d,J=2.46Hz),7.52(1H,dd,J=8.21,4.11Hz),7.65(1H,d,J=2.74Hz),7.94-8.03(2H,m),8.11(1H,s),8.36(1H,dd,J=8.49,1.64Hz),8.86(1H,dd,J=4.38,1.64Hz);$C_{23}H_{23}F_3N_6O$的ESIMS实验值m/z 457.2(M+1)。

[1412] 

306

[1413] N-(1-(3,3-二氟环丁基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺306。

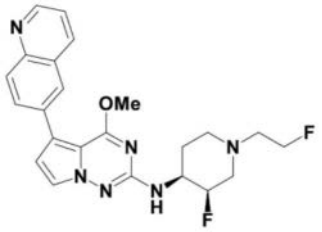
[1414] 白色固体(4mg,0.009mmol,4.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.59(2H,m),1.86-1.97(4H,m),2.32-2.46(2H,m),2.59-2.73(3H,m),2.80(2H,br d,J=11.50Hz),3.56-3.66(1H,m),3.96(3H,s),6.63(1H,d,J=7.94Hz),6.77(1H,d,J=2.46Hz),7.52(1H,dd,J=8.35,4.24Hz),7.65(1H,d,J=2.74Hz),7.94-8.03(2H,m),8.11(1H,s),8.36(1H,dd,J=8.35,1.51Hz),8.86(1H,dd,J=4.11,1.64Hz);$C_{25}H_{26}F_2N_6O$的ESIMS实验值m/z 465.2(M+1)。

[1415] 

310

[1416] N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺310。

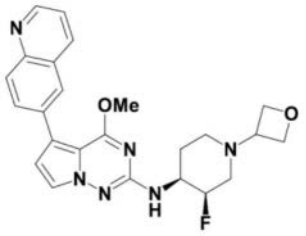
[1417] 灰白色固体(11mg,0.027mmol,88.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69(1H,br dd,J=13.00,3.42Hz),1.93(1H,qd,J=12.18,3.70Hz),2.06(1H,br t,J=10.95Hz),2.12-2.25(1H,m),2.19(3H,s),2.74-2.86(1H,m),3.00-3.11(1H,m),3.69-3.85(1H,m),3.98(3H,s),4.92(1H,d,J=49.90Hz),6.63(1H,d,J=7.67Hz),6.79(1H,d,J=2.46Hz),7.53(1H,dd,J=8.21,4.38Hz),7.65(1H,d,J=2.46Hz),7.95-8.04(2H,m),8.12(1H,s),8.36(1H,dd,J=8.35,1.51Hz),8.86(1H,dd,J=4.11,1.64Hz);$C_{22}H_{23}FN_6O$的ESIMS实验值m/z 407.2(M+1)。

[1418] 

314

[1419] N-((3R,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺314。

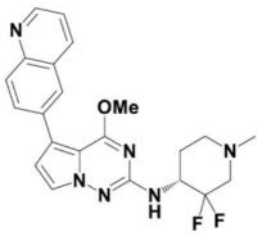
[1420] 灰白色蓬松固体(16mg,0.037mmol,47.7%产率)。^{1}H NMR(500MHz,DMSO-d_6)δppm 1.66-1.77(1H,m),1.93(1H,qd,J=12.21,3.43Hz),2.26(1H,br t,J=11.25Hz),2.39(1H,dd,J=37.60,12.90Hz),2.68(2H,dt,J=28.60,5.25Hz),2.93(1H,br d,J=10.70Hz),3.13-3.22(1H,m),3.73-3.89(1H,m),3.98(3H,s),4.55(2H,dt,J=47.75,4.95Hz),4.93(1H,d,J=49.70Hz),6.64(1H,d,J=7.68Hz),6.79(1H,d,J=2.47Hz),7.53(1H,dd,J=8.23,4.39Hz),7.65(1H,d,J=2.47Hz),7.94-8.04(2H,m),8.12(1H,s),8.36(1H,dd,J=8.23,1.37Hz),8.86(1H,dd,J=4.12,1.37Hz);$C_{23}H_{24}F_2N_6O$的ESIMS实验值m/z 439.2(M+1)。

[1421] 

318

[1422] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺318。

[1423] 米色固体(15mg,0.033mmol,72.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.79(1H,m),1.93(1H,qd,J=12.18,3.15Hz),1.98-2.08(1H,m),2.16(1H,dd,J=37.00,12.60Hz),2.76(1H,br d,J=11.23Hz),2.95-3.05(1H,m),3.50(1H,quin,J=6.43Hz),3.75-3.92(1H,m),3.98(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.95(1H,d,J=49.65Hz),6.69(1H,d,J=7.94Hz),6.79(1H,d,J=2.74Hz),7.49-7.57(1H,m),7.65(1H,d,J=2.74Hz),7.95-8.04(2H,m),8.12(1H,s),8.36(1H,dd,J=8.21,1.64Hz),8.86(1H,dd,J=4.11,1.64Hz);$C_{24}H_{25}FN_6O_2$的ESIMS实验值m/z449.3(M+1)。

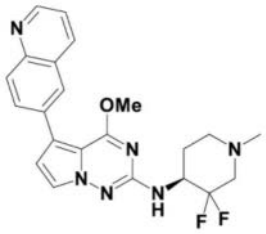
[1424] 

319

[1425] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f]

[1,2,4]三嗪-2-胺319。

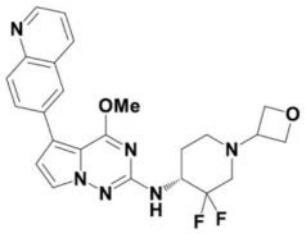
[1426] 灰白色固体(17mg,0.040mmol,74.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.91(2H,m),2.12-2.23(1H,m),2.26(3H,s),2.33-2.46(1H,m),2.79(1H,br d,J=11.77Hz),2.99-3.11(1H,m),3.99(3H,s),4.18-4.33(1H,m),6.81(1H,d,J=2.46Hz),6.83(1H,d,J=9.31Hz),7.53(1H,dd,J=8.21,4.11Hz),7.67(1H,d,J=2.46Hz),7.99(2H,s),8.12(1H,s),8.33-8.40(1H,m),8.86(1H,dd,J=4.24,1.51Hz);$C_{22}H_{22}F_2N_6O$的ESIMS实验值m/z 425.2(M+1)。

[1427] 

320

[1428] (S)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺320。

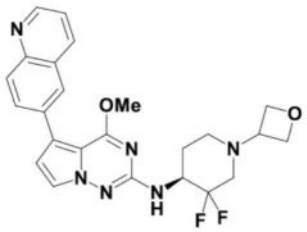
[1429] 黄色固体(11mg,0.026mmol,88.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.92(2H,m),2.13-2.22(1H,m),2.26(3H,s),2.34-2.45(1H,m),2.79(1H,br d,J=11.23Hz),2.99-3.12(1H,m),3.99(3H,s),4.17-4.33(1H,m),6.81(1H,d,J=2.46Hz),6.83(1H,d,J=9.31Hz),7.53(1H,dd,J=8.21,4.11Hz),7.67(1H,d,J=2.46Hz),7.99(2H,s),8.12(1H,s),8.36(1H,d,J=8.21Hz),8.86(1H,d,J=4.11Hz);$C_{22}H_{22}F_2N_6O$的ESIMS实验值m/z 425.2(M+1)。

[1430] 

321

[1431] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺321。

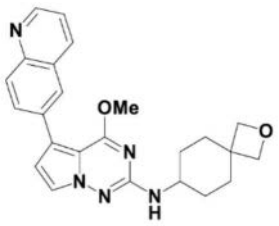
[1432] 灰白色固体(15mg,0.033mmol,72.9%产率)。^{1}H NMR(499MHz,氯仿-d)δppm 1.77-1.87(1H,m),2.19-2.30(2H,m),2.31-2.45(1H,m),2.82-2.90(1H,m),3.05-3.15(1H,m),3.70(1H,quin,J=6.43Hz),4.01(3H,s),4.25-4.41(1H,m),4.63-4.67(1H,m),4.68(1H,d,J=6.30Hz),4.69-4.71(2H,m),4.71-4.73(1H,m),6.70(1H,d,J=2.46Hz),7.41(1H,dd,J=8.35,4.24Hz),7.48(1H,d,J=2.74Hz),7.94-7.99(2H,m),8.10(1H,d,J=8.49Hz),8.18(1H,d,J=7.39Hz),8.90(1H,dd,J=4.11,1.64Hz);$C_{24}H_{24}F_2N_6O_2$的ESIMS实验值m/z 467.2(M+1)。

[1433] 

322

[1434] (S)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺322。

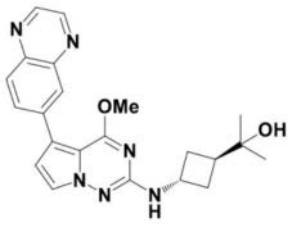
[1435] 灰白色固体(15mg,0.033mmol,72.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.86(1H,m),1.87-1.94(1H,m),2.13-2.20(1H,m),2.37-2.46(1H,m),2.76(1H,br d,J=11.50Hz),2.97-3.07(1H,m),3.61(1H,quin,J=6.37Hz),4.00(3H,s),4.24-4.39(1H,m),4.44(2H,dt,J=15.06,6.16Hz),4.55(2H,td,J=6.57,3.83Hz),6.81(1H,d,J=2.74Hz),6.89(1H,d,J=9.58Hz),7.53(1H,dd,J=8.21,4.11Hz),7.66(1H,d,J=2.74Hz),7.96-8.04(2H,m),8.12(1H,s),8.36(1H,dd,J=8.49,1.64Hz),8.86(1H,dd,J=4.11,1.64Hz);$C_{24}H_{24}F_2N_6O_2$的ESIMS实验值m/z 467.3(M+1)。

[1436] 

326

[1437] 4-甲氧基-5-(喹啉-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺326。

[1438] 灰白色固体(61mg,0.147mmol,53.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.21-1.34(2H,m),1.53(2H,td,J=12.87,3.29Hz),1.82-1.94(2H,m),2.07(2H,br d,J=13.42Hz),3.49-3.61(1H,m),3.95(3H,s),4.24(2H,s),4.32(2H,s),6.50(1H,d,J=7.94Hz),6.76(1H,d,J=2.74Hz),7.52(1H,dd,J=8.21,4.11Hz),7.64(1H,d,J=2.74Hz),7.94-8.03(2H,m),8.10(1H,d,J=1.37Hz),8.35(1H,dd,J=8.49,1.64Hz),8.86(1H,dd,J=4.24,1.78Hz);$C_{24}H_{25}N_5O_2$的ESIMS实验值m/z416.2(M+1)。

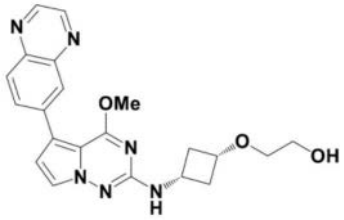
[1439] 

328

[1440] 2-(反-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁基)丙-2-醇328。

[1441] 黄色固体(36mg,0.089mmol,46.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.05

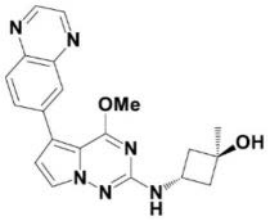
(6H,s),1.93-2.04(2H,m),2.16-2.26(1H,m),2.28-2.36(2H,m),3.97(3H,s),4.05-4.15(1H,m),4.19(1H,s),6.86(1H,d,J＝2.74Hz),7.01(1H,d,J＝6.84Hz),7.66(1H,d,J＝2.46Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.92Hz);$C_{22}H_{24}N_6O_2$的ESIMS实验值m/z 405.2(M+1)。

[1442] 

329

[1443] 2-(顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇329。

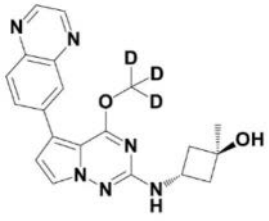
[1444] 黄色固体(25mg,0.062mmol,24.0％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82-1.95(2H,m),2.58-2.72(2H,m),3.31-3.34(2H,m),3.49(2H,q,J＝5.48Hz),3.69-3.76(1H,m),3.76-3.84(1H,m),3.97(3H,s),4.60(1H,t,J＝5.48Hz),6.88(1H,d,J＝2.74Hz),7.07(1H,d,J＝7.39Hz),7.66(1H,d,J＝2.74Hz),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.92Hz),8.93(1H,d,J＝1.92Hz);$C_{21}H_{22}N_6O_3$的ESIMS实验值m/z 407.2(M+1)。

[1445] 

330

[1446] 反-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇330。

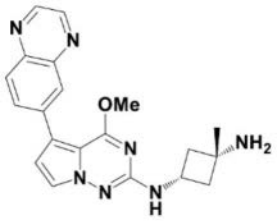
[1447] 淡黄色固体(5mg,0.013mmol,6.9％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28(3H,s),1.95-2.05(2H,m),2.27-2.37(2H,m),3.97(3H,s),4.27(1H,dq,J＝14.78,7.39Hz),4.80(1H,s),6.87(1H,d,J＝2.74Hz),6.99(1H,d,J＝6.84Hz),7.67(1H,d,J＝2.46Hz),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.92Hz);$C_{20}H_{20}N_6O_2$的ESIMS实验值m/z377.2(M+1)。

[1448] 

331

[1449] 反-3-((4-(甲氧基-d_3)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇331。

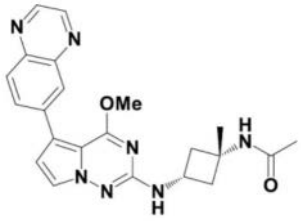
[1450] 黄色固体(5mg,0.013mmol,5.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28(3H,s),1.95-2.06(2H,m),2.28-2.38(2H,m),4.27(1H,dq,J=14.54,7.29Hz),4.80(1H,s),6.87(1H,d,J=2.46Hz),6.99(1H,d,J=6.84Hz),7.67(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{20}H_{17}[^2H_3]N_6O_2$的ESIMS实验值m/z 380.2(M+1)。

[1451] 

332

[1452] 顺-N^1-(4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-3-甲基环丁烷-1,3-二胺332。

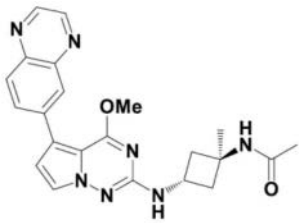
[1453] 黄色固体(64mg,0.171mmol,70.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20(3H,s),1.77(2H,br s),1.87(2H,br dd,J=11.23,8.76Hz),2.29-2.39(2H,m),3.87(1H,dq,J=15.50,7.79Hz),3.97(3H,s),6.85(1H,d,J=7.12Hz),6.86(1H,d,J=2.74Hz),7.68(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.09-8.12(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.64Hz),8.93(1H,d,J=1.64Hz);$C_{20}H_{21}N_7O$的ESIMS实验值m/z 376.3(M+1)。

[1454] 

333

[1455] N-(顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺333。

[1456] 黄色固体(24mg,0.058mmol,98.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.12-2.22(2H,m),2.43(2H,ddd,J=9.58,7.39,2.74Hz),3.97(3H,s),4.04(1H,dq,J=15.40,7.83Hz),6.87(1H,d,J=2.46Hz),7.05(1H,d,J=7.12Hz),7.69(1H,d,J=2.46Hz),8.03(1H,s),8.04-8.08(1H,m),8.09-8.12(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{22}H_{23}N_7O_2$的ESIMS实验值m/z 418.2(M+1)。

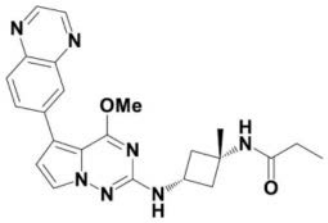
[1457] 

334

[1458] N-(反-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨

基)-1-甲基环丁基)乙酰胺334。

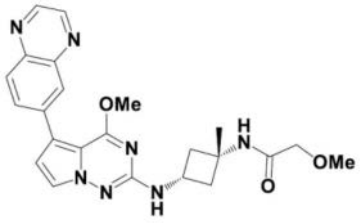
[1459] 黄色固体(96mg,0.230mmol,90.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.82(3H,s),1.90-2.03(2H,m),2.58-2.71(2H,m),3.97(3H,s),4.20(1H,sxt,J=7.83Hz),6.87(1H,d,J=2.74Hz),7.05(1H,d,J=7.39Hz),7.66(1H,d,J=2.74Hz),7.94(1H,s),8.04-8.08(1H,m),8.08-8.13(1H,m),8.23(1H,d,J=1.64Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{22}H_{23}N_7O_2$的ESIMS实验值m/z 418.2(M+1)。

[1460] 

335

[1461] N-(顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)丙酰胺335。

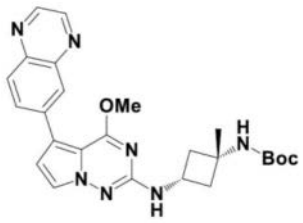
[1462] 黄色固体(27mg,0.063mmol,83.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.98(3H,t,J=7.67Hz),1.38(3H,s),2.02(2H,q,J=7.57Hz),2.13-2.23(2H,m),2.43(2H,ddd,J=9.65,7.46,2.60Hz),3.97(3H,s),4.04(1H,dq,J=15.30,7.77Hz),6.87(1H,d,J=2.46Hz),7.04(1H,d,J=6.84Hz),7.69(1H,d,J=2.74Hz),7.93(1H,s),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{23}H_{25}N_7O_2$的ESIMS实验值m/z432.2(M+1)。

[1463] 

336

[1464] 2-甲氧基-N-(顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺336。

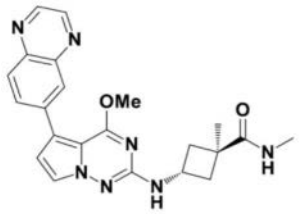
[1465] 黄色固体(27mg,0.060mmol,75.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.41(3H,s),2.14-2.26(2H,m),2.44-2.49(2H,m),3.31(3H,s),3.73(2H,s),3.97(3H,s),4.05(1H,dq,J=15.33,7.85Hz),6.88(1H,d,J=2.46Hz),7.06(1H,d,J=7.12Hz),7.69(1H,d,J=2.74Hz),7.87(1H,s),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{23}H_{25}N_7O_3$的ESIMS实验值m/z 448.2(M+1)。

[1466] 

337

[1467] (顺-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)氨基甲酸三丁酯337。

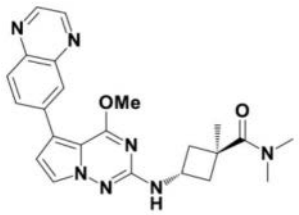
[1468] 琥珀色固体(118mg,0.248mmol,51.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.35(3H,s),1.38(9H,s),2.17(2H,br s),2.32-2.42(2H,m),3.97(3H,s),3.98-4.05(1H,m),6.87(1H,d,J=2.46Hz),6.98-7.09(2H,m),7.68(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{25}H_{29}N_7O_3$的ESIMS实验值m/z 476.3(M+1)。

[1469] 

338

[1470] 反-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺338。

[1471] 黄色固体(27mg,0.065mmol,81.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.32(3H,s),1.85-1.96(2H,m),2.63(3H,d,J=4.65Hz),2.71-2.81(2H,m),3.97(3H,s),4.05(1H,sxt,J=7.99Hz),6.87(1H,d,J=2.74Hz),7.04(1H,d,J=7.39Hz),7.62(1H,q,J=4.29Hz),7.69(1H,d,J=2.46Hz),8.04-8.08(1H,m),8.08-8.12(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{22}H_{23}N_7O_2$的ESIMS实验值m/z 418.2(M+1)。

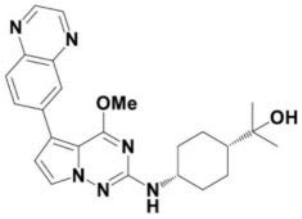
[1472] 

339

[1473] 反-3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,N,1-三甲基环丁烷-1-甲酰胺339。

[1474] 米色固体(24mg,0.056mmol,70.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.40(3H,s),1.93-2.05(2H,m),2.84(3H,br s),2.89(3H,br s),2.90-2.94(2H,m),3.86-3.95(1H,m),3.97(3H,s),6.87(1H,d,J=2.46Hz),7.13(1H,d,J=6.57Hz),7.68(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.08-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=

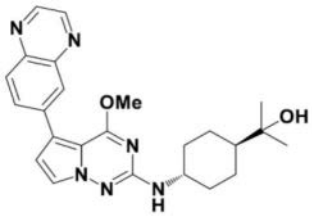
1.92Hz),8.93(1H,d,J＝1.92Hz);$C_{23}H_{25}N_7O_2$的ESIMS实验值m/z 432.2(M+1)。

[1475] 

341

[1476] 2-(顺-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇341。

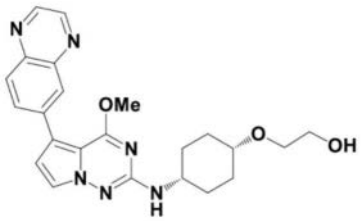
[1477] 黄色固体(30mg,0.069mmol,36.0％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.06(6H,s),1.18-1.23(1H,m),1.33-1.43(2H,m),1.43-1.52(2H,m),1.57(2H,br d,J＝10.40Hz),1.96-2.07(2H,m),3.92-3.97(1H,m),4.00(1H,s),4.00(3H,s),6.48(1H,d,J＝6.30Hz),6.87(1H,d,J＝2.46Hz),7.66(1H,d,J＝2.74Hz),8.04-8.08(1H,m),8.09-8.14(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.92Hz);$C_{24}H_{28}N_6O_2$的ESIMS实验值m/z 433.2(M+1)。

[1478] 

342

[1479] 2-(反-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)丙-2-醇342。

[1480] 黄色固体(16mg,0.037mmol,19.2％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.05(6H,s),1.07-1.15(2H,m),1.16-1.30(3H,m),1.83(2H,br d,J＝12.05Hz),2.04(2H,br d,J＝9.86Hz),3.47-3.59(1H,m),3.97(3H,s),4.03(1H,s),6.55(1H,d,J＝8.21Hz),6.86(1H,d,J＝2.74Hz),7.67(1H,d,J＝2.74Hz),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.92Hz),8.93(1H,d,J＝1.92Hz);$C_{24}H_{28}N_6O_2$的ESIMS实验值m/z 433.3(M+1)。

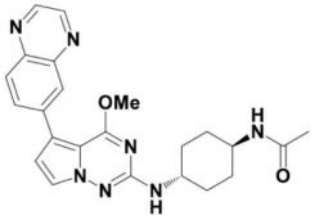
[1481] 

343

[1482] 2-((顺-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇343。

[1483] 白色固体(8.0mg,0.018mmol,7.7％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.57(2H,m),1.60-1.75(4H,m),1.80-1.89(2H,m),3.40(2H,t,J＝5.47Hz),3.48(1H,br d,

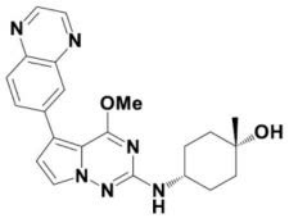
J＝2.19Hz),3.51(2H,q,J＝5.57Hz),3.65(1H,tt,J＝8.25,4.21Hz),3.97(3H,s),4.52(1H,t,J＝5.61Hz),6.59(1H,d,J＝7.67Hz),6.86(1H,d,J＝2.46Hz),7.66(1H,d,J＝2.74Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.64Hz);$C_{23}H_{26}N_6O_3$的ESIMS实验值m/z 435.2(M+1)。

[1484] 

344

[1485] N-(反-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺344。

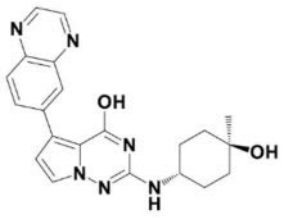
[1486] 黄色固体(5mg,0.012mmol,4.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20-1.30(2H,m),1.31-1.41(2H,m),1.79(3H,s),1.82(2H,br d,J＝10.40Hz),2.01(2H,br d,J＝10.13Hz),3.45-3.53(1H,m),3.53-3.61(1H,m),3.97(3H,s),6.60(1H,d,J＝8.21Hz),6.86(1H,d,J＝2.74Hz),7.68(1H,d,J＝2.46Hz),7.75(1H,d,J＝7.67Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.92Hz);$C_{23}H_{25}N_7O_2$的ESIMS实验值m/z 432.2(M+1)。

[1487] 

345

[1488] 顺-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇345。

[1489] 黄色固体(16mg,0.040mmol,15.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.13(3H,s),1.37(2H,td,J＝13.07,4.24Hz),1.58(2H,br d,J＝12.05Hz),1.61-1.69(2H,m),1.70-1.75(2H,m),3.47-3.60(1H,m),3.97(3H,s),4.01(1H,s),6.56(1H,d,J＝7.94Hz),6.85(1H,d,J＝2.46Hz),7.65(1H,d,J＝2.46Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.92Hz),8.93(1H,d,J＝1.92Hz);$C_{22}H_{24}N_6O_2$的ESIMS实验值m/z 405.2(M+1)。

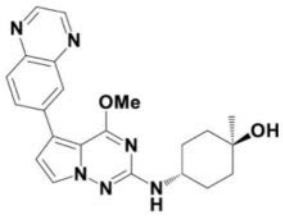
[1490] 

346

[1491] 2-((反-4-羟基-4-甲基环己基)氨基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]

三嗪-4-醇346。

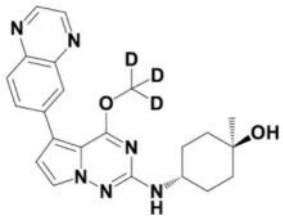
[1492] 黄色固体(10mg,0.026mmol,10.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.40-1.48(4H,m),1.49-1.56(2H,m),1.85-1.96(2H,m),3.63-3.74(1H,m),4.23(1H,s),5.92(1H,br s),6.85(1H,d,J=2.74Hz),7.47(1H,d,J=2.74Hz),8.03(1H,d,J=9.31Hz),8.34(1H,dd,J=9.03,1.92Hz),8.59(1H,d,J=1.64Hz),8.87(1H,d,J=2.19Hz),8.91(1H,d,J=2.19Hz);$C_{21}H_{22}N_6O_2$的ESIMS实验值m/z 391.2(M+1)。

[1493] 

347

[1494] 反-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇347。

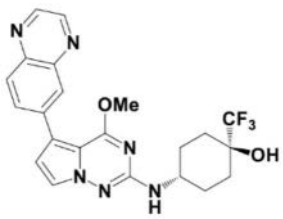
[1495] 黄色固体(26mg,0.064mmol,40.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.54(4H,m),1.56-1.65(2H,m),1.85-1.93(2H,m),3.65(1H,br dd,J=7.94,3.56Hz),3.97(3H,s),4.24(1H,s),6.54(1H,d,J=7.94Hz),6.86(1H,d,J=2.46Hz),7.68(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{22}H_{24}N_6O_2$的ESIMS实验值m/z 405.2(M+1)。

[1496] 

348

[1497] 反-4-((4-(甲氧基-d_3)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇348。

[1498] 黄色固体(38mg,0.093mmol,36.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.37-1.53(4H,m),1.55-1.65(2H,m),1.84-1.92(2H,m),3.66(1H,br dd,J=8.21,3.83Hz),4.24(1H,s),6.53(1H,d,J=7.94Hz),6.86(1H,d,J=2.74Hz),7.68(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{22}H_{21}[^2H_3]N_6O_2$的ESIMS实验值m/z 408.2(M+1)。

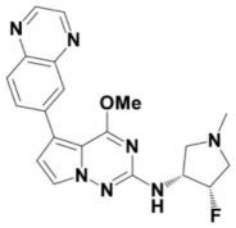
[1499] 

349

[1500] 反-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-

(三氟甲基)环己-1-醇349。

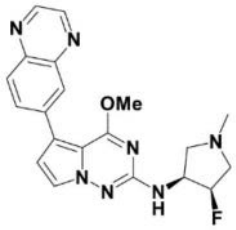
[1501] 灰白色固体(18mg,0.039mmol,16.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.53(2H,br d,J=12.59Hz),1.82-1.90(4H,m),1.90-1.99(2H,m),3.87-3.94(1H,m),4.00(3H,s),5.70(1H,s),6.83(1H,d,J=5.75Hz),6.87(1H,d,J=2.46Hz),7.68(1H,d,J=2.46Hz),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{22}H_{21}F_3N_6O_2$的ESIMS实验值m/z459.2(M+1)。

[1502] 

350

[1503] N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺350。

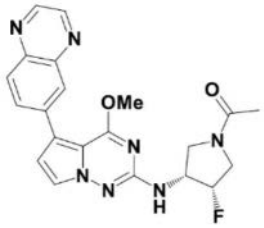
[1504] 黄色固体(33mg,0.084mmol,86.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.31(3H,s),2.55-2.66(1H,m),2.61-2.64(1H,m),2.92(1H,t,J=8.08Hz),3.17(1H,ddd,J=29.85,11.50,4.65Hz),3.99(3H,s),4.21-4.36(1H,m),5.22(1H,dtd,J=55.95,4.95,4.95,1.90Hz),6.82(1H,d,J=7.67Hz),6.91(1H,d,J=2.74Hz),7.70(1H,d,J=2.74Hz),8.05-8.09(1H,m),8.10-8.14(1H,m),8.24(1H,d,J=1.92Hz),8.90(1H,d,J=1.64Hz),8.94(1H,d,J=1.92Hz);$C_{20}H_{20}FN_7O$的ESIMS实验值m/z 394.2(M+1)。

[1505] 

351

[1506] N-((3S,4R)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺351。

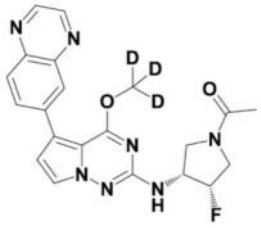
[1507] 黄色固体(21mg,0.053mmol,29.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.31(3H,s),2.56-2.68(2H,m),2.93(1H,t,J=8.08Hz),3.17(1H,ddd,J=29.65,11.80,4.65Hz),3.99(3H,s),4.20-4.37(1H,m),5.22(1H,dtd,J=55.95,4.95,4.95,1.90Hz),6.83(1H,d,J=7.67Hz),6.91(1H,d,J=2.74Hz),7.70(1H,d,J=2.74Hz),8.05-8.09(1H,m),8.10-8.14(1H,m),8.24(1H,d,J=1.64Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.64Hz);$C_{20}H_{20}FN_7O$的ESIMS实验值m/z 394.2(M+1)。

[1508] 

352

[1509] 1-((3S,4R)-3-氟-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮352。

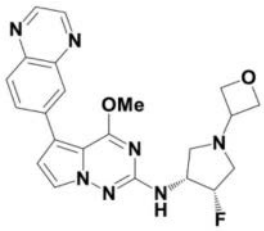
[1510] 黄色固体(43mg,0.102mmol,70.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.92-2.02(3H,m),3.48-3.57(1H,m),3.58-3.76(1H,m),3.79-3.98(2H,m),4.01(3H,d,J=1.64Hz),4.30-4.61(1H,m),5.26-5.51(1H,m),6.93(1H,t,J=2.46Hz),7.14(1H,t,J=6.71Hz),7.71(1H,dd,J=4.11,2.74Hz),8.06-8.10(1H,m),8.10-8.14(1H,m),8.25(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.64Hz);$C_{21}H_{20}FN_7O_2$的ESIMS实验值m/z 422.2(M+1)。

[1511] 

353

[1512] 1-((3S,4R)-3-氟-4-((4-(甲氧基-d_3)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮353。

[1513] 黄色固体(66mg,0.156mmol,71.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.90-2.03(3H,m),3.47-3.57(1H,m),3.59-3.77(1H,m),3.79-3.99(2H,m),4.28-4.62(1H,m),5.38(1H,ddt,J=54.30,37.55,3.05,3.05Hz),6.93(1H,t,J=2.46Hz),7.14(1H,t,J=6.71Hz),7.71(1H,dd,J=3.97,2.60Hz),8.06-8.10(1H,m),8.10-8.15(1H,m),8.25(1H,d,J=1.64Hz),8.90(1H,d,J=1.64Hz),8.94(1H,d,J=1.64Hz);$C_{21}H_{17}[^2H_3]FN_7O_2$的ESIMS实验值m/z 425.2(M+1)。

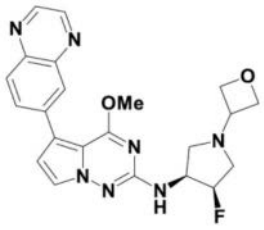
[1514] 

355

[1515] N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺355。

[1516] 黄色固体(7mg,0.016mmol,11.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.70(1H,t,J=9.03Hz),2.78(1H,ddd,J=29.90,12.10,1.40Hz),3.02(1H,t,J=8.35Hz),3.18(1H,

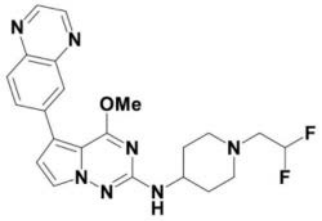
ddd,J＝33.20,12.05,4.40Hz),3.75-3.85(1H,m),4.00(3H,s),4.24-4.40(1H,m),4.47(2H,t,J＝6.02Hz),4.60(2H,t,J＝6.57Hz),5.26(1H,dtd,J＝55.65,4.65,4.65,1.10Hz),6.89(1H,d,J＝7.67Hz),6.91(1H,d,J＝2.74Hz),7.70(1H,d,J＝2.74Hz),8.05-8.09(1H,m),8.10-8.14(1H,m),8.25(1H,d,J＝1.92Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.92Hz);$C_{22}H_{22}FN_7O_2$的ESIMS实验值m/z 436.2(M+1)。

[1517] 

356

[1518] N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺356。

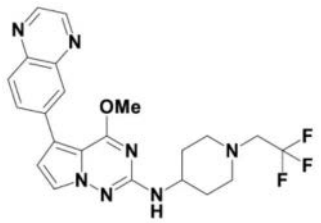
[1519] 黄色固体(25mg,0.057mmol,49.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.70(1H,t,J＝9.03Hz),2.78(1H,ddd,J＝30.15,12.35,1.40Hz),3.02(1H,t,J＝8.35Hz),3.18(1H,ddd,J＝32.90,12.10,4.40Hz),3.74-3.84(1H,m),4.00(3H,s),4.26-4.38(1H,m),4.47(2H,t,J＝6.02Hz),4.60(2H,t,J＝6.57Hz),5.26(1H,dtd,J＝55.65,4.40,4.40,1.10Hz),6.89(1H,d,J＝7.67Hz),6.91(1H,d,J＝2.46Hz),7.70(1H,d,J＝2.46Hz),8.06-8.09(1H,m),8.10-8.14(1H,m),8.25(1H,d,J＝1.64Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.64Hz);$C_{22}H_{22}FN_7O_2$的ESIMS实验值m/z 436.2(M+1)。

[1520] 

362

[1521] N-(1-(2,2-二氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺362。

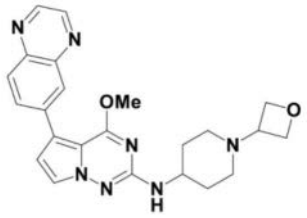
[1522] 黄色固体(27mg,0.061mmol,25.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.48-1.62(2H,m),1.85-1.96(2H,m),2.20-2.33(2H,m),2.72(2H,td,J＝15.74,4.38Hz),2.91(2H,br d,J＝11.77Hz),3.55-3.67(1H,m),3.97(3H,s),6.14(1H,tt,J＝55.95,4.24Hz),6.67(1H,d,J＝7.94Hz),6.87(1H,d,J＝2.46Hz),7.68(1H,d,J＝2.74Hz),8.04-8.08(1H,m),8.08-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.64Hz);$C_{22}H_{23}F_2N_7O$的ESIMS实验值m/z440.2(M+1)。

[1523] 

363

[1524] 4-甲氧基-5-(喹喔啉-6-基)-N-(1-(2,2,2-三氟乙基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺363。

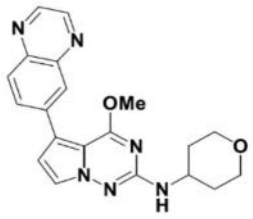
[1525] 黄色固体(13mg,0.028mmol,12.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.47-1.63(2H,m),1.91(2H,br d,J=10.13Hz),2.39-2.49(2H,m),2.93(2H,br d,J=11.77Hz),3.16(2H,q,J=10.31Hz),3.55-3.68(1H,m),3.97(3H,s),6.67(1H,d,J=7.94Hz),6.87(1H,d,J=2.74Hz),7.68(1H,d,J=2.46Hz),8.05-8.08(1H,m),8.09-8.12(1H,m),8.23(1H,d,J=1.64Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{22}H_{22}F_3N_7O$的ESIMS实验值m/z 458.2(M+1)。

