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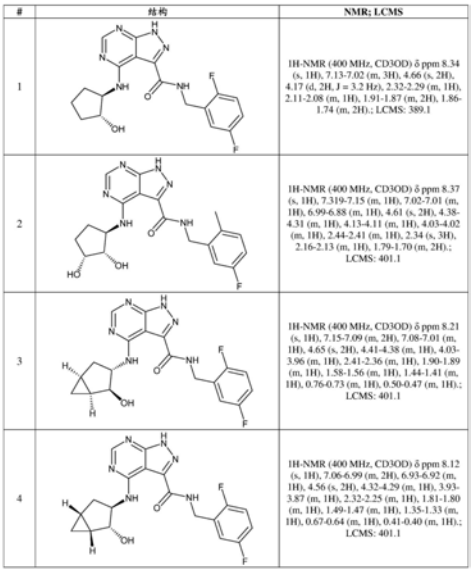
(54)发明名称

适用于治疗与NTRK相关的病症的化合物和组合物

(57)摘要

本发明涉及对野生型NTRK及其抗性突变体具有活性的NTRK抑制剂。



#	结构	NMR; LCMS
1		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.13-7.02 (m, 3H), 4.66 (s, 2H), 4.17 (d, 2H, J = 3.2 Hz), 2.32-2.29 (m, 1H), 2.11-2.08 (m, 1H), 1.91-1.87 (m, 2H), 1.86-1.74 (m, 2H).; LCMS: 389.1
2		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.319-7.15 (m, 1H), 7.02-7.01 (m, 1H), 6.99-6.88 (m, 1H), 4.61 (s, 2H), 4.38-4.31 (m, 1H), 4.13-4.11 (m, 1H), 4.03-4.02 (m, 1H), 2.44-2.41 (m, 1H), 2.34 (s, 3H), 2.16-2.13 (m, 1H), 1.79-1.70 (m, 2H).; LCMS: 401.1
3		1H-NMR (400 MHz, CD3OD) δ ppm 8.21 (s, 1H), 7.15-7.09 (m, 2H), 7.08-7.01 (m, 1H), 4.65 (s, 2H), 4.41-4.38 (m, 1H), 4.03-3.96 (m, 1H), 2.41-2.36 (m, 1H), 1.90-1.89 (m, 1H), 1.58-1.56 (m, 1H), 1.44-1.41 (m, 1H), 0.76-0.73 (m, 1H), 0.50-0.47 (m, 1H).; LCMS: 401.1
4		1H-NMR (400 MHz, CD3OD) δ ppm 8.12 (s, 1H), 7.06-6.99 (m, 2H), 6.93-6.92 (m, 1H), 4.56 (s, 2H), 4.32-4.29 (m, 1H), 3.93-3.87 (m, 1H), 2.32-2.25 (m, 1H), 1.81-1.80 (m, 1H), 1.49-1.47 (m, 1H), 1.35-1.33 (m, 1H), 0.67-0.64 (m, 1H), 0.41-0.40 (m, 1H).; LCMS: 401.1

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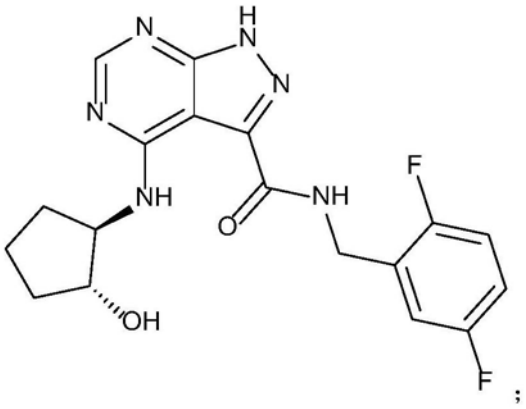
1.一种选自以下化合物中的任意其中之一的化合物,或其药学上可接受的盐:



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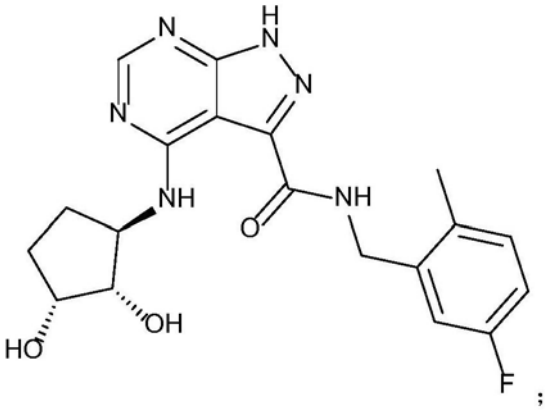

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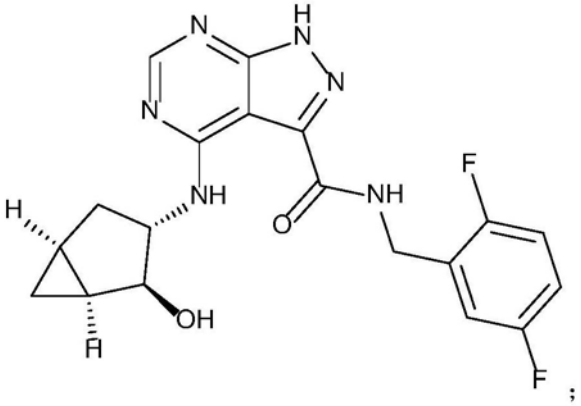

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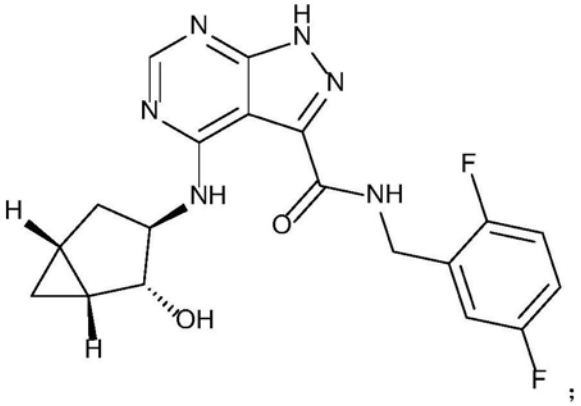

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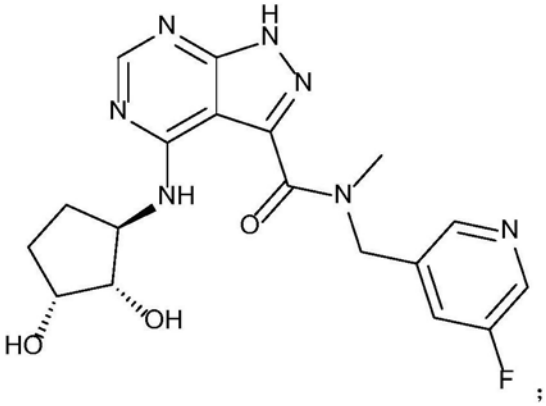

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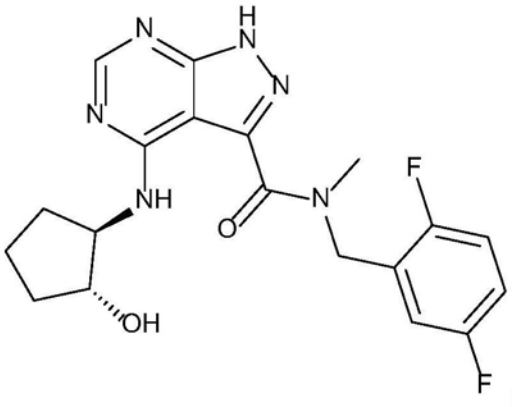

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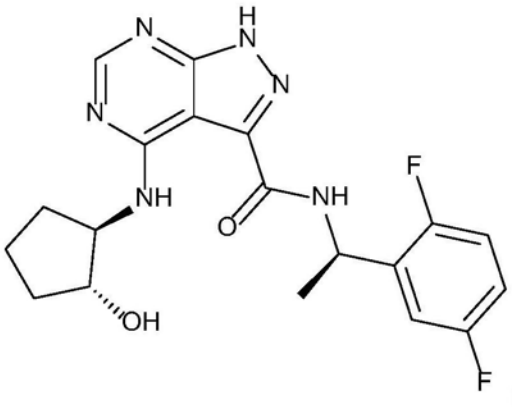

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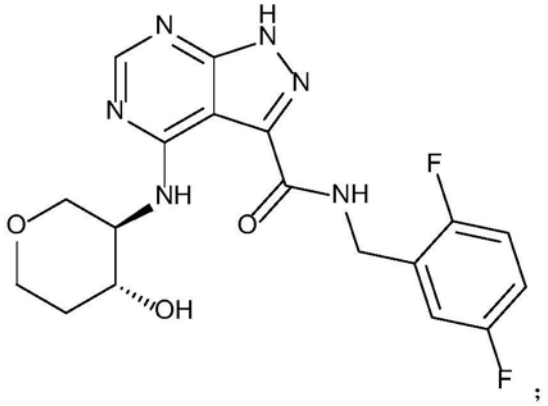
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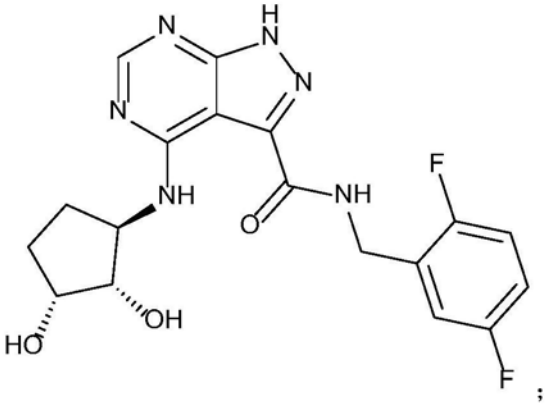
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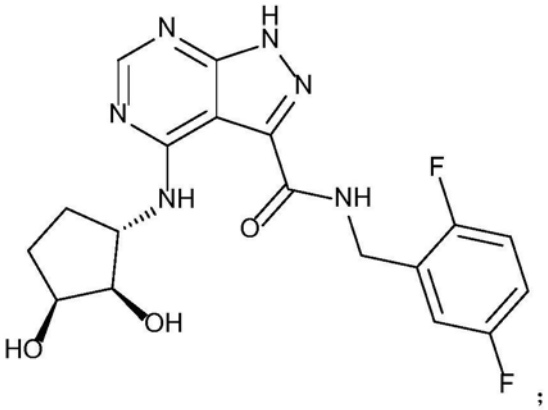
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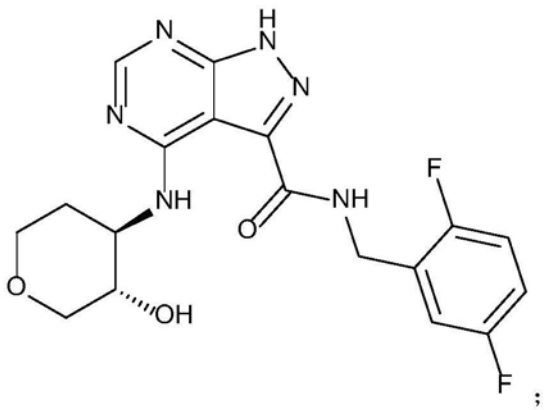
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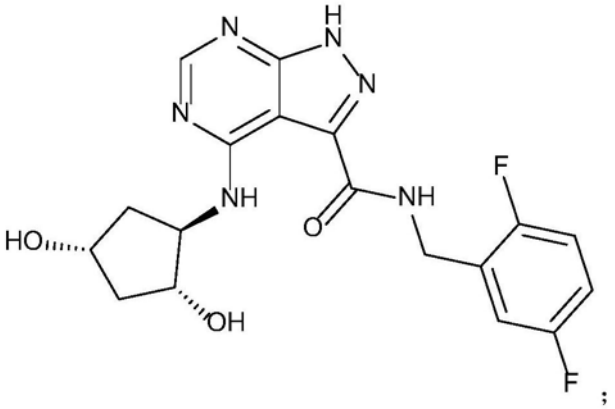

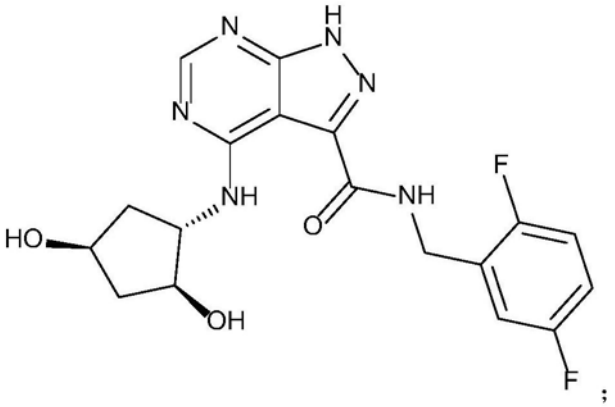

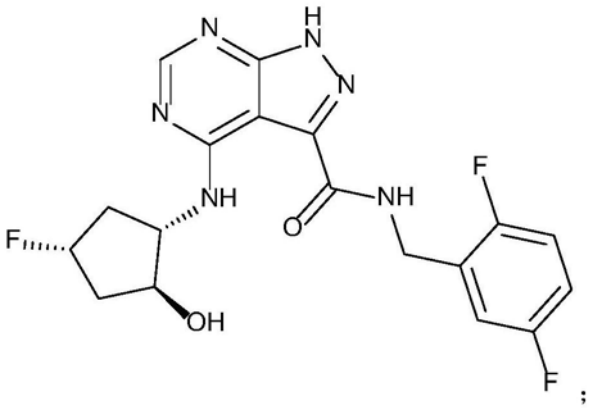

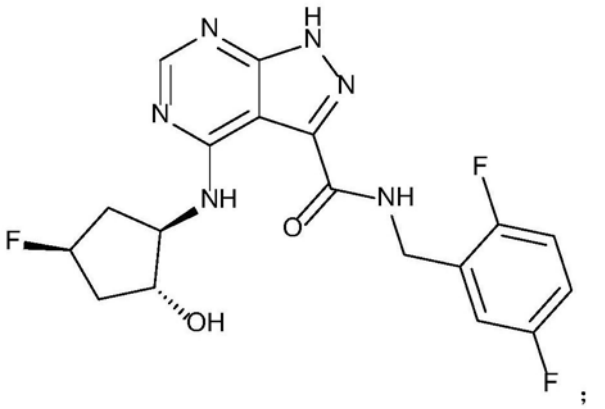

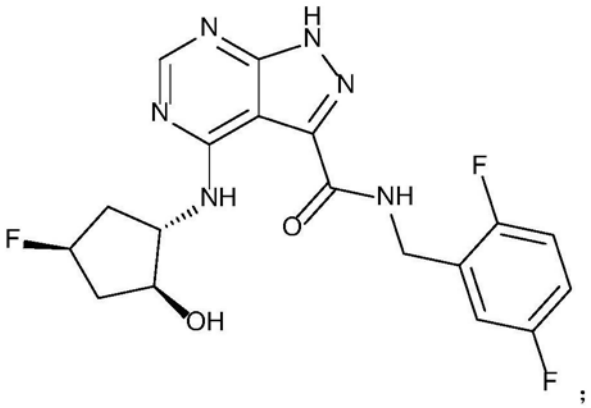

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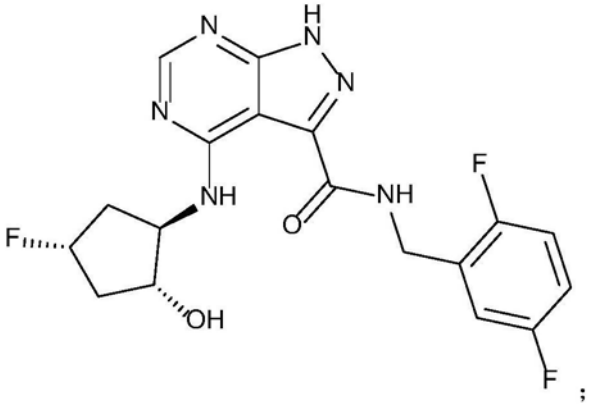

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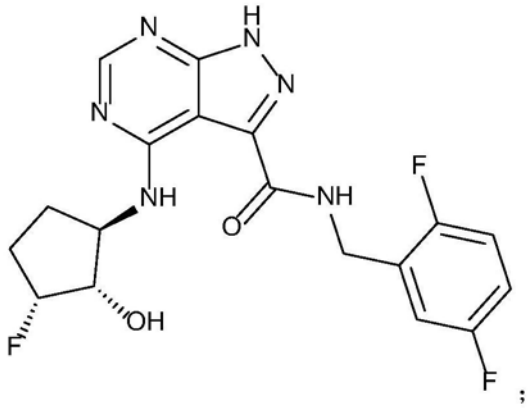

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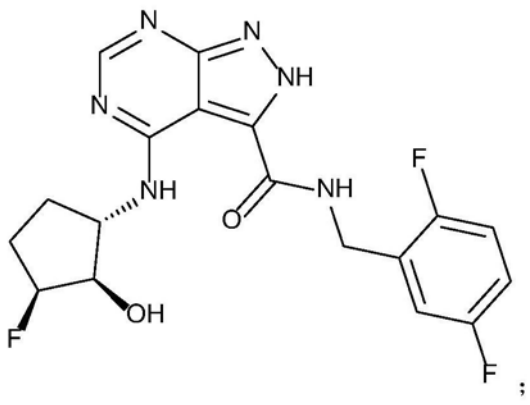

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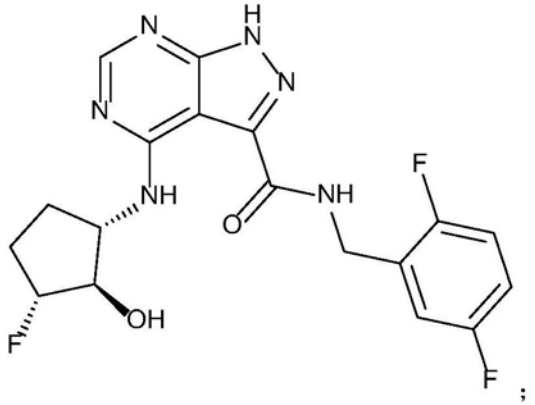
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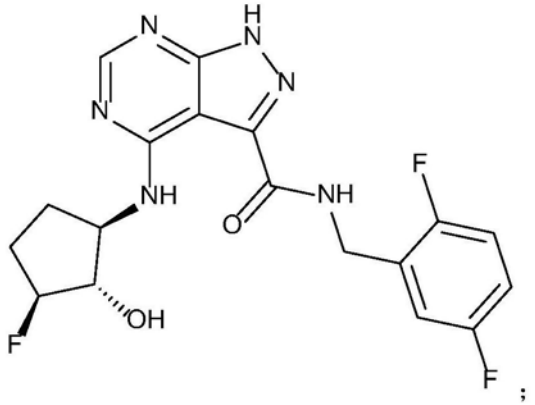
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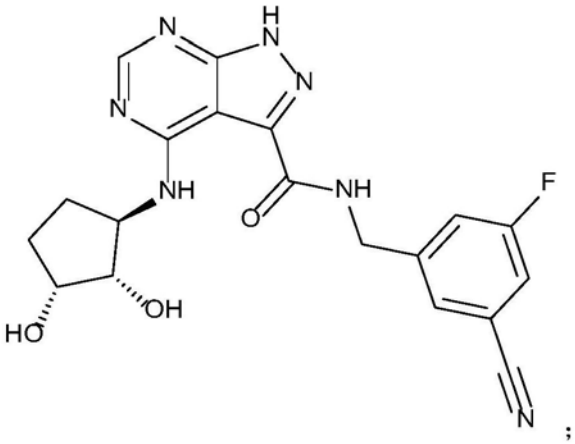
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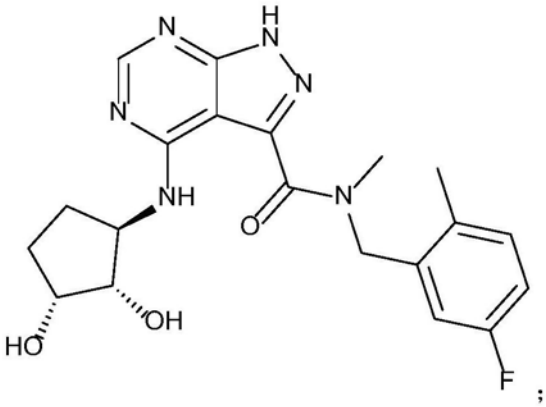
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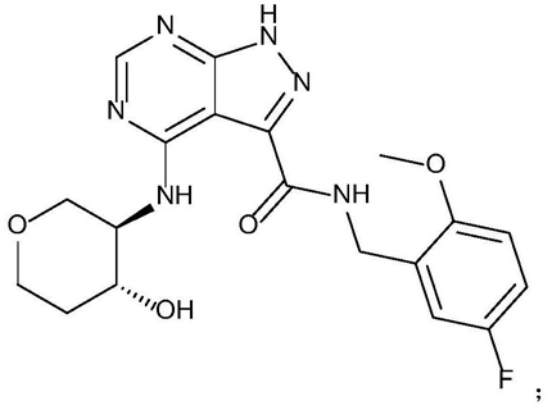

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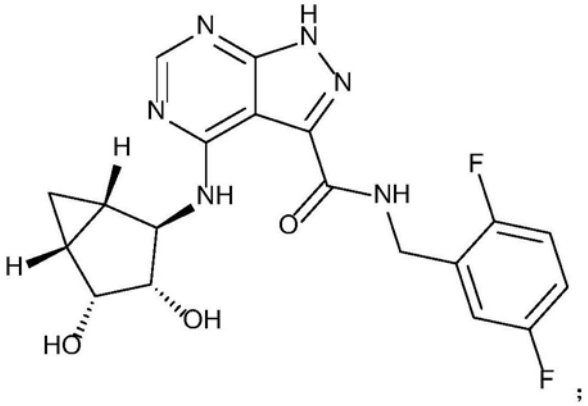

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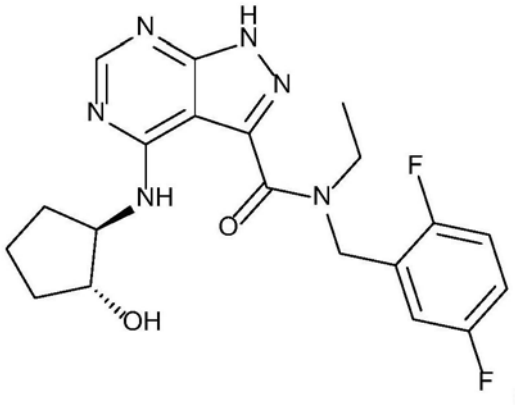

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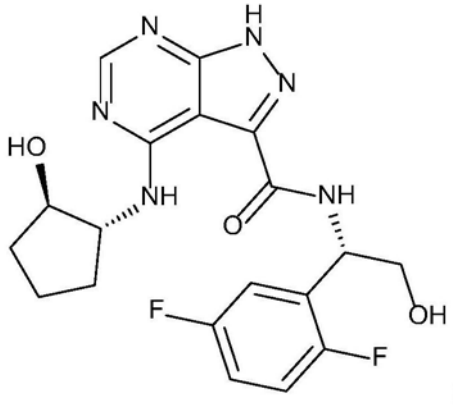

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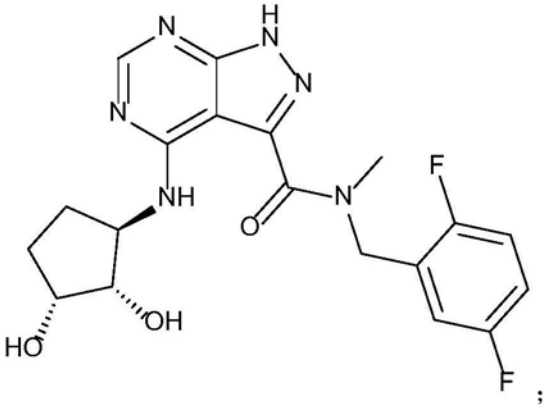

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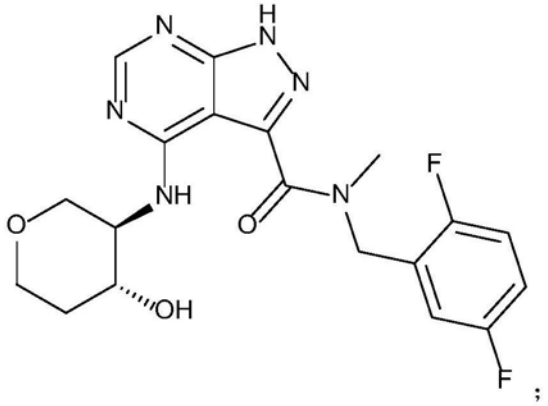

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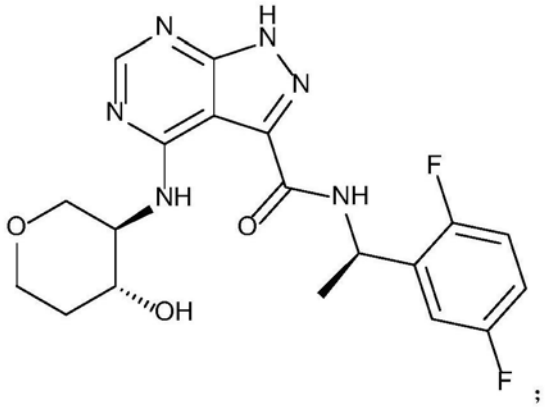

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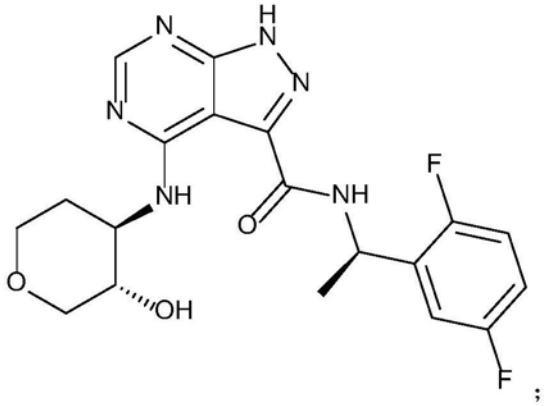

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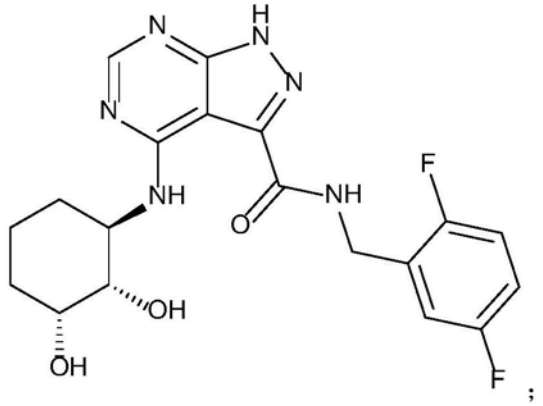

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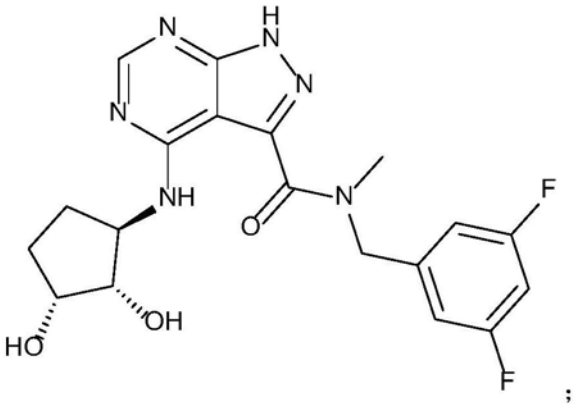

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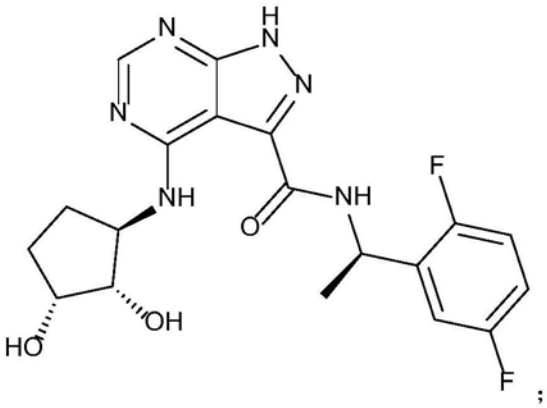

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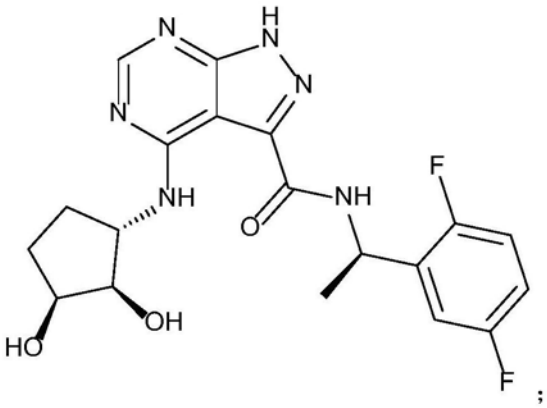

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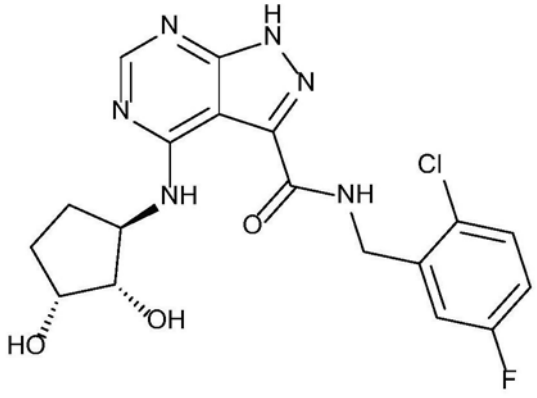
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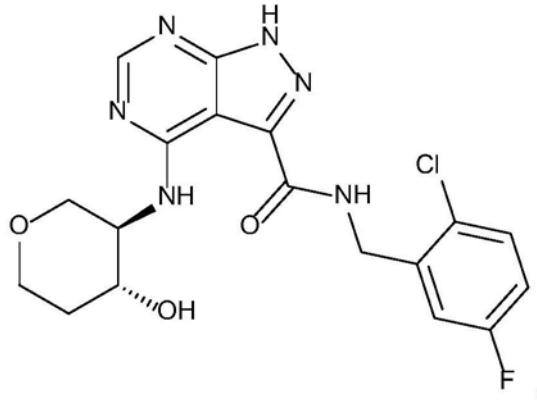
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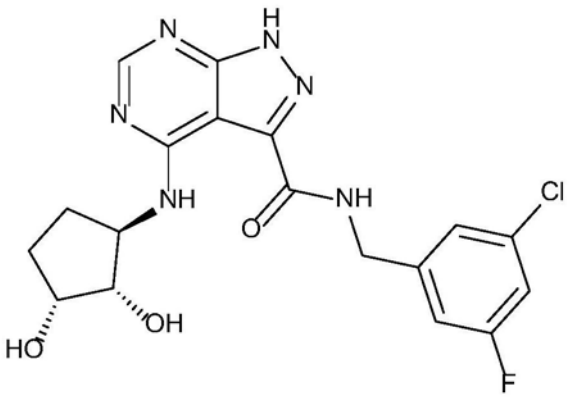
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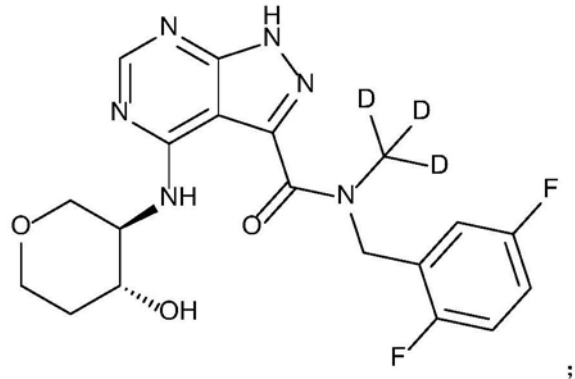
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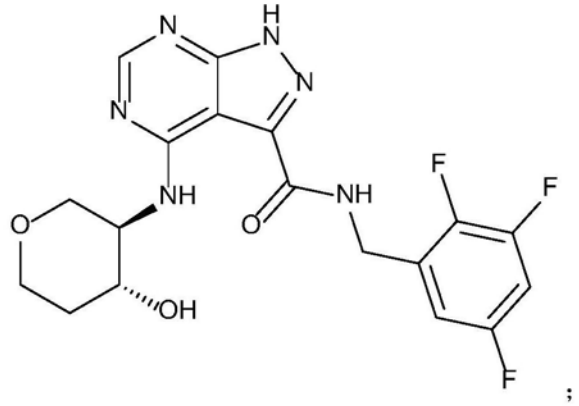
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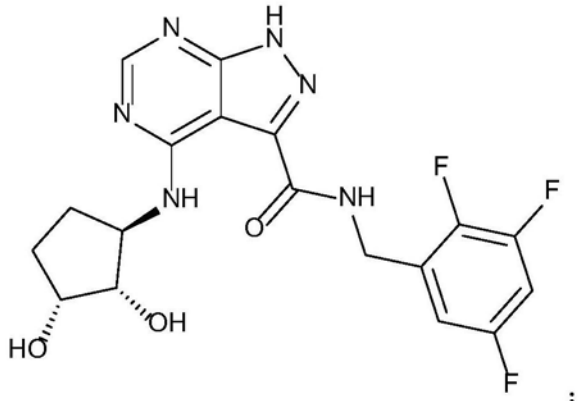
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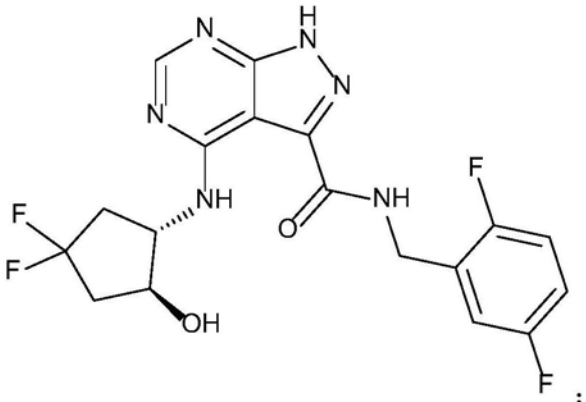
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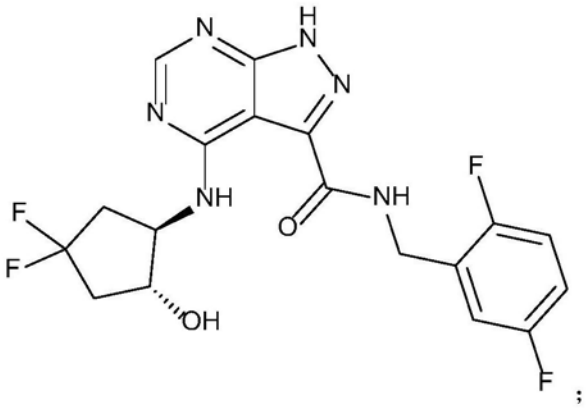
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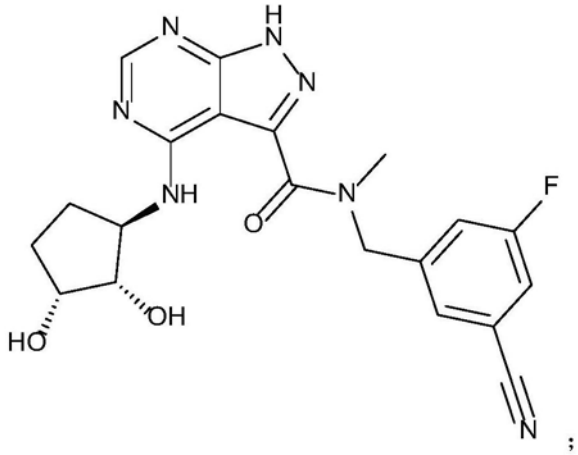
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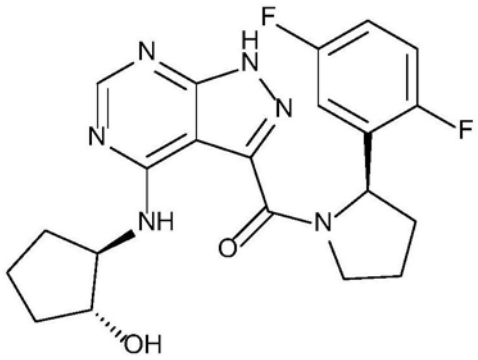
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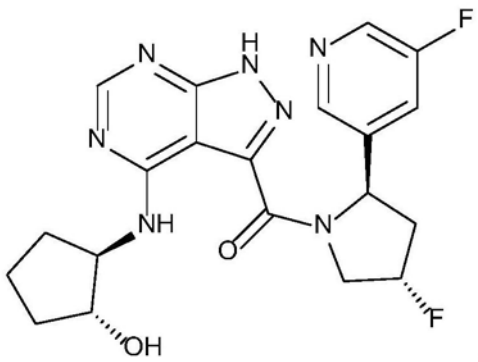
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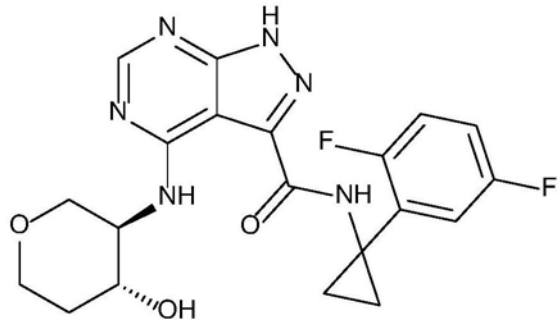
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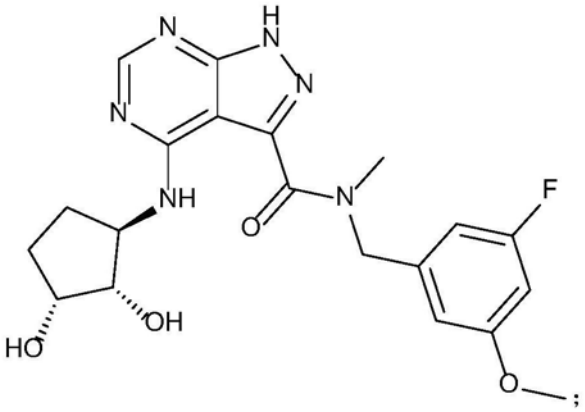

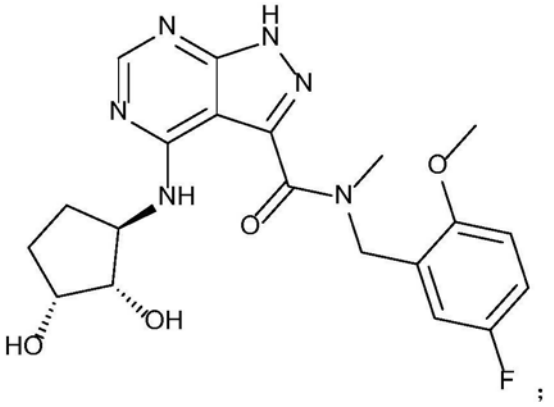

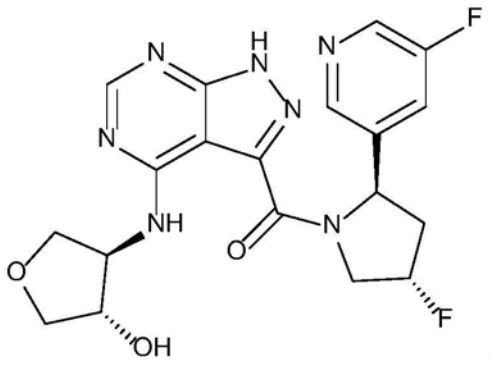

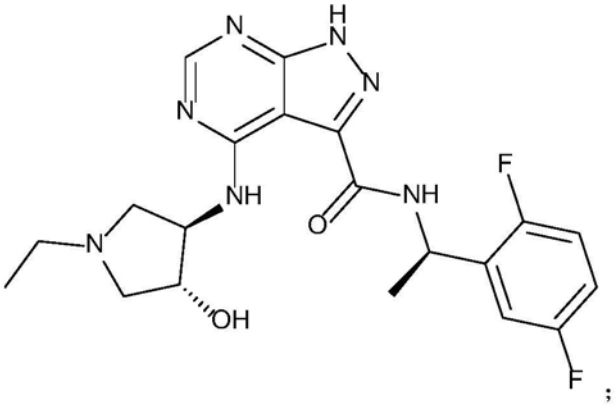

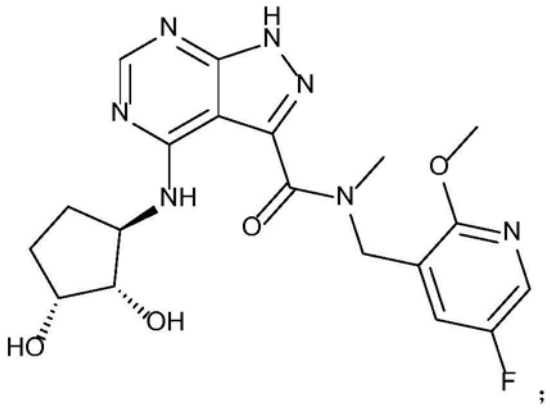

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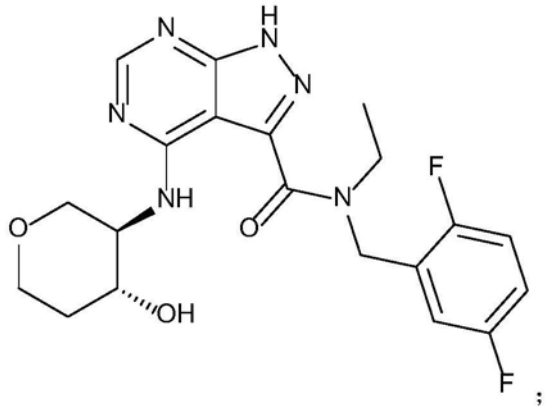

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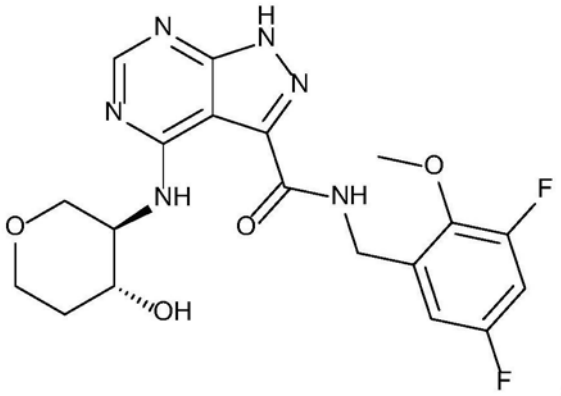

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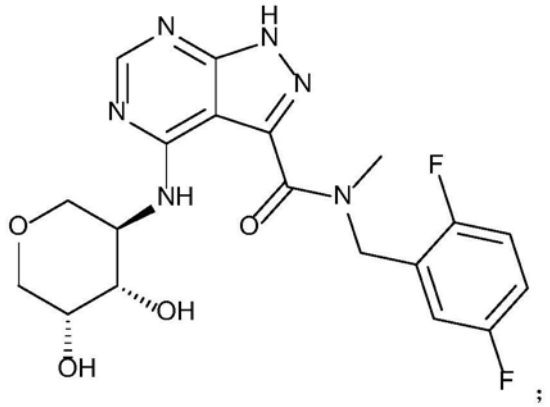

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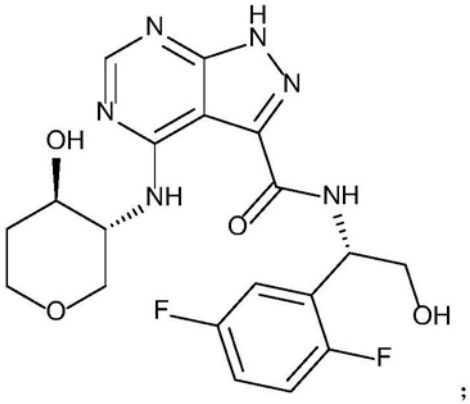

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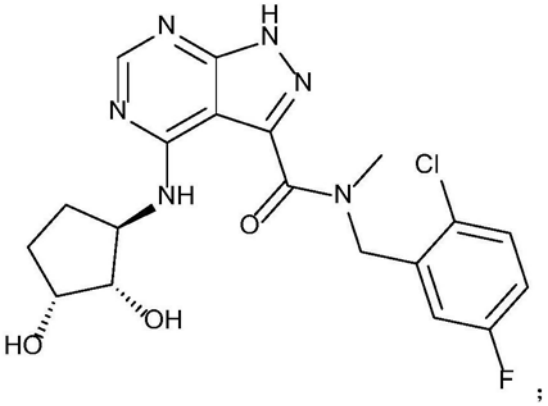

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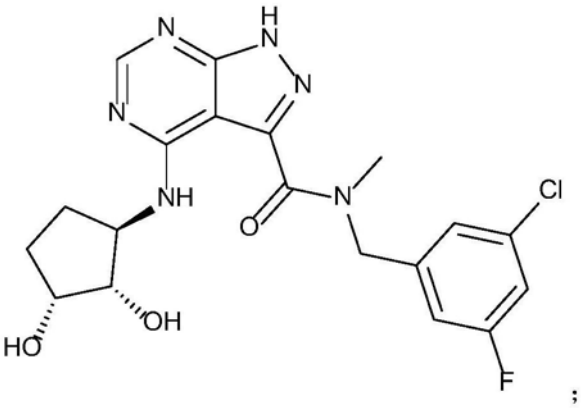

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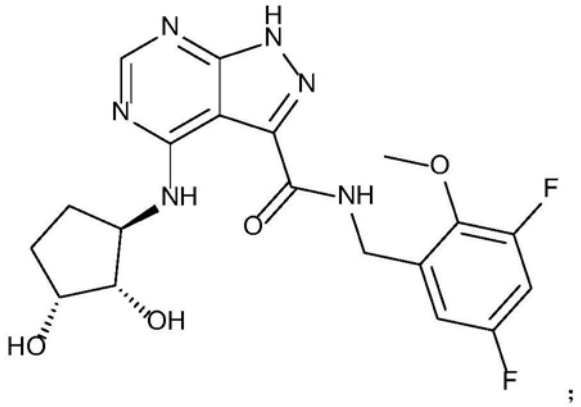

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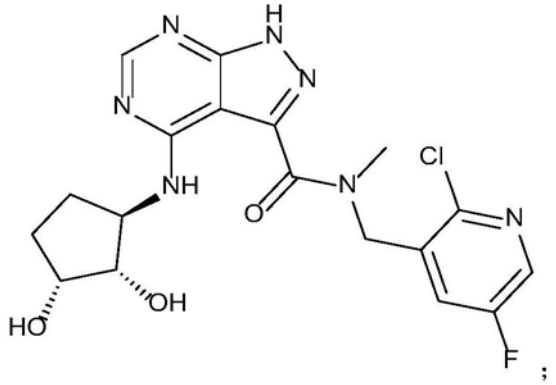
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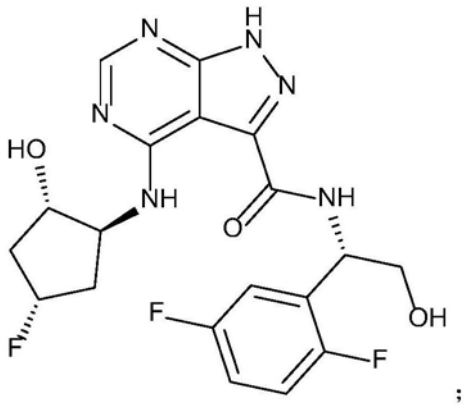
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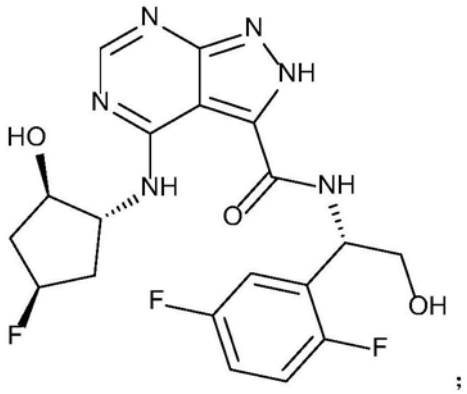
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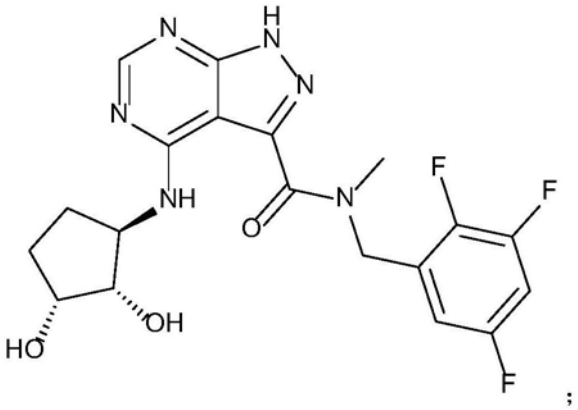
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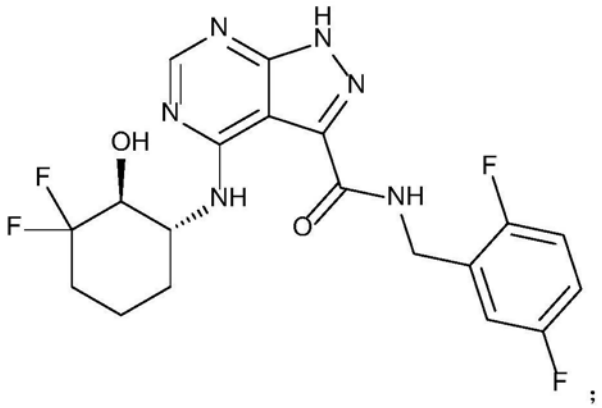
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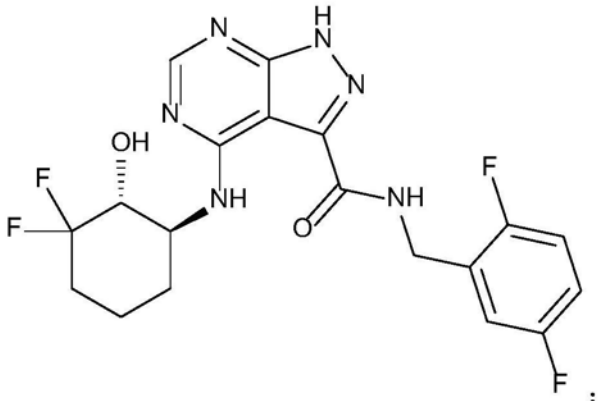
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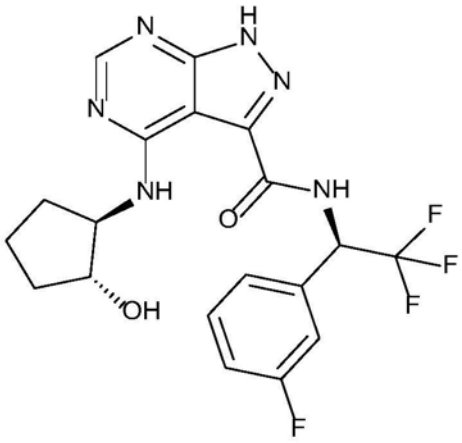
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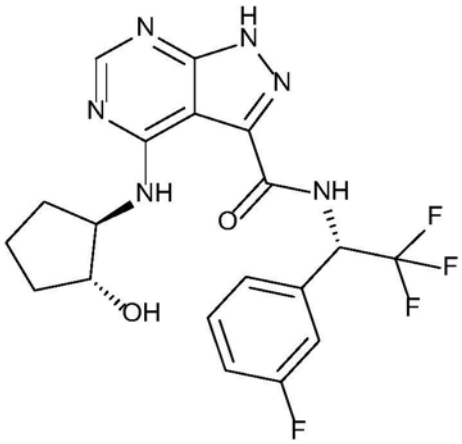
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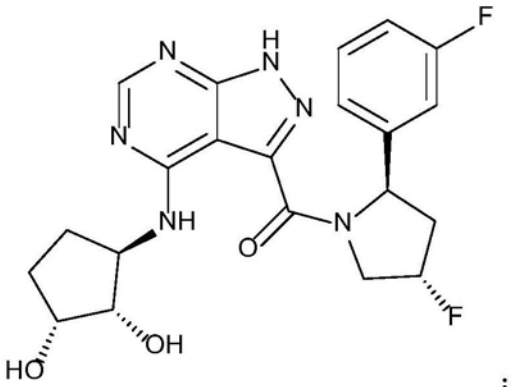

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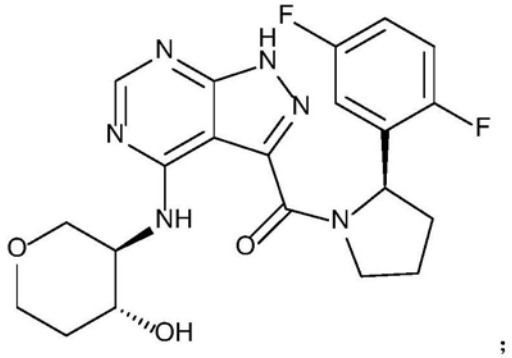

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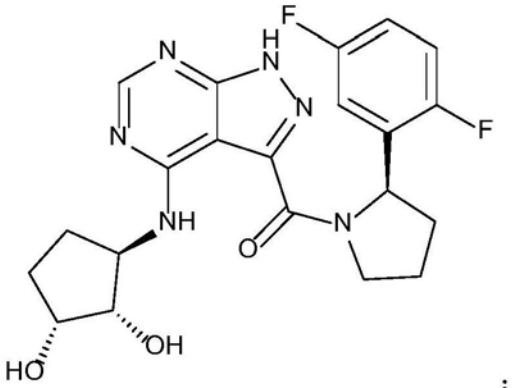

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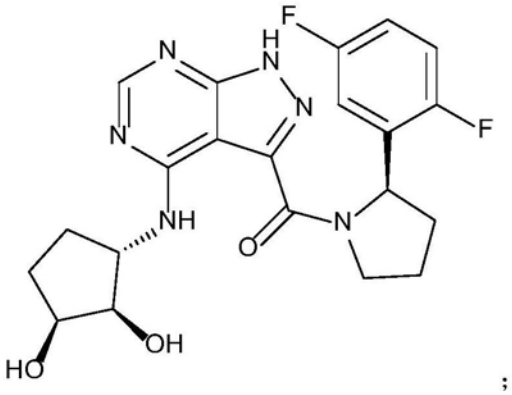

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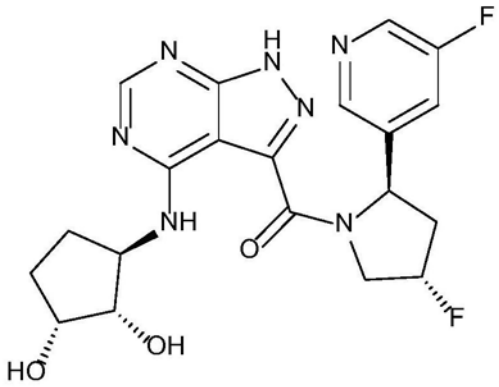

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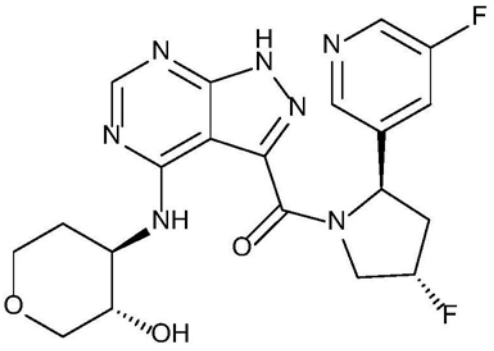

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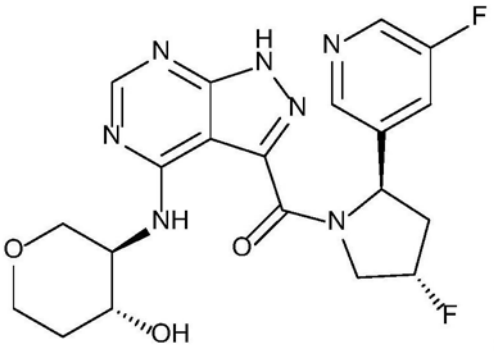

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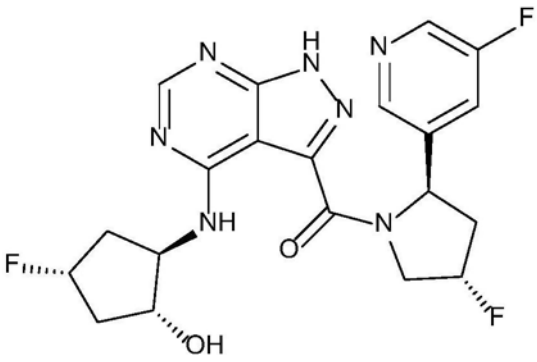

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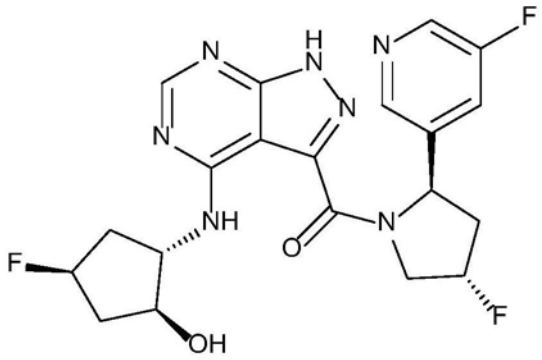

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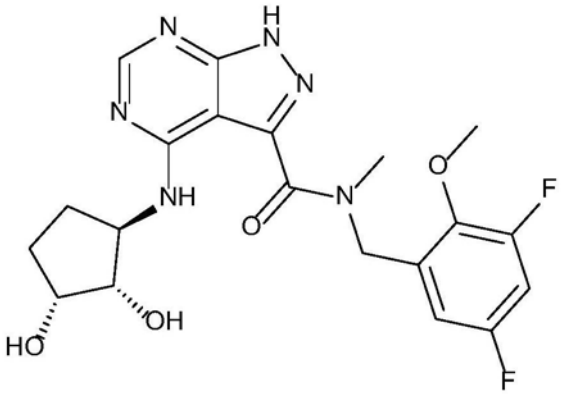

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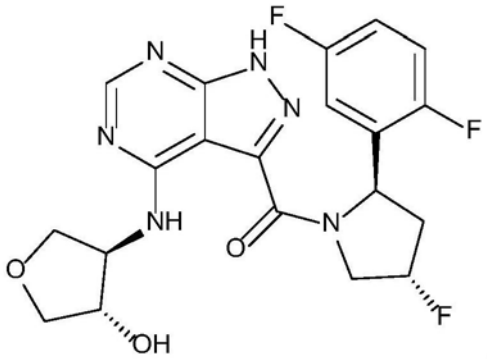

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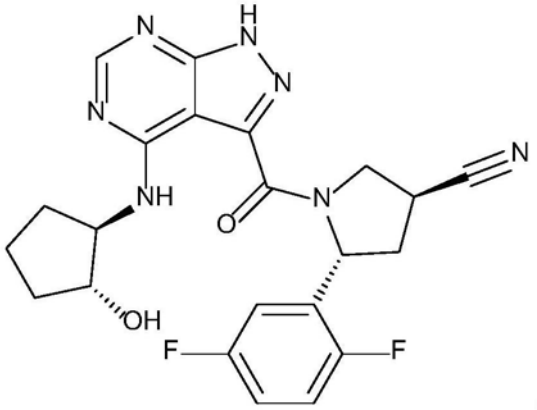

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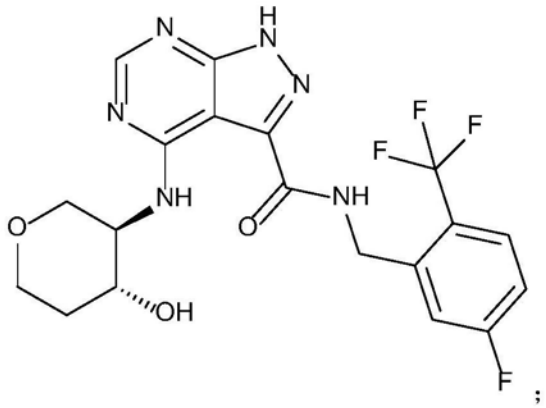
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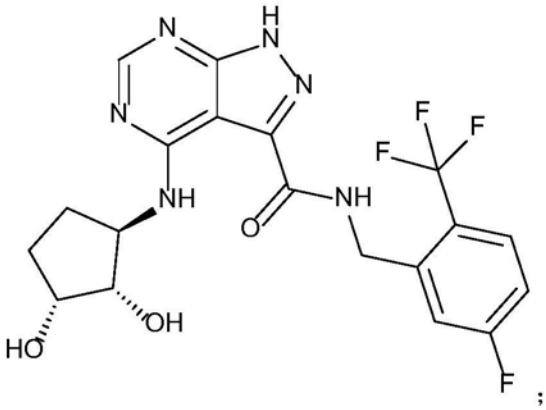
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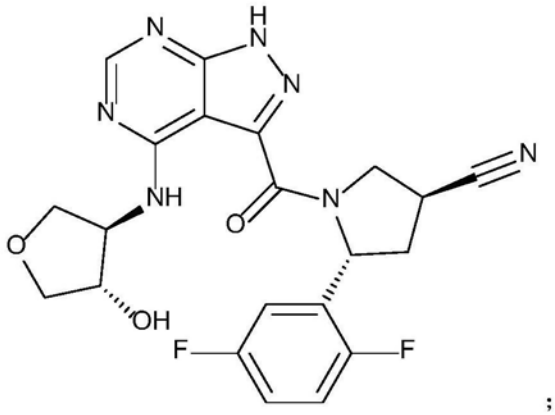
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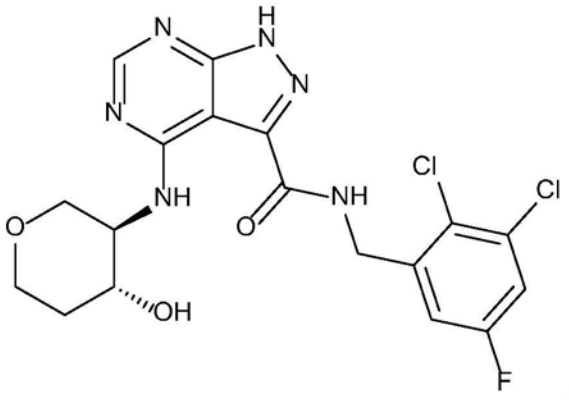
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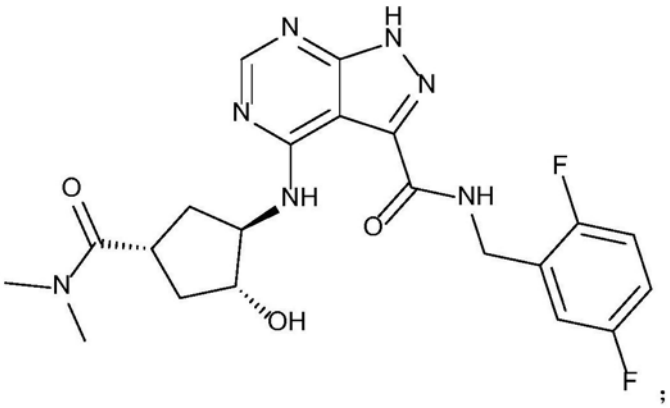