[1526] 

365

[1527] 4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺365。

[1528] 黄色固体(6mg,0.0140mmol,4.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.55(2H,qd,J=11.64,3.15Hz),1.87(2H,br t,J=11.36Hz),1.93(2H,br d,J=11.50Hz),2.70(2H,br d,J=11.23Hz),3.36-3.42(1H,m),3.56-3.68(1H,m),3.97(3H,s),4.42(2H,t,J=6.16Hz),4.53(2H,t,J=6.57Hz),6.69(1H,d,J=7.94Hz),6.86(1H,d,J=2.46Hz),7.67(1H,d,J=2.46Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{23}H_{25}N_7O_2$的ESIMS实验值m/z 432.2(M+1)。

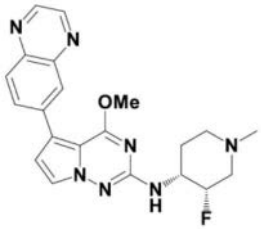
[1529] 

366

[1530] 4-甲氧基-5-(喹喔啉-6-基)-N-(四氢-2H-吡喃-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺366。

[1531] 黄色固体(34mg,0.090mmol,46.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.48-1.61(2H,m),1.91(2H,br dd,J=12.59,2.46Hz),3.40(2H,td,J=11.57,1.78Hz),3.76-3.86(1H,m),3.86-3.92(2H,m),3.98(3H,s),6.74(1H,d,J=7.94Hz),6.87(1H,d,J=

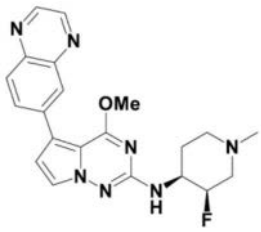
2.74Hz),7.68(1H,d,J＝2.46Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.92Hz),8.93(1H,d,J＝1.64Hz);$C_{20}H_{20}N_6O_2$的ESIMS实验值m/z 377.2(M+1)。

[1532] 

367

[1533] N-((3S,4R)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺367。

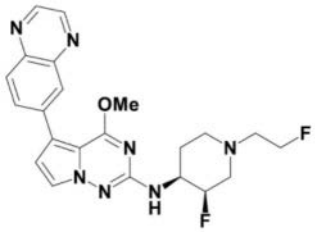
[1534] 浅黄色固体(34mg,0.083mmol,65.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.74(1H,m),1.89-1.99(1H,m),2.02-2.11(1H,m),2.12-2.25(1H,m),2.19(3H,s),2.80(1H,br d,J＝11.22Hz),3.05(1H,br t,J＝10.95Hz),3.69-3.84(1H,m),3.99(3H,s),4.92(1H,d,J＝49.65Hz),6.68(1H,d,J＝7.94Hz),6.89(1H,d,J＝2.74Hz),7.68(1H,d,J＝2.46Hz),8.05-8.09(1H,m),8.09-8.14(1H,m),8.24(1H,d,J＝1.64Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.64Hz);$C_{21}H_{22}FN_7O$的ESIMS实验值m/z 408.2(M+1)。

[1535] 

368

[1536] N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺368。

[1537] 黄色固体(45mg,0.110mmol,43.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76(1H,br d,J＝9.86Hz),1.98(1H,qd,J＝12.41,3.56Hz),2.33(3H,br s),2.34-2.38(1H,m),2.88-3.03(1H,m),3.14-3.27(1H,m),3.27-3.30(1H,m),3.75-3.93(1H,m),3.99(3H,s),5.00(1H,d,J＝49.65Hz),6.78(1H,br d,J＝6.30Hz),6.90(1H,d,J＝2.46Hz),7.67(1H,d,J＝2.46Hz),8.05-8.09(1H,m),8.09-8.14(1H,m),8.24(1H,d,J＝1.92Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.92Hz);$C_{21}H_{22}FN_7O$的ESIMS实验值m/z 408.2(M+1)。

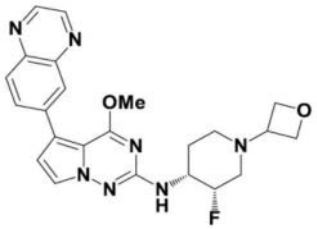
[1538] 

372

[1539] N-((3R,4S)-3-氟-1-(2-氟乙基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并

[2,1-f][1,2,4]三嗪-2-胺372。

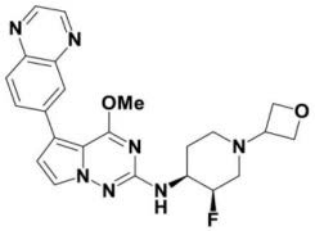
[1540] 浅黄色固体(20mg,0.046mmol,59.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.76(1H,m),1.93(1H,qd,J=12.23,3.83Hz),2.26(1H,br t,J=10.95Hz),2.39(1H,dd,J=37.85,12.38Hz),2.64-2.73(2H,m),2.94(1H,br d,J=11.23Hz),3.13-3.23(1H,m),3.74-3.90(1H,m),3.99(3H,s),4.55(2H,dt,J=48.00,4.95Hz),4.93(1H,d,J=49.95Hz),6.71(1H,d,J=7.67Hz),6.89(1H,d,J=2.74Hz),7.68(1H,d,J=2.74Hz),8.05-8.09(1H,m),8.09-8.14(1H,m),8.24(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.92Hz);$C_{22}H_{23}F_2N_7O$的ESIMS实验值m/z 440.2(M+1)。

[1541] 

373

[1542] N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺373。

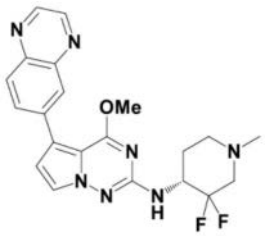
[1543] 黄色固体(39mg,0.087mmol,68.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.79(1H,m),1.93(1H,qd,J=12.09,3.15Hz),1.99-2.08(1H,m),2.10-2.25(1H,m),2.76(1H,br d,J=10.40Hz),2.95-3.06(1H,m),3.50(1H,quin,J=6.37Hz),3.77-3.91(1H,m),3.99(3H,s),4.40(1H,t,J=6.16Hz),4.44-4.49(1H,m),4.54(2H,td,J=6.57,3.01Hz),4.95(1H,d,J=49.65Hz),6.75(1H,d,J=7.67Hz),6.89(1H,d,J=2.46Hz),7.67(1H,d,J=2.46Hz),8.05-8.09(1H,m),8.10-8.13(1H,m),8.24(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.64Hz);$C_{23}H_{24}FN_7O_2$的ESIMS实验值m/z 450.2(M+1)。

[1544] 

374

[1545] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺374。

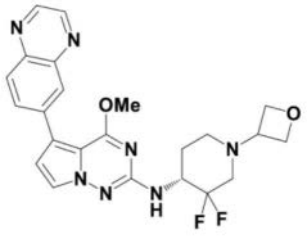
[1546] 黄色固体(51mg,0.114mmol,74.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69-1.79(1H,m),1.93(1H,qd,J=12.14,3.56Hz),2.00-2.07(1H,m),2.09-2.25(1H,m),2.76(1H,br d,J=9.86Hz),2.95-3.06(1H,m),3.50(1H,quin,J=6.30Hz),3.75-3.94(1H,m),3.99(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.95(1H,d,J=49.65Hz),6.76(1H,d,J=7.67Hz),6.89(1H,d,J=2.74Hz),7.67(1H,d,J=2.46Hz),8.06-8.09(1H,m),8.09-8.13(1H,m),8.24(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.92Hz);$C_{23}H_{24}FN_7O_2$的ESIMS实验值m/z 450.25(M+1)。

[1547] 

375

[1548] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺375。

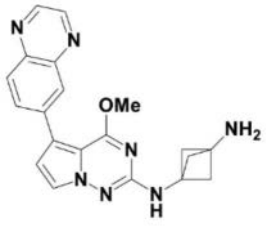
[1549] 黄色固体(14mg,0.033mmol,67.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.78-1.92(2H,m),2.18(1H,td,J=11.02,2.60Hz),2.26(3H,s),2.34-2.44(1H,m),2.79(1H,brd,J=12.05Hz),3.06(1H,td,J=9.86,7.94Hz),4.00(3H,s),4.18-4.33(1H,m),6.89(1H,d,J=9.31Hz),6.91(1H,d,J=2.74Hz),7.69(1H,d,J=2.74Hz),8.06-8.09(1H,m),8.10-8.13(1H,m),8.24(1H,d,J=1.64Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.92Hz);$C_{21}H_{21}F_2N_7O$的ESIMS实验值m/z 426.2(M+1)。

[1550] 

379

[1551] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺379。

[1552] 红棕色蓬松固体(14mg,0.028mmol,67.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.81-1.93(1H,m),1.94-2.03(1H,m),2.18-2.44(1H,m),2.78-2.98(1H,m),3.07-3.28(1H,m),3.60-3.68(1H,m),3.68-3.84(1H,m),4.01(3H,s),4.29-4.44(1H,m),4.45-4.56(2H,m),4.59(2H,br s),6.92(1H,d,J=2.74Hz),6.98-7.08(1H,m),7.68(1H,d,J=2.46Hz),8.06-8.09(1H,m),8.10-8.14(1H,m),8.25(1H,d,J=1.64Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.64Hz);$C_{23}H_{23}F_2N_7O_2$的ESIMS实验值m/z 469.2(M+1)。

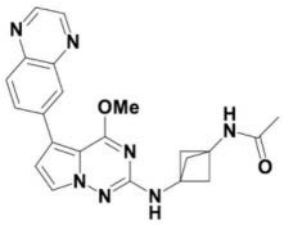
[1553] 

381

[1554] N^1-(4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)双环[1.1.1]戊烷-1,3-二胺381。

[1555] 黄色泡沫(14mg,0.038mmol,42.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.02(6H,s),2.24(2H,br s),3.97(3H,s),6.90(1H,d,J=2.74Hz),7.34(1H,s),7.66(1H,d,J=

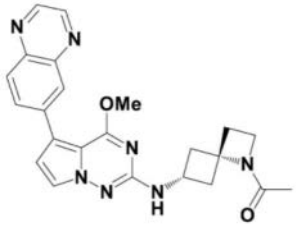
2.74Hz),8.04-8.09(1H,m),8.09-8.13(1H,m),8.24(1H,d,J=1.92Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{20}H_{19}N_7O$的ESIMS实验值m/z 374.2(M+1)。

[1556] 

382

[1557] N-(3-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[1.1.1]戊烷-1-基)乙酰胺382。

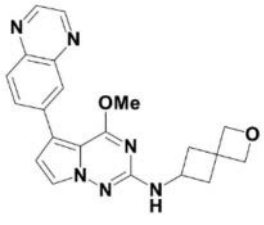
[1558] 黄色固体(10mg,0.024mmol,89.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.78(3H,s),2.28(6H,s),3.97(3H,s),6.91(1H,d,J=2.74Hz),7.48(1H,s),7.69(1H,d,J=2.46Hz),8.05-8.09(1H,m),8.09-8.14(1H,m),8.24(1H,d,J=1.64Hz),8.43(1H,s),8.90(1H,d,J=1.92Hz),8.93(1H,d,J=1.64Hz);$C_{22}H_{21}N_7O_2$的ESIMS实验值m/z416.2(M+1)。

[1559] 

383

[1560] 1-((4s,6r)-6-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-氮杂螺[3.3]庚烷-1-基)乙-1-酮383。

[1561] 黄色固体(20mg,0.047mmol,60.1%产率)。^{1}H NMR(500MHz,DMSO-d_6)δppm 1.74(3H,s),2.27-2.44(2H,m),2.52-2.60(2H,m),2.62-2.70(2H,m),2.84-2.97(2H,m),3.70(1H,br s),4.00(3H,s),6.85(2H,br d,J=2.20Hz),7.63(1H,d,J=2.20Hz),8.04-8.08(1H,m),8.08-8.12(1H,m),8.24(1H,d,J=1.92Hz),8.87(1H,d,J=1.65Hz),8.91(1H,d,J=1.92Hz);$C_{23}H_{23}N_7O_2$的ESIMS实验值m/z 430.2(M+1)。

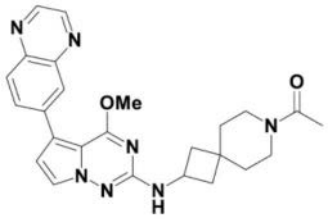
[1562] 

385

[1563] 4-甲氧基-5-(喹喔啉-6-基)-N-(2-氧杂螺[3.3]庚烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺385。

[1564] 浅黄色固体(22mg,0.057mmol,26.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.14-2.24(2H,m),2.62(2H,ddd,J=9.99,7.53,2.74Hz),3.96(3H,s),3.97-4.06(1H,m),4.51(2H,s),4.64(2H,s),6.87(1H,d,J=2.74Hz),7.03(1H,d,J=7.12Hz),7.67(1H,d,J=2.74Hz),8.04-8.08(1H,m),8.08-8.13(1H,m),8.23(1H,d,J=1.64Hz),8.89(1H,d,J=

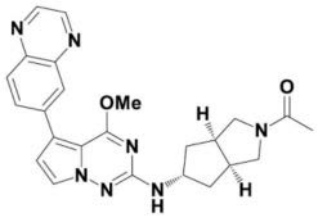
1.64Hz),8.93(1H,d,J＝1.64Hz);$C_{21}H_{20}N_6O_2$的ESIMS实验值m/z 389.2(M+1)。

[1565] 

386

[1566] 1-(2-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-7-氮杂螺[3.5]壬烷-7-基)乙-1-酮386。

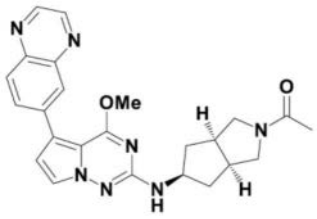
[1567] 灰白色固体(32mg,0.070mmol,41.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.40-1.47(1H,m),1.52(2H,br t,J＝10.13Hz),1.57-1.65(1H,m),1.76-1.86(2H,m),1.94-2.01(3H,m),2.23-2.33(2H,m),3.26-3.33(2H,m),3.36-3.39(1H,m),3.40-3.44(1H,m),3.97(3H,s),4.15-4.27(1H,m),6.87(1H,d,J＝2.74Hz),7.05(1H,t,J＝7.12Hz),7.65-7.71(1H,m),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.92Hz);$C_{25}H_{27}N_7O_2$的ESIMS实验值m/z 458.2(M+1)。

[1568] 

387

[1569] 1-((3aR,5s,6aS)-5-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)六氢环戊并[c]吡咯-2(1H)-基)乙-1-酮387。

[1570] 白色固体(53mg,0.120mmol,99.95%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82-1.91(4H,m),1.95(3H,s),2.73-2.81(1H,m),2.82-2.91(1H,m),3.15(1H,dd,J＝12.32,4.93Hz),3.26(1H,br dd,J＝10.81,4.79Hz),3.52(1H,dd,J＝12.18,8.62Hz),3.65(1H,dd,J＝10.95,8.21Hz),3.94-3.99(3H,m),4.25(1H,sxt,J＝6.63Hz),6.83(1H,d,J＝6.84Hz),6.87(1H,d,J＝2.46Hz),7.68(1H,d,J＝2.74Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.92Hz),8.93(1H,d,J＝1.64Hz);$C_{24}H_{25}N_7O_2$的ESIMS实验值m/z444.2(M+1)。

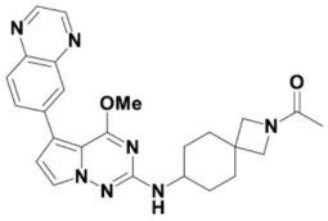
[1571] 

388

[1572] 1-((3aR,5r,6aS)-5-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)六氢环戊并[c]吡咯-2(1H)-基)乙-1-酮388。

[1573] 灰白色固体(55mg,0.124mmol,90.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34-

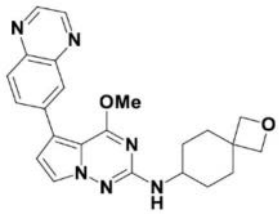
1.48(2H,m),1.95(3H,s),2.24-2.38(2H,m),2.54-2.62(1H,m),2.62-2.72(1H,m),3.35-3.45(3H,m),3.59(1H,dd,J＝10.68,7.94Hz),3.97(3H,s),4.08-4.21(1H,m),6.85-6.90(2H,m),7.66(1H,d,J＝2.74Hz),8.05-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.64Hz),8.89(1H,d,J＝1.92Hz),8.93(1H,d,J＝1.92Hz);$C_{24}H_{25}N_7O_2$的ESIMS实验值m/z 444.2(M+1)。

[1574] 

389

[1575] 1-(7-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮389。

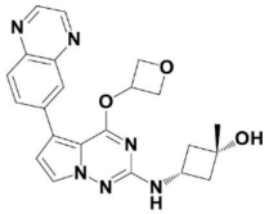
[1576] 灰白色固体(60mg,0.131mmol,82.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.29-1.41(2H,m),1.49-1.62(2H,m),1.73-1.78(3H,m),1.88(4H,br dd,J＝9.58,4.11Hz),3.47(1H,s),3.52(1H,s),3.56-3.67(1H,m),3.75(1H,s),3.81(1H,s),3.97(3H,d,J＝1.10Hz),6.58(1H,dd,J＝16.15,7.94Hz),6.87(1H,d,J＝2.74Hz),7.67(1H,t,J＝2.87Hz),8.04-8.08(1H,m),8.09-8.13(1H,m),8.23(1H,d,J＝1.64Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.64Hz);$C_{25}H_{27}N_7O_2$的ESIMS实验值m/z 458.2(M+1)。

[1577] 

390

[1578] 4-甲氧基-5-(喹喔啉-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺390。

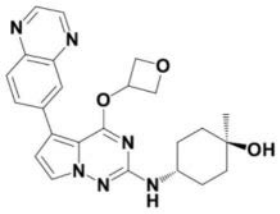
[1579] 黄色固体(39mg,0.094mmol,48.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.20-1.36(2H,m),1.53(2H,td,J＝12.87,3.29Hz),1.88(2H,br dd,J＝13.14,3.29Hz),2.07(2H,br d,J＝12.87Hz),3.48-3.63(1H,m),3.96(3H,s),4.24(2H,s),4.32(2H,s),6.56(1H,d,J＝8.21Hz),6.86(1H,d,J＝2.74Hz),7.67(1H,d,J＝2.74Hz),8.04-8.08(1H,m),8.08-8.13(1H,m),8.23(1H,d,J＝1.92Hz),8.89(1H,d,J＝1.64Hz),8.93(1H,d,J＝1.64Hz);$C_{23}H_{24}N_6O_2$的ESIMS实验值m/z 417.2(M+1)。

[1580] 

391

[1581] 顺-1-甲基-3-((4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁-1-醇391。

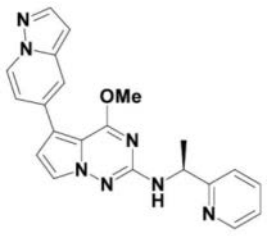
[1582] 黄色固体(10mg,0.024mmol,11.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),1.96-2.04(2H,m),2.28-2.40(2H,m),3.64-3.76(1H,m),4.61(2H,dd,J=7.94,5.20Hz),4.86(2H,t,J=7.26Hz),4.93(1H,s),5.65-5.73(1H,m),6.92-6.95(2H,m),7.71(1H,d,J=2.74Hz),8.10(1H,d,J=8.76Hz),8.19(1H,dd,J=8.76,1.92Hz),8.38(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.95(1H,d,J=1.92Hz);$C_{22}H_{22}N_6O_3$的ESIMS实验值m/z 419.2(M+1)。

[1583] 

392

[1584] 反-1-甲基-4-((4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇392。

[1585] 黄色固体(17mg,0.038mmol,14.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.36-1.50(4H,m),1.54-1.64(2H,m),1.80-1.93(2H,m),3.61(1H,br d,J=3.56Hz),4.25(1H,s),4.62(2H,dd,J=7.53,5.34Hz),4.86(2H,t,J=6.98Hz),5.72(1H,quin,J=5.75Hz),6.50(1H,d,J=7.94Hz),6.93(1H,d,J=2.46Hz),7.71(1H,d,J=2.46Hz),8.10(1H,d,J=8.76Hz),8.20(1H,dd,J=8.76,1.92Hz),8.39(1H,d,J=1.92Hz),8.90(1H,d,J=1.64Hz),8.94(1H,d,J=1.64Hz);$C_{24}H_{26}N_6O_3$的ESIMS实验值m/z 447.2(M+1)。

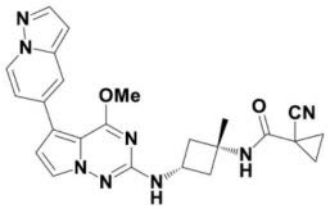
[1586] 

393

[1587] (S)-4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(1-(吡啶-2-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺393。

[1588] 灰白色固体(14mg,0.036mmol,18.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.49

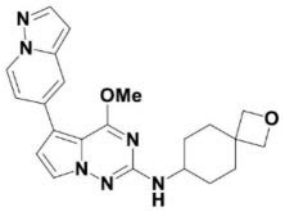
(3H,d,J＝7.12Hz),3.98(3H,s),5.00(1H,quin,J＝7.19Hz),6.58(1H,d,J＝1.64Hz),6.74(1H,d,J＝2.46Hz),7.09(1H,dd,J＝7.39,1.92Hz),7.19(1H,d,J＝7.94Hz),7.23(1H,ddd,J＝7.46,4.86,0.82Hz),7.46(1H,d,J＝7.94Hz),7.55(1H,d,J＝2.74Hz),7.74(1H,td,J＝7.73,1.78Hz),7.79(1H,d,J＝1.10Hz),7.96(1H,d,J＝2.19Hz),8.50-8.54(1H,m),8.61(1H,d,J＝7.12Hz);$C_{21}H_{19}N_7O$的ESIMS实验值m/z 386.2(M+1)。

[1589] 

394

[1590] 1-氰基-N-((1s,3s)-3-((4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺394。

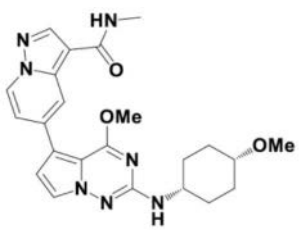
[1591] 米色固体(8mg,0.018mmol,25.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.37(3H,s),1.44-1.49(2H,m),1.49-1.54(2H,m),2.13-2.22(2H,m),2.45(2H,ddd,J＝9.72,7.39,2.60Hz),3.98(3H,s),4.03(1H,sxt,J＝7.78Hz),6.58(1H,dd,J＝2.19,0.82Hz),6.77(1H,d,J＝2.46Hz),7.01(1H,d,J＝6.84Hz),7.10(1H,dd,J＝7.26,2.05Hz),7.64(1H,d,J＝2.46Hz),7.78-7.85(1H,m),7.97(1H,d,J＝2.19Hz),8.29(1H,s),8.62(1H,d,J＝7.39Hz);$C_{24}H_{24}N_8O_2$的ESIMS实验值m/z 457.2(M+1)。

[1592] 

395

[1593] 4-甲氧基-5-(吡唑并[1,5-a]吡啶-5-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺395。

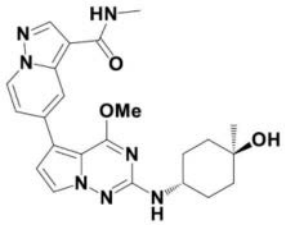
[1594] 米色固体(74mg,0.18mmol,54.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.24-1.31(2H,m),1.52(2H,td,J＝12.94,3.42Hz),1.80-1.92(2H,m),2.02-2.11(2H,m),3.48-3.61(1H,m),3.97(3H,s),4.23(2H,s),4.32(2H,s),6.51(1H,d,J＝7.94Hz),6.56-6.61(1H,m),6.75(1H,d,J＝2.74Hz),7.10(1H,dd,J＝7.26,2.05Hz),7.62(1H,d,J＝2.74Hz),7.80(1H,dd,J＝1.92,0.82Hz),7.96(1H,d,J＝2.19Hz),8.62(1H,d,J＝7.12Hz);$C_{22}H_{24}N_6O_2$的ESIMS实验值m/z 405.2(M+1)。

[1595] 

399

[1596] 5-(4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺399。

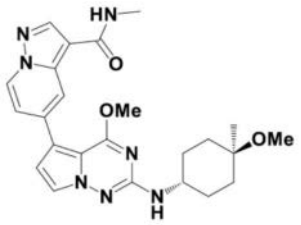
[1597] 米色固体(40mg,0.089mmol,55.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.54(2H,m),1.54-1.65(2H,m),1.66-1.74(2H,m),1.80-1.90(2H,m),2.79(3H,d,J=4.38Hz),3.22(3H,s),3.33-3.38(1H,m),3.58-3.71(1H,m),4.02(3H,s),6.63(1H,d,J=7.67Hz),6.83(1H,d,J=2.74Hz),7.29(1H,dd,J=7.26,2.05Hz),7.64(1H,d,J=2.46Hz),8.10(1H,q,J=4.20Hz),8.45(1H,s),8.49-8.55(1H,m),8.68(1H,d,J=7.39Hz);$C_{23}H_{27}N_7O_3$的ESIMS实验值m/z 450.2(M+1)。

[1598] 

401

[1599] 5-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺401。

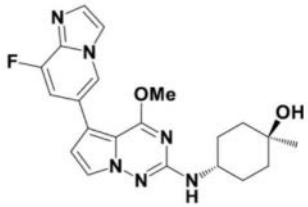
[1600] 米色固体(58mg,0.129mmol,80.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.37-1.54(4H,m),1.57-1.66(2H,m),1.83-1.93(2H,m),2.79(3H,d,J=4.65Hz),3.65(1H,dt,J=7.87,3.87Hz),4.02(3H,s),4.23(1H,s),6.56(1H,d,J=7.94Hz),6.83(1H,d,J=2.74Hz),7.29(1H,dd,J=7.26,2.05Hz),7.65(1H,d,J=2.74Hz),8.10(1H,q,J=4.56Hz),8.45(1H,s),8.52(1H,d,J=1.37Hz),8.68(1H,d,J=7.67Hz);$C_{23}H_{27}N_7O_3$的ESIMS实验值m/z 450.25(M+1)。

[1601] 

405

[1602] 5-(4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基吡唑并[1,5-a]吡啶-3-甲酰胺405。

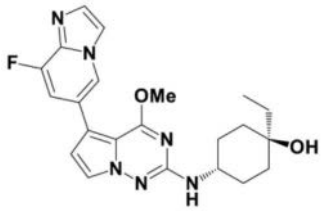
[1603] 灰白色固体(47mg,0.101mmol,63.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.43-1.58(4H,m),1.63-1.73(2H,m),1.79-1.90(2H,m),2.79(3H,d,J=4.65Hz),3.11(3H,s),3.66-3.77(1H,m),4.03(3H,s),6.61(1H,d,J=7.94Hz),6.83(1H,d,J=2.74Hz),7.29(1H,dd,J=7.26,2.05Hz),7.65(1H,d,J=2.74Hz),8.10(1H,q,J=4.56Hz),8.45(1H,s),8.52(1H,dd,J=2.19,0.82Hz),8.65-8.72(1H,m);$C_{24}H_{29}N_7O_3$的ESIMS实验值m/z 464.2(M+1)。

[1604] 

431

[1605] (1r,4r)-4-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇431。

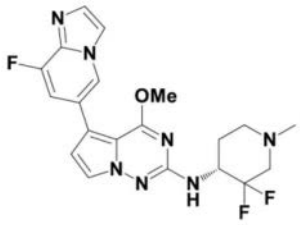
[1606] 灰白色固体(42mg,0.102mmol,32.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.37-1.52(4H,m),1.57-1.65(2H,m),1.82-1.93(2H,m),3.58-3.72(1H,m),3.98(3H,s),4.23(1H,s),6.50(1H,d,J=7.94Hz),6.71(1H,d,J=2.46Hz),7.38(1H,d,J=12.59Hz),7.62(1H,s),7.63(1H,d,J=2.74Hz),8.09(1H,d,J=2.74Hz),8.59(1H,s);$C_{21}H_{23}FN_6O_2$的ESIMS实验值m/z 411.2(M+1)。

[1607] 

433

[1608] (1r,4r)-1-乙基-4-((5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇433。

[1609] 白色固体(10.1mg,0.024mmol,11.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.83(3H,t,J=7.53Hz),1.31-1.39(2H,m),1.39-1.50(4H,m),1.60-1.70(2H,m),1.80-1.89(2H,m),3.68(1H,tt,J=8.18,4.14Hz),3.98(3H,s),6.50(1H,d,J=7.94Hz),6.71(1H,d,J=2.74Hz),7.38(1H,dd,J=12.59,1.37Hz),7.62(1H,d,J=1.37Hz),7.63(1H,d,J=2.46Hz),8.09(1H,dd,J=3.01,1.10Hz),8.59(1H,d,J=1.37Hz);$C_{22}H_{25}FN_6O_2$的ESIMS实验值m/z 425.2(M+1)。

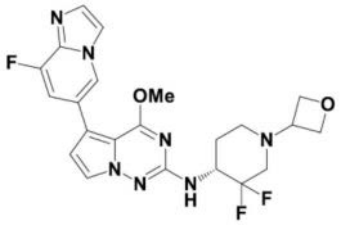
[1610] 

434

[1611] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺434。

[1612] 棕褐色固体(33mg,0.077mmol,32.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.89(2H,m),2.14-2.25(1H,m),2.28(3H,br s),2.35-2.47(1H,m),2.76-2.88(1H,m),3.01-3.15(1H,m),4.01(3H,s),4.19-4.32(1H,m),6.76(1H,d,J=2.74Hz),6.86(1H,br d,J=9.31Hz),7.40(1H,dd,J=12.59,1.37Hz),7.63(1H,s),7.64(1H,d,J=2.46Hz),8.10

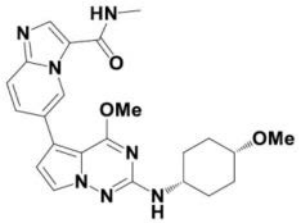
(1H,d,J＝2.46Hz),8.61(1H,d,J＝1.10Hz);$C_{20}H_{20}F_3N_7O$的ESIMS实验值m/z 432.2(M+1)。

[1613] 

435

[1614] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(8-氟咪唑并[1,2-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺435。

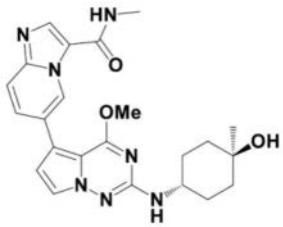
[1615] 棕褐色固体(10mg,0.021mmol,48.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.85(1H,m),1.86-1.92(1H,m),2.12-2.22(1H,m),2.35-2.45(1H,m),2.76(1H,br d,J＝11.50Hz),2.95-3.07(1H,m),3.60(1H,quin,J＝6.30Hz),4.02(3H,s),4.22-4.37(1H,m),4.44(2H,dt,J＝15.26,6.19Hz),4.55(2H,td,J＝6.64,3.70Hz),6.76(1H,d,J＝2.74Hz),6.92(1H,d,J＝9.31Hz),7.40(1H,dd,J＝12.59,1.37Hz),7.62(1H,d,J＝1.09Hz),7.64(1H,d,J＝2.46Hz),8.10(1H,dd,J＝3.01,1.09Hz),8.61(1H,d,J＝1.37Hz);$C_{22}H_{22}F_3N_7O_2$的ESIMS实验值m/z474.2(M+1)。

[1616] 

439

[1617] 6-(4-甲氧基-2-((顺-4-甲氧基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺439。

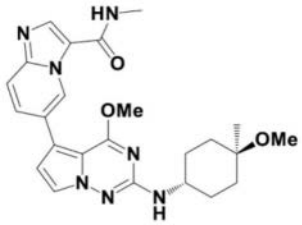
[1618] 米色固体(38mg,0.085mmol,52.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.54(2H,m),1.55-1.65(2H,m),1.66-1.74(2H,m),1.79-1.89(2H,m),2.82(3H,d,J＝4.65Hz),3.22(3H,s),3.33-3.37(1H,m),3.57-3.72(1H,m),4.00(3H,s),6.58(1H,d,J＝7.67Hz),6.74(1H,d,J＝2.74Hz),7.63(1H,d,J＝2.46Hz),7.68(2H,d,J＝1.37Hz),8.27(1H,s),8.43(1H,q,J＝4.56Hz),9.80(1H,t,J＝1.37Hz);$C_{23}H_{27}N_7O_3$的ESIMS实验值m/z 450.2(M+1)。

[1619] 

441

[1620] 6-(2-(((1r,4r)-4-羟基-4-甲基环己基)氨基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺441。

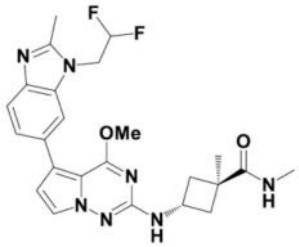
[1621] 灰白色固体(23mg,0.051mmol,31.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.34-1.52(4H,m),1.56-1.66(2H,m),1.82-1.94(2H,m),2.82(3H,d,J=4.38Hz),3.59-3.71(1H,m),4.00(3H,s),4.23(1H,br s),6.51(1H,d,J=7.94Hz),6.75(1H,d,J=2.46Hz),7.64(1H,d,J=2.74Hz),7.68(2H,d,J=1.10Hz),8.26(1H,s),8.43(1H,q,J=4.20Hz),9.80(1H,s);$C_{23}H_{27}N_7O_3$的ESIMS实验值m/z 450.2(M+1)。

[1622] 

445

[1623] 6-(4-甲氧基-2-(((1r,4r)-4-甲氧基-4-甲基环己基)氨基)吡咯并[2,1-f][1,2,4]三嗪-5-基)-N-甲基咪唑并[1,2-a]吡啶-3-甲酰胺445。

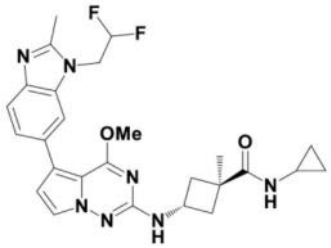
[1624] 棕色固体(33mg,0.071mmol,44.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.41-1.58(4H,m),1.62-1.74(2H,m),1.78-1.91(2H,m),2.82(3H,d,J=4.38Hz),3.11(3H,s),3.71(1H,br d,J=3.56Hz),4.01(3H,s),6.56(1H,d,J=7.67Hz),6.75(1H,d,J=2.46Hz),7.64(1H,d,J=2.46Hz),7.68(2H,d,J=1.37Hz),8.27(1H,s),8.43(1H,q,J=4.11Hz),9.81(1H,t,J=1.37Hz);$C_{24}H_{29}N_7O_3$的ESIMS实验值m/z 464.25(M+1)。

[1625] 

502

[1626] 反-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺502。

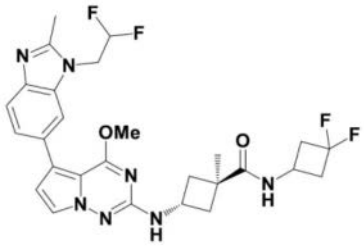
[1627] 白色固体(18mg,0.037mmol,70.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.31(3H,s),1.84-1.94(2H,m),2.57(3H,s),2.62(3H,d,J=4.38Hz),2.73(2H,ddd,J=9.86,7.80,2.60Hz),3.91(3H,s),3.99-4.08(1H,m),4.69-4.84(2H,m),6.48(1H,tt,J=54.30,3.00Hz),6.61(1H,d,J=2.74Hz),6.90(1H,d,J=7.39Hz),7.37(1H,dd,J=8.21,1.37Hz),7.51(1H,d,J=8.21Hz),7.58-7.64(2H,m),7.71(1H,s);$C_{24}H_{27}F_2N_7O_2$的ESIMS实验值m/z 484.2(M+1)。

[1628] 

503

[1629] 反-N-环丙基-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺503。

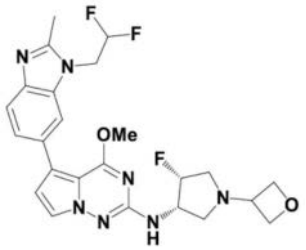
[1630] 白色固体(21mg,0.041mmol,77.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.42-0.49(2H,m),0.58-0.65(2H,m),1.29(3H,s),1.82-1.91(2H,m),2.56(3H,s),2.64-2.70(1H,m),2.71-2.77(2H,m),3.91(3H,s),3.95-4.04(1H,m),4.74(2H,td,J=16.02,2.19Hz),6.47(1H,tt,J=54.30,3.00Hz),6.60(1H,d,J=2.46Hz),6.88(1H,d,J=7.39Hz),7.35(1H,dd,J=8.21,1.64Hz),7.49(1H,d,J=8.21Hz),7.61(1H,d,J=2.46Hz),7.62(1H,d,J=4.38Hz),7.68(1H,s);$C_{26}H_{29}F_2N_7O_2$的ESIMS实验值m/z 510.3(M+1)。