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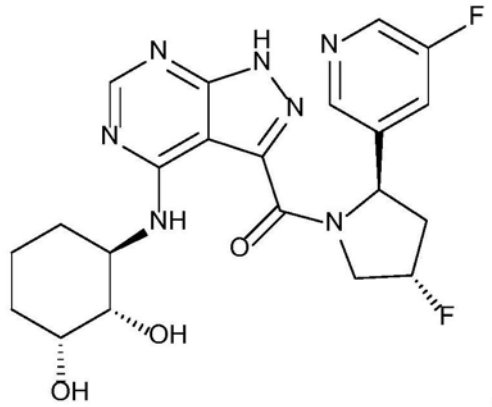

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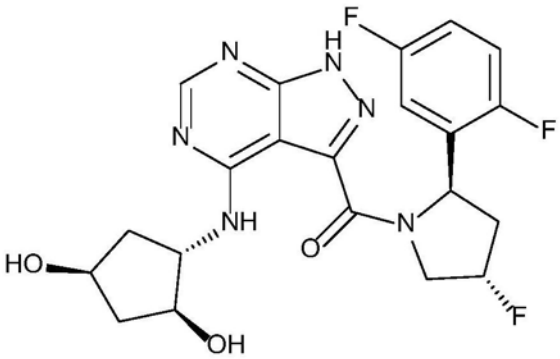

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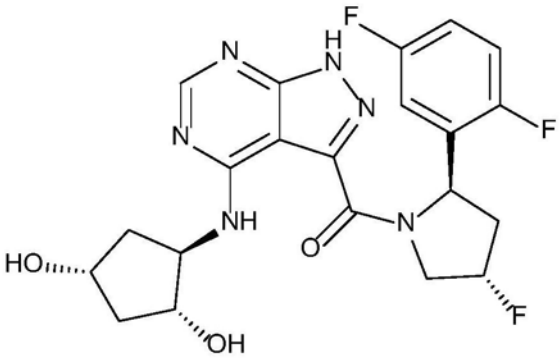

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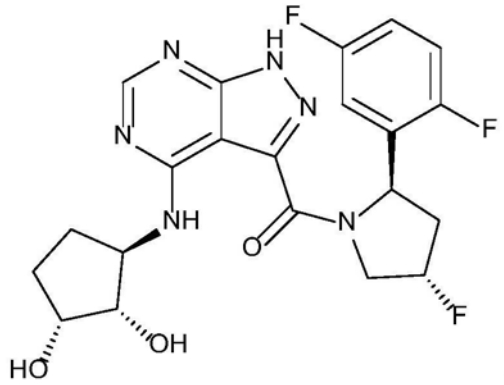

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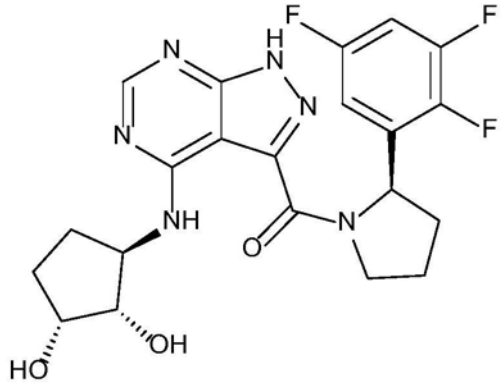

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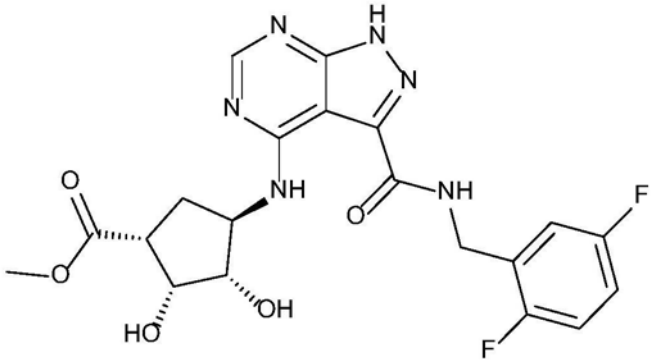

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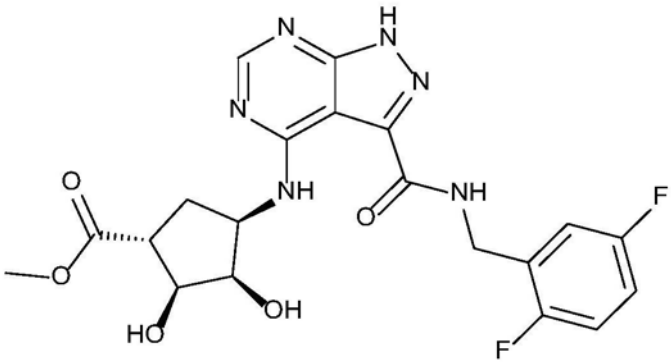

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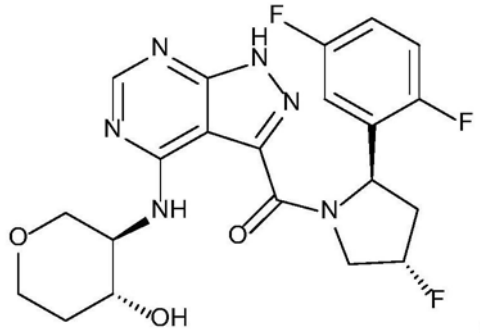
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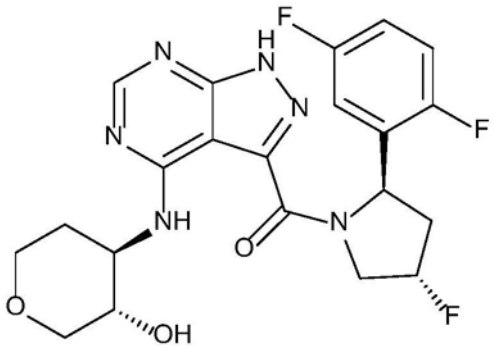
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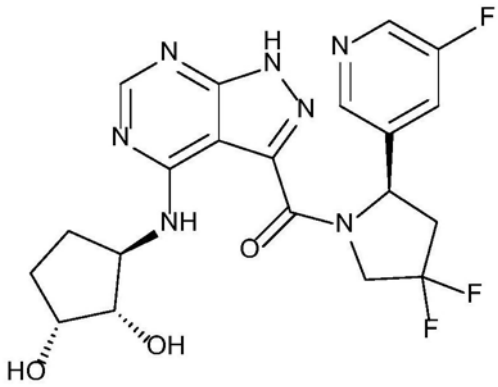
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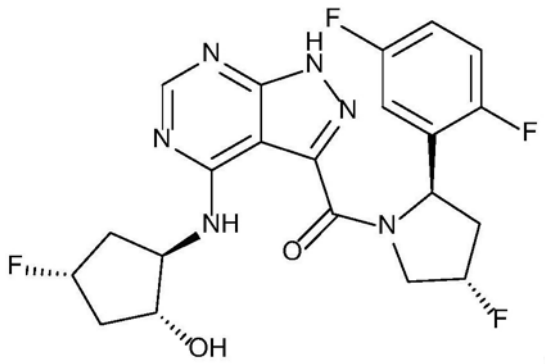
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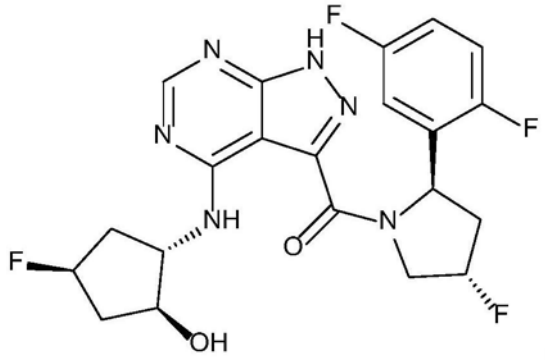

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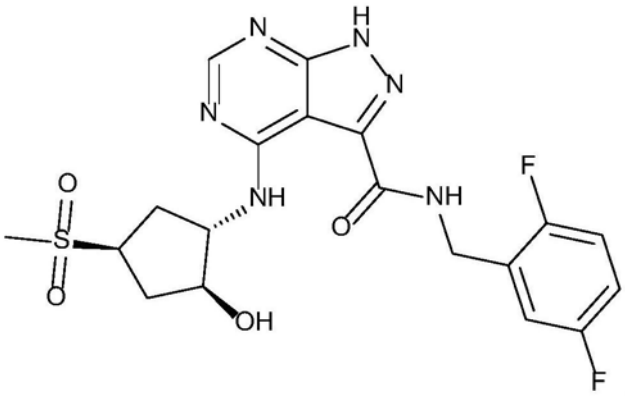

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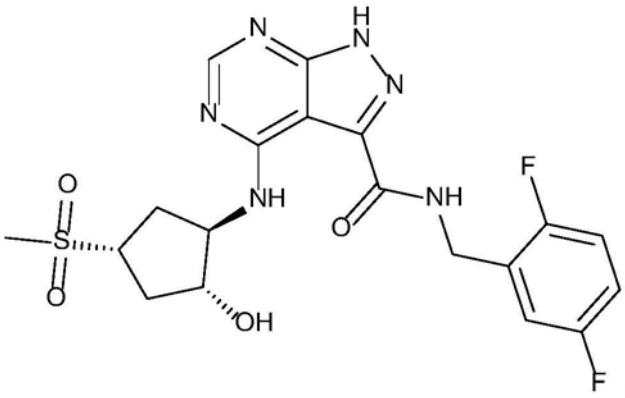

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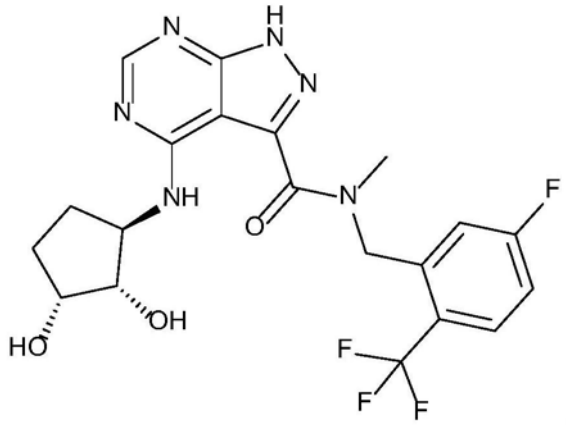

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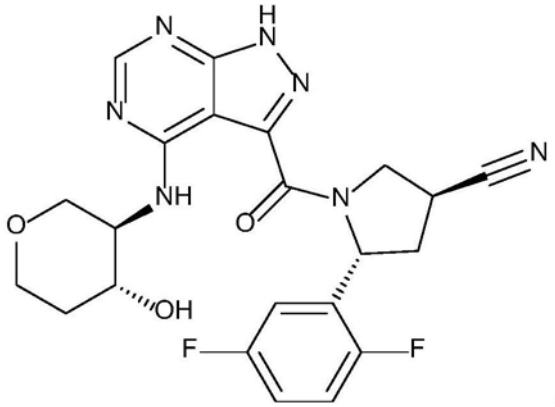

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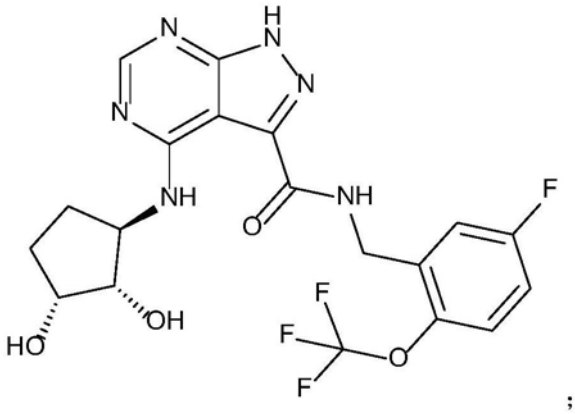

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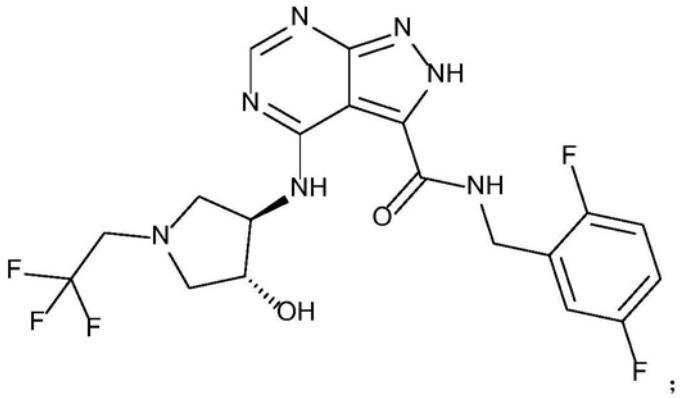

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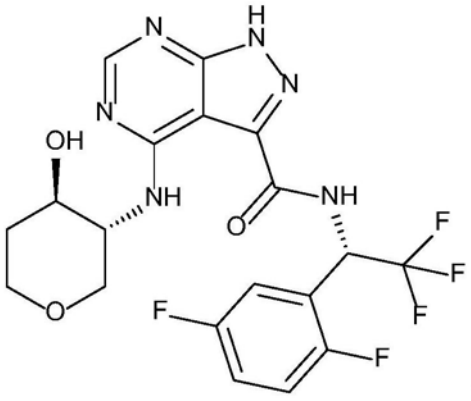

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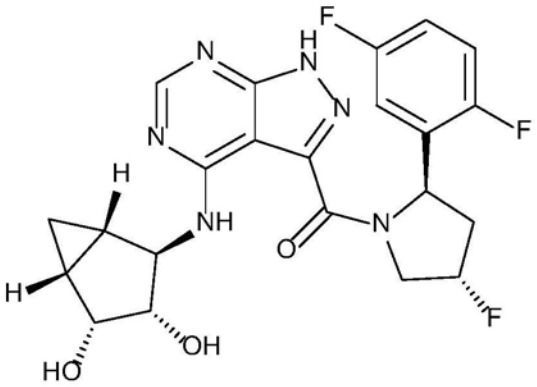

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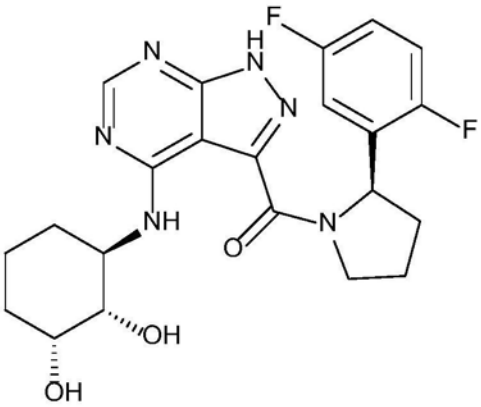

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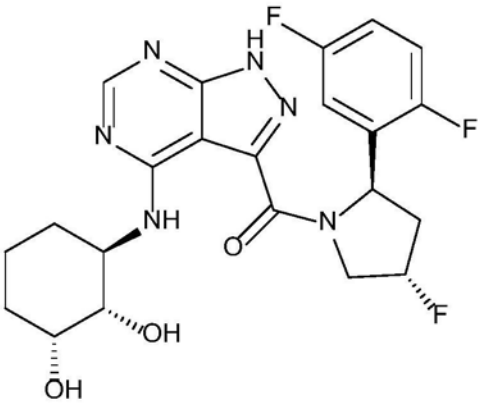

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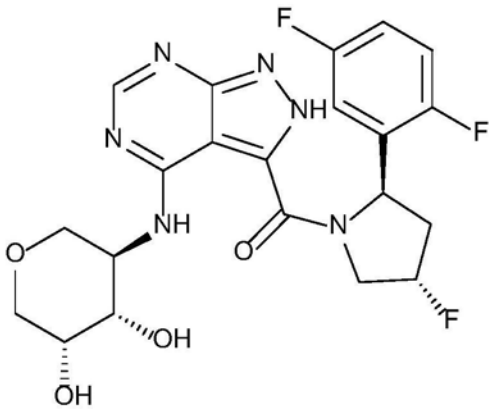

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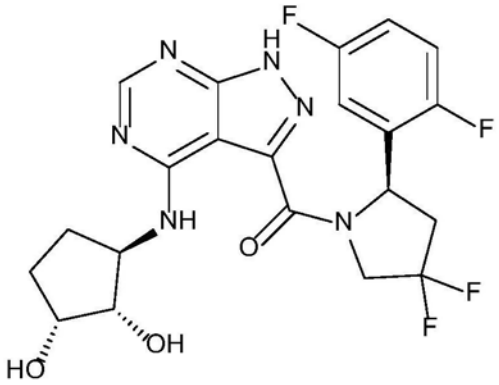

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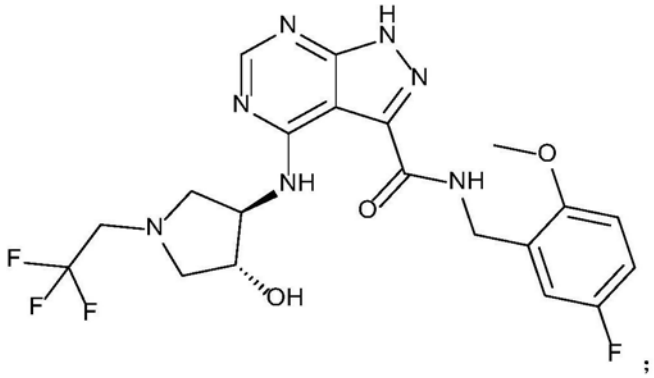

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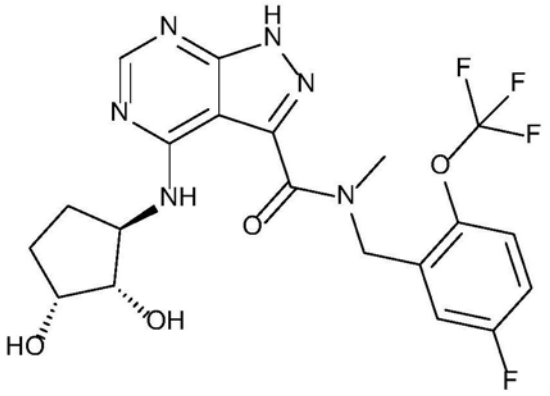

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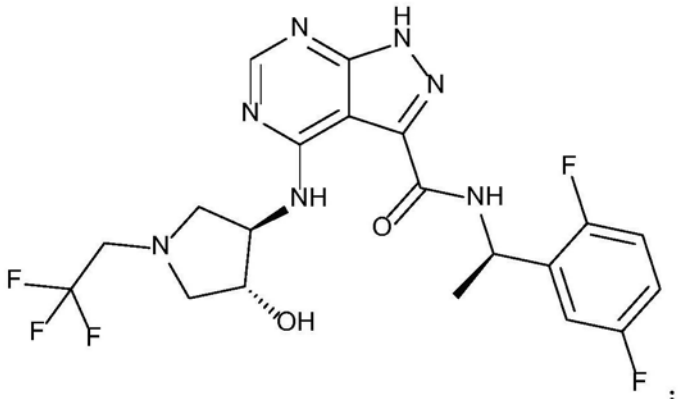

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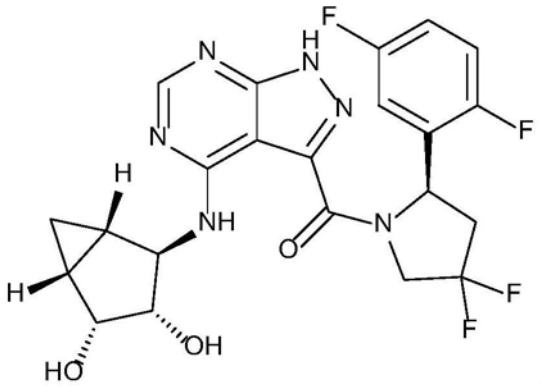

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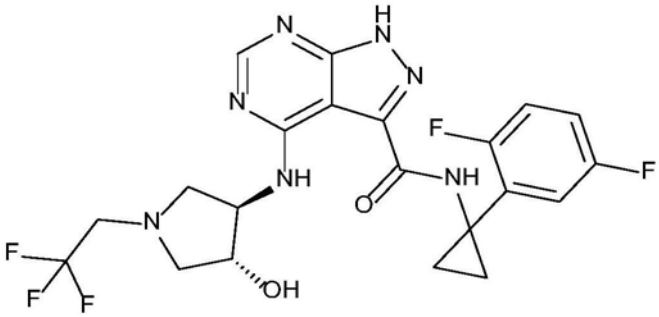

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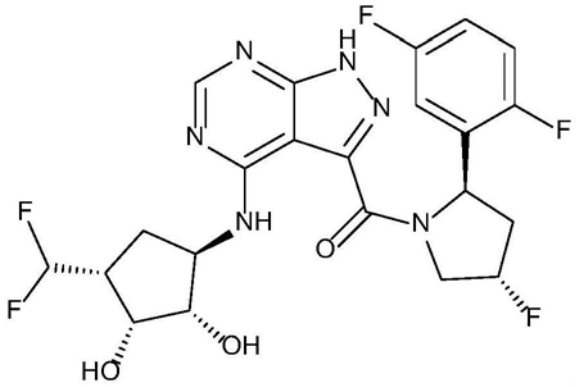

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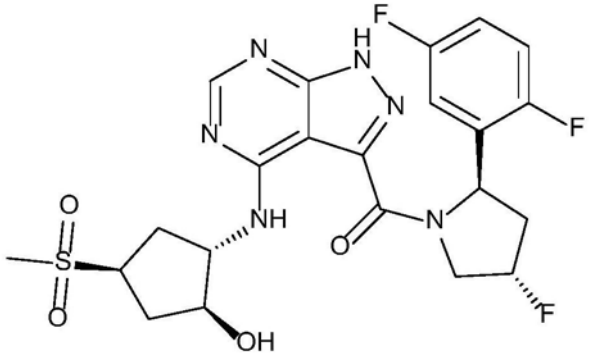

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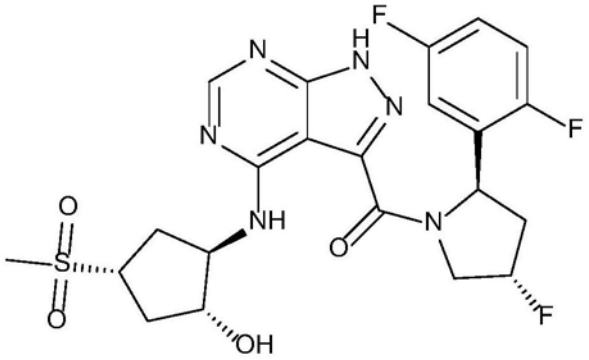

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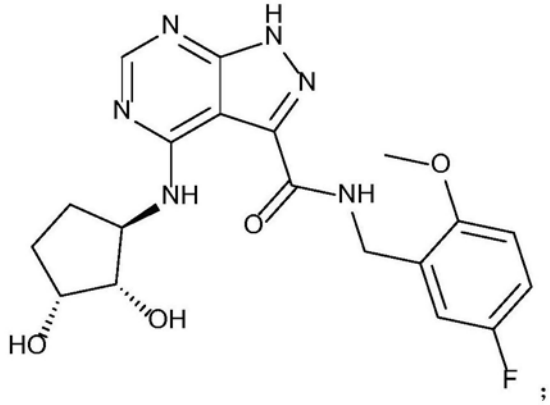

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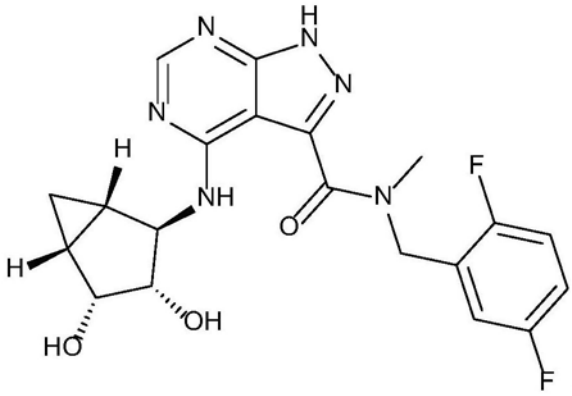

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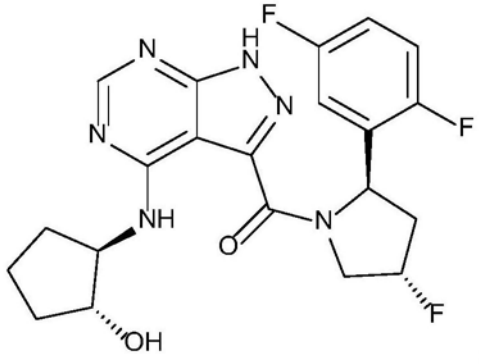

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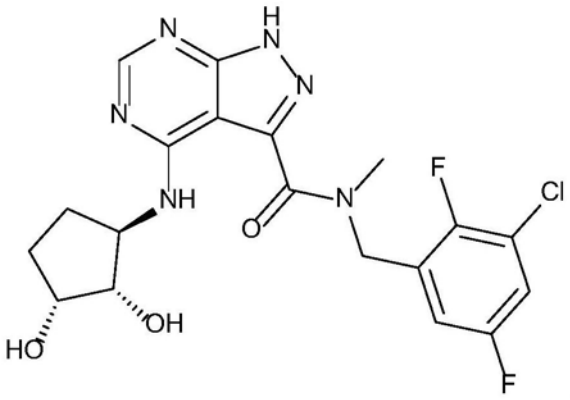
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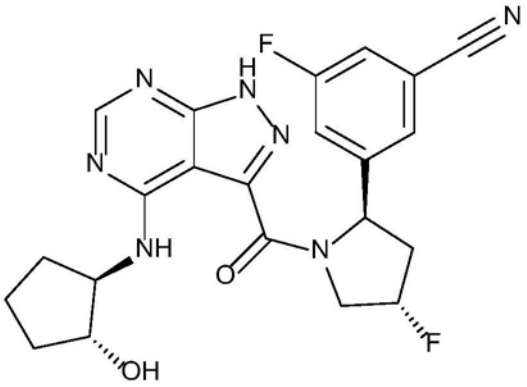
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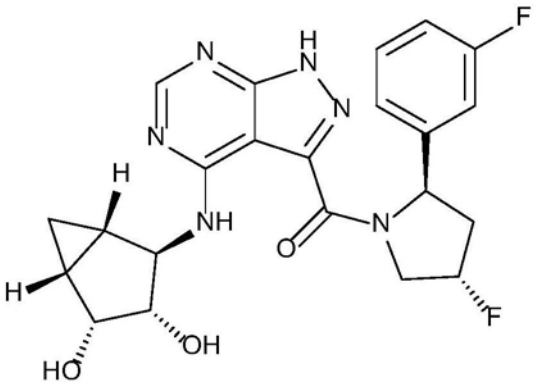
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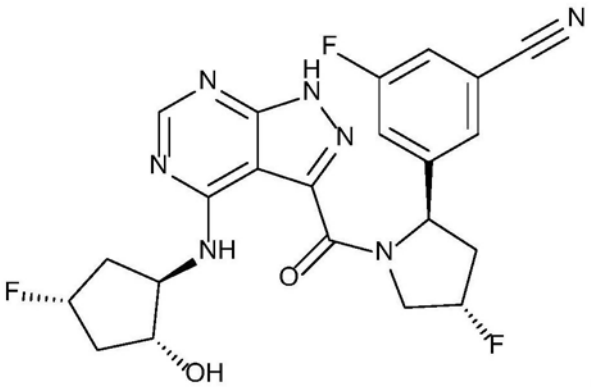
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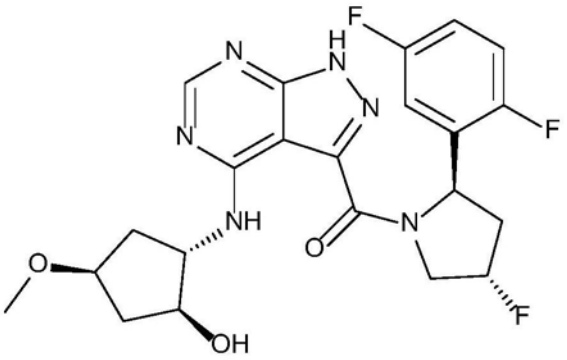
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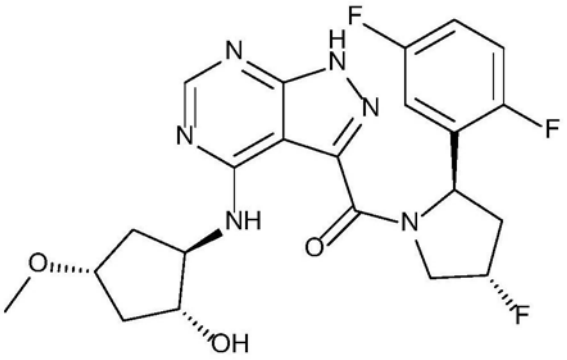
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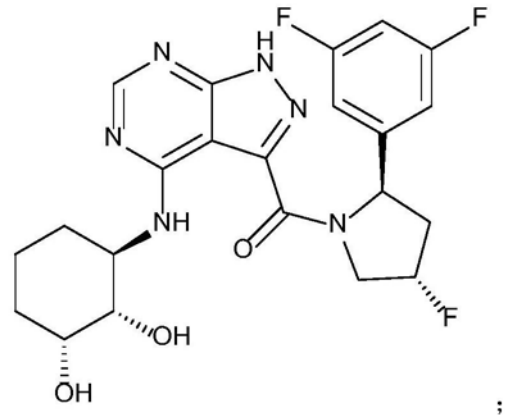
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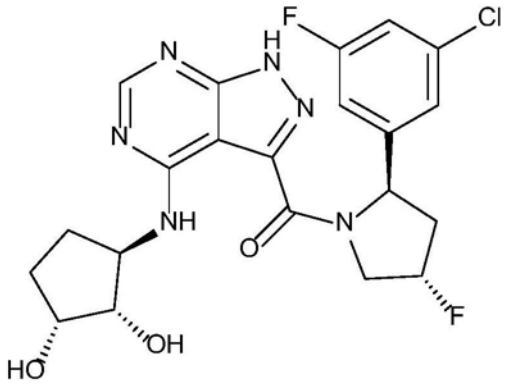
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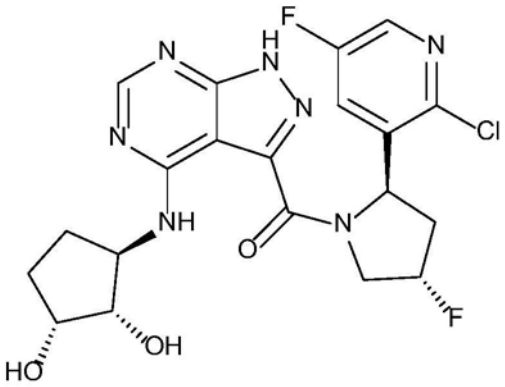

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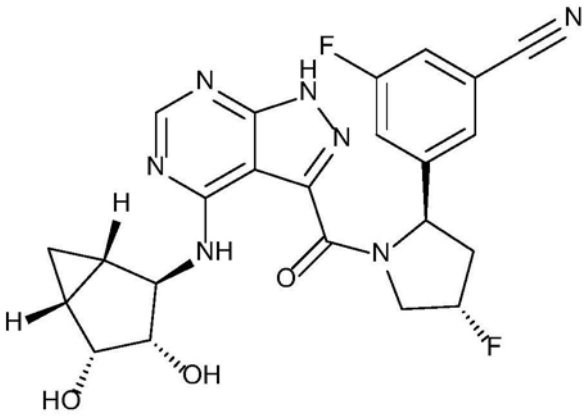

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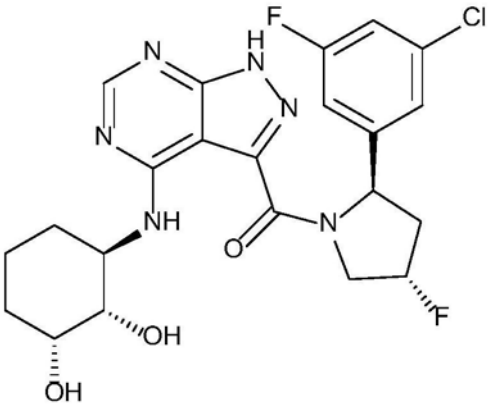

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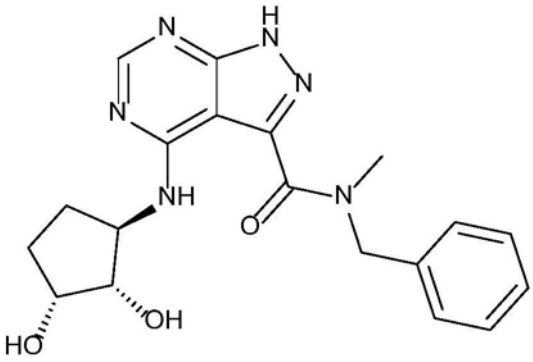

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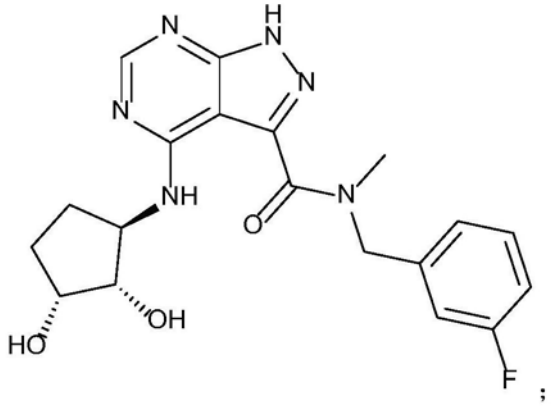

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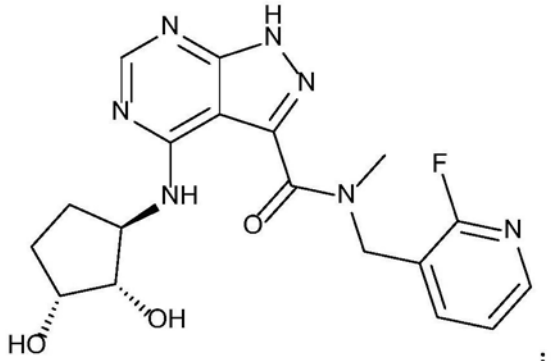

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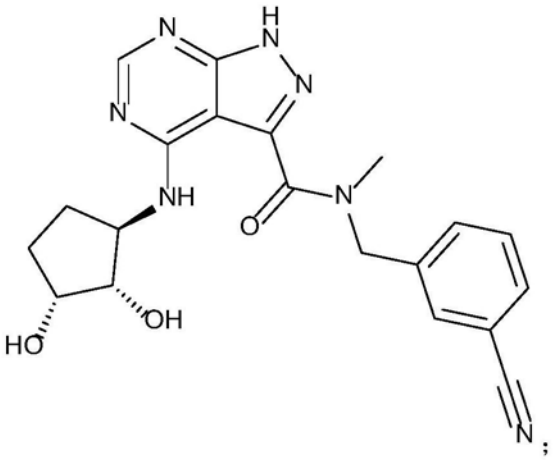

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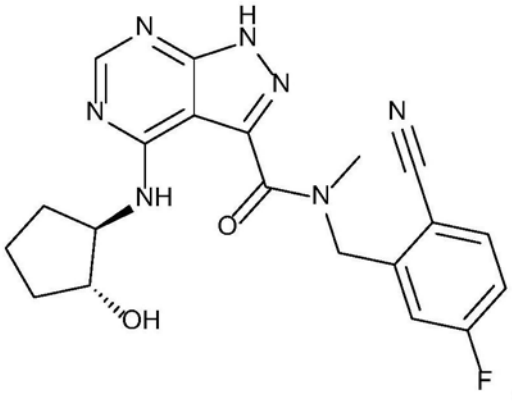

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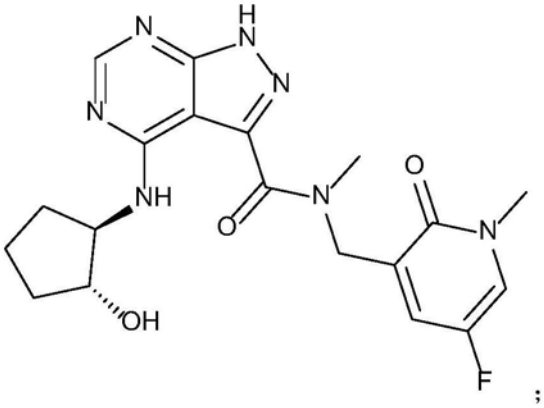
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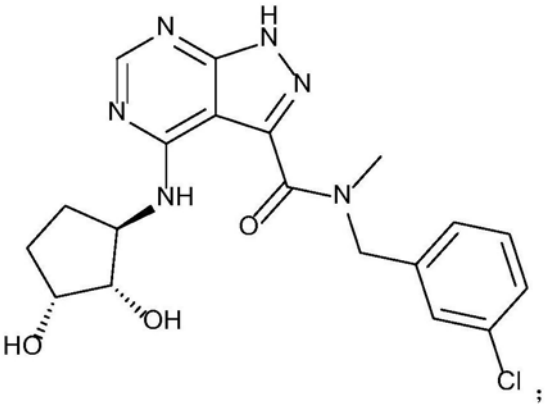
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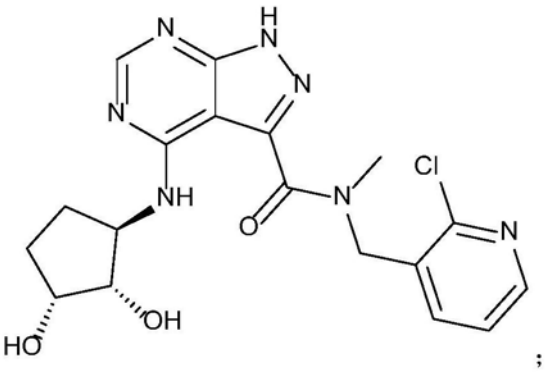
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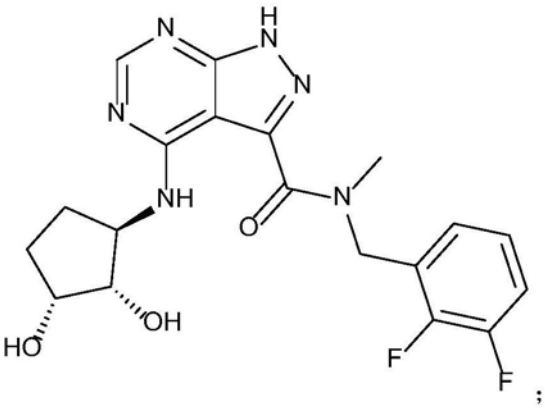
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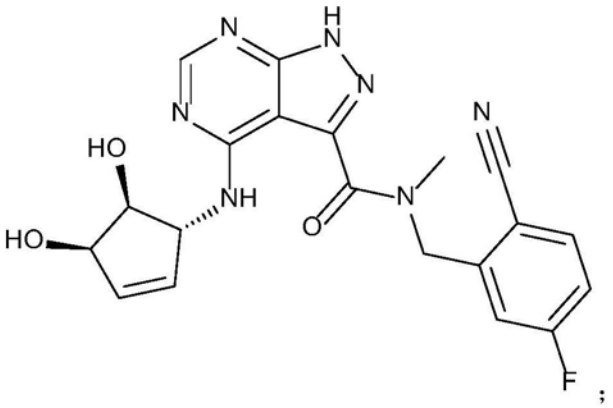

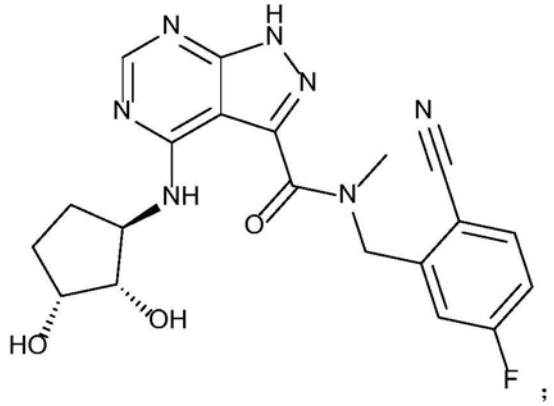

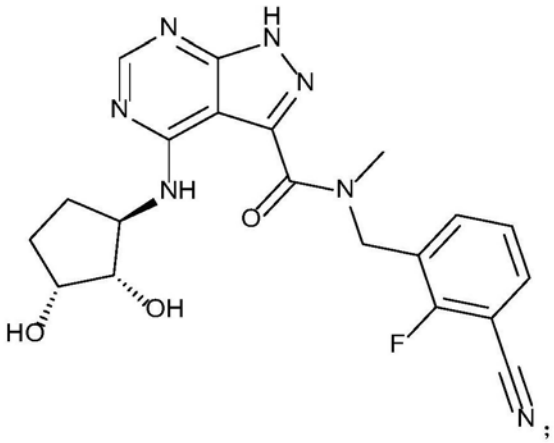

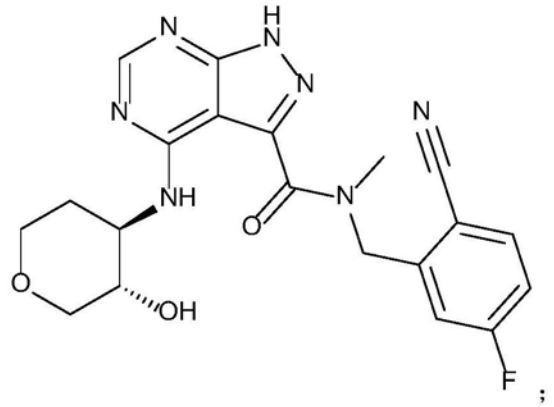

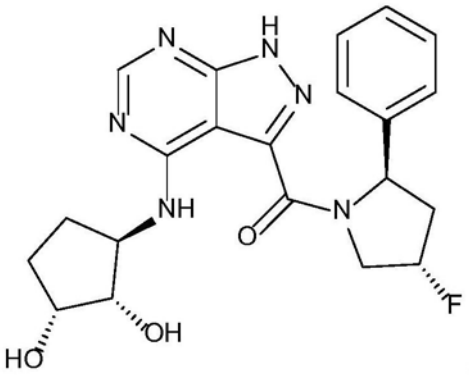

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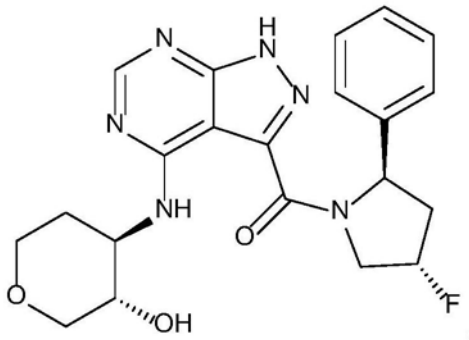

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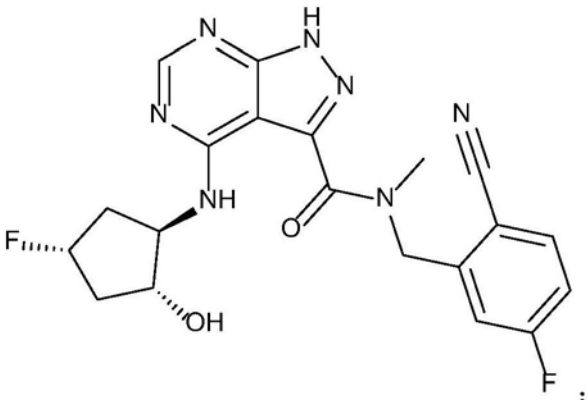

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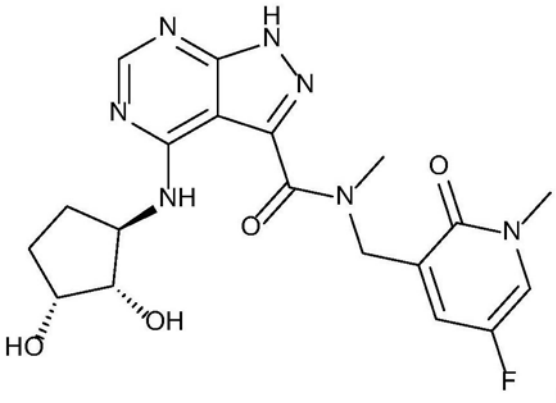

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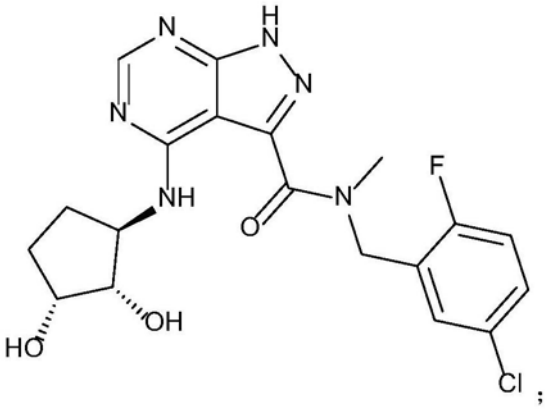

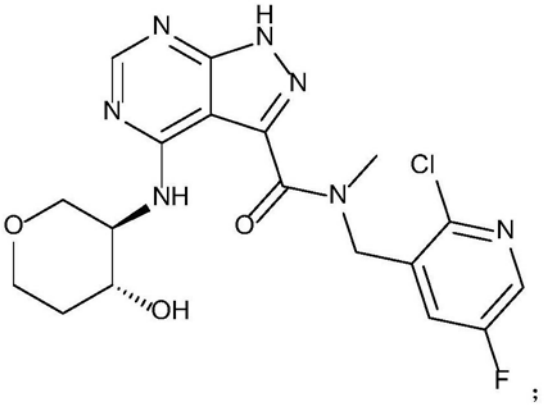

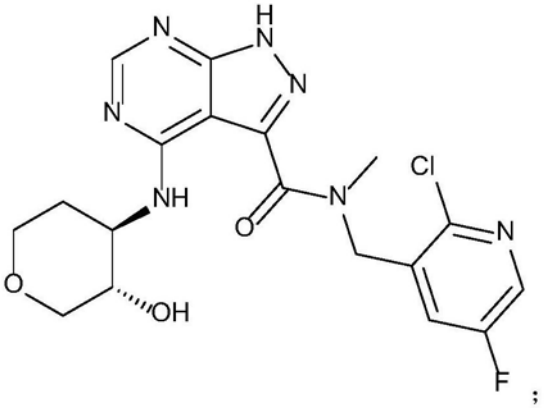

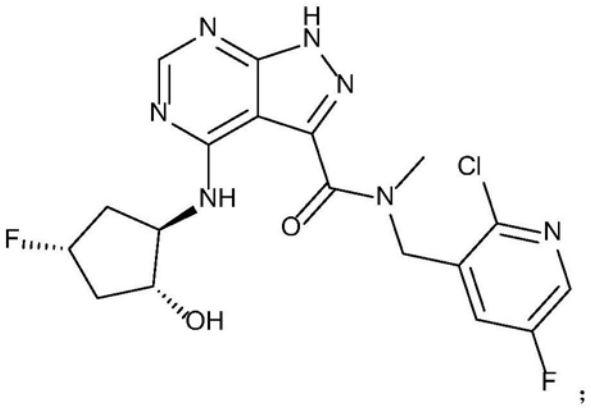

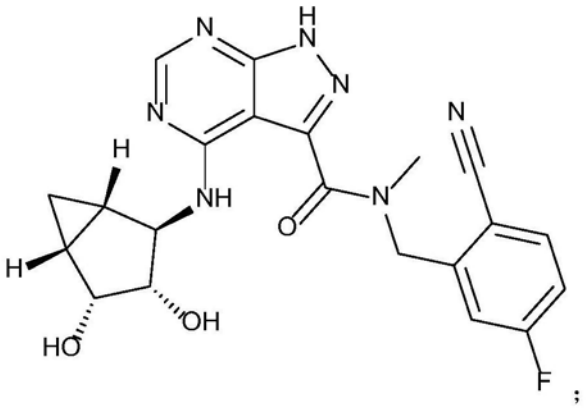
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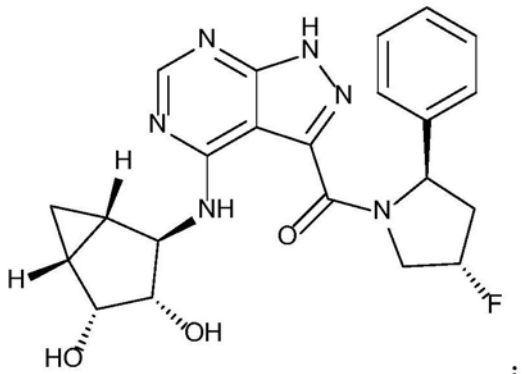
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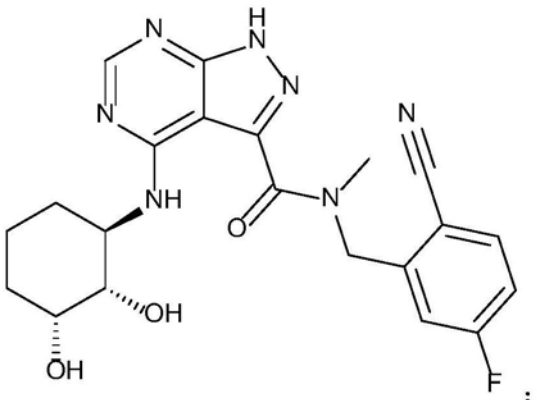
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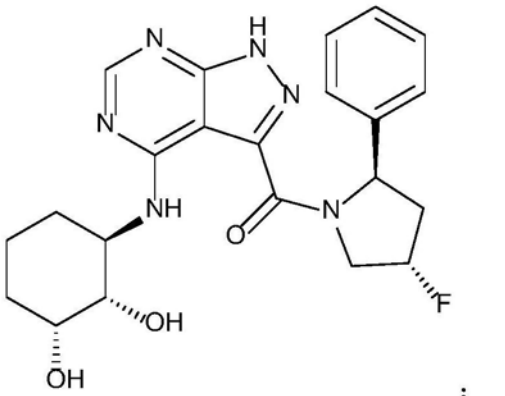
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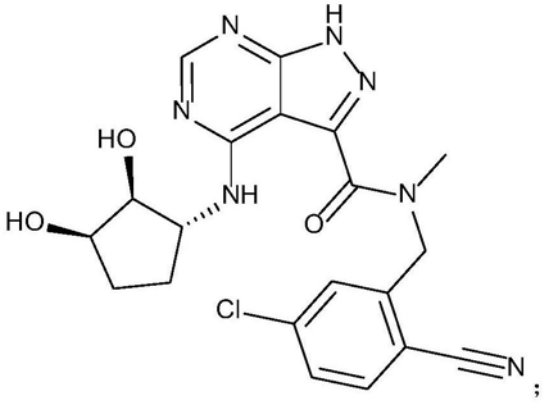

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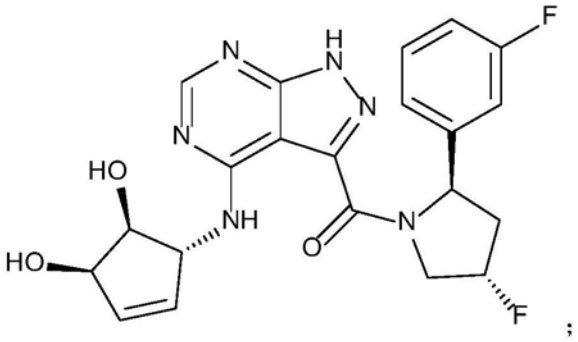

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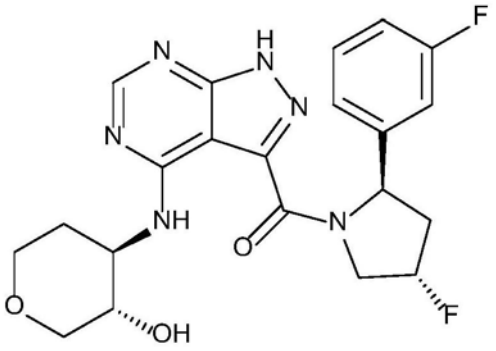

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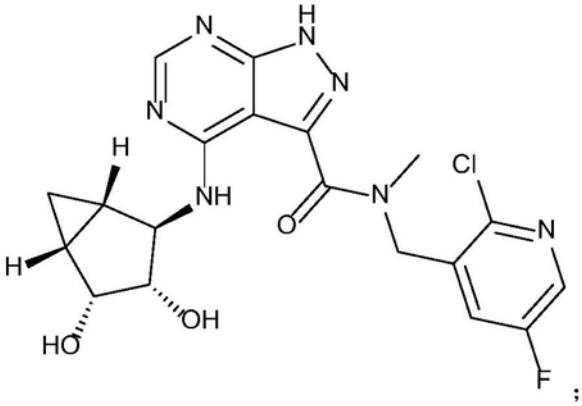

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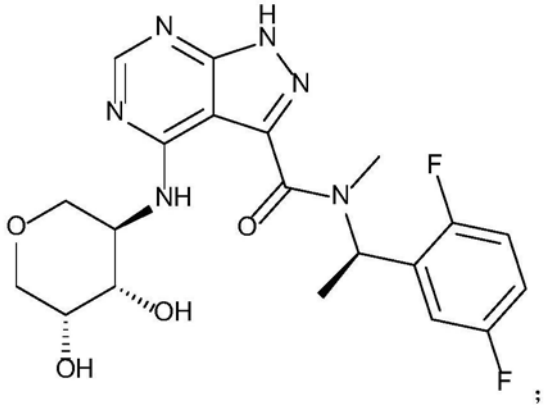

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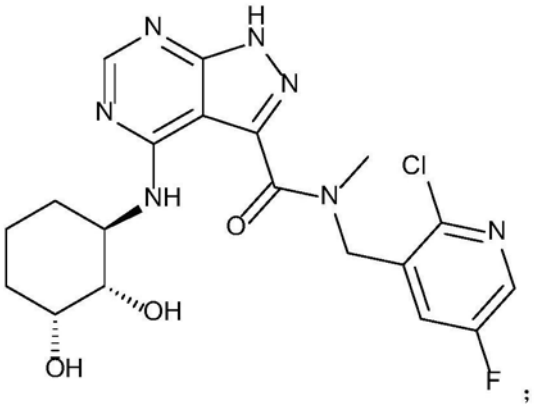

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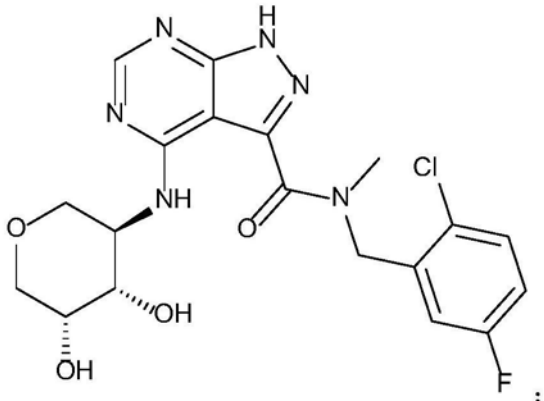

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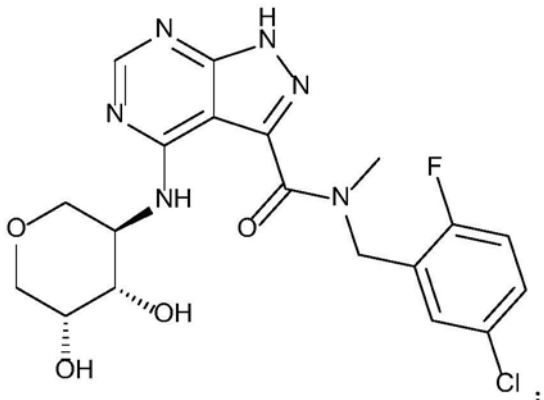

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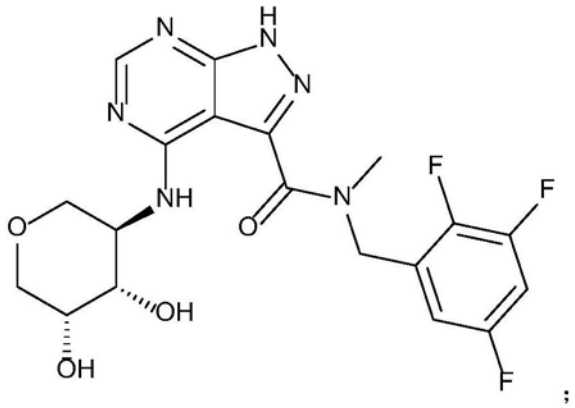

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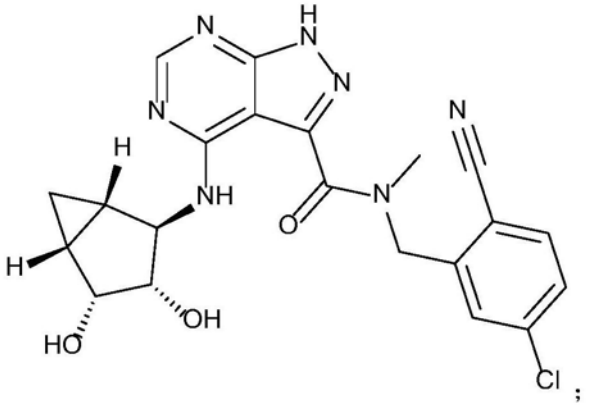

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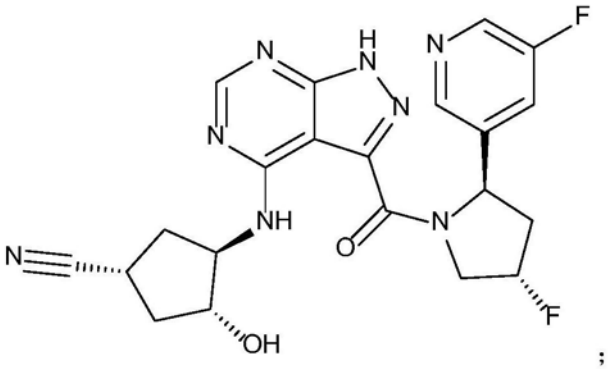

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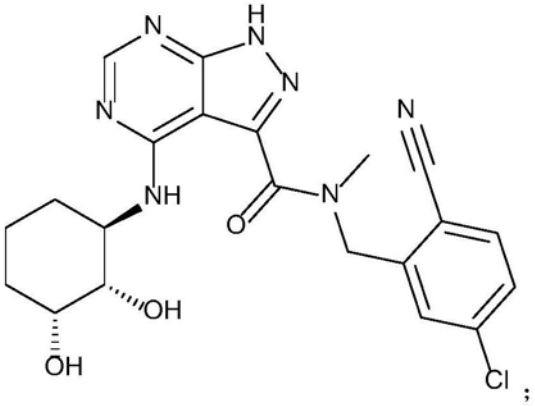

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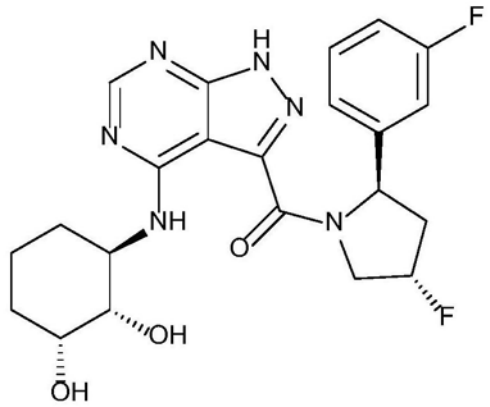
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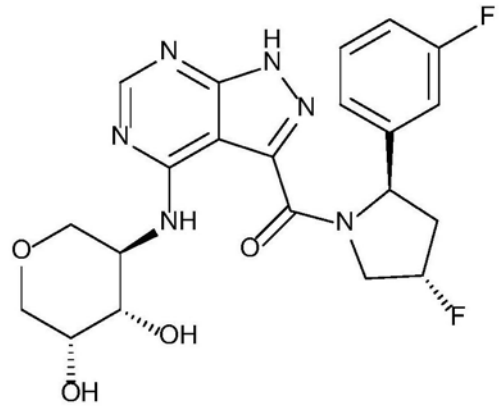
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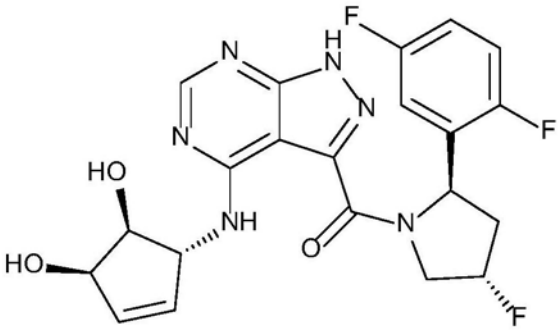
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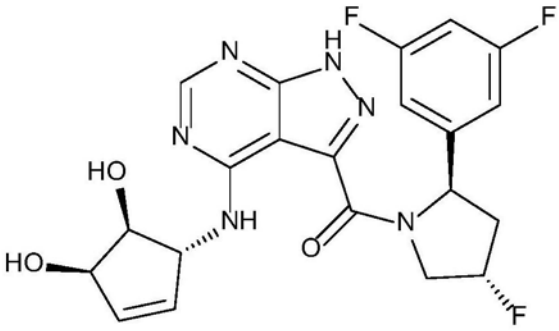
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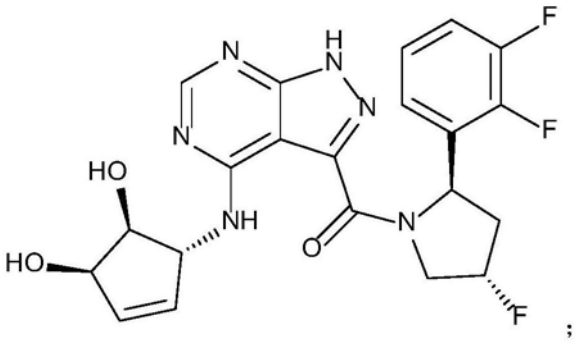

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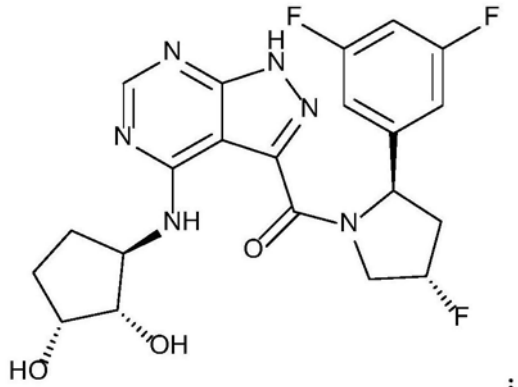

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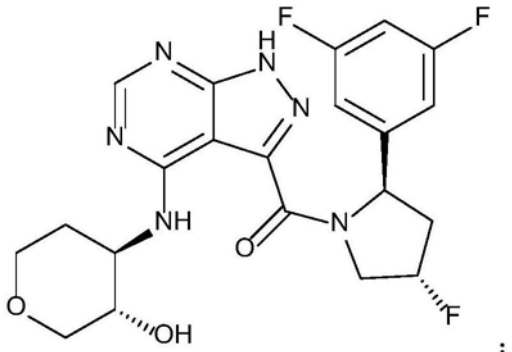

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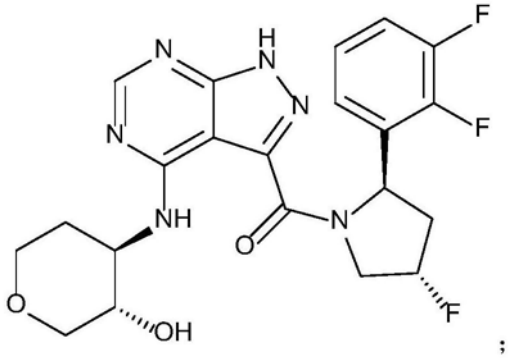

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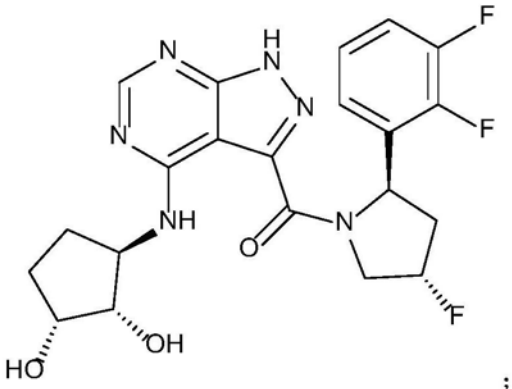

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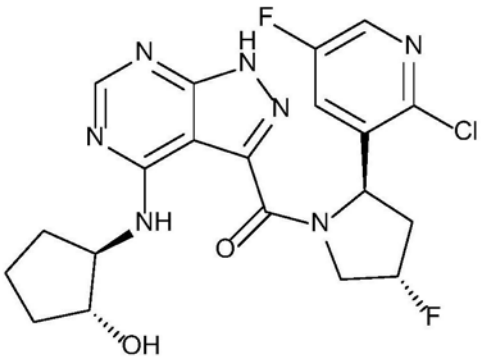

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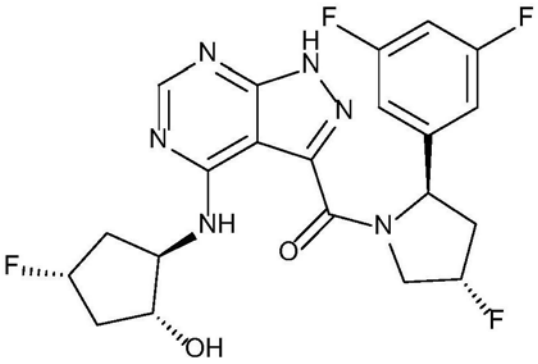

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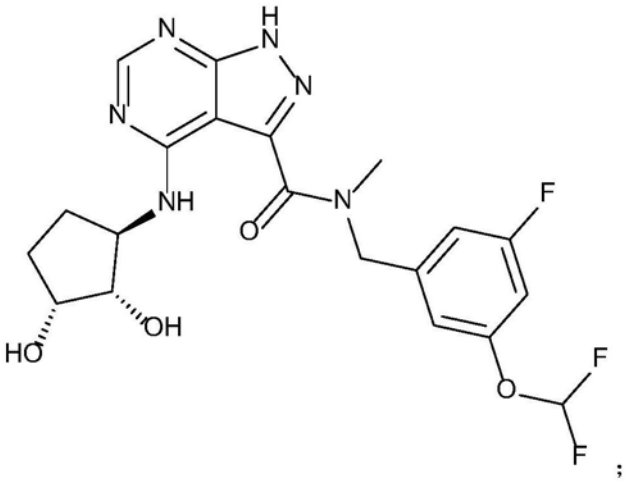

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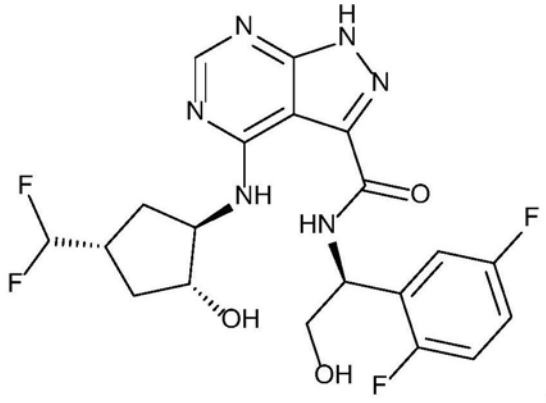
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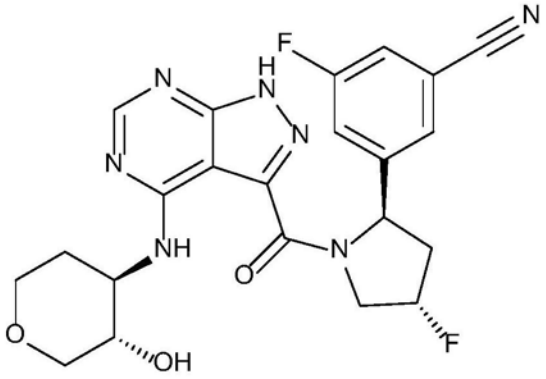
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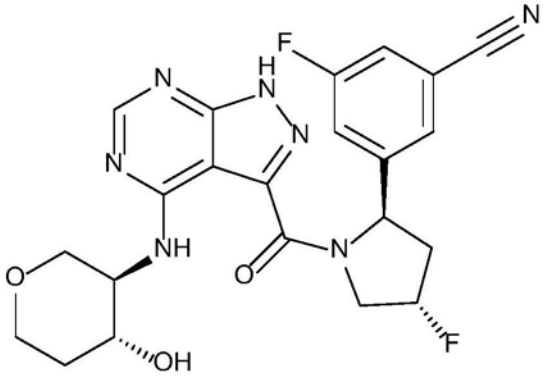
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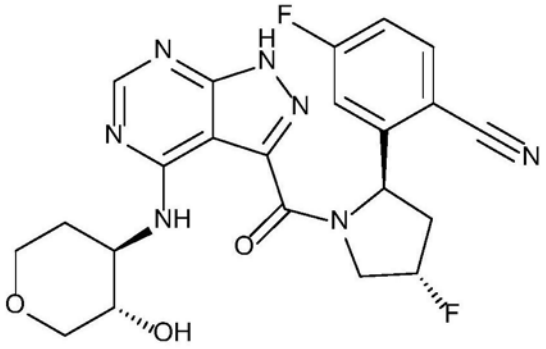
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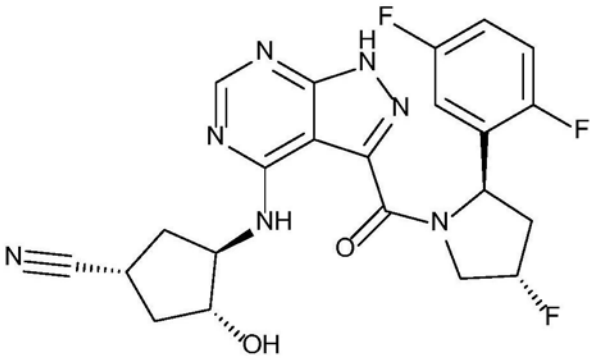

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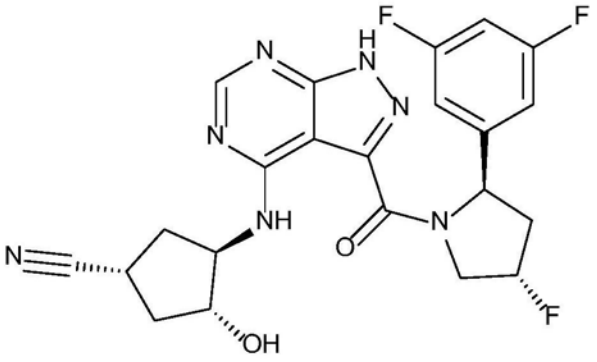

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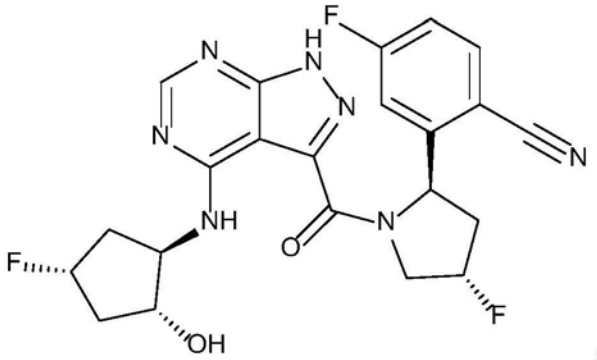

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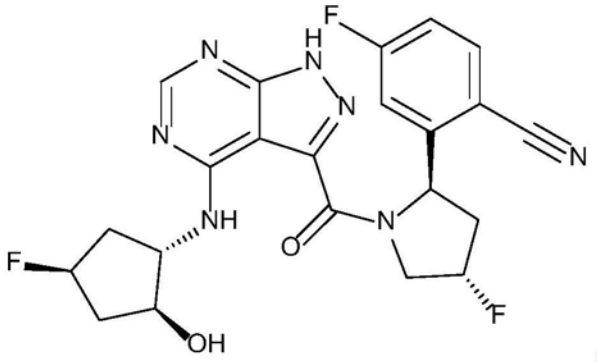

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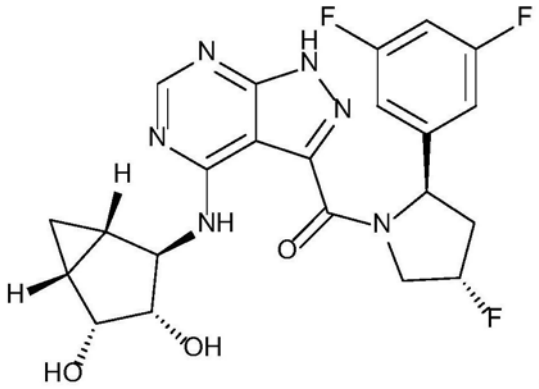

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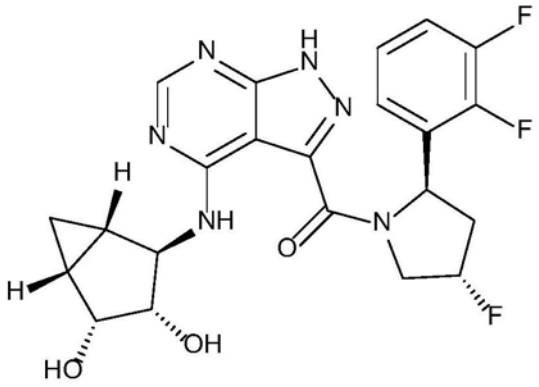

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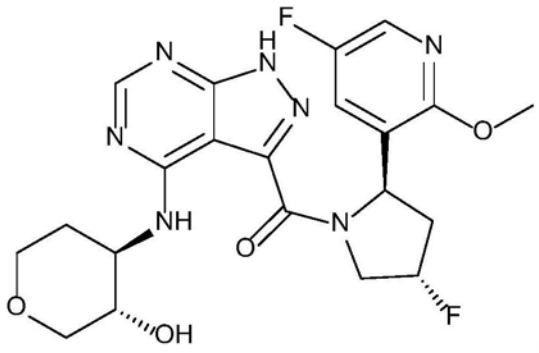

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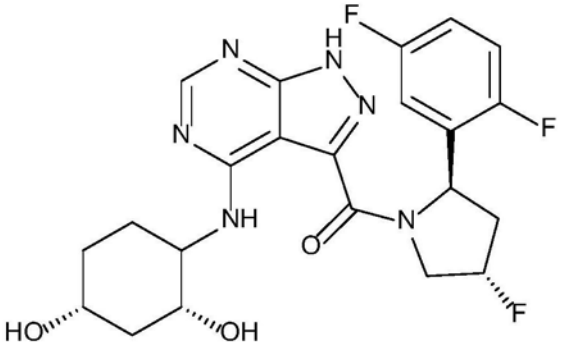

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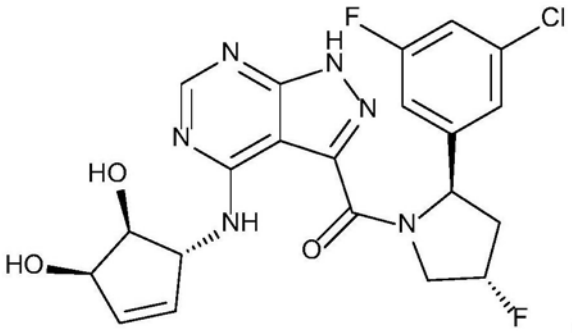
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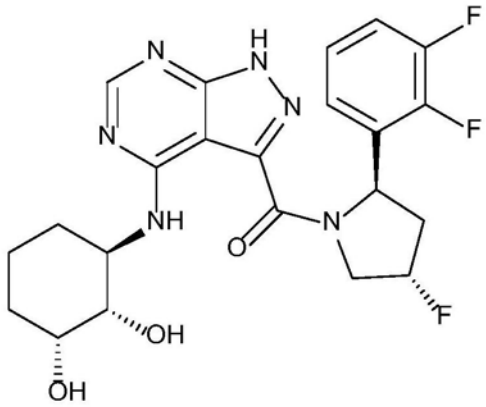
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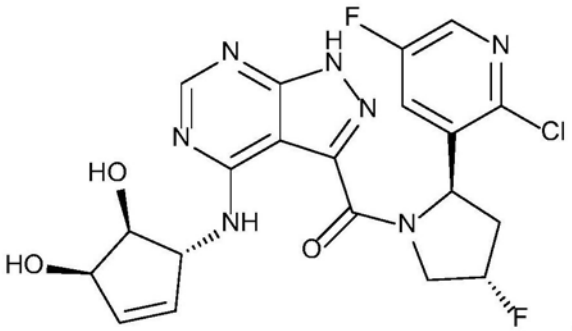
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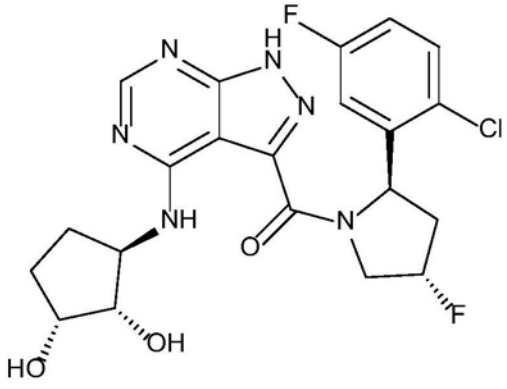
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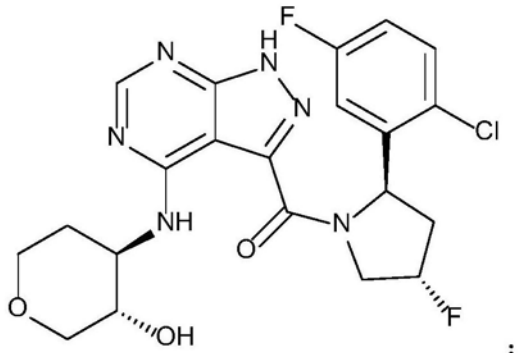
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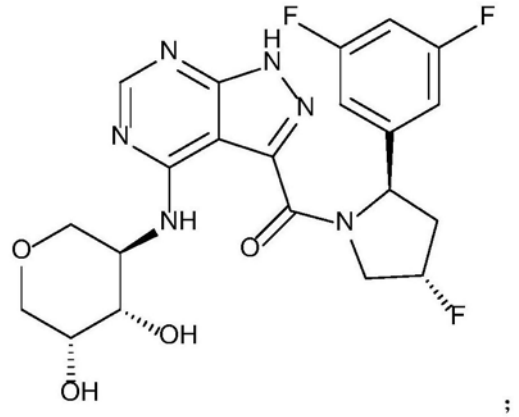
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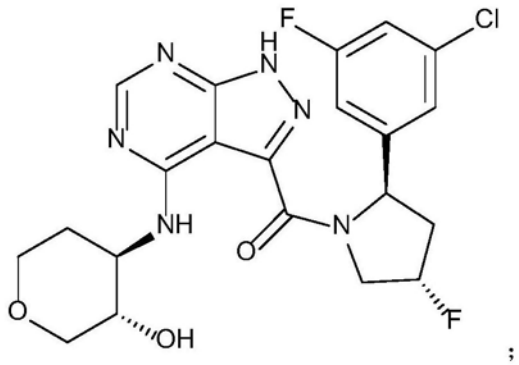
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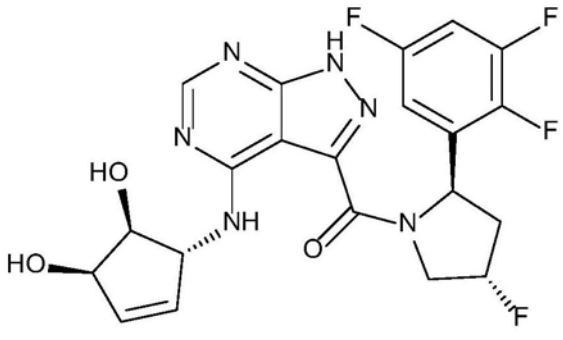
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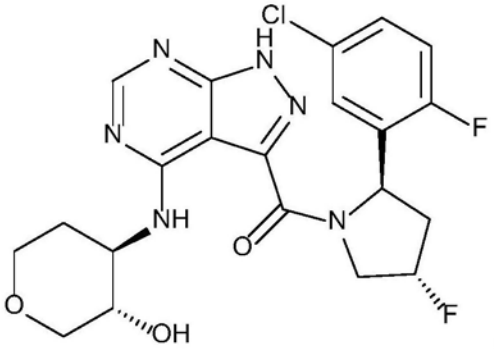
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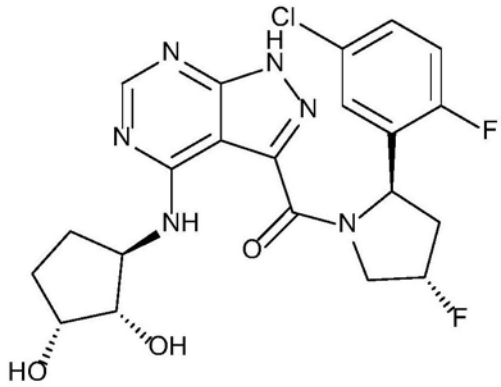
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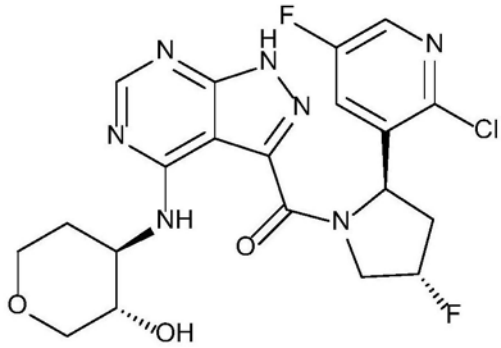
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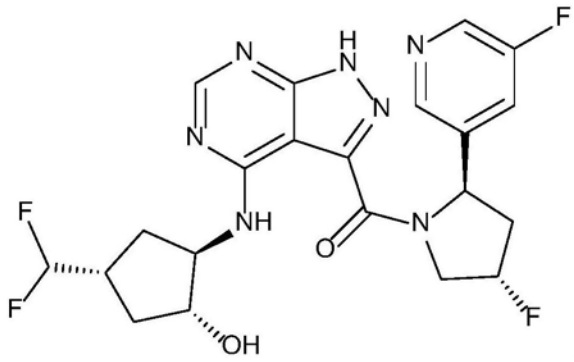
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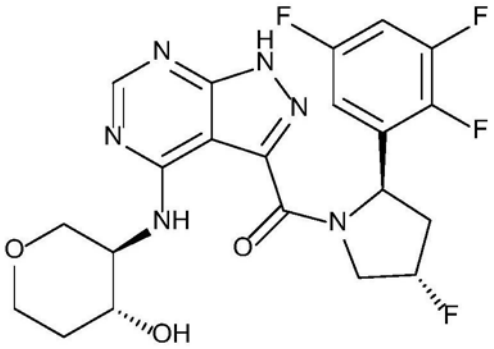
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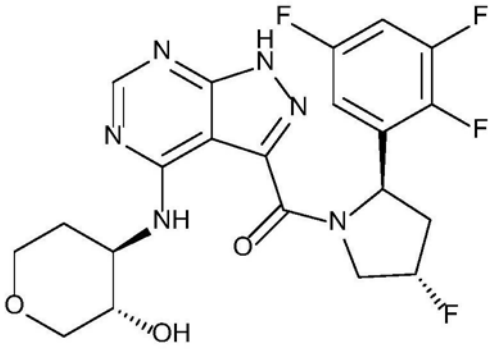
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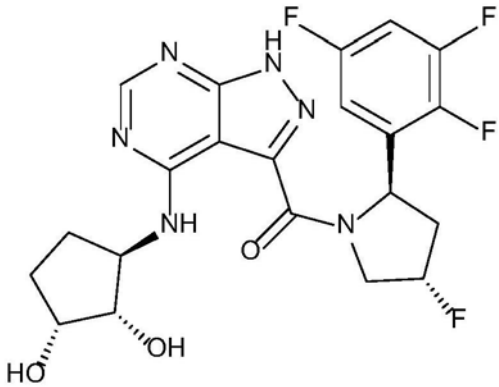
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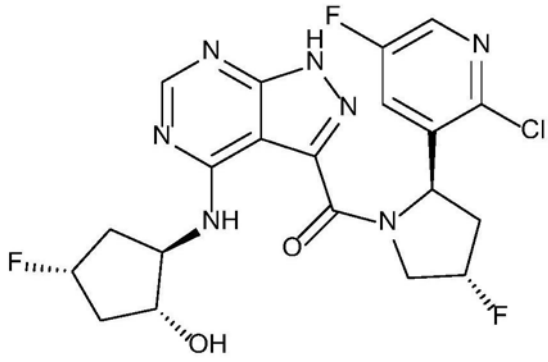
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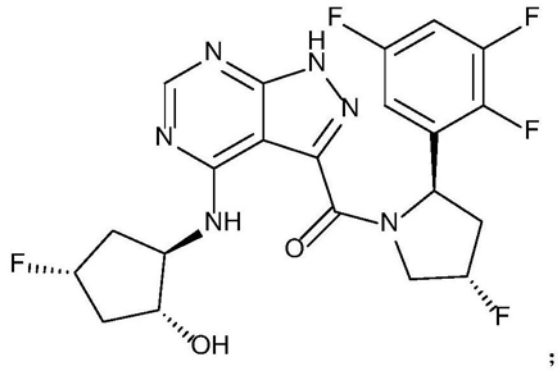

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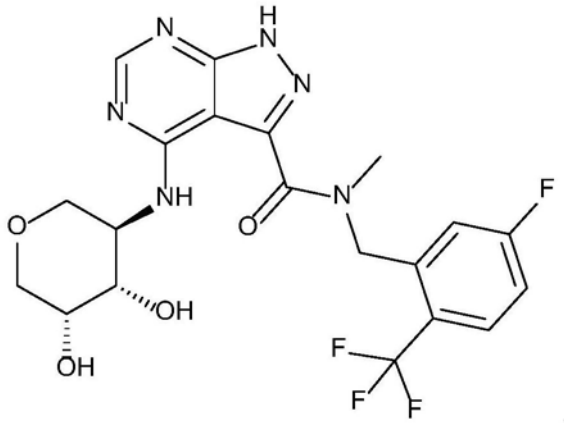

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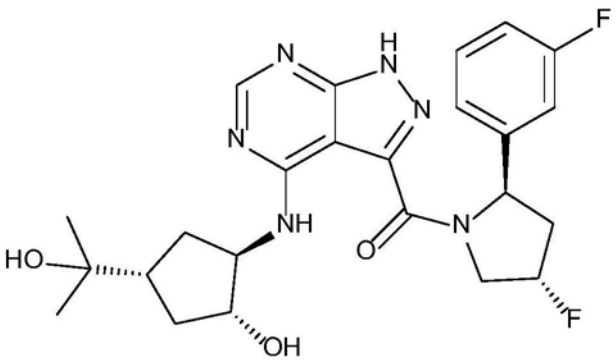

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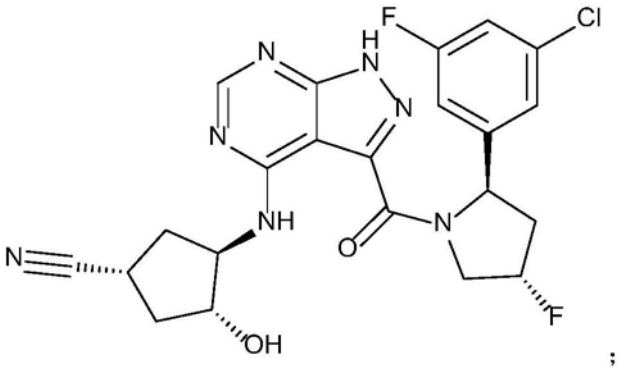

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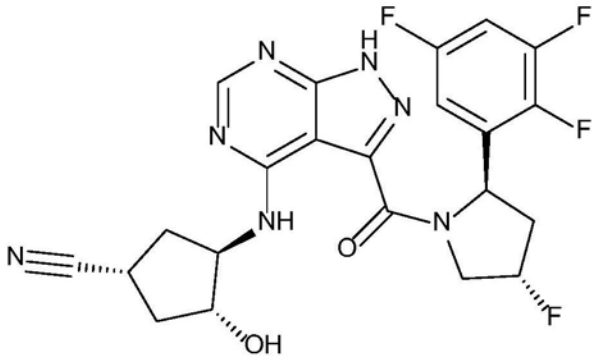

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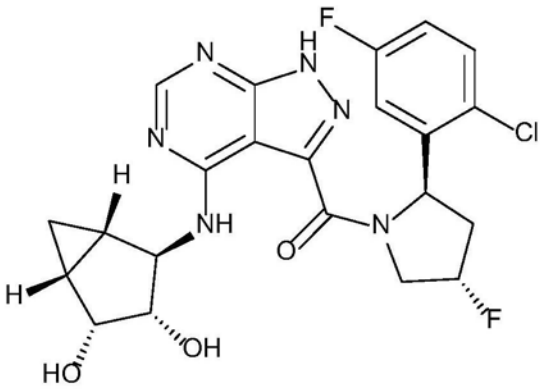

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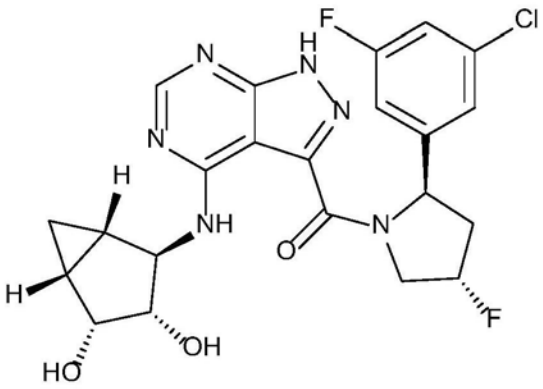

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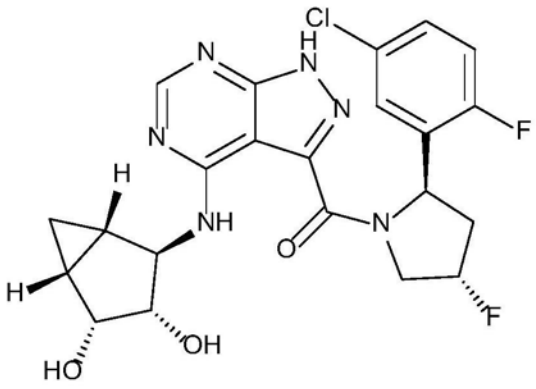

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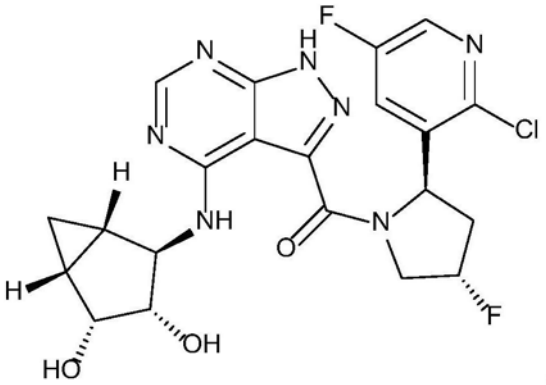

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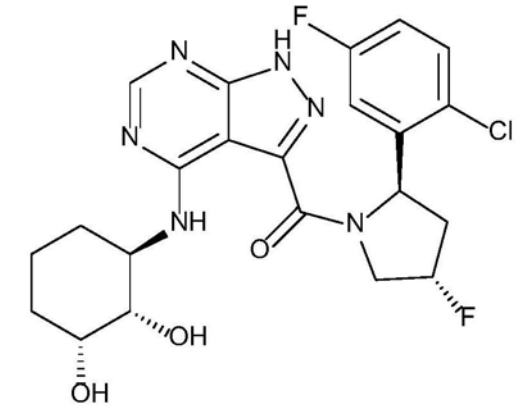

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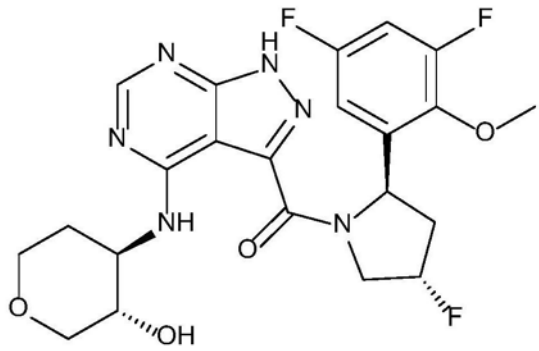

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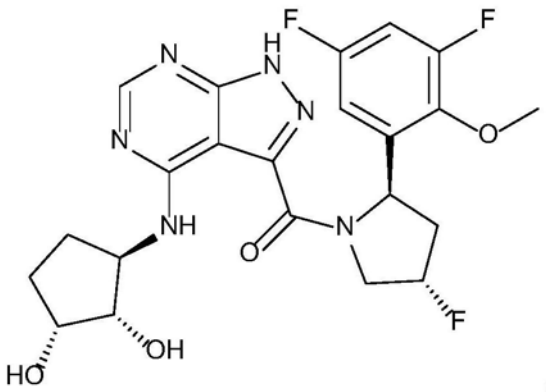

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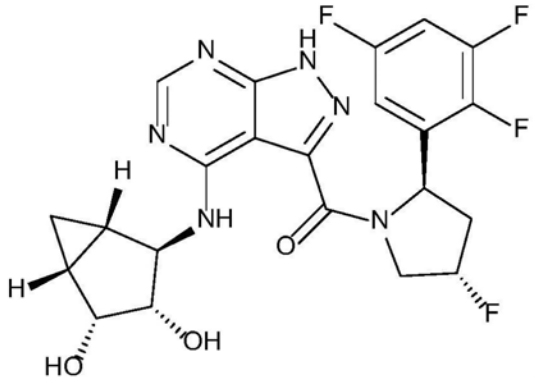

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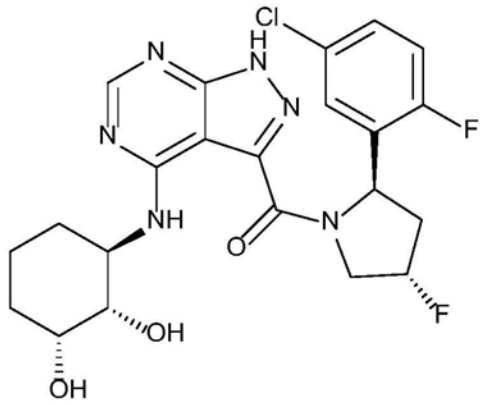

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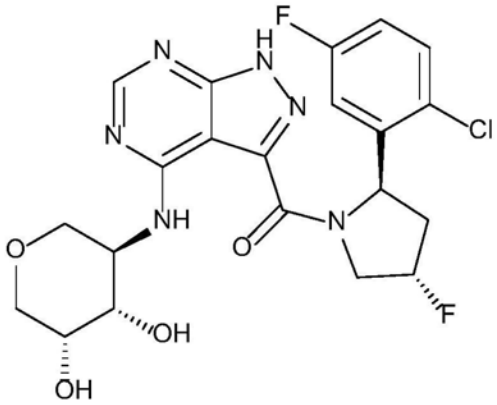

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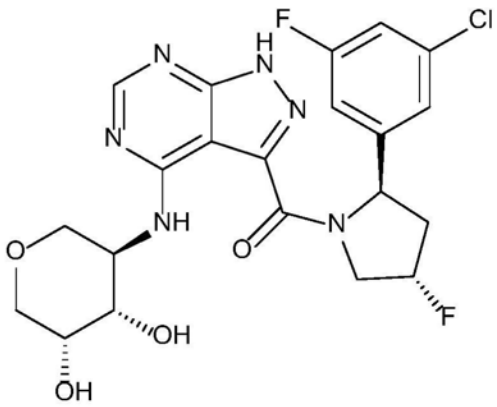

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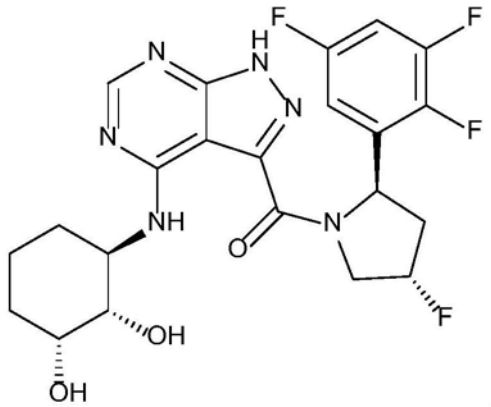

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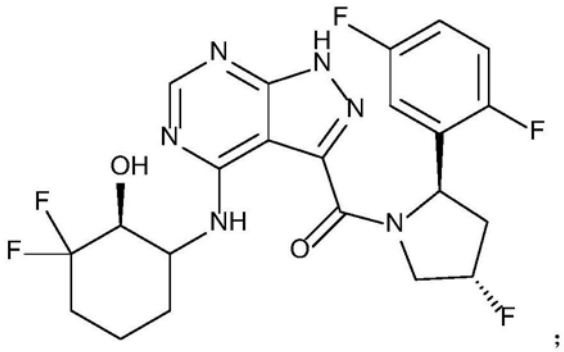

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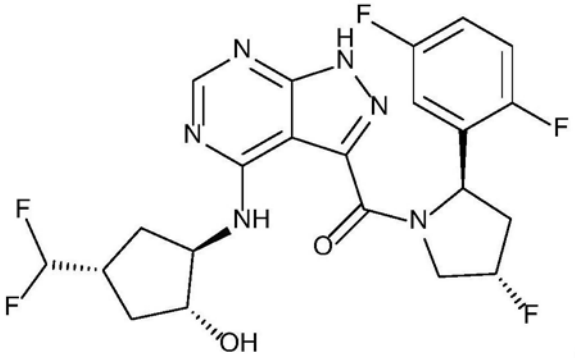

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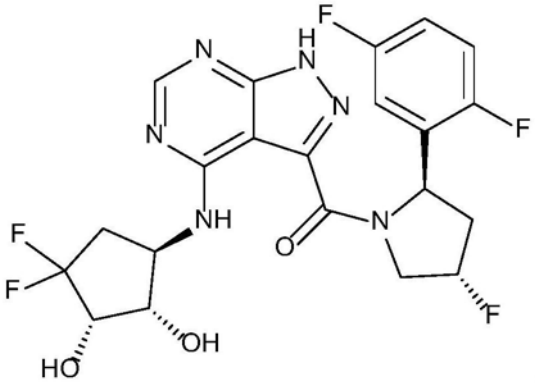

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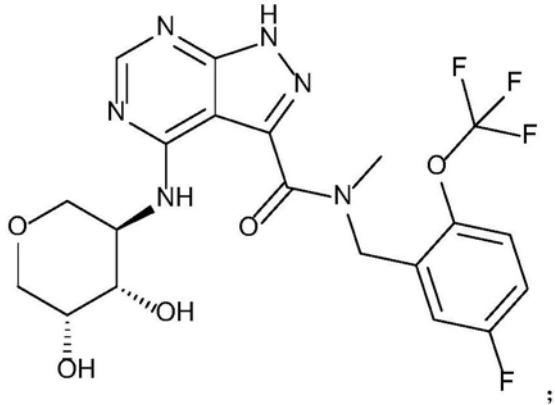

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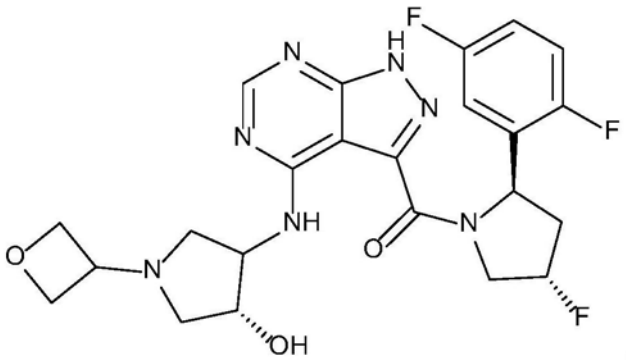

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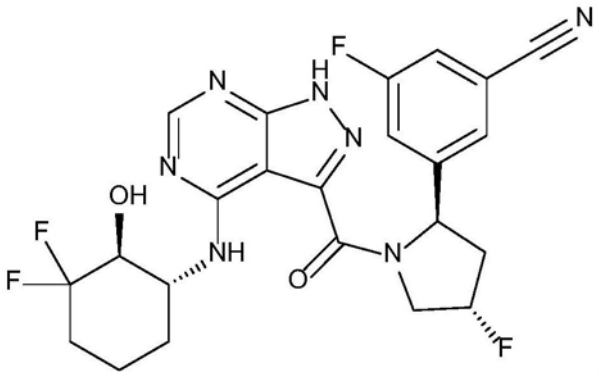

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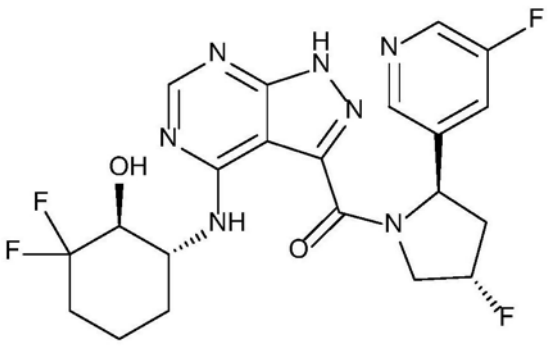

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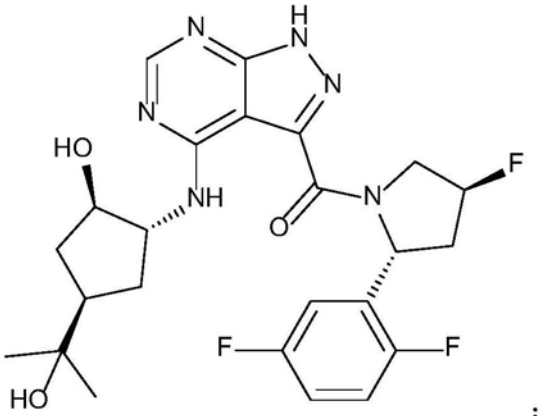

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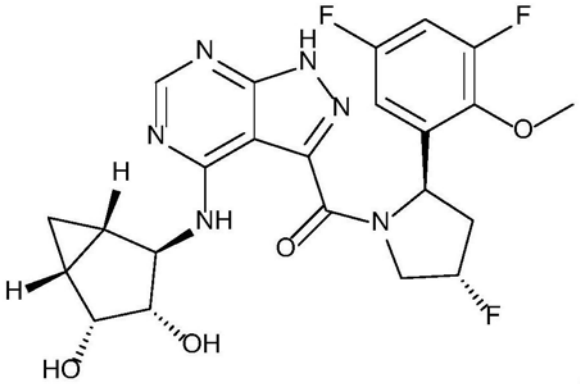

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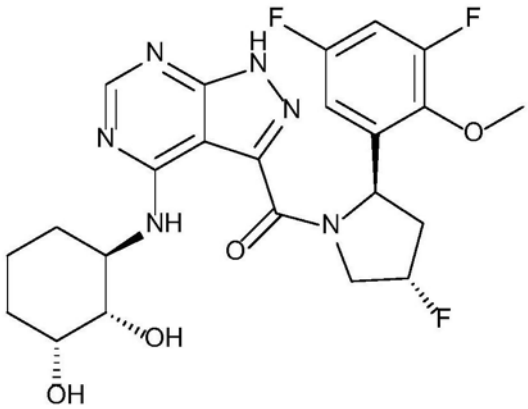

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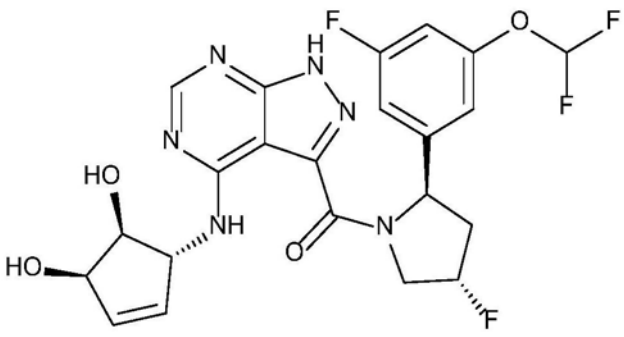

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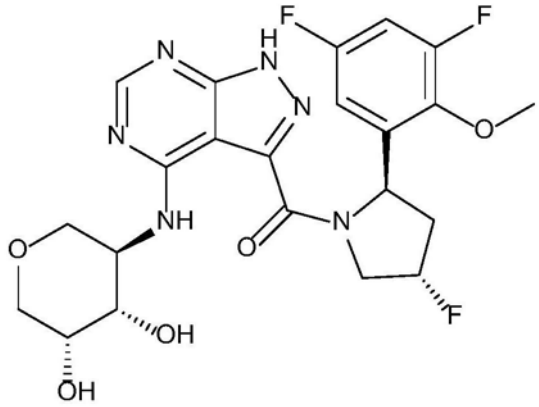

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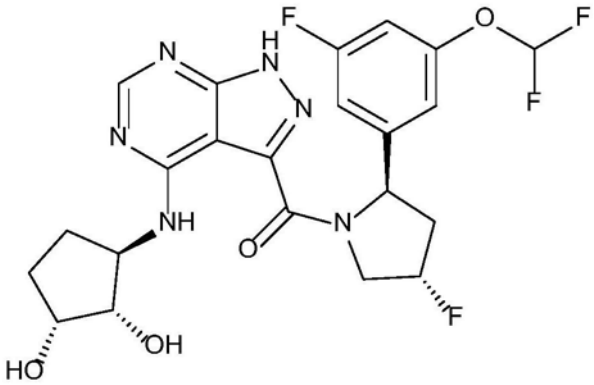

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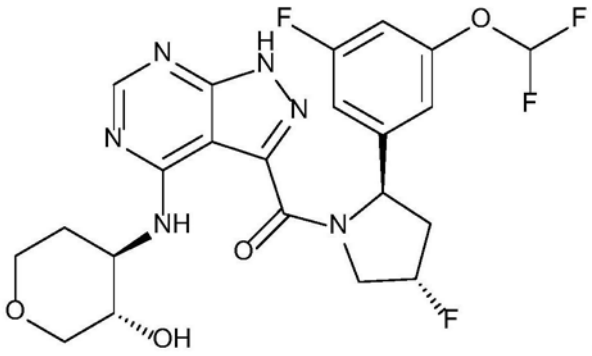

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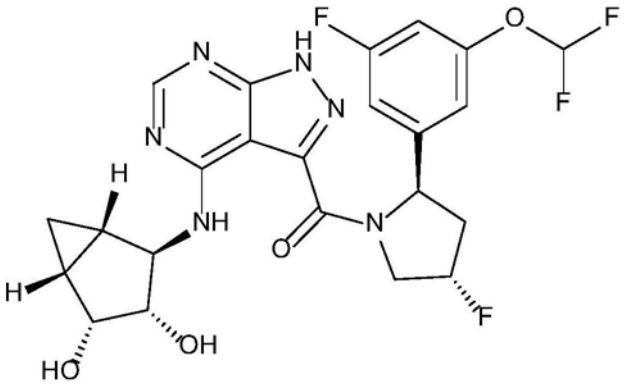

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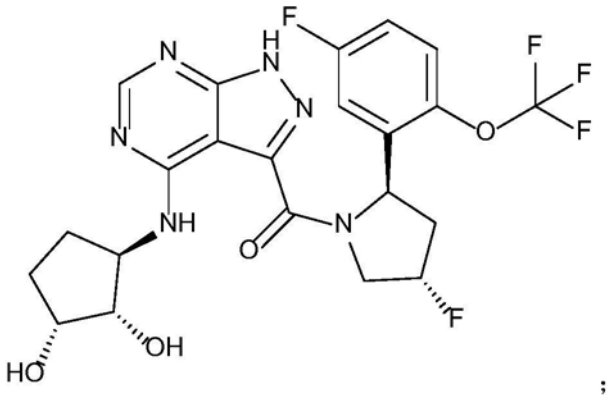

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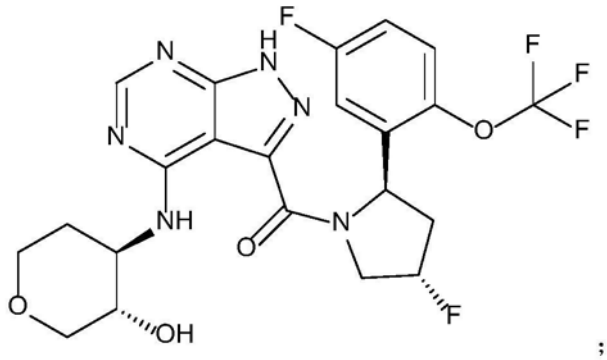

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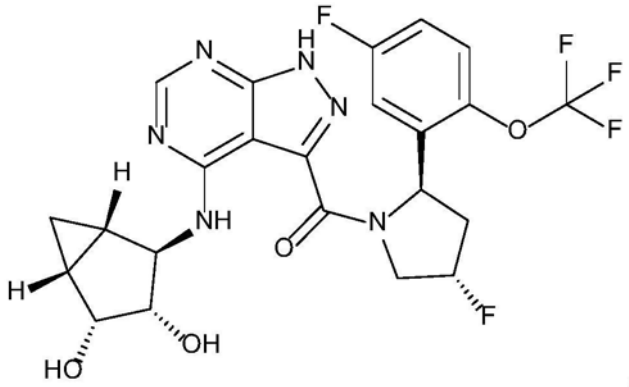

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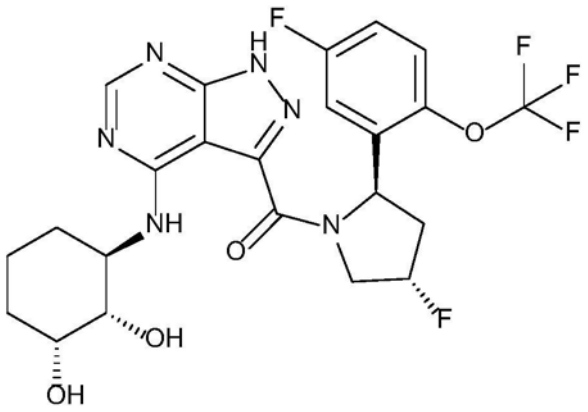

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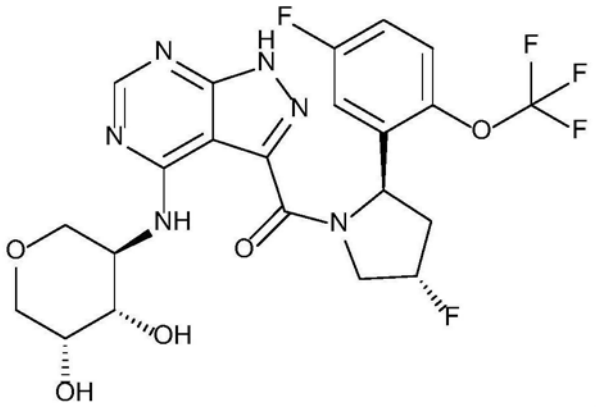

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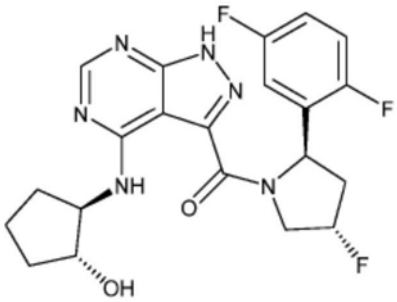
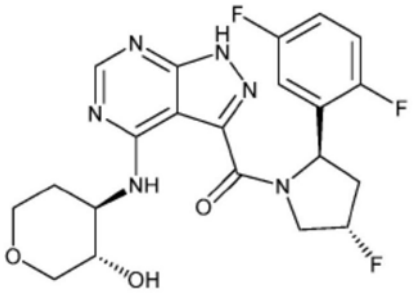
2.一种化合物,其为



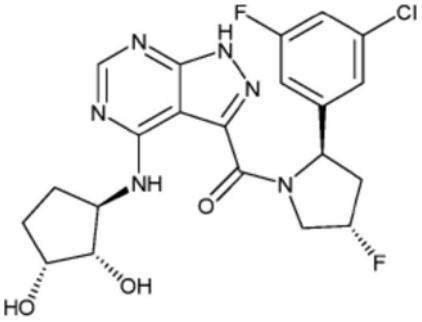
或其药学上可接受的盐。

3.一种化合物,其为



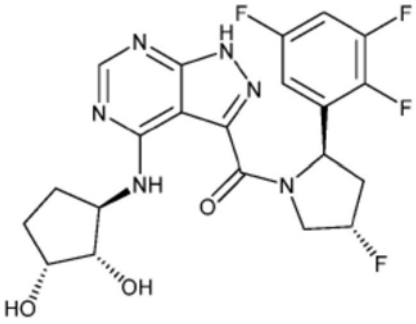
或其药学上可接受的盐。

4.一种化合物,其为



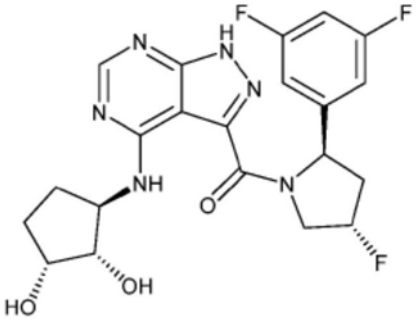
或其药学上可接受的盐。

5.一种化合物,其为



或其药学上可接受的盐。

6.一种化合物,其为



或其药学上可接受的盐。

7.一种药物组合物,其包含:

药学上可接受的载剂;和

如权利要求1至6中任一项所述的化合物,或其药学上可接受的盐。

8.权利要求1至6中任一项中的化合物或其药学上可接受的盐在制备用于治疗患有由异常神经营养酪氨酸受体激酶(NTRK)活性介导的病状的受试者的药物中的应用。

9.权利要求1至6中任一项中的化合物或其药学上可接受的盐在制备用于治疗已对癌症治疗发展抗性的受试者的药物中的应用。

10.权利要求1至6中任一项中的化合物或其药学上可接受的盐在制备用于治疗选自由以下组成的组的病状的药物中的应用:非小细胞肺癌、乳腺癌、黑素瘤、低级和高级神经胶质瘤、胶质母细胞瘤、小儿科星细胞瘤、结直肠癌、乳突甲状腺癌、胰腺癌、头颈部癌、胆管癌、急性髓性白血病、分泌性乳腺癌、唾液癌以及spitz样肿瘤。

适用于治疗与NTRK相关的病症的化合物和组合物

[0001] 优先权要求

[0002] 本申请要求2015年8月26日提交的U.S.S.N.62/210,264的优先权,所述专利以引用的方式整体并入本文。

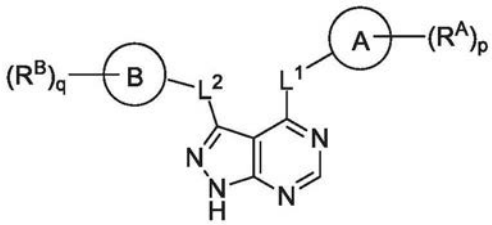
[0003] 先前技术

[0004] 神经营养酪氨酸受体激酶(NTRK)1、2和3为活化参与细胞增殖和存活的多个下游途径的受体酪氨酸激酶(RTK)。由编码这些RTK的基因的异常染色体易位引起的各种基因融合涉及多种癌症的病因,包括高级别和低级别神经胶质瘤、胆管癌、乳突甲状腺癌、结肠癌和非小细胞肺癌。对于激酶融合概貌的基因组学分析识别广泛多种额外癌症类型中的NTRK融合物,包括头颈部鳞状细胞癌、胰腺癌、肉瘤和黑素瘤,从而提供用于部署这些激酶的抑制剂以治疗多个肿瘤学适应症的进一步治疗理论根据。

[0005] 将NTRK融合物识别为某些癌症的潜在病因推进多种NTRK激酶抑制剂的发现和临床研发,以便治疗具有NTRK融合蛋白质的肿瘤。早期临床数据支持此方法在为患有特定人类恶性肿瘤的患者提供益处方面的可行性。然而,最终,尽管存在临床活性的明显迹象,大多数患者的癌症将变得对于激酶抑制剂疗法有抵抗力,导致疾病的复发和进展。通过内在突变的激酶再活化为抗性的常见机制。当发生抗性时,患者的治疗选项往往非常有限。因而需要抑制NTRK,以及其抗性突变体的化合物。

发明内容

[0006] 本发明提供包含式(I)化合物或其药学上可接受的盐的化合物和药物组合物,其中:

[0007] 

式(I)

[0008] 环A和B各自独立地选自芳基、杂芳基、环烷基和杂环基;

[0009] 每个L^1和L^2独立地选自键、-C(O)-、-N(R^1)-、-N(R^1)-C(O)-、-C(O)-N(R^1)-、-(C_1-C_6亚烷基)-N(R^1)-、-N(R^1)-(C_1-C_6亚烷基)-、-N(R^1)-C(O)-(C_1-C_6亚烷基)-以及-C(O)-N(R^1)-(C_1-C_6亚烷基)-;其中每个亚烷基独立地以0-5次出现的R'取代;

[0010] 每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_2-C_6烯基、C_2-C_6炔基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基、杂环烷基、硝基、氰基、-C(O)R^1、-OC(O)R^1、-C(O)OR^1、-(C_1-C_6亚烷基)-C(O)R^1、-SR^1、-S(O)$_2R^1$、-S(O)$_2$-N(R^1)(R^1)、-(C_1-C_6亚烷基)-S(O)$_2R^1$、-(C_1-C_6亚烷基)-S(O)$_2$-N(R^1)(R^1)、-N(R^1)(R^1)、-C(O)-N(R^1)(R^1)、-N(R^1)-C(O)R^1、-N(R^1)-C(O)OR^1、-(C_1-C_6亚烷基)-N

(R^1)-C(O)R^1、-N(R^1)S(O)$_2R^1$以及-P(O)$(R^1)(R^1)$；其中烷基、烯基、炔基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^a取代；或2个R^A或2个R^B与其所连接的碳原子一起形成独立地被0-5次出现的R^a取代的环烷基或杂环基环；

[0011] 每个R^1独立地选自氢、羟基、卤基、硫醇、C_1-C_6烷基、C_1-C_6硫烷基、C_1-C_6烷氧基、C_1-C_6卤烷基、C_1-C_6羟烷基、C_1-C_6杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基，其中烷基、硫烷基、烷氧基、卤烷基、羟烷基、杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^b取代，或者2个R^1与其所连接的原子一起形成独立地以0-5次出现的R^b取代的环烷基或杂环基环；

[0012] 每个R^a和R^b独立地选自C_1-C_6烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6杂烷基、C_1-C_6羟烷基、C_1-C_6烷氧基、环烷基、杂环基以及氰基，其中烷基、卤烷基、杂烷基、羟烷基、烷氧基、环烷基以及杂环基中的每一者独立地以0-5次出现的R'取代；

[0013] 每个R'独立地选自C_1-C_6烷基、C_1-C_6杂烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6羟烷基、环烷基以及氰基；或者2个R'与其所连接的原子一起形成环烷基或杂环基环；

[0014] p为0、1、2、3、4或5；并且

[0015] q为0、1、2、3或4。

[0016] 本文公开的任何化合物可单独或与另一个治疗剂组合用于治疗本文公开的任何疾病。

[0017] 附图简述

[0018] 图1描绘本发明的各种示例性化合物的结构以及其如通过LC-MS确定的NMR峰和质量。

[0019] 发明详述

[0020] 定义

[0021] 如本文使用，术语“患者”、“受试者”、“个体”和“宿主”是指患有或疑似患有与异常NTRK表现(即，通过经由NTRK的信号传导所导致的NTRK活性增加)或生物活性相关的疾病或病症的人类或非人类动物。

[0022] “治疗(Treat/treating)”此疾病或病症是指改善疾病或病症的至少一个症状。这些术语在结合病状诸如癌症来使用时是指以下一种或多种：阻碍癌症生长、导致癌症重量或体积缩小、延长患者的预期存活时间、抑制肿瘤生长、减少肿瘤质量、减少转移性病灶的大小或数目、抑制新转移性病灶的发展、延长存活、延长无进展存活、延长进展时间和/或增强生活品质。

[0023] 术语“预防”在结合病状或疾病诸如癌症使用时是指降低病状或疾病的症状的频率或延迟其发作。因此，预防癌症包括例如相对于未治疗的对照群体减少接受预防性治疗的患者群体中的可检测癌性生长的数目和/或相比于未治疗的对照群体延迟所治疗群体中的可检测癌性生长的出现，例如，以在统计上和/或临床上显著的量。

[0024] 术语“治疗效果”是指通过施用本发明的化合物或组合物在动物(尤其是哺乳动物)并且更具体而言在人类中所引起的有利的局部或全身效果。短语“治疗有效量”意指本发明的化合物或组合物以合理风险比有效于治疗由NTRK的过表达或异常NTRK生物活性所造成的疾病或病状的量。此材料的治疗有效量将根据正在治疗的受试者和疾病病状、所述

受试者的体重和年龄、所述疾病病状的严重性、施用方式及其类似情况来改变，这可由本领域技术人元容易地确定。

[0025] 如本文使用，“发展抗性”意谓在药物首次施用于患者时，患者的症状改善，不论通过肿瘤体积的减少、新病灶的数目减少或医师用于判断疾病进展的一些其他手段来测量；然而，那些症状在某一时点停止改善或甚至恶化。在此时，患者被认为对于药物显现抗性。

[0026] “脂族基团”是指直链、支链或环烃基团并且包括饱和和不饱和基团，诸如烷基、烯基和炔基。

[0027] “亚烷基”是指烷基的二价基团，例如$-CH_2-$、$-CH_2CH_2-$和$CH_2CH_2CH_2-$。

[0028] “烯基”意指含有至少一个双键的脂族基团。

[0029] “烷氧基”意指具有与其所连接的氧基的烷基。代表性烷氧基包括甲氧基、乙氧基、丙氧基、叔丁氧基及其类似基团。术语“卤烷氧基”是指一个或多个氢原子被卤基替代的烷氧基，并包括所有氢已被卤基替代的烷氧基部分(例如，全氟烷氧基)。

[0030] “烷基”是指饱和直链或支链烃的单价基团，诸如1-12、1-10或1-6个碳原子的直链或支链基团，在本文中分别称为C_1-C_{12}烷基、C_1-C_{10}烷基和C_1-C_6烷基。示例性烷基包括但不限于甲基、乙基、丙基、异丙基、2-甲基-1-丙基、2-甲基-2-丙基、2-甲基-1-丁基、3-甲基-1-丁基、2-甲基-3-丁基、2,2-二甲基-1-丙基、2-甲基-1-戊基、3-甲基-1-戊基、4-甲基-1-戊基、2-甲基-2-戊基、3-甲基-2-戊基、4-甲基-2-戊基、2,2-二甲基-1-丁基、3,3-二甲基-1-丁基、2-乙基-1-丁基、丁基、异丁基、叔丁基、戊基、异戊基、新戊基、己基、庚基、辛基等。

[0031] “亚烯基”是指具有两个连接点的烯基。举例而言，“亚乙烯基”表示基团$-CH=CH-$。亚烯基也可为具有一个或多个取代基的未取代形式或取代形式。

[0032] “炔基”是指含有2-12个碳原子并且特征在于具有一个或多个三键的直链或支链烃链。炔基的实例包括但不限于乙炔基、炔丙基和3-己炔基。一个三键碳可任选地为炔基取代基的连接点。

[0033] “亚炔基”是指具有两个连接点的炔基。举例而言，“亚乙炔基”表示基团$-C\equiv C-$。亚炔基也可为具有一个或多个取代基的未取代形式或取代形式。

[0034] “羟亚烷基”或“羟烷基”是指其中亚烷基或烷基氢原子被羟基置换的亚烷基或烷基部分。羟亚烷基或羟烷基包括其中超过一个氢原子已被羟基置换的基团。

[0035] “芳族环系统”为本领域公认的并且是指单环、双环或多环烃环系统，其中至少一个环为芳族。

[0036] “芳基”是指芳族环系统的单价基团。代表性芳基包括完全芳族环系统，诸如苯基、萘基和蒽基，以及其中芳族碳环稠合至一个或多个非芳族碳环的环系统，诸如二氢茚基、邻苯二甲酰亚胺基、萘二甲酰亚胺基或四氢萘基，及其类似基团。

[0037] “芳基烷基”或“芳烷基”是指烷基氢原子被芳基置换的烷基部分。芳烷基包括超过一个氢原子已被芳基置换的基团。“芳基烷基”或“芳烷基”的实例包括苯甲基、2-苯基乙基、3-苯基丙基、9-芴基、二苯甲基和三苯甲基。

[0038] “芳氧基”是指-O-(芳基)，其中杂芳基部分为如本文定义的。

[0039] “卤基”是指任何卤素的基团，例如，-F、-Cl、-Br或-I。

[0040] “卤烷基”和“卤烷氧基”是指被一个或多个卤基或其组合取代的烷基和烷氧基结构。举例而言，术语“氟烷基”和“氟烷氧基”分别包括其中卤基为氟的卤烷基和卤烷氧基。

[0041] “卤亚烷基”是指二价烷基，例如，$-CH_2-$、$-CH_2CH_2-$和$-CH_2CH_2CH_2-$，其中一个或多个氢原子被卤基置换，并且包括其中所有氢被卤基置换的烷基部分。

[0042] “杂烷基”意指任选地取代的烷基，其具有的一个或多个骨架链原子选自不为碳的原子，例如氧、氮、硫、磷或其组合。可给定数值范围，例如C_1-C_6杂烷基是指链中的碳的数目，其在此实例中包括1至6个碳原子。举例而言，$-CH_2OCH_2CH_3$基团被称为“C_3”杂烷基。与分子结构的其余部分的连接可通过杂烷基链中的杂原子或碳达成。“杂亚烷基”意指二价的任选地取代的烷基，其具有的一个或多个骨架链原子选自不为碳的原子，例如氧、氮、硫、磷或其组合。