[1631] 

504

[1632] 反-N-(3,3-二氟环丁基)-3-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺504。

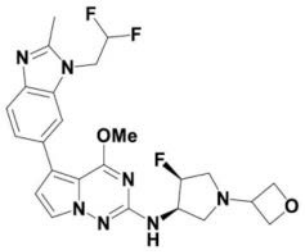
[1633] 白色固体(23mg,0.041mmol,77.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34(3H,s),1.86-1.95(2H,m),2.56(3H,s),2.58-2.71(2H,m),2.76(2H,ddd,J=10.06,8.01,2.46Hz),2.83-2.94(2H,m),3.91(3H,s),4.01(1H,sxt,J=7.94Hz),4.10(1H,dt,J=14.85,7.49Hz),4.68-4.80(2H,m),6.47(1H,tt,J=54.30,3.00Hz),6.60(1H,d,J=2.46Hz),6.91(1H,d,J=7.12Hz),7.35(1H,dd,J=8.21,1.64Hz),7.49(1H,d,J=8.21Hz),7.60(1H,d,J=2.46Hz),7.68(1H,s),8.03(1H,d,J=6.84Hz);$C_{27}H_{29}F_4N_7O_2$的ESIMS实验值m/z 560.25(M+1)。

[1634] 

505

[1635] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺505。

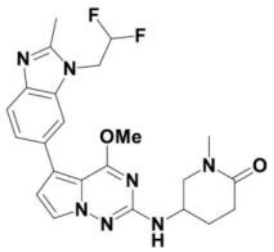
[1636] 白色蓬松固体(14mg,0.028mmol,49.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.56(3H,s),2.68(1H,t,J=9.03Hz),2.77(1H,ddd,J=30.20,12.10,1.40Hz),3.01(1H,t,J=8.35Hz),3.18(1H,ddd,J=33.20,11.91,4.52Hz),3.79(1H,quin,J=6.23Hz),3.94(3H,s),4.23-4.38(1H,m),4.47(2H,t,J=6.02Hz),4.60(2H,t,J=6.57Hz),4.75(2H,td,J=16.02,2.46Hz),5.25(1H,dtd,J=55.65,4.70,4.70,1.35Hz),6.47(1H,tt,J=54.30,3.00Hz),6.65(1H,d,J=2.74Hz),6.72(1H,d,J=7.67Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.61(1H,d,J=2.46Hz),7.70(1H,s);$C_{24}H_{26}F_3N_7O_2$的ESIMS实验值m/z 502.3(M+1)。

[1637] 

506

[1638] 5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺506。

[1639] 白色蓬松固体(17mg,0.034mmol,60.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.56(3H,s),2.68(1H,t,J=9.03Hz),2.77(1H,ddd,J=29.90,12.05,1.37Hz),3.01(1H,t,J=8.35Hz),3.18(1H,ddd,J=33.20,11.91,4.52Hz),3.73-3.84(1H,m),3.94(3H,s),4.23-4.37(1H,m),4.47(2H,t,J=6.02Hz),4.60(2H,t,J=6.57Hz),4.70-4.81(2H,m),5.25(1H,dtd,J=55.65,4.45,4.45,1.23Hz),6.47(1H,tt,J=54.30,3.00Hz),6.65(1H,d,J=2.74Hz),6.72(1H,d,J=7.67Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.61(1H,d,J=2.46Hz),7.70(1H,s);$C_{24}H_{26}F_3N_7O_2$的ESIMS实验值m/z 502.3(M+1)。

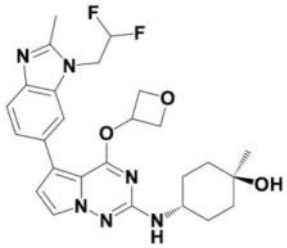
[1640] 

507

[1641] 5-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮507。

[1642] 白色固体(25mg,0.053mmol,40.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.86-1.96(1H,m),1.96-2.04(1H,m),2.26-2.35(1H,m),2.35-2.43(1H,m),2.56(3H,s),2.81(3H,s),3.25(1H,dd,J=11.77,7.67Hz),3.57(1H,dd,J=11.77,4.93Hz),3.94(3H,s),4.04-4.15(1H,m),4.75(2H,td,J=16.02,2.46Hz),6.47(1H,tt,J=54.30,3.00Hz),6.63(1H,d,J=2.74Hz),6.83(1H,d,J=7.39Hz),7.36(1H,dd,J=8.35,1.51Hz),7.50(1H,d,J=8.21Hz),7.62(1H,d,J=2.46Hz),7.70(1H,s);$C_{23}H_{25}F_2N_7O_2$的ESIMS实验值m/z 470.2(M+

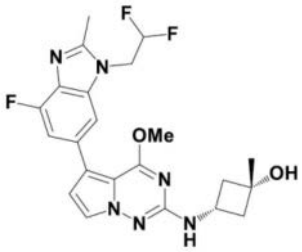
1)。

[1643] 

508

[1644] (1r,4r)-4-((5-(1-(2,2-二氟乙基)-2-甲基-1H-苯并[d]咪唑-6-基)-4-(氧杂环丁烷-3-基氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇508。

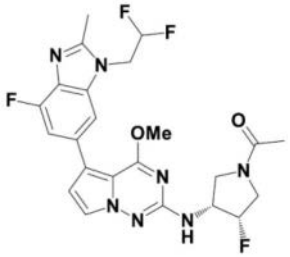
[1645] 白色固体(14mg,0.027mmol,38.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.36-1.50(4H,m),1.54-1.64(2H,m),1.80-1.90(2H,m),2.56(3H,s),3.59(1H,brs),4.25(1H,s),4.51(2H,dd,J=7.67,5.20Hz),4.74(2H,td,J=15.61,2.19Hz),4.84(2H,t,J=6.98Hz),5.67(1H,quin,J=5.68Hz),6.35(1H,d,J=7.94Hz),6.47(1H,tt,J=54.30,3.00Hz),6.64(1H,d,J=2.46Hz),7.45-7.50(1H,m),7.51-7.55(1H,m),7.62(1H,d,J=2.46Hz),7.72(1H,s);$C_{26}H_{30}F_2N_6O_3$的ESIMS实验值m/z 513.3(M+1)。

[1646] 

509

[1647] 顺-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇509。

[1648] 白色固体(8mg,0.017mmol,11.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),1.97-2.07(2H,m),2.31-2.40(2H,m),2.58(3H,s),3.71(1H,sxt,J=7.67Hz),3.93(3H,s),4.78(2H,td,J=16.02,2.46Hz),4.91(1H,s),6.48(1H,tt,J=54.30,3.00Hz),6.66(1H,d,J=2.46Hz),6.88(1H,d,J=6.57Hz),7.19(1H,dd,J=12.32,1.10Hz),7.57(1H,s),7.60(1H,d,J=2.74Hz);$C_{22}H_{23}F_3N_6O_2$的ESIMS实验值m/z 461.2(M+1)。

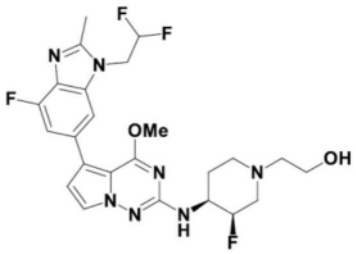
[1649] 

513

[1650] 1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮513。

[1651] 白色固体(30mg,0.059mmol,32.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.93-

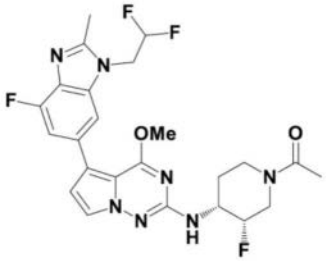
2.01(3H,m),2.58(3H,s),3.47-3.61(1H,m),3.61-3.76(1H,m),3.78-3.85(1H,m),3.86-3.96(1H,m),3.97-3.98(3H,m),4.31-4.58(1H,m),4.78(2H,td,J＝16.08,2.60Hz),5.23-5.48(1H,m),6.49(1H,tt,J＝54.30,3.00Hz),6.72(1H,t,J＝2.33Hz),7.03(1H,t,J＝6.98Hz),7.21(1H,dd,J＝12.18,1.23Hz),7.59(1H,s),7.63(1H,dd,J＝4.11,2.46Hz);$C_{23}H_{23}F_4N_7O_2$的ESIMS实验值m/z 506.2(M+1)。

[1652] 

519

[1653] 2-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-醇519。

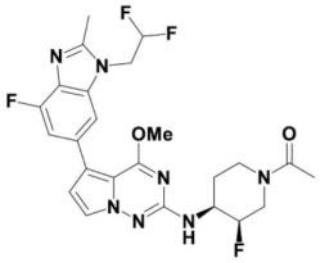
[1654] 白色固体(13mg,0.025mmol,23.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.64-1.72(1H,m),1.90(1H,qd,J＝12.23,3.83Hz),2.17(1H,br t,J＝11.23Hz),2.32(1H,dd,J＝37.55,12.59Hz),2.44(2H,t,J＝6.16Hz),2.58(3H,s),2.91(1H,br d,J＝10.95Hz),3.15(1H,br t,J＝9.72Hz),3.46-3.55(2H,m),3.69-3.86(1H,m),3.95(3H,s),4.41(1H,t,J＝5.34Hz),4.78(2H,td,J＝16.08,2.33Hz),4.89(1H,d,J＝49.65Hz),6.48(1H,tt,J＝54.30,3.00Hz),6.56(1H,d,J＝7.94Hz),6.68(1H,d,J＝2.46Hz),7.20(1H,dd,J＝12.18,1.23Hz),7.58(1H,s),7.60(1H,d,J＝2.46Hz);$C_{24}H_{27}F_4N_7O_2$的ESIMS实验值m/z 522.3(M+1)。

[1655] 

520

[1656] 1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮520。

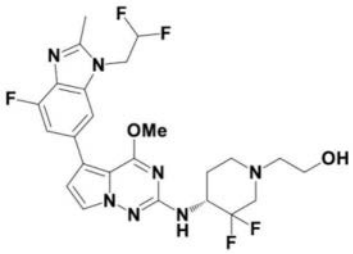
[1657] 蓬松白色固体(5mg,0.010mmol,19.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.73(1H,m),1.74-1.90(1H,m),1.98-2.06(3H,m),2.58(3H,s),2.66-2.97(1H,m),3.17-3.25(1H,m),3.87-4.02(1H,m),3.96(3H,s),4.03-4.16(1H,m),4.39-4.72(1H,m),4.78(2H,td,J＝15.88,2.19Hz),4.99(1H,d,J＝49.65Hz),6.49(1H,tt,J＝54.30,3.00Hz),6.69(1H,d,J＝2.74Hz),6.73(1H,dd,J＝7.80,1.78Hz),7.20(1H,dd,J＝12.18,1.23Hz),7.58(1H,s),7.60(1H,d,J＝2.46Hz);$C_{24}H_{25}F_4N_7O_2$的ESIMS实验值m/z 520.2(M+1)。

[1658] 

521

[1659] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮521。

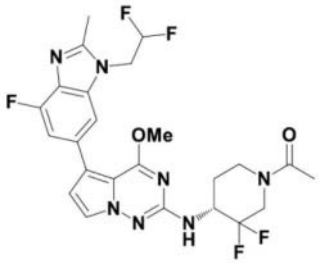
[1660] 白色固体(25mg,0.048mmol,46.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.73(1H,m),1.74-1.90(1H,m),1.98-2.06(3H,m),2.58(3H,s),2.65-2.97(1H,m),3.15-3.26(1H,m),3.86-4.01(1H,m),3.96(3H,s),4.02-4.18(1H,m),4.39-4.73(1H,m),4.78(2H,td,J=16.02,2.46Hz),4.99(1H,d,J=49.55Hz),6.49(1H,tt,J=54.30,3.00Hz),6.69(1H,d,J=2.46Hz),6.73(1H,dd,J=7.67,1.92Hz),7.20(1H,dd,J=12.18,1.23Hz),7.58(1H,s),7.60(1H,d,J=2.46Hz);$C_{24}H_{25}F_4N_7O_2$的ESIMS实验值m/z 520.2(M+1)。

[1661] 

525

[1662] (R)-2-(4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-醇525。

[1663] 白色固体(15mg,0.028mmol,27.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.73-1.88(2H,m),2.25-2.34(1H,m),2.51-2.54(2H,m),2.58(3H,s),2.90(1H,br d,J=11.50Hz),3.13-3.23(1H,m),3.30-3.32(1H,m),3.52(2H,q,J=5.84Hz),3.97(3H,s),4.17-4.32(1H,m),4.49(1H,t,J=5.20Hz),4.78(2H,td,J=16.02,2.19Hz),6.48(1H,tt,J=54.30,3.00Hz),6.70(1H,d,J=2.74Hz),6.77(1H,d,J=9.31Hz),7.20(1H,dd,J=12.18,1.23Hz),7.58(1H,s),7.61(1H,d,J=2.74Hz);$C_{24}H_{26}F_5N_7O_2$的ESIMS实验值m/z 540.2(M+1)。

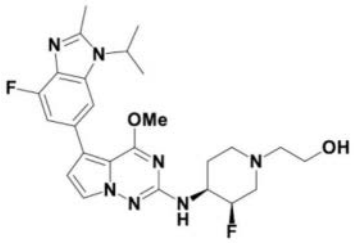
[1664] 

526

[1665] (R)-1-(4-((5-(1-(2,2-二氟乙基)-4-氟-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲

氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮526。

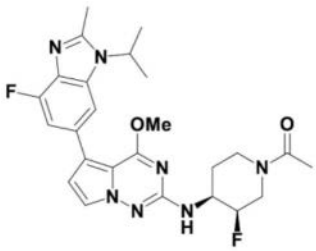
[1666] 白色固体(20mg,0.037mmol,36.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.58-1.83(1H,m),1.84-1.99(1H,m),2.03-2.09(3H,m),2.58(3H,s),2.92-3.05(1H,m),3.63-3.92(1H,m),3.98(3H,s),4.10-4.30(1H,m),4.45-4.60(2H,m),4.78(2H,td,J=16.08,2.33Hz),6.49(1H,tt,J=54.30,3.00Hz),6.71(1H,d,J=2.46Hz),6.95(1H,d,J=9.31Hz),7.21(1H,dd,J=12.18,1.23Hz),7.59(1H,s),7.61(1H,dd,J=2.46,1.37Hz);$C_{24}H_{24}F_5N_7O_2$的ESIMS实验值m/z 538.2(M+1)。

[1667] 

542

[1668] 2-((3R,4S)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-醇542。

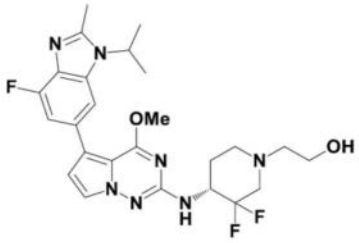
[1669] 白色固体(6mg,0.012mmol,18.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.59(6H,d,J=6.84Hz),1.64-1.72(1H,m),1.90(1H,qd,J=12.27,3.70Hz),2.17(1H,br t,J=10.68Hz),2.32(1H,dd,J=37.25,12.87Hz),2.44(2H,t,J=6.30Hz),2.58(3H,s),2.91(1H,br d,J=10.95Hz),3.15(1H,br t,J=10.13Hz),3.46-3.54(2H,m),4.41(1H,t,J=5.34Hz),4.76(1H,spt,J=6.84Hz),4.89(1H,d,J=49.90Hz),6.55(1H,d,J=7.67Hz),6.69(1H,d,J=2.74Hz),7.12(1H,d,J=12.05Hz),7.59(1H,d,J=2.46Hz),7.64(1H,s);$C_{25}H_{31}F_2N_7O_2$的ESIMS实验值m/z 500.3(M+1)。

[1670] 

544

[1671] 1-((3R,4S)-3-氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮544。

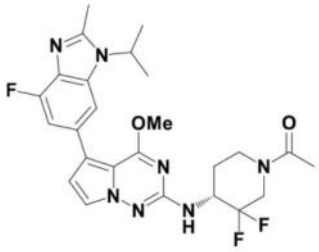
[1672] 白色固体(15mg,0.030mmol,45.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.59(6H,d,J=6.57Hz),1.64-1.89(2H,m),1.97-2.07(3H,m),2.58(3H,s),2.66-2.96(1H,m),3.17-3.26(1H,m),3.83-4.17(2H,m),3.96(3H,s),4.39-4.72(1H,m),4.73-4.81(1H,m),4.92-5.06(1H,m),6.70(1H,d,J=2.74Hz),6.72(1H,d,J=7.94Hz),7.12(1H,dd,J=12.18,1.23Hz),7.59(1H,d,J=2.46Hz),7.64(1H,d,J=1.10Hz);$C_{25}H_{29}F_2N_7O_2$的ESIMS实验值m/z 498.25(M+1)。

[1673] 

549

[1674] (R)-2-(3,3-二氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-醇549。

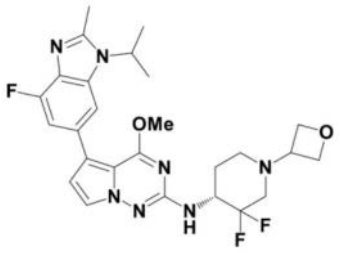
[1675] 白色固体(5mg,0.010mmol,15.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.59(6H,dd,J=6.84,2.19Hz),1.72-1.88(2H,m),2.25-2.34(1H,m),2.44-2.55(1H,m),2.58(3H,s),2.90(1H,br d,J=11.50Hz),3.11-3.22(1H,m),3.52(2H,q,J=5.84Hz),3.97(3H,s),4.17-4.32(1H,m),4.49(1H,t,J=5.34Hz),4.76(1H,spt,J=6.89Hz),6.70(1H,d,J=2.74Hz),6.76(1H,d,J=9.31Hz),7.12(1H,dd,J=12.05,1.10Hz),7.61(1H,d,J=2.74Hz),7.65(1H,d,J=1.10Hz);$C_{25}H_{30}F_3N_7O_2$的ESIMS实验值m/z 518.3(M+1)。

[1676] 

550

[1677] (R)-1-(3,3-二氟-4-((5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮550。

[1678] 白色固体(6mg,0.012mmol,18.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.57-1.61(6H,m),1.62-1.83(1H,m),1.84-1.98(1H,m),2.02-2.10(3H,m),2.58(3H,s),2.93-3.05(1H,m),3.63-3.77(1H,m),3.82-4.21(1H,m),3.98(3H,s),4.22-4.61(2H,m),4.76(1H,spt,J=6.89Hz),6.72(1H,d,J=2.74Hz),6.93(1H,d,J=9.31Hz),7.12(1H,dd,J=12.05,1.10Hz),7.60(1H,dd,J=2.46,1.37Hz),7.65(1H,d,J=1.10Hz);$C_{25}H_{28}F_3N_7O_2$的ESIMS实验值m/z 516.2(M+1)。

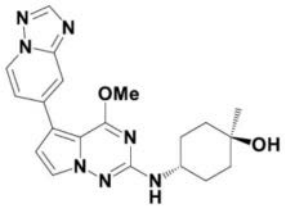
[1679] 

551

[1680] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺551。

[1681] 白色固体(8mg,0.015mmol,23.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.59(6H,

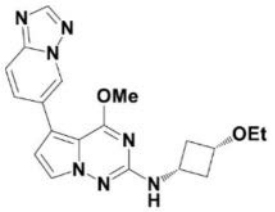
dd,J＝6.98,2.05Hz),1.75-1.85(1H,m),1.85-1.93(1H,m),2.16(1H,br t,J＝10.40Hz),2.34-2.47(1H,m),2.58(3H,s),2.76(1H,br d,J＝11.77Hz),2.96-3.07(1H,m),3.60(1H,quin,J＝6.23Hz),3.97(3H,s),4.24-4.37(1H,m),4.44(2H,dt,J＝14.92,6.23Hz),4.55(2H,td,J＝6.64,3.42Hz),4.76(1H,spt,J＝6.89Hz),6.71(1H,d,J＝2.74Hz),6.83(1H,d,J＝9.58Hz),7.12(1H,dd,J＝12.18,0.96Hz),7.60(1H,d,J＝2.74Hz),7.65(1H,d,J＝1.10Hz);$C_{26}H_{30}F_3N_7O_2$的ESIMS实验值m/z 530.25(M+1)。

[1682] 

554

[1683] (1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-7-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇554。

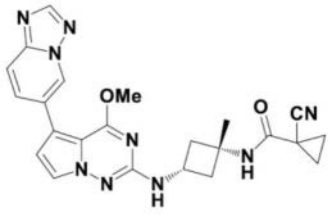
[1684] 白色固体(6.4mg,0.016mmol,8.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.37-1.53(4H,m),1.57-1.65(2H,m),1.84-1.93(2H,m),3.65(1H,br dd,J＝8.08,3.70Hz),3.99(3H,s),4.23(1H,s),6.58(1H,d,J＝7.94Hz),6.88(1H,d,J＝2.74Hz),7.44(1H,dd,J＝7.12,1.64Hz),7.67(1H,d,J＝2.74Hz),7.95(1H,dd,J＝1.92,0.82Hz),8.46(1H,s),8.89(1H,dd,J＝7.12,0.82Hz);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[1685] 

555

[1686] 5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(顺-3-乙氧基环丁基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺555。

[1687] 灰白色固体(9mg,0.024mmol,32.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.10(3H,t,J＝6.98Hz),1.80-1.91(2H,m),2.59-2.70(2H,m),3.34(2H,q,J＝7.10Hz),3.65-3.72(1H,m),3.74-3.84(1H,m),3.96(3H,s),6.81(1H,d,J＝2.74Hz),7.05(1H,d,J＝7.39Hz),7.63(1H,d,J＝2.74Hz),7.80-7.86(1H,m),7.87-7.92(1H,m),8.49(1H,s),9.03-9.10(1H,m);$C_{19}H_{21}N_7O_2$的ESIMS实验值m/z 380.2(M+1)。

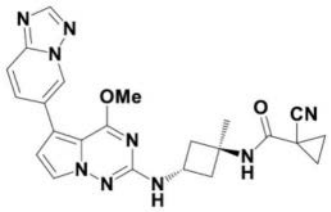
[1688] 

562

[1689] N-((1s,3s)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-

f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-1-氰基环丙烷-1-甲酰胺562。

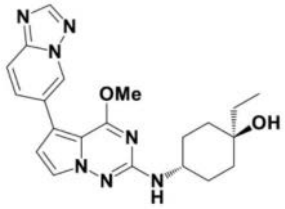
[1690] 米色固体(8mg,0.018mmol,25.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.37(3H,s),1.43-1.49(2H,m),1.49-1.55(2H,m),2.18(2H,br dd,J=11.64,9.17Hz),2.45(2H,ddd,J=9.86,7.39,2.46Hz),3.96(3H,s),4.03(1H,sxt,J=7.78Hz),6.81(1H,d,J=2.74Hz),7.03(1H,d,J=7.12Hz),7.67(1H,d,J=2.46Hz),7.82-7.86(1H,m),7.87-7.92(1H,m),8.29(1H,s),8.49(1H,s),9.04-9.11(1H,m);$C_{23}H_{23}N_9O_2$的ESIMS实验值m/z 458.2(M+1)。

[1691] 

563

[1692] N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)-1-氰基环丙烷-1-甲酰胺563。

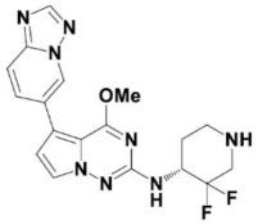
[1693] 米色固体(7mg,0.015mmol,22.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.37(3H,s),1.48-1.57(4H,m),1.93-2.06(2H,m),2.67-2.78(2H,m),3.96(3H,s),4.18(1H,sxt,J=7.72Hz),6.80(1H,d,J=2.74Hz),7.05(1H,d,J=6.84Hz),7.67(1H,d,J=2.74Hz),7.81-7.86(1H,m),7.87-7.92(1H,m),8.05(1H,s),8.49(1H,s),9.02-9.10(1H,m);$C_{23}H_{23}N_9O_2$的ESIMS实验值m/z 458.2(M+1)。

[1694] 

567

[1695] (1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇567。

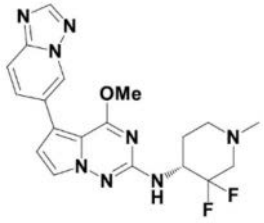
[1696] 灰白色固体(25mg,0.061mmol,36.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.83(3H,t,J=7.39Hz),1.31-1.39(2H,m),1.40-1.45(2H,m),1.46(2H,q,J=7.57Hz),1.58-1.69(2H,m),1.80-1.90(2H,m),3.68(1H,tt,J=8.01,4.04Hz),3.96(3H,s),3.99(1H,s),6.51(1H,d,J=7.67Hz),6.79(1H,d,J=2.46Hz),7.65(1H,d,J=2.74Hz),7.81-7.85(1H,m),7.87-7.91(1H,m),8.49(1H,s),9.06(1H,s);$C_{21}H_{25}N_7O_2$的ESIMS实验值m/z 408.2(M+1)。

[1697] 

575

[1698] (R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(3,3-二氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺575。

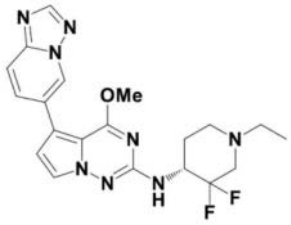
[1699] 灰白色固体(86mg,0.215mmol,53.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69(1H,qd,J=11.82,3.70Hz),1.80-1.89(1H,m),2.60(1H,br t,J=11.64Hz),2.81(1H,dd,J=29.65,13.46Hz),2.93(1H,br d,J=12.87Hz),3.06-3.19(1H,m),4.00(3H,s),4.25-4.42(1H,m),6.83(1H,d,J=2.46Hz),6.89(1H,d,J=9.31Hz),7.67(1H,d,J=2.46Hz),7.82-7.87(1H,m),7.88-7.93(1H,m),8.50(1H,s),9.08(1H,s);$C_{18}H_{18}F_2N_8O$的ESIMS实验值m/z 401.2(M+1)。

[1700] 

576

[1701] (R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺576。

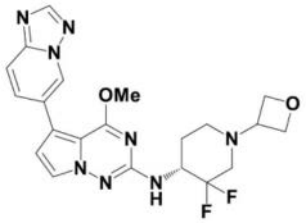
[1702] 蓬松白色固体(12mg,0.027mmol,71.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.94(2H,m),2.10-2.47(5H,m),2.73-2.94(1H,m),3.00-3.20(1H,m),4.00(3H,s),4.21-4.41(1H,m),6.84(1H,d,J=2.74Hz),6.89-6.99(1H,m),7.67(1H,d,J=2.74Hz),7.80-7.87(1H,m),7.88-7.94(1H,m),8.50(1H,s),9.05-9.12(1H,m);$C_{19}H_{20}F_2N_8O$的ESIMS实验值m/z 415.2(M+1)。

[1703] 

577

[1704] (R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺577。

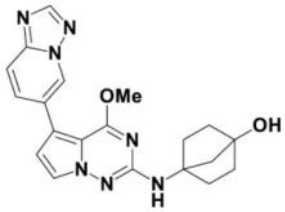
[1705] 蓬松白色固体(16mg,0.034mmol,55.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.01(3H,br s),1.71-1.94(2H,m),2.10-2.24(1H,m),2.29-2.48(3H,m),2.80-2.94(1H,m),3.01-3.18(1H,m),4.00(3H,s),4.18-4.36(1H,m),6.79-6.94(2H,m),7.66(1H,br s),7.82-7.87(1H,m),7.88-7.95(1H,m),8.50(1H,s),9.09(1H,s);$C_{20}H_{22}F_2N_8O$的ESIMS实验值m/z 429.2(M+1)。

[1706] 

578

[1707] (R)-5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺578。

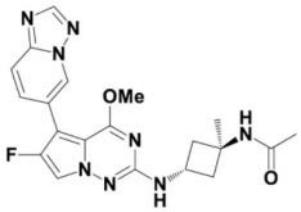
[1708] 蓬松白色固体(18mg,0.039mmol,63.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.86(1H,m),1.86-1.93(1H,m),2.10-2.22(1H,m),2.40(1H,dd,J=26.30,11.77Hz),2.76(1H,br d,J=11.22Hz),2.95-3.08(1H,m),3.60(1H,quin,J=6.30Hz),4.00(3H,s),4.23-4.37(1H,m),4.44(2H,dt,J=15.19,6.23Hz),4.55(2H,td,J=6.57,3.83Hz),6.84(1H,d,J=2.74Hz),6.94(1H,d,J=9.31Hz),7.66(1H,d,J=2.74Hz),7.80-7.87(1H,m),7.88-7.95(1H,m),8.50(1H,s),9.08(1H,s);$C_{21}H_{22}F_2N_8O_2$的ESIMS实验值m/z 457.2(M+1)。

[1709] 

582

[1710] 4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇582。

[1711] 灰白色固体(3mg,0.008mmol,4.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.51-1.63(2H,m),1.66-1.79(2H,m),1.85(2H,s),1.86-1.92(2H,m),1.98-2.11(2H,m),3.96(3H,s),4.89(1H,s),6.77(1H,s),6.80(1H,d,J=2.74Hz),7.62(1H,d,J=2.74Hz),7.80-7.86(1H,m),7.87-7.91(1H,m),8.49(1H,s),9.03-9.10(1H,m);$C_{20}H_{21}N_7O_2$的ESIMS实验值m/z 392.2(M+1)。

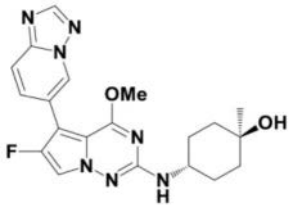
[1712] 

585

[1713] N-((1r,3r)-3-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺585。

[1714] 灰白色固体(6mg,0.014mmol,27.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.35(3H,s),1.81(3H,s),1.89-2.00(2H,m),2.58-2.70(2H,m),3.92(3H,s),4.17(1H,sxt,J=7.72Hz),7.13(1H,d,J=7.12Hz),7.77-7.82(1H,m),7.83(1H,d,J=3.01Hz),7.88(1H,d,J=9.86Hz),7.93(1H,s),8.53(1H,s),9.05(1H,s);$C_{20}H_{21}FN_8O_2$的ESIMS实验值m/z 425.2(M+

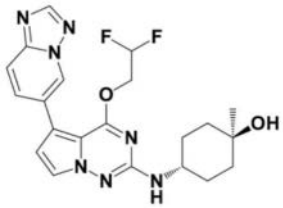
1)。

[1715] 

589

[1716] (1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇589。

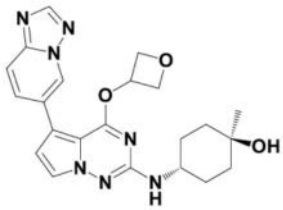
[1717] 灰白色固体(7mg,0.017mmol,23.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.36-1.51(4H,m),1.55-1.65(2H,m),1.81-1.90(2H,m),3.58-3.68(1H,m),3.92(3H,s),4.25(1H,s),6.63(1H,d,J=7.94Hz),7.78-7.82(1H,m),7.86(1H,d,J=3.01Hz),7.88(1H,dd,J=9.31,0.82Hz),8.53(1H,s),9.05(1H,s);$C_{20}H_{22}FN_7O_2$的ESIMS实验值m/z 412.2(M+1)。

[1718] 

616

[1719] (1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(2,2-二氟乙氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇616。

[1720] 白色固体(2.92mg,0.007mmol)。^{1}H NMR(400MHz,溶剂)δppm1.28(3H,s),1.46-1.66(4H,m),1.69-1.80(2H,m),1.99-2.10(2H,m),3.68-3.82(1H,m),4.69(2H,td,J=14.07,3.75Hz),6.18(1H,tt,J=55.00,3.76Hz),6.77(1H,d,J=2.63Hz),7.57(1H,d,J=2.50Hz),7.75(1H,d,J=9.13Hz),7.96(1H,dd,J=9.26,1.38Hz),8.41(1H,s),8.94(1H,s);$C_{21}H_{23}F_2N_7O_2$的ESIMS实验值m/z 444.3(M+1)。

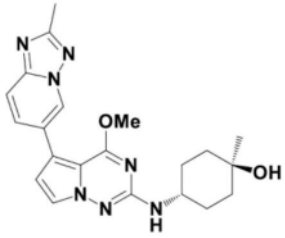
[1721] 

621

[1722] (1r,4r)-4-((5-([1,2,4]三唑并[1,5-a]吡啶-6-基)-4-(氧杂环丁烷-3-基氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇621。

[1723] 白色固体(11mg,0.025mmol,35.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.36-1.48(4H,m),1.55-1.64(2H,m),1.80-1.90(2H,m),3.59(1H,br d,J=3.83Hz),4.25(1H,s),4.61(2H,dd,J=7.53,5.34Hz),4.86(2H,t,J=7.12Hz),5.69(1H,quin,J=5.75Hz),6.48(1H,d,J=7.94Hz),6.86(1H,d,J=2.74Hz),7.69(1H,d,J=

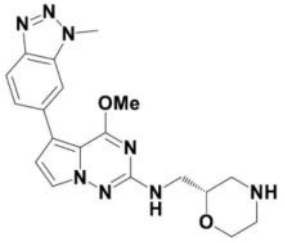
2.74Hz),7.88(1H,d,J＝9.31Hz),7.98(1H,dd,J＝9.31,1.64Hz),8.51(1H,s),9.21(1H,s);$C_{22}H_{25}N_7O_3$的ESIMS实验值m/z 436.2(M+1)。

[1724] 

622

[1725] (1r,4r)-4-((4-甲氧基-5-(2-甲基-[1,2,4]三唑并[1,5-a]吡啶-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环已-1-醇622。

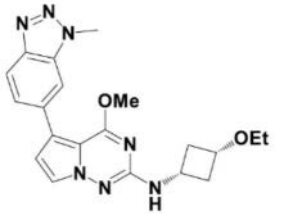
[1726] 白色固体(34mg,0.083mmol,35.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.37-1.52(4H,m),1.55-1.66(2H,m),1.82-1.93(2H,m),2.48(3H,s),3.64(1H,brd,J＝4.11Hz),3.96(3H,s),4.23(1H,s),6.51(1H,d,J＝7.67Hz),6.76(1H,d,J＝2.74Hz),7.65(1H,d,J＝2.74Hz),7.68(1H,d,J＝9.03Hz),7.82(1H,dd,J＝9.31,1.64Hz),8.94(1H,s);$C_{21}H_{25}N_7O_2$的ESIMS实验值m/z 408.2(M+1)。

[1727] 

623

[1728] (S)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-N-(吗啉-2-基甲基)吡咯并[2,1-f][1,2,4]三嗪-2-胺623。

[1729] 白色固体(54mg,0.137mmol,94.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.59(1H,dd,J＝12.32,10.68Hz),2.80(1H,td,J＝12.05,3.56Hz),2.86-2.94(1H,m),3.06(1H,br d,J＝11.77Hz),3.20-3.26(1H,m),3.28-3.32(1H,m),3.54(1H,td,J＝11.64,2.46Hz),3.75(1H,dtd,J＝10.23,6.04,6.04,2.05Hz),3.85(1H,dd,J＝11.77,2.19Hz),3.96(3H,s),4.31(3H,s),6.74(1H,t,J＝6.02Hz),6.76(1H,d,J＝2.46Hz),7.61(1H,dd,J＝8.76,1.37Hz),7.65(1H,d,J＝2.74Hz),7.94(1H,s),7.98(1H,d,J＝8.76Hz);$C_{19}H_{22}N_8O_2$的ESIMS实验值m/z 395.2(M+1)。

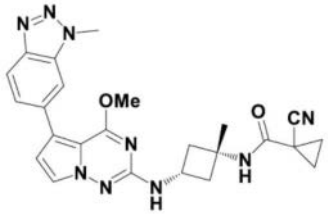
[1730] 

624

[1731] N-(顺-3-乙氧基环丁基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)

吡咯并[2,1-f][1,2,4]三嗪-2-胺624。

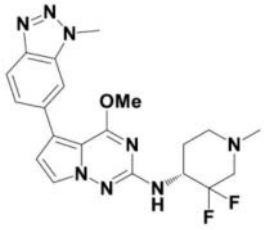
[1732] 米色固体(23mg,0.059mmol,30.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.10(3H,t,J=6.98Hz),1.81-1.93(2H,m),2.64(2H,tdt,J=9.02,9.02,6.74,2.53,2.53Hz),3.34(2H,q,J=6.85Hz),3.65-3.73(1H,m),3.74-3.84(1H,m),3.95(3H,s),4.31(3H,s),6.75(1H,d,J=2.46Hz),7.01(1H,d,J=7.39Hz),7.58-7.62(1H,m),7.62(1H,d,J=2.74Hz),7.94(1H,s),7.95-7.99(1H,m);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[1733] 