[0043] “碳环环系统”是指单环、双环或多环烃环系统，其中每个环为完全饱和的或含有一个或多个不饱和单位，但是其中没有环是芳族环。

[0044] “碳环基”是指碳环环系统的单价基团。代表性碳环基团包括环烷基(例如，环戊基、环丁基、环戊基、环己基及其类似基团)以及环烯基(例如，环戊烯基、环己烯基、环戊二烯基及其类似基团)。

[0045] “环烷基”是指具有3至12个碳的环状、双环、三环或多环非芳族烃基团。任何可取代环原子皆可被取代(例如被一个或多个取代基取代)。环烷基可含有稠环或螺环。稠环为共享共同碳原子的环。环烷基部分的实例包括但不限于环丙基、环己基、甲基环己基、金刚烷基和降冰片基。在一些实施方案中，环烷基为双环[3.1.0]己基。

[0046] “环烷基烷基”是指-(环烷基)-烷基，其中环烷基和烷基为如本文公开的。“环烷基烷基”通过环烷基与母体分子结构键合。

[0047] “杂芳族环系统”为本领域公认的并且是指单环、双环或多环环系统，其中至少一个环为芳族并且包含至少一个杂原子(例如，N、O或S)；并且其中没有其他环为杂环基(如以下定义)。在某些情况下，作为芳族并包含杂原子的环在此环中含有1、2、3或4个环杂原子。

[0048] “杂芳基”是指杂芳族环系统的单价基团。代表性杂芳基包括环系统，其中(i)每个环包含杂原子并且为芳族，例如，咪唑基、噁唑基、噻唑基、三唑基、吡咯基、呋喃基、噻吩基吡唑基、吡啶基、吡嗪基、哒嗪基、嘧啶基、吲嗪基、嘌呤基、萘啶基和蝶啶基；(ii)每个环为芳族或碳环基，至少一个芳族环包含杂原子并且至少一个其他环为烃环，或者例如吲哚基、异吲哚基、苯并噻吩基、苯并呋喃基、二苯并呋喃基、吲唑基、苯并咪唑基、苯并噻唑基、喹啉基、异喹啉基、噌啉基、酞嗪基、喹唑啉基、喹喔啉基、咔唑基、吖啶基、吩嗪基、吩噻嗪基、吩噁嗪基、吡啶并[2,3-b]-1,4-噁嗪-3-(4H)-酮、5,6,7,8-四氢喹啉基以及5,6,7,8-四氢异喹啉基；并且(iii)每个环为芳族或碳环基，并且至少一个芳族环与另一个芳族环共享桥头杂原子，例如，4H-喹嗪基。

[0049] “杂环环系统”是指单环、双环和多环系统，其中至少一个环为饱和或部分不饱和的(但并非芳族)并且包含至少一个杂原子。杂环环系统可在任何杂原子或碳原子处连接至其侧基以得到稳定结构并且任一环原子均可任选地被取代。

[0050] “杂环基”是指杂环环系统的单价基团。代表性杂环基包括环系统，其中(i)每个环为非芳族并且至少一个环包含杂原子，例如，四氢呋喃基、四氢吡喃基、四氢噻吩基、吡咯烷基、吡咯烷酮基、哌啶基、吡咯啉基、十氢喹啉基、噁唑烷基、哌嗪基、二氧杂环己烷、二氧杂环戊烷、二氮杂卓基、氧氮杂卓基、硫氮杂卓基、吗啉基和奎宁环基；(ii)至少一个环为非芳族并且包含杂原子并且至少一个其他环为芳族碳环，例如，1,2,3,4-四氢喹啉基、1,2,3,4-

四氢异喹啉基;并且(iii)至少一个环为非芳族并且包含杂原子并且至少一个其他环为芳族并且包含杂原子,例如,3,4-二氢-1H-吡喃并[4,3-c]吡啶和1,2,3,4-四氢-2,6-萘啶。

[0051] “杂环基烷基”是指被杂环基团取代的烷基。

[0052] “氰基”是指-CN基团。

[0053] “硝基”是指基团-NO_2。

[0054] “羟基(hydroxy)”或“羟基(hydroxyl)”是指基团-OH。

[0055] “羟亚烷基”是指二价烷基,例如,-CH_2-、-CH_2CH_2-和-$CH_2CH_2CH_2$-,其中一个或多个氢原子被羟基置换,并且包括其中所有氢被羟基置换的烷基部分。

[0056] “取代的”无论是否前置有术语“任选地”都意指指定部分的一个或多个氢被适合取代基置换。除非另外指示,否则“任选取代的”基团可在基团的每个可取代位置处具有适合取代基,并且当任何给定结构中的超过一个位置可被超过一个选自指定组的取代基取代时,在每个位置的取代基可以相同或不同。在本发明下设想的取代基的组合优选地为使得形成稳定或化学可行化合物的组合。如本文所用的术语“稳定”是指化合物在经受允许其产生、检测以及在某些实施方案中允许其回收、纯化和用于本文公开的一种或多种目的的条件时基本上不会改变。

[0057] 如本文所用,当例如烷基、m、n等的各表述在任何结构中出现超过一次时,其定义旨在独立于其在相同结构中的其他位置的定义。

[0058] 本发明的某些化合物可以特定几何或立体异构形式存在。本发明涵盖所有这些化合物,包括属于本发明范围内的顺式-和反式-异构物、R-和S-对映异构物、非对映异构物、(D)-异构物、(L)-异构物、其外消旋混合物及其他混合物。额外不对称碳原子可存在于取代基诸如烷基中。所有这些异构物以及其混合物旨在包括于本发明中。

[0059] 如果例如需要本发明的化合物的特定对映异构物,其可通过不对称合成或通过使用手性助剂衍生化来制备,其中将所得非对映异构混合物分离并且辅助基团裂解以提供纯的所需对映异构物。或者,当分子含有碱性官能基(诸如氨基)或酸性官能基(诸如羧基)时,使用合适光学活性酸或碱来形成非对映异构盐,随后将由此形成的非对映异构物通过在本领域中熟知的分级结晶或色谱方法来拆分,并且随后回收纯对映异构物。

[0060] 除非另外指示,否则当公开的化合物由未规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,应理解其表示所述化合物的所有可能的立体异构物以及其对映异构混合物。可使用以下所示的等式计算组合物的“对映异构过量”或“对映异构过量%”。在以下所示的实例中,组合物含有90%的一种对映异构物(例如S-对映异构物)和10%的另一种对映异构物(即R-对映异构物)。

[0061] ee=(90-10)/100=80%。

[0062] 因此,认为含有90%的一种对映异构物和10%的另一种对映异构物的组合物具有80%的对映异构过量。

[0063] 本文所述的化合物或组合物可含有至少50%、75%、90%、95%或99%对映异构过量的一种形式的化合物,例如,S-对映异构物。换言之,此类组合物含有相对于R对映异构物而言对映异构过量的S对映异构物。

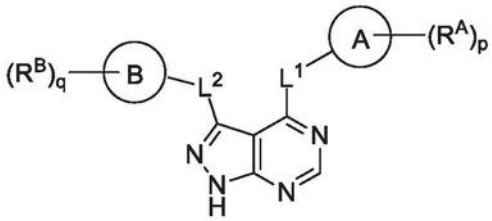
[0064] 本文所述的化合物也可在构成这些化合物的一个或多个原子处含有非天然比例的原子同位素。举例而言,化合物可用放射性同位素(例如像氘(^2H)、氚(^3H)、碘-13(^{13}C)或

碳-14(^{14}C))进行放射性标记。本文公开的化合物的所有同位素变化形式,无论是否具有放射性,都旨在涵盖在本发明的范围内。另外,本文描述的化合物的所有互变异构形式旨在处于本发明的范围内。

[0065] 化合物可呈游离碱形式呈盐形式而适用。代表性盐包括氢溴酸盐、盐酸盐、硫酸盐、硫酸氢盐、磷酸盐、硝酸盐、乙酸盐、戊酸盐、油酸盐、棕榈酸盐、硬脂酸盐、月桂酸盐、苯甲酸盐、乳酸盐、磷酸盐、甲苯磺酸盐、柠檬酸盐、马来酸盐、富马酸盐、琥珀酸盐、酒石酸盐、萘甲酸盐、甲磺酸盐、葡庚糖酸盐、乳糖醛酸盐和月桂基磺酸盐及其类似物。(参见例如Berge等人(1977)"Pharmaceutical Salts",J.Pharm.Sci.66:1-19。)

[0066] 化合物

[0067] 本发明提供式(I)化合物或其立体异构物、对映异构物、互变异构物或同位素标记形式,或任何前述材料的药学上可接受的盐,其中:

[0068] 

[0069] 式(I)

[0070] 环A和B各自独立地选自芳基、杂芳基、环烷基和杂环基;

[0071] 每个L^1和L^2独立地选自键、-C(O)-、-N(R^1)-、-N(R^1)-C(O)-、-C(O)-N(R^1)-、-(C_1-C_6亚烷基)-N(R^1)-、-N(R^1)-(C_1-C_6亚烷基)-、-N(R^1)-C(O)-(C_1-C_6亚烷基)-以及-C(O)-N(R^1)-(C_1-C_6亚烷基)-;其中每个亚烷基独立地以0-5次出现的R'取代;

[0072] 每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_2-C_6烯基、C_2-C_6炔基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基、杂环烷基、硝基、氰基、-C(O)R^1、-OC(O)R^1、-C(O)OR^1、-(C_1-C_6亚烷基)-C(O)R^1、-SR^1、-S(O)$_2R^1$、-S(O)$_2$-N(R^1)(R^1)、-(C_1-C_6亚烷基)-S(O)$_2R^1$、-(C_1-C_6亚烷基)-S(O)$_2$-N(R^1)(R^1)、-N(R^1)(R^1)、-C(O)-N(R^1)(R^1)、-N(R^1)-C(O)R^1、-N(R^1)-C(O)OR^1、-(C_1-C_6亚烷基)-N(R^1)-C(O)R^1、-N(R^1)S(O)$_2R^1$以及-P(O)(R^1)(R^1);其中烷基、烯基、炔基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^a取代;或者2个R^A或2个R^B与其所连接的碳原子一起形成独立地以0-5次出现的R^a取代的环烷基或杂环基环;

[0073] 每个R^1独立地选自氢、羟基、卤基、硫醇、C_1-C_6烷基、C_1-C_6硫烷基、C_1-C_6烷氧基、C_1-C_6卤烷基、C_1-C_6羟烷基、C_1-C_6杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基,其中烷基、硫烷基、烷氧基、卤烷基、羟烷基、杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^b取代,或者2个R^1与其所连接的原子一起形成独立地以0-5次出现的R^b取代的环烷基或杂环基环;

[0074] 每个R^a和R^b独立地选自C_1-C_6烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6杂烷基、C_1-C_6羟烷基、C_1-C_6烷氧基、环烷基、杂环基以及氰基,其中烷基、卤烷基、杂烷基、羟烷基、烷氧基、环烷基以及杂环基中的每一者独立地以0-5次出现的R'取代;

[0075] 每个R'独立地选自C_1-C_6烷基、C_1-C_6杂烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6羟烷基、

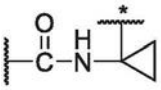
环烷基以及氰基;或者2个R'与其所连接的原子一起形成环烷基或杂环基环;并且

[0076] p为0、1、2、3、4或5;并且

[0077] q为0、1、2、3或4。

[0078] 在一些实施方案中,环A为环烷基。在一些实施方案中,环A为5元或6元环烷基环。在一些实施方案中,环A为环戊基或环己基。在一些实施方案中,环A为杂环基。在一些实施方案中,环A为5元或6元杂环基。在一些实施方案中,环A为四氢吡喃基、四氢呋喃基或吡咯烷基。在一些实施方案中,环A为环烯基环。在一些实施方案中,环A为环戊烯基。

[0079] 在一些实施方案中,环B为芳基。在一些实施方案中,环B为苯基。在一些实施方案中,环B为杂芳基。在一些实施方案中,环B为吡啶基。在一些实施方案中,环B为杂环基。在一些实施方案中,环B为吡咯烷基。

[0080] 在一些实施方案中,L^1为键、-C(O)-或-N(R^1)-;并且L^2为-N(R^1)-C(O)-(C_1-C_6亚烷基)-或-C(O)-N(R^1)-(C_1-C_6亚烷基)-。在一些实施方案中,L^1为-NH-并且L^2为-C(O)-NH-CH(CH_2OH)-*、-C(O)-N(CH_3)-CH_2-*、-C(O)-N(CH_3)-CH(CH_3)-*、-C(O)N(CH_2CH_3)CH_2-*、-C(O)NHCH(CH_3)-*、-C(O)N(CD_3)CH_2-*、-C(O)NHCH(CF_3)-*以及  ,其中"*"表示结合至环B的L^2的一部分。在一些实施方案中,L^1为-NH-,L^2为-C(O)-并且环B为吡咯烷基。在一些实施方案中,L^1为-NH-,L^2为-C(O)-并且环B为吡咯烷-1-基。

[0081] 在一些实施方案中,每个R^1独立地选自氢和以0-5次出现的R^b取代的C_1-C_6烷基。在一些实施方案中,每个R^1独立地选自氢和-CH_3。

[0082] 在一些实施方案中,每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、硝基、氰基、-C(O)R^1、-OC(O)R^1、-C(O)OR^1、-SR^1、-S(O)$_2R^1$、-S(O)$_2$-N(R^1)(R^1)、-N(R^1)(R^1)、-C(O)-N(R^1)(R^1)、-N(R^1)-C(O)R^1、-N(R^1)-C(O)OR^1以及-N(R^1)S(O)$_2R^1$;其中烷基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基以及杂芳基中的每一者独立地以0-5次出现的R^a取代;或者2个R^A或2个R^B与其所连接的碳原子一起形成独立地以0-5次出现的R^a取代的环烷基或杂环基环。

[0083] 在一些实施方案中,每个R^A独立地选自羟基、C_1-C_6烷基、C_1-C_6烷氧基、卤基、-C(O)-N(R^1)(R^1)、-C(O)OR^1、-S(O)$_2R^1$以及C_1-C_6卤烷基。在一些实施方案中,每个R^A另外且独立地选自-CN、氧杂环丁烷基和C_1-C_6羟烷基,或结合至环A上的相邻环碳原子的两个R^A结合在一起以形成稠合至环A的C_3-C_6环烷基。在一些实施方案中,每个R^A独立地选自羟基、氟代、氧杂环丁烷-3-基、-CHF_2、-CH_2CH_3、-C(CH_3)$_2$OH、-OCH_3、-C(O)N(CH_3)$_2$、-C(O)OCH_3、-S(O)$_2CH_3$;或者结合至环A上的相邻环碳原子的两个R^A结合在一起以形成稠合至环A的环丙基。

[0084] 在一些实施方案中,每个R^B独立地选自卤基、C_1-C_6烷基、氰基、C_1-C_6烷氧基、芳基、杂芳基以及C_1-C_6卤烷氧基。在一些实施方案中,每个R^B另外选自氧基。

[0085] 在一些实施方案中,环B为吡咯烷基并且至少一个R^B为任选地取代的芳基或杂芳基。在一些实施方案中,环B为吡咯烷基并且至少一个R^B为任选地取代的苯基或吡啶基。

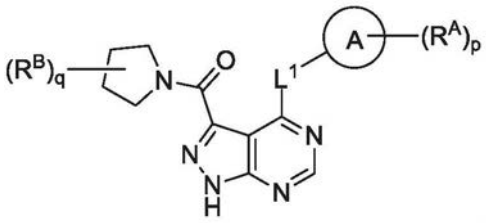
[0086] 在一些实施方案中,环B为吡咯烷基,并且至少一个R^B选自2,3,5-三氟苯基、2,3-二氟苯基、2,5-二氟苯基、2-氯-5-氟苯基、2-氯-5-氟吡啶-3-基、2-氰基-5-氟苯基、2-氟-5-氯苯基、2-甲氧基-3,5-二氟苯基、2-甲氧基-5-氟吡啶-3-基、2-三氟甲氧基-5-氟苯基、

3,5-二氟苯基、3-氯-5-氟苯基、3-氰基-5-氟苯基、3-二氟甲氧基-5-氟苯基、3-氟苯基、5-氟吡啶-3-基以及苯基。

[0087] 在一些实施方案中，环B为吡咯烷基并且一个额外R^B，如果存在，则为氟代。

[0088] 在一些实施方案中，环B不同于吡咯烷基，并且每个R^B独立地选自氯代、氟代、氧基、$-CH_3$、$-CF_3$、-CN、$-OCH_3$、$-OCF_3$以及$-OCHF_2$。

[0089] 在另一方面中，本发明提供式(Ia)化合物：

[0090]  (Ia)，或其立体异构物、对映异构物、互变异构物或同位素标记形式，或任何前述材料的药学上可接受的盐，其中：

[0091] 环A选自芳基、杂芳基、环烷基以及杂环基；

[0092] L^1独立地选自键、$-C(O)-$、$-N(R^1)-$、$-N(R^1)-C(O)-$、$-C(O)-N(R^1)-$、$-(C_1-C_6$亚烷基$)-N(R^1)-$、$-N(R^1)-(C_1-C_6$亚烷基$)-$、$-N(R^1)-C(O)-(C_1-C_6$亚烷基$)-$以及$-C(O)-N(R^1)-(C_1-C_6$亚烷基$)-$；其中每个亚烷基独立地以0-5次出现的R'取代；

[0093] 每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_2-C_6烯基、C_2-C_6炔基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基、杂环烷基、硝基、氰基、$-C(O)R^1$、$-OC(O)R^1$、$-C(O)OR^1$、$-(C_1-C_6$亚烷基$)-C(O)R^1$、$-SR^1$、$-S(O)_2R^1$、$-S(O)_2-N(R^1)(R^1)$、$-(C_1-C_6$亚烷基$)-S(O)_2R^1$、$-(C_1-C_6$亚烷基$)-S(O)_2-N(R^1)(R^1)$、$-N(R^1)(R^1)$、$-C(O)-N(R^1)(R^1)$、$-N(R^1)-C(O)R^1$、$-N(R^1)-C(O)OR^1$、$-(C_1-C_6$亚烷基$)-N(R^1)-C(O)R^1$、$-N(R^1)S(O)_2R^1$以及$-P(O)(R^1)(R^1)$；其中烷基、烯基、炔基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^a取代；或者2个R^A或2个R^B与其所连接的碳原子一起形成独立地以0-5次出现的R^a取代的环烷基或杂环基环；

[0094] 每个R^1独立地选自氢、羟基、卤基、硫醇、C_1-C_6烷基、C_1-C_6硫烷基、C_1-C_6烷氧基、C_1-C_6卤烷基、C_1-C_6羟烷基、C_1-C_6杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基，其中烷基、硫烷基、烷氧基、卤烷基、羟烷基、杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^b取代，或者2个R^1与其所连接的原子一起形成独立地以0-5次出现的R^b取代的环烷基或杂环基环；

[0095] 每个R^a和R^b独立地选自C_1-C_6烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6杂烷基、C_1-C_6羟烷基、C_1-C_6烷氧基、环烷基、杂环基以及氰基，其中烷基、卤烷基、杂烷基、羟烷基、烷氧基、环烷基以及杂环基中的每一者独立地以0-5次出现的R'取代；

[0096] 每个R'独立地选自C_1-C_6烷基、C_1-C_6杂烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6羟烷基、环烷基以及氰基；或者2个R'与其所连接的原子一起形成环烷基或杂环基环；并且

[0097] p为0、1、2、3、4或5；并且

[0098] q为0、1、2、3或4。

[0099] 在一些实施方案中，环A为环烷基。在一些实施方案中，环A为5元或6元环烷基环。在一些实施方案中，环A为环戊基或环己基。在一些实施方案中，环A为杂环基。在一些实施

方案中，环A为5元或6元杂环基。在一些实施方案中，环A为四氢吡喃、四氢呋喃或吡咯烷基。在一些实施方案中，环A为环烯基环。在一些实施方案中，环A为环戊烯基。

[0100] 在一些实施方案中，L^1为一键、-C(O)-或-N(R^1)-。在一些实施方案中，L^1为-NH-。

[0101] 在一些实施方案中，每个R^1独立地选自氢和以0-5次出现的R^b取代的C_1-C_6烷基。在一些实施方案中，每个R^1独立地选自氢和-CH_3。

[0102] 在一些实施方案中，每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、硝基、氰基、-C(O)R^1、-OC(O)R^1、-C(O)OR^1、-SR^1、-S(O)$_2R^1$、-S(O)$_2$-N(R^1)(R^1)、-N(R^1)(R^1)、-C(O)-N(R^1)(R^1)、-N(R^1)-C(O)R^1、-N(R^1)-C(O)OR^1以及-N(R^1)S(O)$_2R^1$；其中烷基、烯基、炔基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^a取代；或2个R^A或2个R^B与其连接的碳原子一起形成独立地以0-5次出现的R^a取代的环烷基或杂环基环。

[0103] 在一些实施方案中，每个R^A独立地选自羟基、C_1-C_6烷基、C_1-C_6烷氧基、卤基、-C(O)-N(R^1)(R^1)、-C(O)OR^1、-S(O)$_2R^1$和C_1-C_6卤烷基。在一些实施方案中，每个R^A另外且独立地选自-CN、氧杂环丁烷基和C_1-C_6羟烷基，或者结合至环A上的相邻环碳原子的两个R^A结合在一起以形成稠合至环A的C_3-C_6环烷基。在一些实施方案中，每个R^A独立地选自羟基、氟代、氧杂环丁烷-3-基、-CHF_2、-CH_2CH_3、-C(CH_3)$_2$OH、-OCH_3、-C(O)N(CH_3)$_2$、-C(O)OCH_3、-S(O)$_2CH_3$；或者结合至环A上的相邻环碳原子的两个R^A结合在一起以形成稠合至环A的环丙基。

[0104] 在一些实施方案中，每个R^B独立地选自卤基、C_1-C_6烷基、氰基、C_1-C_6烷氧基、芳基、杂芳基以及C_1-C_6卤烷氧基。在一些实施方案中，每个R^B另外选自氧基。

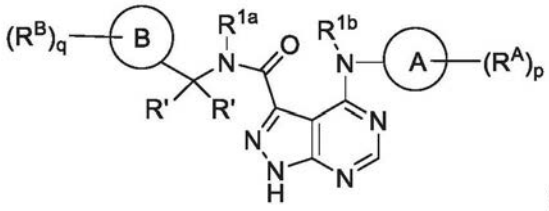
[0105] 在一些实施方案中，在环B为吡咯烷基时，至少一个R^B选自2,3,5-三氟苯基、2,3-二氟苯基、2,5-二氟苯基、2-氯-5-氟苯基、2-氯-5-氟吡啶-3-基、2-氰基-5-氟苯基、2-氟-5-氯苯基、2-甲氧基-3,5-二氟苯基、2-甲氧基-5-氟吡啶-3-基、2-三氟甲氧基-5-氟苯基、3,5-二氟苯基、3-氯-5-氟苯基、3-氰基-5-氟苯基、3-二氟甲氧基-5-氟苯基、3-氟苯基、5-氟吡啶-3-基以及苯基。

[0106] 在一些实施方案中，当环B为吡咯烷基时，一个额外R^B，如果存在，为氟代。

[0107] 在一些实施方案中，p为0、1或2。

[0108] 在一些实施方案中，q为1、2或3。

[0109] 在另一方面中，本发明提供式(II)化合物：

[0110] 

(II)，或其立体异构物、对映异构物、互变异构物或同位素标记形式，或任何前述材料的药学上可接受的盐，其中：

[0111] 环A和B各自独立地选自芳基、杂芳基、环烷基和杂环基；

[0112] 每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_2-C_6烯基、C_2-C_6炔基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基、杂环烷基、硝基、氰基、-C(O)R^1、-OC(O)R^1、-C(O)OR^1、-(C_1-C_6亚烷基)-C(O)R^1、-

SR^1、$-S(O)_2R^1$、$-S(O)_2-N(R^1)(R^1)$、$-(C_1-C_6$亚烷基$)-S(O)_2R^1$、$-(C_1-C_6$亚烷基$)-S(O)_2-N(R^1)(R^1)$、$-N(R^1)(R^1)$、$-C(O)-N(R^1)(R^1)$、$-N(R^1)-C(O)R^1$、$-N(R^1)-C(O)OR^1$、$-(C_1-C_6$亚烷基$)-N(R^1)-C(O)R^1$、$-N(R^1)S(O)_2R^1$以及$-P(O)(R^1)(R^1)$；其中烷基、烯基、炔基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基、杂芳基、芳氧基、芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^a取代；或者2个R^A或2个R^B与其所连接的碳原子一起形成独立地以0-5次出现的R^a取代的环烷基或杂环基环；

[0113] 每个R^1独立地选自氢、羟基、卤基、硫醇、C_1-C_6烷基、C_1-C_6硫烷基、C_1-C_6烷氧基、C_1-C_6卤烷基、C_1-C_6羟烷基、C_1-C_6杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基，其中烷基、硫烷基、烷氧基、卤烷基、羟烷基、杂烷基、环烷基、环烷基烷基、杂芳烷基、杂环基以及杂环烷基中的每一者独立地以0-5次出现的R^b取代，或者2个R^1与其所连接的原子一起形成独立地以0-5次出现的R^b取代的环烷基或杂环基环；

[0114] R^{1a}选自氢、C_1-C_6烷基和氘化C_1-C_6烷基；

[0115] R^{1b}选自氢和C_1-C_6烷基；

[0116] 每个R^a和R^b独立地选自C_1-C_6烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6杂烷基、C_1-C_6羟烷基、C_1-C_6烷氧基、环烷基、杂环基以及氰基，其中烷基、卤烷基、杂烷基、羟烷基、烷氧基、环烷基以及杂环基中的每一者独立地以0-5次出现的R'取代；

[0117] 每个R'独立地选自C_1-C_6烷基、C_1-C_6杂烷基、卤基、羟基、C_1-C_6卤烷基、C_1-C_6羟烷基、环烷基以及氰基；或者2个R'与其所连接的原子一起形成环烷基或杂环基环；并且

[0118] p为0、1、2、3、4或5；并且

[0119] q为0、1、2、3或4。

[0120] 在一些实施方案中，环A为环烷基。在一些实施方案中，环A为5元或6元环烷基环。在一些实施方案中，环A为环戊基或环己基。在一些实施方案中，环A为杂环基。在一些实施方案中，环A为5元或6元杂环基。在一些实施方案中，环A为四氢吡喃、四氢呋喃或吡咯烷基。在一些实施方案中，环A为环烯基环。在一些实施方案中，环A为环戊烯基。

[0121] 在一些实施方案中，环B为芳基。在一些实施方案中，环B为苯基。在一些实施方案中，B为杂芳基。在一些实施方案中，环B为吡啶基。

[0122] 在一些实施方案中，每个R^1独立地选自氢和以0-5次出现的R^b取代的C_1-C_6烷基。

[0123] 在一些实施方案中，R^{1a}为氢、$-CH_3$、$-CD_3$或$-CH_2CH_3$。

[0124] 在一些实施方案中，R^{1b}为氢。

[0125] 在一些实施方案中，每个R^A和R^B独立地选自羟基、C_1-C_6烷基、C_1-C_6烷氧基、卤基、C_1-C_6杂烷基、C_1-C_6卤烷基、C_1-C_6卤烷氧基、C_1-C_6羟烷基、环烷基、芳基、杂芳基、硝基、氰基、$-C(O)R^1$、$-OC(O)R^1$、$-C(O)OR^1$、$-SR^1$、$-S(O)_2R^1$、$-S(O)_2-N(R^1)(R^1)$、$-N(R^1)(R^1)$、$-C(O)-N(R^1)(R^1)$、$-N(R^1)-C(O)R^1$、$-N(R^1)-C(O)OR^1$以及$-N(R^1)S(O)_2R^1$；其中烷基、烷氧基、杂烷基、卤烷基、卤烷氧基、羟烷基、环烷基、芳基以及杂芳基中的每一者独立地以0-5次出现的R^a取代；或者2个R^A或2个R^B与其所连接的碳原子一起形成独立地以0-5次出现的R^a取代的环烷基或杂环基环。

[0126] 在一些实施方案中，每个R^A独立地选自羟基、C_1-C_6烷基、C_1-C_6烷氧基、卤基、$-C(O)-N(R^1)(R^1)$、$-C(O)OR^1$、$-S(O)_2R^1$以及C_1-C_6卤烷基。在一些实施方案中，每个R^A另外且独立地选自-CN、氧杂环丁烷基和C_1-C_6羟烷基，或者结合至环A上的相邻环碳原子的两个R^A结合在一

起以形成稠合至环A的C_3-C_6环烷基。在一些实施方案中，每个R^A独立地选自羟基、氟代、氧杂环丁烷-3-基、-CHF_2、-CH_2CH_3、-$C(CH_3)_2OH$、-OCH_3、-$C(O)N(CH_3)_2$、-$C(O)OCH_3$、-$S(O)_2CH_3$；或者结合至环A上的相邻环碳原子的两个R^A结合在一起以形成稠合至环A的环丙基。

[0127] 在一些实施方案中，每个R^B独立地选自卤基、C_1-C_6烷基、氰基、C_1-C_6烷氧基、芳基、杂芳基以及C_1-C_6卤烷氧基。在一些实施方案中，每个R^B另外选自氧基。在一些实施方案中，每个R^B独立地选自氯代、氟代、氧基、-CH_3、-CF_3、-CN、-OCH_3、-OCF_3以及-$OCHF_2$。

[0128] 在一些实施方案中，每个R'独立地选自C_1-C_6烷基、C_1-C_6卤烷基和C_1-C_6羟烷基；或者2个R'与其所连接的原子一起形成环烷基或杂环基环。在一些实施方案中，一个R'为氢，并且另一个R'选自氢、C_1-C_6烷基、C_1-C_6卤烷基和C_1-C_6羟烷基；或者2个R'与其所连接的原子一起形成环烷基环。在一些实施方案中，一个R'为氢，并且另一个R'选自氢、-CH_2OH、-CH_3或-CF_3，或者2个R'与其所连接的原子一起形成环丙-1,1-二基环。

[0129] 在一些实施方案中，p为0、1或2。

[0130] 在一些实施方案中，q为0、1、2或3。

[0131] 虽然，如上所述，式(I)、(Ia)或(II)中的变量的各种实施方案及其方面可选自一组化学部分，但是本发明还包括以下情况作为其另外的实施方案和方面，其中此变量：a)选自此组中的化学部分的任何子集；并且为b)此组的任何单一成员。

[0132] 虽然对于式(I)、(Ia)和(II)中的每个变量个别地阐明(或暗示，如先前段落中论述)其各种实施方案和方面，但是本发明涵盖式(I)、(Ia)和(II)中的每种变量的不同实施方案和方面的所有可能组合。

[0133] 本发明的示例性化合物的结构以及NMR和LCMS数据示出在图1中。在某些实施方案中，本发明的化合物选自由以下组成的组：图1中的任一种化合物及其药学上可接受的盐、溶剂化物、水合物、互变异构物、立体异构物以及同位素标记的衍生物。

[0134] 本发明还提供含有药学上可接受的载剂和任何式(I)、(Ia)和(II)化合物的药物组合物。

[0135] 这些化合物的药学上可接受的盐也预期用于本文所述的用途。

[0136] “药学上可接受的盐”是指保持其生物性质并且没有毒性或在其他方面不合药物用途需要的本发明的化合物的任何盐。药学上可接受的盐可从在本领域中熟知的各种有机和无机抗衡离子衍生并且包括。这些盐包括：(1)与有机酸或无机酸所形成的酸加成盐，诸如盐酸、氢溴酸、硫酸、硝酸、磷酸、氨基磺酸、乙酸、三氟乙酸、三氯乙酸、丙酸、己酸、环戊基丙酸、乙醇酸、戊二酸、丙酮酸、乳酸、丙二酸、琥珀酸、山梨酸、抗坏血酸、苹果酸、马来酸、富马酸、酒石酸、柠檬酸、苯甲酸、3-(4-羟基苯甲酰基)苯甲酸、苦味酸、肉桂酸、扁桃酸、邻苯二甲酸、月桂酸、甲磺酸、乙磺酸、1,2-乙烷-二磺酸、2-羟基乙磺酸、苯磺酸、4-氯苯磺酸、2-萘磺酸、4-甲苯磺酸、樟脑酸、樟脑磺酸、4-甲基双环[2.2.2]-辛-2-烯-1-羧酸、葡庚糖酸、3-苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡萄糖酸、苯甲酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸、环己基氨基磺酸、奎尼酸、黏康酸及其类似酸；或者(2)当存在于母体化合物中的酸性质子(a)置换为金属离子(例如碱金属离子、碱土金属离子或铝离子)或碱金属或碱土金属氢氧化物(诸如氢氧化钠、氢氧化钾、氢氧化钙、氢氧化镁、氢氧化铝、氢氧化锂、氢氧化锌和氢氧化钡、氨)或者(b)与有机碱配位时所形成的盐，所述有机碱诸如脂族、脂环族或芳族有机胺，诸如氨、甲胺、二甲胺、二乙胺、甲基吡啶、乙醇胺、二乙醇胺、三乙醇

胺、乙二胺、赖氨酸、精氨酸、鸟氨酸、胆碱、N,N′-二苄基乙烯-二胺、氯普鲁卡因、二乙醇胺、普鲁卡因、N-苄基苯乙胺、N-甲基葡萄胺哌嗪、三(羟甲基)-氨基甲烷、四甲基氢氧化铵及其类似物。药学上可接受的盐仅举例而言还包括钠、钾、钙、镁、铵、四烷基铵及其类似物，并且当化合物含有碱性官能度时，包括无毒有机酸或无机酸的盐，诸如盐酸盐、氢溴酸盐、酒石酸盐、甲磺酸盐、苯磺酸盐、乙酸盐、马来酸盐、草酸盐等。

[0137] 药物组合物

[0138] 本发明的药物组合物包含一种或多种本发明的化合物和一种或多种生理上或药学上可接受的载剂。术语“药学上可接受的载剂”是指参与携带或运输任何主题组合物或其组分的药学上可接受的材料、组合物或媒介物，诸如液体或固体填充剂、稀释剂、赋形剂、溶剂或封装材料。每种载剂必须在与主题组合物及其组分相容并且不伤害患者的意义上是“可接受的”。可充当药学上可接受的载剂的材料的一些实例包括：(1)糖，诸如乳糖、葡萄糖和蔗糖；(2)淀粉，诸如玉米淀粉和马铃薯淀粉；(3)纤维素及其衍生物，诸如羧甲基纤维素钠、乙基纤维素和乙酸纤维素；(4)粉末状黄蓍胶；(5)麦芽；(6)明胶；(7)滑石；(8)赋形剂，诸如可可脂和栓剂蜡；(9)油，诸如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；(10)二醇，诸如丙二醇；(11)多元醇，诸如甘油、山梨糖醇、甘露糖醇和聚乙二醇；(12)酯，诸如油酸乙酯和月桂酸乙酯；(13)琼脂；(14)缓冲剂，诸如氢氧化镁和氢氧化铝；(15)海藻酸；(16)无热原水；(17)等张生理盐水；(18)林格氏溶液(Ringer′s solution)；(19)乙醇；(20)磷酸盐缓冲溶液；以及(21)用于药物制剂中的其他无毒相容材料。

[0139] 本发明的组合物可经口、胃肠外、通过吸入喷雾剂、局部、经直肠、经鼻、经颊、经阴道或通过植入储存器施用。如本文所用的术语“胃肠外”包括皮下、静脉内、肌肉内、关节内、滑膜内、胸骨内、鞘内、肝内、病灶内和颅内注射或输注技术。在一些实施方案中，本发明的组合物经口、腹膜内或静脉内施用。本发明的组合物的无菌可注射形式可为水性或油性悬浮液。这些悬浮液可根据本领域中已知的技术使用适合分散剂或湿润剂和悬浮剂来配制。无菌可注射制剂也可为于无毒胃肠外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液，例如呈于1,3-丁二醇中的溶液形式。可采用的可接受的媒介物和溶剂尤其为水、林格氏溶液和等张氯化钠溶液。此外，无菌非挥发性油通常用作溶剂或悬浮介质。

[0140] 出于此目的，可采用任何温和的不挥发性油，包括合成的单甘油酯或二甘油酯。脂肪酸(诸如油酸)及其甘油酯衍生物适用于制备可注射剂，天然药学上可接受的油诸如橄榄油或蓖麻油亦如此，尤其呈其聚氧乙基化形式。这些油溶液或悬浮液也可含有长链醇稀释剂或分散剂，诸如羧甲基纤维素或通常用于配制药学上可接受的剂型(包括乳液和悬浮液)的类似分散剂。通常用于制造药学上可接受的固体、液体或其他剂型的其他常用表面活性剂(诸如吐温(Tween)、斯盘(Span))和其他乳化剂或生物可用性增强剂也可用于配制目的。

[0141] 本发明的药学上可接受的组合物可以任何口腔可接受的剂型经口施用，所述剂型包括但不限于胶囊、片剂、水性悬浮液或溶液。在供经口使用的片剂的情况下，通常使用的载剂包括乳糖和玉米淀粉。还通常添加润滑剂诸如硬脂酸镁。对于以胶囊形式进行的经口施用，适合的稀释剂包括乳糖和干燥玉米淀粉。当水性悬浮液为经口使用所需时，使活性成分与乳化剂和悬浮剂组合。必要时，还可添加某些甜味剂、调味剂或着色剂。

[0142] 或者，本发明的药学上可接受的组合物可以用于经直肠施用的栓剂形式施用。这些组合物可通过将药剂与在室温下为固体但在直肠温度下为液体的适合非刺激性赋形剂

混合来制备并且因此将在直肠中熔融以释放药物。这些材料包括可可脂、蜂蜡和聚乙二醇。

[0143] 本发明的药学上可接受的组合物也可以局部施用，尤其当治疗目标包括通过局部应用可易于接近的区域或器官时，包括眼、皮肤或下肠道疾病。易于制备适合的局部制剂以用于这些区域或器官中的每一个。用于下肠道的局部应用可以直肠栓剂制剂(参见上文)形式或以适合灌肠剂制剂形式实现。还可使用局部经皮贴片。

[0144] 对于局部应用，药学上可接受的组合物可以配制为含有悬浮或溶解于一种或多种载剂中的活性组分的适合软膏剂形式。用于局部施用本发明的化合物的载剂包括但不限于矿物油、液体凡士林、白凡士林、丙二醇、聚氧化乙烯、聚氧化丙烯化合物、乳化蜡以及水。或者，药学上可接受的组合物可以配制为含有悬浮或溶解于一种或多种药学上可接受的载剂中的活性组分的适合洗剂或乳膏剂。适合载剂包括但不限于矿物油、脱水山梨醇单硬脂酸酯、聚山梨醇酯60、十六烷基酯蜡、鲸蜡硬脂醇(cetearyl alcohol)、2-辛基十二烷醇、苯甲醇以及水。

[0145] 本发明的药学上可接受的组合物也可通过经鼻气雾剂或吸入剂施用。这些组合物根据药物制剂领域中熟知的技术制备并且可采用苯甲醇或其他适合防腐剂、增强生物可用性的吸收促进剂、氟碳化合物和/或其他常规增溶剂或分散剂制备成盐水中的溶液。

[0146] 本发明的化合物可与载剂材料组合以产生呈单一剂型的组合物的量将根据所治疗宿主和特定施用模式而变化。优选地，应配制所述组合物以使得可向接受这些组合物的患者施用在0.01-100mg/kg体重/天之间的剂量的抑制剂。

[0147] 剂量

[0148] 本发明的化合物(包括药学上可接受的盐和氘化变体)的毒性和治疗功效变体可通过在细胞培养物或实验动物中的标准药物程序来确定。LD_{50}为对于50％群体致死的剂量。ED_{50}为在50％群体中治疗有效的剂量。毒性作用与治疗作用之间的剂量比率(LD_{50}/ED_{50})为治疗指数。优选展现较大治疗指数的化合物。当可使用显示毒副作用的化合物时，应谨慎设计将此类化合物靶向受影响组织的位置的递送系统以便使对未感染细胞的潜在损害最小化从而减少副作用。

[0149] 从细胞培养测定和/或动物研究获得的数据可用于配制用于人类的剂量范围。这些化合物的剂量优选地在循环浓度范围内，包括具有极低或没有毒性的ED_{50}。所述剂量可根据所使用的剂型和所使用的施用途径而在此范围内变化。对于任何化合物，治疗有效剂量可最初从细胞培养测定估计。剂量可在动物模型中配制以实现循环血浆浓度范围，包括如在细胞培养物中所确定的IC_{s0}(即，实现症状的一半最大抑制的测试化合物的浓度)。此信息可用于更准确地确定在人类中的有用剂量。血浆中的水平可例如通过高效液相色谱来测量。

[0150] 还应理解用于任何特定患者的特定剂量和治疗方案将取决于多种因素，包括所用的特定化合物的活性、年龄、体重、一般健康状况、性别、膳食、施用时间、排泄速率、药物组合以及治疗医师的判断和所治疗特定疾病的严重性。本发明的化合物在组合物中的量也将取决于组合物中的特定化合物。

[0151] 治疗

[0152] NTRK融合物涉及多种类型的癌症。这些融合物具有与受体的天然或野生型形式的受体相同的完整NTRK激酶结构域；因此，如本文使用，具有与野生型NTRK相同的激酶结构域

的任何NTRK蛋白质(NTRK1、2或3)被称为“野生型NTRK”。突变可在NTRK激酶结构域中发生，从而导致突变体对于激酶抑制剂疗法具有抗性。这些抗性突变可使用结构生物学和计算分析，以及通过检查其中序列变化产生不同氨基酸的密码子的密码子序列来预测。或者，给定抑制剂的抗性突变可在实验上通过施用该抑制剂(例如，已知NTRK野生型抑制剂)并且使细胞暴露于突变促进剂(诸如ENU)来识别。将细胞洗涤，然后用递增浓度(2-100X增殖IC_{50})的选定化合物来铺板。然后，在3-4周后收集具有细胞向外生长的孔。具体而言，通过两种方法来识别NTRK融合物内的氨基酸位置595(NTRK1 wt编号)处的突变，其实现从甘氨酸至精氨酸残基的变化(迄今称为‘G595R’)。此突变随后证明对于临床上评估的两种NTRK抑制剂赋予显著抗性(在下表中示出)。如表中示出，化合物对于野生型NTRK具有活性，但是对于NTRK融合物的G595R突变形式的活性显著地较小。

[0153]

化合物	NTRK wt 酶分析 IC_{50} (nM)	NTRK wt 细胞 GI_{50} (nM)	NTRK G595R 细胞 GI_{50} (nM)
厄洛替尼	0.6	2	2700
TSR-011	2.3	32	12000
克唑替尼	9.3	87	9000

[0154] 因此，在另一方面，本发明提供一种治疗患有由异常神经营养酪氨酸受体激酶(NTRK)活性介导的病状的受试者的方法，其包括向受试者施用治疗有效量的本文所述的化合物或化合物的药物组合物。

[0155] 本发明提供抑制野生型NTRK和NTRK的抗性G595R突变体的化合物。

[0156] 在另一方面中，本发明提供治疗对于癌症治疗显现抗性的受试者的方法，包含向受试者施用治疗有效量的化合物或本文所述化合物的药物组合物。

[0157] 此外，相对于其他激酶，抑制剂可对野生型NTRK具有选择性，由此导致与抑制其他激酶相关的毒性减少。因为其对于野生型和突变体NTRK的活性，本文描述的化合物可用于治疗患有与异常NTRK活性相关的病状的患者。所述化合物也可用于治疗各种癌症。在一些实施方案中，癌症选自非小细胞肺癌、乳腺癌、黑素瘤、低级和高级神经胶质瘤、胶质母细胞瘤、小儿科星细胞瘤、结直肠癌、乳突甲状腺癌、胰腺癌、头颈部癌、胆管癌、急性髓性白血病、分泌乳腺癌、唾液癌症以及spitz样肿瘤。

[0158] 化合物也可用于治疗对于野生型NTRK抑制剂发展抗性的患者，或具有突变形式的NTRK(诸如G595R突变体)的患者。方法包括施用对于NTRK抗性突变体具有活性的本发明的化合物或组合物的步骤。“活性”意指在生物化学测定中对于至少一种抗性突变体测量时，化合物具有小于1μM、500nM、250nM、100nM、75nM、50nM、25nM、10nM或5nM的IC_{50}。

[0159] 本文所述的化合物和组合物可单独或与其他化合物(包括其他NTRK调控化合物或其他治疗剂)组合来施用。在一些实施方案中，本发明的化合物或组合物可与一种或多种选自以下的化合物组合施用：卡博替尼(COMETRIQ)、凡德他尼(CALPRESA)、索拉非尼(NEXAVAR)、舒尼替尼(SUTENT)、瑞格非尼(STAVARGA)、帕纳替尼(ICLUSIG)、贝伐单抗(AVASTIN)、克唑替尼(XALKORI)或吉非替尼(IRESSA)。本发明的化合物或组合物可通过相同或不同施用途径与其他治疗剂同时或依次施用。本发明的化合物可与其他治疗剂一起包含在单一制剂中或在单独的制剂中。

[0160] 合成

[0161] 本发明的化合物(包括其盐和N-氧化物)可使用已知的有机合成技术制备并且可根据众多可能的合成途径(诸如以下流程中的合成途径)中的任一种来合成。用于制备本发明的化合物的反应可在适合溶剂中进行,所述溶剂可由有机合成领域技术人员容易选择。在进行反应的温度下,例如在可范围为溶剂冷冻温度至溶剂沸腾温度的温度下,适当的溶剂可大体上不与起始材料(反应物)、中间体或产物反应。给定反应可在一种溶剂或超过一种溶剂的混合物中进行。根据特定反应步骤,适于特定反应步骤的溶剂可由技术人员选择。

[0162] 制备本发明的化合物可涉及各种化学基团的保护和脱保护。保护和脱保护的需要和合适保护基团的选择可通过本领域技术人员容易地确定。保护基团的化学可发现于例如Wuts和Greene,Protective Groups in Organic Synthesis,第4版,John Wiley&Sons:New Jersey,(2006)中,其以引用方式整体并入本文。

[0163] 反应可根据在本领域中已知的任何合适方法进行监测。举例而言,产物形成可通过光谱手段进行监测,诸如核磁共振(NMR)光谱学(例如,^{1}H或^{13}C)、红外线(IR)光谱学、分光光度测定法(例如,UV-可见光)、质谱法(MS)或通过色谱方法诸如高效液相色谱(HPLC)或薄层色谱(TLC)。用于化合物表征的分析仪器和方法:

[0164] LC-MS:除非另外指示,否则所有液相色谱-质谱(LC-MS)数据(分析样品的纯度和身份)都用Agilent 1260型LC系统获得,所述系统使用利用ES-API电离的Agilent 6120型质谱仪,配备有在摄氏22.4℃下的Agilent Poroshel 120(EC-C18,2.7um粒度,3.0×50mm尺寸)反相柱。流动相由含0.1%甲酸的水和含0.1%甲酸的乙腈的溶剂混合物组成。利用在4分钟过程内从95%水性/5%有机至5%水性/95%有机流动相的恒定梯度。流速在1mL/min下恒定。

[0165] 制备型LC-MS:在配备有在摄氏22.4℃下的Luna 5u C18(2)100A,AXIA填充的250 x 21.2mm反相柱的Shimadzu Discovery VP®制备型系统上进行制备型HPLC。流动相由含0.1%甲酸的水和含0.1%甲酸的乙腈的溶剂混合物组成。利用在25分钟过程中从95%水性/5%有机至5%水性/95%有机流动相的恒定梯度。流速在20mL/min下恒定。在微波中执行的反应在Biotage启动器微波单元中以此方式进行。

[0166] 手性HPLC:拆分手性混合物的制备HPLC在配备有Chiralpak AS-H柱(5mm,3.0cm id x 25cm L)的Thar SFC预-80仪器中执行。流动相由SFC CO_2(A)和MeOH/0.1%NH_4OH(B)组成。67%至33%(B)的恒定梯度在65g/min的流速下使用100巴的系统背压来保持。分离进展通过220nm的波长下的UV检测来监测。

[0167] 硅胶色谱:硅胶色谱在Teledyne Isco CombiFlash® Rf单元或Biotage® Isolera Four单元上执行。

[0168] 质子NMR:除非另外指示,否则所有^{1}H NMR光谱都用Varian 400MHz Unity Inova 400MHz NMR仪器(采集时间=3.5秒,伴有1秒延迟;16至64次扫描)获得。当表征时,所有质子均在DMSO-d_6溶剂中以关于残余DMSO(2.50ppm)的百万分率(ppm)形式加以报导。

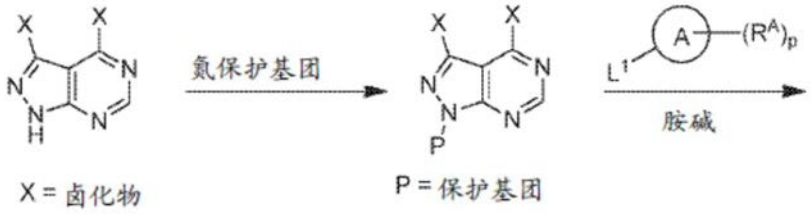
实施例

[0169] 以下实施例旨在为示例性的,并且不意图以任何方式具有限制性。

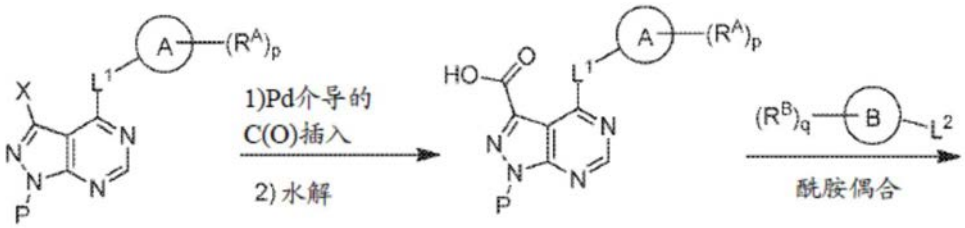
[0170] 以下流程意图提供关于制备本发明的化合物的一般性指导。本领域技术人员将理

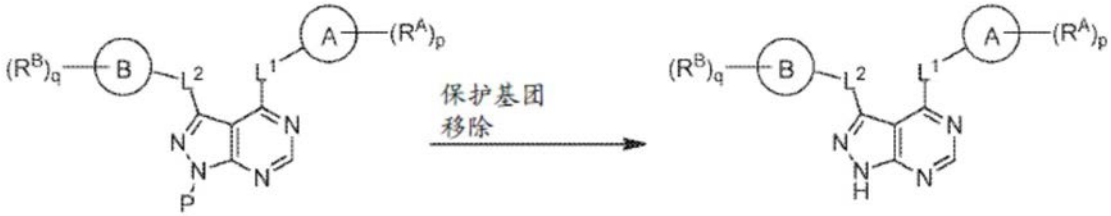
解可使用制备各种本发明的化合物的有机化学的一般知识对所述流程中所示的制剂进行修改或优化。

[0171] 一般合成1：



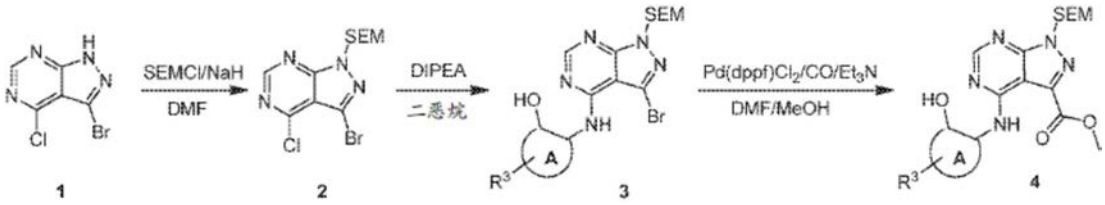
[0172]



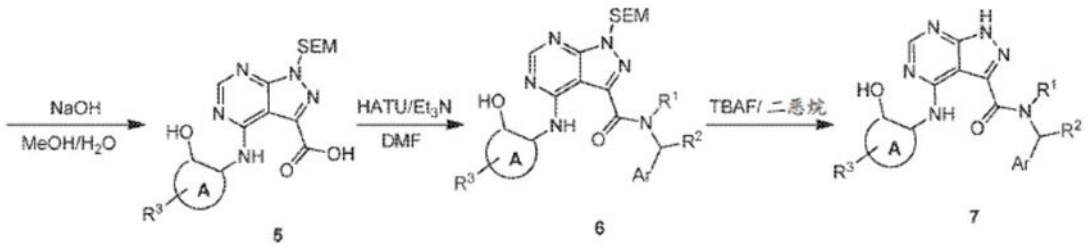


[0173] 对于某些化合物，一般合成开始于二卤化物取代的1H-吡唑并[3,4-d]嘧啶的合适氮保护(P)。氮保护的双环可在合适条件下，例如在亲核芳族取代反应条件下，使用碱(诸如二异丙基乙胺(DIPEA))，在极性溶剂诸如二噁烷中，在嘧啶环上的卤化物处使用适当取代的环A取代以提供被环A取代的双环。吡唑环的卤化物可在钯介导的羰基插入反应条件下取代，随后水解以提供所得羧酸。羧酸可在合适偶合条件下，例如在酰胺偶合反应条件下与环B反应以提供被环A和B取代的氮保护化合物。移除保护基可提供式I化合物。

[0174] 合成方案1：



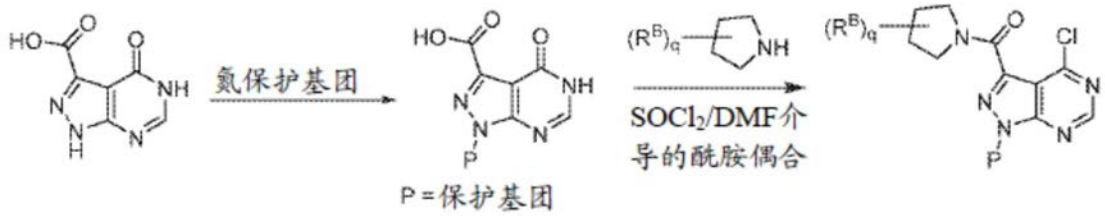
[0175]



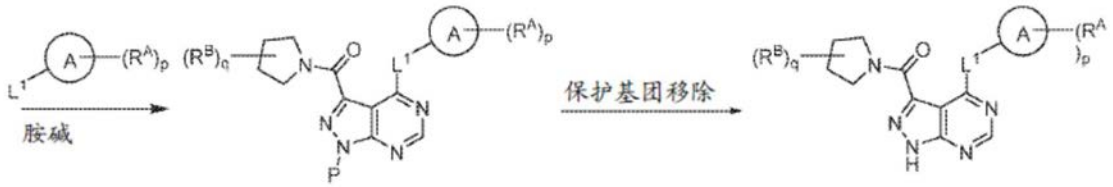
[0176] 稍微更具体形式的一般合成流程1在以上合成方案1中示出。合成方案开始于3-溴-4-氯-1H-吡唑并[3,4-d]嘧啶1的SEM基团保护。SEM保护的杂环2可在亲核芳族取代反应条件下在极性溶剂诸如二噁烷中使用碱诸如二异丙基乙胺(DIPEA)，使用氨基醇取代以提

供胺取代的杂环3。3-溴吡唑并嘧啶3在DMF-MeOH溶剂混合物中经受钯介导的羰基插入反应以提供甲酯4。在通过NaOH处理来水解酯之后，羧酸5在酰胺偶合反应条件下与苄胺或吡咯烷反应以提供SEM保护的化合物6。SEM保护基可使用TBAF或在酸性条件下移除以提供最终化合物7。以下描述的化合物使用一般合成1、2或3来制备，如分别在合成方案1、2或3中进一步详述。

[0177] 一般合成2

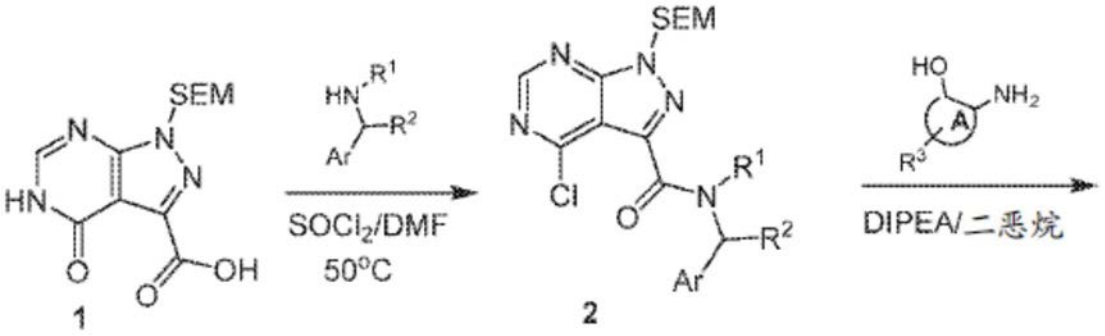


[0178]

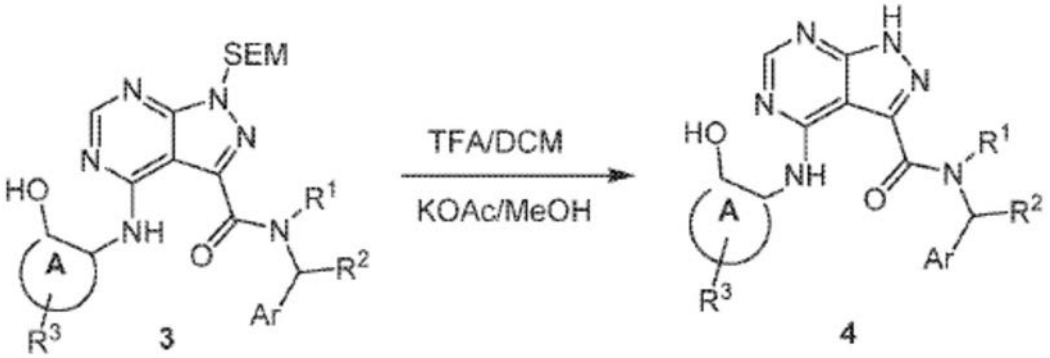


[0179] 对于某些化合物，一般合成开始于4-氧基-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-3-羧酸的合适氮保护(P)。氮保护的双环可在氯化试剂诸如亚硫酰氯存在下氯化并与胺偶合。所得化合物可在合适条件下，例如在亲核芳族取代反应条件下，使用碱诸如二异丙基乙胺(DIPEA)，在极性溶剂诸如二噁烷中，在嘧啶环上的卤化物处使用适当取代的环A取代以提供用环A取代的双环。移除保护基可提供式I化合物。以下描述的化合物可使用此一般合成来制备。此外，手性HPLC可用于拆分式I、(Ia)、(Ia-1)、(Ia-2)、(Ib)、(Ib-1、(Ib-2)、II、(IIa)、(IIb)、(IIc)化合物的手性混合物。

[0180] 合成方案2

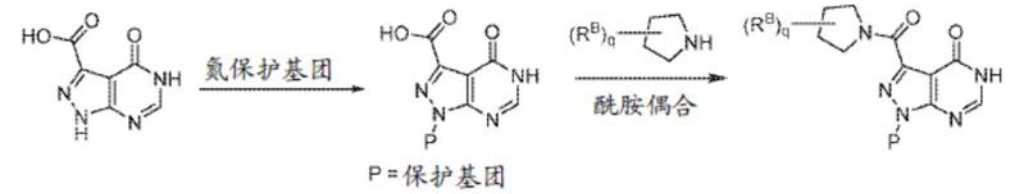


[0181]

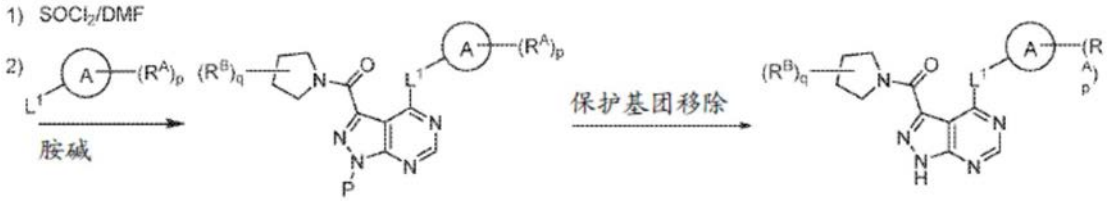


[0182] 稍微更具体形式的一般合成流程2在以上合成方案2中示出。合成方案开始于SEM保护的4-氧基-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-3-羧酸1,其可使用亚硫酰氯/DMF氯化,并且然后在轻微加热下与苄胺或吡咯烷偶合以提供SEM保护的化合物2。SEM保护的杂环2可在亲核芳族取代反应条件下,在极性溶剂诸如二噁烷中使用碱诸如二异丙基乙胺(DIPEA),使用氨基醇取代以提供胺取代的杂环3。SEM保护基可使用TBAF或在酸性条件下移除以提供最终化合物4。

[0183] 一般合成3

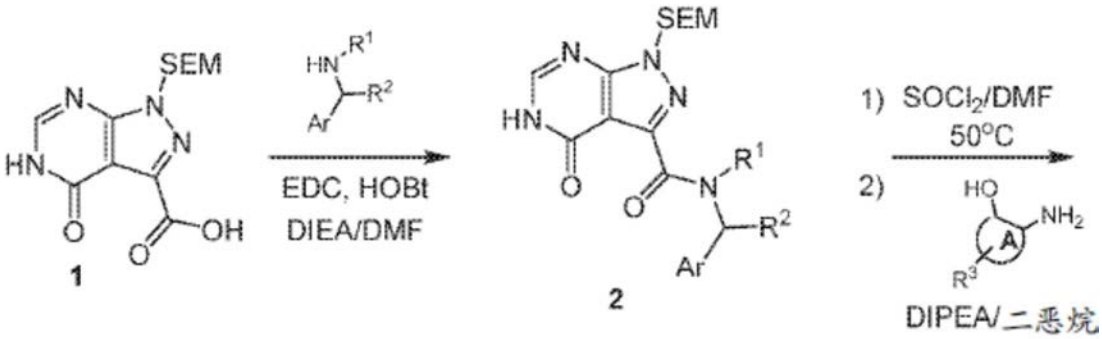


[0184]

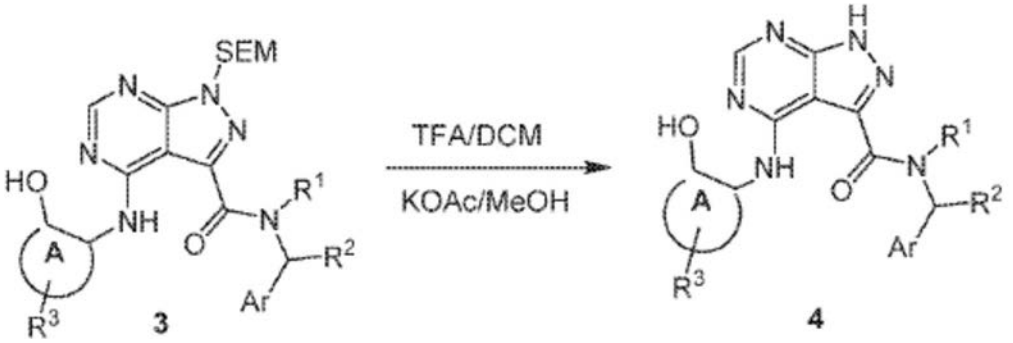


[0185] 对于某些化合物,一般合成开始于4-氧基-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-3-羧酸的合适氮保护(P)。羧酸可使用酰胺偶合条件来偶合至胺。所得化合物可使用亚硫酰氯来氯化,随后在合适条件下,例如在亲核芳族取代反应条件下,使用碱诸如二异丙基乙胺(DIPEA),在极性溶剂诸如二噁烷中,在嘧啶环上的卤化物处使用适当取代的环A取代以提供被环A取代的双环。移除保护基可提供式I化合物。以下描述的化合物可使用此一般合成来制备。此外,手性HPLC可用于拆分式I、(Ia)、(Ia-1)、(Ia-2)、(Ib)、(Ib-1、(Ib-2)、II、(IIa)、(IIb)、(IIc)化合物的手性混合物。

[0186] 合成方案3



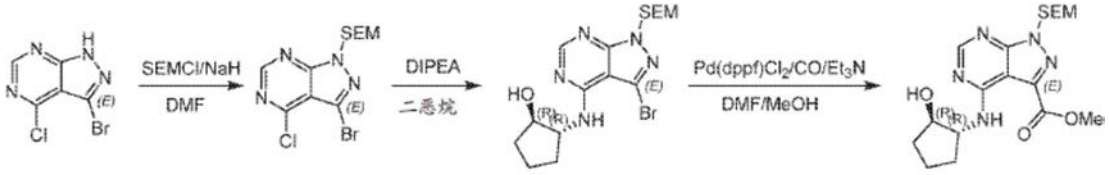
[0187]



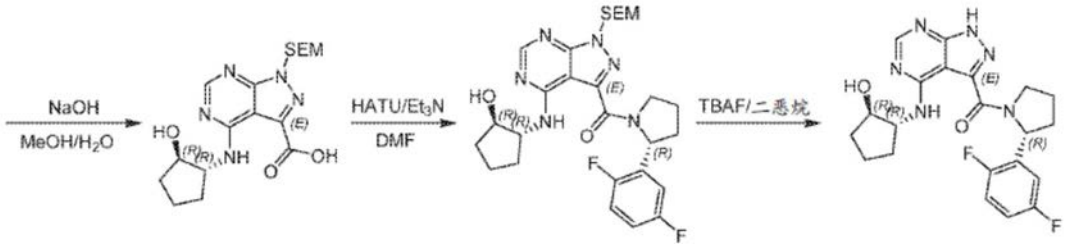
[0188] 稍微更具体形式的一般合成流程3在以上合成方案3中示出。合成方案开始于SEM保护的4-氧基-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-3-羧酸1,其可在酰胺偶合条件下与苄胺或吡咯烷偶合。SEM保护的杂环2可使用亚硫酰氯/DMF来氯化,并且然后在亲核芳族取代反应条件下在极性溶剂诸如二噁烷中使用碱诸如二异丙基乙胺(DIPEA),使用氨基醇取代以提供胺取代的杂环3。SEM保护基可使用TBAF或在酸性条件下移除以提供最终化合物4。

[0189] 图1列出的所有化合物,以及本发明的其他化合物使用三种一般合成流程之一和以上描绘的方案来制备。此外,手性HPLC可用于拆分式I、(Ia)、(Ia-1)、(Ia-2)、(Ib)、(Ib-1、(Ib-2)、II、(IIa)、(IIb)、(IIc)化合物的手性混合物。某些特定合成实施例在实施例中阐明。

[0190] 实施例1.合成化合物45

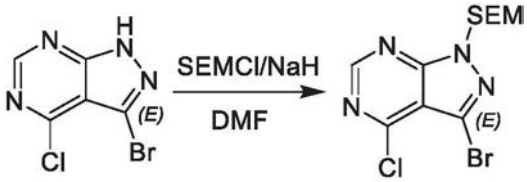


[0191]



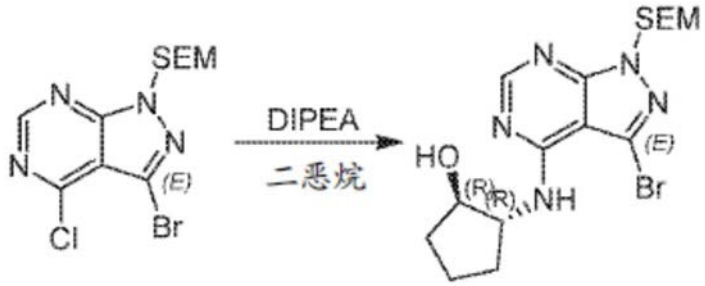
[0192] 步骤1:合成3-溴-4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶

[0193]



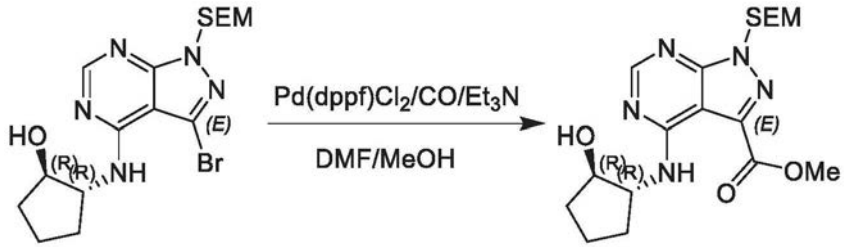
[0194] 在0℃下向3-溴-4-氯-1H-吡唑并[3,4-d]嘧啶(10.00g,42.84mmol)于DMF(50.00mL)中的溶液分批添加NaH(2.57g,64.25mmol)。在搅拌0.5h之后,在0℃下将SEM-Cl(8.57g,51.40mmol)逐滴添加至反应物历时0.5h。将反应物缓慢加温至25℃并且搅拌16h。在TLC(PE:EtOAc=1:1,R_f=0.88)显示反应完成之后,通过50mL的H_2O来缓慢淬灭反应。将混合物用EtOAc(50mL*3)萃取,并且将有机层用盐水(20mL*3)洗涤,在Na_2SO_4上干燥并浓缩。通过硅胶柱色谱(PE:EtOAc=20:1)纯化残余物以得到呈无色油状的3-溴-4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶(6.20g,产率:39.80%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 8.83(s,1H),5.82(s,2H),3.70(t,2H,J=8.4Hz),0.97(t,2H,J=8.4Hz),0.00(s,9H)。

[0195] 步骤2:合成(1R,2R)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)环戊-1-醇

[0196] 

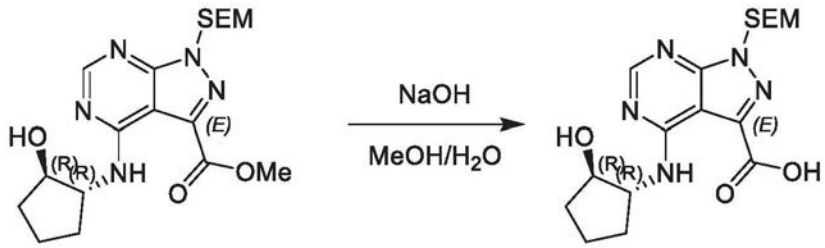
[0197] 向3-溴-4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶(2.50g,6.87mmol)和(1R,2R)-2-氨基环戊醇盐酸盐(945.38mg,6.87mmol)于二噁烷(15mL)中的混合物中添加DIPEA(1.78g,13.74mmol),将反应混合物在70℃下搅拌16h。一旦TLC(PE:EtOAc=5:1)显示起始材料完全消耗,就将混合物真空浓缩并且通过硅胶柱色谱(PE:EtOAc=30:1～10:1)纯化以提供呈黄色油状的(1R,2R)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)环戊-1-醇(2.10g,4.41mmol,产率:64.22%)。^{1}H-NMR(400MHz,CD_3OD)δppm 8.41(s,1H),6.26(s,1H),5.70(s,2H),4.13-4.12(m,2H),3.69-3.65(m,2H),2.40-2.39(m,1H),2.20-2.18(m,1H),1.95-1.84(m,2H),1.72-1.61(m,2H),0.97(d,2H,J=4.0Hz),0.00(s,9H)。

[0198] 步骤3:合成4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯

[0199] 

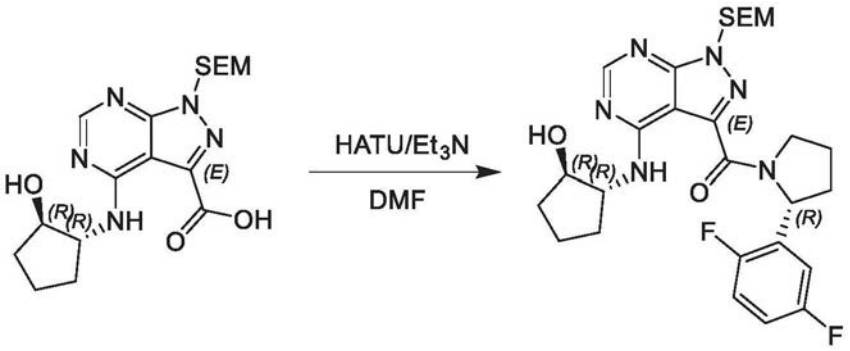
[0200] 向(1R,2R)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)环戊-1-醇(2.10g,4.90mmol)于DMF(10mL)和MeOH(15mL)中的混合物中一次性添加Pd(dppf)Cl_2(717.07mg,980.00umol)和Et_3N(1.49g,14.70mmol),并且将反应混合物在70℃下在CO(50psi)气氛下搅拌30h。一旦TLC(PE:EtOAc=1:1)和LCMS显示起始材料完全消耗,将混合物过滤并且将滤液真空浓缩以获得呈黄色油状的4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯(2.70g,粗产物),其未进一步纯化即直接使用。^{1}H-NMR(400MHz,$CDCl_3$)δppm 8.85(s,1H),8.45(s,1H),5.83(s,2H),4.14(br.s,2H),4.10(s,3H),3.70(t,2H,J=8.4Hz),2.40-2.38(m,1H),2.20-2.17(m,1H),1.93-1.79(m,4H),0.98(t,2H,J=8.4Hz),0.00(s,9H)。

[0201] 步骤4:合成4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸

[0202] 

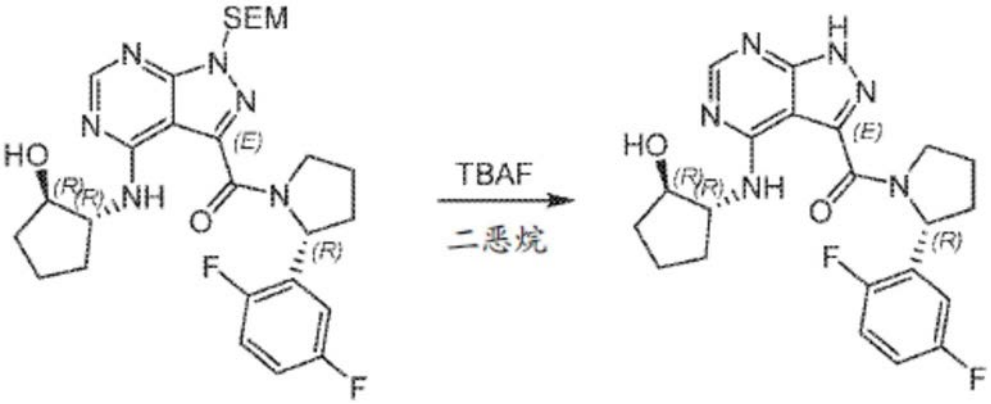
[0203] 向甲基4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(2.70g,6.63mmol)于MeOH(10mL)中的混合物中添加H_2O(10mL),随后一次性添加NaOH(530.01mg,13.25mmol)。然后,将反应混合物在26℃下搅拌16h。一旦LCMS和TLC(PE:EtOAc=1:1)显示起始材料完全消耗,就通过在真空中浓缩来移除MeOH并且将残余物用EtOAc(8mL*2)洗涤。然后,添加HCl水溶液(1N)直至pH<7并且观察到白色沉淀物的形成。通过过滤来收集固体并且在真空中干燥以提供呈白色固体状的4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(1.20g,产率:37.89%)。^{1}H-NMR(400MHz,CD_3OD)δppm 8.40(s,1H),5.80(s,2H),4.37-4.32(m,1H),4.22-4.19(m,1H),3.75(t,2H,J=8.0Hz),2.39-2.36(m,1H),2.11-2.06(m,1H),1.96-1.91(m,2H),1.78-1.73(m,2H),0.95(t,2H,J=8.0Hz),0.00(s,9H)。

[0204] 步骤5:合成((R)-2-(2,5-二氟苯基)吡咯烷-1-基)(4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮

[0205] 

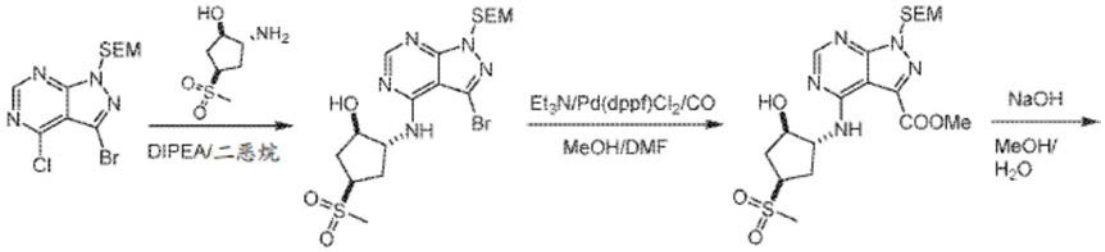
[0206] 在20℃下向4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(100.00mg,254.12umol)和(2R)-2-(2,5-二氟苯基)吡咯烷(55.87mg,304.95umol)于DMF(2mL)中的混合物中添加HATU(144.94mg,381.18umol)和Et_3N(128.57mg,1.27mmol),并且在20℃下将反应物搅拌16h。在LCMS显示反应完成之后,将H_2O(5mL)添加至混合物,并且将反应物用EtOAc(10mL*3)萃取并且用盐水(5mL*3)洗涤。然后,将有机层在Na_2SO_4上干燥并且浓缩。通过制备型TLC(PE:EtOAc=1:1,R_f=0.5)纯化残余物以得到呈无色油状的((R)-2-(2,5-二氟苯基)吡咯烷-1-基)(4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(20.00mg,产率:14.09%)。

[0207] 步骤6:合成((R)-2-(2,5-二氟苯基)吡咯烷-1-基)(4-(((1R,2R)-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮

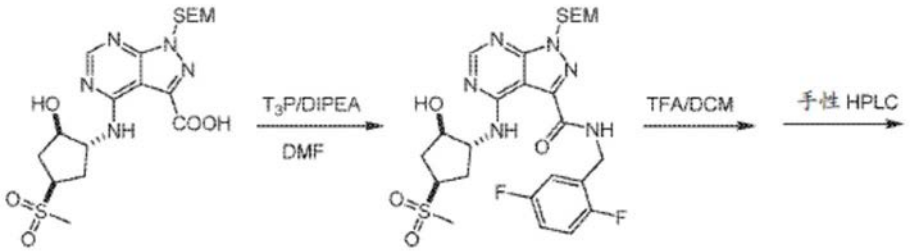
[0208] 

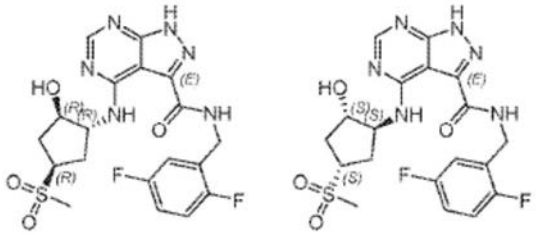
[0209] 在20℃下向((R)-2-(2,5-二氟苯基)吡咯烷-1-基)(4-(((1R,2R)-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(20.00mg,35.80umol)于二噁烷(20mL)中的溶液中添加TBAF(80.61mg,358.00umol),并且在80℃下将反应物加热16h。在TLC(EtOAc,R_f=0.1)显示反应完成之后,将溶液浓缩并且将10mL的H_2O添加至残余物。将溶液用EtOAc(10mL*3)萃取,并且将有机层在Na_2SO_4上干燥并且浓缩。通过酸性制备型HPLC(MeOH/H_2O/TFA溶剂系统)纯化残余物以得到呈棕色固体状的((R)-2-(2,5-二氟苯基)吡咯烷-1-基)(4-(((1R,2R)-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(11.10mg,产率:72.37%)。

[0210] 实施例2.合成化合物97和化合物98



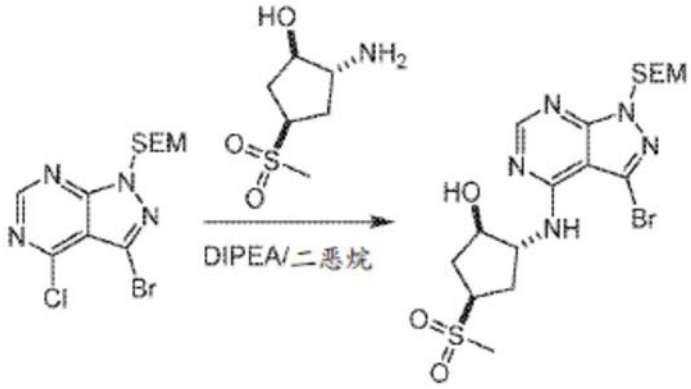
[0211]





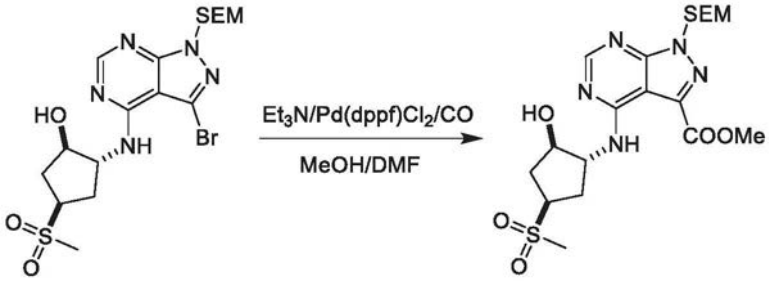
[0212] 步骤1:合成(1R,2R,4R)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-(甲磺酰基)环戊-1-醇

[0213]



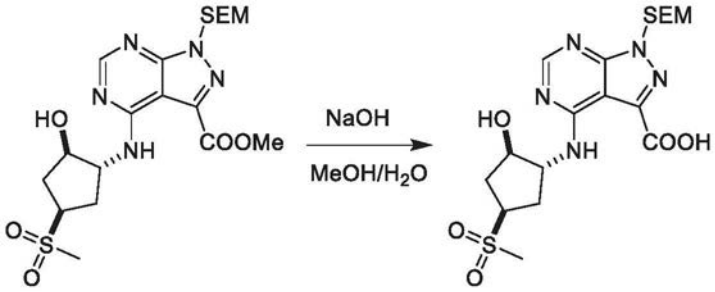
[0214] 向3-溴-4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶(300.00mg,824.83umol)于二噁烷(10.00mL)中的混合物中添加DIPEA(319.80mg,2.47mmol)和(1R,2R,4R)-2-氨基-4-(甲磺酰基)环戊-1-醇(195.71mg,907.31umol),并且将混合物在90℃下搅拌32h。在LCMS显示反应完成之后,将混合物浓缩以移除1,4-二噁烷,并且将残余物溶解于DCM(20mL)中。将有机层用水(10mL*4)洗涤,在Na_2SO_4上干燥,并且浓缩以得到呈白色固体状的(1R,2R,4R)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-(甲磺酰基)环戊-1-醇(350.00mg,产率:83.78%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 8.43(s,1H),6.23(br.s,1H),5.71(s,2H),4.50(br.s,1H),4.26-4.24(m,1H),3.70-3.66(m,3H),2.97(br.s,4H),2.65(m,1H),2.37-2.20(m,2H),0.97(t,2H,J=8.4Hz),0.00(s,9H)。

[0215] 步骤2:合成4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯

[0216] 

[0217] 向(1R,2R,4R)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-(甲磺酰基)环戊-1-醇(350.00mg,691.03umol)于MeOH(10.00mL)/DMF(2.00mL)中的混合物中添加Et3N(139.85mg,1.38mmol)和Pd(dppf)Cb(25.28mg,34.55umol)。在添加之后,将混合物在75℃下在CO(50Psi)下搅拌16h。一旦LCMS显示反应完成,将混合物浓缩以得到粗产物,通过制备型TLC(PE:EtOAc=0:1)纯化所述粗产物以得到呈红色固体状的4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯(250.00mg,产率:74.50%)。

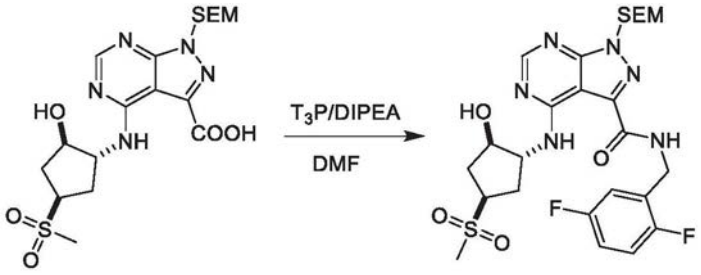
[0218] 步骤3:合成4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸

[0219] 

[0220] 向4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯(250.00mg,514.80umol)于MeOH(10.00mL)/H_2O(5.00mL)中的混合物中添加NaOH(41.18mg,1.03mmol),将其在20℃下搅拌16h。一旦LCMS显示反应完成,就将混合物浓缩以移除MeOH。将水层用EtOAc(3mL*2)洗涤并

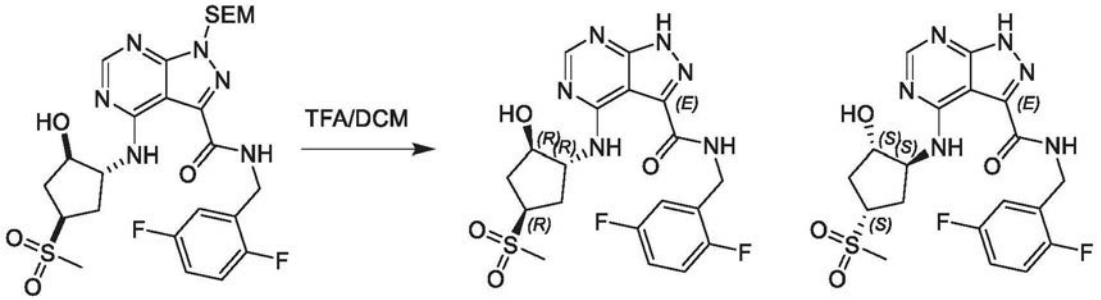
且通过HCl(1M)酸化直至pH＝4为止，然后将混合物过滤并且将滤饼在真空下干燥以提供呈黑色/棕色固体状的4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(180.00mg，产率：74.14％)。^{1}H-NMR(400MHz，$CDCl_3$)δppm 8.47(s,1H)，5.77(s,2H)，4.43-4.40(m,1H)，4.17-4.12(m,1H)，3.85-8.82(m,1H)，3.69(t,2H,J＝8.4Hz)，3.03(s,3H)，2.45-2.41(m,2H)，1.99-1.91(m,2H)，0.92(t,2H,J＝8.4Hz)，0.00(s,9H)。

[0221] 步骤4：合成N-(2,5-二氟苄基)-4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0222] 

[0223] 向4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(60.00mg，127.23umol)于DMF(2.00mL)中的混合物中添加DIPEA(16.44mg，127.23umol)、(2,5-二氟苯基)甲胺(36.42mg，254.46umol)和T_3P(40.48mg，127.23umol)。在添加之后，将混合物在20℃下搅拌1h，其中LCMS显示反应完成。将混合物添加至水(4mL)中并且用EtOAc(5mL*3)萃取，并且将有机层在Na_2SO_4上干燥并浓缩以得到呈红色油状的N-(2,5-二氟苄基)-4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(50.00mg，粗产物)。

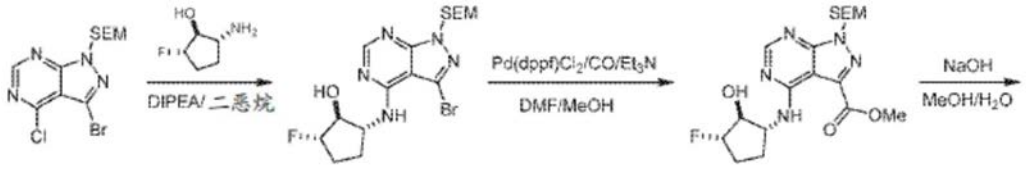
[0224] 步骤5：合成N-(2,5-二氟苄基)-4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0225] 

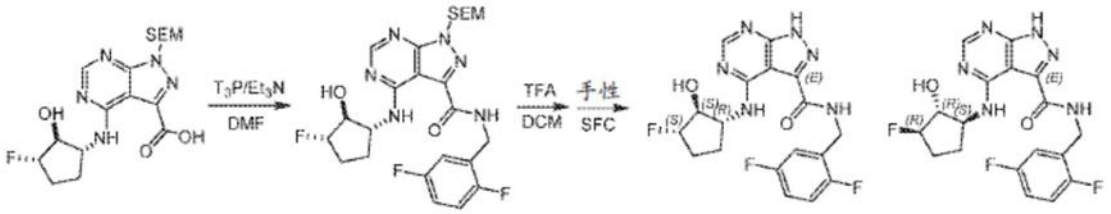
[0226] 在20℃下，将DCM(5.00mL)中的N-(2,5-二氟苄基)-4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(50.00mg，83.79umol)在TFA(5.00mL)的混合物中搅拌16h，然后LCMS显示反应完成。将混合物浓缩以得到粗产物，通过制备型HPLC(TFA)和手性HPLC来纯化所述粗产物(拆分异构物的保留时间分别为7.46min和9.20min)。获得呈白色固体状的N-(2,5-二氟苄基)-4-(((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(2.80mg，产率：7.16％)和N-(2,5-二氟苄基)-4-(((1S,2S,4S)-2-羟基-4-(甲磺酰基)环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(4.00mg，产率：10.23％)。这些化合物的

LC-MS条件如下:流速=0.8mL·min^{-1},流动相:从99%[水+0.375‰v/v TFA]和1%[CH_3CN+0.188‰v/v TFA],在此条件下历时0.4min,然后在3.0min内变化至10%[水+0.375‰v/v TFA]和90%[CH_3CN+0.188‰v/v TFA],然后在0.45min内变化至100%[CH_3CN+0.188‰v/v TFA],最后在0.01min内变化至99%[水+0.375‰v/v TFA]和1%[CH_3CN+0.188‰v/v TFA],然后在此条件下历时0.64min;纯度分别为98.887%和96.551%。

[0227] 实施例3.合成化合物20和化合物21

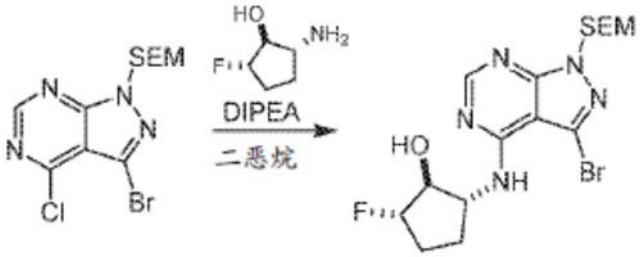


[0228]



[0229] 步骤1:(1S,2R,5S)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-5-氟环戊-1-醇

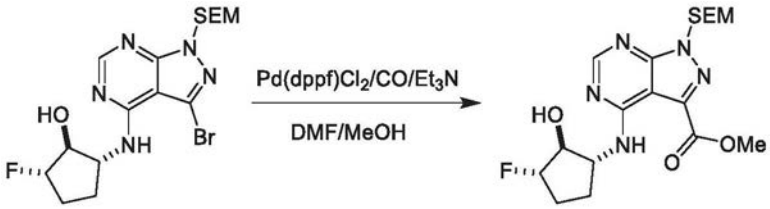
[0230]



[0231] 向3-溴-4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶(600.00mg,1.65mmol)和2-氨基-5-氟-环戊醇(196.58mg,1.65mmol)于二噁烷(15mL)中的混合物中添加DIPEA(426.49mg,3.30mmol)。将混合物在110℃下搅拌16h,然后TLC(PE/EtOAc=1:1)显示反应完成。将混合物冷却至25℃并且在减压下在50℃下浓缩。向残余物中添加EtOAc(50mL),并且将有机相用H_2O(20mL*3)洗涤,在Na_2SO_4上干燥,过滤并且真空浓缩以提供(1S,2R,5S)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-5-氟环戊-1-醇(600.00mg,粗产物)。残余物未进一步纯化即直接用于下一步骤中。

[0232] 步骤2:4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯

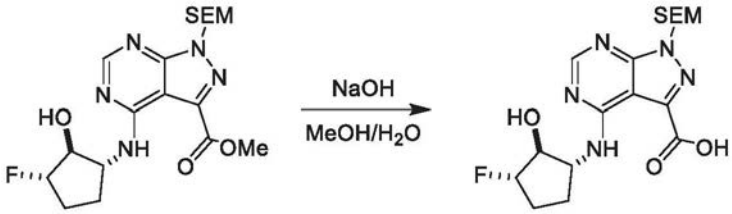
[0233]



[0234] 在N_2下,向(1S,2R,5S)-2-((3-溴-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡

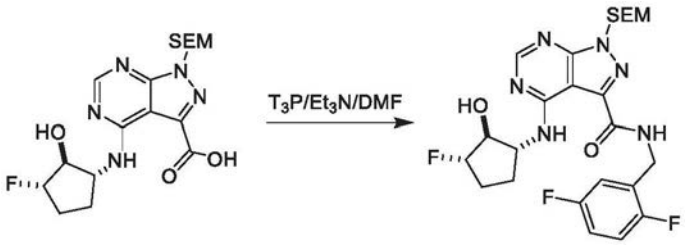
唑并[3,4-d]嘧啶-4-基)氨基)-5-氟环戊-1-醇(600.00mg,1.34mmol)于MeOH/DMF(20mL,v:v=2/1)中的溶液中添加Pd(dppf)Cl_2(49.17mg,67.21umol)和Et3N(408.03mg,4.03mmol)。在真空下将悬浮液脱气并且用CO吹扫几次。在70℃下将混合物在CO(50psi)下搅拌16h,然后TLC(PE/EtOAc=1:1)显示起始材料完全消耗。将反应混合物过滤并且将滤液浓缩以提供4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯(700.00mg,粗产物)。所述粗产物未进一步纯化即使用。

[0235] 步骤3:4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸

[0236] 

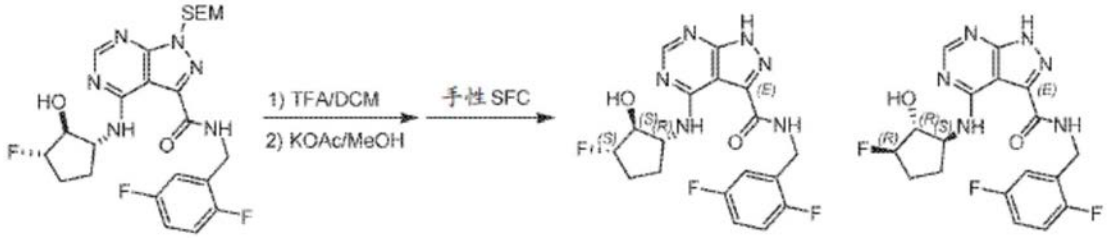
[0237] 向4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸甲酯(700.00mg,1.65mmol)于MeOH/H_2O(15mL,v/v=2/1)中的溶液中一次性添加NaOH(132.00mg,3.30mmol),将其在25℃下搅拌2h。在LCMS显示反应完成之后,将混合物在40℃下减压浓缩。将水相调整至pH=4并且过滤以提供呈白色固体状的4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(700.00mg,粗产物)。

[0238] 步骤4:N-(2.5-二氟苄基)-4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0239] 

[0240] 在25℃下向4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(100.00mg,243.01umol)和T_3P(231.97mg,729.04umol)的混合物中添加DMF(2.00mL)中的Et_3N(49.18mg,486.03umol),随后在10min之后一次性添加(2,5-二氟苯基)甲胺(69.57mg,486.03umol)。在25℃下将混合物搅拌16h。在LCMS显示反应完成之后,将混合物在60℃下在减压下浓缩以提供N-(2,5-二氟苄基)-4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(200mg,粗产物)。残余物未纯化并且直接使用。

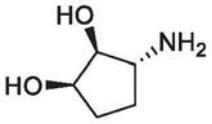
[0241] 步骤5:N-(2,5-二氟苄基)-4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺和N-(2,5-二氟苄基)-4-(((1S,2R,3R)-3-氟-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0242] 

[0243] 将N-(2,5-二氟苄基)-4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(200.00mg,372.70umol)于TFA/DCM(15.00mL,v/v=1/1)中的混合物在25℃下搅拌3h,然后在30℃下在减压下浓缩。向残余物中添加MeOH(20mL)和KOAc(100mg),并且将混合物在25℃下搅拌16h。一旦LCMS显示反应完成,就将混合物在30℃下在减压下浓缩。通过酸性制备型HPLC纯化残余物,随后进行手性制备型HPLC以提供呈白色固体状的N-(2,5-二氟苄基)-4-(((1R,2S,3S)-3-氟-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(25.00mg,产率:16.51%)和呈灰色固体状的N-(2,5-二氟苄基)-4-(((1S,2R,3R)-3-氟-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(30.00mg,产率:19.81%)。这些化合物的LC-MS条件如下:流速=0.8mL·min^{-1},流动相:从95%[水+10mM NH_4HCO_3]和5%CH_3CN,在此条件下历时0.4min,然后在2.6min内变化至10%[水+10mM NH_4HCO_3]和90%CH_3CN,然后在0.85min内变化至100%CH_3CN,最后在0.01min内变化至95%[水+10mM NH_4HCO_3]和5%CH_3CN,然后在此条件下历时0.64min。分别为97.125%纯度和97.690%纯度。

[0244] 合成胺中间物

[0245] 实施例4:合成(1R,2S,3R)-3-氨基环戊烷-1,2-二醇

[0246] 

[0247] 步骤1:(3aS,4S,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇

[0248] 向(3aR,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-酮(92.00g,596.78mmol,1.00当量)于MeOH(2.00L)中的溶液中添加Pd-C(10%,12g)。在真空下将悬浮液脱气并且用H_2吹扫几次。将混合物在20℃下在H_2(30psi)下搅拌4h,在此时TLC(PE:EtOAc=3:1)显示起始材料完全消耗。将反应混合物过滤,并且在0℃下向滤液分批添加$NaBH_4$(34.09g,901.14mmol,1.51当量),并且将所得混合物在20℃下搅拌0.5h。然后将混合物浓缩,并且向残余物添加H_2O(500mL)。将混合物用EtOAc(500mL*3)萃取,在Na_2SO_4上干燥,并且浓缩以得到呈黄色油状的(3aS,4S,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(84.00g,产率:88.98%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.60(t,1H,J=5.2Hz),4.39(t,1H,J=5.6Hz),3.83(br.s,1H),2.37-2.35(m,1H),1.88-1.76(m,2H),1.65-1.56(m,1H),1.48(s,3H),1.45-1.36(m,1H),1.33(s,3H)。

[0249] 步骤2:2-((3aS,4R,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮

[0250] 在N_2下,向(3aS,4S,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(70.00g,442.51mmol,1.00当量)、异吲哚啉-1,3-二酮(80.00g,543.74mmol,1.23当量)和PPh_3(175.00g,667.20mmol,1.51当量)于干燥甲苯(1.00L)中的搅拌混合物中逐滴添加

DIAD(135.00g,667.62mmol,1.51当量)。将所得混合物在80℃下在N_2下搅拌20h。在TLC(PE:EtOAc=3:1)显示起始材料完全消耗之后,将混合物浓缩,并且通过硅胶柱色谱(PE:EtOAc=80:1/50:1/20:1/10:1)纯化残余物以得到呈白色固体状的2-((3aS,4R,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(90.00g,产率:70.79%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.82-7.80(m,2H),7.72-7.70(m,2H),5.03-4.96(m,2H),4.61-4.60(m,1H),2.28-2.20(m,2H),1.94-1.85(m,2H),1.50(s,3H),1.31(s,3H)

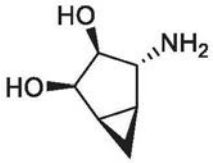
[0251] 步骤3:3aS,4R,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺

[0252] 将2-((3aS,4R,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(90.00g,313.25mmol,1.00当量)和$NH_2NH_2.H_2O$(32.00g,626.50mmol,2.00当量)于EtOH(600.00mL)中的混合物在80℃下搅拌16h。在TLC(PE:EtOAc=3:1)显示起始材料完全消耗之后,将混合物过滤并浓缩,并且将EtOH(500mL)添加至残余物。在浓缩以移除溶剂之后,添加PE(1000mL)并且将混合物过滤并浓缩以得到呈黄色油状的(3aS,4R,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺(41.00g,粗产物),其在静置时固化为黄色晶体。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.72(t,1H,J=5.2Hz),4.18(d,1H,J=5.6Hz),3.39(d,1H,J=4.0Hz),2.01-1.93(m,2H),1.78-1.77(m,1H),1.40(s,3H),1.38-1.35(m,1H),1.26(s,3H),1.10(br.s,2H)。

[0253] 步骤4:(1R,2S,3R)-3-氨基环戊烷-1,2-二醇盐酸盐

[0254] 将(3aS,4R,6aR)-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺(10.00g,63.61mmol,1.00当量)于H_2O(55.00mL)和HCl(5.00mL,12M)中的混合物在20℃下搅拌2h。TLC(EtOAc:MeOH=10:1)显示起始材料完全消耗。将混合物浓缩以得到呈黄色固体状的(1R,2S,3R)-3-氨基环戊烷-1,2-二醇盐酸盐(9.20g,产率:94.15%)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.03(br.s,1H),3.90(dd,1H,J=8.4,4.4Hz),3.48-3.41(m,1H),2.25-2.19(m,1H),2.05-2.02(m,1H),1.75-1.65(m,1H),1.58-1.56(m,1H)。

[0255] 实施例5:合成(1R,2R,3S,4R,5S)-4-氨基二环[3.1.0]己烷-2,3-二醇

[0256] 

[0257] 步骤1:(3aS,4S,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇

[0258] 向(3aR,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-酮(90.00g,583.81mmol,1.00当量)和$CeCl_3.7H_2O$(240.00g,644.16mmol,1.10当量)于MeOH(2.00L)中的0℃搅拌混合物中分批添加$NaBH_4$(44.00g,1.16mol,1.99当量)历时0.5h。在添加之后,在18℃下将混合物搅拌0.5h。TLC(PE:EtOAc=3:1)显示起始材料完全消耗。将混合物浓缩,并且向残余物中添加EtOAc(2000mL)并且将溶液在18℃下搅拌0.5h。然后将混合物过滤,将滤液在Na_2SO_4上干燥并且浓缩以得到呈淡黄色油状的粗产物(3aS,4S,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(79.00g,粗产物),其未进一步纯化即直接用于下一步骤中。^{1}H-NMR(400MHz,$CDCl_3$)δppm 5.88(s,2H),5.01(d,1H,J=5.6Hz),4.74(t,1H,J=5.6Hz),4.55(dd,1H,J=9.6,5.6Hz),2.76(d,1H,J=9.6Hz),1.43

(s,3H),1.40(s,3H)。

[0259] 步骤2:3aR,3bR,4aS,5S,5aS)-2,2-二甲基六氢环丙[3,4]环戊[1,2-d][1,3]间二氧杂环戊烯-5-醇

[0260] 向(3aS,4S,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(40.00g,256.11mmol,1.00当量)于DCM(50.00mL)中的0℃搅拌混合物中逐滴添加$ZnEt_2$(1M,1.00L,3.90当量)。在15min之后,将CH_2I_2(550.00g,2.05mol,8.02当量)添加至混合物中,将其在20℃下搅拌16h。TLC(PE:EtOAc=1:1)显示起始材料消耗。通过饱和NH_4Cl溶液(200mL)淬灭混合物,随后添加H_2O(500mL)。将混合物用DCM(500mL*5)萃取,并且将合并的有机层在Na_2SO_4中干燥并且浓缩以得到粗产物。通过硅胶柱色谱(PE:EtOAc=0:1/100:1/80:1/50:1/20:1/10:1/5:1)纯化粗产物以得到呈淡黄色油状的(3aR,3bR,4aS,5S,5aS)-2,2-二甲基六氢环丙[3,4]-环戊[1,2-d][1,3]间二氧杂环戊烯-5-醇(18.00g,产率:41.29%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.87(t,1H,J=6.0Hz),4.53-4.45(m,2H),2.34(br.s,1H),1.85-1.82(m,1H),1.64-1.62(m,1H),1.54(s,3H),1.28(s,3H),0.98-0.94(m,1H),0.63-0.60(m,1H)。

[0261] 步骤3:2-((3aR,3bR,4aS,5R,5aS)-2,2-二甲基六氢环丙[3,4]环戊[1,2-d][1,3]间二氧杂环戊烯-5-基)异吲哚啉-1,3-二酮

[0262] 在N_2下向(3aR,3bR,4aS,5S,5aS)-2,2-二甲基六氢环丙[3,4]-环戊[1,2-d][1,3]间二氧杂环戊烯-5-醇(10.00g,58.75mmol,1.00当量)、异吲哚啉-1,3-二酮(12.00g,81.56mmol,1.39当量)和PPh_3(24.00g,91.50mmol,1.56当量)于干燥甲苯(500.00mL)中的搅拌混合物中逐滴添加DIAD(20.00g,98.91mmol,1.68当量)。将所得混合物在80℃下在N_2下搅拌20h。TLC(PE:EtOAc=3:1)显示起始材料完全消耗。将混合物浓缩,并且通过硅胶柱色谱(PE:EtOAc=80:1/50:1/30:1/20:1/10:1)纯化残余物以得到呈淡黄色油状的2-((3aR,3bR,4aS,5R,5aS)-2,2-二甲基六氢环丙[3,4]-环戊[1,2-d][1,3]间二氧杂环戊烯-5-基)异吲哚啉-1,3-二酮(14.00g,产率:79.61%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.86-7.83(m,2H),7.74-7.72(m,2H),5.37-5.34(m,1H),4.78-4.76(m,1H),4.73(s,1H),2.01-1.95(m,1H),1.51(s,3H),1.47-1.42(m,1H),1.24(s,3H),0.85-0.79(m,2H)。

[0263] 步骤4:(3aR,3bR,4aS,5R,5aS)-2,2-二甲基六氢环丙[3,4]环戊[1,2-d][1,3]间二氧杂环戊烯-5-胺

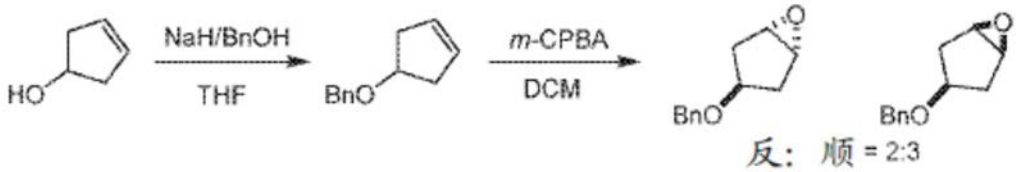
[0264] 将2-((3aR,3bR,4aS,5R,5aS)-2,2-二甲基六氢环丙[3,4]-环戊[1,2-d][1,3]间二氧杂环戊烯-5-基)异吲哚啉-1,3-二酮(14.00g,46.77mmol,1.00当量)和$NH_2NH_2.H_2O$(4.78g,93.54mmol,2.00当量)于EtOH(200.00mL)中的混合物在70℃下搅拌16h。TLC(PE:EtOAc=3:1)显示起始材料完全消耗。过滤混合物,将滤液浓缩,并且向残余物中添加EtOAc(20mL)。然后过滤混合物,并且浓缩以得到呈黄色油状的(3aR,3bR,4aS,5R,5aS)-2,2-二甲基六氢环丙[3,4]环戊[1,2-d][1,3]间二氧杂环戊烯-5-胺(7.00g,产率:88.45%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 5.06-5.03(m,1H),4.30(d,1H,J=6.8Hz),3.45(s,1H),1.73-1.71(m,1H),1.48(s,3H),1.43-1.39(m,1H),1.25(s,3H),0.74-0.67(m,2H)。

[0265] 步骤5:(1R,2R,3S,4R,5S)-4-氨基二环[3.1.0]己烷-2,3-二醇*HCl

[0266] 将(3aR,3bR,4aS,5R,5aS)-2,2-二甲基六氢环丙[3,4]环戊[1,2-d][1,3]间二氧杂环戊烯-5-胺(1.00g,63.61mmol,1.00当量)于H_2O(5.500mL)和HCl(0.5mL,12M)中的混合

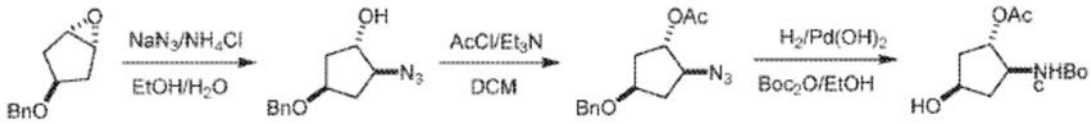
物在15℃下搅拌2h。TLC(EtOAc:MeOH=10:1)显示起始材料完全消耗。将混合物浓缩以得到呈黄色固体状的(1R,2R,3S,4R,5S)-4-氨基二环[3.1.0]己烷-2,3-二醇*HCl(780mg g,产率:79.9%)。

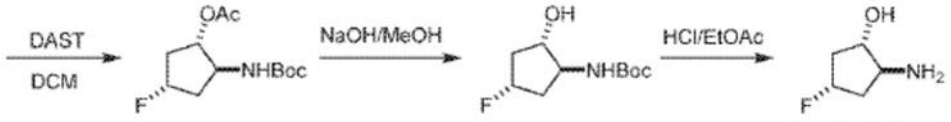
[0267] 实施例6:合成(1S,2S,4S)-2-氨基-4-氟环戊-1-醇(相对立体化学)



反: 顺 = 2:3

[0268]

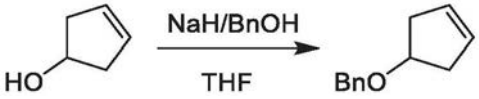




(相对立体化学)

[0269] 步骤1:((环戊-3-烯-1-基氧基)甲基)苯

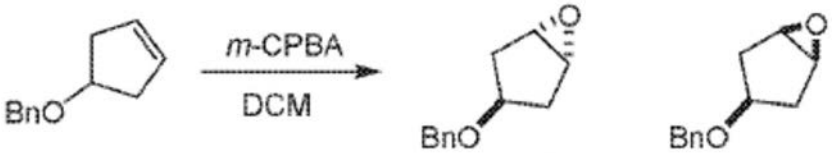
[0270]



[0271] 在0℃下向环戊-3-烯-1-醇(60.00g,713.27mmol)于THF(600.00mL)中的混合物中分批添加NaH(37.09g,927.25mmol)。在起泡停止之后,在0℃下在45min时间段内逐滴添加溴甲基苯(158.59g,927.25mmol),然后加温至25℃并且搅拌16h。TLC(PE/EtOAc=50/1)显示反应完成。在低于5℃的温度下,用MeOH(120mL)淬灭过量NaH。将混合物加温至25℃,用H_2O(600.00mL)稀释,并且分离两个层。将水层用乙酸乙酯(200mL*3)萃取。将合并的有机相用盐水(200mL)洗涤,在Na_2SO_4上干燥,过滤并且真空浓缩。通过硅胶色谱(PE/EtOAc=1/0)纯化残余物以提供呈黄色油状的((环戊-3-烯-1-基氧基)甲基)苯(120.00g,产率:96.56%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.38-7.28(m,5H),5.72(s,2H),4.52(s,2H),4.35-4.30(m,1H),2.64-2.59(m,2H),2.50-2.46(m,2H)。

[0272] 步骤2:(1R,3S,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷和(1R,3r,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷

[0273]



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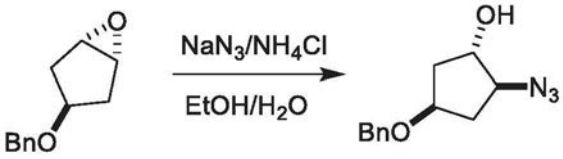
[0274] 在0℃下向((环戊-3-烯-1-基氧基)甲基)苯(120.00g,688.71mmol)于DCM(600.00mL)中的混合物中一次性添加m-CPBA(297.68g,1.38mol)。在25℃下将混合物搅拌

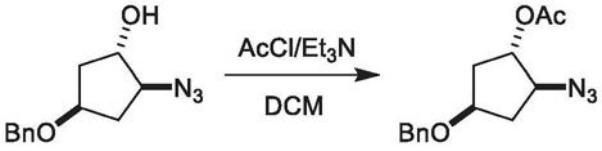
16h。TLC(PE:EtOAc＝20:1)显示反应完成。将混合物过滤并且通过添加饱和Na_2SO_3水溶液来减少过量m-CPBA直至观察到阴性碘化淀粉测试为止。将混合物过滤并且真空浓缩。通过硅胶色谱(PE:EtOAc＝1:0,20:1)纯化残余物以提供呈黄色油状的(1R,3R,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷(56.00g,产率:42.74%)和(1R,3S,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷(37.00g,产率:28.24%)。对(1R,3S,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷进行光谱分析。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.31-7.20(m,5H),4.36(s,2H),3.84-3.74(m,1H),3.43(s,2H),2.51-2.35(m,2H),1.66-1.57(m,2H)。对(1R,3R,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷进行光谱分析^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.31-7.15(m,5H),4.36(s,2H),3.85-3.74(m,1H),3.43(s,2H),2.51-2.35(m,2H),1.66-1.60(m,2H)。

[0275] 步骤3:(1S,2S,4R)-2-叠氮基-4-(苄氧基)环戊-1-醇

[0276] 

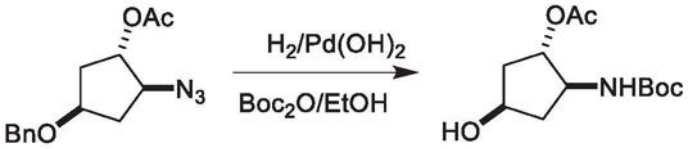
[0277] 在25℃下向(1R,3S,5S)-3-(苄氧基)-6-氧杂双环[3.1.0]己烷(20.00g,105.13mmol)于EtOH(760.00mL)和H_2O(230.00mL)中的混合物中一次性添加NH_4Cl(20.98g,392.13mmol)、NaN_3(24.00g,369.17mmol)。将混合物加热至80℃并且搅拌16小时。TLC(PE:EtOAc＝10:1)显示反应完成。将混合物冷却至25℃并且通过N_2来移除EtOH,并且使用DCM(100mL*3)萃取水相。将合并的有机相用H_2O(30mL*3洗涤),在Na_2SO_4上干燥,过滤并且真空浓缩以提供呈黄色油状的(1S,2S,4R)-2-叠氮基-4-(苄氧基)环戊-1-醇(23.00g,产率:93.79%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.43-7.28(m,5H),4.58-4.47(m,2H),4.27-4.25(m,1H),4.11-4.08(m,1H),3.66-3.61(m,1H),2.49-2.44(m,2H),2.16-2.13(m,1H),1.89(br.s,1H),1.87-1.80(m,2H)。

[0278] 步骤4:(1S,2S,4R)-2-叠氮基-4-(苄氧基)环戊基乙酸酯

[0279] 

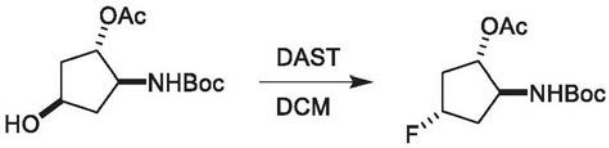
[0280] 在0℃下在30分钟时间段内在N_2下,向(1S,2S,4R)-2-叠氮基-4-(苄氧基)环戊-1-醇(22.90g,98.17mmol)、Et3N(59.60g,589.02mmol)于DCM(550mL)中的溶液中逐滴添加乙酰氯(38.53g,490.85mmol)于DCM(50mL)中的溶液,在此期间将温度保持在5℃以下。然后将反应混合物加温至25℃并且搅拌16h。TLC(PE:tOAc＝10:1)显示起始材料完全消耗。通过缓慢添加H_2O(100mL)来淬灭反应物。将有机相用饱和盐水(50mL)洗涤,在Na_2SO_4上干燥,过滤并且在真空中浓缩。通过硅胶柱色谱(PE:EtOAc＝100:1,50:1)纯化残余物以提供呈黄色油状的(1S,2S,4R)-2-叠氮基-4-(苄氧基)环戊基乙酸酯(17.00g,产率:62.90%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.37-7.28(m,5H),5.24-5.12(m,1H),4.51(s,2H),4.14-4.11(m,1H),3.88-3.85(m,1H),2.45-2.40(m,1H),2.36-2.32(m,1H),2.07(s,3H),1.95-1.88(m,2H)。

[0281] 步骤5:(1S,2S,4R)-2-((叔丁氧羰基)氨基)-4-羟环戊基乙酸酯

[0282] 

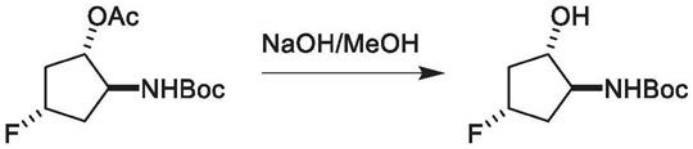
[0283] 在N_2下向(1S,2S,4R)-2-叠氮基-4-(苄氧基)环戊基乙酸酯(8.80g,31.97mmol)于EtOH(100.00mL)中的溶液中添加Pd(OH)$_2$(4.42g,31.97mmol)。在真空下将悬浮液脱气并且用H_2吹扫几次。将混合物在H_2(50psi)下在70℃下搅拌32h。TLC(PE:EtOAc=2:1)显示起始材料完全消耗。过滤反应混合物并且浓缩滤液。通过硅胶色谱(PE:EtOAc=10:1,2:1)纯化粗产物以得到呈黄色固体状的(1S,2S,4R)-2-((叔丁氧羰基)氨基)-4-羟环戊基乙酸酯(3.80g,产率:45.84%)。

[0284] 步骤6:(1S,2S,4S)-2-((叔丁氧羰基)氨基)-4-氟环戊基乙酸酯

[0285] 

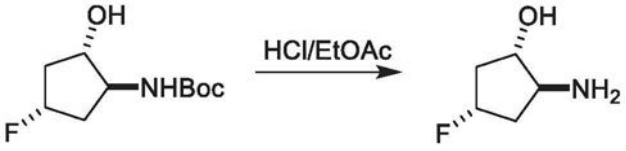
[0286] 在-70℃下在N_2下向(1S,2S,4R)-2-((叔丁氧羰基)氨基)-4-羟环戊基乙酸酯(2.57g,9.91mmol)于DCM(150.00mL)中的混合物中逐滴添加DAST(2.40g,14.87mmol)。在-70℃下将混合物搅拌30min。TLC(PE:EtOAc=2:1)显示反应完成。将混合物冷却至0℃并且添加$NaHCO_3$(5mL,10%)水溶液并且将其搅拌10min。将水相用EtOAc(15mL*2)萃取,并且将合并的有机相用盐水(10mL)洗涤,在Na_2SO_4上干燥,过滤,并且真空浓缩。通过硅胶色谱(PE:AtOAc=20:1,10:1)纯化粗产物以得到呈黄色油状的(1S,2S,4S)-2-((叔丁氧羰基)氨基)-4-氟环戊基乙酸酯(700.00mg,产率:27.03%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 5.14(s,0.5H),5.00(br.s,1H),4.71(s,0.5H),4.14-4.13(m,1H),2.49-2.47(m,2H),2.07-1.94(m,3H),1.81-1.74(m,2H),1.43-1.41(m,9H)。

[0287] 步骤7:((1S,2S,4S)-4-氟-2-羟环戊基)氨基甲酸叔丁酯

[0288] 

[0289] 向(1S,2S,4S)-2-((叔丁氧羰基)氨基)-4-氟环戊基乙酸酯(700.00mg,2.68mmol)于MeOH(20.00mL)中的混合物中一次性添加NaOH(160.80mg,4.02mmol)。在25℃下将混合物搅拌1h。TLC(PE:EtOAc=3:1)显示反应完成。将混合物在30℃下在减压下浓缩以提供呈白色固体状的((1S,2S,4S)-4-氟-2-羟环戊基)氨基甲酸叔丁酯(650.00mg,粗产物)。

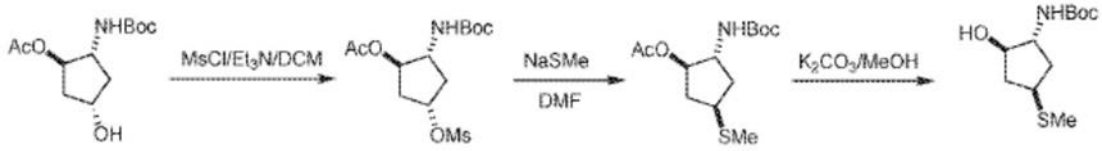
[0290] 步骤8:(1S,2S,4S)-2-氨基-4-氟环戊-1-醇(相对立体化学)

[0291] 

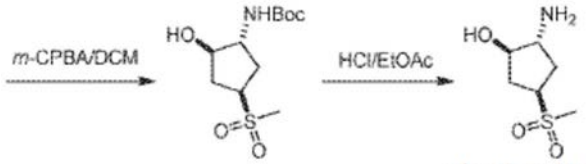
[0292] 将((1S,2S,4S)-4-氟-2-羟环戊基)氨基甲酸叔丁酯(650.00mg,2.96mmol)于MeOH/HCl(20.00mL,4M)中的混合物在25℃下搅拌1h。TLC(PE:EtOAc=2:1)显示反应完成。将混合物在30℃下在减压下浓缩以提供呈白色固体状的(1S,2S,4S)-2-氨基-4-氟环戊-1-

醇(相对立体化学)(400.00mg,产率:86.85%)。^{1}H-NMR(400MHz,DMSO-d_6)δppm 8.38(br.s,3H),5.09(d,1H,J=53.6Hz),4.09-4.03(m,1H),3.34-3.30(m,1H),2.44-2.39(m,1H),2.21-2.16(m,1H),1.95-1.87(m,1H),1.75-1.66(m,1H)。

[0293] 实施例7:合成(1R,2R,4R)-2-氨基-4-(甲磺酰基)环戊-1-醇(相对立体化学)



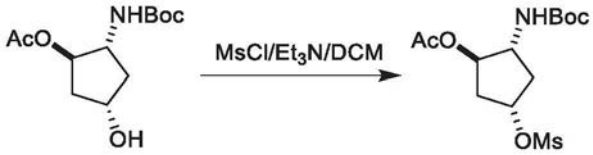
[0294]



(相对立体化学)

[0295] 步骤1:制备(1R,2R,4S)-2-((叔丁氧羰基)氨基)-4-((甲磺酰基)氧基)环戊基乙酸酯

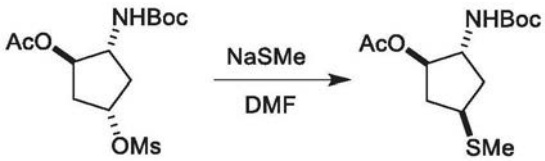
[0296]



[0297] 在0℃下向(1R,2R,4S)-2-((叔丁氧羰基)氨基)-4-羟环戊基乙酸酯(3.00g,11.57mmol)和Et_3N(4.68g,46.28mmol)于DCM(50.00mL)中的混合物中逐滴添加MsCl(3.98g,34.71mmol),然后在20℃下将混合物搅拌3h。TLC(PE:EtOAc=1:1)显示反应完成。将混合物用水(100mL*3)洗涤,然后将有机层在Na_2SO_4上干燥并且浓缩以得到呈黄色固体状的(1R,2R,4S)-2-((叔丁氧羰基)氨基)-4-((甲磺酰基)氧基)环戊基乙酸酯(3.5g,粗产物:100%)。

[0298] 步骤2:(1R,2R,4R)-2-((叔丁氧羰基)氨基)-4-(甲硫)环戊基乙酸酯

[0299]



[0300] 向(1R,2R,4S)-2-((叔丁氧羰基)氨基)-4-((甲磺酰基)氧基)环戊基乙酸酯(3.50g,10.37mmol)于DMF(30.00mL)中的混合物中添加NaSMe(4.36g,12.45mmol)。然后,将混合物在90℃下搅拌2h,并且TLC(PE:EtOAc=2:1)显示反应完成。将混合物浓缩以得到呈黄色固体状的粗(1R,2R,4R)-2-((叔丁氧基羰基)氨基)-4-(甲硫)环戊基乙酸酯(3.00g,粗产物100%)。

[0301] 步骤3:((1R,2R,4R)-2-羟基-4-(甲硫)环戊基)氨基甲酸叔丁酯

[0302] 

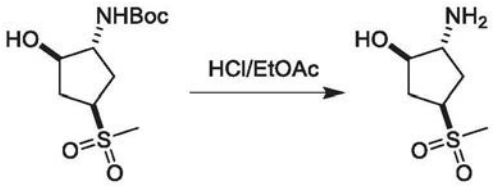
[0303] 向(1R,2R,4R)-2-((叔丁氧羰基)氨基)-4-(甲硫)环戊基乙酸酯(3.00g,10.37mmol)于MeOH(100.00mL)中的混合物中添加K_2CO_3(2.87g,20.74mmol)。在25℃下将混合物搅拌16h。TLC(PE:EtOAc=2:1)显示反应完成。将混合物浓缩并且通过硅胶柱色谱(PE:EtOAc=5:1-1:1)纯化以得到呈白色固体状的((1R,2R,4R)-2-羟基-4-(甲硫)-环戊基)氨基甲酸叔丁酯(1.60g,产率:62.38%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.10-3.99(m,2H),3.85(br.s,1H),3.14-3.11(m,1H),2.50-2.46(m,1H),2.17-2.10(m,4H),1.86-1.82(m,1H),1.81-1.67(m,1H),1.45(s,9H)。

[0304] 步骤4:((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基甲酸叔丁酯

[0305] 

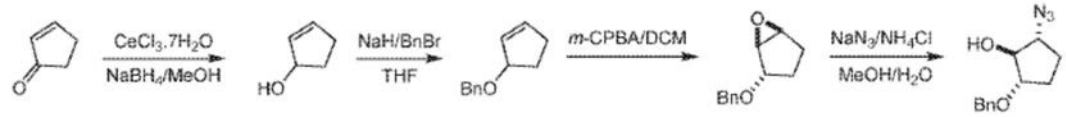
[0306] 向((1R,2R,4R)-2-羟基-4-(甲硫)环戊基)氨基甲酸叔丁酯(1.60g,6.47mmol)于DCM(100.00mL)中的混合物中添加m-CPBA(3.49g,16.18mmol)。在25℃下将混合物搅拌16h。在TLC(PE:EtOAc=2:1)显示起始材料完全消耗之后,将混合物用饱和Na_2SO_3(aq.20mL)和饱和$NaHCO_3$(aq.20mL*3)洗涤。然后将有机层在Na_2SO_4上干燥,浓缩,用PE(10mL)洗涤,过滤,并且将滤饼在真空下干燥以得到呈白色固体状的((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基甲酸叔丁酯(1.70g,产率:94.06%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.62(br.s,1H),4.07-4.04(m,1H),3.81-3.79(m,1H),3.48-3.45(m,1H),2.82(s,3H),2.57-2.40(m,2H),2.11-2.07(m,1H),1.90-1.87(m,2H),1.38(s,9H)。