625

[1734] 1-氰基-N-((1s,3s)-3-((4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)环丙烷-1-甲酰胺625。

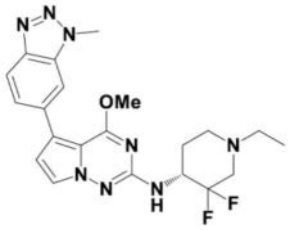
[1735] 灰白色固体(9mg,0.019mmol,28.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.43-1.49(2H,m),1.49-1.54(2H,m),2.14-2.23(2H,m),2.45(2H,ddd,J=9.79,7.46,2.74Hz),3.95(3H,s),4.04(1H,sxt,J=7.78Hz),4.31(3H,s),6.75(1H,d,J=2.46Hz),6.99(1H,d,J=7.12Hz),7.60(1H,dd,J=8.76,1.64Hz),7.65(1H,d,J=2.46Hz),7.94(1H,s),7.97(1H,dd,J=8.62,0.68Hz),8.29(1H,s);$C_{24}H_{25}N_9O_2$的ESIMS实验值m/z 472.2(M+1)。

[1736] 

626

[1737] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺626。

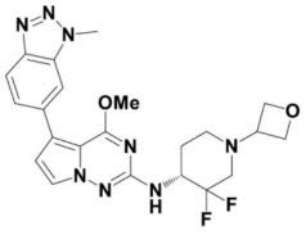
[1738] 蓬松白色固体(6mg,0.013mmol,35.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.90(2H,m),2.12-2.23(1H,m),2.28(3H,br s),2.34-2.46(1H,m),2.75-2.88(1H,m),3.01-3.15(1H,m),3.98(3H,s),4.19-4.30(1H,m),4.31(3H,s),6.78(1H,d,J=2.46Hz),6.84(1H,br d,J=6.84Hz),7.62(1H,dd,J=8.62,1.51Hz),7.66(1H,d,J=2.46Hz),7.95(1H,s),7.98(1H,d,J=8.76Hz);$C_{20}H_{22}F_2N_8O$的ESIMS实验值m/z 429.2(M+1)。

[1739] 

627

[1740] (R)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺627。

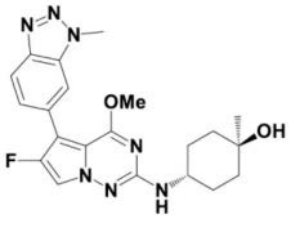
[1741] 蓬松白色固体(14mg,0.032mmol,52.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.01(3H,t,J=7.26Hz),1.72-1.83(1H,m),1.84-1.92(1H,m),2.18(1H,br t,J=10.40Hz),2.33-2.42(1H,m),2.45(2H,q,J=7.12Hz),2.88(1H,br d,J=11.77Hz),3.07-3.18(1H,m),3.98(3H,s),4.20-4.30(1H,m),4.31(3H,s),6.78(1H,d,J=2.46Hz),6.83(1H,d,J=9.31Hz),7.60-7.63(1H,m),7.66(1H,d,J=2.46Hz),7.95(1H,s),7.98(1H,d,J=8.49Hz);$C_{21}H_{24}F_2N_8O$的ESIMS实验值m/z 443.2(M+1)。

[1742] 

628

[1743] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺628。

[1744] 蓬松白色固体(22mg,0.047mmol,52.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.75-1.86(1H,m),1.87-1.94(1H,m),2.11-2.22(1H,m),2.41(1H,dd,J=27.15,11.55Hz),2.76(1H,br d,J=11.23Hz),2.96-3.07(1H,m),3.60(1H,quin,J=6.23Hz),3.99(3H,s),4.25-4.37(1H,m),4.31(3H,s),4.44(2H,dt,J=15.06,6.16Hz),4.55(2H,td,J=6.64,3.70Hz),6.78(1H,d,J=2.46Hz),6.89(1H,d,J=9.31Hz),7.62(1H,dd,J=8.76,1.64Hz),7.65(1H,d,J=2.46Hz),7.95(1H,s),7.98(1H,d,J=8.76Hz);$C_{22}H_{24}F_2N_8O_2$的ESIMS实验值m/z 471.2(M+1)。

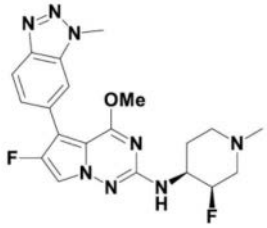
[1745] 

629

[1746] 反-4-((6-氟-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇629。

[1747] 灰白色固体(10.5mg,0.025mmol,27.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm

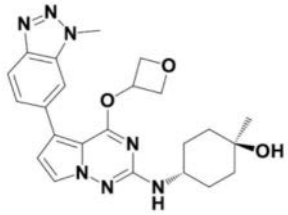
1.14(3H,s),1.37-1.52(4H,m),1.56-1.66(2H,m),1.82-1.92(2H,m),3.63(1H,dt,J＝8.21,4.11Hz),3.90(3H,s),4.24(1H,s),4.31(3H,s),6.59(1H,d,J＝7.94Hz),7.52(1H,d,J＝8.76Hz),7.84(1H,d,J＝2.74Hz),7.90(1H,s),8.02(1H,d,J＝8.76Hz);$C_{21}H_{24}FN_7O_2$的ESIMS实验值m/z 426.2(M+1)。

[1748] 

630

[1749] 6-氟-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺630。

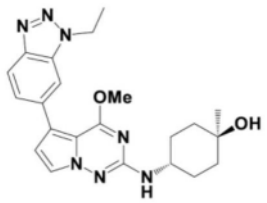
[1750] 白色固体(7.6mg,0.018mmol,19.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.63-1.72(1H,m),1.86-1.98(1H,m),2.01-2.10(1H,m),2.17(1H,dd,J＝37.55,12.87Hz),2.19(3H,s),2.80(1H,br d,J＝10.95Hz),3.00-3.11(1H,m),3.66-3.83(1H,m),3.92(3H,s),4.32(3H,s),4.89(1H,d,J＝50.20Hz),6.74(1H,d,J＝7.67Hz),7.52(1H,d,J＝8.76Hz),7.83(1H,d,J＝3.01Hz),7.91(1H,s),8.03(1H,d,J＝8.49Hz);$C_{20}H_{22}F_2N_8O$的ESIMS实验值m/z 429.2(M+1)。

[1751] 

631

[1752] (1r,4r)-1-甲基-4-((5-(1-甲基-1H-苯并[d][1,2,3]三唑-6-基)-4-(氧杂环丁烷-3-基氧基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇631。

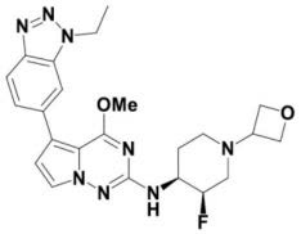
[1753] 灰白色固体(11mg,0.025mmol,34.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.36-1.52(4H,m),1.54-1.65(2H,m),1.79-1.93(2H,m),3.60(1H,br s),4.25(1H,s),4.32(3H,s),4.56(2H,dd,J＝7.39,5.20Hz),4.85(2H,t,J＝6.98Hz),5.70(1H,quin,J＝5.61Hz),6.45(1H,br d,J＝7.67Hz),6.79(1H,d,J＝2.46Hz),7.68(1H,d,J＝2.46Hz),7.69-7.73(1H,m),8.01(1H,d,J＝8.76Hz),8.04(1H,s);$C_{23}H_{27}N_7O_3$的ESIMS实验值m/z 450.2(M+1)。

[1754] 

639

[1755] (1r,4r)-4-((5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇639。

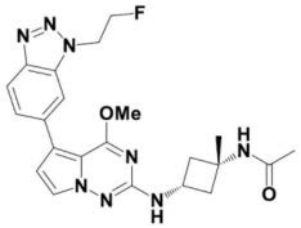
[1756] 蓬松白色固体(6mg,0.014mmol,29.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.50(4H,m),1.54(3H,t,J=7.26Hz),1.57-1.63(2H,m),1.84-1.93(2H,m),3.65(1H,dt,J=8.08,3.90Hz),3.95(3H,s),4.23(1H,s),4.75(2H,q,J=7.12Hz),6.49(1H,d,J=7.94Hz),6.74(1H,d,J=2.46Hz),7.57-7.62(1H,m),7.64(1H,d,J=2.46Hz),7.97-7.99(2H,m);$C_{22}H_{27}N_7O_2$的ESIMS实验值m/z 422.2(M+1)。

[1757] 

646

[1758] 5-(1-乙基-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺646。

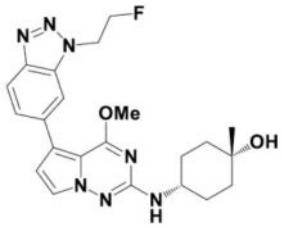
[1759] 灰白色固体(2mg,0.004mmol,25.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.54(3H,t,J=7.39Hz),1.68-1.78(1H,m),1.92(1H,qd,J=12.14,3.29Hz),1.98-2.06(1H,m),2.16(1H,dd,J=37.30,12.59Hz),2.76(1H,br d,J=10.68Hz),2.99(1H,br t,J=10.13Hz),3.49(1H,quin,J=6.30Hz),3.74-3.91(1H,m),3.97(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.75(2H,q,J=7.12Hz),4.94(1H,d,J=49.60Hz),6.69(1H,d,J=7.67Hz),6.77(1H,d,J=2.74Hz),7.59-7.62(1H,m),7.64(1H,d,J=2.74Hz),7.97-8.00(2H,m);$C_{23}H_{27}FN_8O_2$的ESIMS实验值m/z 467.25(M+1)。

[1760] 

653

[1761] N-((1s,3s)-3-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺653。

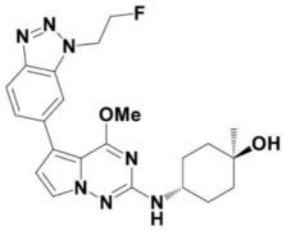
[1762] 白色固体(12mg,0.027mmol,21.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.11-2.21(2H,m),2.42(2H,ddd,J=9.58,7.39,2.46Hz),3.93(3H,s),4.03(1H,sxt,J=7.78Hz),4.94(3H,dt,J=47.15,4.65Hz),5.08(2H,dt,J=27.70,4.70Hz),6.73(1H,d,J=2.46Hz),6.99(1H,d,J=6.84Hz),7.61(1H,dd,J=8.76,1.37Hz),7.65(1H,d,J=2.46Hz),7.98-8.04(3H,m);$C_{22}H_{25}FN_8O_2$的ESIMS实验值m/z 453.2(M+1)。

[1763] 

658

[1764] (1s,4s)-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇658。

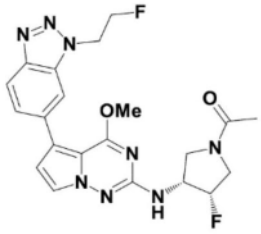
[1765] 白色固体(10mg,0.023mmol,23.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.37(2H,td,J=13.00,4.38Hz),1.58(2H,br d,J=12.05Hz),1.61-1.74(4H,m),3.46-3.58(1H,m),3.93(3H,s),4.00(1H,s),4.94(2H,dt,J=47.20,4.65Hz),5.07(2H,dt,J=27.95,4.65Hz),6.50(1H,d,J=7.94Hz),6.71(1H,d,J=2.74Hz),7.61(1H,dd,J=8.62,1.51Hz),7.61(1H,d,J=2.46Hz),7.99(1H,s),8.00(1H,d,J=8.49Hz);$C_{22}H_{26}FN_7O_2$的ESIMS实验值m/z 440.2(M+1)。

[1766] 

659

[1767] (1r,4r)-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇659。

[1768] 蓬松白色固体(3mg,0.007mmol,14.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.51(4H,m),1.56-1.65(2H,m),1.82-1.92(2H,m),3.65(1H,dt,J=7.73,3.94Hz),3.94(3H,s),4.23(1H,s),4.94(2H,dt,J=47.20,4.65Hz),5.07(2H,dt,J=27.70,4.65Hz),6.49(1H,d,J=7.94Hz),6.72(1H,d,J=2.46Hz),7.61(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.46Hz),7.99(1H,s),8.00(1H,d,J=8.76Hz);$C_{22}H_{26}FN_7O_2$的ESIMS实验值m/z 440.2(M+1)。

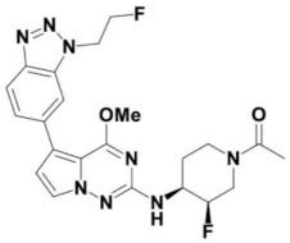
[1769] 

660

[1770] 1-((3S,4R)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮660。

[1771] 白色固体(17mg,0.037mmol,20.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.93-

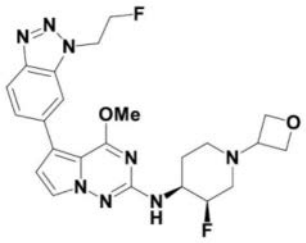
2.01(3H,m),3.46-3.58(1H,m),3.59-3.76(1H,m),3.77-3.85(1H,m),3.85-3.96(1H,m),3.96-3.99(3H,m),4.29-4.59(1H,m),4.94(2H,dt,J＝47.15,4.65Hz),5.08(2H,dt,J＝27.95,4.65Hz),5.24-5.50(1H,m),6.79(1H,t,J＝2.46Hz),7.09(1H,dd,J＝7.12,5.75Hz),7.61-7.65(1H,m),7.68(1H,dd,J＝3.97,2.60Hz),8.00-8.04(2H,m);$C_{21}H_{22}F_2N_8O_2$的ESIMS实验值m/z 457.2(M+1)。

[1772] 

664

[1773] 1-((3R,4S)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮664。

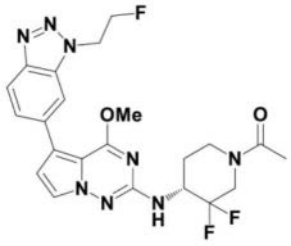
[1774] 蓬松白色固体(15mg,0.032mmol,64.1％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.92(2H,m),1.97-2.06(3H,m),2.66-3.00(1H,m),3.36-3.52(1H,m),3.86-4.18(2H,m),3.96(3H,s),4.41-4.75(1H,m),4.94(2H,dt,J＝47.20,4.65Hz),4.94(1H,br s),5.08(2H,dt,J＝27.95,4.65Hz),6.76(1H,d,J＝2.74Hz),6.80(1H,dd,J＝7.80,3.15Hz),7.62(1H,dd,J＝8.62,1.51Hz),7.65(1H,d,J＝2.74Hz),7.99-8.03(2H,m);$C_{22}H_{24}F_2N_8O_2$的ESIMS实验值m/z 471.2(M+1)。

[1775] 

666

[1776] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺666。

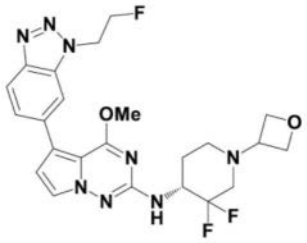
[1777] 灰白色固体(2mg,0.004mmol,14.9％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67-1.78(1H,m),1.87-1.97(1H,m),1.99-2.05(1H,m),2.16(1H,dd,J＝37.00,12.59Hz),2.72-2.79(1H,m),2.99(1H,br t,J＝10.54Hz),3.49(1H,quin,J＝6.30Hz),3.76-3.91(1H,m),3.96(3H,s),4.40(1H,t,J＝6.16Hz),4.46(1H,t,J＝6.16Hz),4.54(2H,td,J＝6.43,3.01Hz),4.94(2H,dt,J＝47.45,4.65Hz),5.08(2H,dt,J＝28.00,4.65Hz),6.70(1H,d,J＝7.67Hz),6.75(1H,d,J＝2.46Hz),7.62(1H,dd,J＝8.62,1.51Hz),7.64(1H,d,J＝2.74Hz),7.99-8.03(2H,m);$C_{23}H_{26}F_2N_8O_2$的ESIMS实验值m/z 485.2(M+1)。

[1778] 

669

[1779] (R)-1-(3,3-二氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮669。

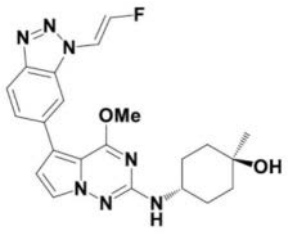
[1780] 蓬松白色固体(7mg,0.014mmol,32.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.58-1.84(1H,m),1.85-2.00(1H,m),2.02-2.10(3H,m),2.99(1H,br t,J=11.09Hz),3.63-3.92(1H,m),3.98(3H,s),4.10-4.31(1H,m),4.46-4.63(2H,m),4.94(2H,dt,J=47.20,4.65Hz),5.08(2H,dt,J=28.00,4.65Hz),6.78(1H,d,J=2.74Hz),7.00(1H,d,J=9.31Hz),7.61-7.64(1H,m),7.65(1H,dd,J=2.46,1.37Hz),8.00-8.04(2H,m);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

[1781] 

670

[1782] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺670。

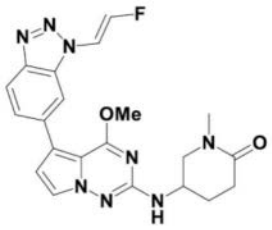
[1783] 浅黄色固体(8mg,0.016mmol,33.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.86(1H,m),1.86-1.93(1H,m),2.12-2.23(1H,m),2.34-2.47(1H,m),2.76(1H,br d,J=11.77Hz),2.97-3.06(1H,m),3.60(1H,quin,J=6.30Hz),3.97(3H,s),4.24-4.38(1H,m),4.44(2H,dt,J=15.13,6.26Hz),4.55(2H,td,J=6.57,3.83Hz),4.94(2H,dt,J=46.90,4.65Hz),5.08(2H,dt,J=27.70,4.65Hz),6.77(1H,d,J=2.74Hz),6.90(1H,d,J=9.31Hz),7.61-7.64(1H,m),7.65(1H,d,J=2.46Hz),8.00-8.03(2H,m);$C_{23}H_{25}F_3N_8O_2$的ESIMS实验值m/z 503.2(M+1)。

[1784] 

672

[1785] (1r,4r)-4-((5-(1-((E)-2-氟乙烯基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇672。

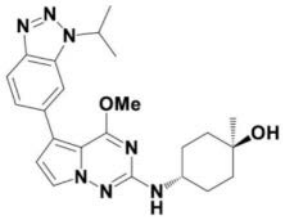
[1786] 黄色固体(7mg,0.016mmol,23.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.51(4H,m),1.57-1.66(2H,m),1.82-1.93(2H,m),3.59-3.71(1H,m),3.94(3H,s),4.23(1H,s),6.51(1H,d,J=7.94Hz),6.74(1H,d,J=2.74Hz),7.34(1H,dd,J=60.90,4.10Hz),7.45(1H,dd,J=18.62,3.83Hz),7.65(1H,d,J=2.46Hz),7.69(1H,d,J=9.03Hz),7.92(1H,s),8.08(1H,d,J=8.76Hz);$C_{22}H_{24}FN_7O_2$的ESIMS实验值m/z 438.2(M+1)。

[1787] 

673

[1788] (E)-5-((5-(1-(2-氟乙烯基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮673。

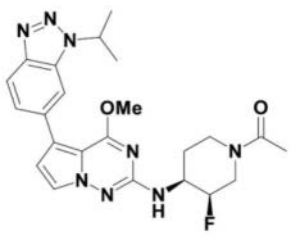
[1789] 白色固体(2mg,0.005mmol,4.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82-2.06(2H,m),2.23-2.43(2H,m),2.81(3H,br s),3.20-3.28(1H,m),3.56(1H,br s),3.96(3H,br s),4.10(1H,br s),6.78(1H,br s),6.95(1H,br s),7.34(1H,d,J=63.35Hz),7.45(1H,br d,J=17.25Hz),7.68(2H,br s),7.93(1H,br s),8.08(1H,br d,J=3.01Hz);$C_{21}H_{21}FN_8O_2$的ESIMS实验值m/z 437.2(M+1)。

[1790] 

681

[1791] (1r,4r)-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇681。

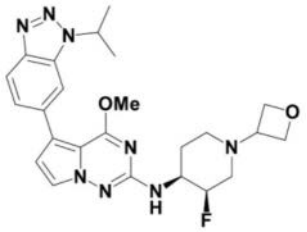
[1792] 蓬松白色固体(2.7mg,0.006mmol,10.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.39-1.51(4H,m),1.57-1.63(2H,m),1.67(6H,d,J=6.57Hz),1.84-1.91(2H,m),3.65(1H,br dd,J=7.80,3.97Hz),3.94(3H,s),4.23(1H,s),5.24(1H,spt,J=6.71Hz),6.48(1H,d,J=7.94Hz),6.74(1H,d,J=2.46Hz),7.58(1H,dd,J=8.76,1.37Hz),7.64(1H,d,J=2.46Hz),7.98(1H,d,J=8.49Hz),8.00(1H,s);$C_{23}H_{29}N_7O_2$的ESIMS实验值m/z 436.2(M+1)。

[1793] 

686

[1794] 1-((3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮686。

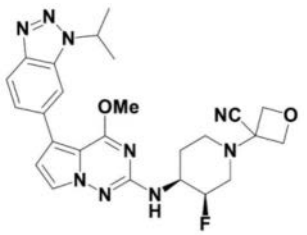
[1795] 蓬松白色固体(9mg,0.019mmol,54.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67(6H,d,J=6.84Hz),1.69-1.74(1H,m),1.74-1.92(1H,m),1.97-2.06(3H,m),2.67-2.98(1H,m),3.18-3.51(1H,m),3.86-4.18(2H,m),3.96(3H,s),4.38-4.76(1H,m),4.99(1H,d,J=49.90Hz),5.24(1H,spt,J=6.71Hz),6.78(1H,d,J=2.74Hz),6.78-6.81(1H,m),7.59(1H,dd,J=8.62,1.51Hz),7.64(1H,d,J=2.46Hz),7.99(1H,d,J=8.76Hz),8.02(1H,s);$C_{23}H_{27}FN_8O_2$的ESIMS实验值m/z 467.3(M+1)。

[1796] 

688

[1797] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺688。

[1798] 蓬松白色固体(11mg,0.023mmol,24.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67(6H,d,J=6.57Hz),1.70-1.77(1H,m),1.88-1.97(1H,m),1.99-2.06(1H,m),2.16(1H,dd,J=37.00,12.59Hz),2.71-2.80(1H,m),2.95-3.04(1H,m),3.49(1H,quin,J=6.37Hz),3.74-3.90(1H,m),3.96(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.43,3.01Hz),4.94(1H,d,J=49.90Hz),5.24(1H,spt,J=6.75Hz),6.69(1H,d,J=7.94Hz),6.77(1H,d,J=2.74Hz),7.59(1H,dd,J=8.76,1.37Hz),7.64(1H,d,J=2.46Hz),7.99(1H,d,J=8.76Hz),8.02(1H,s);$C_{24}H_{29}FN_8O_2$的ESIMS实验值m/z 481.25(M+1)。

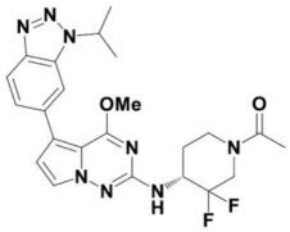
[1799] 

690

[1800] 3-((3R,4S)-3-氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)氧杂环丁烷-3-甲腈690。

[1801] 蓬松白色固体(10mg,0.020mmol,21.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67(6H,d,J=6.84Hz),1.82(1H,br dd,J=12.32,3.01Hz),2.00(1H,qd,J=12.37,3.70Hz),2.09-2.18(1H,m),2.26(1H,dd,J=36.20,12.32Hz),2.78-2.86(1H,m),3.00-3.11(1H,m),3.79-3.95(1H,m),3.97(3H,s),4.52(1H,d,J=6.84Hz),4.65(1H,d,J=7.12Hz),4.76(2H,t,J=6.84Hz),5.04(1H,d,J=49.35Hz),5.24(1H,spt,J=6.75Hz),6.78(1H,d,J=2.46Hz),6.81(1H,d,J=7.67Hz),7.59(1H,dd,J=8.76,1.37Hz),7.66(1H,d,J=2.46Hz),7.99(1H,d,J=8.49Hz),8.02(1H,s);$C_{25}H_{28}FN_9O_2$的ESIMS实验值m/z 506.2

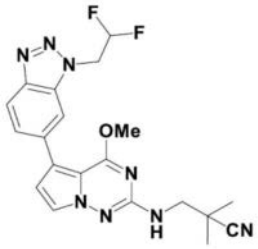
(M+1)。

[1802] 

691

[1803] (R)-1-(3,3-二氟-4-((5-(1-异丙基-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮691。

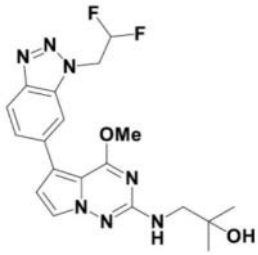
[1804] 蓬松白色固体(11mg,0.023mmol,67.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67(6H,d,J=6.84Hz),1.72-1.84(1H,m),1.85-2.00(1H,m),2.02-2.10(3H,m),2.95-3.43(2H,m),3.64-3.91(1H,m),4.10-4.31(1H,m),4.46-4.61(1H,m),5.24(1H,spt,J=6.71Hz),6.80(1H,d,J=2.74Hz),7.00(1H,d,J=9.31Hz),7.60(1H,dd,J=8.76,1.37Hz),7.65(1H,dd,J=2.46,1.37Hz),7.99(1H,d,J=8.76Hz),8.03(1H,s);$C_{23}H_{26}F_2N_8O_2$的ESIMS实验值m/z 485.2(M+1)。

[1805] 

695

[1806] 3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2,2-二甲基丙腈695。

[1807] 灰白色固体(30mg,0.070mmol,35.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(6H,s),3.49(2H,d,J=6.57Hz),3.98(3H,s),5.30(2H,td,J=15.88,2.74Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),7.14(1H,t,J=6.71Hz),7.63-7.66(1H,m),7.67(1H,d,J=2.46Hz),8.04(1H,d,J=8.21Hz),8.04(1H,s);$C_{20}H_{20}F_2N_8O$的ESIMS实验值m/z 427.2(M+1)。

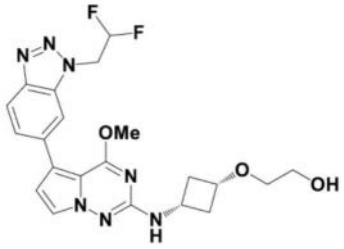
[1808] 

696

[1809] 1-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-甲基丙-2-醇696。

[1810] 灰白色固体(6mg,0.014mmol,15.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.16

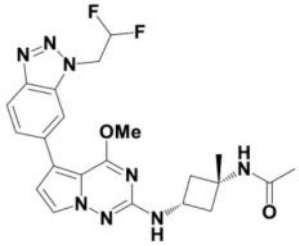
(6H,s),3.23(2H,d,J＝6.02Hz),3.96(3H,s),4.56(1H,s),5.30(2H,td,J＝15.95,2.87Hz),6.21(1H,br t,J＝5.89Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.74(1H,d,J＝2.74Hz),7.63-7.65(1H,m),7.64(1H,d,J＝2.74Hz),8.02(1H,s),8.03-8.05(1H,m);$C_{19}H_{21}F_2N_7O_2$的ESIMS实验值m/z 418.1(M+1)。

[1811] 

699

[1812] 2-(顺-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇699。

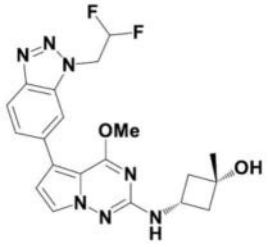
[1813] 蓬松白色固体(3.5mg,0.008mmol,19.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.81-1.94(2H,m),2.59-2.70(2H,m),3.33-3.35(2H,m),3.48(2H,q,J＝5.29Hz),3.70-3.75(1H,m),3.75-3.82(1H,m),3.94(3H,s),4.60(1H,t,J＝5.48Hz),5.30(2H,td,J＝15.88,2.74Hz),6.60(2H,tt,J＝54.30,3.00Hz),6.73(1H,d,J＝2.46Hz),7.03(1H,d,J＝7.39Hz),7.63(1H,d,J＝2.46Hz),7.62-7.65(1H,m),8.01-8.04(2H,m);$C_{21}H_{23}F_2N_7O_3$的ESIMS实验值m/z 460.2(M+1)。

[1814] 

702

[1815] N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺702。

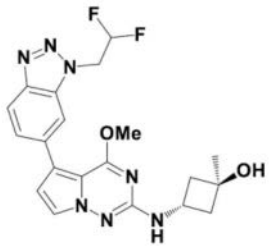
[1816] 白色固体(16mg,0.034mmol,27.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.12-2.23(2H,m),2.42(2H,ddd,J＝9.58,7.39,2.74Hz),3.93(3H,s),4.03(1H,sxt,J＝7.78Hz),5.30(2H,td,J＝15.95,2.87Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.73(1H,d,J＝2.74Hz),7.00(1H,d,J＝6.84Hz),7.63(1H,dd,J＝8.62,1.51Hz),7.66(1H,d,J＝2.74Hz),7.99-8.05(3H,m);$C_{22}H_{24}F_2N_8O_2$的ESIMS实验值m/z 471.2(M+1)。

[1817] 

710

[1818] (1s,3s)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇710。

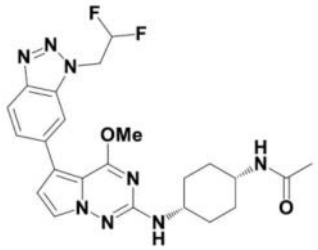
[1819] 蓬松白色固体(18mg,0.042mmol,39.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27(3H,s),2.02(2H,td,J=8.90,2.46Hz),2.32-2.40(2H,m),3.72(1H,dq,J=15.16,7.72Hz),3.93(3H,s),4.91(1H,s),5.30(2H,td,J=15.95,2.87Hz),6.60(1H,tt,J=54.30,3.00Hz),6.72(1H,d,J=2.74Hz),6.94(1H,d,J=6.57Hz),7.63(1H,dd,J=8.76,1.64Hz),7.65(1H,d,J=2.74Hz),7.99-8.06(2H,m);$C_{20}H_{21}F_2N_7O_2$的ESIMS实验值m/z 430.15(M+1)。

[1820] 

711

[1821] (1r,3r)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁-1-醇711。

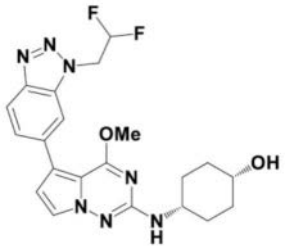
[1822] 蓬松白色固体(20mg,0.047mmol,43.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.28(3H,s),1.95-2.05(2H,m),2.27-2.35(2H,m),3.93(3H,s),4.26(1H,dq,J=14.82,7.38Hz),4.79(1H,s),5.30(2H,td,J=15.95,2.87Hz),6.60(1H,tt,J=54.30,3.00Hz),6.72(1H,d,J=2.74Hz),6.95(1H,d,J=6.84Hz),7.63(1H,dd,J=8.80,1.35Hz),7.64(1H,d,J=2.74Hz),8.01-8.04(2H,m);$C_{20}H_{21}F_2N_7O_2$的ESIMS实验值m/z 430.2(M+1)。

[1823] 

717

[1824] N-(顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺717。

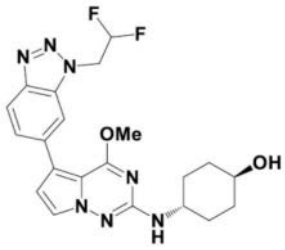
[1825] 白色固体(5.83mg,0.012mmol)。^{1}H NMR(400MHz,DMSO-d_6)δppm 1.50-1.59(2H,m),1.60-1.72(4H,m),1.73-1.80(2H,m),1.81(3H,s),3.68(2H,br s),3.95(3H,s),5.30(2H,td,J=15.85,2.69Hz),6.46(1H,d,J=6.38Hz),6.60(1H,tt,J=54.30,3.00Hz),6.73(1H,d,J=2.63Hz),7.62-7.66(2H,m),7.70(1H,br d,J=7.00Hz),8.00-8.05(2H,m);$C_{23}H_{26}F_2N_8O_2$的ESIMS实验值m/z 485.0(M+1)。

[1826] 

718

[1827] 顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇718。

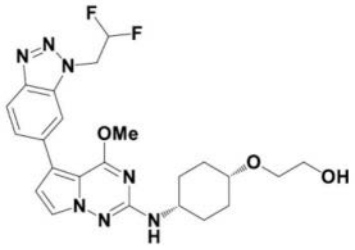
[1828] 蓬松白色固体(9mg,0.020mmol,14.7％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.46-1.54(2H,m),1.61-1.69(4H,m),1.70-1.79(2H,m),3.56-3.67(1H,m),3.73(1H,br d,J＝2.19Hz),3.94(3H,s),4.34(1H,d,J＝3.01Hz),5.30(2H,td,J＝15.95,2.87Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.53(1H,d,J＝7.39Hz),6.71(1H,d,J＝2.46Hz),7.64(1H,dd,J＝8.50,1.65Hz),7.63(1H,d,J＝2.46Hz),8.01-8.05(2H,m);$C_{21}H_{23}F_2N_7O_2$的ESIMS实验值m/z 444.2(M+1)。

[1829] 

719

[1830] 反-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇719。

[1831] 蓬松白色固体(7mg,0.016mmol,11.4％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.17-1.40(4H,m),1.79-1.89(2H,m),1.92-2.01(2H,m),3.35-3.46(1H,m),3.49-3.59(1H,m),3.93(3H,s),4.55(1H,d,J＝4.38Hz),5.30(2H,td,J＝15.95,2.87Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.51(1H,d,J＝8.21Hz),6.71(1H,d,J＝2.46Hz),7.64(1H,dd,J＝8.76,1.64Hz),7.65(1H,d,J＝2.46Hz),8.02(1H,d,J＝9.86Hz),8.02(1H,s);$C_{21}H_{23}F_2N_7O_2$的ESIMS实验值m/z 444.2(M+1)。

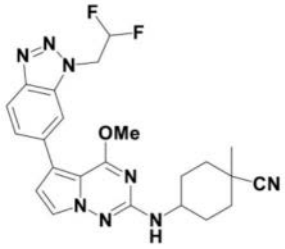
[1832] 

720

[1833] 2-((顺-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇720。

[1834] 白色固体(7.47mg,0.015mmol)。^{1}H NMR(400MHz,DMSO-d_6)δppm 1.46-1.57(2H,m),

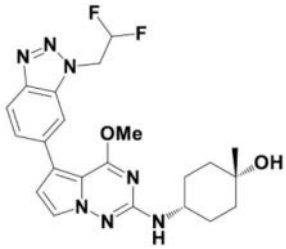
1.62-1.73(4H,m),1.78-1.89(2H,m),3.40(2H,t,J＝5.50Hz),3.48-3.54(2H,m),3.58-3.72(2H,m),3.94(3H,s),4.52(1H,t,J＝5.50Hz),5.30(2H,td,J＝15.86,2.51Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.54(1H,d,J＝7.70Hz),6.71(1H,d,J＝2.57Hz),7.61-7.66(2H,m),7.99-8.05(2H,m);$C_{23}H_{27}F_2N_7O_3$的ESIMS实验值m/z488.2(M+1)。

[1835] 

721

[1836] 4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈721。

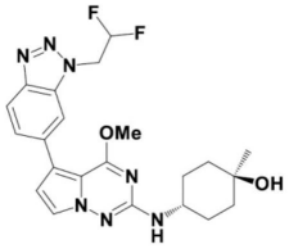
[1837] 白色固体(15mg,0.032mmol,51.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34(3H,s),1.45-1.63(4H,m),1.95(2H,br d,J＝10.68Hz),1.99-2.08(2H,m),3.56-3.63(1H,m),3.94(3H,s),5.30(2H,td,J＝15.88,2.74Hz),6.61(1H,tt,J＝54.30,3.00Hz),6.72(1H,d,J＝2.46Hz),6.78(1H,d,J＝7.94Hz),7.62(1H,d,J＝2.74Hz),7.63-7.66(1H,m),8.01-8.05(2H,m);$C_{23}H_{24}F_2N_8O$的ESIMS实验值m/z 467.2(M+1)。

[1838] 

724

[1839] (1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇724。

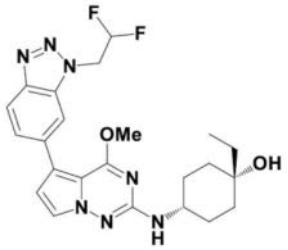
[1840] 蓬松白色固体(15mg,0.033mmol,34.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.37(2H,td,J＝13.07,4.52Hz),1.58(2H,br d,J＝12.32Hz),1.61-1.69(2H,m),1.69-1.75(2H,m),3.46-3.59(1H,m),3.93(3H,s),4.00(1H,s),5.30(2H,td,J＝15.88,2.74Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.51(1H,d,J＝7.94Hz),6.71(1H,d,J＝2.74Hz),7.62(1H,d,J＝2.46Hz),7.62-7.65(1H,m),8.00-8.04(2H,m);$C_{22}H_{25}F_2N_7O_2$的ESIMS实验值m/z 458.2(M+1)。

[1841] 

725

[1842] (1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇725。

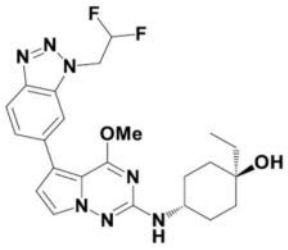
[1843] 蓬松白色固体(9mg,0.020mmol,55.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.53(4H,m),1.56-1.65(2H,m),1.81-1.93(2H,m),3.60-3.72(1H,m),3.94(3H,s),4.23(1H,s),5.30(2H,td,J=15.88,2.74Hz),6.50(1H,d,J=7.94Hz),6.60(1H,tt,J=54.30,3.00Hz),6.72(1H,s),7.62-7.65(1H,m),7.65(1H,d,J=2.74Hz),8.01-8.04(2H,m);$C_{22}H_{25}F_2N_7O_2$的ESIMS实验值m/z 458.2(M+1)。

[1844] 

726

[1845] (1s,4s)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇726。

[1846] 蓬松白色固体(24mg,0.051mmol,36.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.85(3H,t,J=7.53Hz),1.30(2H,td,J=13.21,3.97Hz),1.37(2H,q,J=7.39Hz),1.56(2H,br d,J=12.32Hz),1.60-1.70(2H,m),1.71-1.77(2H,m),3.45-3.59(1H,m),3.80(1H,s),3.93(3H,s),5.30(2H,td,J=15.81,2.87Hz),6.60(1H,tt,J=54.30,3.00Hz),6.54(1H,d,J=7.94Hz),6.71(1H,d,J=2.74Hz),7.62(1H,d,J=2.46Hz),7.64(1H,dd,J=8.76,1.64Hz),8.00-8.04(2H,m);$C_{23}H_{27}F_2N_7O_2$的ESIMS实验值m/z 472.2(M+1)。

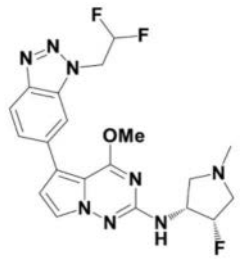
[1847] 

727

[1848] (1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-乙基环己-1-醇727。

[1849] 蓬松白色固体(28mg,0.059mmol,42.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm

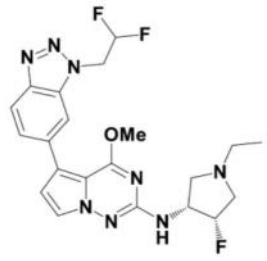
0.83(3H,t,J＝7.39Hz),1.32-1.39(2H,m),1.40-1.46(2H,m),1.47(2H,q,J＝7.39Hz),1.60-1.71(2H,m),1.80-1.91(2H,m),3.69(1H,tt,J＝8.08,4.11Hz),3.94(3H,s),3.98(1H,s),5.30(2H,td,J＝15.95,2.87Hz),6.49(1H,d,J＝7.94Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.72(1H,d,J＝2.46Hz),7.64(1H,dd,J＝8.50,1.65Hz),7.65(1H,d,J＝2.74Hz),8.00-8.06(2H,m);$C_{23}H_{27}F_2N_7O_2$的ESIMS实验值m/z 472.2(M+1)。

[1850] 

730

[1851] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-4-氟-1-甲基吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺730。

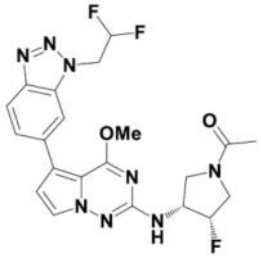
[1852] 蓬松白色固体(12mg,0.027mmol,58.1％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.31(3H,s),2.60(1H,ddd,J＝31.55,11.64,2.05Hz),2.61(1H,br t,J＝8.90Hz),2.92(1H,t,J＝8.08Hz),3.17(1H,ddd,J＝29.35,11.50,4.93Hz),3.96(3H,s),4.20-4.36(1H,m),5.14-5.28(1H,m),5.25-5.35(2H,m),6.61(1H,tt,J＝54.30,3.00Hz),6.76(1H,d,J＝2.74Hz),6.78(1H,d,J＝7.67Hz),7.64(1H,dd,J＝8.90,0.96Hz),7.67(1H,d,J＝2.74Hz),8.04(1H,d,J＝8.21Hz),8.03(1H,s);$C_{20}H_{21}F_3N_8O$的ESIMS实验值m/z 447.2(M+1)。

[1853] 

732

[1854] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-1-乙基-4-氟吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺732。

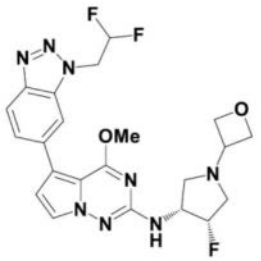
[1855] 蓬松白色固体(2mg,0.004mmol,6.3％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.03(3H,t,J＝7.26Hz),2.47-2.54(2H,m),2.59-2.70(2H,m),2.97(1H,t,J＝8.21Hz),3.18(1H,ddd,J＝30.95,11.91,4.79Hz),3.96(3H,s),4.19-4.33(1H,m),5.13-5.27(1H,m),5.27-5.35(2H,m),6.61(1H,tt,J＝54.30,3.00Hz),6.75-6.77(1H,m),6.76(1H,d,J＝2.74Hz),7.63-7.66(1H,m),7.67(1H,d,J＝2.46Hz),8.04(1H,d,J＝7.94Hz),8.03(1H,s);$C_{21}H_{23}F_3N_8O$的ESIMS实验值m/z 461.2(M+1)。

[1856] 

734

[1857] 1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮734。

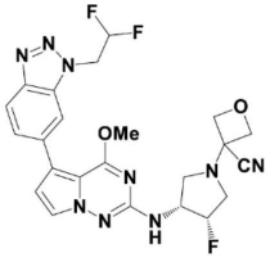
[1858] 蓬松白色固体(19mg,0.040mmol,69.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.92-2.02(3H,m),3.47-3.75(2H,m),3.78-3.96(2H,m),3.97(3H,d,J=1.37Hz),4.30-4.59(1H,m),5.25-5.48(3H,m),6.61(1H,tt,J=54.30,3.00Hz),6.78(1H,t,J=2.46Hz),7.10(1H,dd,J=7.12,5.20Hz),7.63-7.67(1H,m),7.68(1H,dd,J=3.97,2.60Hz),8.03-8.06(2H,m);$C_{21}H_{21}F_3N_8O_2$的ESIMS实验值m/z 475.2(M+1)。

[1859] 

739

[1860] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺739。

[1861] 蓬松白色固体(14mg,0.029mmol,27.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.69(1H,t,J=9.17Hz),2.77(1H,ddd,J=30.20,12.10,1.40Hz),3.02(1H,t,J=8.35Hz),3.18(1H,ddd,J=32.90,12.05,4.38Hz),3.79(1H,quin,J=6.16Hz),3.96(3H,s),4.23-4.37(1H,m),4.47(2H,t,J=6.02Hz),4.60(2H,t,J=6.57Hz),5.18-5.32(1H,m),5.31(2H,td,J=15.95,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.77(1H,d,J=2.46Hz),6.84(1H,d,J=7.67Hz),7.63-7.66(1H,m),7.67(1H,d,J=2.46Hz),8.04(1H,d,J=8.21Hz),8.04(1H,s);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

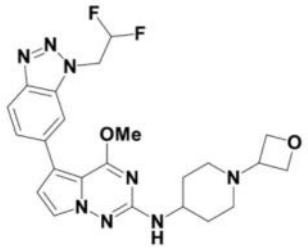
[1862] 

741

[1863] 3-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧

基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)氧杂环丁烷-3-甲腈741。

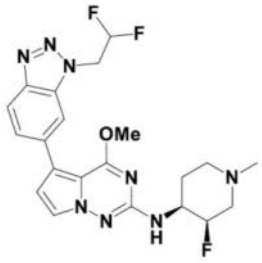
[1864] 蓬松白色固体(14mg,0.027mmol,26.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.82(1H,t,J=9.05Hz),2.88(1H,ddd,J=29.60,11.77,0.82Hz),3.09(1H,t,J=8.35Hz),3.26(1H,ddd,J=34.05,12.05,4.38Hz),3.97(3H,s),4.32-4.46(1H,m),4.58(1H,d,J=6.84Hz),4.62(1H,d,J=6.84Hz),4.81(2H,d,J=6.84Hz),5.26-5.41(3H,m),6.61(1H,tt,J=54.30,3.00Hz),6.78(1H,d,J=2.46Hz),7.02(1H,d,J=7.39Hz),7.63-7.67(1H,m),7.69(1H,d,J=2.74Hz),8.04(1H,br d,J=8.21Hz),8.04(1H,s);$C_{23}H_{22}F_3N_9O_2$的ESIMS实验值m/z 514.2(M+1)。

[1865] 

750

[1866] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)哌啶-4-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺750。

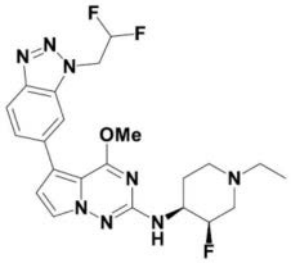
[1867] 蓬松白色固体(4mg,0.008mmol,6.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.54(2H,qd,J=11.64,3.42Hz),1.86(2H,br t,J=11.50Hz),1.92(2H,br d,J=11.50Hz),2.69(2H,br d,J=11.50Hz),3.35-3.42(1H,m),3.54-3.66(1H,m),3.94(3H,s),4.42(2H,t,J=6.02Hz),4.50-4.57(2H,m),5.30(2H,td,J=15.95,2.87Hz),6.60(1H,tt,J=54.30,3.00Hz),6.65(1H,d,J=7.94Hz),6.72(1H,d,J=2.46Hz),7.64(1H,br dd,J=8.50,1.65Hz),7.64(1H,d,J=2.74Hz),8.03(1H,d,J=10.40Hz),8.02(1H,s);$C_{23}H_{26}F_2N_8O_2$的ESIMS实验值m/z 485.2(M+1)。

[1868] 

754

[1869] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺754。

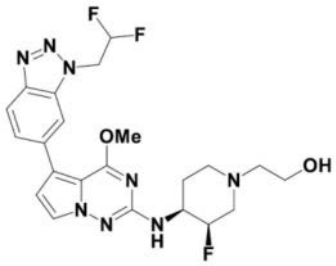
[1870] 蓬松白色固体(3mg,0.007mmol,19.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.64-1.74(1H,m),1.93(1H,qd,J=12.32,3.56Hz),2.02-2.10(1H,m),2.18(1H,dd,J=37.85,12.32Hz),2.19(3H,s),2.80(1H,br d,J=11.23Hz),3.00-3.10(1H,m),3.69-3.85(1H,m),3.95(3H,s),4.92(1H,d,J=50.20Hz),5.30(2H,td,J=15.95,2.87Hz),6.60(1H,tt,J=54.30,3.00Hz),6.64(1H,d,J=7.67Hz),6.75(1H,d,J=2.74Hz),7.63-7.66(1H,m),7.65(1H,d,J=2.46Hz),8.01-8.05(2H,m);$C_{21}H_{23}F_3N_8O$的ESIMS实验值m/z 461.2(M+1)。

[1871] 

755

[1872] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-1-乙基-3-氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺755。

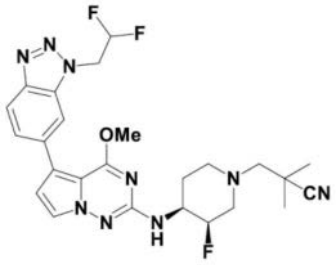
[1873] 蓬松白色固体(2.6mg,0.006mmol,12.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.00(3H,t,J=7.12Hz),1.66-1.75(1H,m),1.90(1H,qd,J=12.23,3.56Hz),2.06(1H,br t,J=11.09Hz),2.19(1H,dd,J=37.85,12.32Hz),2.37(2H,q,J=7.30Hz),2.89(1H,br d,J=10.95Hz),3.08-3.17(1H,m),3.71-3.86(1H,m),3.95(3H,s),4.92(1H,d,J=49.90Hz),5.30(2H,td,J=15.95,2.87Hz),6.60(1H,tt,J=54.30,3.00Hz),6.63(1H,d,J=7.94Hz),6.75(1H,d,J=2.74Hz),7.63-7.65(1H,m),7.65(1H,d,J=2.74Hz),8.01-8.05(2H,m);$C_{22}H_{25}F_3N_8O$的ESIMS实验值m/z 475.2(M+1)。

[1874] 

756

[1875] 2-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-醇756。

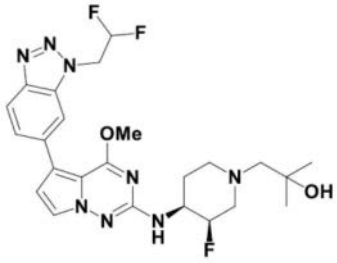
[1876] 蓬松白色固体(8mg,0.016mmol,37.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.63-1.72(1H,m),1.85-1.97(1H,m),2.14-2.22(1H,m),2.32(1H,dd,J=37.55,12.59Hz),2.44(2H,t,J=6.30Hz),2.91(1H,br d,J=11.77Hz),3.16(1H,br dd,J=11.23,10.13Hz),3.50(2H,t,J=6.30Hz),3.71-3.88(1H,m),3.95(3H,s),4.42(1H,br s),4.90(1H,d,J=50.15Hz),5.30(2H,td,J=15.95,2.87Hz),6.60(2H,tt,J=54.30,3.00Hz),6.63(1H,d,J=7.94Hz),6.74(1H,d,J=2.74Hz),7.62-7.66(2H,m),8.01-8.05(2H,m);$C_{22}H_{25}F_3N_8O_2$的ESIMS实验值m/z 491.2(M+1)。

[1877] 

757

[1878] 3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2,2-二甲基丙腈757。

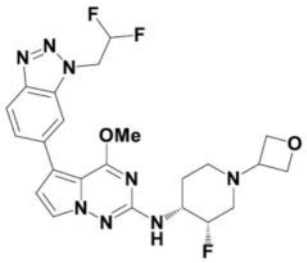
[1879] 蓬松白色固体(2mg,0.004mmol,20.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.16(6H,s),1.65-1.74(1H,m),1.86-1.98(1H,m),2.02-2.10(1H,m),2.13-2.25(1H,m),2.19(2H,s),2.75-2.83(1H,m),2.99-3.08(1H,m),3.70-3.86(1H,m),4.46(3H,s),4.91(1H,d,J=50.20Hz),5.29(2H,td,J=15.67,3.15Hz),6.59(1H,tt,J=54.30,3.00Hz),6.70(1H,d,J=7.67Hz),6.74(1H,d,J=2.46Hz),7.70(1H,d,J=2.74Hz),7.71(1H,dd,J=8.50,1.65Hz),7.98(1H,s),8.00(1H,d,J=8.49Hz);$C_{25}H_{28}F_3N_9O$的ESIMS实验值m/z 528.3(M+1)。

[1880] 

758

[1881] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)-2-甲基丙-2-醇758。

[1882] 蓬松白色固体(2mg,0.004mmol,26.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.09(6H,s),1.60-1.69(1H,m),1.95(1H,qd,J=12.46,3.70Hz),2.26-2.32(1H,m),2.33-2.46(1H,m),2.98(1H,br d,J=10.13Hz),3.25-3.29(1H,m),3.33(2H,s),3.70-3.85(1H,m),3.95(3H,s),4.08(1H,br s),4.86(1H,d,J=49.65Hz),5.30(2H,td,J=16.02,2.74Hz),6.60(1H,tt,J=54.30,3.00Hz),6.61(1H,d,J=7.94Hz),6.74(1H,d,J=2.46Hz),7.63-7.66(1H,m),7.65(1H,d,J=2.46Hz),8.01-8.05(2H,m);$C_{24}H_{29}F_3N_8O_2$的ESIMS实验值m/z 519.2(M+1)。

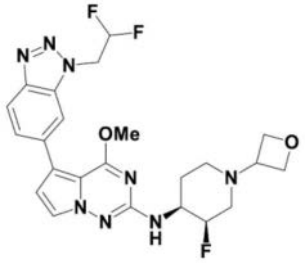
[1883] 

761

[1884] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺761。

[1885] 蓬松白色固体(11mg,0.022mmol,32.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.78(1H,m),1.92(1H,qd,J=12.18,3.42Hz),1.99-2.06(1H,m),2.16(1H,dd,J=37.05,12.59Hz),2.76(1H,br d,J=9.31Hz),2.94-3.05(1H,m),3.50(1H,quin,J=6.30Hz),3.74-3.91(1H,m),3.96(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.94(1H,d,J=49.65Hz),5.30(2H,td,J=15.88,2.74Hz),6.60(1H,tt,J=54.30,3.00Hz),6.70(1H,d,J=7.94Hz),6.75(1H,d,J=2.74Hz),7.64

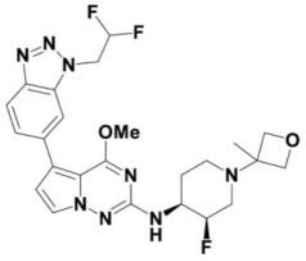
(1H,dd,J＝8.76,1.64Hz),7.64(1H,d,J＝2.74Hz),8.01-8.05(2H,m);$C_{23}H_{25}F_3N_8O_2$的ESIMS实验值m/z503.2(M+1)。

[1886] 

762

[1887] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺762。

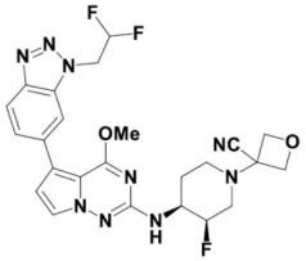
[1888] 蓬松白色固体(12mg,0.024mmol,18.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.78(1H,m),1.92(1H,qd,J＝12.09,3.42Hz),1.99-2.06(1H,m),2.16(1H,dd,J＝37.05,12.59Hz),2.76(1H,br d,J＝9.86Hz),2.94-3.04(1H,m),3.50(1H,quin,J＝6.43Hz),3.75-3.91(1H,m),3.96(3H,s),4.40(1H,t,J＝6.16Hz),4.46(1H,t,J＝6.16Hz),4.54(2H,td,J＝6.57,3.01Hz),4.94(1H,d,J＝49.90Hz),5.30(2H,td,J＝15.95,2.87Hz),6.61(1H,tt,J＝54.30,3.00Hz),6.70(1H,d,J＝7.94Hz),6.75(1H,d,J＝2.74Hz),7.64(1H,dd,J＝8.50,1.35Hz),7.64(1H,d,J＝2.74Hz),8.01-8.05(2H,m);$C_{23}H_{25}F_3N_8O_2$的ESIMS实验值m/z503.2(M+1)。

[1889] 

764

[1890] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(3-甲基氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺764。

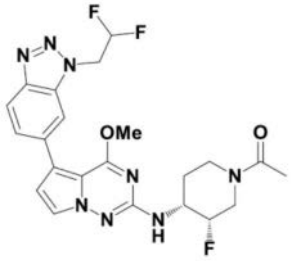
[1891] 蓬松白色固体(1mg,0.002mmol,5.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.29(3H,s),1.69-1.78(1H,m),1.91(1H,qd,J＝11.96,3.83Hz),2.20(1H,br t,J＝10.81Hz),2.35(1H,dd,J＝35.35,11.77Hz),2.54-2.59(1H,m),2.75-2.84(1H,m),3.74-3.90(1H,m),3.96(3H,s),4.13(2H,dd,J＝7.26,5.61Hz),4.34(1H,d,J＝5.48Hz),4.42(1H,d,J＝5.75Hz),4.93(1H,d,J＝49.90Hz),5.30(2H,td,J＝15.95,2.87Hz),6.61(1H,tt,J＝54.30,3.00Hz),6.70(1H,d,J＝7.94Hz),6.75(1H,d,J＝2.74Hz),7.64(1H,dd,J＝8.80,1.35Hz),7.64(1H,d,J＝2.74Hz),8.01-8.05(2H,m);$C_{24}H_{27}F_3N_8O_2$的ESIMS实验值m/z517.25(M+1)。

[1892] 

769

[1893] 3-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)氧杂环丁烷-3-甲腈769。

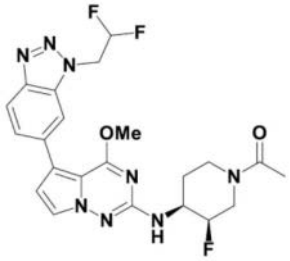
[1894] 蓬松白色固体(14mg,0.027mmol,20.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82(1H,br dd,J=13.00,3.15Hz),2.00(1H,qd,J=12.32,3.83Hz),2.10-2.17(1H,m),2.26(1H,dd,J=36.20,12.05Hz),2.77-2.86(1H,m),3.00-3.11(1H,m),3.79-3.94(1H,m),3.97(3H,s),4.52(1H,d,J=7.12Hz),4.65(1H,d,J=7.12Hz),4.76(2H,t,J=6.84Hz),5.04(1H,d,J=49.90Hz),5.30(2H,td,J=15.95,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.46Hz),6.82(1H,d,J=7.67Hz),7.63-7.66(1H,m),7.67(1H,d,J=2.46Hz),8.02-8.05(2H,m);$C_{24}H_{24}F_3N_9O_2$的ESIMS实验值m/z 528.2(M+1)。

[1895] 

770

[1896] 1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮770。

[1897] 蓬松白色固体(8mg,0.016mmol,32.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.65-1.74(1H,m),1.75-1.92(1H,m),1.98-2.06(3H,m),2.67-2.98(1H,m),3.17-3.26(1H,m),3.87-4.04(1H,m),3.96(3H,s),4.04-4.17(1H,m),4.42-4.74(1H,m),4.99(1H,d,J=48.80Hz),5.30(2H,td,J=15.95,2.87Hz),6.61(2H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.80(1H,dd,J=7.80,2.60Hz),7.63-7.66(1H,m),7.65(1H,d,J=2.46Hz),8.02-8.05(2H,m);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

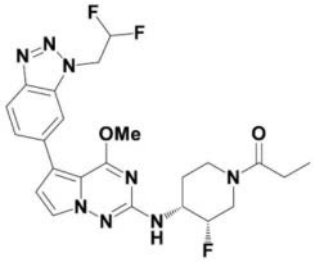
[1898] 

771

[1899] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧

基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮771。

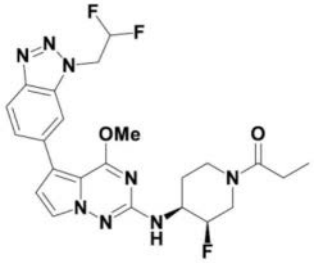
[1900] 蓬松白色固体(7mg,0.014mmol,53.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.64-1.90(2H,m),1.97-2.08(3H,m),2.66-3.28(1H,m),2.82-3.50(1H,m),3.86-4.02(1H,m),3.96(3H,s),4.02-4.17(1H,m),4.41-4.75(1H,m),5.00(1H,d,J=49.90Hz),5.30(2H,td,J=15.88,2.74Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.81(1H,dd,J=7.80,3.42Hz),7.63-7.66(1H,m),7.65(1H,d,J=2.74Hz),8.02-8.05(2H,m);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z489.2(M+1)。

[1901] 

772

[1902] 1-((3S,4R)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)丙-1-酮772。

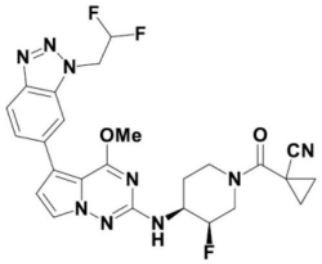
[1903] 蓬松白色固体(7mg,0.014mmol,27.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.00(3H,t,J=7.39Hz),1.66-1.89(2H,m),2.26-2.41(2H,m),2.67-2.98(1H,m),3.14-3.23(1H,m),3.90-4.05(1H,m),3.96(3H,s),4.05-4.22(1H,m),4.43-4.79(1H,m),4.99(1H,d,J=49.65Hz),5.30(2H,td,J=15.88,2.74Hz),6.61(2H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.46Hz),6.79(1H,d,J=7.67Hz),7.64(1H,dd,J=6.30,1.35Hz),7.65(1H,s),8.01-8.06(2H,m);$C_{23}H_{25}F_3N_8O_2$的ESIMS实验值m/z 503.2(M+1)。

[1904] 

773

[1905] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)丙-1-酮773。

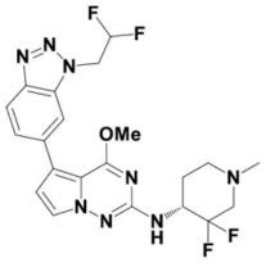
[1906] 蓬松白色固体(9.1mg,0.018mmol,46.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.00(3H,t,J=7.39Hz),1.66-1.90(2H,m),2.24-2.42(2H,m),2.69-3.00(1H,m),3.12-3.24(1H,m),3.91-4.00(1H,m),3.96(3H,s),4.04-4.22(1H,m),4.43-4.78(1H,m),4.99(1H,d,J=49.35Hz),5.30(2H,td,J=15.88,2.74Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.79(1H,d,J=7.94Hz),7.63-7.66(2H,m),8.02-8.05(2H,m);$C_{23}H_{25}F_3N_8O_2$的ESIMS实验值m/z 503.2(M+1)。

[1907] 

776

[1908] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-羰基)环丙烷-1-甲腈776。

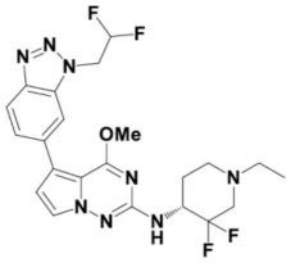
[1909] 米色固体(4mg,0.007mmol,23.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.23(2H,s),1.35-1.52(1H,m),1.52-1.65(2H,m),1.63-1.75(1H,m),1.75-1.94(1H,m),1.94-2.12(1H,m),3.96(3H,s),4.05-4.17(1H,m),4.26-4.38(1H,m),4.51-4.62(1H,m),5.09(1H,d,J=48.55Hz),5.30(2H,td,J=15.81,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.88(1H,br s),7.63-7.67(2H,m),8.02-8.06(2H,m);$C_{25}H_{24}F_3N_9O_2$的ESIMS实验值m/z 540.2(M+1)。

[1910] 

777

[1911] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺777。

[1912] 灰白色固体(7mg,0.015mmol,31.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.75-1.89(2H,m),2.18(1H,td,J=11.16,2.87Hz),2.26(3H,s),2.38(1H,ddd,J=27.15,11.50,1.40Hz),2.79(1H,br d,J=11.77Hz),2.99-3.12(1H,m),3.97(3H,s),4.17-4.32(1H,m),5.30(2H,td,J=15.95,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.46Hz),6.84(1H,d,J=9.31Hz),7.63-7.66(1H,m),7.66(1H,d,J=2.46Hz),8.03(1H,s),8.04(1H,d,J=6.57Hz);$C_{21}H_{22}F_4N_8O$的ESIMS实验值m/z 479.2(M+1)。

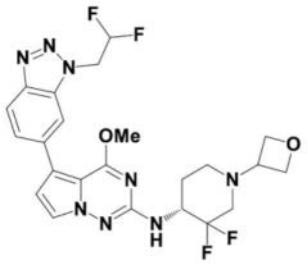
[1913] 

780

[1914] (R)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-(1-乙基-3,3-二

氟哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺780。

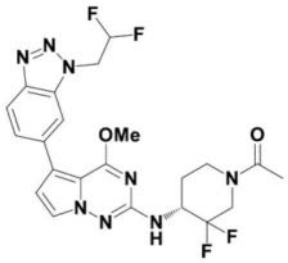
[1915] 灰白色固体(8mg,0.016mmol,36.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.01(3H,t,J=7.26Hz),1.73-1.83(1H,m),1.84-1.90(1H,m),2.12-2.24(1H,m),2.34-2.43(1H,m),2.45(2H,q,J=7.12Hz),2.88(1H,br d,J=12.05Hz),3.05-3.17(1H,m),3.97(3H,s),4.19-4.35(1H,m),5.30(2H,td,J=15.88,2.74Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.85(1H,d,J=9.58Hz),7.63-7.66(1H,m),7.66(1H,d,J=2.74Hz),8.03(1H,s),8.04(1H,d,J=6.55Hz);$C_{22}H_{24}F_4N_8O$的ESIMS实验值m/z 493.25(M+1)。

[1916] 

785

[1917] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺785。

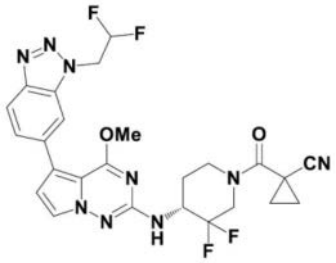
[1918] 灰白色固体(8mg,0.015mmol,22.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.86(1H,m),1.86-1.93(1H,m),2.12-2.22(1H,m),2.41(1H,ddd,J=26.60,11.50,1.65Hz),2.76(1H,br d,J=11.50Hz),2.95-3.08(1H,m),3.60(1H,quin,J=6.30Hz),3.97(3H,s),4.24-4.37(1H,m),4.44(2H,dt,J=15.06,6.16Hz),4.55(2H,td,J=6.57,3.56Hz),5.30(2H,td,J=15.88,2.74Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.46Hz),6.91(1H,d,J=9.31Hz),7.63-7.66(1H,m),7.66(1H,d,J=2.46Hz),8.03(1H,s),8.04(1H,d,J=6.30Hz);$C_{23}H_{24}F_4N_8O_2$的ESIMS实验值m/z 521.2(M+1)。

[1919] 

788

[1920] (R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮788。

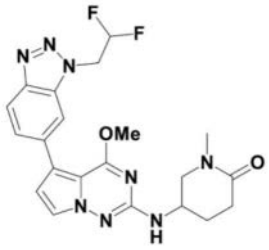
[1921] 蓬松白色固体(20mg,0.040mmol,79.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.58-1.84(1H,m),1.85-2.00(1H,m),2.02-2.10(3H,m),3.32(1H,s),3.39-3.78(1H,m),3.84-4.30(1H,m),3.98(3H,s),4.10-4.61(2H,m),5.30(2H,td,J=15.81,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.77(1H,d,J=2.74Hz),7.01(1H,d,J=9.31Hz),7.63-7.67(2H,m),8.02-8.06(2H,m);$C_{22}H_{22}F_4N_8O_2$的ESIMS实验值m/z 507.2(M+1)。

[1922] 

791

[1923] (R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-羰基)环丙烷-1-甲腈791。

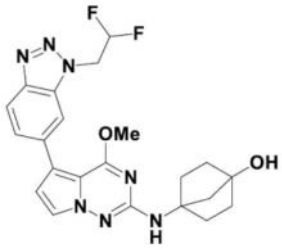
[1924] 灰白色固体(3mg,0.005mmol,13.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36-1.52(2H,m),1.61-1.81(3H,m),1.86-2.08(2H,m),3.04-3.11(1H,m),3.98(3H,s),4.18-4.31(1H,m),4.38-4.49(1H,m),4.56-4.70(1H,m),5.30(2H,td,J=15.74,2.74Hz),6.61(1H,tt,J=54.30,3.00Hz),6.78(1H,d,J=2.46Hz),7.08(1H,br d,J=9.31Hz),7.64-7.66(1H,m),7.67(1H,d,J=2.74Hz),8.03(1H,s),8.04-8.06(1H,m);$C_{25}H_{23}F_4N_9O_2$的ESIMS实验值m/z 558.2(M+1)。

[1925] 

793

[1926] 5-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮793。

[1927] 白色固体(11mg,0.024mmol,22.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.87-1.96(1H,m),1.97-2.04(1H,m),2.27-2.35(1H,m),2.36-2.44(1H,m),2.81(3H,s),3.26(1H,dd,J=11.77,7.67Hz),3.57(1H,dd,J=11.91,4.52Hz),3.96(3H,s),4.05-4.15(1H,m),5.30(2H,td,J=15.95,2.60Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.46Hz),6.94(1H,d,J=7.12Hz),7.63-7.66(1H,m),7.68(1H,d,J=2.74Hz),8.02-8.05(2H,m);$C_{21}H_{22}F_2N_8O_2$的ESIMS实验值m/z457.2(M+1)。

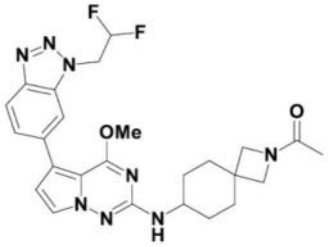
[1928] 

798

[1929] 4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇798。

[1930] 蓬松白色固体(2.4mg,0.005mmol,3.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm

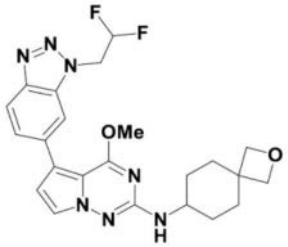
1.52-1.63(2H,m),1.65-1.77(2H,m),1.86(2H,s),1.87-1.93(2H,m),1.99-2.09(2H,m),3.93(3H,s),4.88(1H,s),5.30(2H,td,J＝16.02,3.01Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.73(1H,d,J＝2.74Hz),6.75(1H,s),7.61(1H,d,J＝2.46Hz),7.64(1H,dd,J＝8.62,1.51Hz),8.01-8.04(2H,m);$C_{22}H_{23}F_2N_7O_2$的ESIMS实验值m/z 456.2(M+1)。

[1931] 

799

[1932] 1-(7-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2-氮杂螺[3.5]壬烷-2-基)乙-1-酮799。

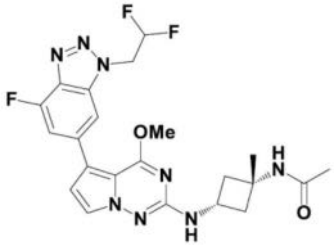
[1933] 白色固体(8mg,0.016mmol,8.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.27-1.41(2H,m),1.50-1.61(2H,m),1.73-1.78(3H,m),1.82-1.94(4H,m),3.45-3.54(2H,m),3.55-3.64(1H,m),3.72-3.82(2H,m),3.93(3H,d,J＝1.10Hz),5.30(2H,td,J＝15.74,2.46Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.53(1H,dd,J＝16.43,7.94Hz),6.72(1H,d,J＝2.46Hz),7.62-7.65(2H,m),8.00-8.05(2H,m);$C_{25}H_{28}F_2N_8O_2$的ESIMS实验值m/z 511.2(M+1)。

[1934] 

801

[1935] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺801。

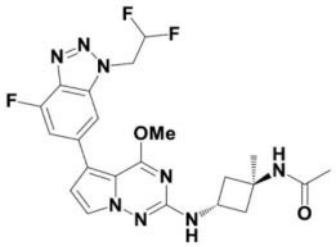
[1936] 无色半固体(2mg,0.004mmol,4.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.41-1.49(1H,m),1.53(2H,td,J＝12.94,3.42Hz),1.83-1.92(2H,m),1.96-2.03(1H,m),2.07(2H,br d,J＝12.87Hz),3.49-3.61(1H,m),3.93(3H,s),4.24(2H,s),4.32(2H,s),5.30(2H,td,J＝15.88,3.01Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.51(1H,d,J＝8.21Hz),6.72(1H,d,J＝2.74Hz),7.63(1H,dd,J＝8.80,1.35Hz),7.64(1H,d,J＝2.74Hz),8.02(1H,d,J＝9.86Hz),8.02(1H,s);$C_{23}H_{25}F_2N_7O_2$的ESIMS实验值m/z 470.2(M+1)。

[1937] 

805

[1938] N-((1s,3s)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺805。

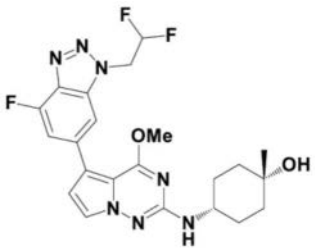
[1939] 白色固体(16mg,0.033mmol,26.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.12-2.21(2H,m),2.42(2H,ddd,J=9.65,7.32,2.46Hz),3.96(3H,s),4.03(1H,sxt,J=7.72Hz),5.34(2H,td,J=15.88,2.74Hz),6.62(1H,tt,J=54.30,3.00Hz),6.78(1H,d,J=2.46Hz),7.05(1H,d,J=6.84Hz),7.50(1H,dd,J=12.18,0.96Hz),7.66(1H,d,J=2.46Hz),7.90(1H,s),8.02(1H,s);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