[0307] 步骤5:(1R,2R,4R)-2-氨基-4-(甲磺酰基)环戊-1-醇(相对立体化学)

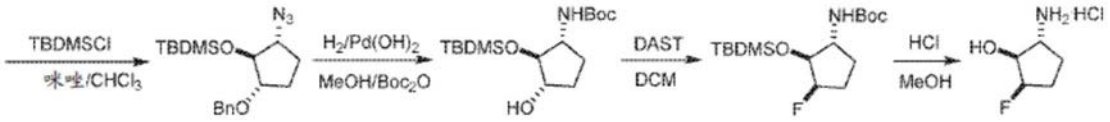
[0308] 

[0309] 将((1R,2R,4R)-2-羟基-4-(甲磺酰基)环戊基)氨基甲酸叔丁酯(1.2g,4.30mmol)于HCl/MeOH(10.00mL)中的混合物在25℃下搅拌16h,然后LCMS显示反应完成,并且将混合物浓缩以得到呈黄色固体状的(1R,2R,4R)-2-氨基-4-(甲磺酰基)环戊-1-醇(1.0g,粗产物:100%)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.11-4.07(m,2H),3.76(br.s,1H),2.94(s,3H),2.53(br.s,2H),1.99(br.s,2H)。

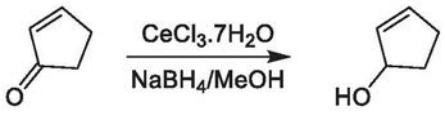
[0310] 实施例8:合成(1S,2R,5R)-2-氨基-5-氟环戊-1-醇盐酸盐(相对立体化学)



[0311]

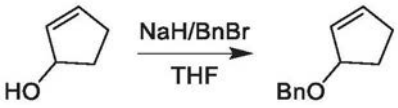


[0312] 步骤1:环戊-2-烯-1-醇

[0313] 

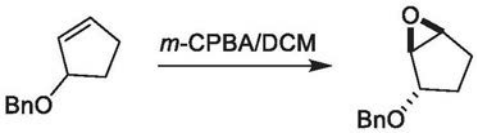
[0314] 在15℃下向$CeCl_3.7H_2O$(24.00g,64.42mmol)于MeOH(120.00mL)中的混合物中添加环戊-2-烯-1-酮(5.00g,60.90mmol)。在5min之后,在0℃下将$NaBH_4$(4.61g,121.80mmol)分批添加至混合物。将所得混合物在25℃下搅拌1h,然后TLC(PE:EtOAc=5:1)显示生成多个点并且部分起始材料保留。通过H_2O(100mL)淬灭反应物并且将有机溶剂在真空中浓缩。向残余物中添加H_2O(300mL),随后用MTBE(200mL*3)萃取。将合并的有机层在Na_2SO_4上干燥并且在真空下浓缩以得到呈棕色油状的粗产物环戊-2-烯-1-醇(3.00g,粗产物)。其未进一步纯化即直接用于下一步骤中。^{1}H-NMR(400MHz,$CDCl_3$)δppm 5.91(d,1H,J=4.8Hz),5.77-5.76(m,1H),4.79(d,1H,J=3.6Hz),2.47-2.42(m,1H),2.21-2.15(m,2H),1.64-1.59(m,1H)。

[0315] 步骤2:((环戊-2-烯-1-基氧基)甲基)苯

[0316] 

[0317] 在0℃下向环戊-2-烯-1-醇(9.00g,106.99mmol)于THF(200.00mL)中的混合物中分批添加NaH(6.80g,170.11mmol)。在添加之后,将混合物在20℃下搅拌0.5h,然后在0℃下将BnBr(20.00g,116.94mmol)逐滴添加至混合物中。在20℃下将所得混合物搅拌2h。TLC(PE:EtOAc=20:1)显示形成新材料(R_f=0.6,254nm)。在此时点,添加H_2O(20mL),随后用EtOAc(20mL*3)萃取。将合并的有机物在Na_2SO_4上干燥并且浓缩以得到粗产物,通过硅胶柱色谱(PE:EtOAc=1:0/100:1/80:1)纯化所述粗产物以得到呈黄色油状的((环戊-2-烯-1-基氧基)甲基)苯(8.00g,产率:42.91%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.34-7.25(m,5H),6.02(br.s,1H),5.88(br.s,1H),4.66(br.s,1H),4.55-4.47(m,2H),2.52-4.48(m,1H),2.27-2.24(m,1H),2.16-2.13(m,1H),1.87-1.84(m,1H)。

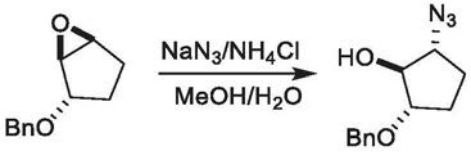
[0318] 步骤3:(1S,2S,5S)-2-(苄氧基)-6-氧杂双环[3.1.0]己烷

[0319] 

[0320] 在0℃下向((环戊-2-烯-1-基氧基)甲基)苯(8.50g,29.27mmol)于DCM(50.00mL)中的混合物中分批添加m-CPBA(13.50g,58.67mmol)。在25℃下将混合物搅拌4h。一旦TLC(PE:EtOAc=10:1)显示起始材料完全消耗,就过滤混合物,将滤液浓缩并且通过硅胶柱色

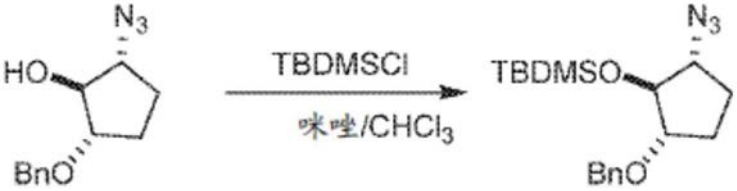
谱(PE:EtOAc=1:0/100:1/80:1/50:1)纯化以得到粗产物。然后添加DCM(20mL),将混合物过滤,并且将H_2O(20mL)和Na_2CO_3(500mg)添加至滤液,随后在25℃下将混合物搅拌0.5h。然后将混合物用DCM(20mL*3)萃取,在Na_2SO_4上干燥,并且浓缩以得到呈无色油状的(1S,2S,5S)-2-(苄氧基)-6-氧杂双环[3.1.0]己烷(2.40g,产率:43.10%),其通过NOE证实。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.37-7.26(m,5H),4.61-4.51(m,2H),4.09(d,1H,J=5.2Hz),3.55(br.s,1H),3.49(br.s,1H),1.99-1.95(m,1H),1.87-1.75(m,2H),1.54-1.52(m,1H)。

[0321] 步骤4:(1S,2R,5S)-2-叠氮基-5-(苄氧基)环戊-1-醇

[0322] 

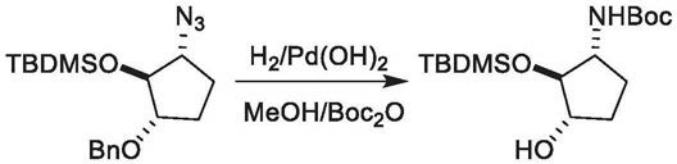
[0323] 向(1S,2S,5S)-2-(苄氧基)-6-氧杂双环[3.1.0]己烷(2.40g,12.62mmol)和NH_4Cl(1.55g,29.03mmol)于H_2O(3.00mL)和MeOH(24.00mL)中的混合物中添加NaN_3(4.10g,63.10mmol),将其在80℃下搅拌16h。在TLC(PE:EtOAc=10:1)显示起始材料消耗之后,通过N_2干燥有机溶剂并且将残余物用H_2O(20mL)稀释,用DCM(20mL*3)萃取。将合并的有机相用H_2O(10mL*3)洗涤,在Na_2SO_4上干燥,并且浓缩以得到呈棕色油状的(1S,2R,5S)-2-叠氮基-5-(苄氧基)环戊-1-醇(2.60g,产率:88.32%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.42-7.31(m,5H),4.64-4.55(m,2H),4.02-3.99(m,1H),3.82-3.80(m,1H),3.66-3.63(m,1H),2.25(br.s,1H),2.07-2.01(m,2H),1.80-1.77(m,2H)。

[0324] 步骤5:(((1S,2R,5S)-2-叠氮基-5-(苄氧基)环戊基)氧基)(叔丁基)二甲基硅烷

[0325] 

[0326] 将(1S,2R,5S)-2-叠氮基-5-(苄氧基)环戊-1-醇(2.50g,10.72mmol)、咪唑(1.61g,23.69mmol)和TBDMSCl(2.42g,16.08mmol)于$CHCl_3$(5.00mL)中的混合物在80℃下搅拌16h。一旦TLC(PE:EtOAc=10:1)显示起始材料完全消耗,将混合物浓缩并通过硅胶柱色谱(PE:EtOAc=1:0/100:1/80:1)纯化以得到呈无色油状的(((1S,2R,5S)-2-叠氮基-5-(苄氧基)环戊基)氧基)(叔丁基)二甲基硅烷(3.00g,产率:80.52%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.24-7.15(m,5H),4.40(d,2H,J=2.4Hz),3.88-3.86(m,1H),3.63-3.61(m,1H),3.47-3.43(m,1H),1.94-1.82(m,2H),1.70-1.65(m,2H),0.79(s,9H),0.03(s,3H),0.00(s,3H)。

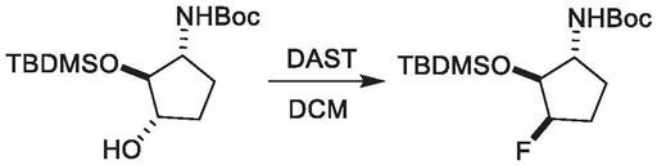
[0327] 步骤6:((1R,2S,3S)-2-((叔丁基二甲基甲硅烷基)氧基)-3-羟环戊基)氨基甲酸叔丁酯

[0328] 

[0329] 向(((1S,2R,5S)-2-叠氮基-5-(苄氧基)环戊基)氧基)(叔丁基)二甲基硅烷

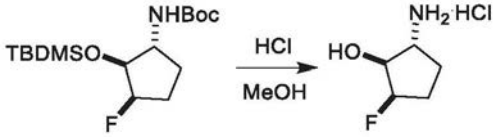
(2.90g,8.34mmol)和Boc_2O(2.20g,10.10mmol)于MeOH(50.00mL)中的混合物中添加$Pd(OH)_2$(1.50g,5.42mmol),将其在50℃下在H_2(50psi)下搅拌20h。在TLC(PE:EtOAc=3:1)显示起始材料完全消耗之后,过滤混合物,并将滤液浓缩并且通过硅胶柱色谱(PE:EtOAc=10:1/8:1/5:1)纯化滤液以得到呈白色固体状的((1R,2S,3S)-2-((叔丁基二甲基甲硅烷基)氧基)-3-羟环戊基)氨基甲酸叔丁酯(2.10g,产率:75.95%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.81(br.s,1H),3.89-3.88(m,1H),3.70-3.67(m,2H),2.06-1.89(m,2H),1.58-1.56(m,2H),1.35(s,9H),0.79(s,9H),0.02(s,3H),0.00(s,3H)。

[0330] 步骤7:((1R,2S,3R)-2-((叔丁基二甲基甲硅烷基)氧基)-3-氟环戊基)氨基甲酸叔丁酯

[0331] 

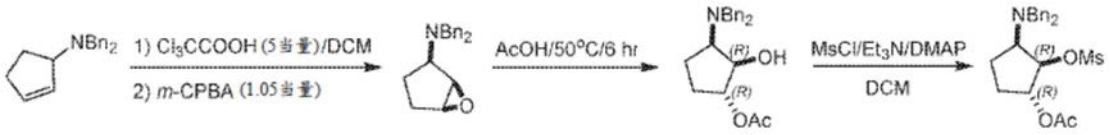
[0332] 在-70℃下向((1R,2S,3S)-2-((叔丁基二甲基甲硅烷基)氧基)-3-羟环戊基)氨基甲酸叔丁酯(1.10g,3.32mmol)于DCM(50.00mL)中的混合物添加DAST(1.61g,9.96mmol)。将反应混合物在-70℃下搅拌1h并且在25℃下搅拌1小时。在TLC(PE:EtOAc=5:1,R_f=0.6)显示反应完成之后,将冰水(5mL)添加至反应物中。将溶液用DCM(20mL*3)萃取并且用盐水(30mL)洗涤。将有机层在Na_2SO_4上干燥并且浓缩。通过硅胶柱色谱(PE:EtOAc=100:1)纯化残余物以得到呈白色固体状的((1R,2S,3R)-2-((叔丁基二甲基甲硅烷基)氧基)-3-氟环戊基)氨基甲酸叔丁酯(100.00mg,产率:9.03%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.64(d,1H,J=54.4Hz),4.26(br.s,1H),3.90-3.86(m,1H),3.76-3.68(m,1H),2.11-1.79(m,4H),1.34(s,9H),0.81(s,9H),0.00(s,6H)。

[0333] 步骤8:(1S,2R,5R)-2-氨基-5-氟环戊-1-醇盐酸盐(相对立体化学)

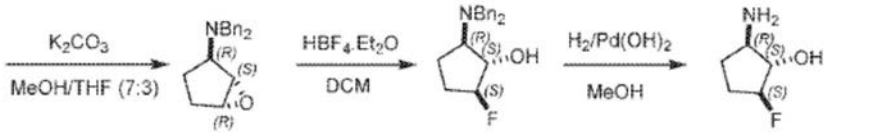
[0334] 

[0335] 将((1R,2S,3R)-2-((叔丁基二甲基甲硅烷基)氧基)-3-氟环戊基)氨基甲酸叔丁酯(100.00mg,299.84umol)于HCl/MeOH(20.00mL,4M)中的溶液在25℃下搅拌16h。TLC(PE:EtOAc=5:1,R_f=0)显示反应完成。通过N_2干燥溶液,并且获得呈黄色固体状的(1S,2R,5R)-2-氨基-5-氟环戊-1-醇盐酸盐(相对立体化学)(45.00mg,产率:96.45%)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.93-4.89(m,1H),3.98-3.88(m,1H),3.52-3.47(m,1H),2.30-2.00(m,3H),1.66-1.62(m,1H)。

[0336] 实施例9:合成(1S,2R,5S)-2-氨基-5-氟环戊-1-醇(相对立体化学)

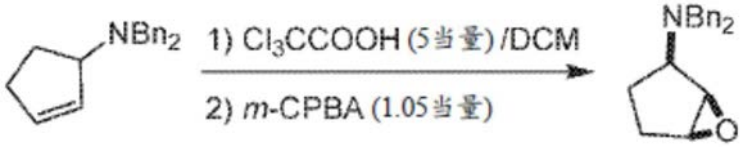


[0337]



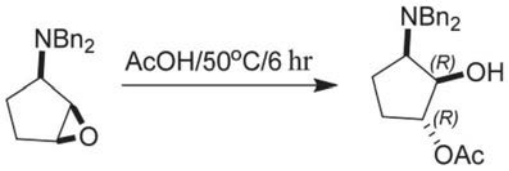
(相对立体化学)

[0338] 步骤1:(1R,2R,5S)-N,N-联苄基-6-氧杂双环[3.1.0]己-2-胺

[0339] 

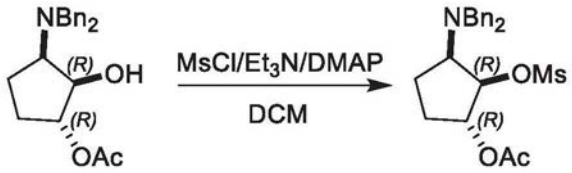
[0340] 将Cl_3CCOOH(154.72g,949.20mmol)添加至N,N-联苄基环戊-2-烯-1-胺(50.00g,189.84mmol)于DCM(640mL)中的搅拌溶液中并且将所得混合物在20℃下搅拌0.1h。一次性添加m-CPBA(43.00g,199.33mmol)并且将反应混合物在20℃下持续搅拌16h。在TLC(PE:EtOAc=10:1)显示反应完成之后,将混合物用DCM(500mL)稀释并且添加Na_2SO_3饱和水溶液直至碘化淀粉纸指示没有留下m-CPBA为止。添加$NaHCO_3$(500mL)饱和水溶液并且将各层分离。将有机层用$NaHCO_3$(200mL*2)水溶液洗涤,然后干燥,浓缩,并且通过硅胶柱色谱(PE:EtOAc=100:1-50:1)纯化以得到呈白色固体状的(1R,2R,5S)-N,N-联苄基-6-氧杂双环[3.1.0]己-2-胺(30.00g,产率:56.56%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.41(d,4H,J=7.2Hz),7.31(t,4H,J=7.6Hz),7.25-7.22(m,2H),3.86-3.70(m,4H),3.44(s,1H),3.32(s,1H),3.28-3.24(m,1H),2.04-2.01(m,1H),1.54-1.45(m,3H)。

[0341] 步骤2:(1R,2R,3R)-3-(联苄基氨基)-2-羟环戊基乙酸酯

[0342] 

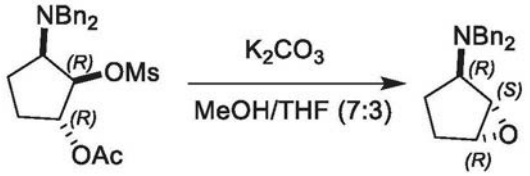
[0343] 将(1R,2R,5S)-N,N-联苄基-6-氧杂双环[3.1.0]己-2-胺(30.00g,107.38mmol,1.00当量)于AcOH(200mL)中的溶液在50℃下搅拌16h。在TLC(PE:EtOAc=10:1)显示反应完成之后,将混合物浓缩以移除AcOH,将残余物溶解于DCM(100mL)中,并且将有机层用$NaHCO_3$(100mL*3)水溶液洗涤,并且在Na_2SO_4上干燥并浓缩。通过硅胶柱色谱(PE:EtOAc=100:1-50:1)纯化残余物以得到呈白色固体状的(1R,2R,3R)-3-(联苄基氨基)-2-羟环戊基乙酸酯(20.00g,产率:54.87%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.36-7.28(m,10H),5.05-5.02(m,1H),4.05(d,1H,J=4.0Hz),3.81-3.69(m,4H),3.27-3.24(m,1H),2.40-2.36(m,1H),2.07(s,3H),1.97-1.94(m,1H),1.78-1.73(m,1H),1.60-1.54(m,1H)。

[0344] 步骤3:(1R,2R,3R)-3-(联苄基氨基)-2-((甲磺酰基)氧基)环戊基乙酸酯

[0345] 

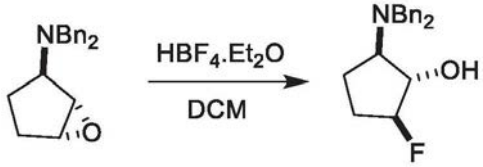
[0346] 将MsCl(8.10g,70.71mmol)逐滴添加至(1R,2R,3R)-3-(联苄基氨基)-2-羟环戊基乙酸酯(20.00g,58.92mmol)、Et_3N(18.48g,182.66mmol)和DMAP(719.83mg,5.89mmol)于DCM(200mL)中的混合物中。在添加之后,将混合物在20℃下搅拌16h。在TLC(PE:EtOAc=10:1)显示反应完成之后,将混合物用水(100mL*2)洗涤,将有机层在Na_2SO_4上干燥,并且通过硅胶柱色谱(PE:EtOAc=80:1-60:1)纯化以得到呈白色固体状的(1R,2R,3R)-3-(联苄基氨基)-2-((甲磺酰基)氧基)环戊基乙酸酯(15.00g,产率:60.97%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.41(d,4H,J=7.6Hz),7.33(t,4H,J=6.8Hz),7.31-7.25(m,2H),5.16-5.13(m,1H),5.01-5.00(m,1H),3.92-3.81(m,4H),3.37-3.32(m,1H),3.15(s,3H),2.33-2.30(m,1H),2.01(s,3H),1.98-1.91(m,2H),1.56-1.53(m,1H)。

[0347] 步骤4:(1S,2R,5R)-N,N-联苄基-6-氧杂双环[3.1.0]己-2-胺

[0348] 

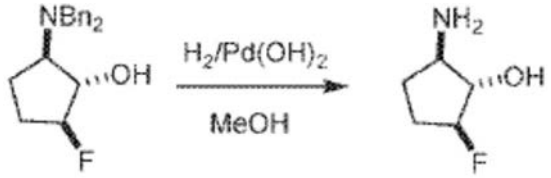
[0349] 将K_2CO_3(5.96g,43.11mmol)添加至(1R,2R,3R)-3-(联苄基氨基)-2-((甲磺酰基)氧基)环戊基乙酸酯(15.00g,35.93mmol)于MeOH(70mL)/THF(30mL)中的混合物中。在20℃下将混合物搅拌16h。在TLC(PE:EtOAc=10:1)显示反应完成之后,将混合物浓缩以移除MeOH和THF。然后将混合物溶解于DCM(20mL)中,将有机层用水(10mL*2)洗涤,在Na_2SO_4上干燥,并且浓缩以得到呈白色固体状的(1S,2R,5R)-N,N-联苄基-6-氧杂双环[3.1.0]己-2-胺(10.00g,产率:99.62%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.37(d,4H,J=7.6Hz),7.32(d,4H,J=7.2Hz),7.29-7.23(m,2H),3.73-3.69(m,2H),3.53-3.41(m,5H),2.06-2.00(m,1H),1.91-1.90(m,1H),1.87-1.76(m,1H),1.51-1.48(m,1H)。

[0350] 步骤5:(1S,2R,5S)-2-(联苄基氨基)-5-氟环戊-1-醇

[0351] 

[0352] 向(1S,2R,5R)-N,N-联苄基-6-氧杂双环[3.1.0]己-2-胺(6.50g,23.27mmol)于DCM(200mL)中的混合物中添加HBF_4/Et_2O(7.54g,46.53mmol),并且将混合物在30℃下搅拌0.2h。在TLC显示反应完成之后,将混合物添加至Na_2CO_3(100mL)并且用DCM(200mL*2)萃取。将有机层在Na_2SO_4上干燥,浓缩,并且通过硅胶柱色谱(PE:EtOAc=60:1至20:1)纯化以得到呈白色固体状的(1S,2R,5S)-2-(联苄基氨基)-5-氟环戊-1-醇(1.80g,产率:25.84%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.38-7.22(m,10H),4.81-4.67(m,1H),4.23-4.15(m,1H),3.83-3.55(m,4H),3.04-2.98(m,1H),1.93-1.79(m,4H)。

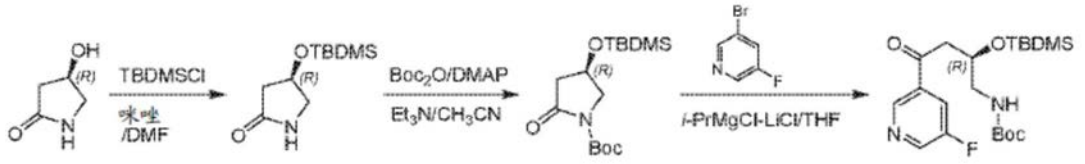
[0353] 步骤6:(1S,2R,5S)-2-氨基-5-氟环戊-1-醇(相对立体化学)

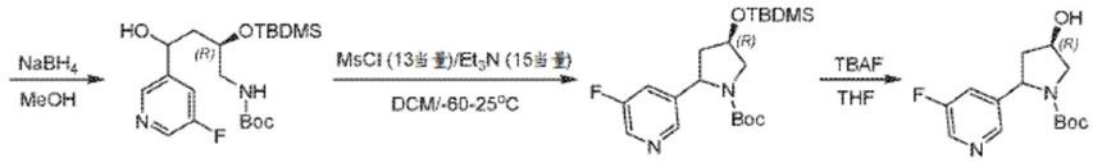
[0354] 

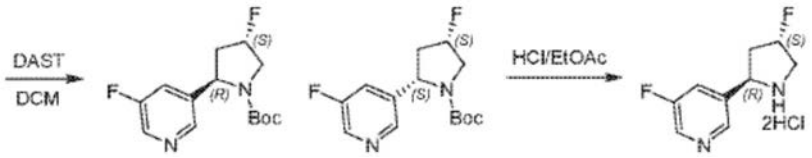
(相对立体化学)

[0355] 向(1S,2R,5S)-2-(联苄基氨基)-5-氟环戊-1-醇(1.60g,5.34mmol)于MeOH(10mL)中的混合物中添加$Pd(OH)_2$(500.00mg,3.61mmol),并且将混合物在30℃下在H_2(30psi)下搅拌16h。在TLC显示反应完成之后,通过硅藻土过滤混合物并且将滤液浓缩以得到呈白色固体状的(1S,2R,5S)-2-氨基-5-氟环戊-1-醇(600.00mg,产率:94.31%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.93-4.77(m,1H),3.92-3.84(m,1H),3.10-3.04(m,1H),2.07-1.98(m,3H),1.64-1.61(m,1H)。

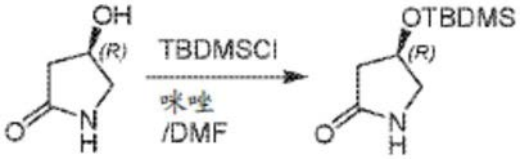
[0356] 实施例10:合成3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶



[0357] 



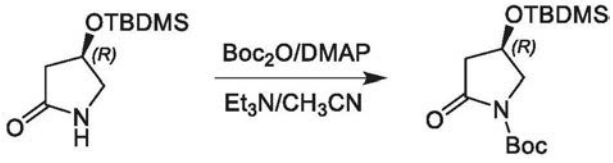
[0358] 步骤1:(R)-4-((叔丁基二甲基甲硅烷基)氧基)吡咯烷-2-酮

[0359] 

[0360] 在0℃下向(R)-4-羟吡咯烷-2-酮(9.0g,89.1mmol)于DMF(50mL)中的混合物中一次性添加咪唑(9.09g,134mmol)和TBDMSCl(14.1g,93.6mmol)。在25℃下将反应混合物搅拌3h。TLC(DCM/MeOH=10/1,R_f=0.8)显示反应完成,然后添加水(200mL),通过过滤收集所得沉淀物并且在真空中干燥以得到呈白色固体状的(R)-4-((叔丁基二甲基甲硅烷基)氧基)吡咯烷-2-酮(15.5g,产率:80.7%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 5.90(br.s,1H),4.55-4.53(m,1H),3.60-3.56(m,1H),3.24-3.21(m,1H),2.56-2.50(m,1H),2.28-2.23(m,1H),0.87-0.85(m,9H),0.06-0.00(m,6H)。

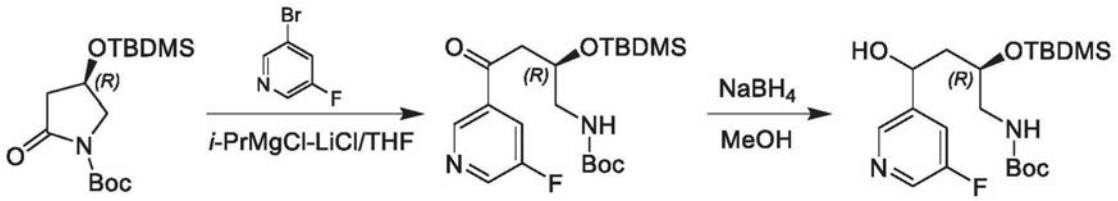
[0361] 步骤2:制备(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧基吡咯烷-1-羧酸叔丁

酯

[0362] 

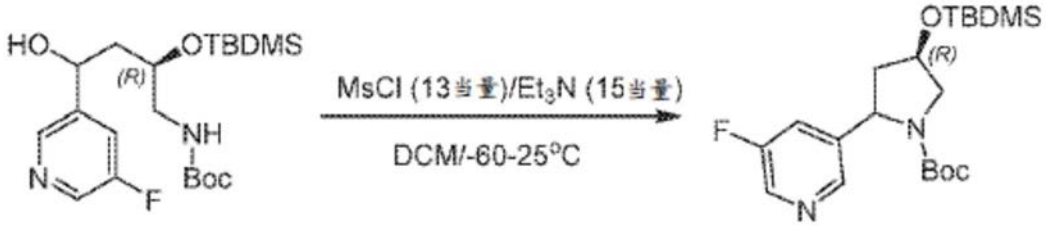
[0363] 在0℃下向(R)-4-((叔丁基二甲基甲硅烷基)氧基)吡咯烷-2-酮(15.5g,72.0mmol)于CH_3CN(150mL)中的混合物中一次性添加Et_3N(8.72g,86.4mmol)、DMAP(4.39g,36mmol)和Boc_2O(20.4g,93.7mmol)。将反应混合物在25℃下搅拌10h。TLC(PE/EtOAc=3/1)显示反应完成,然后添加水(600mL),通过过滤收集所得沉淀物并且在真空中干燥以得到呈粉红色固体状的(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧基吡咯烷-1-羧酸叔丁酯(19.2g,产率:84.6%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.33-4.30(m,1H),3.81-3.77(m,1H),3.56-3.54(m,1H),2.67-2.61(m,1H),2.41-2.37(m,1H),1.46(s,9H),0.80(s,9H),0.00(s,6H)。

[0364] 步骤3:((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯

[0365] 

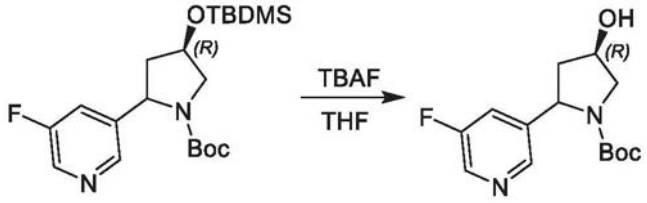
[0366] 在0℃下在30分钟内向3-溴-5-氟-吡啶(3.35g,19.02mmol,1.20当量)于THF(40.00mL)中的混合物中逐滴添加i-PrMgCl-LiCl(1.3M,17.56mL,1.44当量)(放热)。在添加之后,在1h内温度升高至25℃并且在25℃下搅拌30分钟。TLC(PE/EtOAc=10/1)显示生成新的点,这指示Mg试剂成功地制备。然后在-78℃下在30分钟内将于THF(50mL)中的(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧基吡咯烷-1-羧酸叔丁酯(5.00g,15.85mmol,1.00当量)逐滴添加至溶液。使混合物在1h内加温至25℃,然后在25℃下搅拌16h。TLC(PE/EtOAc=3/1)显示起始材料完全消耗并且检测到所需产物(R)-(2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-氧代丁基)氨基甲酸叔丁酯。通过在0℃下添加MeOH(50mL)来淬灭反应物。在0℃下添加$NaBH_4$(1.20g,31.70mmol,2.00当量),然后将混合物在25℃下搅拌4h。TLC(PE/EtOAc=2/1)和LCMS显示反应完成。将合并的反应混合物(4个平行反应)通过NH_4Cl(400mL)水溶液淬灭并且用EtOAc(600mL*3)萃取。将合并的有机物在Na_2SO_4上干燥并且在真空中浓缩,并且通过HPLC纯化残余物以得到呈黄色油状的((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯(1.24g,产率:18.91%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 8.26-8.22(m,2H),7.37(d,1H,J=8.8Hz),4.95-4.88(m,2H),4.69(br.s,1H),4.00-3.98(m,2H),3.23-3.10(m,2H),1.73(br.s,2H),1.32(s,9H),0.80-0.79(m,9H),0.00(s,6H)。

[0367] 步骤4:(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0368] 

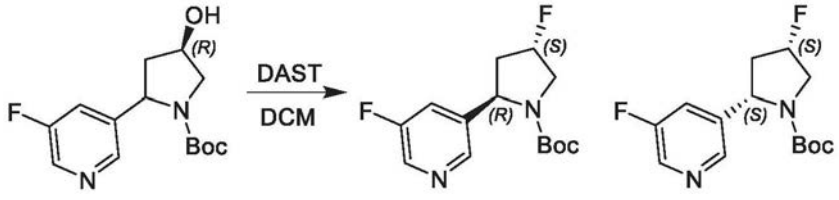
[0369] 在-60℃下在0.5h内向((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯(8.70g,20.98mmol,1.00当量)和Et_3N(31.84g,314.70mmol,15.00当量)于DCM(500.00mL)中的混合物中逐滴添加MsCl(31.24g,272.74mmol,13.00当量)。然后将混合物在-60℃下搅拌1h,并且将反应混合物加温至25℃并且搅拌18h。LCMS显示起始材料完全消耗。然后将混合物用H_2O(200mL*3)洗涤,并且将水相用DCM(200mL*4)萃取。将合并的有机层在Na_2SO_4上干燥并且在真空中浓缩以得到呈黑色/棕色油状的粗产物(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(8.30g,粗产物),其未纯化即直接使用。

[0370] 步骤5:(4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0371] 

[0372] 在25℃下向(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(8.30g,20.93mmol,1.00当量)于THF(250.00mL)中的混合物中添加TBAF(9.43g,41.86mmol,2.00当量)。在25℃下将混合物搅拌16h。在TLC(PE/EtOAc=1/1)显示反应完成之后,将混合物浓缩并且将残余物溶解于EtOAc(600mL)中,用水(200mL*5)洗涤,在Na_2SO_4上干燥,并浓缩。通过PLC纯化粗产物以得到呈棕色黑色油状的(4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(4.70g,16.65mmol,产率:79.54%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 8.37-8.33(m,2H),7.48(br.s,1H),5.09-4.89(m,1H),4.56-4.54(m,1H),3.80-3.65(m,2H),2.63-2.43(m,1H),2.03-1.96(m,1H),1.56-1.20(m,9H)。

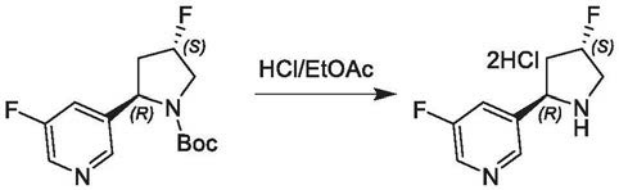
[0373] 步骤6:(2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0374] 

[0375] 在-78℃下在0.5h内向(4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(4.70g,16.65mmol,1.00当量)于DCM(150.00mL)中的混合物中逐滴添加DAST(29.52g,183.15mmol,11.00当量)。将反应混合物在-78℃下搅拌2h,然后将其加温至25℃并且搅拌20h。在TLC(PE/EtOAc=0/1)显示起始材料完全消耗之后,将混合物冷却至0℃并且通过饱和$NaHCO_3$溶液(100mL)来逐滴淬灭。将有机相分离并且在Na_2SO_4上干燥,浓缩以得到残余物,然后通过硅胶柱色谱(PE:EtOAc从10:1、8:1至5:1,然后3:1)纯化以得到呈白色固体状的(2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.38g,4.85mmol,产率:

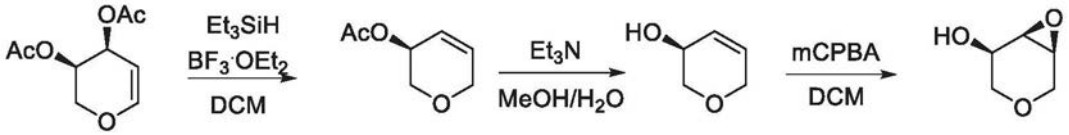
29.15%,R_f=0.53)和呈黄色油状的(2S,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.36g,4.78mmol,产率:28.73%,R_f=0.43)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 8.31-8.27(m,2H),7.20-7.18(m,1H),5.18(d,1H,J=51.6Hz),4.97-4.88(m,1H),4.04-4.00(m,1H),3.64(dd,1H,J=38.8,12.8Hz),2.67(dd,1H,J=15.6,6.8Hz),1.97-1.67(m,1H),1.56-1.12(m,9H)。

[0376] 步骤7:3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶

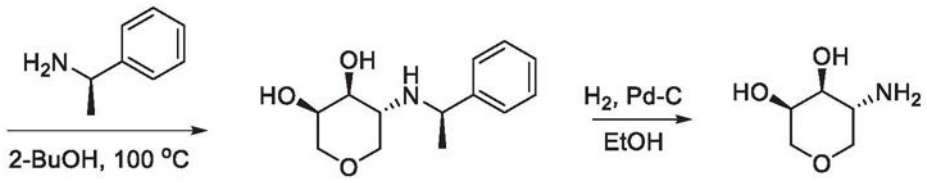
[0377] 

[0378] 在0℃下向(2R,4S)-4-氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.38g,4.85mmol,1.00当量)于EtOAc(10mL)中的混合物中逐滴添加HCl/EtOAc(40.00mL,4M)。将混合物加温至25℃并且搅拌3h。在TLC(PE:EtOAc=1:1)显示反应完成之后,将溶剂蒸发以得到呈棕色固体状的3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)吡啶(1.25g,4.86mmol,产率:100.00%)。^{1}H-NMR(400MHz,CD_3OD)δppm 8.84-8.81(m,2H),8.31(d,1H,J=9.2Hz),5.62(dt,1H,J=52.0,2.4Hz),5.23-5.18(m,1H),4.00-3.95(m,1H),3.88-3.71(m,1H),2.67(td,1H,J=16.0,6.0Hz),1.69-1.59(m,1H)。

[0379] 实施例11:合成(3R,4S,5R)-5-氨基四氢-2H-吡喃-3,4-二醇



[0380]



[0381] 步骤1:(S)-3,6-二氢-2H-吡喃-3-基乙酸酯

[0382] 将(3R,4S)-3,4-二氢-2H-吡喃-3,4-二基二乙酸酯(2.9g,14.49mmol)溶解于DCM(15ml)中,并且在N_2下在室温下搅拌。添加三乙基硅烷(2.55ml,15.93mmol)并且搅拌5分钟。逐滴添加$BF_3.OEt_2$(1.836ml,14.49mmol)并且继续搅拌30分钟。将反应混合物用30ml饱和碳酸氢盐淬灭,并且分离各层。将合并的有机层在硫酸钠上干燥并且将溶剂移除。通过快速色谱(0-30%Hex/EtOAc)纯化残余物。回收呈透明油状的(S)-3,6-二氢-2H-吡喃-3-基乙酸酯(1.9g,92%产率)。^{1}H NMR(400MHz,DMSO-d6)δ6.10(dddt,J=10.2,3.2,2.1,1.0Hz,1H),5.84(ddt,J=10.1,4.3,2.1Hz,1H),4.96(dtd,J=4.3,2.7,1.5Hz,1H),4.16-3.89(m,2H),3.73(t,J=2.9Hz,2H),2.01(d,J=0.9Hz,3H)。

[0383] 步骤2:(S)-3,6-二氢-2H-吡喃-3-醇

[0384] 将(S)-3,6-二氢-2H-吡喃-3-基乙酸酯(1.9g,13.37mmol)溶解于MeOH(30ml)和水(20ml)中。添加三乙胺(7ml,50.2mmol)并且在室温下搅拌30min。将溶剂在减压下移除。然

后将残余水用EtOAc萃取三次。将有机层合并，在硫酸钠上干燥并且将溶剂移除。回收呈透明油状的(S)-3,6-二氢-2H-吡喃-3-醇(1.1g,10.99mmol,82％产率)。所述粗产物未进一步纯化而继续使用。

[0385] 步骤3:(1S,5R,6R)-3,7-二氧杂双环[4.1.0]庚-5-醇

[0386] 将(S)-3,6-二氢-2H-吡喃-3-醇(1.1g,10.99mmol)溶解于CH_2Cl_2(20ml)中并且将其冷却至0℃。分批添加mCPBA(4.55g,13.18mmol)。在加温至室温的同时将反应混合物搅拌过夜。将反应混合物的白色沉淀物过滤掉，保留洗脱剂，将溶剂移除并且用乙醚研磨。重复此步骤。残余物(1S,5R,6R)-3,7-二氧杂双环[4.1.0]庚-5-醇(1.2g,100％产率)未进一步纯化而继续使用。

[0387] 步骤4:(3R,4S,5R)-5-(((R)-1-苯基乙基)氨基)四氢-2H-吡喃-3,4-二醇

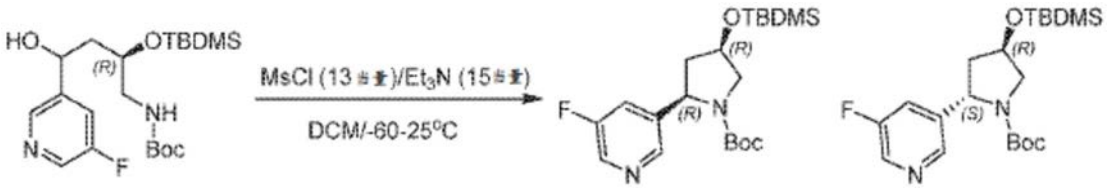
[0388] 将(1S,5R,6R)-3,7-二氧杂双环[4.1.0]庚-5-醇(1.26g,10.85mmol)、(R)-1-苯基乙胺(1.658ml,13.02mmol)溶解于2-BuOH(15ml)中。将反应混合物加热至100℃，持续18小时。将反应混合物冷却至室温，移除溶剂，并且然后在ISCO 0-100％EtOAc上纯化残余物。将级分合并，将溶剂移除，并且然后将残余物用MTBE处理并搅拌过夜。将有机混合物的白色沉淀物过滤掉。回收(3R,4S,5R)-5-(((R)-1-苯基乙基)氨基)四氢-2H-吡喃-3,4-二醇(0.350g,14％产率)。^{1}H NMR(400MHz,DMSO-d_6)δ7.38-7.24(m,4H),7.22-7.12(m,1H),4.61(d,J＝5.6Hz,1H),4.46(d,J＝4.8Hz,1H),3.88(q,J＝6.5Hz,1H),3.64(tt,J＝5.0,2.8Hz,1H),3.47(dd,J＝11.4,4.7Hz,1H),3.39(ddd,J＝8.4,5.6,3.1Hz,1H),3.31(s,2H),3.29(t,J＝3.0Hz,1H),3.25(d,J＝2.5Hz,0H),2.79(dd,J＝11.1,7.8Hz,1H),2.57(td,J＝7.8,3.9Hz,1H),1.86(s,1H),1.21(d,J＝6.6Hz,3H)。

[0389] 步骤5:(3R,4S,5R)-5-氨基四氢-2H-吡喃-3,4-二醇

[0390] 将(3R,4S,5R)-5-(((R)-1-苯基乙基)氨基)四氢-2H-吡喃-3,4-二醇(0.350g,1.475mmol)溶解于EtOH(3ml)中并且添加Pd-C(0.031g,0.295mmol)。将反应混合物在H_2气球下搅拌过夜。通过硅藻土过滤反应混合物并且将溶剂移除以得到呈米黄色固体状的(3R,4S,5R)-5-氨基四氢-2H-吡喃-3,4-二醇(0.190g,1.427mmol,97％产率)。所述粗产物未进一步纯化即继续使用。LCMS(M+H)134。

[0391] 实施例12.(R)-3-(4,4-二氟吡咯烷-2-基)-5-氟吡啶

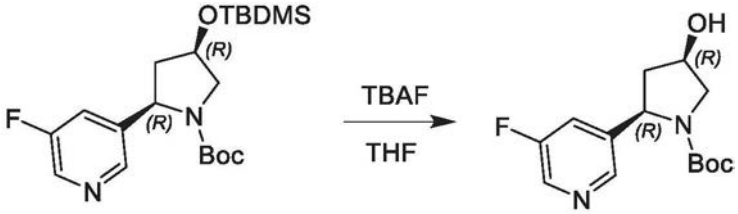
[0392] 步骤1:(2R,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0393] 

[0394] 在-60℃下在30分钟内向((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(5-氟吡啶-3-基)-4-羟基丁基)氨基甲酸叔丁酯(6.80g,16.40mmol)和Et_3N(24.89g,246.00mmol)于DCM(500.00mL)中的混合物中逐滴添加MsCl(24.42g,213.20mmol)。在-60℃下将混合物搅拌1h。将反应混合物加温至25℃并且再搅拌18h。将混合物用H_2O(200mL*3)洗涤。将水相用DCM(200mL*4)萃取。将合并的有机层在Na_2SO_4上干燥并且在真空中浓缩。通过硅胶色谱(PE:EtOAc＝50/1,20/1,10/1)纯化残余物以提供呈棕色油状的(2S,4R)-4-((叔丁基二甲

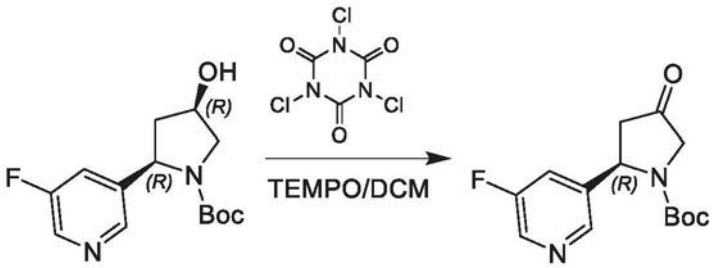
基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(2.70g,产率:41.52%)和(2R,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(2.40g,产率:36.89%)。1H-NMR(400MHz,CDCl3)δppm 8.40(br.s,2H),7.56-7.45(m,1H),5.11-4.94(m,2H),4.53(br.s,1H),3.85-3.79(m,1H),3.66-3.53(m,1H),2.62-2.58(m,1H),2.04-2.01(m,1H),1.56(s,3H),1.32(s,6H),0.99-0.88(m,9H),0.18-0.00(m,6H)。

[0395] 步骤2:(2R,4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0396] 

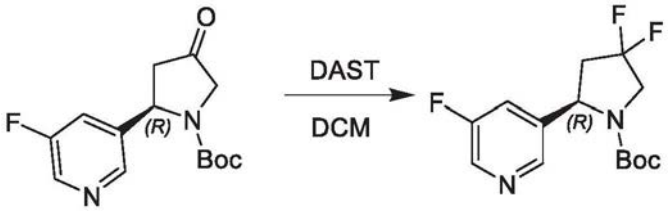
[0397] 在25℃下向(2R,4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(2.40g,6.05mmol)于THF(60.00mL)中的混合物中一次性添加TBAF(3.16g,12.10mmol)。将混合物在50℃下在减压下浓缩。将残余物添加至水(20mL)中。将水相用乙酸乙酯(30mL*3)萃取。将合并的有机相用饱和盐水(20mL*2)洗涤,在Na_2SO_4上干燥,过滤并且在真空中浓缩。通过硅胶色谱(PE:EtOAc=20/1,10/1,1/3)纯化残余物以提供呈黄色固体状的(2R,4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.30g,产率:76.11%)。1H-NMR(400MHz,CDCl3)δppm 8.26(d,2H,J=12.8Hz),7.39(br.s,1H),4.95-4.81(m,1H),4.48-4.47(m,1H),3.73(br.s,1H),3.56-3.53(m,1H),2.55(br.s,1H),1.97-1.98(m,1H),1.65-1.16(m,9H)。

[0398] 步骤3:(R)-2-(5-氟吡啶-3-基)-4-氧基吡咯烷-1-羧酸叔丁酯

[0399] 

[0400] 在-10℃下向(2R,4R)-2-(5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.30g,4.60mmol)和三氯异氰酸(1.10g,4.60mmol)的混合物中添加TEMPO(72.41mg,460.49umol)。将混合物在-10℃下搅拌15min,然后加温至25℃并且搅拌1h。TLC(EtOAc)显示反应完成。将有机相用$NaHCO_3$(20mL*2)洗涤,在Na_2SO_4上干燥,过滤并且在真空中浓缩。通过硅胶色谱(石油醚/乙酸乙酯=50/1,10/1)纯化残余物以提供呈棕色油状的(R)-2-(5-氟吡啶-3-基)-4-氧基吡咯烷-1-羧酸叔丁酯(1.10g,产率:85.32%)。

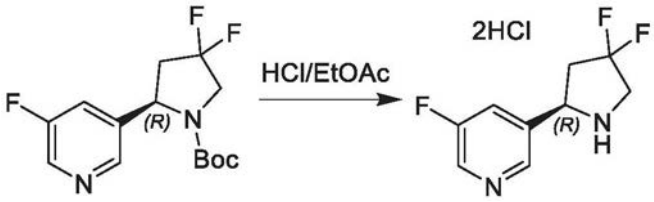
[0401] 步骤4:(R)-4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0402] 

[0403] 在-70℃下在N_2下向(R)-2-(5-氟吡啶-3-基)-4-氧基吡咯烷-1-羧酸叔丁酯

(1.00g,3.57mmol)于DCM(100.00mL)中的混合物中逐滴添加DAST(14.39g,89.25mmol)。在-70℃下将混合物搅拌30min。然后在25℃下将混合物搅拌16h。在0℃下通过$NaHCO_3$饱和水溶液来缓慢淬灭反应混合物并且将水相用DCM(50mL*4)萃取。将合并的有机相用饱和盐水(30mL)洗涤,在Na_2SO_4上干燥,过滤并且在真空中浓缩。通过硅胶色谱(石油醚/乙酸乙酯=100/1,30/1)纯化残余物以提供呈棕色油状的(R)-4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.00g,产率:92.66%)。1H-NMR(400MHz,CDCl3)δppm 8.40(s,1H),8.34(s,1H),7.30-7.21(m,1H),5.06(br.s,1H),4.14-3.85(m,2H),2.91-2.84(m,1H),2.39-2.32(m,1H),1.43-1.14(m,9H)。

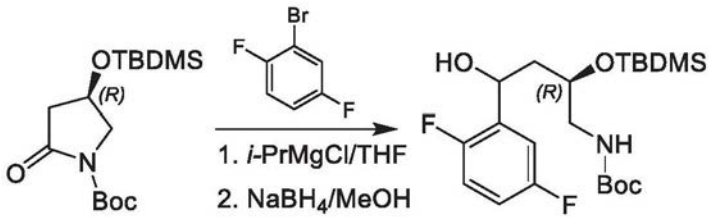
[0404] 步骤5:(R)-3-(4,4-二氟吡咯烷-2-基)-5-氟吡啶

[0405] 

[0406] 在25℃下将(R)-4,4-二氟-2-(5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(1.00g,3.31mmol)于HCl/EtOAc(50.00mL,4M)中的混合物搅拌2h。将混合物在30℃下在减压下浓缩以提供呈白色固体状的呈双HCl盐形式的(R)-3-(4,4-二氟吡咯烷-2-基)-5-氟吡啶(840.00mg,产率:92.25%)。1H-NMR(400MHz,MeOD)δppm8.68-8.63(m,1H),7.97(d,1H,J=9.2Hz),5.26-5.21(m,1H),4.03-3.90(m,2H),3.13-2.92(m,2H)。

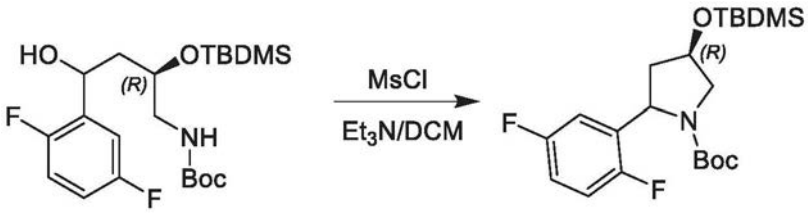
[0407] 实施例13.(3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-腈

[0408] 步骤1:((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(2,5-二氟苯基)-4-羟基丁基)氨基甲酸叔丁酯

[0409] 

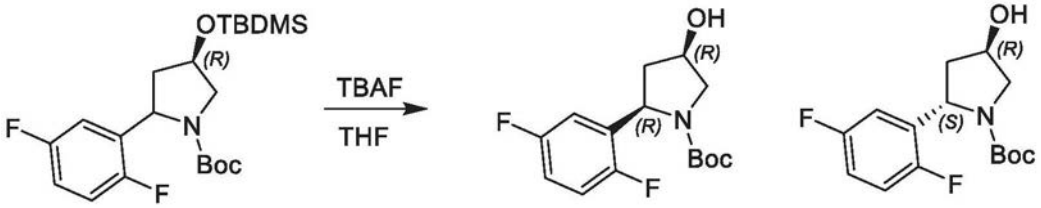
[0410] 在0℃下在N_2下,向2-溴-1,4-二氟苯(3.01g,15.60mmol,1.20当量)于THF(15mL)中的溶液中逐滴添加异丙基氯化镁复合物(2.27g,15.60mmol,1.20当量)。将反应物在15℃下搅拌1h以制备(2,5-二氟苯基)溴化镁(23mL)。在0℃下在30分钟内向(R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-氧基吡咯烷-1-羧酸叔丁酯(4.10g,13.00mmol,1.00当量)于THF(50mL)中的溶液中逐滴添加(2,5-二氟苯基)溴化镁(23mL)。在0℃下将反应混合物搅拌1h。在0℃下将甲醇(20mL)添加至混合物,随后添加$NaBH_4$(738mg,19.50mmol,1.50当量)。将混合物在0℃下搅拌1h,然后倾倒至10%NH_4Cl水溶液。将混合物用EtOAc(20mL*2)萃取,将合并的有机层用盐水洗涤,在Na_2SO_4上干燥,过滤并浓缩。通过中压液相色谱(MPLC)纯化粗产物以得到((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(2,5-二氟苯基)-4-羟基丁基)氨基甲酸叔丁酯(2.22g,5.14mmol,39.6%产率)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.17-7.15(m,1H),6.86-6.79(m,2H),5.11-5.06(m,1H),4.70(br.s,1H),4.02-3.98(m,1H),3.69(br.s,0.5H),3.46(br.s,0.5H),3.33-3.14(m,2H),1.80-1.69(m,2H),1.35(s,9H),0.84-0.82(9H,m),0.04-0.03(6H,m)。

[0411] 步骤2:(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯

[0412] 

[0413] 在-60℃下在N_2下,向((2R)-2-((叔丁基二甲基甲硅烷基)氧基)-4-(2,5-二氟苯基)-4-羟基丁基)氨基甲酸叔丁酯(13.40g,31.05mmol,1.00当量)和Et_3N(9.43g,93.14mmol,3.00当量)于DCM(50mL)中的溶液中逐滴添加甲磺酰氯(5.33g,46.57mmol,1.50当量)。将混合物在-60℃下搅拌2h并且在15℃下搅拌16h。LCMS显示起始材料完全消耗。将反应混合物用DCM(30mL*2)萃取并且将合并的有机物用盐水(50mL)洗涤,在Na_2SO_4上干燥并过滤,浓缩以得到(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(12.00g,26.11mmol,产率:84.10%,90%纯度),其未进一步纯化即直接使用。

[0414] 步骤3:(2R,4R)-2-(2,5-二氟苯基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0415] 

[0416] 在15℃下向(4R)-4-((叔丁基二甲基甲硅烷基)氧基)-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(4.50g,10.88mmol,1.00当量)于THF(30mL)中的溶液中添加TBAF/THF(1M,14.15mL,1.30当量)。在15℃下将混合物搅拌16h。TLC(PE:EtOAc=3:1)显示起始材料完全消耗。通过H_2O(50mL)淬灭反应混合物,将其用EtOAc(30mL*2)萃取并且将合并的有机物用盐水(10mL)洗涤,在Na_2SO_4上干燥,过滤并在真空中浓缩。通过中性制备型HPLC纯化残余物以提供呈白色固体状的(2R,4R)-2-(2,5-二氟苯基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.00g,3.34mmol,产率:30.70%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.04-6.80(m,3H),5.10-5.00(m,1H),4.43(s,1H),3.75(br.s,1H),3.53-3.49(m,1H),2.53(br.s,1H),1.93-1.90(m,1H),1.40-1.16(m,9H)。

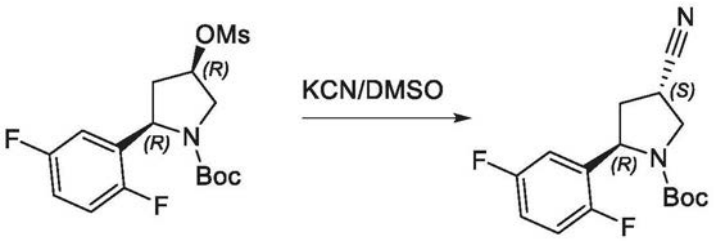
[0417] 步骤4:(2R,4R)-2-(2,5-二氟苯基)-4-((甲磺酰基)氧基)吡咯烷-1-羧酸叔丁酯

[0418] 

[0419] 在0℃下向(2R,4R)-2-(2,5-二氟苯基)-4-羟基吡咯烷-1-羧酸叔丁酯(3.00g,10.02mmol,1.00当量)和Et_3N(2.03g,20.04mmol,2.00当量)于DCM(80.00mL)中的混合物中逐滴添加MsCl(1.61g,14.03mmol,1.40当量)。在18℃下将混合物搅拌2h。通过H_2O(30mL)淬灭混合物。通过DCM(50mL*3)萃取水相。将合并的有机层在Na_2SO_4上干燥并且在减压下浓缩。获得呈棕色固体状的(2R,4R)-2-(2,5-二氟苯基)-4-((甲磺酰基)氧基)吡咯烷-1-羧酸叔

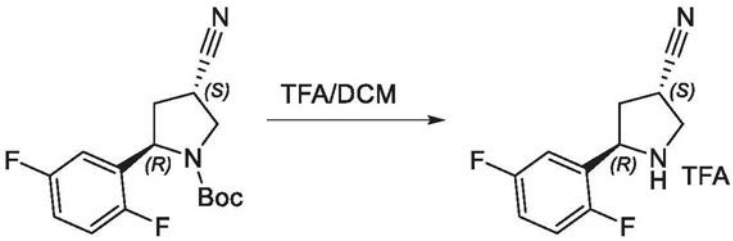
丁酯(3.60g,9.54mmol,产率:95.20%)。

[0420] 步骤5:(2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯

[0421] 

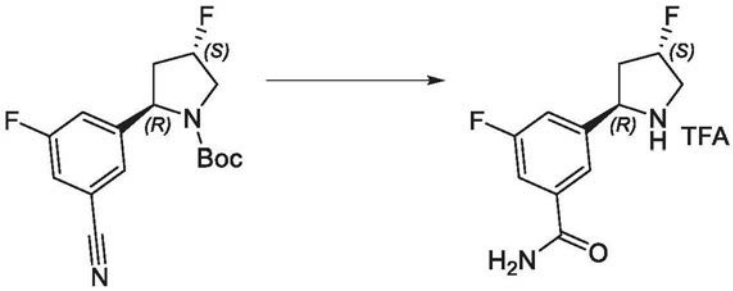
[0422] 向(2R,4R)-2-(2,5-二氟苯基)-4-((甲磺酰基)氧基)吡咯烷-1-羧酸叔丁酯(3.60g,9.54mmol,1.00当量)于DMSO(20.00mL)中的混合物中一次性添加KCN(745.49mg,11.45mmol,1.20当量)。在90℃下将混合物搅拌3h。将80mL的H2O添加至混合物,并且通过EtOAc(80mL*4)萃取混合物。在减压下浓缩合并的有机层。通过硅胶色谱(PE/EtOAc=40:1、30:1、10:1)纯化残余物。获得呈浅绿色液体状的(2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(1.60g,5.19mmol,产率:54.40%)。

[0423] 步骤6:(3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-腈

[0424] 

[0425] 将(2R,4S)-4-氰基-2-(2,5-二氟苯基)吡咯烷-1-羧酸叔丁酯(800.00mg,2.59mmol,1.00当量)于TFA(4.00mL)/DCM(20.00mL)中的混合物在18℃下搅拌3h。将混合物在N_2下干燥。获得呈淡黄色固体状的(3S,5R)-5-(2,5-二氟苯基)吡咯烷-3-腈(780.00mg,2.42mmol,产率:93.44%)。

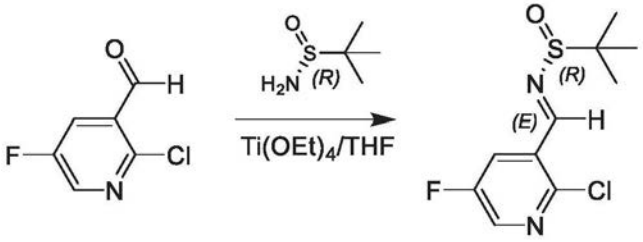
[0426] 实施例14.3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酰胺

[0427] 

[0428] 将3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苄腈(0.050g,0.240mmol)(如WO 2012/034095中制备)溶解于TFA(0.800ml,10.38mmol)和H_2SO_4(0.200ml,3.75mmol)中并且在室温下搅拌过夜。将反应混合物用冰水(3ml)稀释并且通过过滤分离固体,并且直接使用所述固体。

[0429] 实施例15.2-氯-5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)吡啶

[0430] 步骤1:(S,Z)-N-((2-氯-5-氟吡啶-3-基)亚甲基)-2-甲基丙烷-2-亚磺酰胺

[0431] 

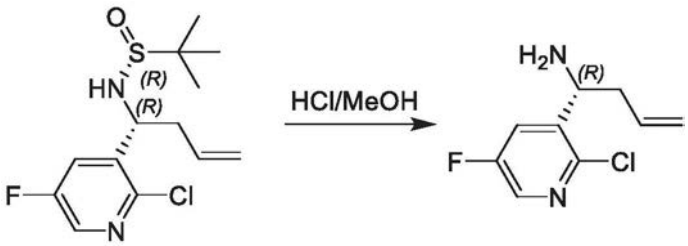
[0432] 在0℃下将2-氯-5-氟烟碱醛(20g,125mmol)溶解于THF(150ml)中。添加(R)-2-甲基丙烷-2-亚磺酰胺(16.71g,138mmol),随后逐滴添加四乙醇钛(22.88ml,150mmol)。搅拌反应混合物,同时加温至RT。在3小时之后,将反应混合物冷却至0℃,并且添加150ml盐水并且搅拌20分钟。通过硅藻土过滤混合物。将水层分离并丢弃。将有机层在Na_2SO_4上干燥并且将溶剂移除以得到(S,Z)-N-((2-氯-5-氟吡啶-3-基)亚甲基)-2-甲基丙烷-2-亚磺酰胺(32g,122mmol,97%产率),其未进一步纯化即继续使用。LCMS:263M+H。

[0433] 步骤2:(R)-N-((R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)-2-甲基丙烷-2-亚磺酰胺

[0434] 

[0435] 将(R,E)-N-((2-氯-5-氟吡啶-3-基)亚甲基)-2-甲基丙烷-2-亚磺酰胺(32.9g,125mmol)溶解于HMPA(100ml)中并且冷却至0℃。在0℃下添加锌(16.37g,250mmol)、烯丙基溴(21.67ml,250mmol)和水(2.256ml,125mmol)并且将反应混合物加温至RT过夜。LCMS显示完全转化成所需产物。在RT下添加100ml水并且搅拌30分钟。添加30ml的MBTE,随后添加60ml的10%柠檬酸并且将反应混合物搅拌30分钟。通过硅藻土过滤混合物并用MTBE洗涤。将有机层用10%柠檬酸、水和盐水洗涤。将溶剂在真空下移除以得到呈橙色油状的(R)-N-((R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)-2-甲基丙烷-2-亚磺酰胺(14.5g,47.6mmol,38.0%产率)。LCMS:305M+H。

[0436] 步骤3:(R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-胺,HCl

[0437] 

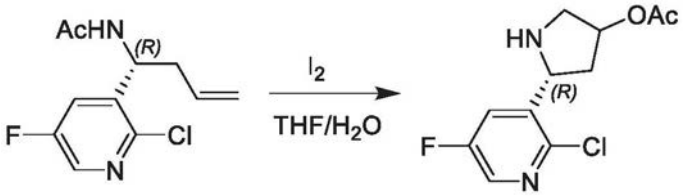
[0438] 将(R)-N-((R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)-2-甲基丙烷-2-亚磺酰胺(7.5g,24.61mmol)溶解于10ml的MeOH中。添加HCl(二噁烷中的4M)(30.8ml,123mmol)并且在RT下搅拌1h。在真空下移除溶剂并且将残余物用DCM稀释并用NaHCO3饱和水溶液洗涤。将各层分离并且将有机层用Na_2SO_4干燥并在真空下移除溶剂。回收呈固体状的(R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-胺,HCl(5.83g,24.59mmol,100%产率)。LCMS:201M+H。