[1940] 

806

[1941] N-((1r,3r)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺806。

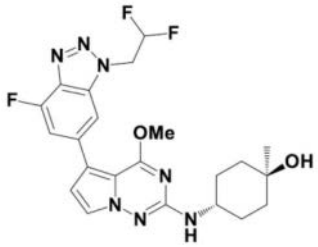
[1942] 白色固体(5mg,0.010mmol,13.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.81(3H,s),1.91-2.00(2H,m),2.59-2.68(2H,m),3.95(3H,s),4.19(1H,sxt,J=7.78Hz),5.34(2H,td,J=15.88,2.74Hz),6.62(1H,tt,J=54.30,3.00Hz),6.78(1H,d,J=2.74Hz),7.05(1H,d,J=7.39Hz),7.50(1H,dd,J=12.18,0.96Hz),7.64(1H,d,J=2.46Hz),7.89(1H,s),7.93(1H,s);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

[1943] 

810

[1944] (1s,4s)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇810。

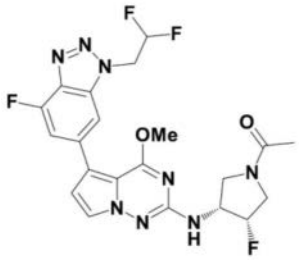
[1945] 白色固体(15mg,0.032mmol,32.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.37(2H,td,J=13.00,4.38Hz),1.53-1.62(2H,m),1.63-1.74(4H,m),3.47-3.57(1H,m),3.96(3H,s),4.00(1H,s),5.34(2H,td,J=15.88,2.74Hz),6.62(1H,tt,J=54.30,3.00Hz),6.56(1H,d,J=8.21Hz),6.76(1H,d,J=2.46Hz),7.50(1H,dd,J=12.05,1.10Hz),7.63(1H,d,J=2.46Hz),7.90(1H,s);$C_{22}H_{24}F_3N_7O_2$的ESIMS实验值m/z 476.2(M+1)。

[1946] 

811

[1947] (1r,4r)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇811。

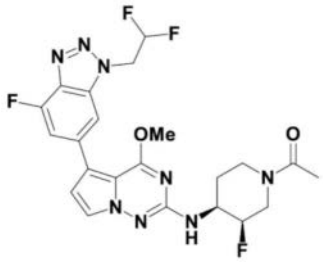
[1948] 蓬松白色固体(14mg,0.029mmol,61.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.52(4H,m),1.56-1.64(2H,m),1.83-1.92(2H,m),3.64(1H,br dd,J=8.62,3.97Hz),3.96(3H,s),4.23(1H,s),5.34(2H,td,J=15.95,2.60Hz),6.62(1H,tt,J=54.30,3.00Hz),6.54(1H,d,J=7.94Hz),6.77(1H,d,J=2.46Hz),7.50(1H,dd,J=12.05,0.82Hz),7.66(1H,d,J=2.74Hz),7.90(1H,s);$C_{22}H_{24}F_3N_7O_2$的ESIMS实验值m/z 476.2(M+1)。

[1949] 

812

[1950] 1-((3R,4S)-3-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-4-氟吡咯烷-1-基)乙-1-酮812。

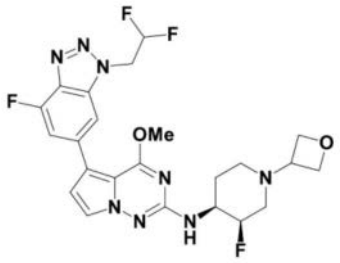
[1951] 白色固体(30mg,0.061mmol,33.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.93-2.01(3H,m),3.47-3.64(1H,m),3.65-3.77(1H,m),3.78-3.85(1H,m),3.86-3.97(1H,m),3.98-4.01(3H,m),4.36-4.56(1H,m),5.25-5.48(1H,m),5.35(2H,td,J=16.02,3.01Hz),6.62(1H,tt,J=54.30,3.00Hz),6.84(1H,t,J=2.46Hz),7.14(1H,dd,J=7.26,4.24Hz),7.52(1H,dd,J=12.18,0.96Hz),7.69(1H,dd,J=3.83,2.74Hz),7.92(1H,s);$C_{21}H_{20}F_4N_8O_2$的ESIMS实验值m/z 493.2(M+1)。

[1952] 

816

[1953] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮816。

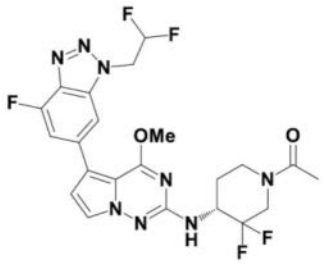
[1954] 蓬松白色固体(10mg,0.020mmol,39.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.66-1.73(1H,m),1.74-1.93(1H,m),1.98-2.06(3H,m),2.67-2.98(1H,m),3.17-3.26(1H,m),3.87-4.04(1H,m),3.98(3H,s),4.04-4.17(1H,m),4.41-4.76(1H,m),4.99(1H,d,J=49.65Hz),5.34(2H,td,J=15.88,2.74Hz),6.62(1H,tt,J=54.30,3.00Hz),6.81(1H,d,J=2.46Hz),6.85(1H,dd,J=7.67,3.29Hz),7.51(1H,dd,J=12.05,1.10Hz),7.66(1H,d,J=2.74Hz),7.91(1H,s);$C_{22}H_{22}F_4N_8O_2$的ESIMS实验值m/z 507.2(M+1)。

[1955] 

818

[1956] 5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺818。

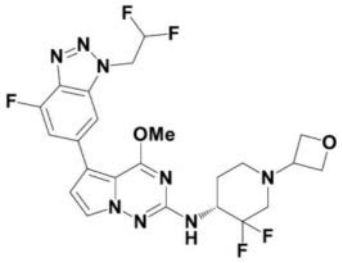
[1957] 蓬松白色固体(4mg,0.008mmol,23.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.77(1H,m),1.92(1H,qd,J=12.00,3.42Hz),1.98-2.06(1H,m),2.16(1H,dd,J=37.30,12.05Hz),2.76(1H,br d,J=10.13Hz),2.94-3.03(1H,m),3.49(1H,quin,J=6.23Hz),3.74-3.91(1H,m),3.98(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.50,3.15Hz),4.93(1H,d,J=49.35Hz),5.34(2H,td,J=15.95,2.87Hz),6.62(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=7.94Hz),6.80(1H,d,J=2.74Hz),7.51(1H,dd,J=12.18,0.96Hz),7.65(1H,d,J=2.46Hz),7.91(1H,s);$C_{23}H_{24}F_4N_8O_2$的ESIMS实验值m/z 521.2(M+1)。

[1958] 

821

[1959] (R)-1-(4-((5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮821。

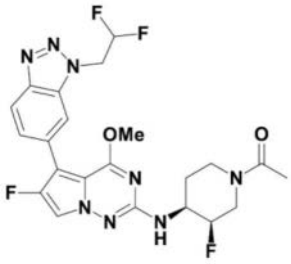
[1960] 蓬松白色固体(11mg,0.021mmol,44.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.58-1.84(1H,m),1.85-1.99(1H,m),2.03-2.09(3H,m),2.94-3.04(1H,m),3.64-3.92(1H,m),4.00(3H,s),4.09-4.31(1H,m),4.46-4.61(2H,m),5.34(2H,td,J=15.88,2.46Hz),6.62(1H,tt,J=54.30,3.00Hz),6.83(1H,d,J=2.74Hz),7.06(1H,d,J=9.31Hz),7.52(1H,dd,J=12.18,0.96Hz),7.67(1H,dd,J=2.46,1.37Hz),7.92(1H,s);$C_{22}H_{21}F_5N_8O_2$的ESIMS实验值m/z 525.2(M+1)。

[1961] 

822

[1962] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(1-(2,2-二氟乙基)-4-氟-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺822。

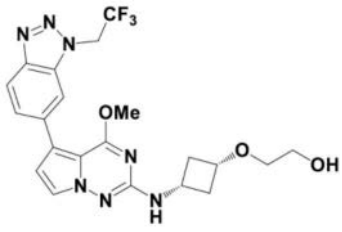
[1963] 蓬松白色固体(3mg,0.006mmol,11.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.86(1H,m),1.86-1.93(1H,m),2.12-2.21(1H,m),2.40(1H,dd,J=26.90,11.88Hz),2.76(1H,br d,J=11.50Hz),2.96-3.07(1H,m),3.60(1H,quin,J=6.23Hz),4.00(3H,s),4.23-4.37(1H,m),4.44(2H,dt,J=15.19,6.23Hz),4.55(2H,td,J=6.64,3.70Hz),5.34(2H,td,J=15.88,2.74Hz),6.62(2H,tt,J=54.30,3.00Hz),6.82(1H,d,J=2.74Hz),6.96(1H,d,J=9.31Hz),7.52(1H,dd,J=12.05,1.10Hz),7.67(1H,d,J=2.46Hz),7.91(1H,s);$C_{23}H_{23}F_5N_8O_2$的ESIMS实验值m/z 539.2(M+1)。

[1964] 

856

[1965] 1-((3R,4S)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-6-氟-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-3-氟哌啶-1-基)乙-1-酮856。

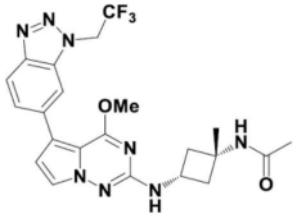
[1966] 白色固体(4mg,0.008mmol,21.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67-1.73(1H,m),1.74-1.90(1H,m),1.98-2.06(3H,m),2.66-2.98(1H,m),3.13-3.26(1H,m),3.87-4.01(1H,m),3.91(3H,s),4.02-4.16(1H,m),4.39-4.76(1H,m),4.97(1H,d,J=49.40Hz),5.32(2H,td,J=16.02,2.74Hz),6.59(1H,tt,J=54.30,3.00Hz),6.91(1H,dd,J=7.67,4.11Hz),7.57(1H,d,J=8.76Hz),7.83(1H,d,J=3.01Hz),7.99(1H,s),8.09(1H,d,J=8.76Hz);$C_{22}H_{22}F_4N_8O_2$的ESIMS实验值m/z 507.2(M+1)。

[1967] 

904

[1968] 2-(顺-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环丁氧基)乙-1-醇904。

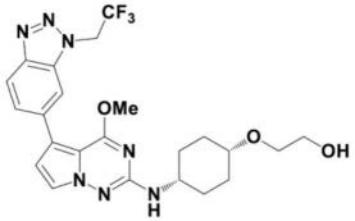
[1969] 蓬松白色固体(1.8mg,0.004mmol,9.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.81-1.95(2H,m),2.59-2.71(2H,m),3.36-3.43(2H,m),3.48(2H,br s),3.69-3.75(1H,m),3.75-3.81(1H,m),3.93(3H,s),5.87(2H,q,J=9.13Hz),6.73(1H,d,J=2.46Hz),7.05(1H,d,J=7.39Hz),7.63(1H,d,J=2.46Hz),7.65-7.69(1H,m),8.07(1H,d,J=8.76Hz),8.09(1H,s);$C_{21}H_{22}F_3N_7O_3$的ESIMS实验值m/z 478.2(M+1)。

[1970] 

905

[1971] N-((1s,3s)-3-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺905。

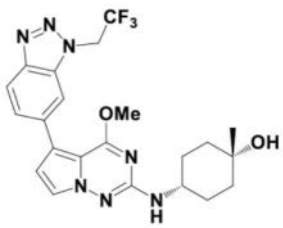
[1972] 白色固体(18mg,0.037mmol,29.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.12-2.22(2H,m),2.42(2H,ddd,J=9.58,7.39,2.46Hz),3.93(3H,s),4.03(1H,sxt,J=7.72Hz),5.87(2H,q,J=9.03Hz),6.73(1H,d,J=2.46Hz),7.02(1H,d,J=6.84Hz),7.67(1H,dd,J=8.50,1.65Hz),7.66(1H,d,J=2.74Hz),8.02(1H,s),8.07(1H,d,J=8.76Hz),8.09(1H,s);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

[1973] 

909

[1974] 2-((顺-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)氧基)乙-1-醇909。

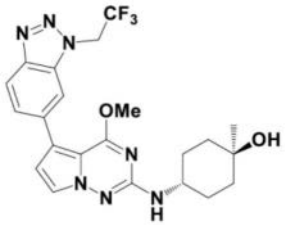
[1975] 白色固体(14.88mg,0.029mmol,%产率)。^{1}H NMR(400MHz,DMSO-d_6)δppm 1.40-1.57(2H,m),1.61-1.76(4H,m),1.78-1.90(2H,m),3.38-3.43(2H,m),3.48-3.54(2H,m),3.57-3.71(2H,m),3.93(3H,s),4.52(1H,t,J=5.44Hz),5.87(2H,q,J=9.01Hz),6.56(1H,br d,J=7.46Hz),6.71(1H,d,J=2.57Hz),7.64(1H,d,J=2.57Hz),7.67(1H,dd,J=8.68,1.22Hz),8.07(1H,d,J=8.68Hz),8.09(1H,s);$C_{23}H_{26}F_3N_7O_3$的ESIMS实验值m/z 506.2(M+1)。

[1976] 

910

[1977] (1s,4s)-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇910。

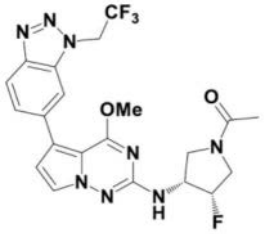
[1978] 白色固体(15mg,0.032mmol,32.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.12(3H,s),1.37(2H,td,J=13.07,4.24Hz),1.58(2H,br d,J=12.05Hz),1.61-1.75(4H,m),3.45-3.56(1H,m),3.92(3H,s),4.00(1H,s),5.87(2H,q,J=8.94Hz),6.53(1H,d,J=7.94Hz),6.71(1H,d,J=2.74Hz),7.63(1H,d,J=2.46Hz),7.67(1H,dd,J=8.76,1.37Hz),8.06(1H,d,J=8.76Hz),8.09(1H,s);$C_{22}H_{24}F_3N_7O_2$的ESIMS实验值m/z 476.2(M+1)。

[1979] 

911

[1980] (1r,4r)-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇911。

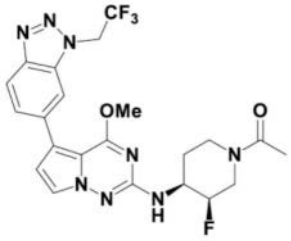
[1981] 蓬松白色固体(15mg,0.032mmol,65.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.38-1.51(4H,m),1.56-1.66(2H,m),1.83-1.93(2H,m),3.65(1H,dt,J=7.87,3.87Hz),3.93(3H,s),4.24(1H,s),5.87(2H,q,J=8.94Hz),6.51(1H,d,J=7.94Hz),6.71(1H,d,J=2.74Hz),7.66(1H,d,J=2.46Hz),7.66-7.68(1H,m),8.07(1H,d,J=8.76Hz),8.09(1H,s);$C_{22}H_{24}F_3N_7O_2$的ESIMS实验值m/z 476.2(M+1)。

[1982] 

912

[1983] 1-((3S,4R)-3-氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)吡咯烷-1-基)乙-1-酮912。

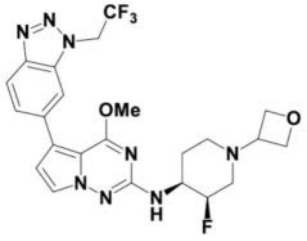
[1984] 白色固体(18mg,0.037mmol,20.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.92-2.02(3H,m),3.47-3.56(1H,m),3.58-3.75(1H,m),3.79-3.86(1H,m),3.86-3.95(1H,m),3.95-3.98(3H,m),4.28-4.60(1H,m),5.22-5.51(1H,m),5.88(2H,q,J=8.94Hz),6.78(1H,t,J=2.46Hz),7.11(1H,dd,J=7.12,5.20Hz),7.67-7.70(2H,m),8.08(1H,d,J=8.76Hz),8.11(1H,s);$C_{21}H_{20}F_4N_8O_2$的ESIMS实验值m/z493.2(M+1)。

[1985] 

916

[1986] 1-((3R,4S)-3-氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮916。

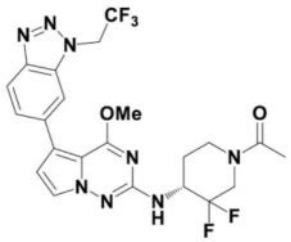
[1987] 蓬松白色固体(12mg,0.024mmol,47.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67-1.74(1H,m),1.74-1.91(1H,m),1.98-2.06(3H,m),2.67-2.99(1H,m),3.16-3.26(1H,m),3.88-4.02(1H,m),3.95(3H,s),4.03-4.17(1H,m),4.40-4.75(1H,m),5.00(1H,d,J=49.65Hz),5.88(2H,q,J=9.22Hz),6.75(1H,d,J=2.74Hz),6.82(1H,dd,J=7.67,3.01Hz),7.66(1H,d,J=2.46Hz),7.68(1H,dd,J=8.76,1.64Hz),8.08(1H,d,J=8.76Hz),8.10(1H,s);$C_{22}H_{22}F_4N_8O_2$的ESIMS实验值m/z 507.2(M+1)。

[1988] 

918

[1989] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺918。

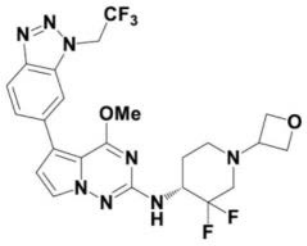
[1990] 蓬松白色固体(10mg,0.019mmol,45.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.78(1H,m),1.87-1.97(1H,m),1.99-2.06(1H,m),2.16(1H,dd,J=37.00,12.59Hz),2.76(1H,br d,J=10.95Hz),2.94-3.05(1H,m),3.49(1H,quin,J=6.30Hz),3.73-3.90(1H,m),3.95(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.43,3.01Hz),4.94(1H,d,J=49.60Hz),5.87(2H,q,J=8.94Hz),6.73(1H,d,J=7.94Hz),6.74(1H,d,J=2.74Hz),7.65(1H,d,J=2.46Hz),7.67(1H,dd,J=8.49,1.37Hz),8.07(1H,d,J=8.76Hz),8.10(1H,s);$C_{23}H_{24}F_4N_8O_2$的ESIMS实验值m/z 521.2(M+1)。

[1991] 

921

[1992] (R)-1-(3,3-二氟-4-((4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮921。

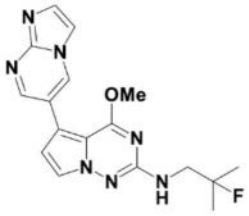
[1993] 蓬松白色固体(7mg,0.013mmol,43.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.58-1.84(1H,m),1.84-2.01(1H,m),2.03-2.09(3H,m),2.99(1H,br t,J=11.36Hz),3.61-3.90(1H,m),3.97(3H,s),4.10-4.31(1H,m),4.45-4.63(2H,m),5.88(2H,q,J=9.22Hz),6.77(1H,d,J=2.46Hz),7.03(1H,d,J=9.03Hz),7.67(1H,dd,J=2.60,1.23Hz),7.67-7.70(1H,m),8.08(1H,d,J=8.76Hz),8.11(1H,s);$C_{22}H_{21}F_5N_8O_2$的ESIMS实验值m/z 525.2(M+1)。

[1994] 

922

[1995] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺922。

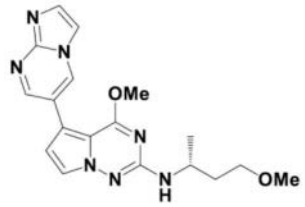
[1996] 蓬松白色固体(3mg,0.006mmol,11.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.86(1H,m),1.86-1.93(1H,m),2.12-2.20(1H,m),2.41(1H,dd,J=27.15,11.23Hz),2.76(1H,br d,J=11.77Hz),2.95-3.08(1H,m),3.61(1H,quin,J=6.09Hz),3.96(3H,s),4.22-4.37(1H,m),4.44(2H,dt,J=15.19,6.09Hz),4.55(2H,td,J=6.57,3.56Hz),5.87(2H,q,J=9.03Hz),6.76(1H,d,J=2.74Hz),6.93(1H,d,J=9.31Hz),7.66(1H,d,J=2.74Hz),7.68(1H,dd,J=8.80,1.35Hz),8.08(1H,d,J=8.76Hz),8.11(1H,s);$C_{23}H_{23}F_5N_8O_2$的ESIMS实验值m/z 539.2(M+1)。

[1997] 

924

[1998] N-(2-氟-2-甲基丙基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺924。

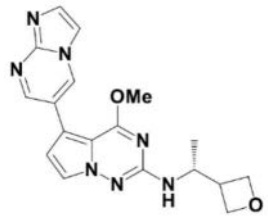
[1999] 米色固体(6mg,0.017mmol,8.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.37(6H,d,J=21.40Hz),3.47(2H,dd,J=18.89,6.57Hz),4.00(3H,s),6.79(1H,d,J=2.74Hz),6.86(1H,t,J=6.43Hz),7.67(1H,d,J=2.46Hz),7.73(1H,d,J=1.10Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.10(1H,d,J=2.46Hz);$C_{17}H_{18}FN_7O$的ESIMS实验值m/z 356.2(M+1)。

[2000] 

926

[2001] (R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(4-甲氧基丁烷-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺926。

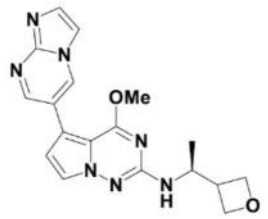
[2002] 米色固体(4mg,0.011mmol,5.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.16(3H,d,J=6.57Hz),1.63-1.73(1H,m),1.77-1.88(1H,m),3.22(3H,s),3.36-3.45(2H,m),3.88-3.96(1H,m),3.97(3H,s),6.58(1H,d,J=8.49Hz),6.77(1H,d,J=2.46Hz),7.66(1H,d,J=2.46Hz),7.75(1H,br s),7.95(1H,br s),8.74(1H,d,J=2.19Hz),9.10(1H,d,J=1.64Hz);$C_{18}H_{21}N_7O_2$的ESIMS实验值m/z 368.2(M+1)。

[2003] 

927

[2004] (R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺927。

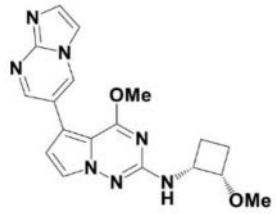
[2005] 米色固体(13mg,0.036mmol,17.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.10(3H,d,J=6.57Hz),3.04-3.14(1H,m),3.98(3H,s),4.14-4.26(1H,m),4.35(1H,t,J=6.30Hz),4.43(1H,t,J=6.16Hz),4.58-4.65(2H,m),6.70(1H,d,J=8.76Hz),6.78(1H,d,J=2.46Hz),7.69(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[2006] 

928

[2007] (S)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(氧杂环丁烷-3-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺928。

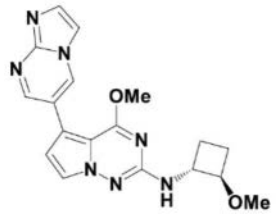
[2008] 灰白色固体(14mg,0.038mmol,19.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.10(3H,d,J=6.57Hz),3.04-3.17(1H,m),4.15-4.26(1H,m),4.35(1H,t,J=6.16Hz),4.43(1H,t,J=6.16Hz),4.55-4.66(2H,m),6.70(1H,d,J=8.49Hz),6.78(1H,d,J=2.46Hz),7.69(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[2009] 

929

[2010] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1R,2S)-2-甲氧基环丁基)吡咯并[2,1-f][1,2,4]三嗪-2-胺929。

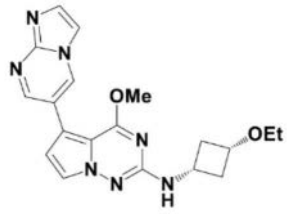
[2011] 白色固体(10mg,0.027mmol,27.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.92-2.05(3H,m),2.05-2.12(1H,m),3.19(3H,s),4.00(3H,s),4.00-4.04(1H,m),4.30-4.41(1H,m),6.59(1H,d,J=7.67Hz),6.79(1H,d,J=2.74Hz),7.68(1H,d,J=2.46Hz),7.73(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.10(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[2012] 

930

[2013] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1R,2R)-2-甲氧基环丁基)吡咯并[2,1-f][1,2,4]三嗪-2-胺930。

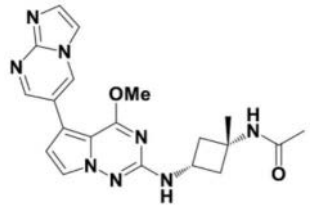
[2014] 灰白色固体(25mg,0.068mmol,41.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38-1.48(2H,m),1.95-2.02(1H,m),2.02-2.10(1H,m),3.22(3H,s),3.81(1H,q,J=7.48Hz),3.98(3H,s),4.06-4.16(1H,m),6.79(1H,d,J=2.46Hz),7.19(1H,d,J=8.76Hz),7.68(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.10Hz),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[2015] 

931

[2016] N-(顺-3-乙氧基环丁基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺931。

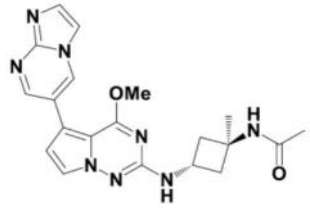
[2017] 灰白色固体(10mg,0.026mmol,13.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.10(3H,t,J=6.98Hz),1.79-1.92(2H,m),2.57-2.69(2H,m),3.33-3.37(2H,m),3.64-3.72(1H,m),3.74-3.83(1H,m),3.97(3H,s),6.78(1H,d,J=2.46Hz),7.07(1H,d,J=7.39Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.74Hz);$C_{19}H_{21}N_7O_2$的ESIMS实验值m/z 380.2(M+1)。

[2018] 

934

[2019] N-((1s,3s)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺934。

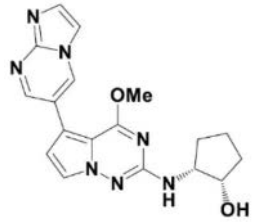
[2020] 米色固体(26mg,0.064mmol,93.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.12-2.21(2H,m),2.42(2H,ddd,J=9.58,7.39,2.74Hz),3.97(3H,s),3.98-4.07(1H,m),6.77(1H,d,J=2.74Hz),7.05(1H,d,J=7.12Hz),7.68(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.02(1H,s),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{22}N_8O_2$的ESIMS实验值m/z407.2(M+1)。

[2021] 

935

[2022] N-((1r,3r)-3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺935。

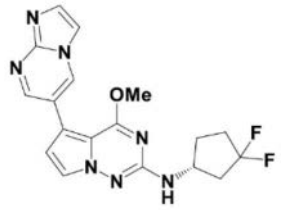
[2023] 灰白色固体(26mg,0.064mmol,93.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(3H,s),1.81(3H,s),1.90-2.00(2H,m),2.58-2.69(2H,m),3.97(3H,s),4.19(1H,sxt,J=7.78Hz),6.77(1H,d,J=2.46Hz),7.05(1H,d,J=7.12Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),7.94(1H,s),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{22}N_8O_2$的ESIMS实验值m/z 407.2(M+1)。

[2024] 

942

[2025] (1S,2R)-2-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环戊-1-醇942。

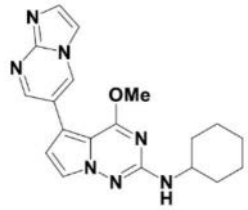
[2026] 米色固体(16mg,0.044mmol,26.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.46-1.56(1H,m),1.57-1.67(2H,m),1.69-1.77(1H,m),1.77-1.86(1H,m),1.92-2.01(1H,m),3.79-3.91(1H,m),3.98(3H,s),4.09-4.19(1H,m),4.74(1H,d,J=4.38Hz),5.98(1H,d,J=7.67Hz),6.79(1H,d,J=2.46Hz),7.68(1H,d,J=2.46Hz),7.73(1H,s),7.93(1H,s),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.15(M+1)。

[2027] 

943

[2028] (R)-N-(3,3-二氟环戊基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺943。

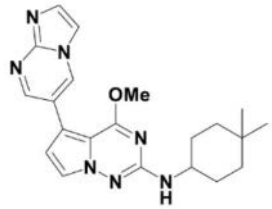
[2029] 白色固体(17mg,0.044mmol,26.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.82(1H,dq,J=12.25,8.42Hz),2.02-2.23(3H,m),2.23-2.35(1H,m),2.54-2.62(1H,m),3.98(3H,s),4.23(1H,sxt,J=7.34Hz),6.80(1H,d,J=2.46Hz),7.07(1H,d,J=6.84Hz),7.70(1H,d,J=2.46Hz),7.73(1H,s),7.93(1H,s),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{17}F_2N_7O$的ESIMS实验值m/z 386.2(M+1)。

[2030] 

944

[2031] N-环己基-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺944。

[2032] 米色固体(43mg,0.118mmol,59.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.08-1.19(1H,m),1.21-1.38(4H,m),1.54-1.65(1H,m),1.70-1.78(2H,m),1.95(2H,br d,J=10.40Hz),3.53-3.65(1H,m),3.97(3H,s),6.58(1H,d,J=8.21Hz),6.76(1H,d,J=2.74Hz),7.66(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.92(1H,d,J=1.10Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{19}H_{21}N_7O$的ESIMS实验值m/z 364.15(M+1)。

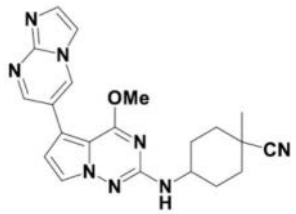
[2033] 

947

[2034] N-(4,4-二甲基环己基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺947。

[2035] 灰白色固体(12mg,0.031mmol,15.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.93(3H,s),0.93(3H,s),1.26(2H,td,J=13.21,3.70Hz),1.35-1.43(1H,m),1.44-1.54(1H,m),1.62-1.72(1H,m),1.73-1.83(2H,m),1.90(1H,br d,J=3.56Hz),3.48-3.61(1H,m),3.97(3H,s),6.56(1H,d,J=8.21Hz),6.76(1H,d,J=2.74Hz),7.65(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=

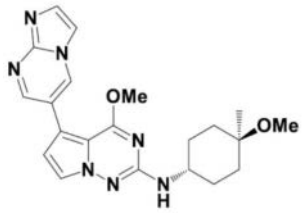
2.46Hz)；$C_{21}H_{25}N_7O$的ESIMS实验值m/z 392.2(M+1)。

[2036] 

948

[2037] 4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己烷-1-甲腈948。

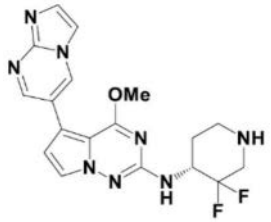
[2038] 灰白色固体(34mg,0.085mmol,42.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34(3H,s),1.45-1.60(4H,m),1.95(2H,br d,J=10.68Hz),2.00-2.07(2H,m),3.52-3.65(1H,m),3.98(3H,s),6.77(1H,d,J=2.46Hz),6.83(1H,d,J=7.94Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.10Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz)；$C_{21}H_{22}N_8O$的ESIMS实验值m/z 403.2(M+1)。

[2039] 

954

[2040] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-((1r,4r)-4-甲氧基-4-甲基环己基)吡咯并[2,1-f][1,2,4]三嗪-2-胺954。

[2041] 灰白色固体(22mg,0.054mmol,27.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.14(3H,s),1.42-1.57(4H,m),1.63-1.74(2H,m),1.78-1.90(2H,m),3.11(3H,s),3.65-3.77(1H,m),3.98(3H,s),6.60(1H,d,J=7.94Hz),6.77(1H,d,J=2.74Hz),7.67(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz)；$C_{21}H_{25}N_7O_2$的ESIMS实验值m/z 408.2(M+1)。

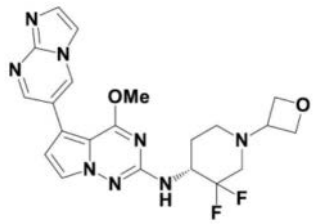
[2042] 

964

[2043] (R)-N-(3,3-二氟哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺964。

[2044] 米色固体(18mg,0.045mmol,75.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.69(1H,qd,J=11.96,3.56Hz),1.79-1.90(1H,m),2.55-2.67(1H,m),2.81(1H,dd,J=29.35,14.00Hz),2.93(1H,br d,J=12.05Hz),3.06-3.15(1H,m),4.01(3H,s),4.26-4.41(1H,m),6.80(1H,d,J=2.74Hz),6.91(1H,d,J=9.31Hz),7.68(1H,d,J=2.46Hz),7.73(1H,d,J=

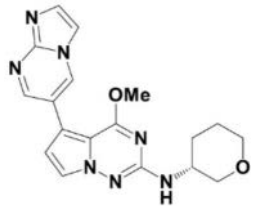
1.37Hz),7.93(1H,d,J＝1.37Hz),8.74(1H,d,J＝2.46Hz),9.10(1H,d,J＝2.46Hz);$C_{18}H_{18}F_2N_8O$的ESIMS实验值m/z 401.2(M+1)。

[2045] 

968

[2046] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺968。

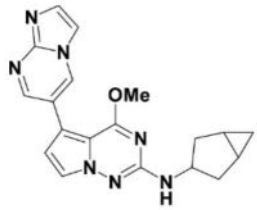
[2047] 灰白色固体(15mg,0.033mmol,72.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.86(1H,m),1.86-1.92(1H,m),2.12-2.22(1H,m),2.35-2.46(1H,m),2.76(1H,br d,J＝11.50Hz),2.96-3.08(1H,m),3.60(1H,quin,J＝6.30Hz),4.01(3H,s),4.23-4.37(1H,m),4.44(2H,dt,J＝15.19,6.23Hz),4.55(2H,td,J＝6.57,3.83Hz),6.81(1H,d,J＝2.46Hz),6.96(1H,d,J＝9.31Hz),7.68(1H,d,J＝2.46Hz),7.73(1H,d,J＝1.37Hz),7.93(1H,d,J＝1.37Hz),8.74(1H,d,J＝2.46Hz),9.10(1H,d,J＝2.46Hz);$C_{21}H_{22}F_2N_8O_2$的ESIMS实验值m/z 457.(M+1)。

[2048] 

975

[2049] (R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(四氢-2H-吡喃-3-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺975。

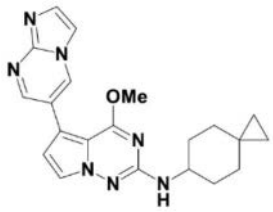
[2050] 白色固体(7mg,0.019mmol,11.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.53-1.65(2H,m),1.67-1.76(1H,m),1.99(1H,br d,J＝7.39Hz),3.11(1H,t,J＝9.99Hz),3.23-3.30(1H,m),3.70-3.80(2H,m),3.94(1H,br dd,J＝10.54,3.15Hz),3.98(3H,s),6.66(1H,d,J＝7.94Hz),6.78(1H,d,J＝2.46Hz),7.69(1H,d,J＝2.46Hz),7.72(1H,d,J＝0.82Hz),7.93(1H,d,J＝1.10Hz),8.73(1H,d,J＝2.46Hz),9.09(1H,d,J＝2.46Hz);$C_{18}H_{19}N_7O_2$的ESIMS实验值m/z 366.2(M+1)。

[2051] 

976

[2052] N-(双环[3.1.0]己烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺976。

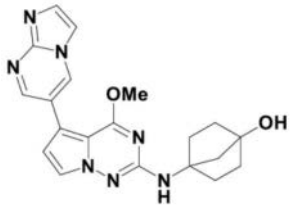
[2053] 米色固体(18mg,0.050mmol,25.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.39(1H,q,J=4.11Hz),0.55(1H,td,J=8.08,4.93Hz),1.26-1.30(2H,m),1.74(2H,dd,J=13.69,3.01Hz),2.18-2.28(2H,m),3.97(3H,s),4.18(1H,tdt,J=8.30,8.30,5.51,2.91,2.91Hz),6.62(1H,d,J=5.48Hz),6.76(1H,d,J=2.46Hz),7.65(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.92(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{19}H_{19}N_7O$的ESIMS实验值m/z 362.2(M+1)。

[2054] 

977

[2055] 5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(螺[2.5]辛烷-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺977。

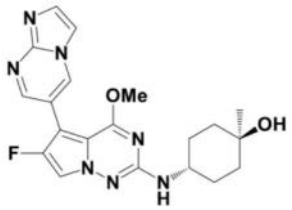
[2056] 灰白色固体(8mg,0.021mmol,10.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.17-0.25(2H,m),0.26-0.35(2H,m),0.98(2H,br d,J=13.42Hz),1.45(2H,qd,J=11.65,3.30Hz),1.67-1.79(2H,m),1.88-1.97(2H,m),3.57-3.73(1H,m),3.98(3H,s),6.64(1H,d,J=8.21Hz),6.76(1H,d,J=2.46Hz),7.67(1H,d,J=2.74Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{21}H_{23}N_7O$的ESIMS实验值m/z 390.2(M+1)。

[2057] 

978

[2058] 4-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)双环[2.2.1]庚-1-醇978。

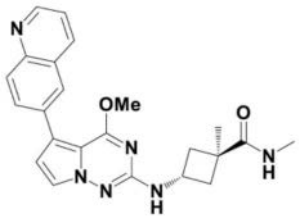
[2059] 米色固体(17mg,0.043mmol,21.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.57(2H,td,J=9.79,3.70Hz),1.65-1.77(2H,m),1.85(2H,s),1.87-1.93(2H,m),1.97-2.07(2H,m),3.97(3H,s),4.89(1H,s),6.77(1H,d,J=2.46Hz),6.79(1H,s),7.63(1H,d,J=2.46Hz),7.72(1H,d,J=1.10Hz),7.93(1H,d,J=1.10Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{21}N_7O_2$的ESIMS实验值m/z 392.2(M+1)。

[2060] 

996

[2061] (1r,4r)-4-((6-氟-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇996。

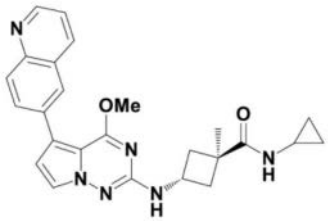
[2062] 灰白色固体(1mg,0.002mmol,4.3%产率)。^{1}H NMR(499MHz,METHANOL-d_4)δppm 1.28(3H,s),1.48-1.56(2H,m),1.56-1.63(2H,m),1.68-1.78(2H,m),1.98-2.09(2H,m),3.74(1H,tt,J=8.80,4.21Hz),4.01(3H,s),4.58(1H,br s),7.54(1H,d,J=3.01Hz),7.75(1H,s),7.88(1H,s),8.72(1H,d,J=2.19Hz),9.00(1H,d,J=2.19Hz);$C_{20}H_{22}FN_7O_2$的ESIMS实验值m/z 412.2(M+1)。

[2063] 

1038

[2064] 反-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-N,1-二甲基环丁烷-1-甲酰胺1038。

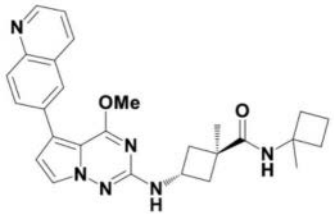
[2065] 黄色固体(23mg,0.055mmol,44.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.32(3H,s),1.85-1.95(2H,m),2.63(3H,d,J=4.65Hz),2.71-2.80(2H,m),3.95(3H,s),4.05(1H,sxt,J=7.94Hz),6.77(1H,d,J=2.46Hz),6.99(1H,d,J=7.39Hz),7.52(1H,dd,J=8.21,4.11Hz),7.62(1H,q,J=4.11Hz),7.66(1H,d,J=2.74Hz),7.94-8.03(2H,m),8.10(1H,d,J=1.37Hz),8.36(1H,dd,J=8.35,1.51Hz),8.86(1H,br d,J=2.74Hz);$C_{23}H_{24}N_6O_2$的ESIMS实验值m/z 417.2(M+1)。

[2066] 

1039

[2067] 反-N-环丙基-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺1039。

[2068] 淡黄色固体(20mg,0.045mmol,36.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 0.42-0.48(2H,m),0.58-0.64(2H,m),1.30(3H,s),1.84-1.90(2H,m),2.68(1H,tq,J=7.41,3.91Hz),2.72-2.78(2H,m),3.95(3H,s),3.96-4.06(1H,m),6.77(1H,d,J=2.74Hz),6.98(1H,d,J=7.39Hz),7.53(1H,dd,J=8.35,4.24Hz),7.63(1H,d,J=4.11Hz),7.67(1H,d,J=2.46Hz),7.94-8.04(2H,m),8.11(1H,s),8.37(1H,dd,J=8.21,1.37Hz),8.87(1H,br d,J=2.46Hz);$C_{25}H_{26}N_6O_2$的ESIMS实验值m/z 443.2(M+1)。

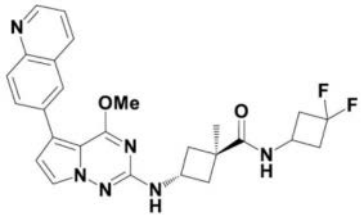
[2069] 

1040

[2070] 反-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基-N-(1-甲基环丁基)环丁烷-1-甲酰胺1040。

[2071] 棕褐色固体(21mg,0.045mmol,36.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.33(3H,s),1.39(3H,s),1.71-1.82(2H,m),1.83-1.97(4H,m),2.16-2.28(2H,m),2.71-2.82(2H,m),3.96(3H,s),3.97-4.04(1H,m),6.77(1H,d,J=2.74Hz),6.97(1H,br d,J=7.12Hz),7.51

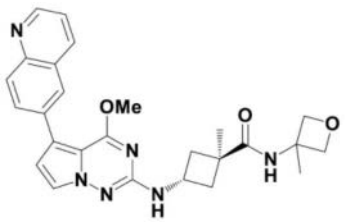
[2072] -7.56(2H,m),7.67(1H,d,J=2.74Hz),7.95-8.04(2H,m),8.12(1H,s),8.38(1H,br d,J=7.94Hz),8.84-8.92(1H,m);$C_{27}H_{30}N_6O_2$的ESIMS实验值m/z 471.3(M+1)。

[2073] 

1041

[2074] 反-N-(3,3-二氟环丁基)-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁烷-1-甲酰胺?1041

[2075] 黄色固体(33mg,0.067mmol,54.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.34(3H,s),1.87-1.98(2H,m),2.58-2.71(2H,m),2.77(2H,ddd,J=9.99,7.80,2.46Hz),2.83-2.96(2H,m),3.96(3H,s),3.99-4.06(1H,m),4.07-4.15(1H,m),6.78(1H,d,J=2.74Hz),7.02(1H,br d,J=7.12Hz),7.59(1H,dd,J=8.21,4.11Hz),7.67(1H,d,J=2.46Hz),8.02(2H,s),8.04(1H,d,J=6.84Hz),8.14(1H,s),8.45(1H,br d,J=7.94Hz),8.91(1H,br d,J=3.01Hz);$C_{26}H_{26}F_2N_6O_2$的ESIMS实验值m/z 493.25(M+1)。

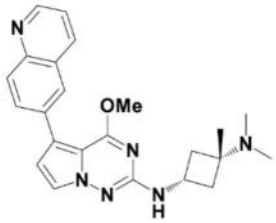
[2076] 

1042

[2077] 反-3-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基-N-(3-甲基氧杂环丁烷-3-基)环丁烷-1-甲酰胺1042。

[2078] 棕褐色固体(21mg,0.044mmol,35.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.35(3H,s),1.52(3H,s),1.87-1.98(2H,m),2.71-2.80(2H,m),3.96(3H,s),4.05(1H,sxt,J=7.94Hz),4.31(2H,d,J=6.30Hz),4.60(2H,d,J=6.30Hz),6.77(1H,d,J=2.74Hz),7.00

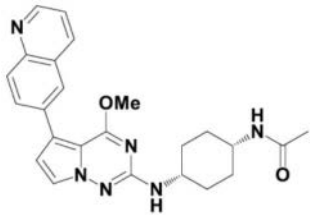
(1H,d,J＝7.39Hz),7.46-7.57(1H,m),7.67(1H,d,J＝2.46Hz),7.93-8.03(2H,m),8.08(1H,s),8.10(1H,d,J＝1.37Hz),8.36(1H,dd,J＝8.21,1.64Hz),8.86(1H,dd,J＝4.24,1.78Hz);$C_{26}H_{28}N_6O_3$的ESIMS实验值m/z 473.3(M+1)。

[2079] 

1043

[2080] 顺-N3-(4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)-N1,N1,1-三甲基环丁烷-1,3-二胺1043。

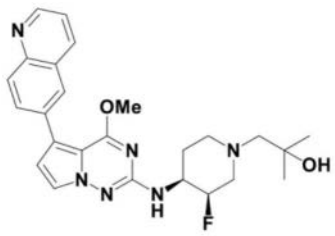
[2081] 米色固体(28mg,0.070mmol,57.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.07(3H,s),1.82-1.92(2H,m),2.03(6H,s),2.15-2.25(2H,m),3.92-4.03(1H,m),3.96(3H,s),6.77(1H,d,J＝2.74Hz),6.96(1H,d,J＝7.12Hz),7.52(1H,dd,J＝8.35,4.24Hz),7.65(1H,d,J＝2.46Hz),7.94-8.03(2H,m),8.11(1H,s),8.36(1H,dd,J＝8.35,1.51Hz),8.86(1H,dd,J＝4.38,1.64Hz);$C_{23}H_{26}N_6O$的ESIMS实验值m/z403.25(M+1)。

[2082] 

1044

[2083] N-(顺-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺1044。

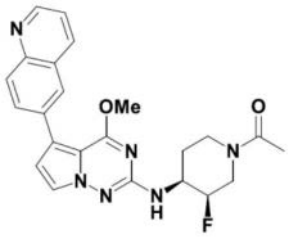
[2084] 白色固体(4.16mg,0.010mmol)。^{1}H NMR(400MHz,DMSO-d_6)δppm 1.50-1.60(2H,m),1.60-1.73(4H,m),1.73-1.81(2H,m),1.81(3H,s),3.40-3.47(1H,m),3.68(2H,br s),3.97(3H,s),6.46(1H,d,J＝6.38Hz),6.77(1H,d,J＝2.63Hz),7.53(1H,dd,J＝8.32,4.19Hz),7.65(1H,d,J＝2.63Hz),7.73(1H,br d,J＝7.00Hz),7.99(2H,s),8.11(1H,s),8.36(1H,dd,J＝8.25,1.50Hz),8.86(1H,dd,J＝4.19,1.69Hz);$C_{24}H_{26}N_6O_2$的ESIMS实验值m/z 431.1(M+1)。

[2085] 

1045

[2086] 1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇1045。

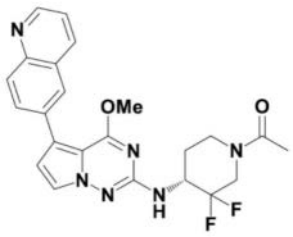
[2087] 白色固体(5mg,0.011mmol,14.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.10(6H,s),1.61-1.71(1H,m),1.95(1H,qd,J=12.18,3.42Hz),2.20-2.29(2H,m),2.29-2.35(1H,m),2.43(1H,dd,J=37.55,12.87Hz),2.98(1H,br d,J=12.32Hz),3.23-3.30(2H,m),3.71-3.86(1H,m),3.98(3H,s),4.08(1H,br s),4.87(1H,d,J=49.90Hz),6.59(1H,d,J=7.94Hz),6.79(1H,d,J=2.74Hz),7.53(1H,dd,J=8.21,4.11Hz),7.65(1H,d,J=2.46Hz),7.95-8.03(2H,m),8.11(1H,d,J=1.37Hz),8.36(1H,dd,J=8.35,1.78Hz),8.86(1H,dd,J=4.24,1.78Hz);$C_{25}H_{29}FN_6O_2$的ESIMS实验值m/z 465.3(M+1)。

[2088] 

1047

[2089] 1-((3R,4S)-3-氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮1047。

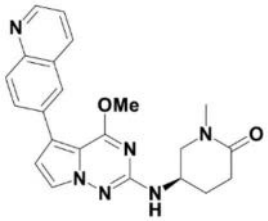
[2090] 淡橙色固体(20mg,0.046mmol,60.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67-1.75(1H,m),1.75-1.91(1H,m),1.99-2.07(3H,m),2.67-2.97(1H,m),3.15-3.27(1H,m),3.87-3.95(1H,m),3.98(3H,s),4.03-4.17(1H,m),4.40-4.77(1H,m),5.00(1H,d,J=49.35Hz),6.80(2H,d,J=2.46Hz),7.53(1H,dd,J=8.21,4.11Hz),7.65(1H,d,J=2.74Hz),7.96-8.02(2H,m),8.12(1H,s),8.36(1H,dd,J=8.21,1.64Hz),8.86(1H,dd,J=4.38,1.64Hz);$C_{23}H_{23}FN_6O_2$的ESIMS实验值m/z 435.2(M+1)。

[2091] 

1048

[2092] (R)-1-(3,3-二氟-4-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮1048。

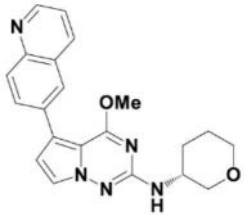
[2093] 淡黄色固体(5mg,0.011mmol,37.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.55-1.85(1H,m),1.86-2.01(1H,m),2.03-2.10(3H,m),2.92-3.06(1H,m),3.80-3.94(1H,m),4.00(3H,s),4.11-4.32(1H,m),4.46-4.62(2H,m),6.82(1H,d,J=2.74Hz),7.00(1H,d,J=9.31Hz),7.53(1H,dd,J=8.21,4.11Hz),7.66(1H,dd,J=2.46,1.37Hz),7.94-8.04(2H,m),8.12(1H,s),8.37(1H,dd,J=8.35,1.51Hz),8.87(1H,dd,J=4.24,1.78Hz);$C_{23}H_{22}F_2N_6O_2$的ESIMS实验值m/z 453.2(M+1)。

[2094] 

1049

[2095] (R)-5-((4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮1049。

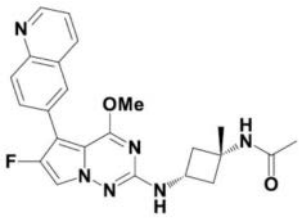
[2096] 米色固体(23mg,0.057mmol,44.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.88-1.97(1H,m),1.97-2.04(1H,m),2.27-2.36(1H,m),2.37-2.44(1H,m),2.81(3H,s),3.26(1H,dd,J=12.05,7.67Hz),3.58(1H,dd,J=12.05,4.38Hz),3.98(3H,s),4.05-4.17(1H,m),6.80(1H,d,J=2.74Hz),6.92(1H,d,J=7.39Hz),7.53(1H,dd,J=8.21,4.11Hz),7.69(1H,d,J=2.74Hz),7.94-8.04(2H,m),8.12(1H,s),8.36(1H,dd,J=8.35,1.51Hz),8.86(1H,dd,J=4.11,1.64Hz);$C_{22}H_{22}N_6O_2$的ESIMS实验值m/z 403.2(M+1)。

[2097] 

1050

[2098] (R)-4-甲氧基-5-(喹啉-6-基)-N-(四氢-2H-吡喃-3-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1050。

[2099] 灰白色固体(59mg,0.157mmol,46.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.51-1.63(2H,m),1.67-1.76(1H,m),1.95-2.04(1H,m),3.06-3.17(1H,m),3.25-3.32(1H,m),3.72-3.81(2H,m),3.93-3.98(1H,m),3.96(3H,s),6.60(1H,d,J=8.21Hz),6.78(1H,d,J=2.46Hz),7.52(1H,dd,J=8.35,4.24Hz),7.67(1H,d,J=2.46Hz),7.94-8.03(2H,m),8.11(1H,s),8.36(1H,dd,J=8.35,1.51Hz),8.86(1H,dd,J=4.24,1.78Hz);$C_{21}H_{21}N_5O_2$的ESIMS实验值m/z 376.2(M+1)。

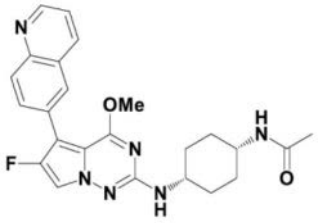
[2100] 

1052

[2101] N-(顺-3-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环丁基)乙酰胺1052。

[2102] 灰白色固体(14mg,0.032mmol,90.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.38(3H,s),1.76(3H,s),2.11-2.21(2H,m),2.42(2H,ddd,J=9.65,7.46,2.60Hz),3.91(3H,s),4.01(1H,sxt,J=7.83Hz),7.09(1H,d,J=6.84Hz),7.55(1H,dd,J=8.35,4.24Hz),

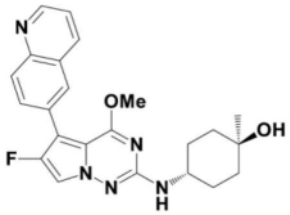
7.85(1H,d,J＝2.74Hz),7.88(1H,dd,J＝8.76,1.64Hz),8.01-8.05(2H,m),8.06(1H,s),8.39(1H,dd,J＝8.49,1.10Hz),8.90(1H,dd,J＝4.24,1.78Hz);$C_{23}H_{23}FN_6O_2$的ESIMS实验值m/z 435.2(M+1)。

[2103] 

1054

[2104] N-(顺-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己基)乙酰胺1054。

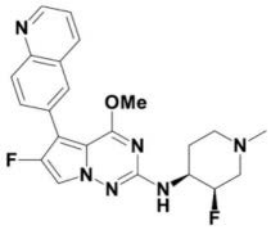
[2105] 灰白色固体(8.6mg,0.019mmol,70.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.50-1.59(2H,m),1.61-1.72(4H,m),1.73-1.81(2H,m),1.81(3H,s),3.67(2H,br d,J＝3.29Hz),3.93(3H,s),6.56(1H,d,J＝6.30Hz),7.50-7.59(1H,m),7.70(1H,d,J＝7.12Hz),7.84(1H,d,J＝2.74Hz),7.89(1H,dd,J＝8.76,1.64Hz),8.03(1H,d,J＝8.76Hz),8.07(1H,s),8.39(1H,dd,J＝8.35,1.23Hz),8.90(1H,dd,J＝4.11,1.64Hz);$C_{24}H_{25}FN_6O_2$的ESIMS实验值m/z 449.2(M+1)。

[2106] 

1056

[2107] 反-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇1056。

[2108] 灰白色固体(9.7mg,0.023mmol,30.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.36-1.53(4H,m),1.56-1.65(2H,m),1.80-1.92(2H,m),3.63(1H,br dd,J＝8.21,3.83Hz),3.91(3H,s),4.23(1H,s),6.59(1H,d,J＝7.94Hz),7.55(1H,dd,J＝8.35,4.24Hz),7.85(1H,d,J＝2.74Hz),7.89(1H,dd,J＝8.76,1.64Hz),8.03(1H,d,J＝8.76Hz),8.06(1H,s),8.39(1H,dd,J＝8.49,1.10Hz),8.90(1H,dd,J＝4.11,1.64Hz);$C_{23}H_{24}FN_5O_2$的ESIMS实验值m/z 422.2(M+1)。

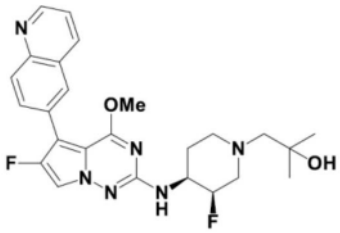
[2109] 

1057

[2110] 6-氟-N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,

1-f][1,2,4]三嗪-2-胺1057。

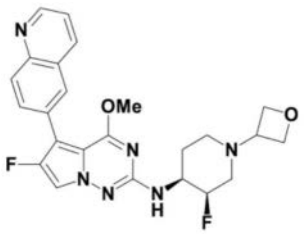
[2111] 白色固体(6mg,0.014mmol,18.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.64-1.73(1H,m),1.93(1H,qd,J=12.23,3.83Hz),2.06(1H,br t,J=11.09Hz),2.17(1H,dd,J=37.60,12.59Hz),2.19(3H,s),2.80(1H,br d,J=11.23Hz),3.05(1H,br t,J=10.54Hz),3.69-3.83(1H,m),3.93(3H,s),4.90(1H,d,J=49.65Hz),6.74(1H,d,J=7.67Hz),7.55(1H,dd,J=8.35,4.24Hz),7.84(1H,d,J=2.74Hz),7.89(1H,dd,J=8.62,1.51Hz),8.04(1H,d,J=8.76Hz),8.07(1H,s),8.39(1H,dd,J=8.49,1.09Hz),8.90(1H,dd,J=4.11,1.64Hz);$C_{22}H_{22}F_2N_6O$的ESIMS实验值m/z 425.2(M+1)。

[2112] 

1058

[2113] 1-((3R,4S)-3-氟-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)-2-甲基丙-2-醇1058。

[2114] 白色固体(3mg,0.006mmol,23.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.09(6H,s),1.60-1.70(1H,m),1.95(1H,qd,J=12.18,3.70Hz),2.20-2.28(2H,m),2.29-2.35(1H,m),2.37-2.48(1H,m),2.92-3.03(1H,m),3.23-3.31(1H,m),3.68-3.85(1H,m),3.93(3H,s),4.08(1H,s),4.85(1H,d,J=49.60Hz),6.71(1H,d,J=7.67Hz),7.55(1H,dd,J=8.21,4.11Hz),7.84(1H,d,J=3.01Hz),7.89(1H,dd,J=8.62,1.78Hz),8.04(1H,d,J=8.76Hz),8.07(1H,s),8.40(1H,d,J=8.49Hz),8.90(1H,dd,J=4.11,1.64Hz);$C_{25}H_{28}F_2N_6O_2$的ESIMS实验值m/z 483.2(M+1)。

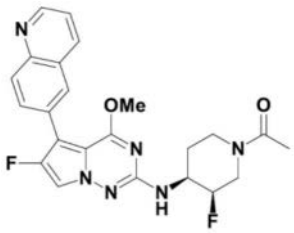
[2115] 

1059

[2116] 6-氟-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1059。

[2117] 白色固体(14mg,0.030mmol,21.2%产率)。^{1}H NMR(500MHz,DMSO-d_6)δppm 1.67-1.77(1H,m),1.92(1H,qd,J=12.21,3.43Hz),1.98-2.06(1H,m),2.15(1H,dd,J=36.80,12.62Hz),2.76(1H,br d,J=10.15Hz),2.99(1H,br t,J=10.02Hz),3.49(1H,quin,J=6.31Hz),3.71-3.88(1H,m),3.93(3H,s),4.40(1H,t,J=6.17Hz),4.46(1H,t,J=6.17Hz),4.54(2H,td,J=6.52,2.88Hz),4.92(1H,d,J=49.45Hz),6.81(1H,d,J=7.96Hz),7.55(1H,dd,J=8.23,4.12Hz),7.84(1H,d,J=3.02Hz),7.89(1H,dd,J=8.64,1.51Hz),8.04

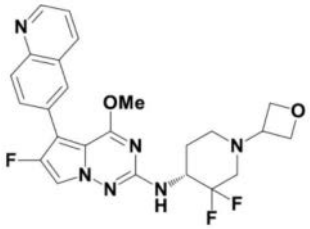
(1H,d,J＝8.78Hz),8.07(1H,s),8.36-8.43(1H,m),8.90(1H,dd,J＝4.12,1.65Hz);$C_{24}H_{24}F_2N_6O_2$的ESIMS实验值m/z 467.2(M+1)。

[2118] 

1061

[2119] 1-((3R,4S)-3-氟-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮1061。

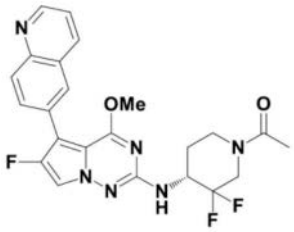
[2120] 棕褐色固体(7mg,0.016mmol,63.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.67-1.74(1H,m),1.74-1.91(1H,m),2.00(3H,s),2.66-2.97(1H,m),3.86-4.17(3H,m),3.93(3H,s),4.41-4.76(1H,m),4.98(1H,d,J＝49.35Hz),6.90(1H,dd,J＝7.80,3.15Hz),7.55(1H,dd,J＝8.35,4.24Hz),7.83(1H,d,J＝3.01Hz),7.90(1H,dd,J＝8.62,1.51Hz),8.04(1H,d,J＝8.76Hz),8.08(1H,s),8.40(1H,dd,J＝8.35,1.23Hz),8.90(1H,dd,J＝4.24,1.78Hz);$C_{23}H_{22}F_2N_6O_2$的ESIMS实验值m/z453.2(M+1)。

[2121] 

1062

[2122] (R)-N-(3,3-二氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1062。

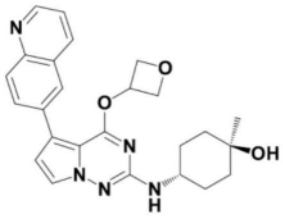
[2123] 黄色固体(1.6mg,0.003mmol,14.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.75-1.96(2H,m),2.13-2.24(1H,m),2.74-2.83(1H,m),2.98-3.10(1H,m),3.62(1H,br d,J＝6.02Hz),3.95(3H,s),3.96(1H,s),4.20-4.37(1H,m),4.45(2H,dt,J＝14.99,6.19Hz),4.56(2H,td,J＝6.57,3.83Hz),7.02(1H,d,J＝9.31Hz),7.58(1H,dd,J＝8.21,4.11Hz),7.82-7.88(1H,m),7.92(1H,br d,J＝8.76Hz),8.05(1H,d,J＝8.49Hz),8.10(1H,s),8.44(1H,d,J＝7.94Hz),8.93(1H,br s);$C_{24}H_{23}F_3N_6O_2$的ESIMS实验值m/z 485.2(M+1)。

[2124] 

1064

[2125] (R)-1-(3,3-二氟-4-((6-氟-4-甲氧基-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮1064。

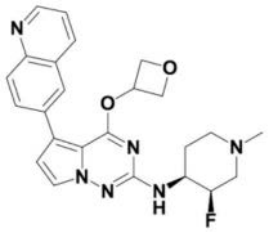
[2126] 灰白色固体(7.7mg,0.016mmol,70.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.55-1.83(1H,m),1.85-2.00(1H,m),2.03-2.10(3H,m),2.92-3.04(1H,m),3.61-3.91(1H,m),3.95(3H,s),4.12-4.31(1H,m),4.44-4.60(2H,m),7.10(1H,dd,J=9.31,1.92Hz),7.51-7.60(1H,m),7.85(1H,t,J=2.33Hz),7.90(1H,dd,J=8.76,1.64Hz),8.04(1H,d,J=8.76Hz),8.08(1H,s),8.40(1H,dd,J=8.49,1.09Hz),8.90(1H,dd,J=4.11,1.64Hz);$C_{23}H_{21}F_3N_6O_2$的ESIMS实验值m/z 471.2(M+1)。

[2127] 

1089

[2128] (1r,4r)-1-甲基-4-((4-(氧杂环丁烷-3-基氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)环己-1-醇1089。

[2129] 白色固体(20mg,0.045mmol,27.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.37-1.48(4H,m),1.55-1.65(2H,m),1.81-1.90(2H,m),3.55-3.67(1H,m),4.25(1H,s),4.56(2H,dd,J=7.80,5.34Hz),4.86(2H,t,J=7.12Hz),5.66-5.74(1H,m),6.44(1H,d,J=7.67Hz),6.82(1H,d,J=2.46Hz),7.51-7.57(1H,m),7.69(1H,d,J=2.46Hz),7.98-8.05(1H,m),8.06-8.12(1H,m),8.21(1H,d,J=1.92Hz),8.36(1H,dd,J=8.35,1.23Hz),8.87(1H,dd,J=4.11,1.64Hz);$C_{25}H_{27}N_5O_3$的ESIMS实验值m/z 446.2(M+1)。

[2130] 

1090

[2131] N-((3R,4S)-3-氟-1-甲基哌啶-4-基)-4-(氧杂环丁烷-3-基氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1090。

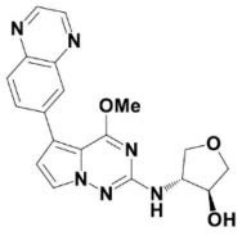
[2132] 灰白色固体(19mg,0.042mmol,21.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.63-1.75(1H,m),1.90(1H,qd,J=12.23,3.56Hz),2.06(1H,br t,J=11.36Hz),2.18(1H,dd,J=37.85,12.87Hz),2.19(3H,s),2.80(1H,br d,J=12.05Hz),3.00-3.10(1H,m),3.64-3.82(1H,m),4.57(2H,dd,J=7.53,5.34Hz),4.87(1H,d,J=49.60Hz),4.85-4.89(2H,m),5.71(1H,quin,J=5.75Hz),6.64(1H,d,J=7.94Hz),6.85(1H,d,J=2.46Hz),7.54(1H,dd,J=8.35,4.24Hz),7.69(1H,d,J=2.46Hz),8.01-8.04(1H,m),8.07-8.11(1H,m),8.22(1H,d,J=1.92Hz),8.36(1H,dd,J=8.35,1.23Hz),8.87(1H,dd,J=4.24,1.78Hz);$C_{24}H_{25}FN_6O_2$的ESIMS实验值m/z 449.2(M+1)。

[2133] 

1091

[2134] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-(氧杂环丁烷-3-基氧基)-5-(喹啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1091。

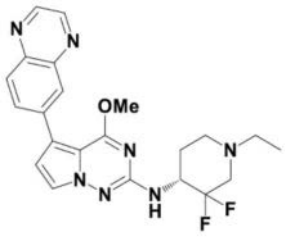
[2135] 棕褐色固体(14mg,0.030mmol,15.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.72-1.90(2H,m),2.12-2.23(1H,m),2.26(3H,s),2.39(1H,dd,J=26.90,12.05Hz),2.79(1H,brd,J=11.50Hz),2.99-3.11(1H,m),4.09-4.27(1H,m),4.57(2H,ddd,J=12.73,7.26,5.48Hz),4.88(2H,q,J=7.12Hz),5.73(1H,quin,J=5.75Hz),6.84(1H,br d,J=9.31Hz),6.87(1H,d,J=2.46Hz),7.54(1H,dd,J=8.21,4.11Hz),7.70(1H,d,J=2.74Hz),7.99-8.06(1H,m),8.07-8.14(1H,m),8.23(1H,d,J=2.19Hz),8.37(1H,dd,J=8.35,1.23Hz),8.87(1H,dd,J=4.11,1.64Hz);$C_{24}H_{24}F_2N_6O_2$的ESIMS实验值m/z 467.2(M+1)。

[2136] 

1093

[2137] (3S,4R)-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)四氢呋喃-3-醇1093。

[2138] 黄色固体(30mg,0.079mmol,33.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 3.55(1H,dd,J=9.31,1.92Hz),3.66-3.72(1H,m),3.92(1H,dd,J=9.31,4.65Hz),3.99(3H,s),4.01-4.06(2H,m),4.27(1H,dt,J=3.76,2.09Hz),5.19(1H,d,J=3.83Hz),6.89(1H,d,J=2.74Hz),6.96(1H,d,J=5.48Hz),7.71(1H,d,J=2.46Hz),8.05-8.09(1H,m),8.09-8.13(1H,m),8.24(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.92Hz);$C_{19}H_{18}N_6O_3$的ESIMS实验值m/z 379.2(M+1)。

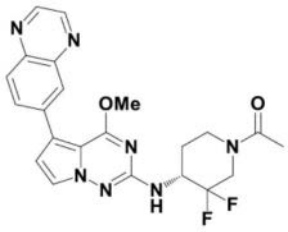
[2139] 

1095

[2140] (R)-N-(1-乙基-3,3-二氟哌啶-4-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1095。

[2141] 蓬松黄色固体(8mg,0.017mmol,49.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.02

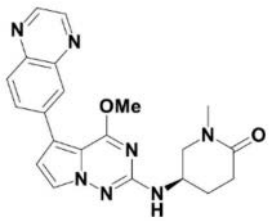
(3H,br s),1.79(1H,br d,J＝10.95Hz),1.87(1H,br s),2.12-2.25(1H,m),2.37-2.49(3H,m),2.88(1H,br d,J＝9.58Hz),3.12(1H,br dd,J＝4.38,1.64Hz),4.01(3H,s),4.20-4.36(1H,m),6.85-6.96(2H,m),7.69(1H,br d,J＝2.19Hz),8.05-8.09(1H,m),8.10-8.14(1H,m),8.25(1H,d,J＝1.92Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.92Hz);$C_{22}H_{23}F_2N_7O$的ESIMS实验值m/z 440.2(M+1)。

[2142] 

1096

[2143] (R)-1-(3,3-二氟-4-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)乙-1-酮1096。

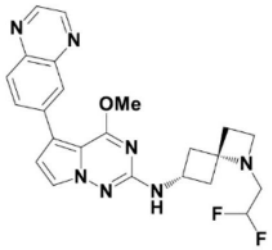
[2144] 蓬松黄色固体(4mg,0.009mmol,60.5％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.57-1.85(1H,m),1.86-2.02(1H,m),2.03-2.11(3H,m),3.33-3.43(1H,m),3.65-3.94(1H,m),3.98-4.05(3H,m),4.10-4.64(3H,m),6.92(1H,d,J＝2.74Hz),7.05(1H,d,J＝9.31Hz),7.69(1H,dd,J＝2.46,1.37Hz),8.05-8.09(1H,m),8.10-8.14(1H,m),8.25(1H,d,J＝1.92Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.64Hz);$C_{22}H_{21}F_2N_7O_2$的ESIMS实验值m/z 454.2(M+1)。

[2145] 

1097

[2146] (R)-5-((4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基哌啶-2-酮1097。

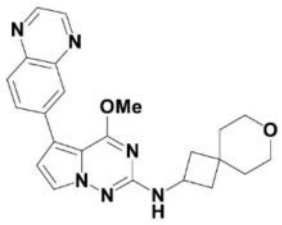
[2147] 黄色固体(26mg,0.064mmol,33.5％产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.88-1.96(1H,m),1.97-2.05(1H,m),2.27-2.36(1H,m),2.37-2.45(1H,m),2.81(3H,s),3.26(1H,dd,J＝12.05,7.67Hz),3.58(1H,dd,J＝11.64,4.79Hz),3.99(3H,s),4.06-4.17(1H,m),6.90(1H,d,J＝2.74Hz),6.98(1H,d,J＝7.39Hz),7.71(1H,d,J＝2.74Hz),8.06-8.09(1H,m),8.10-8.13(1H,m),8.24(1H,d,J＝1.64Hz),8.90(1H,d,J＝1.92Hz),8.94(1H,d,J＝1.64Hz);$C_{21}H_{21}N_7O_2$的ESIMS实验值m/z 404.2(M+1)。

[2148] 

1099

[2149] N-((4s,6r)-1-(2,2-二氟乙基)-1-氮杂螺[3.3]庚烷-6-基)-4-甲氧基-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1099。

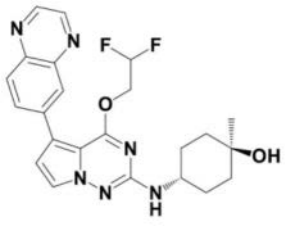
[2150] 黄色固体(1mg,0.024mmol,31.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.11-2.22(4H,m),2.41(2H,ddd,J=9.31,6.98,2.87Hz),2.83(2H,td,J=16.08,4.24Hz),3.17(2H,t,J=6.71Hz),3.87-3.96(1H,m),3.97(3H,s),6.00(1H,tt,J=56.25,4.40Hz),6.88(1H,d,J=2.74Hz),6.92(1H,d,J=7.94Hz),7.68(1H,d,J=2.74Hz),8.05-8.08(1H,m),8.09-8.12(1H,m),8.23(1H,d,J=1.64Hz),8.89(1H,d,J=1.92Hz),8.93(1H,d,J=1.92Hz);$C_{23}H_{23}F_2N_7O$的ESIMS实验值m/z 452.2(M+1)。

[2151] 

1100

[2152] 4-甲氧基-5-(喹喔啉-6-基)-N-(7-氧杂螺[3.5]壬烷-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1100。

[2153] 黄色固体(18mg,0.043mmol,44.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.48-1.54(2H,m),1.56-1.63(2H,m),1.76-1.85(2H,m),2.24-2.34(2H,m),3.42-3.48(2H,m),3.51-3.59(2H,m),3.97(3H,s),4.19(1H,sxt,J=7.83Hz),6.87(1H,d,J=2.74Hz),7.04(1H,d,J=7.12Hz),7.68(1H,d,J=2.74Hz),8.05-8.08(1H,m),8.08-8.13(1H,m),8.23(1H,d,J=1.92Hz),8.89(1H,d,J=1.64Hz),8.93(1H,d,J=1.92Hz);$C_{23}H_{24}N_6O_2$的ESIMS实验值m/z 417.2(M+1)。

[2154] 

1130

[2155] (1r,4r)-4-((4-(2,2-二氟乙氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇1130。