[0439] 步骤4:(R)-N-(1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)乙酰胺

[0440] 

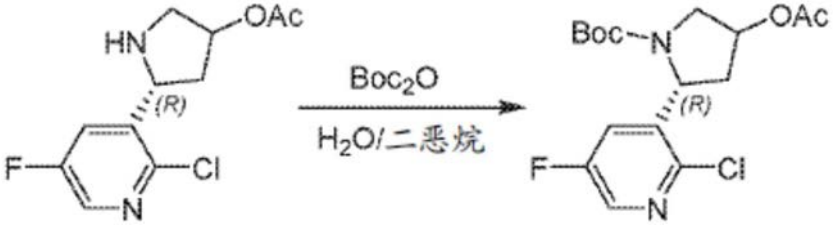
[0441] 在0℃下向DCM(70.3ml)中的(R)-1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-胺·HCl(5.83g,24.59mmol)中添加TEA(4.11ml,29.5mmol)和乙酸酐(2.320ml,24.59mmol)。将混合物搅拌2小时。将反应混合物倾倒至饱和$NaHCO_3$水溶液中并且用DCM萃取。将有机层用盐水洗涤、在$MgSO_4$上干燥并且在减压下浓缩。回收(R)-N-(1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)乙酰胺(5.97g,24.60mmol,100%产率)并且未进一步纯化即继续使用。LCMS:243M+H。

[0442] 步骤5:(5R)-5-(2-氯-5-氟吡啶-3-基)吡咯烷-3-基乙酸酯

[0443] 

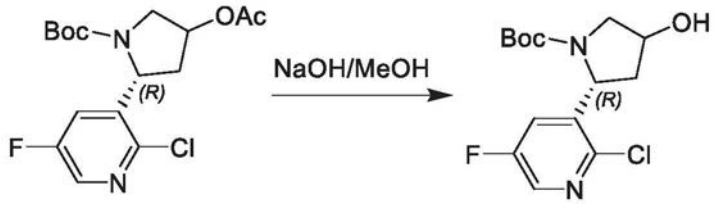
[0444] 将(R)-N-(1-(2-氯-5-氟吡啶-3-基)丁-3-烯-1-基)乙酰胺(5.97g,24.60mmol)溶解于THF(56.2ml)和水(14.06ml)中,随后添加I_2(18.73g,73.8mmol)并且在RT下搅拌过夜。将粗反应物用饱和$NaHCO_3$和$Na_2S_2O_3$溶液稀释并且用EtOAc萃取两次。将水层用饱和$NaHCO_3$水溶液碱化并且用EtOAc萃取以获得呈淡黄色油状的(5R)-5-(2-氯-5-氟吡啶-3-基)吡咯烷-3-基乙酸酯(5.9g,22.81mmol,93%产率)。LCMS:259M+H。

[0445] 步骤6:(2R)-4-乙酰氧基-2-(2-氯-5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯

[0446] 

[0447] 向(5R)-5-(2-氯-5-氟吡啶-3-基)吡咯烷-3-基乙酸酯(5.9g,22.81mmol)于二噁烷(76ml)和水(76ml)中的溶液中添加BOC-酐(7.94ml,34.2mmol),随后谨慎添加2N NaOH(7ml)以达到pH～9。在RT下将反应混合物搅拌1小时。将反应混合物用水稀释并且用EtOAc萃取三次。将有机层在Na_2SO_4上干燥并且将溶剂在真空下移除以得到(2R)-4-乙酰氧基-2-(2-氯-5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(3.5g,9.75mmol,42.8%产率),其未进一步纯化即继续使用。LCMS:359M+H。

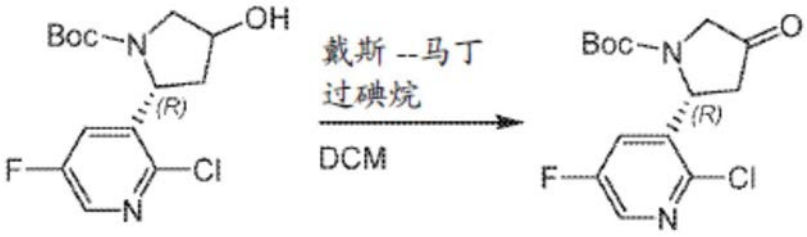
[0448] 步骤7:(2R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0449] 

[0450] 将(2R)-4-乙酰氧基-2-(2-氯-5-氟吡啶-3-基)吡咯烷-1-羧酸叔丁酯(3.5g,

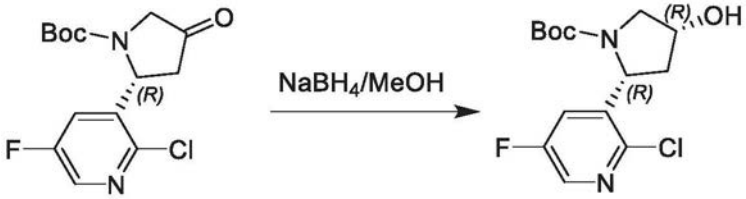
9.75mmol)溶解于MeOH(48.8ml)中,随后添加2M NaOH(5.37ml,10.73mmol)并且将反应混合物在RT下搅拌2小时。将溶剂在真空下移除并且将水层用1N HCl中和,并且用EtOAc萃取三次。将合并的有机层在Na_2SO_4上干燥。将溶剂在真空下移除并且通过硅胶色谱(0-70%Hex/EtOAc)纯化残余物以得到(2R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(2.1g,6.63mmol,68.0%产率)。LCMS:317M+H。

[0451] 步骤8:(R)-2-(2-氯-5-氟吡啶-3-基)-4-氧基吡咯烷-1-羧酸叔丁酯

[0452] 

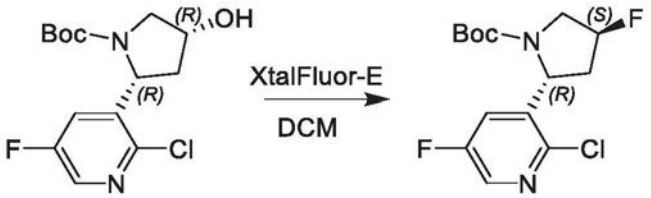
[0453] 将(2R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(2.1g,6.63mmol)溶解于DCM(66.3ml)中并且添加$NaHCO_3$(0.557g,6.63mmol),随后添加戴斯-马丁过碘烷(8.44g,19.89mmol)。将反应混合物搅拌过夜。添加水(0.119ml,6.63mmol),随后添加戴斯-马丁过碘烷(8.44g,19.89mmol)并且搅拌18小时。用饱和$NaHCO_3$水溶液将pH调整至~7并且用DCM x3萃取。将有机层合并,在Na_2SO_4上干燥并且将溶剂在真空下移除。通过快速色谱(0-70%Hex/EtOAc)纯化残余物以得到(R)-2-(2-氯-5-氟吡啶-3-基)-4-氧基吡咯烷-1-羧酸叔丁酯(1.6g,5.08mmol,77%产率)。LCMS:315M+H。

[0454] 步骤9:(2R,4R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0455] 

[0456] 将(R)-2-(2-氯-5-氟吡啶-3-基)-4-氧基吡咯烷-1-羧酸叔丁酯(1.6g,5.08mmol)悬浮于乙醇(33.9ml)中并且冷却至0℃。分批添加$NaBH_4$(0.096g,2.54mmol)并且在0℃下搅拌45分钟。用饱和NH_4Cl缓慢淬灭反应物并且将其加温至RT,并且将溶液用DCM x3萃取。将有机层合并并且在Na_2SO_4上干燥。通过快速色谱(0-70%Hex/EtOAc)纯化残余物以得到(2R,4R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.446g,4.57mmol,90%产率)。LCMS:317M+H。

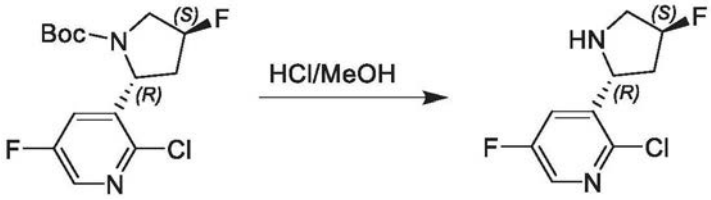
[0457] 步骤10:(2R,4S)-2-(2-氯-5-氟吡啶-3-基)-4-氟吡咯烷-1-羧酸叔丁酯

[0458] 

[0459] 将(2R,4R)-2-(2-氯-5-氟吡啶-3-基)-4-羟基吡咯烷-1-羧酸叔丁酯(1.0g,3.16mmol)溶解于DCM(25ml)中并且冷却至-78℃。添加TEA-HF(1.098ml,9.47mmol)并且搅拌10分钟。添加XtalFluor-E(1.446g,6.31mmol)并且在10分钟之后将反应混合物转移至冰浴并且将其加温至0℃。在2小时之后,将反应混合物用DCM稀释并且用饱和$NaHCO_3$水溶液淬

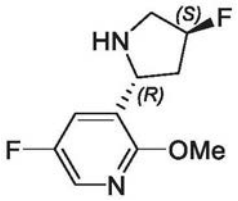
灭。将有机层分离，并且将溶剂在真空下移除。通过ISCO(0-50％Hex/EtOAc；12g柱)纯化残余物以得到呈白色固体状的(2R,4S)-2-(2-氯-5-氟吡啶-3-基)-4-氟吡咯烷-1-羧酸叔丁酯(0.805g,2.53mmol,80％产率)。LCMS:319M+H。

[0460] 步骤11:2-氯-5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)吡啶,HCl

[0461] 

[0462] 将(2R,4S)-2-(2-氯-5-氟吡啶-3-基)-4-氟吡咯烷-1-羧酸叔丁酯(0.805g,2.53mmol,80％产率)溶解于EtOAc(5ml)中并且添加4N HCl/二噁烷(3ml)。在RT下将反应混合物搅拌1小时。将沉淀物过滤掉，用醚洗涤，并且在高真空下干燥过夜以得到呈米黄色固体状的2-氯-5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)吡啶,HCl(0.612g,2.399mmol,76％产率)。LCMS:219M+H。

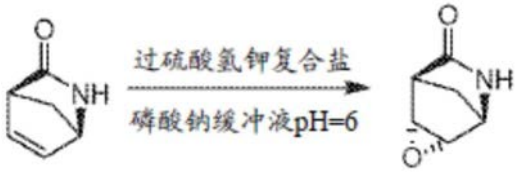
[0463] 实施例16.5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)-2-甲氧基吡啶

[0464] 

[0465] 将5-氟-3-((2R,4S)-4-氟吡咯烷-2-基)-2-甲氧基吡啶以与3-氟-5-((2R,4S)-4-氟吡咯烷-2-基)苯甲酰胺相同的方式来制备，用5-氟-2-甲氧基烟碱醛替换2-氯-5-氟烟碱醛。

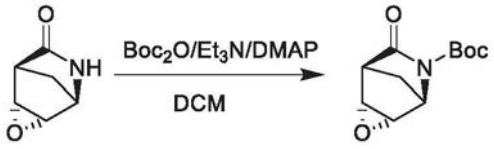
[0466] 实施例17.(1R,3R,4R)-3-氨基-4-羟基环戊烷-1-羧酸甲酯

[0467] 步骤1:(1S,2R,4S,5R)-3-氧杂-6-氮杂三环[3.2.1.02,4]辛-7-酮

[0468] 

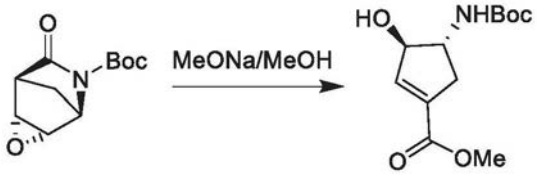
[0469] 在0℃下在5h内向(1R,4S)-2-氮杂双环[2.2.1]庚-5-烯-3-酮(30.00g,274.90mmol,1.00当量)于NaH_2PO_4(395.00mL,0.2M)和Na_2HPO_4(55.00mL,0.2M)中的溶液中分批添加H_2O(450.00mL)和过硫酸氢钾复合盐(669.31g,4.40mol,16.00当量)，并且通过添加NaOH水溶液(12M)来保持pH＝6并且将温度保持于0℃。在添加之后，将混合物在0℃下再搅拌2h,TLC(PE:EtOAc＝1:1)显示起始材料完全消耗，将混合物过滤并且将水相用DCM(400mL*5)萃取，将合并的有机层在Na_2SO_4上干燥，真空浓缩以获得呈黄色固体状的(1S,2R,4S,5R)-3-氧杂-6-氮杂三环[3.2.1.02,4]辛-7-酮(9.00g,71.93mmol,产率:26.16％)。^{1}H-NMR(400MHz,$CDCl_3$)δppm5.96(br.s,1H),3.86(s,1H),3.62(1H,d,J＝3.2Hz),3.53(1H,d,J＝2.8Hz),2.86(s,1H),1.82(d,1H,J＝9.6Hz),1.64(d,1H,J＝10.0Hz)。

[0470] 步骤2:(1S,2R,4S,5R)-7-氧基-3-氧杂-6-氮杂三环[3.2.1.02,4]辛烷-6-羧酸叔丁酯

[0471] 

[0472] 向(1S,2R,4S,5R)-3-氧杂-6-氮杂三环[3.2.1.02,4]辛-7-酮(9.00g,71.93mmol,1.00当量)于DCM(100.00mL)中的溶液中添加Boc_2O(17.27g,79.12mmol,1.10当量)、Et_3N(8.73g,86.32mmol,1.20当量)和DMAP(878.71mg,7.19mmol,0.10当量),将混合物在25℃下搅拌16h,LCMS显示起始材料完全消耗,将混合物用NH_4Cl水溶液(100mL*3)洗涤,将合并的有机层在Na_2SO_4上干燥,在真空中浓缩,使用硅胶柱色谱(PE:EtOAc=5:1～1:1)纯化粗产物以获得呈黄色固体状的(1S,2R,4S,5R)-7-氧基-3-氧杂-6-氮杂三环[3.2.1.02,4]辛烷-6-羧酸叔丁酯(12.00g,53.28mmol,产率:74.07%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.56(s,1H),3.71(d,1H,J=2.8Hz),3.54(d,1H,J=2.8Hz),3.00(s,1H),1.75(d,1H,J=10.0Hz),1.57(d,1H,J=10.8Hz),1.46(s,9H)。

[0473] 步骤3:(3R,4R)-4-((叔丁氧羰基)氨基)-3-羟基环戊-1-烯-1-羧酸甲酯

[0474] 

[0475] 在0℃下将Na(3.37mg,146.50umol,0.01当量)添加至MeOH(10.00mL),然后将溶液在0℃下搅拌0.5h,将溶液添加至MeOH(30.00mL)中的(1S,2R,4S,5R)-7-氧基-3-氧杂-6-氮杂三环[3.2.1.02,4]辛烷-6-羧酸叔丁酯(3.30g,14.65mmol,1.00当量),并且然后将混合物在16℃下搅拌13.5h,LCMS显示起始材料完全消耗,用乙酸(5mL)淬灭反应物,并且然后用$NaHCO_3$(20mL*3)洗涤,将有机层在Na_2SO_4上干燥,并且在真空中浓缩,用PE(20mL)洗涤粗产物以获得呈白色固体状的(3R,4R)-4-((叔丁氧羰基)氨基)-3-羟基环戊-1-烯-1-羧酸甲酯(2.10g,8.16mmol,产率:55.72%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 6.65(s,1H),4.98(s,1H),4.81(d,1H,J=2.8Hz),4.46(s,1H),3.98-3.92(m,1H),3.75(s,3H),3.07-3.01(m,1H),2.36-2.29(m,1H),1.45(s,9H)。

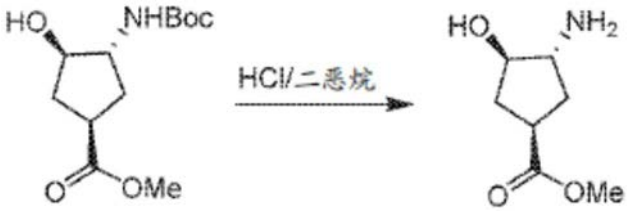
[0476] 步骤4:(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸甲酯

[0477] 

[0478] 将(3R,4R)-4-((叔丁氧羰基)氨基)-3-羟基环戊-1-烯-1-羧酸甲酯(2.00g,7.77mmol,1.00当量)、(1Z,5Z)-环辛-1,5-二烯;(2S,5S)-1-[2-[(2S,5S)-2,5-二甲基磷杂环戊烷-1-基]乙基]-2,5-二甲基-磷杂环戊烷;铑(1+);三氟甲磺酸酯(48.08mg,77.74umol,0.01当量)于MeOH(50.00mL)中的混合物脱气并且用H_2吹扫3次,并且然后将混合物在55℃下在H_2(40psi)气氛下搅拌16h,TLC(PE:EtOAc=1:1)显示起始材料消耗,将混合物真空浓缩,并且然后溶解于EtOAc(5mL)中,然后向混合物中添加PE(20mL),形成白色固体,将沉淀物收集,在真空中干燥,将固体溶解于MeOH(7mL)中,并且用酸性制备型-HPLC

(HCl)纯化以获得呈黄色油的(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸甲酯(750.00mg,2.89mmol,产率:37.23%),所述结构通过手性HPLC和^{1}H-NMR来证实。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.04-3.99(m,1H),3.80-3.77(m,1H),3.70(s,3H),2.93-2.91(m,1H),2.48-2.44(m,1H),2.43-2.35(m,1H),1.92-1.89(m,1H),1.87-1.69(m,1H),1.45(s,9H)。

[0479] 实施例18.合成(1R,3R,4R)-3-氨基-4-羟基环戊烷-1-羧酸甲酯

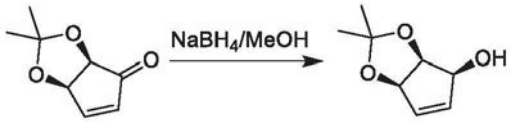
[0480] 

[0481] 在19℃下将HCl/二噁烷(10.00mL,4M)中的(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸甲酯(700.00mg,2.70mmol,1.00当量)搅拌5h,LCMS显示起始材料消耗,将混合物在真空中浓缩以获得呈黄色油状的(1R,3R,4R)-3-氨基-4-羟基环戊烷-1-羧酸甲酯(500.00mg,2.56mmol,产率:94.66%)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.09-4.05(m,1H),3.75-3.66(m,3H),3.37-3.33(m,1H),3.06-3.04(m,1H),2.45-2.37(m,2H),1.87-1.81(m,2H)。

[0482] LC-MS(流动相:从95%[水+0.375‰v/v TFA]和5%[CH_3CN+0.188‰v/v TFA],在此条件下历时0.25min,然后在10.0min内变化至15%[CH_3CN+0.188‰v/v TFA],在此条件下历时5min,最后在0.01min内变化至95%[水+0.375‰v/v TFA]和5%[CH_3CN+0.188‰v/v TFA],然后在此条件下历时5min。流量自始自终为1.0mL·min^{-1})纯度为98.803%,Rt=0.893min,MS计算值:159.2,MS实验值:160.1($[M+1]^+$)。

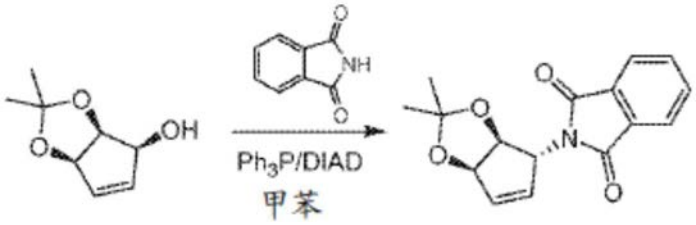
[0483] 实施例19.(3aS,4R,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺

[0484] 步骤1:(3aS,4S,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇

[0485] 

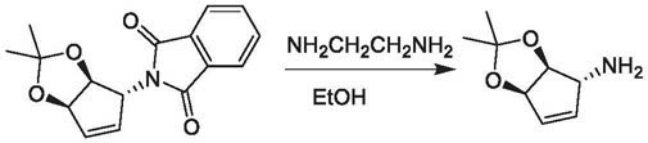
[0486] 将(3aR,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-酮(50.00g,324.34mmol,1.00当量)溶解于MeOH(1.00L)中,然后添加$CeCl_3.7H_2O$(120.84g,324.34mmol,30.83mL,1.00当量)。将混合物冷却至0℃。然后在0℃下在1.5h内分批添加$NaBH_4$(24.54g,648.68mmol,2.00当量)。在添加之后,通过TLC(PE/EtOAc=5/1)检查反应完成。通过饱和NH_4Cl(1000mL)淬灭反应物,将其用DCM(500mL*5)萃取。将合并的有机层在Na_2SO_4上干燥并且在45℃下在真空中浓缩。获得呈黄色液体状的(3aS,4S,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(50.66g,324.37mmol,产率:100.00%),其未纯化即直接使用。

[0487] 步骤2:2-((3aS,4R,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮

[0488] 

[0489] 在20℃下向(3aS,4S,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(8.00g,51.22mmol,1.00当量)和异吲哚啉-1,3-二酮(9.04g,61.46mmol,1.20当量)于甲苯(250.00mL)中的混合物中添加PPh_3(20.15g,76.83mmol,1.50当量)。然后在0℃下将DIAD(15.54g,76.83mmol,1.50当量)逐滴添加至混合物。在添加之后,使混合物达到80℃并且搅拌16h。TLC(PE/EtOAc=5/1)显示反应完成。浓缩混合物。通过硅胶柱色谱(PE/EtOAc=25/1至15/1)纯化残余物。所获得产物为呈黄色油状的粗产物,在TLC上有一些极性点。因此,添加80mL的MeOH并且产生白色沉淀物并通过过滤收集。获得呈白色固体状的2-((3aS,4R,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(9.60g,33.65mmol,产率:65.70%)。

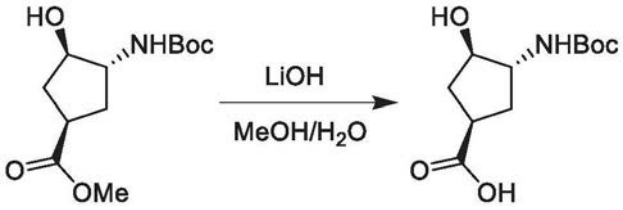
[0490] 步骤3:(3aS,4R,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺

[0491] 

[0492] 向2-((3aS,4R,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(9.52g,33.37mmol,1.00当量)于EtOH(300.00mL)中的混合物中添加乙烷-1,2-二胺(4.01g,66.74mmol,2.00当量)。在80℃下将反应混合物搅拌16h。产生许多白色沉淀物。TLC(PE/EtOAc=5/1)显示起始材料完全消耗。将沉淀物过滤。向滤液中添加300mL的NaOH(0.5M)。将混合物用DCM(200mL*5)萃取,在Na_2SO_4上干燥并浓缩。获得呈黄色油状的(3aS,4R,6aR)-2,2-二甲基-3a,6a-二氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺(4.90g,31.57mmol,产率:94.62%)。

[0493] 实施例20.(1R,3R,4R)-3-氨基-4-羟基环戊烷-1-腈

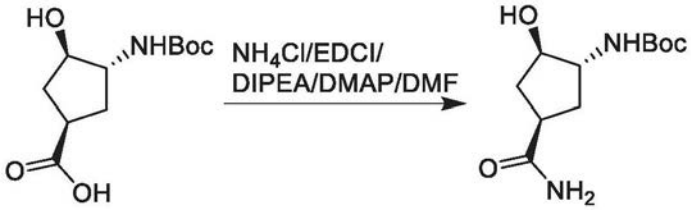
[0494] 步骤1:(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸

[0495] 

[0496] 在15℃下将(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸甲酯(5.00g,19.28mmol,1.00当量)、$LiOH.H_2O$(2.43g,57.85mmol,3.00当量)于MeOH(10.00mL)和H_2O(10.00mL)中的混合物搅拌16h,TLC(PE:EtOAc=1:1)显示反应完成,向混合物中添加稀释的HCl(1M)直至pH=6为止,并且真空浓缩,然后将混合物溶解于DCM(15mL)和EtOAc(5mL)中,将混合物过滤,并且将滤液真空浓缩以获得呈白色固体状的产物(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸(6.50g,粗产物)。^{1}H-NMR(400MHz,CD_3OD)δppm

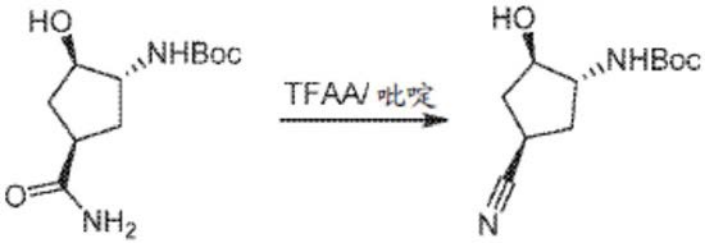
3.95-3.90(m,1H),3.74-3.69(m,1H),2.91-2.87(m,1H),2.32-2.22(m,2H),1.82-1.72(m,2H),1.45(s,9H)。

[0497] 步骤2:((1R,2R,4R)-4-氨甲酰基-2-羟环戊基)氨基甲酸叔丁酯

[0498] 

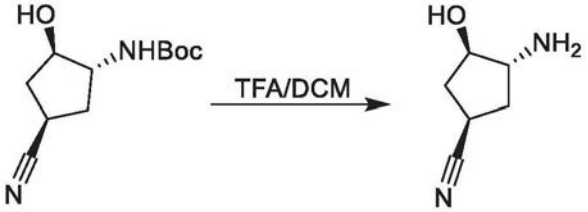
[0499] 向(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸(3.00g,12.23mmol,1.00当量)于DMF(40.00mL)中的混合物中添加HATU(6.05g,15.90mmol,1.30当量)、DIPEA(4.74g,36.69mmol,3.00当量)和NH_4Cl(1.96g,36.69mmol,3.00当量),然后将混合物在15℃下搅拌32h,LCMS显示反应完成,将混合物真空浓缩以获得((1R,2R,4R)-4-氨甲酰基-2-羟环戊基)氨基甲酸叔丁酯(11g,粗产物)(建立2个批次并且在一起纯化)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.58(br.s,1H),3.96-3.94(m,1H),3.77-3.75(m,1H),2.25-2.20(m,2H),1.79-1.75(m,2H),1.44(s,9H)。

[0500] 步骤3:((1R,2R,4R)-4-氰基-2-羟环戊基)氨基甲酸叔丁酯

[0501] 

[0502] 在0℃下向((1R,2R,4R)-4-氨甲酰基-2-羟环戊基)氨基甲酸叔丁酯(2.00g,8.19mmol,1.00当量)、吡啶(1.94g,24.56mmol,3.00当量)于THF(3.00mL)中的混合物中逐滴添加TFAA(2.58g,12.28mmol,1.50当量),然后混合物在0℃下搅拌0.5h,然后在15℃下向混合物中添加Et_3N(2.49g,24.56mmol,3.00当量),并且将混合物在15℃下搅拌0.5h,并且向混合物中添加TFAA(2.58g,12.28mmol,1.50当量),并且将混合物在15℃下搅拌0.5h,LCMS显示反应完成,将混合物真空浓缩,通过制备型HPLC(TFA,MS)纯化以获得呈无色油状的((1R,2R,4R)-4-氰基-2-羟环戊基)氨基甲酸叔丁酯(380.00mg,1.68mmol,产率:20.51%)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.07-3.97(m,1H),3.79-3.78(m,0.5H),3.51-3.49(m,0.5H),3.19-3.05(m,1H),2.44-2.35(m,0.5H),2.33-2.28(m,1.5H),1.97-1.94(m,1H),1.92-1.82(m,1H),1.41(s,9H)。

[0503] 步骤4:(1R,3R,4R)-3-氨基-4-羟基环戊烷-1-腈

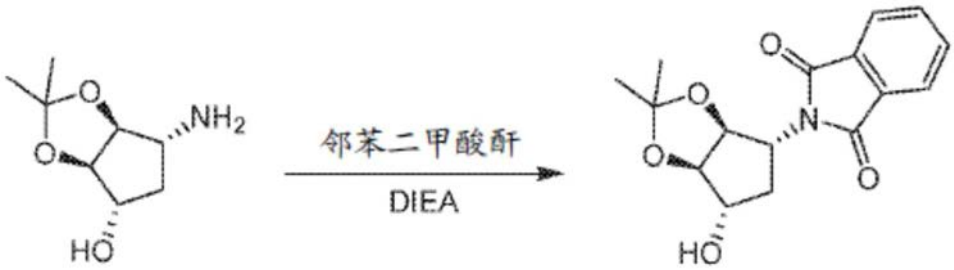
[0504] 

[0505] 将((1R,2R,4R)-4-氰基-2-羟环戊基)氨基甲酸叔丁酯(800.00mg,3.54mmol,1.00当量)于TFA(5.00mL)和DCM(5.00mL)中的混合物在20℃下搅拌2h,LCMS显示反应完成,将混

合物真空浓缩以获得呈无色油状的(1R,3R,4R)-3-氨基-4-羟基环戊烷-1-腈(545.00mg,2.27mmol,产率:64.10%)。^{1}H-NMR(400MHz,CD_3OD)δppm 4.12-4.06(m,1H),3.51-3.47(m,1H),3.23-3.20(m,1H),2.48-2.42(m,2H),2.11-2.10(m,1H),1.94-1.90(m,1H)。

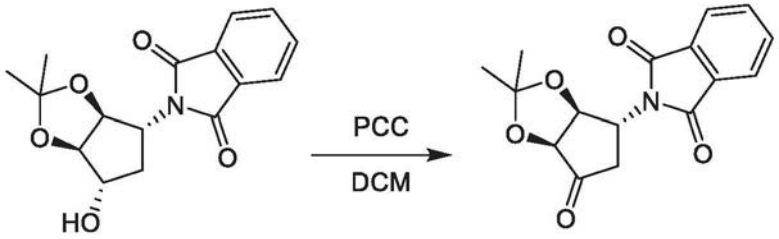
[0506] 实施例21.(3aS,4R,6aS)-6,6-二氟-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺

[0507] 步骤1:2-((3aS,4R,6S,6aR)-6-羟基-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮

[0508] 

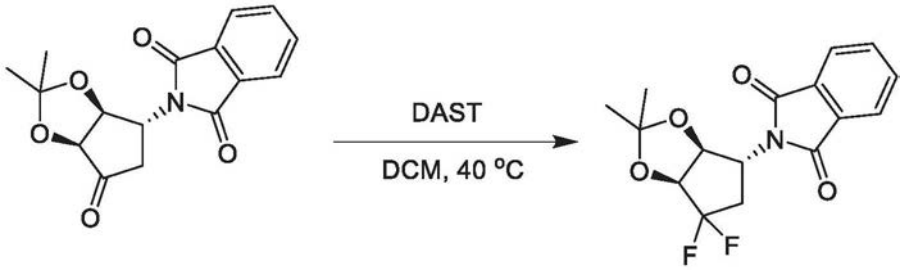
[0509] 将(3aR,4S,6R,6aS)-6-氨基-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-醇(0.43g,2.46mmol,1.00当量)、邻苯二甲酸酐(0.36g,2.46mmol,1当量)和DIEA(0.65mL,3.7mmol,1.5当量)于甲苯(6.2mL)中的混合物在100℃下搅拌9h。LCMS显示反应完成。将EtOAc添加至反应混合物,并且然后用饱和碳酸氢钠水溶液(15mL)洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥,在真空中浓缩。通过硅胶柱色谱(己烷/EtOAc)纯化残余物以获得呈白色固体状的产物2-((3aS,4R,6S,6aR)-6-羟基-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(0.62g,83%)。

[0510] 步骤2:2-((3aS,4R,6aS)-2,2-二甲基-6-氧基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮

[0511] 

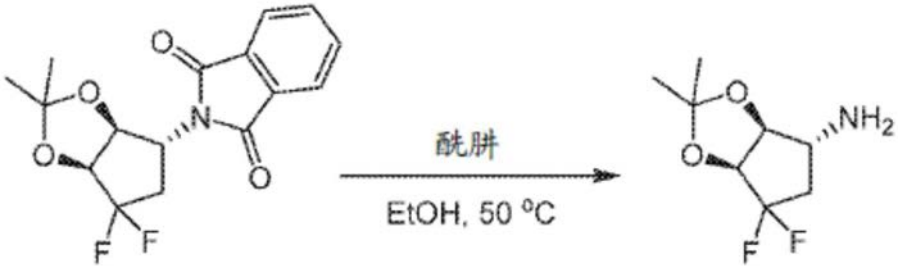
[0512] 向2-((3aS,4R,6S,6aR)-6-羟基-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(0.20g,0.68mmol,1.00当量)于DCM(4.5mL)中的溶液中添加PCC(0.29g,1.35mmol,2当量)并且将溶液在23℃下搅拌16h。添加另一个等分试样的PCC(0.15g,0.67mmol)并且将反应再持续16小时。LCMS显示反应完成。将EtOAc添加至反应混合物,并且然后通过硅藻土垫过滤。将残余物浓缩,然后通过硅胶柱色谱(己烷/EtOAc)纯化以获得呈灰白色固体状的产物2-((3aS,4R,6aS)-2,2-二甲基-6-氧基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(0.19g,94%)。

[0513] 步骤3:2-((3aS,4R,6aS)-6,6-二氟-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮

[0514] 

[0515] 向2-((3aS,4R,6aS)-2,2-二甲基-6-氧基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(0.16g,0.53mmol,1.00当量)于DCM(3.5mL)中的溶液中添加DAST(0.42g,2.64mmol,5当量)并且将溶液在回流下搅拌16h。添加另一个等分试样的DAST(0.42g,2.64mmol,5当量)并且将反应在23℃下再持续16小时。将反应混合物用DCM稀释并且用饱和碳酸氢钠溶液洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥,在真空中浓缩。通过硅胶柱色谱(己烷/EtOAc)纯化残余物以获得产物2-((3aS,4R,6aS)-6,6-二氟-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(0.065g,38%)。

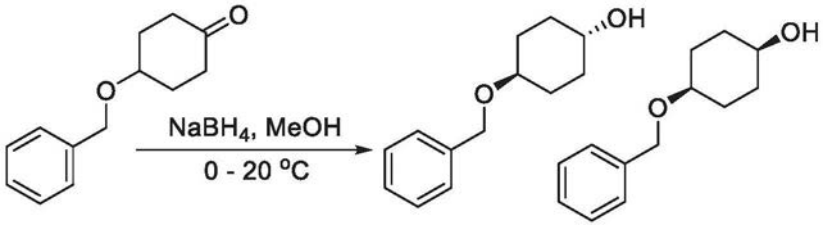
[0516] 步骤4:(3aS,4R,6aS)-6,6-二氟-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺

[0517] 

[0518] 向2-((3aS,4R,6aS)-6,6-二氟-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-基)异吲哚啉-1,3-二酮(0.065g,0.2mmol,1.00当量)于乙醇(1.8mL)中的溶液中添加一水合肼(0.015mL,0.3mmol,1.5当量)并且将溶液在50℃下搅拌2h,然后在70℃下再搅拌2小时。使用最小体积乙醇来过滤非均相反应混合物。然后将滤液浓缩并且分离的粗产物(3aS,4R,6aS)-6,6-二氟-2,2-二甲基四氢-4H-环戊[d][1,3]间二氧杂环戊烯-4-胺未进一步纯化即用于下一个步骤中。

[0519] 实施例22.合成(1R,3R,4R)-4-氨基环己烷-1,3-二醇

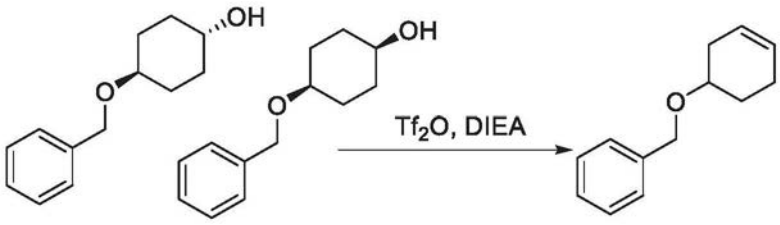
[0520] 步骤1:(1r,4r)-4-(苄氧基)环己醇和(1s,4s)-4-(苄氧基)环己醇

[0521] 

[0522] 在10min时间段期间,向4-(苄氧基)环己酮(31.0g,152mmol)于500mL甲醇中的冰浴冷却溶液中,分多批添加硼氢化钠(5.78g,153mmol),然后将溶液在20℃下搅拌2h。然后通过饱和氯化铵水溶液(50mL)淬灭混合物,将其浓缩并且将残余物溶解于200mL水中并且用乙酸乙酯(200mL x 3)萃取,将合并的有机相在硫酸钠上干燥,然后在真空中浓缩以得到

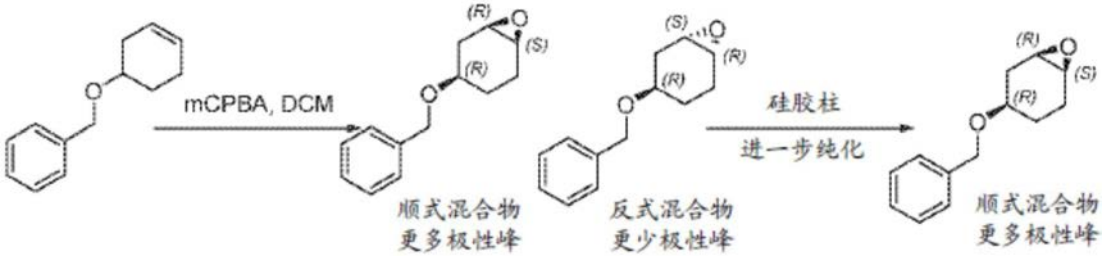
呈淡黄色油状的标题产物(1r,4r)-4-(苄氧基)环己醇和(1s,4s)-4-(苄氧基)环己醇(31.0g,粗产物),其未进一步纯化即直接用于下一个步骤。MS(ES+)$C_{13}H_{18}O_2$需要值:206,实验值:207$[M+H]^+$。

[0523] 步骤2:((环己-3-烯基氧基)甲基)苯

[0524] 

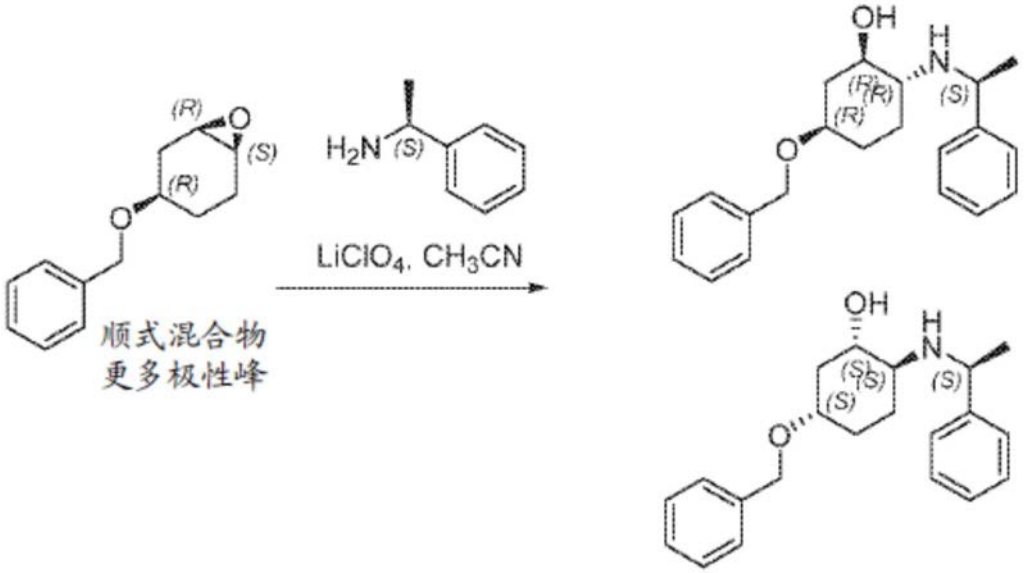
[0525] 在30min时间段期间,向(1r,4r)-4-(苄氧基)环己醇和(1s,4s)-4-(苄氧基)环己醇(30.0g,145mmol)以及N,N-二异丙基乙胺(28.1g,218mmol)于1200mL二氯甲烷中的冰浴冷却溶液中逐滴添加三氟甲磺酸酐(30.7g,109mmol),然后将溶液在25℃下搅拌18h。然后将混合物在真空中浓缩并且使用硅胶柱色谱以石油醚:乙酸乙酯=12:1洗脱来纯化残余物以得到呈黄色油状的标题化合物(28.0g,产率100%)。MS(ES+)$C_{13}H_{16}O$需要值:188,实验值:189$[M+H]^+$。

[0526] 步骤3:(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷

[0527] 

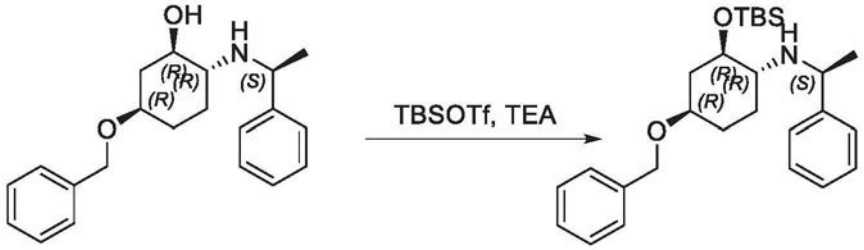
[0528] 在0℃下使用间氯过氧苯甲酸(21.9g,127mmol)处理((环己-3-烯基氧基)甲基)苯(12.0g,63.7mmol)于二氯甲烷(200mL)中的溶液。将反应混合物在0℃下搅拌2h,然后在室温下搅拌15min。将洗涤的(10%亚硫酸钠水溶液、5%氢氧化钠水溶液、然后为水)有机溶液蒸发,提供液体残余物,使用硅胶柱色谱以己烷:异丙醚:乙酸乙酯=65:28:7洗脱来分离所述残余物以得到呈黄色油状的标题化合物(4.18g,产率32%)。反式-(1S,3R,6R)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷在TLC上显示更小极性并且首先洗脱。顺式-(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷其次洗脱。MS(ES+)$C_{13}H_{16}O_2$需要值:204,实验值:205$[M+H]^+$。

[0529] 步骤4:(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇

[0530] 

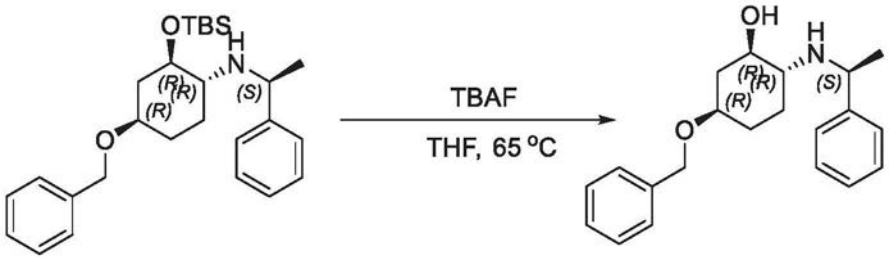
[0531] 将高氯酸锂(7.27g,68.4mmol)添加至(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷(7.0g,34.2mmol)于120mL 4A-MS干燥乙腈中的冰浴冷却搅拌溶液中,将浴移除并且在15min时间段期间逐滴添加(S)-1-苯基乙胺(5.58g,46.1mmol),然后将溶液在25℃下搅拌18h。然后将混合物在200mL水中稀释并且用乙酸乙酯(200mL x 3)萃取,将合并的有机相在硫酸钠上干燥,然后浓缩并且使用硅胶柱色谱以石油醚:乙酸乙酯:三乙胺=98:0:2～49:49:2洗脱来纯化残余物以得到呈黄色油状的标题化合物(3.5g,产率31%)。(1S,2S,5S)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇在TLC上显示更小极性,并且首先洗脱。(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇其次洗脱。MS(ES+)$C_{21}H_{27}NO_2$需要值:325,实验值:326$[M+H]^+$。

[0532] 步骤5:(1R,2R,4R)-4-(苄氧基)-2-(叔丁基二甲基甲硅烷基氧基)-N-((S)-1-苯基乙基)环己胺

[0533] 

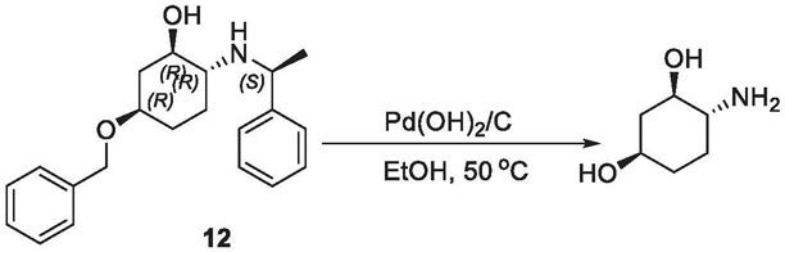
[0534] 将三氟甲磺酸叔丁基二甲基甲硅烷基酯(13.0g,49.5mmol)添加至(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇(5.4g,16.5mmol)和三乙胺(5.0g,49.5mmol)于100mL干燥二氯甲烷中的冰浴冷却的搅拌溶液中。在30min之后,将此用碳酸氢钠的饱和水溶液洗涤,在硫酸钠上干燥。移除溶剂,并且使用硅胶柱色谱以石油醚:乙酸乙酯=100:0～70:30洗脱来纯化残余物以得到呈黄色油状的标题化合物(5.4g,产率71%)。MS(ES+)$C_{27}H_{41}NO_2Si$需要值:439,实验值:440$[M+H]^+$。

[0535] 步骤7:(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇

[0536] 

[0537] 在室温下,将四丁基氟化铵(2.66g,10.2mmol)添加至(1R,2R,4R)-4-(苄氧基)-2-(叔丁基二甲基甲硅烷基氧基)-N-((S)-1-苯基乙基)环己胺(1.5g,3.41mmol)于50mL干燥氧杂环戊烷中的搅拌溶液中。然后在65℃下将此溶液搅拌2h。然后将混合物在真空中浓缩并且将残余物在200mL水中稀释并且用乙酸乙酯(200mL x 3)萃取,将合并的有机相用水和饱和氯化钠水溶液洗涤,在硫酸钠上干燥。移除溶剂,并且使用硅胶柱色谱以石油醚:乙酸乙酯=100:0～70:30洗脱来纯化残余物以得到呈无色油状的标题化合物(0.75g,产率68%)。MS(ES+)$C_{21}H_{27}NO_2$需要值:325,实验值:326$[M+H]^+$。

[0538] 步骤8:(1R,3R,4R)-4-氨基环己烷-1,3-二醇

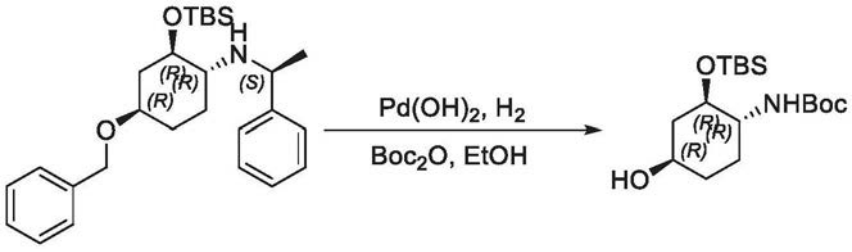
[0539] 

12

[0540] 在室温下,将活性碳上的10%氢氧化钯(697mg,催化剂)添加至(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇(650mg,1.99mmol)于15mL乙醇中的溶液。然后在50℃下在氢气下将此溶液搅拌20h。然后将混合物冷却并且通过硅藻土过滤,将滤饼用甲醇:二氯甲烷=1:10洗涤,将滤液在真空下浓缩并且将残余物在20mL甲醇:二氯甲烷=1:10溶液中稀释并且浓缩,在高真空下干燥,然后在-20℃下冷却以得到呈白色晶体状的标题化合物(240mg,产率92%)。MS(ES+)$C_6H_{13}NO_2$需要值:131,实验值:132$[M+H]^+$。^{1}H-NMR(400MHz,6d-DMSO)δppm 4.62-4.49(m,2H),3.42-3.33(m,2H,J=3.2Hz),2.93-2.86(m,1H),2.25-2.18(m,1H),1.98-1.92(m,1H),1.72-1.59(m,3H),1.13-1.03(m,2H),0.97-0.90(m,1H)。

[0541] 实施例23.合成(1R,2R)-2-(叔丁基二甲基甲硅烷基氧基)-4-氧环己基氨基甲酸叔丁酯

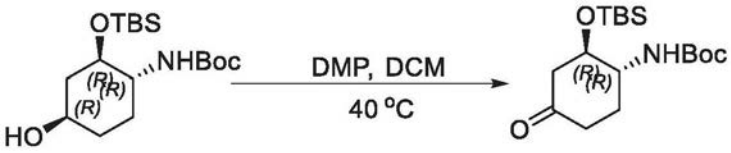
[0542] 步骤1:(1R,2R,4R)-2-(叔丁基二甲基甲硅烷基氧基)-4-羟基环己基氨基甲酸叔丁酯

[0543] 

[0544] 在室温下,将活性碳上的10%氢氧化钯(1.9g,催化剂)添加至来自先前实施例的(1R,2R,4R)-4-(苄氧基)-2-(叔丁基二甲基甲硅烷基氧基)-N-((S)-1-苯基乙基)环己胺

(2.0g,4.54mmol)和二碳酸二-叔丁酯(3.95g,18.1mmol)于60mL乙醇中的溶液中。然后在50℃下在氢气下将此溶液搅拌20h。然后将混合物冷却并且通过硅藻土过滤,将滤饼用甲醇:二氯甲烷=1:10洗涤,将滤液在真空中浓缩并且将残余物在20mL甲醇:二氯甲烷=1:10溶液中稀释并且浓缩,在高真空下干燥,以得到呈无色油状的标题化合物(1.2g,产率77%)。MS(ES+)$C_{17}H_{35}NO_4Si$需要值:345,实验值:346$[M+H]^+$。

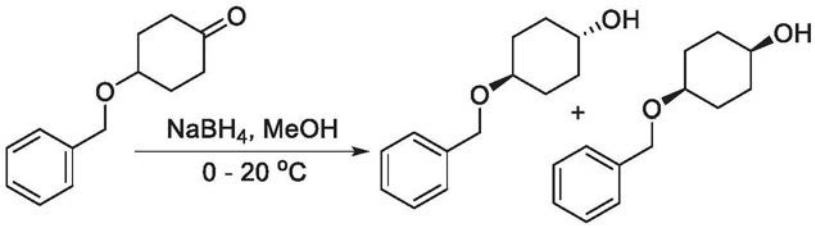
[0545] 步骤2:(1R,2R)-2-(叔丁基二甲基甲硅烷基氧基)-4-氧环己基氨基甲酸叔丁酯

[0546] 

[0547] 在室温下,将1,1,1-三乙酰氧基-1,1-二氢-1,2-苯碘酰基-3(1H)-酮(戴斯-马丁过碘烷,4.11g,9.71mmol)添加至(1R,2R,4R)-2-(叔丁基二甲基甲硅烷基氧基)-4-羟基环己基氨基甲酸叔丁酯(1.4g,4.05mmol)于50mL二氯甲烷中的溶液中。然后在40℃下在氮气下将此溶液搅拌3h。然后将混合物在真空下浓缩并且使用硅胶柱色谱以石油醚:乙酸乙酯=100:0～95:5洗脱来纯化残余物以得到呈黄色油状的标题化合物(1.2g,产率86%)。MS(ES+)$C_{17}H_{33}NO_4Si$需要值:343,实验值:344$[M+H]^+$。^{1}H-NMR(400MHz,$CDCl_3$)δppm 4.70-4.49(br.,1H),4.10-3.90(br.s,1H),3.79-3.65(br.,1H),2.64(dd,1H,J=14.4,4.0Hz),2.42-2.28(m,4H),1.46(s,9H),0.87(s,9H),0.08(d,6H,J=6.8Hz)。

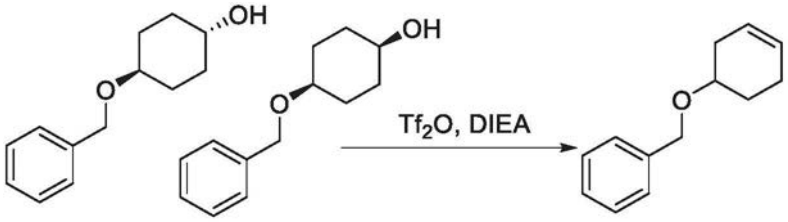
[0548] 实施例23.合成(1R,2R)-2-(叔丁基二甲基甲硅烷基氧基)-4-氧环己基氨基甲酸叔丁酯和(1R,3R,4R)-4-氨基环己烷-1,3-二醇

[0549] 步骤1:(1R,4R)-4-(苄氧基)环己醇和(1S,4S)-4-(苄氧基)环己醇:

[0550] 

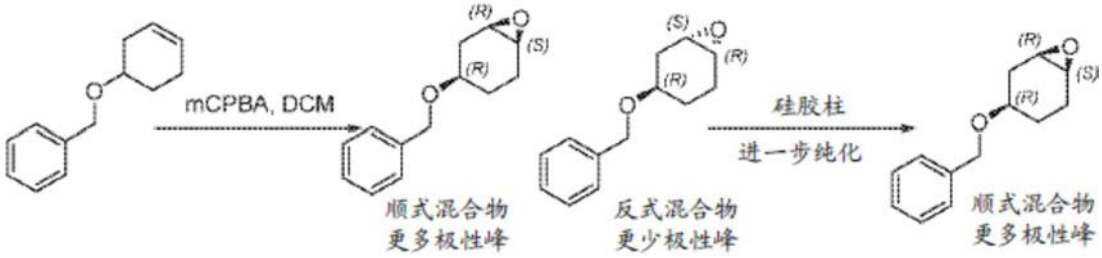
[0551] 在10min时间段期间,向4-(苄氧基)环己酮(31.0g,152mmol)于500mL甲醇中的冰浴冷却溶液中,分多批添加硼氢化钠(5.78g,153mmol),然后将溶液在20℃下搅拌2h。然后通过饱和氯化铵水溶液(50mL)淬灭混合物,将其浓缩并且将残余物溶解于200mL水中并且用乙酸乙酯(200mL x 3)萃取,将合并的有机相在硫酸钠上干燥,然后在真空下浓缩以得到呈淡黄色油状的标题产物(1R,4R)-4-(苄氧基)环己醇和(1S,4S)-4-(苄氧基)环己醇(31.0g,粗产物),其未进一步纯化即直接用于下一个步骤。MS(ES+)$C_{13}H_{18}O_2$需要值:206,实验值:207$[M+H]^+$。

[0552] 步骤2:((环己-3-烯基氧基)甲基)苯:

[0553] 

[0554] 在30min时间段期间，向(1R,4R)-4-(苄氧基)环己醇和(1S,4S)-4-(苄氧基)环己醇(30.0g,145mmol)和N,N-二异丙基乙胺(28.1g,218mmol)于1200mL二氯甲烷中的冰浴冷却溶液中逐滴添加三氟甲磺酸酐(30.7g,109mmol)，然后将溶液在25℃下搅拌18h。然后将混合物在真空中浓缩并且使用硅胶柱色谱以石油醚:乙酸乙酯＝12:1洗脱来纯化残余物以得到呈黄色油状的标题化合物(28.0g，产率100％)。MS(ES+)$C_{13}H_{16}O$需要值:188，实验值:189$[M+H]^+$。

[0555] 步骤3:(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷:

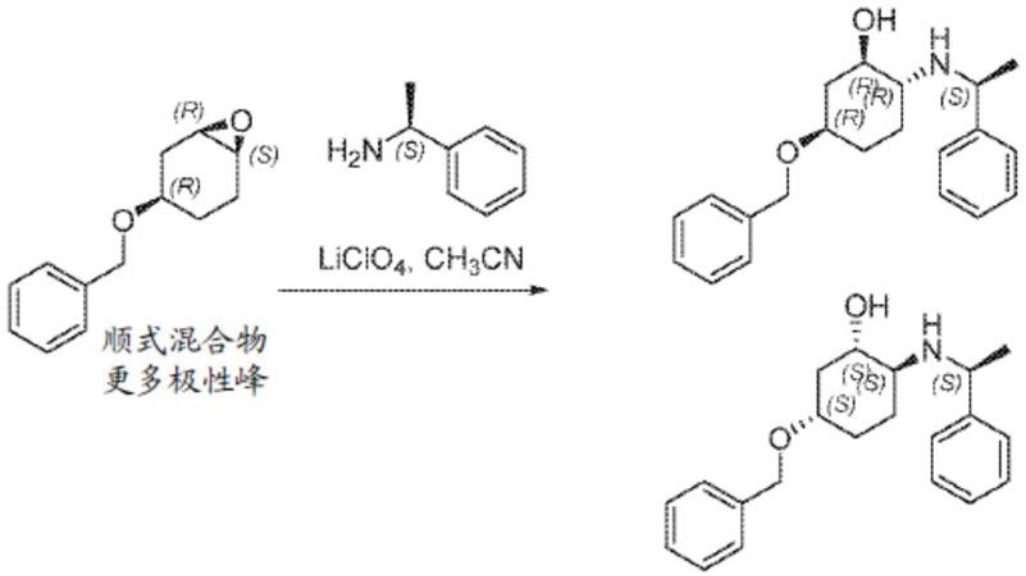
[0556] 

[0557] 在0℃下使用间氯过氧苯甲酸(21.9g,127mmol)处理((环己-3-烯基氧基)甲基)苯(12.0g,63.7mmol)于二氯甲烷(200mL)中的溶液。将反应混合物在0℃下搅拌2h，并且然后在室温下搅拌15min。将洗涤的(10％亚硫酸钠水溶液、5％氢氧化钠水溶液、然后为水)有机溶液蒸发，提供液体残余物，使用硅胶柱色谱以己烷:异丙醚:乙酸乙酯＝65:28:7洗脱来分离所述残余物以得到呈黄色油状的标题化合物(4.18g，产率32％)。反式-(1S,3R,6R)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷在TLC上显示更小极性并且首先洗脱。顺式-(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷其次洗脱。MS(ES+)$C_{13}H_{16}O_2$需要值:204，实验值:205$[M+H]^+$。

[0558] 顺式-(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷:^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.35-7.27(m,5H),4.56-4.45(m,2H),3.35-3.29(m,1H),3.12-3.09(m,2H),2.37-2.32(m,1H),2.25-2.20(m,1H),1.89-1.68(m,3H),1.49-1.44(m,1H)。

[0559] 反式-(1S,3R,6R)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷:^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.35-7.27(m,5H),4.48(dd,2H,J＝28.0,12.4Hz),3.56-3.52(m,1H),3.19-3.17(m,2H),2.24-2.18(m,1H),2.15-2.07(m,1H),2.00-1.91(m,2H),1.64-1.53(m,2H)。

[0560] 步骤3:(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇:

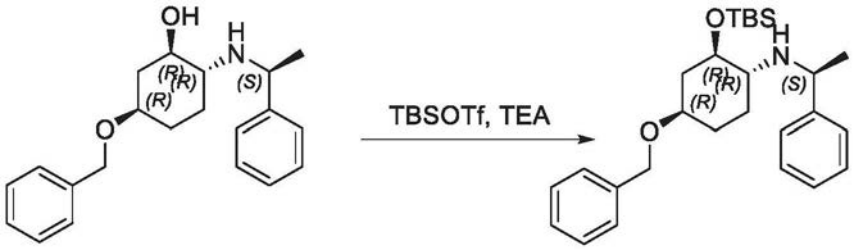
[0561] 

[0562] 将高氯酸锂(7.27g,68.4mmol)添加至(1R,3R,6S)-3-(苄氧基)-7-氧杂-双环[4.1.0]庚烷(7.0g,34.2mmol)于120mL 4A-MS干燥乙腈中的冰浴冷却搅拌溶液中,将浴移除并且在15min时间段期间逐滴添加(S)-1-苯基乙胺(5.58g,46.1mmol),然后将溶液在25℃下搅拌18h。然后将混合物在200mL水中稀释并且用乙酸乙酯(200mL x 3)萃取,将合并的有机相在硫酸钠上干燥,然后浓缩并且使用硅胶柱色谱以石油醚:乙酸乙酯:三乙胺=98:0:2～49:49:2洗脱来纯化残余物以得到呈黄色油状的标题化合物(3.5g,产率31%)。(1S,2S,5S)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇在TLC上显示更小极性,并且首先洗脱。(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇其次洗脱。MS(ES+)$C_{21}H_{27}NO_2$需要值:325,实验值:326$[M+H]^+$。

[0563] (1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇:^{1}H-NMR(400MHz,$CDCl_3$)δ ppm 7.35-7.24(m,10H),4.52(d,2H,J=2.0Hz),3.97(q,1H,J=6.8Hz),3.42-3.34(m,1H),3.19-3.12(m,1H),2.39(dd,1H,J=12.0,2.4Hz),2.16(dd,1H,J=12.0,3.6Hz),2.09-2.00(m,2H),1.65-1.49(m,1H),1.35(d,3H,J=6.4Hz),1.28-1.15(m,2H),0.90(qd,1H,J=13.2,3.6Hz)。

[0564] (1S,2S,5S)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇:^{1}H-NMR(400MHz,$CDCl_3$)δ ppm 7.36-7.22(m,10H),4.54(d,2H,J=3.2Hz),3.90(q,1H,J=6.4Hz),3.44-3.35(m,1H),3.15-3.09(m,1H),2.51-2.45(m,1H),2.43-2.36(m,1H),2.04-1.99(m,1H),1.95-1.90(m,1H),1.47-1.29(m,3H),1.34(d,3H,J=6.4Hz),0.82(qd,1H,J=13.2,3.2Hz)。

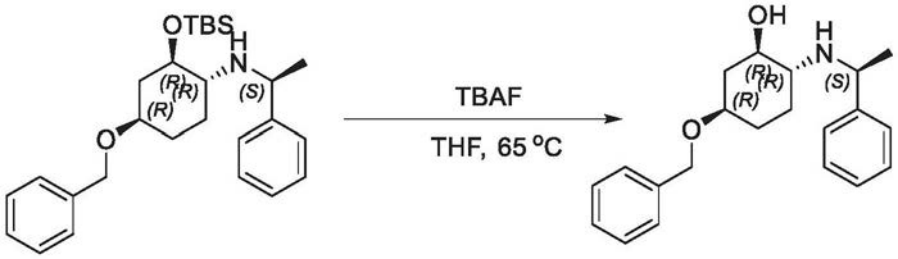
[0565] 步骤4:合成(1R,2R,4R)-4-(苄氧基)-2-(叔丁基二甲基甲硅烷基氧基)-N-((S)-1-苯基乙基)环己胺:

[0566] 