[2156] 白色固体(10.45mg,0.023mmol)。^{1}H NMR(400MHz,DMSO-d_6)δppm 0.47(3H,s),

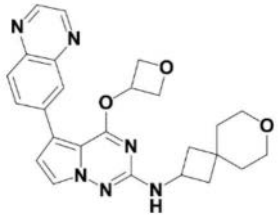
0.62-0.85(4H,m),0.87-1.01(2H,m),1.18-1.31(2H,m),2.88-3.02(1H,m),3.86(2H,td,J=13.88,3.88Hz),5.35(1H,tt,J=55.00,3.84Hz),5.99(1H,d,J=2.63Hz),6.76(1H,d,J=2.63Hz),7.19-7.26(1H,m),7.28-7.36(1H,m),7.42(1H,d,J=1.75Hz),8.01(1H,d,J=1.88Hz),8.05(1H,d,J=1.88Hz);$C_{23}H_{24}F_2N_6O_2$的ESIMS实验值m/z 455.1(M+1)。

[2157] 

1136

[2158] (R)-N-(3,3-二氟-1-甲基哌啶-4-基)-4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1136。

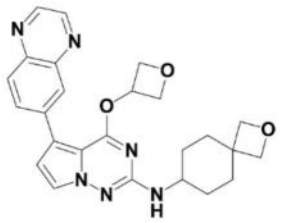
[2159] 棕褐色固体(16mg,0.034mmol,15.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.73-1.90(2H,m),2.13-2.24(1H,m),2.26(3H,s),2.39(1H,dd,J=27.45,11.25Hz),2.79(1H,br d,J=11.50Hz),3.00-3.12(1H,m),4.13-4.29(1H,m),4.62(2H,ddd,J=16.22,7.60,5.48Hz),4.88(2H,q,J=6.94Hz),5.70-5.80(1H,m),6.89(1H,br d,J=9.31Hz),6.97(1H,d,J=2.46Hz),7.73(1H,d,J=2.74Hz),8.11(1H,d,J=8.76Hz),8.21(1H,dd,J=8.76,1.92Hz),8.40(1H,d,J=1.92Hz),8.91(1H,d,J=1.92Hz),8.95(1H,d,J=1.92Hz);$C_{23}H_{23}F_2N_7O_2$的ESIMS实验值m/z 468.2(M+1)。

[2160] 

1137

[2161] 4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)-N-(7-氧杂螺[3.5]壬烷-2-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1137。

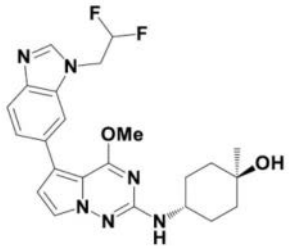
[2162] 米色固体(20mg,0.044mmol,40.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.45-1.55(2H,m),1.56-1.63(2H,m),1.72-1.84(2H,m),2.22-2.33(2H,m),3.42-3.49(2H,m),3.50-3.59(2H,m),4.16(1H,sxt,J=7.88Hz),4.61(2H,dd,J=7.67,5.20Hz),4.87(2H,t,J=7.12Hz),5.71(1H,quin,J=5.68Hz),6.94(1H,d,J=2.74Hz),6.98(1H,d,J=7.39Hz),7.71(1H,d,J=2.74Hz),8.10(1H,d,J=8.76Hz),8.19(1H,dd,J=8.76,1.92Hz),8.39(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.95(1H,d,J=1.92Hz);$C_{25}H_{26}N_6O_3$的ESIMS实验值m/z 459.25(M+1)。

[2163] 

1138

[2164] 4-(氧杂环丁烷-3-基氧基)-5-(喹喔啉-6-基)-N-(2-氧杂螺[3.5]壬烷-7-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1138。

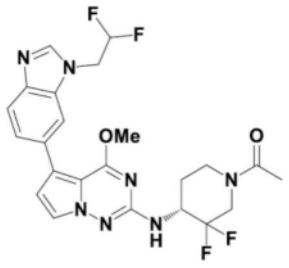
[2165] 黄色固体(14mg,0.031mmol,28.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.18-1.31(2H,m),1.53(2H,td,J=12.87,3.29Hz),1.86(2H,br dd,J=13.28,3.15Hz),2.07(2H,br d,J=13.14Hz),3.47-3.59(1H,m),4.24(2H,s),4.32(2H,s),4.62(2H,dd,J=7.67,5.48Hz),4.85(2H,t,J=7.12Hz),5.70(1H,quin,J=5.75Hz),6.50(1H,d,J=7.94Hz),6.93(1H,d,J=2.74Hz),7.70(1H,d,J=2.74Hz),8.10(1H,d,J=8.76Hz),8.19(1H,dd,J=8.76,1.92Hz),8.39(1H,d,J=1.92Hz),8.90(1H,d,J=1.92Hz),8.94(1H,d,J=1.92Hz);$C_{25}H_{26}N_6O_3$的ESIMS实验值m/z 459.25(M+1)。

[2166] 

1139

[2167] (1r,4r)-4-((5-(1-(2,2-二氟乙基)-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-1-甲基环己-1-醇1139。

[2168] 蓬松白色固体(11mg,0.024mmol,49.9%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.15(3H,s),1.37-1.53(4H,m),1.56-1.66(2H,m),1.82-1.93(2H,m),3.64(1H,br dd,J=8.21,3.56Hz),3.92(3H,s),4.23(1H,s),4.81(2H,td,J=15.95,2.87Hz),6.47(1H,tt,J=54.30,3.00Hz),6.39(1H,d,J=7.94Hz),6.61(1H,d,J=2.46Hz),7.42(1H,dd,J=8.35,1.51Hz),7.60(1H,d,J=2.46Hz),7.63(1H,d,J=8.49Hz),7.80(1H,s),8.20(1H,s);$C_{23}H_{26}F_2N_6O_2$的ESIMS实验值m/z 457.2(M+1)。

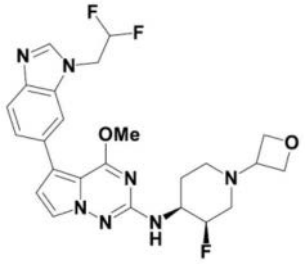
[2169] 

1140

[2170] (R)-1-(4-((5-(1-(2,2-二氟乙基)-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,

1-f][1,2,4]三嗪-2-基)氨基)-3,3-二氟哌啶-1-基)乙-1-酮1140。

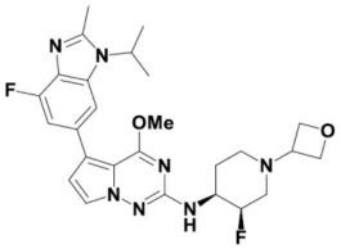
[2171] 蓬松白色固体(5mg,0.010mmol,32.4%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.57-1.83(1H,m),1.85-2.00(1H,m),2.03-2.09(3H,m),2.93-3.06(1H,m),3.61-3.92(2H,m),3.96(3H,s),4.09-4.31(1H,m),4.45-4.62(2H,m),4.81(2H,td,J=16.15,3.01Hz),6.48(1H,tt,J=54.30,3.00Hz),6.67(1H,d,J=2.46Hz),6.91(1H,d,J=9.31Hz),7.43(1H,dd,J=8.35,1.51Hz),7.61(1H,dd,J=2.46,1.37Hz),7.64(1H,d,J=8.21Hz),7.82(1H,s),8.21(1H,s);$C_{23}H_{23}F_4N_7O_2$的ESIMS实验值m/z 506.2(M+1)。

[2172] 

1141

[2173] 5-(1-(2,2-二氟乙基)-1H-苯并[d]咪唑-6-基)-N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1141。

[2174] 蓬松白色固体(13mg,0.026mmol,61.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.68-1.75(1H,m),1.91(1H,qd,J=12.14,3.56Hz),1.98-2.06(1H,m),2.16(1H,dd,J=37.55,12.32Hz),2.76(1H,br d,J=11.23Hz),2.95-3.05(1H,m),3.49(1H,quin,J=6.30Hz),3.71-3.89(1H,m),3.94(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.81(2H,td,J=15.95,2.87Hz),4.94(1H,d,J=50.50Hz),6.47(1H,tt,J=54.85,3.30Hz),6.60(1H,d,J=7.94Hz),6.65(1H,d,J=2.74Hz),7.42(1H,dd,J=8.49,1.64Hz),7.60(1H,d,J=2.46Hz),7.64(1H,d,J=8.49Hz),7.81(1H,s),8.21(1H,s);$C_{24}H_{26}F_3N_7O_2$的ESIMS实验值m/z 502.2(M+1)。

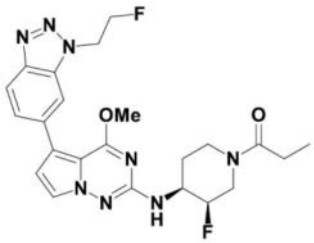
[2175] 

1142

[2176] N-((3R,4S)-3-氟-1-(氧杂环丁烷-3-基)哌啶-4-基)-5-(4-氟-1-异丙基-2-甲基-1H-苯并[d]咪唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1142。

[2177] 白色固体(14mg,0.027mmol,41.6%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.59(6H,d,J=6.84Hz),1.69-1.78(1H,m),1.85-1.97(1H,m),1.97-2.06(1H,m),2.15(1H,dd,J=36.75,12.59Hz),2.58(3H,s),2.76(1H,br d,J=11.22Hz),2.94-3.04(1H,m),3.49(1H,quin,J=6.43Hz),3.73-3.91(1H,m),3.96(3H,s),4.40(1H,t,J=6.16Hz),4.46(1H,t,J=6.16Hz),4.54(2H,td,J=6.57,3.01Hz),4.76(1H,spt,J=6.94Hz),4.93(1H,d,J=49.65Hz),6.62(1H,d,J=7.94Hz),6.69(1H,d,J=2.46Hz),7.12(1H,dd,J=12.05,

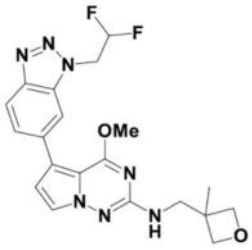
1.10Hz),7.59(1H,d,J＝2.74Hz),7.64(1H,d,J＝1.09Hz);$C_{26}H_{31}F_2N_7O_2$的ESIMS实验值m/z 512.3(M+1)。

[2178] 

1143

[2179] 1-((3R,4S)-3-氟-4-((5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)哌啶-1-基)丙-1-酮1143。

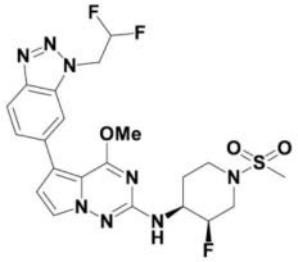
[2180] 蓬松白色固体(8.8mg,0.018mmol,46.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.00(3H,t,J＝7.39Hz),1.67-1.90(2H,m),2.27-2.42(2H,m),2.70-2.99(1H,m),3.13-3.22(1H,m),3.91-4.00(1H,m),3.96(3H,s),4.05-4.22(1H,m),4.44-4.77(1H,m),4.94(2H,dt,J＝47.15,4.65Hz),4.99(1H,d,J＝49.35Hz),5.08(2H,dt,J＝27.70,4.65Hz),6.76(1H,d,J＝2.46Hz),6.78(1H,d,J＝7.67Hz),7.62(1H,dd,J＝8.62,1.51Hz),7.65(1H,d,J＝2.74Hz),8.01(1H,d,J＝10.40Hz),8.01(1H,s);$C_{23}H_{26}F_2N_8O_2$的ESIMS实验值m/z 485.2(M+1)。

[2181] 

1144

[2182] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基-N-((3-甲基氧杂环丁烷-3-基)甲基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1144。

[2183] 白色固体(33mg,0.077mmol,38.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.30(3H,s),3.46(2H,d,J＝6.02Hz),3.96(3H,s),4.22(2H,d,J＝5.75Hz),4.51(2H,d,J＝5.75Hz),5.30(2H,td,J＝15.95,2.87Hz),6.60(1H,tt,J＝54.30,3.00Hz),6.73(1H,d,J＝2.74Hz),6.95(1H,t,J＝6.16Hz),7.63-7.66(1H,m),7.64(1H,d,J＝2.46Hz),8.01-8.05(2H,m);$C_{20}H_{21}F_2N_7O_2$的ESIMS实验值m/z 430.2(M+1)。

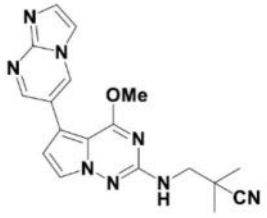
[2184] 

1145

[2185] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3R,4S)-3-氟-1-(甲

基磺酰基)哌啶-4-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1145。

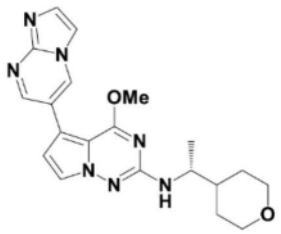
[2186] 蓬松白色固体(6mg,0.011mmol,33.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.77-1.88(1H,m),1.96(1H,qd,J=12.50,4.38Hz),2.93(3H,s),3.02(1H,td,J=12.25,2.60Hz),3.20(1H,dd,J=37.55,12.59Hz),3.61-3.70(1H,m),3.80-3.89(1H,m),3.90-4.04(1H,m),3.96(3H,s),5.05(1H,d,J=49.10Hz),5.30(2H,td,J=15.95,2.87Hz),6.61(1H,tt,J=54.30,3.00Hz),6.76(1H,d,J=2.74Hz),6.88(1H,d,J=7.94Hz),7.63(1H,d,J=2.46Hz),7.64-7.66(1H,m),8.02-8.05(2H,m);$C_{21}H_{23}F_3N_8O_3S$的ESIMS实验值m/z 525.15(M+1)。

[2187] 

1146

[2188] 3-((5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-基)氨基)-2,2-二甲基丙腈1146。

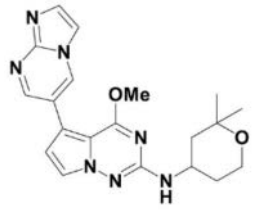
[2189] 米色固体(20mg,0.055mmol,27.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.36(6H,s),3.49(2H,d,J=6.57Hz),4.02(3H,s),6.81(1H,d,J=2.74Hz),7.17(1H,t,J=6.57Hz),7.69(1H,d,J=2.46Hz),7.73(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.10(1H,d,J=2.46Hz);$C_{18}H_{18}N_8O$的ESIMS实验值m/z 363.3(M+1)。

[2190] 

1147

[2191] (R)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基-N-(1-(四氢-2H-吡喃-4-基)乙基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1147。

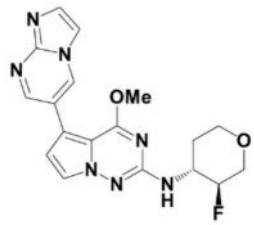
[2192] 米色固体(14mg,0.036mmol,17.8%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.13(3H,d,J=6.57Hz),1.20-1.33(3H,m),1.58-1.65(1H,m),1.66-1.73(2H,m),3.18-3.30(2H,m),3.69(1H,br dd,J=14.92,7.26Hz),3.83-3.92(2H,m),3.98(3H,s),6.61(1H,d,J=9.03Hz),6.76(1H,d,J=2.46Hz),7.64(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.08(1H,d,J=2.46Hz);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[2193] 

1148

[2194] N-(2,2-二甲基四氢-2H-吡喃-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1148。

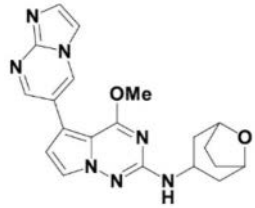
[2195] 灰白色固体(20mg,0.051mmol,25.5%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.16(3H,s),1.22(3H,s),1.32(1H,t,J=12.32Hz),1.35-1.43(1H,m),1.81-1.86(1H,m),1.87-1.92(1H,m),3.59-3.71(2H,m),3.91-4.02(1H,m),3.98(3H,s),6.64(1H,d,J=8.21Hz),6.77(1H,d,J=2.46Hz),7.66(1H,d,J=2.46Hz),7.72(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.73(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{20}H_{23}N_7O_2$的ESIMS实验值m/z 394.2(M+1)。

[2196] 

1149

[2197] N-((3S,4R)-3-氟四氢-2H-吡喃-4-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1149。

[2198] 灰白色固体(14mg,0.037mmol,18.3%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.55-1.68(1H,m),2.03-2.13(1H,m),3.39-3.44(1H,m),3.44-3.51(1H,m),3.80-3.88(1H,m),3.98-4.02(1H,m),4.00(3H,s),4.05-4.10(1H,m),4.58(1H,dtd,J=48.55,8.21,8.21,4.38Hz),6.80(1H,d,J=2.74Hz),7.03(1H,d,J=8.21Hz),7.69(1H,d,J=2.46Hz),7.73(1H,d,J=1.37Hz),7.93(1H,d,J=1.37Hz),8.74(1H,d,J=2.46Hz),9.09(1H,d,J=2.46Hz);$C_{18}H_{18}FN_7O_2$的ESIMS实验值m/z 384.2(M+1)。

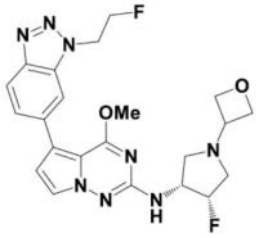
[2199] 

1150

[2200] N-(8-氧杂双环[3.2.1]辛烷-3-基)-5-(咪唑并[1,2-a]嘧啶-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1150。

[2201] 灰白色固体(7mg,0.018mmol,9.0%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 1.76-1.82(2H,m),1.87-1.92(2H,m),2.00-2.07(2H,m),2.11-2.18(2H,m),3.78-3.87(1H,m),4.00(3H,s),4.27(2H,br s),6.62(1H,d,J=4.11Hz),6.78(1H,d,J=2.46Hz),7.67(1H,d,

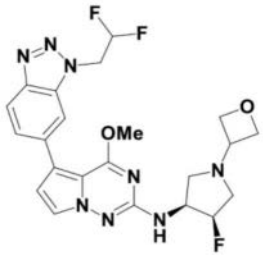
J＝2.74Hz),7.72(1H,d,J＝1.37Hz),7.93(1H,d,J＝1.64Hz),8.74(1H,d,J＝2.46Hz),9.09(1H,d,J＝2.46Hz);$C_{20}H_{21}N_7O_2$的ESIMS实验值m/z 392.15(M+1)。

[2202] 

1151

[2203] N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-5-(1-(2-氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1151。

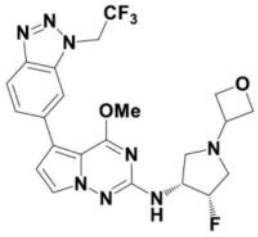
[2204] 蓬松白色固体(6mg,0.013mmol,18.2%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.68(1H,t,J＝9.03Hz),2.77(1H,ddd,J＝29.90,12.05,1.10Hz),3.02(1H,t,J＝8.35Hz),3.18(1H,ddd,J＝33.20,12.05,4.38Hz),3.79(1H,quin,J＝6.16Hz),3.96(3H,s),4.22-4.38(1H,m),4.47(2H,t,J＝6.02Hz),4.60(2H,t,J＝6.57Hz),4.94(2H,dt,J＝47.15,4.65Hz),5.08(2H,dt,J＝28.00,4.65Hz),5.25(1H,dtd,J＝55.95,4.65,4.65,1.40Hz),6.77(1H,d,J＝2.74Hz),6.82(1H,d,J＝7.67Hz),7.61-7.64(1H,m),7.66(1H,d,J＝2.46Hz),8.00-8.03(2H,m);$C_{22}H_{24}F_2N_8O_2$的ESIMS实验值m/z 471.2(M+1)。

[2205] 

1152

[2206] 5-(1-(2,2-二氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)-N-((3S,4R)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基吡咯并[2,1-f][1,2,4]三嗪-2-胺1152。

[2207] 蓬松白色固体(15mg,0.031mmol,43.7%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.69(1H,t,J＝9.03Hz),2.77(1H,ddd,J＝29.90,12.05,1.37Hz),3.02(1H,t,J＝8.35Hz),3.18(1H,ddd,J＝33.20,12.05,4.38Hz),3.74-3.84(1H,m),3.96(3H,s),4.24-4.38(1H,m),4.47(2H,t,J＝6.02Hz),4.55-4.64(2H,m),5.25(1H,dtd,J＝55.95,4.65,4.65,1.40Hz),5.31(2H,td,J＝15.81,2.87Hz),6.61(1H,tt,J＝54.30,3.00Hz),6.77(1H,d,J＝2.46Hz),6.84(1H,d,J＝7.67Hz),7.63-7.66(1H,m),7.67(1H,d,J＝2.74Hz),8.04(1H,d,J＝7.94Hz),8.04(1H,d,J＝1.10Hz);$C_{22}H_{23}F_3N_8O_2$的ESIMS实验值m/z 489.2(M+1)。

[2208] 

1153

[2209] N-((3R,4S)-4-氟-1-(氧杂环丁烷-3-基)吡咯烷-3-基)-4-甲氧基-5-(1-(2,2,2-三氟乙基)-1H-苯并[d][1,2,3]三唑-6-基)吡咯并[2,1-f][1,2,4]三嗪-2-胺1153。

[2210] 蓬松白色固体(10mg,0.020mmol,28.1%产率)。^{1}H NMR(499MHz,DMSO-d_6)δppm 2.69(1H,t,J=9.03Hz),2.77(1H,ddd,J=29.90,12.05,1.37Hz),3.02(1H,t,J=8.35Hz),3.18(1H,ddd,J=32.90,11.91,4.52Hz),3.74-3.84(1H,m),3.95(3H,s),4.23-4.39(1H,m),4.47(2H,t,J=6.02Hz),4.60(2H,t,J=6.57Hz),5.25(1H,dtd,J=55.95,4.65,4.65,1.40Hz),5.88(2H,q,J=9.13Hz),6.77(1H,d,J=2.46Hz),6.86(1H,d,J=7.67Hz),7.68(1H,dd,J=8.62,1.51Hz),7.68(1H,d,J=2.74Hz),8.08(1H,d,J=8.49Hz),8.11(1H,s);$C_{22}H_{22}F_4N_8O_2$的ESIMS实验值m/z 507.2(M+1)。

[2211] 实施例12.

[2212] 如下文所述,使用针对DYRK1A激酶活性的测定程序筛选代表性化合物。

[2213] 将各化合物溶解于DMSO中作为10mM储备液并用于制备化合物源板。进行连续稀释(1:3,11点剂量反应曲线,从10μM至0.00016μM)并且使用ECHO 550(Labcyte,Sunnyvale,CA)将化合物转移至1536孔黑壁圆底板(Corning)中。

[2214] DYRK1A激酶测定是使用Ser/Thr 18肽Z-lyte测定试剂盒根据制造商说明书(Life Technologies-Thermo-Fisher的分公司)进行。这是一种非放射性测定,使用香豆素与荧光素之间的荧光共振能量转移(FRET)以检测激酶活性,其表示为香豆素发射/荧光素发射的比率。

[2215] 简而言之,重组DYRK1A激酶、ATP和Ser/Thr肽18在1X激酶缓冲液中分别制备成0.25μg/mL、15μM和4μM的最终浓度。使混合物与代表性化合物一起在室温下温育一小时。所有反应都一式两份进行。未磷酸化(“0%对照”)和磷酸化(“100%对照”)形式的Ser/Thr 18充当对照反应。另外,操作星形孢菌素的11点剂量反应曲线(1uM最高)以充当阳性化合物对照。

[2216] 温育后,将显影试剂A在显影缓冲液中稀释,然后添加至反应物中并使其在室温下进一步温育一小时。在Ex400Em 455处读取板以检测香豆素信号,并且在Ex400Em 520处读取以测量所述信号(EnVision多标签板读取器,PerkinElmer)。

[2217] 发射比率(Em)计算为香豆素(C)发射信号(在445nm处)/荧光素(F)发射信号(在520nm处)的比率。然后使用下式计算磷酸化百分比:[1-((Em比率X F100%)-C100%)/((C0%-C100%)+(Em比率X(F100%-F0%)))]。生成剂量反应曲线,并且使用在Dotmatics’Studies软件(Bishops Stortford,UK)中拟合的非线性回归曲线计算抑制浓度(IC_{50})值。

[2218] 表2显示如本文所描述的代表性式I化合物的所测量活性。

[2219] 表2.

[2220]

化合物	EC_{50} (μM)	化合物	EC_{50} (μM)	化合物	EC_{50} (μM)	化合物	EC_{50} (μM)
1	0.0224	**209**	0.0088	**386**	0.0009	**762**	0.0013
3	0.0015	**210**	0.0015	**387**	0.0007	**764**	0.0004
4	0.0011	**211**	0.0066	**388**	0.0012	**769**	0.0029
6	0.0011	**212**	0.0014	**389**	0.0013	**770**	0.0015
7	0.0046	**214**	0.0022	**390**	0.0030	**771**	0.0001
8	0.0006	**217**	0.0093	**391**	0.0072	**772**	0.0020
9	9.9633	**218**	0.0029	**392**	0.0014	**773**	0.0007
10	0.0938	**222**	0.0035	**393**	0.1779	**776**	0.0005
13	0.0055	**223**	0.0016	**394**	0.0021	**777**	0.0016
15	0.0337	**224**	0.0113	**395**	0.0062	**780**	0.0019
16	0.0344	**225**	0.0117	**399**	0.0035	**785**	0.0005
17	0.0175	**226**	0.0032	**401**	0.0027	**788**	0.0007
18	0.0074	**227**	0.0036	**405**	0.0007	**791**	0.0022
19	0.0141	**228**	0.0034	**431**	0.0023	**793**	0.0013
20	0.0034	**229**	0.0019	**433**	0.0026	**798**	0.0003
24	0.0143	**230**	0.0042	**434**	0.0049	**799**	0.0017
26	0.0071	**231**	0.0072	**435**	0.0089	**801**	0.0032
27	9.9633	**233**	0.0068	**439**	0.0023	**805**	0.0016
29	0.0092	**236**	0.0005	**441**	0.0011	**806**	0.0014
30	0.0221	**239**	0.0029	**445**	0.0021	**810**	0.0109
31	0.0077	**242**	0.0044	**502**	0.0014	**811**	0.0017
34	0.0062	**243**	0.0012	**503**	0.0023	**812**	0.0028
36	0.0121	**245**	0.0007	**504**	0.0014	**816**	0.0028
37	0.0025	**250**	0.0006	**505**	0.0038	**818**	0.0008
39	0.0029	**252**	0.0025	**506**	0.0023	**821**	0.0019
40	0.0016	**254**	0.0018	**507**	0.0031	**822**	0.0018
43	0.0013	**257**	0.0004	**508**	0.0243	**856**	0.0019
44	0.0032	**258**	0.0008	**509**	0.0014	**904**	0.0018
45	0.0093	**261**	0.1532	**513**	0.0028	**905**	0.0004
49	0.0026	**262**	0.0032	**519**	0.0027	**910**	0.0077
51	0.0067	**263**	0.1117	**520**	0.0030	**911**	0.0021
52	0.0052	**264**	0.0035	**521**	0.0026	**912**	0.0008
53	0.0007	**265**	0.0589	**525**	0.0024	**916**	0.0014
54	0.0012	**266**	0.0029	**526**	0.0016	**918**	0.0007
55	0.0067	**267**	0.0048	**542**	0.0011	**921**	0.0014
56	0.0013	**268**	0.0050	**544**	0.0009	**922**	0.0009

[2221]

61	0.0049	**269**	0.0023	**549**	0.0026	**924**	0.0021
62	0.0085	**270**	0.0051	**550**	0.0016	**926**	0.0056
63	0.0046	**271**	0.0038	**551**	0.0016	**927**	0.0012
67	0.0056	**272**	0.0013	**554**	0.0077	**928**	0.0020
74	0.0052	**273**	0.0018	**555**	0.0050	**929**	0.0198
80	0.0562	**274**	0.0010	**562**	0.0011	**930**	0.0069
91	0.0016	**275**	0.0034	**563**	0.0010	**931**	0.0015
92	0.0626	**276**	0.0006	**567**	0.0037	**934**	0.0016
93	0.1944	**277**	0.0633	**575**	0.0069	**935**	0.0012
94	0.0041	**280**	0.0334	**576**	0.0073	**942**	0.0189
95	0.0082	**281**	0.0066	**577**	0.0064	**943**	0.0036
96	0.0010	**282**	0.0136	**578**	0.0080	**944**	0.0015
97	0.0011	**283**	0.1099	**582**	0.0409	**947**	0.0022
98	0.0256	**284**	0.2352	**585**	0.0022	**948**	0.0004
99	0.0045	**287**	0.0022	**589**	0.0009	**954**	0.0009
102	0.0019	**288**	0.0026	**616**	0.0029	**964**	0.0043
103	0.0059	**290**	0.0018	**621**	0.0354	**968**	0.0028
104	0.0012	**304**	0.0143	**622**	0.0141	**975**	0.0076
107	0.0009	**305**	0.0807	**623**	0.0051	**976**	0.0025
108	0.0033	**306**	0.0282	**624**	0.0086	**977**	0.0018
109	0.0010	**310**	0.0047	**625**	0.0009	**978**	0.0024
112	0.0026	**314**	0.0041	**626**	0.0027	**996**	0.0029
113	0.0033	**318**	0.0042	**627**	0.0039	**1038**	0.0005
114	0.0019	**319**	0.0022	**628**	0.0063	**1039**	0.0017
122	0.0016	**320**	0.0082	**629**	0.0024	**1040**	0.0027
124	0.0028	**321**	0.0021	**630**	0.0049	**1041**	0.0009
127	0.0022	**322**	0.0066	**631**	0.0245	**1042**	0.0012
129	0.0026	**326**	0.0073	**639**	0.0013	**1043**	0.0028
137	0.0019	**328**	0.0054	**646**	0.0034	**1044**	0.0032
138	0.0043	**329**	0.0019	**653**	0.0013	**1045**	0.0045
139	0.0069	**330**	0.0023	**658**	0.0045	**1047**	0.0021
140	0.0107	**331**	0.0012	**659**	0.0009	**1048**	0.0013
141	0.0218	**332**	0.0028	**660**	<0.0002	**1049**	0.0049
142	0.0027	**333**	0.0011	**664**	0.0016	**1050**	0.0135
143	0.0108	**334**	0.0009	**666**	0.0011	**1052**	0.0045
148	0.0018	**335**	0.0020	**669**	0.0016	**1054**	0.0020
149	0.0015	**336**	0.0013	**670**	0.0008	**1056**	0.0011
151	0.0017	**337**	0.0115	**672**	0.0059	**1057**	0.0017
159	0.0029	**338**	0.0012	**673**	0.0053	**1058**	0.0023
161	0.0030	**339**	0.0048	**681**	0.0019	**1059**	0.0019
164	0.0021	**341**	0.0093	**686**	0.0034	**1061**	0.0009
168	0.0027	**342**	0.0032	**688**	0.0023	**1062**	0.0037
169	0.0021	**343**	0.0007	**690**	0.0078	**1064**	0.0020
170	0.0086	**344**	0.0018	**691**	0.0014	**1089**	0.0045
171	0.0029	**345**	0.0037	**695**	0.0013	**1090**	0.0057
172	0.0025	**346**	0.0344	**696**	0.0013	**1091**	0.0018
173	0.0017	**347**	0.0017	**699**	0.0014	**1093**	0.0043

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174	0.0030	**348**	0.0023	**702**	0.0012	**1095**	0.0040
187	0.1003	**349**	0.0066	**710**	0.0009	**1096**	0.0030
188	0.0503	**350**	0.0014	**711**	0.0005	**1097**	0.0027
189	0.0188	**351**	0.0081	**717**	0.0023	**1099**	0.0007
190	0.0115	**352**	0.0022	**718**	0.0005	**1100**	0.0067
191	0.0053	**353**	0.0022	**719**	0.0003	**1130**	0.0008
192	0.0009	**355**	0.0027	**721**	0.0057	**1136**	0.0038
193	0.0199	**356**	0.0088	**724**	0.0011	**1137**	0.0048
194	0.0022	**362**	0.0060	**725**	0.0006	**1138**	0.0033
195	0.0039	**363**	0.0401	**726**	0.0018	**1139**	0.0005
196	0.0011	**365**	0.0028	**727**	0.0028	**1140**	0.0013
197	0.0296	**366**	0.0025	**730**	0.0046	**1141**	0.0014
198	0.0045	**367**	0.0033	**732**	0.0010	**1142**	0.0023
199	0.0057	**368**	0.0040	**734**	0.0008	**1143**	0.0018
200	0.0038	**372**	0.0041	**739**	0.0046	**1144**	0.0020
201	0.0020	**373**	0.0029	**741**	0.0012	**1145**	0.0014
202	0.0109	**374**	0.0029	**750**	0.0003	**1146**	0.0020
203	0.0075	**375**	0.0033	**754**	0.0017	**1147**	0.0027
204	0.0035	**379**	0.0033	**755**	0.0023	**1148**	0.0006
205	0.0043	**381**	0.0025	**756**	0.0014	**1149**	0.0045
206	0.0004	**382**	0.0018	**757**	0.0367	**1150**	0.0044
207	0.0013	**383**	0.0014	**758**	0.0011		
208	0.0005	**385**	0.0017	**761**	0.0017		

[2223] 实施例13.

[2224] 使用下文所述的针对tau磷酸化活性的测定程序筛选代表性化合物。

[2225] 将在补充有10％ FBS(Corning,35-011-CV)和青霉素/链霉素(Thermo Fisher Scientific,15140163)的DMEM(Thermo Fisher Scientific,10566024)中培养的HEK293T细胞(ATCC,CRL3216),以8.1x10^6个细胞/烧瓶接种于75cm^2烧瓶中。然后使用脂染胺3000(Thermo Fisher Scientific,L30000015)以5μg DYRK1A(NM_001396)人类、未加标签的克隆(OriGene,SC314641)和2.5μg MAPT(441a.a.Tau基因)(NM_005910)人类、未加标签的克隆(OriGene,TP313312)短暂转染HEK293T细胞,并且在加湿温育箱中在37℃和5％ CO^2下温育20-30小时。温育后,收集经DYRK1A和MAPT表达载体转染的HEK293T细胞并且在BioCoat聚-D赖氨酸包被的96孔板(Corning,354461)中以3x10^4个细胞/孔接种。

[2226] 使用下文所述的评估Thr212处的减少的Tau磷酸化(pThr212)的细胞测定程序筛选以上合成的化合物。

[2227] 将各化合物溶解于DMSO(Sigma-Aldrich,D8418-100 mL)中作为10mM储备液。将10mM储备液按1:3、10点剂量反应曲线连续稀释并且以20μM至1.1nM范围内的最终浓度添加至细胞中。将细胞用化合物一式两份地处理并且在加湿温育箱中在37℃和5％ CO^2下温育18-24小时。

[2228] 在过夜化合物处理后,用补充有1X Halt磷酸酶抑制剂混合液(Thermo Fisher Scientific,78427)和1X Halt蛋白酶抑制剂混合液(Thermo Fisher Scientific,78438)的1X Alpha Surefire Ultra裂解缓冲液(Perkin Elmer,ALSU-LB-100ML)裂解细胞。将裂

解物以12,000g短暂离心10min以去除任何细胞碎片,并且将5μL裂解物分配至384孔Opti板(Perkin Elmer,6007290)中以用于在phosphoTau(Thr212)AlphaLISA测定中测量Tau磷酸化。将供体抗体经生物素标记的HT7Tau(Thermo Fisher Scientific,MN1000B)和接受体抗体pThr212Tau(Thermo Fisher Scientific,44740G)二者以3nM的最终浓度添加至细胞裂解物中并在室温下温育1小时。在用供体和接受体抗体温育裂解物后,以10ug/mL最终浓度添加抗兔IgG(Fc特异性)AlphaLISA接受体珠粒(Perkin Elmer,AL104C)并在室温下避光温育1小时。最后,以40ug/mL最终浓度添加AlphaScreen链霉亲和素供体珠粒(PerkinElmer,6760002)并在室温下避光温育1小时。在EnVision多标签板读取器(Perkin Elmer)上在Ex=665nm处和在Em=615nm处读取板。使用磷酸化Tau(Thr212)AlphaLISA信号标绘,绘制曲线拟合,并且在Prism(GraphPad)中测定各化合物的EC_{50}。

[2229] 表3显示如本文所描述的代表性式I化合物的所测量活性。

[2230] 表3.

[2231]

化合物	pTau (Thr212) EC_{50} (μM)	化合物	pTau (Thr212) EC_{50} (μM)	化合物	pTau (Thr212) EC_{50} (μM)	化合物	pTau (Thr212) EC_{50} (μM)
1	0.0216	**56**	0.0357	**257**	0.0151	**318**	0.0754
3	0.1966	**192**	0.0181	**258**	0.0089	**352**	0.0394
20	0.1068	**194**	0.1071	**272**	0.0134	**392**	0.0252
44	0.0482	**200**	0.1299	**276**	0.0101	**431**	0.1288
54	0.0257	**210**	0.0197	**310**	0.1090	**943**	0.0575