[0567] 将三氟甲磺酸叔丁基二甲基甲硅烷基酯(13.0g,49.5mmol)添加至(1R,2R,5R)-5-

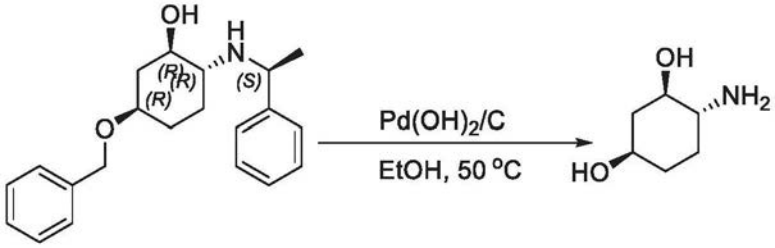
(苄氧基)-2-((S)-1-苯基乙氨基)环己醇(5.4g,16.5mmol)和三乙胺(5.0g,49.5mmol)于100mL干燥二氯甲烷中的冰浴冷却的搅拌溶液中。在30min之后,将此用碳酸氢钠的饱和水溶液洗涤,在硫酸钠上干燥。移除溶剂,并且使用硅胶柱色谱以石油醚:乙酸乙酯=100:0～70:30洗脱来纯化残余物以得到呈黄色油状的标题化合物(5.4g,产率71%)。MS(ES+)$C_{27}H_{41}NO_2Si$需要值:439,实验值:440[M+H]$^+$。

[0568] 步骤5:(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇:

[0569] 

[0570] 在室温下,将四丁基氟化铵(2.66g,10.2mmol)添加至(1R,2R,4R)-4-(苄氧基)-2-(叔丁基二甲基甲硅烷基氧基)-N-((S)-1-苯基乙基)环己胺(1.5g,3.41mmol)于50mL干燥氧杂环戊烷中的搅拌溶液中。然后在65℃下将此溶液搅拌2h。然后将混合物在真空中浓缩并且将残余物在200mL水中稀释并用乙酸乙酯(200mL x 3)萃取,将合并的有机相用水和饱和氯化钠水溶液洗涤,在硫酸钠上干燥。移除溶剂,并且使用硅胶柱色谱以石油醚:乙酸乙酯=100:0～70:30洗脱来纯化残余物以得到呈无色油状的标题化合物(0.75g,产率68%)。MS(ES+)$C_{21}H_{27}NO_2$需要值:325,实验值:326[M+H]$^+$。

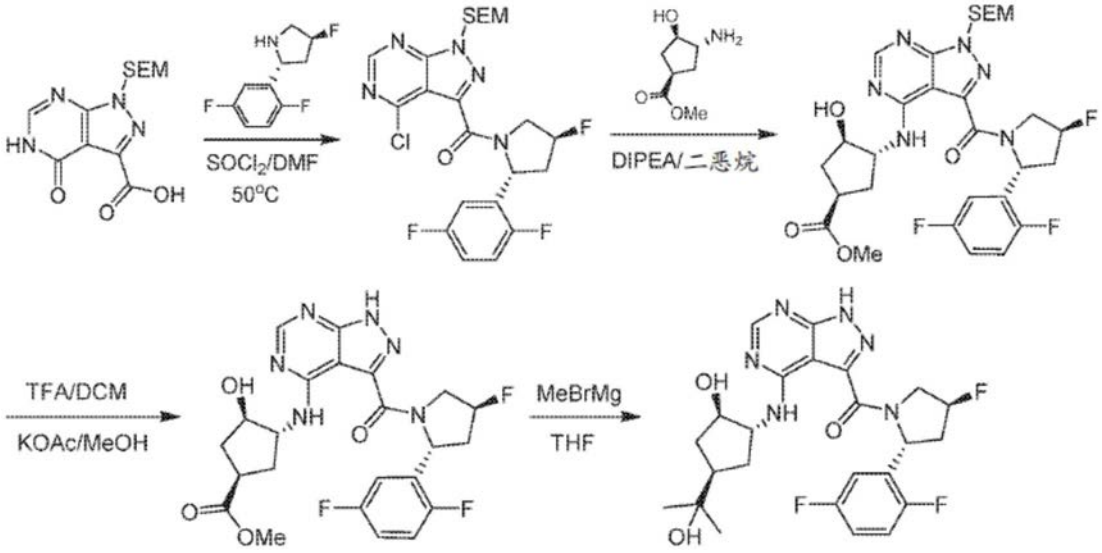
[0571] 步骤6:(1R,3R,4R)-4-氨基环己烷-1,3-二醇:

[0572] 

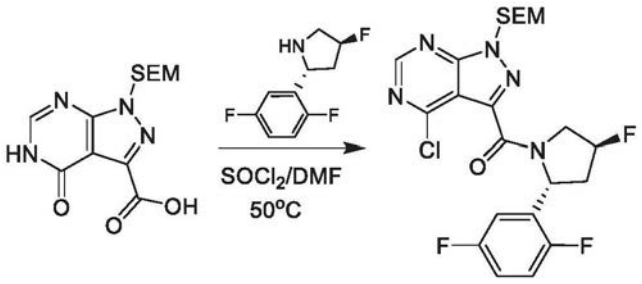
[0573] 在室温下,将活性碳上的10%氢氧化钯(697mg,催化剂)添加至(1R,2R,5R)-5-(苄氧基)-2-((S)-1-苯基乙氨基)环己醇(650mg,1.99mmol)于15mL乙醇中的溶液中。然后在50℃下在氢气下将此溶液搅拌20h。然后将混合物冷却并且通过硅藻土过滤,将滤饼用甲醇:二氯甲烷=1:10洗涤,将滤液在真空下浓缩并且将残余物在20mL甲醇:二氯甲烷=1:10溶液中稀释并且浓缩,在高真空下干燥,然后在-20℃下冷却以得到呈白色晶体状的标题化合物(240mg,产率92%)。MS(ES+)$C_6H_{13}NO_2$需要值:131,实验值:132[M+H]$^+$。

[0574] (1R,3R,4R)-4-氨基环己烷-1,3-二醇:^{1}H-NMR(400MHz,6J-DMSO)δppm 4.62-4.49(m,2H),3.42-3.33(m,2H,J=3.2Hz),2.93-2.86(m,1H),2.25-2.18(m,1H),1.98-1.92(m,1H),1.72-1.59(m,3H),1.13-1.03(m,2H),0.97-0.90(m,1H)。

[0575] 实施例24:合成化合物232:

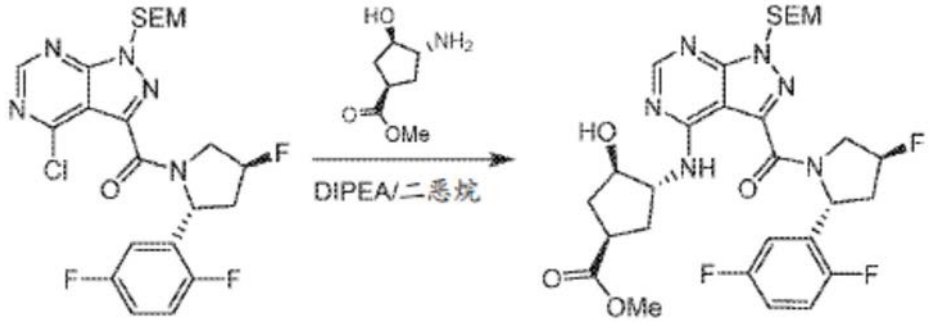
[0576] 

[0577] 步骤1：(4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮

[0578] 

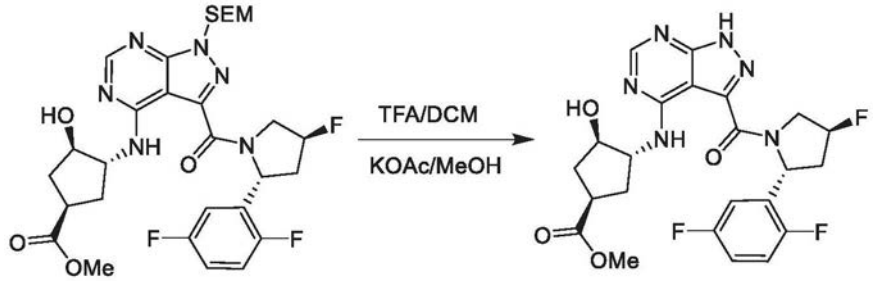
[0579] 在15℃下向4-氧基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-4,5-二氢-1H-吡唑并[3,4-d]嘧啶-3-羧酸(1.00g,3.22mmol,1.00当量)于$SOCl_2$(164.00g,1.38mol,428.11当量)中的溶液中添加DMF(235.49mg,3.22mmol,1.00当量)。将反应物在50℃下加热16h。TLC(PE:EtOAc＝3:1,R_f＝0.8和0.7)显示反应完成。浓缩混合物。将残余物冷却至-10℃并且溶解于DCM(25.00mL)中。将Et_3N(1.63g,16.10mmol,5.00当量)和(2R,4S)-2-(2,5-二氟苯基)-4-氟-吡咯烷(497.40mg,2.09mmol,0.65当量,HCl)添加至反应。在0℃下将反应物搅拌0.2h。TLC(PE:EtOAc＝3:1,R_f＝0.38)显示反应完成。将溶液用盐水(5mL)洗涤,在Na_2SO_4上干燥并且浓缩。通过制备型-TLC(PE:EtOAc＝10:1)纯化残余物以得到呈黄色固体状的(4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮(400.00mg,产率:24.26%)。

[0580] 步骤2：(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷-1-羧酸甲酯

[0581] 

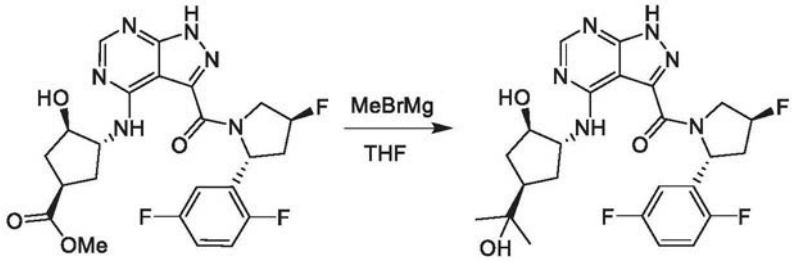
[0582] 向(4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮(200.00mg,390.63umol,1.00当量)和(1R,3R,4R)-3-氨基-4-羟基-环戊烷羧酸甲酯(80.24mg,410.16umol,1.05当量,HCl)于二噁烷(10.00mL)中的溶液中添加DIPEA(151.46mg,1.17mmol,3.00当量)。将反应物在90℃下加热5h。LCMS显示反应完成。将溶液浓缩。通过制备型-TLC(PE:EtOAc=2:1)纯化残余物以得到呈黄色固体状的(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷-1-羧酸甲酯(120.00mg,产率:48.40%)。

[0583] 步骤3:(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷-1-羧酸甲酯

[0584] 

[0585] 在15℃下,向(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷-1-羧酸甲酯(120.00mg,189.06umol,1.00当量)于DCM(3.00mL)中的溶液中添加TFA(3.00mL)。在15℃下将反应物搅拌16h。LCMS显示起始材料消耗。检测到极少(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-(羟甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷羧酸甲酯。将反应物浓缩。将残余物溶解于MeOH(20.00mL)中。将KOAc(185.54mg,1.89mmol,10.00当量)添加至反应物中。将反应物在50℃下加热16h。LCMS显示反应完成。将溶液浓缩。将残余物溶解于EtOAc(20mL)中并且用盐水(10mL)洗涤,在Na_2SO_4上干燥并且浓缩以得到呈红色固体状的(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷-1-羧酸甲酯(80.00mg,粗产物),其未纯化即用于下一个步骤中。

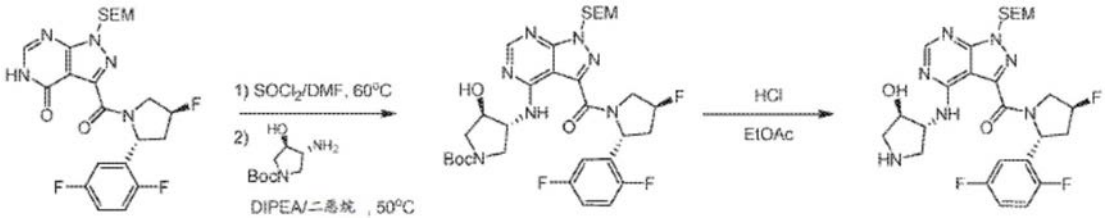
[0586] 步骤4:((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((1R,2R,4R)-2-羟基-4-(2-羟丙-2-基)环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮

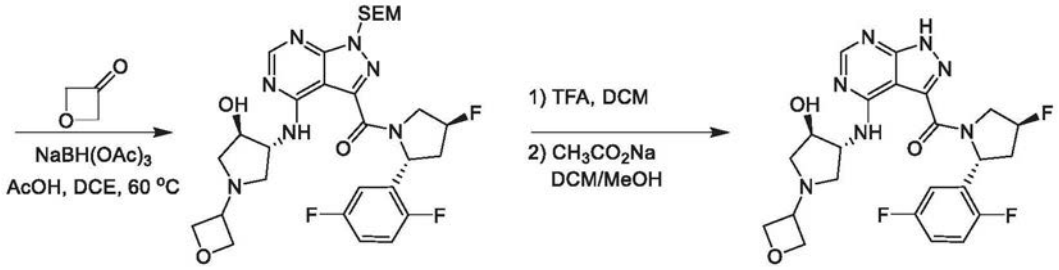
[0587] 

[0588] 在-70℃下,向(1R,3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基环戊烷-1-羧酸甲酯(80.00mg,158.59umol,1.00当量)于THF(20.00mL)中的溶液中添加MeMgBr(3M,1.59mL,30.00当量)。将反应物缓慢加温至15℃并且搅拌2h。TLC(EtOAc,R_f=0.24)和LCMS显示反应完成。将溶液用1NHCl水溶液中和至pH=7。将反应混合物浓缩。通过中性制备型-HPLC纯化残余物以得到呈黄色固体状的((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((1R,2R,4R)-2-羟基-4-(2-羟丙-2-基)环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(17.40mg,产率:21.75%)。

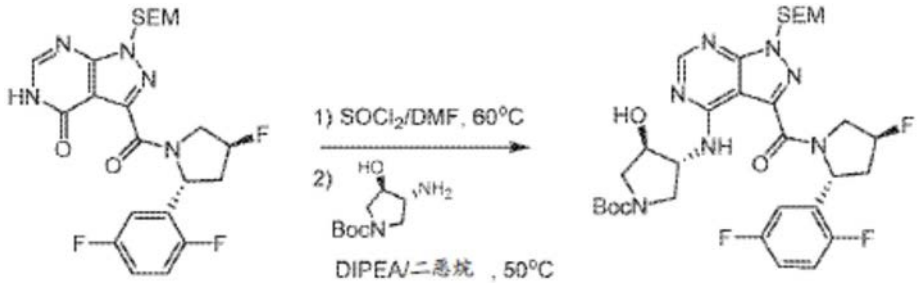
[0589] 对于此化合物和以下化合物156,LC-MS条件如下:(流动相:从99%[水+0.375‰v/v TFA]和1%[CH_3CN+0.188‰v/v TFA],在此条件下历时0.4min,然后在3.0min内变化至10%[水+0.375‰v/v TFA]和90%[CH_3CN+0.188‰v/v TFA],然后在0.45min内变化至100%[CH_3CN+0.188‰v/v TFA],最后在0.01min内变化至99%[水+0.375‰v/v TFA]和1%[CH_3CN+0.188‰v/v TFA],然后在此条件下历时0.64min。流量自始自终为0.8mL·min^{-1}。)纯度为99.870%

[0590] 实施例25.合成化合物229:

[0591] 

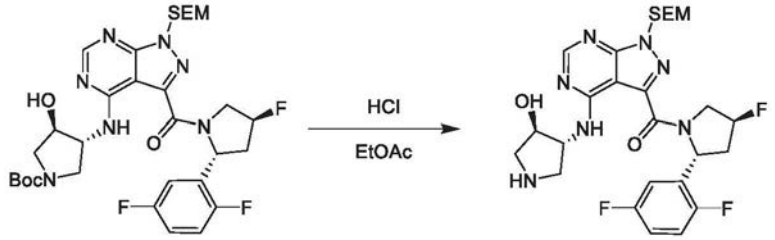
[0592] 

[0593] 步骤1:(3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基吡咯烷-1-羧酸叔丁酯

[0594] 

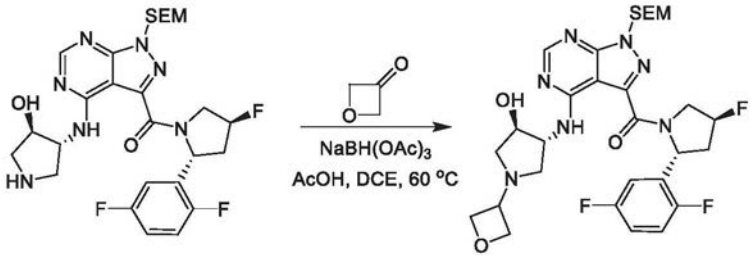
[0595] 在50℃下,将3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮(0.085g,0.17mmol,1当量)的溶液与亚硫酰氯(0.031mL,0.43mmol,2.5当量)和DCM(0.7mL)中的几滴DMF一起搅拌3小时。LCMS指示SM完全消耗成氯代杂环中间物。将反应混合物在冰上冷却并且添加二噁烷(0.7mL),随后添加DIEA(0.21mL,1.21mmol,7当量)和(3R,4R)-3-氨基-4-羟基吡咯烷-1-羧酸叔丁酯(0.05g,0.26mmol,1.5当量)。接着在70℃下将反应混合物搅拌3小时。LCMS指示反应完成。然后将反应混合物用DCM稀释并且用饱和碳酸氢钠溶液洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥并且在真空中浓缩。通过硅胶柱色谱(已烷/EtOAc)纯化残余物以获得产物(3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基吡咯烷-1-羧酸叔丁酯(0.084g,72%)。

[0596] 步骤2:((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟吡咯烷-3-基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮

[0597] 

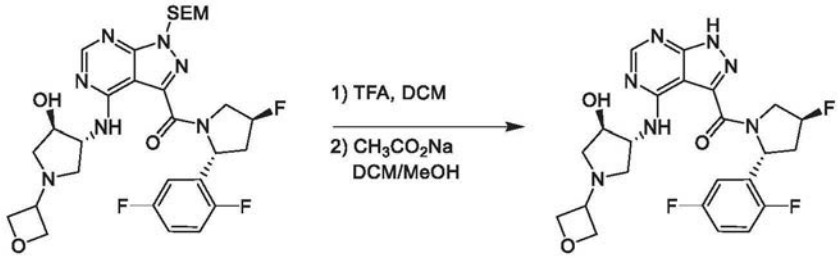
[0598] 使用二噁烷(4M,0.9mL,3.72mmol,30当量)中的HCl处理(3R,4R)-3-((3-((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-羰基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-4-基)氨基)-4-羟基吡咯烷-1-羧酸酯(0.084g,0.12mmol,1当量)于EtOAc(1.25mL)中的溶液。在23℃下搅拌4小时之后,LCMS指示反应完成。将反应混合物用EtOAc稀释并且用饱和碳酸氢钠溶液洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥,在真空中浓缩。粗产物((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟吡咯烷-3-基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮未进一步纯化即用于下一个步骤中。

[0599] 步骤3:((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟基-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮

[0600] 

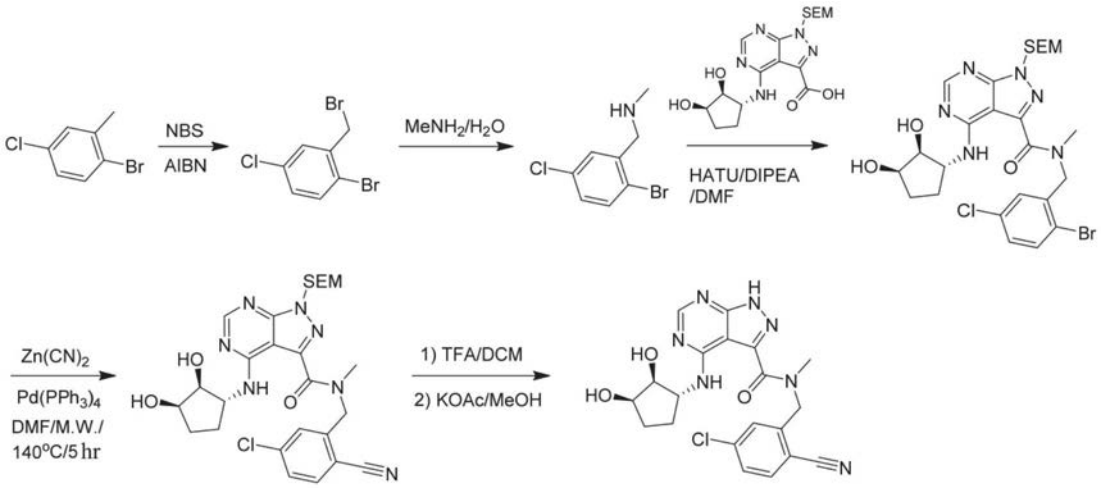
[0601] 向((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟吡咯烷-3-基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(0.036g,0.062mmol,1当量)于DCE(0.5mL)中的溶液中添加几滴乙酸(2μL,0.031mmol,0.5当量),随后添加氧杂环丁烷-3-酮(0.015mL,0.21mmol,3.3当量)并且将反应混合物在60℃下加热2小时。添加三乙酰氧基硼氢化钠(0.033g,0.16mmol,2.5当量)并且将溶液在23℃下搅拌24小时。LCMS指示反应完成。将反应混合物用EtOAc稀释并且用饱和碳酸氢钠溶液洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥,在真空中浓缩。然后,通过硅胶柱色谱(DCM/MeOH)纯化残余物以分离产物((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟基-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(0.030g,75%)。

[0602] 步骤4:((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟基-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮

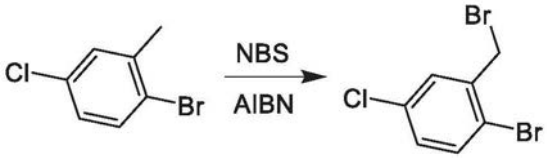
[0603] 

[0604] 将((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟基-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(0.060g,0.095mmol,1当量)于DCM(1mL)中的溶液用TFA(0.73mL,9.5mmol,100当量)处理16小时。将反应混合物用DCM稀释并且用饱和碳酸氢钠水溶液洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥,并且在真空中浓缩。向DCM/MeOH(1/1,1mL)中的中间物中添加乙酸钠(0.016g,0.19mmol,2当量)并且将反应物在23℃下搅拌2小时。将反应混合物用DCM稀释并且用饱和碳酸氢钠溶液洗涤。将合并的有机层用饱和盐水溶液洗涤,在Na_2SO_4上干燥,在真空中浓缩。然后,首先通过硅胶柱色谱(含有10%NH_4OH的DCM/MeOH)然后通过制备-TLC来纯化残余物以分离产物((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)(4-(((3R,4R)-4-羟基-1-(氧杂环丁烷-3-基)吡咯烷-3-基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)甲酮(0.034g,70%)。

[0605] 实施例26.合成化合物156

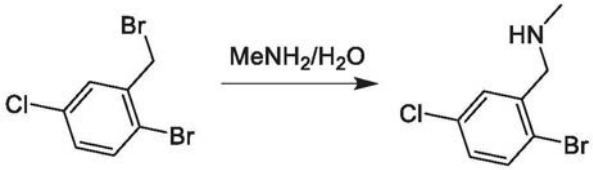
[0606] 

[0607] 步骤1:1-溴-2-(溴甲基)-4-氯苯

[0608] 

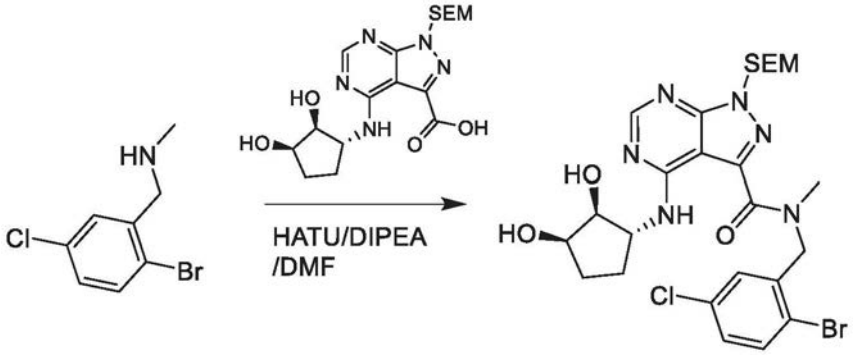
[0609] 在90℃下,将1-溴-4-氯-2-甲苯(3.00g,14.60mmol,1.00当量)、NBS(2.34g,13.14mmol,0.90当量)和AIBN(239.75mg,1.46mmol,0.10当量)于CCl_4(20.00mL)中的溶液搅拌12h。将溶液在真空中浓缩以得到呈黄色固体状的粗产物1-溴-2-(溴甲基)-4-氯苯(5.40g,粗产物),其未进一步纯化即用于下一个步骤中。

[0610] 步骤2:1-(2-溴-5-氯苯基)-N-甲基甲胺

[0611] 

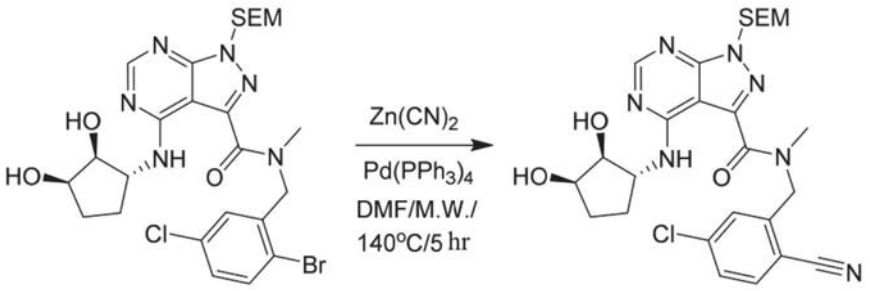
[0612] 在25℃下,将1-溴-2-(溴甲基)-4-氯苯(5.40g,18.99mmol,1.00当量)于$MeNH_2/H_2O$(30.00mL)中的溶液搅拌15h。当反应完成时,用EtOAc(50mL*3)萃取产物,将合并的有机层在真空中浓缩以得到粗产物。通过硅胶柱色谱(PE:EtOAc=5:1至1:1)纯化粗产物以获得呈灰白色固体状的1-(2-溴-5-氯苯基)-N-甲基甲胺(1.00g,产率:22.45%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.45(d,1H,J=8.8Hz),7.40-7.39(m,1H),7.10(dd,1H,J=8.4,2.4Hz),3.79(s,2H),2.46(s,3H)。

[0613] 步骤3:N-(2-溴-5-氯苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0614] 

[0615] 向1-(2-溴-5-氯苯基)-N-甲基甲胺(500.00mg,1.22mmol,1.00当量)和4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-羧酸(314.98mg,1.34mmol,1.10当量)于DMF(5.00mL)中的溶液中添加DIPEA(315.35mg,2.44mmol,2.00当量)和HATU(556.66mg,1.46mmol,1.20当量),将所得混合物在25℃下搅拌15h。当反应完成时,添加H_2O(20mL),通过EtOAc(20mL*3)萃取产物,将合并的有机层在真空中浓缩以得到粗产物。通过制备型-TLC(EtOAc)纯化粗产物以获得呈红色油状的N-(2-溴-5-氯苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(520.00mg,产率:81.20%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 9.77(br.s,0.5H),9.49(br.s,0.5H),8.45(d,1H,J=11.4Hz),7.63(dd,1H,J=8.4,4.4Hz),7.33-7.31(m,1H),7.26-7.25(m,1H),5.87(s,1H),5.67(s,1H),5.46(s,1H),4.98(s,1H),4.45-4.44(m,1H),4.31-4.29(m,1H),4.03-4.02(m,1H),3.79(t,1H,J=8.0Hz),3.71(s,1.5H),3.55(t,1H,J=8.0Hz),3.29(s,1.5H),3.16(d,1H,J=6.0Hz),2.65-2.61(m,1H),2.05-1.83(m,2H),1.05(t,1H,J=8.4Hz),0.90(t,1H,J=8.0Hz),0.07(s,4.5H),0.00(s,4.5H)。

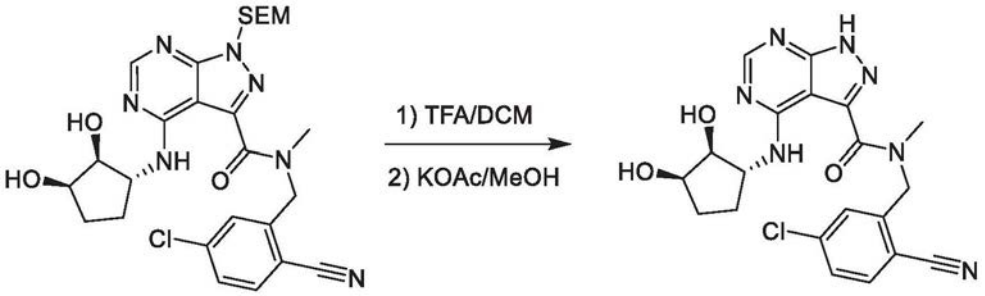
[0616] 步骤4:N-(5-氯-2-氰基苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0617] 

[0618] 将N-(2-溴-5-氯苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(420.00mg,670.91umol,1.00当量)、$Zn(CN)_2$(630.22mg,5.37mmol,340.66uL,8.00当量)和$Pd(PPh_3)_4$(77.53mg,67.09umol,0.10当量)的混合物溶解于密封管中的DMF(3.00mL)中,将其在140℃下用微波辐射3h。在3h之后,LCMS显示起始材料未完全消耗,因此添加更多$Zn(CN)_2$(2当量)和$Pd(PPh_3)_4$(0.1当量),将其在150℃下再用微波辐射2h。当反应完成时,添加H_2O(15mL),通过EtOAC(20mL*3)萃取产物。在无水Na_2SO_4干燥上合并的有机层并且将其浓缩得到粗产物。通过制备型-TLC(EtOAc)纯化粗产物以获得呈黄色油状的N-(5-氯-2-氰基苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡

唑并[3,4-d]嘧啶-3-甲酰胺(520.00mg,粗产物,包括PPh_3O)。^1H-NMR(400MHz,$CDCl_3$)δppm 9.72(br.s,0.5H),9.44(br.s,0.5H),8.45(d,1H,J=6.4Hz),7.79-7.54(m,3H),5.86(s,1H),5.70(s,1H),5.67(s,1H),5.11(s,1H),4.45-4.44(m,1H),4.30-4.29(m,1H),4.03-4.02(m,1H),3.81-3.76(m,2.5H),3.59(t,1H,J=8.0Hz),3.32(s,1.5H),3.18-3.16(m,1H),2.19-1.86(m,3H),1.04(t,1H,J=8.0Hz),0.92(t,1H,J=8.0Hz),0.06(s,4.5H),0.00(s,4.5H)。

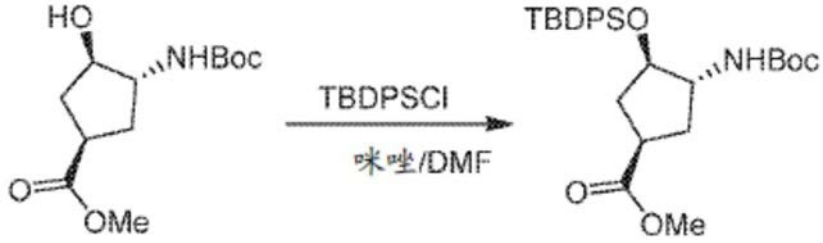
[0619] 步骤5:N-(5-氯-2-氰基苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺

[0620] 

[0621] 向混合溶剂TFA(10.00mL)和DCM(10.00mL)中添加N-(5-氯-2-氰基苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(520.00mg,908.88umol,1.00当量),将所得混合物在25℃下搅拌1h。通过N_2蒸发溶剂以得到粗产物。将粗产物溶解于MeOH(15.00mL)中,通过$NaHCO_3$调整至pH=7-8,并且添加KOAc(178.39mg,1.82mmol,2.00当量),将其在50℃下搅拌2h。当反应完成时,将混合物在真空中浓缩以得到粗产物,将其溶解于EtOAc(50mL)中,通过H_2O(15mL*3)洗涤。将有机层在真空中浓缩以得到粗产物,通过酸性制备型-HPLC(TFA)纯化所述粗产物以获得呈白色固体状的N-(5-氯-2-氰基苄基)-4-(((1R,2S,3R)-2,3-二羟基环戊基)氨基)-N-甲基-1H-吡唑并[3,4-d]嘧啶-3-甲酰胺(171.00mg,产率:33.85%,TFA)。

[0622] 实施例27.合成化合物226

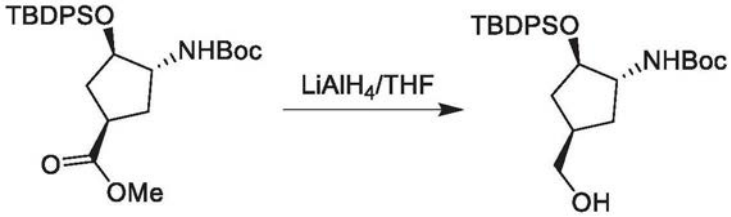
[0623] 步骤1:(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-((叔丁基二苯基甲硅烷基)氧基)环戊烷-1-羧酸甲酯:

[0624] 

[0625] 在0℃下,向(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-羟基环戊烷-1-羧酸甲酯(1.50g,5.78mmol,1.00当量)和咪唑(590.74mg,8.67mmol,1.50当量)于DMF(10.00mL)中的溶液中添加TBDPSCl(1.67g,6.07mmol,1.05当量)。在15℃下将反应物搅拌16h。TLC(PE:EtOAc=5:1,R_f=0.43)显示反应完成。将溶液倾倒至水(20mL)中并且用EtOAc(10mL*3)萃取。将有机层在Na_2SO_4上干燥并且浓缩。将残余物从PE(1mL)重结晶以得到呈白色固体状的(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-((叔丁基二苯基甲硅烷基)氧基)环戊烷-1-羧酸甲酯(2.80g,产率:97.40%)。^1H-NMR(400MHz,$CDCl_3$)δppm7.69-7.64(m,4H),7.43-7.37(m,

6H),4.10(br.s,1H),3.92-3.97(m,2H),3.66(s,3H),2.75-2.71(m,1H),2.46-2.43(m,1H),2.01-1.95(m,2H),1.65-1.61(m,1H),1.40(s,9H),1.05(s,9H)。

[0626] 步骤2:((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(羟甲基)环戊基)氨基甲酸叔丁酯:

[0627] 

[0628] 在-30℃下,向(1R,3R,4R)-3-((叔丁氧羰基)氨基)-4-((叔丁基二苯基甲硅烷基)氧基)环戊烷-1-羧酸甲酯(2.80g,5.63mmol,1.00当量)于THF(30.00mL)中的溶液中添加$LiAlH_4$(427.32mg,11.26mmol,2.00当量)。将反应物缓慢加温至15℃并且搅拌2h。TLC(PE:EtOAc=3:1,R_f=0.24)显示反应完成。在0℃下,将反应物用0.43mL的H_2O和0.43mL的10%NaOH水溶液淬灭。将混合物过滤并且将滤液浓缩。将残余物用PE(5mL)洗涤。将固体收集。获得呈白色固体状的((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(羟甲基)环戊基)氨基甲酸叔丁酯(2.30g,产率:86.98%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.69-7.65(m,4H),7.43-7.38(m,6H),4.11-4.10(m,1H),3.89(br.s,2H),3.54(br.s,2H),2.14-2.10(m,1H),1.97-1.89(m,2H),1.62-1.58(m,1H),1.39(s,9H),1.06(s,9H)。

[0629] 步骤3:((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-甲酰基环戊基)氨基甲酸叔丁酯:

[0630] 

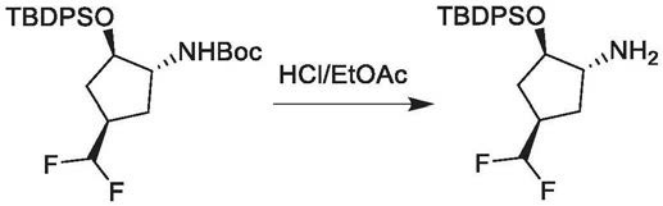
[0631] 在0℃下向((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(羟甲基)环戊基)氨基甲酸叔丁酯(2.30g,4.90mmol,1.00当量)于DCM(50.00mL)中的溶液中添加戴斯-马丁过碘烷试剂(3.12g,7.35mmol,1.50当量)。在15℃下将反应物搅拌16h。TLC(PE:EtOAc=3:1,R_f=0.7)显示反应完成。在0℃下,将反应物用饱和$NaHCO_3$(30mL)水溶液淬灭并且用DCM(30mL)萃取。将有机层在Na_2SO_4上干燥并且浓缩。通过硅胶柱色谱(PE:EtOAc=30:1)纯化残余物。获得呈黄色油状的((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-甲酰基环戊基)氨基甲酸叔丁酯(900.00mg,产率:39.27%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 9.55(s,1H),7.61-7.56(m,4H),7.37-7.31(m,6H),4.08(d,1H,J=7.2Hz),3.93-3.89(m,1H),3.79(br.s,1H),2.62-2.55(m,1H),2.44-2.40(m,1H),1.86-1.83(m,2H),1.57-1.52(m,1H),1.34(s,9H),0.97(s,9H)。

[0632] 步骤4:((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊基)氨基甲酸叔丁酯:

[0633] 

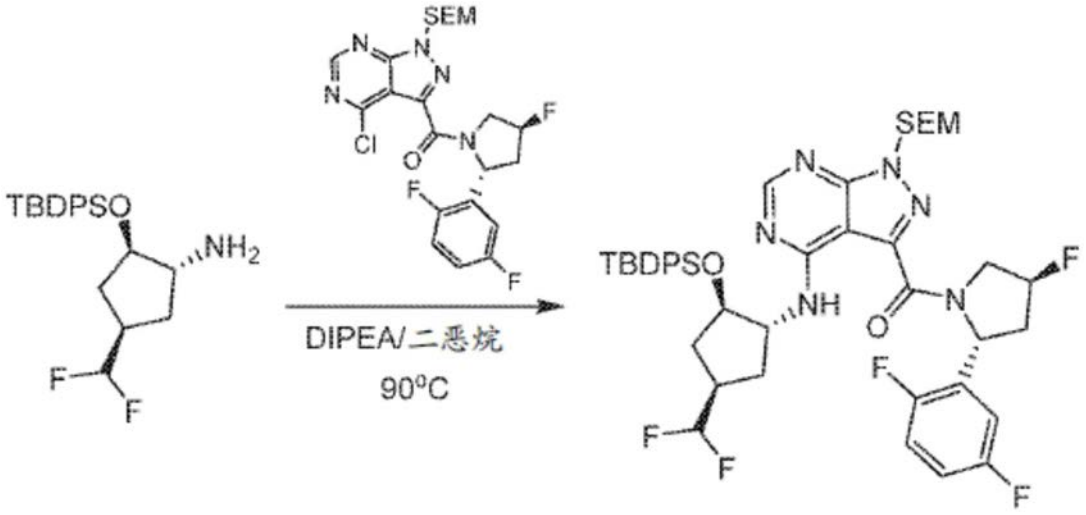
[0634] 在0℃下,向((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-甲酰基环戊基)氨基甲酸叔丁酯(900.00mg,1.92mmol,1.00当量)于DCM(50.00mL)中的溶液中添加DAST(928.45mg,5.76mmol,3.00当量)。在15℃下将反应物搅拌5h。TLC(PE:EtOAc=3:1,R_f=0.6)显示反应完成。将溶液用饱和$NaHCO_3$水溶液(20mL)淬灭并且用DCM(20mL)萃取。将有机层在Na_2SO_4上干燥并且浓缩。通过硅胶柱色谱(PE:EtOAc=30:1～20:1)纯化残余物。获得呈黄色油状的((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊基)氨基甲酸叔丁酯(250.00mg,产率:26.59%)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.62-7.56(m,4H),7.34-7.31(m,6H),5.76-5.43(m,1H),3.88-3.82(m,2H),2.30-2.24(m,1H),2.07-2.04(m,1H),1.80-1.75(m,1H),1.65-1.57(m,1H),1.33(s,9H),0.99(s,9H)。

[0635] 步骤5:(1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊-1-胺:

[0636] 

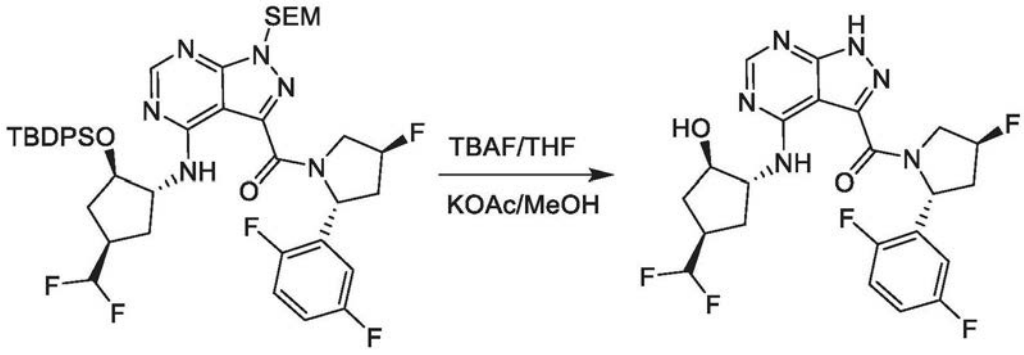
[0637] 在15℃下,向((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊基)氨基甲酸叔丁酯(50.00mg,102.11umol,1.00当量)于EtOAc(2.00mL)中的溶液中添加HCl/EtOAc(10.00Ml,4M)。在15℃下将反应物搅拌1h。TLC(PE:EtOAc=3:1,R_f=0.05)显示反应完成。通过N_2将溶剂吹干。残余物未进一步纯化。获得呈黄色油状的(1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊-1-胺(40.00mg,产率:91.95%,HCl)。^{1}H-NMR(400MHz,$CDCl_3$)δppm 7.70-7.68(m,4H),7.49-7.43(m,6H),5.81(td,1H,J=57.2,4.8Hz),4.25(dd,1H,J=12.0,5.6Hz),3.50(dd,1H,J=13.2,6.4Hz),2.22-2.19(m,1H),1.80-1.74(m,2H),1.66-1.63(m,1H),1.08(s,9H)。

[0638] 步骤6:(4-(((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮:

[0639] 

[0640] 向(1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊-1-胺(40.00mg,93.89umol,1.00当量,HCl)和(4-氯-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮(48.07mg,93.89umol,1.00当量)于二噁烷(10.00mL)中的溶液中添加DIPEA(60.67mg,469.45umol,5.00当量)。将反应物在90℃下加热0.5h。LCMS显示反应完成。将溶液浓缩。通过制备型-TLC(PE:EtOAc=3:1)纯化残余物。获得呈黄色油状的(4-(((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮(38.00mg,产率:46.78%)。

[0641] 步骤7:(4-(((1R,2R,4R)-4-(二氟甲基)-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮(化合物226):

[0642] 

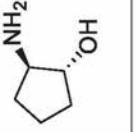
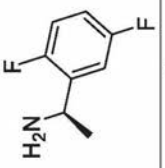
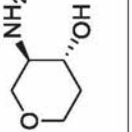
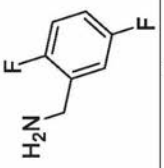
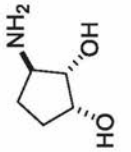
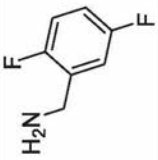
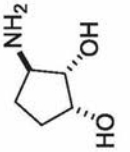
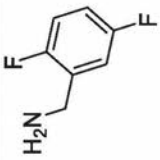
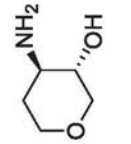
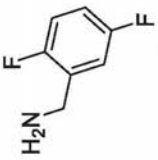
[0643] 在50℃下将(4-(((1R,2R,4R)-2-((叔丁基二苯基甲硅烷基)氧基)-4-(二氟甲基)环戊基)氨基)-1-((2-(三甲基甲硅烷基)乙氧基)甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮(38.00mg,43.93umol,1.00当量)于TBAF/THF(5.00mL)中的溶液加热2h。LCMS显示留下(4-(((1R,2R,4R)-4-(二氟甲基)-2-羟环戊基)氨基)-1-(羟甲基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮。将反应混合物浓缩。将残余物溶解于EtOAc(20mL)中并且用盐水(10mL*2)洗涤。将有机层浓缩并且溶解于MeOH(20.00mL)中。将KOAc(21.56mg,219.65umol,5.00当量)添加至反应物中。将反应物在50℃下加热16h。LCMS显示反应完成。将溶液浓缩。通过制备型-HPLC(MeOH/TFA系统)纯化残余物。获得呈黄色固体状的(13.50mg,产率:

50.34％,TFA)的(4-(((1R,2R,4R)-4-(二氟甲基)-2-羟环戊基)氨基)-1H-吡唑并[3,4-d]嘧啶-3-基)((2R,4S)-2-(2,5-二氟苯基)-4-氟吡咯烷-1-基)甲酮。

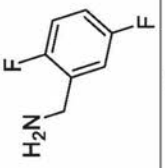
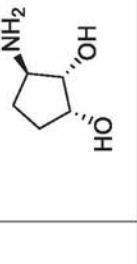
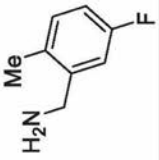
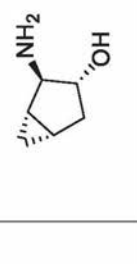
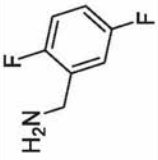
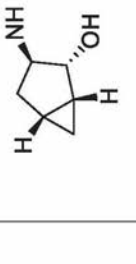
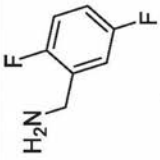
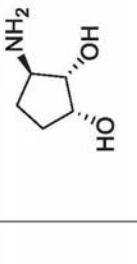
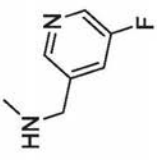
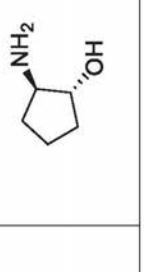
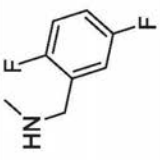
[0644] 实施例28.合成其他化合物

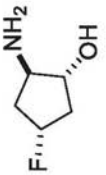
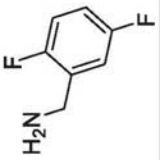
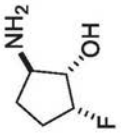
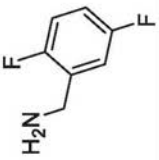
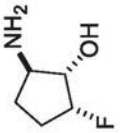
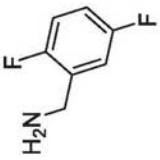
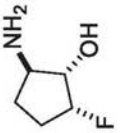
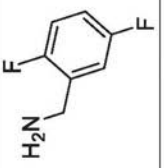
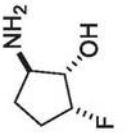
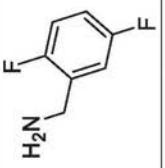
[0645] 本发明的额外化合物使用与以上实施例阐明的技术类似的技术来合成。下表指示基于每种化合物(“Cmpd”)的合成的特定实施例(“实施例”)以及用于合成每种特定化合物的合适氨基醇和胺。

[0646] 表1.用于合成示例性化合物的方案和中间物。

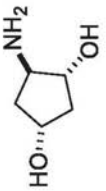
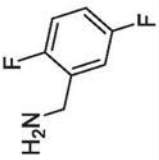
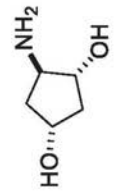
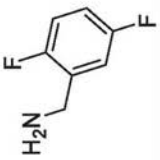
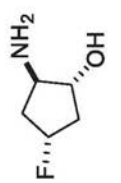
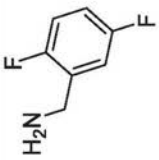
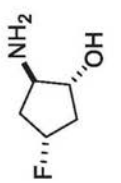
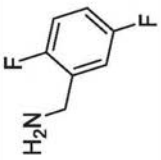
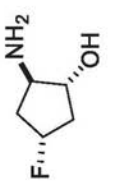
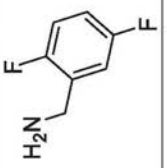
Cmpd	氨基醇	胺	实施例
7			1
8			1
9			2
10			2
11			1

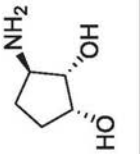
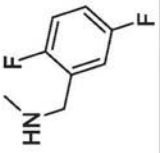
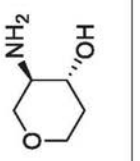
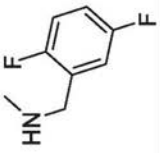
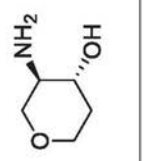
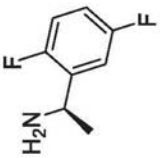
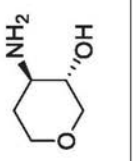
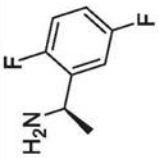
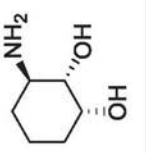
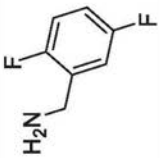
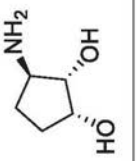
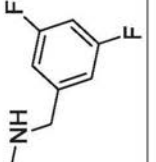
[0647]

Cmpd	氨基醇	胺	实施例
1			1
2			1
3			1
4			1
5			1
6			1

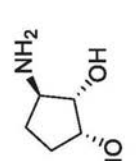
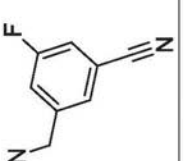
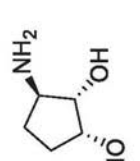
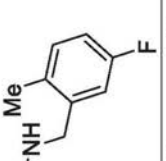
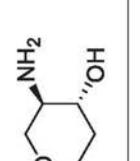
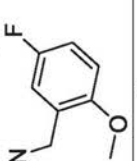
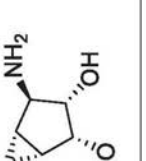
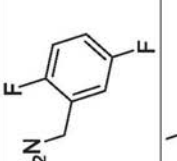
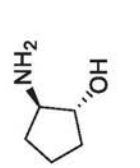
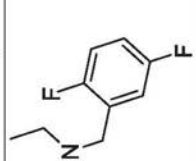
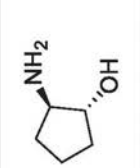
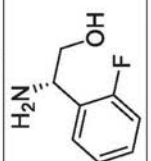
Cmpd	氨基醇	胺	实施例
17			3
18			3
19			3
20			3
21			3

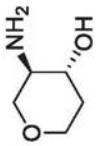
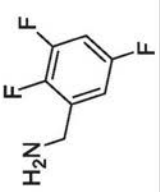
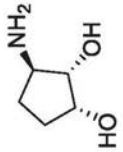
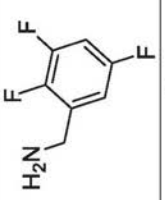
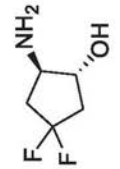
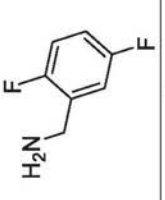
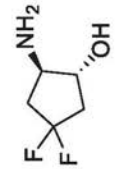
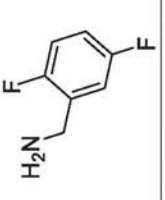
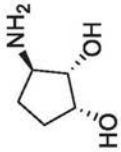
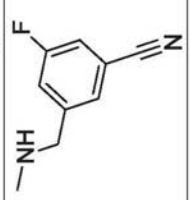
[0648]

Cmpd	氨基醇	胺	实施例
12			2
13			2
14			3
15			3
16			3

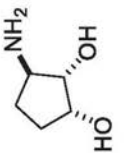
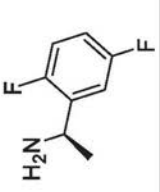
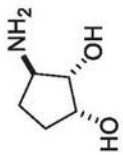
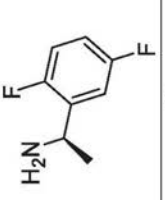
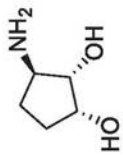
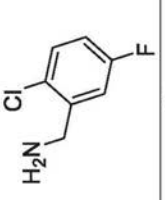
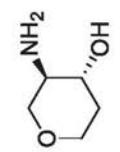
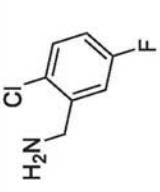
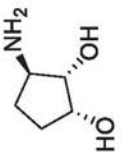
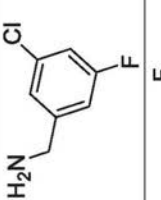
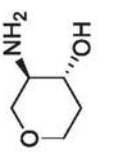
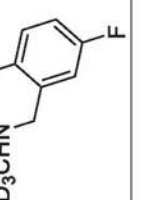
Cmpd	氨基醇	胺	实施例
28			1
29			1
30			1
31			1
32			1
33			1

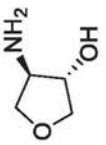
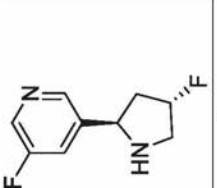
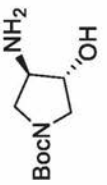
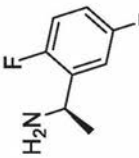
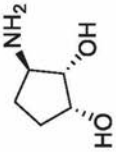
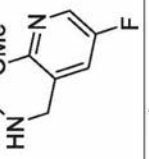
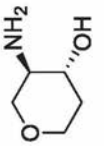
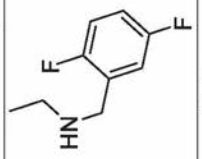
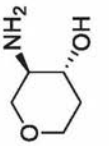
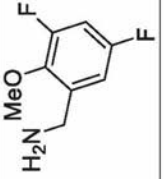
[0649]

Cmpd	氨基醇	胺	实施例
22			1
23			1
24			1
25			1
26			1
27			1

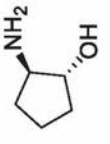
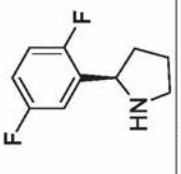
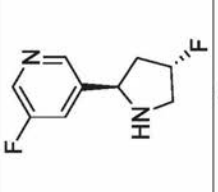
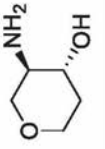
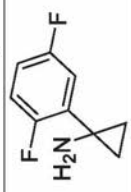
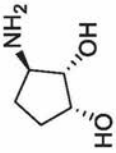
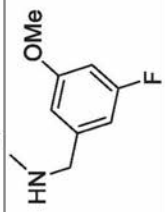
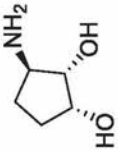
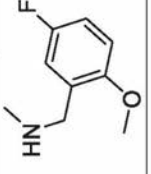
Cmpd	氨基醇	胺	实施例
40			1
41			1
42			1
43			1
44			1

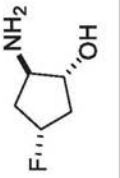
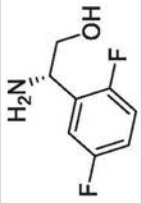
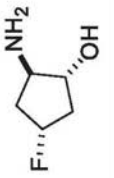
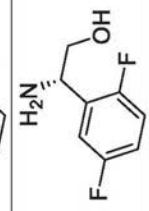
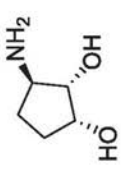
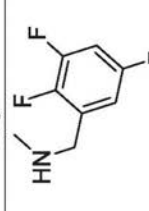
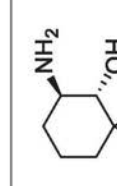
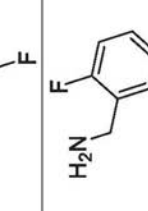
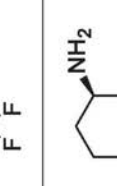
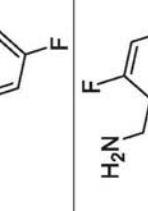
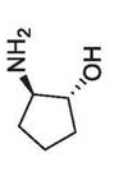
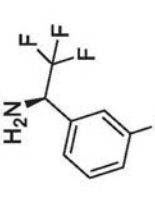
[0650]

Cmpd	氨基醇	胺	实施例
34			2
35			2
36			1
37			1
38			1
39			1

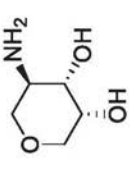
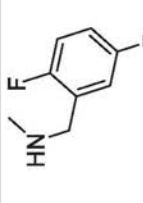
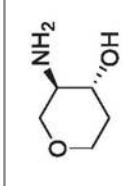
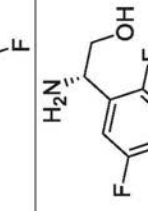
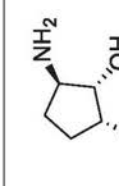
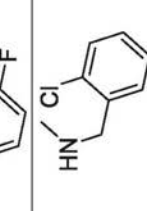
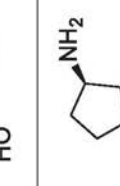
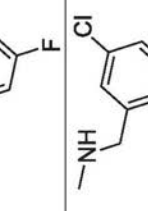
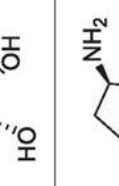
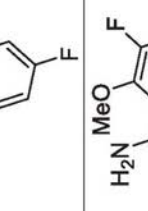
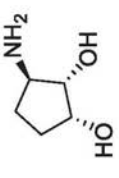
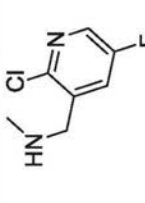
Cmpd	氨基醇	胺	实施例
50			1
51			23
52			1
53			1
54			1

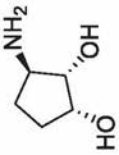
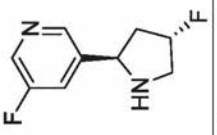
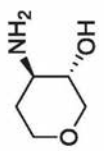
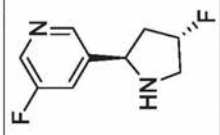
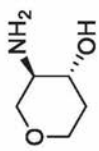
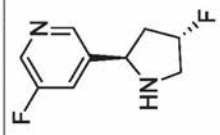
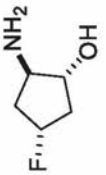
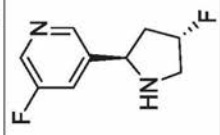
[0651]

Cmpd	氨基醇	胺	实施例
45			1
46			1
47			1
48			1
49			1

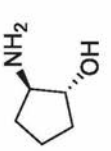
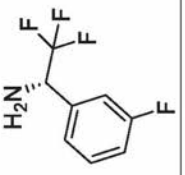
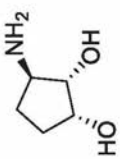
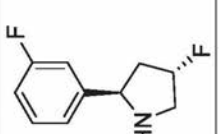
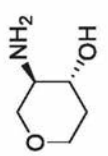
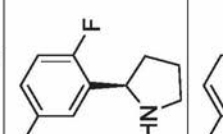
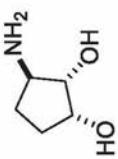
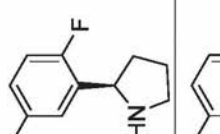
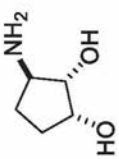
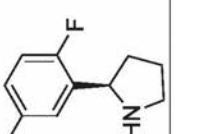
Cmpd	氨基醇	胺	实施例
61			3
62			3
63			1
64			1
65			1
66			2

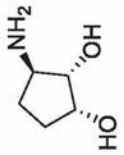
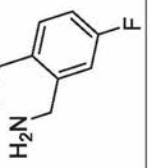
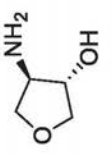
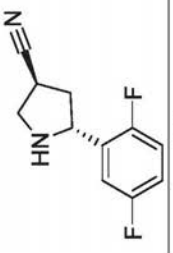
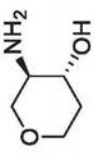
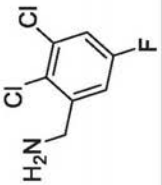
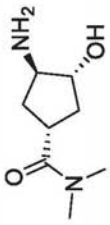
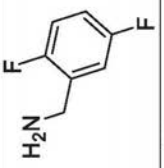
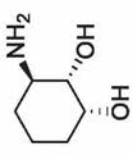
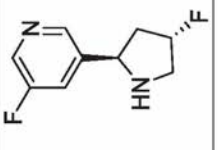
[0652]

Cmpd	氨基醇	胺	实施例
55			1
56			1
57			1
58			1
59			1
60			1

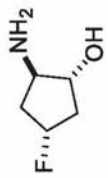
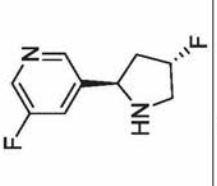
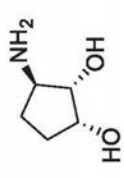
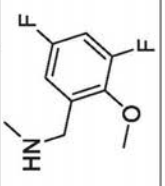
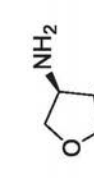
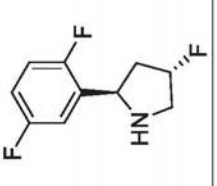
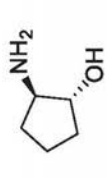
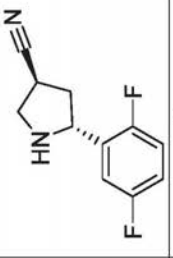
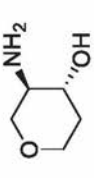
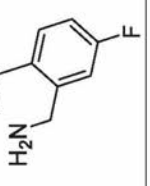
Cmpd	氨基醇	胺	实施例
72			1
73			1
74			1
75			3

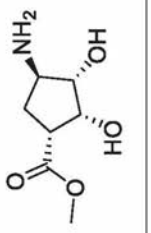
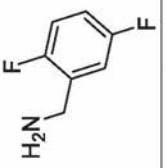
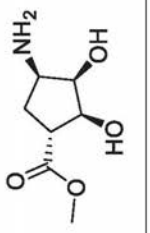
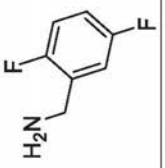
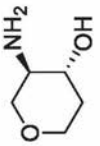
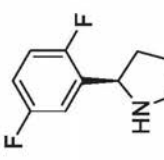
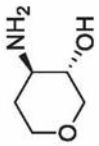
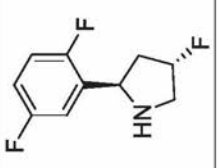
[0653]

Cmpd	氨基醇	胺	实施例
67			2
68			1
69			1
70			2
71			2

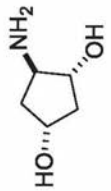
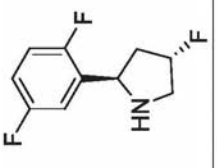
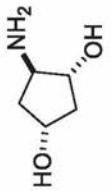
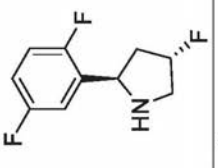
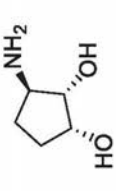
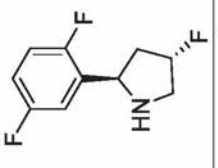
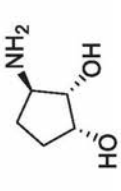
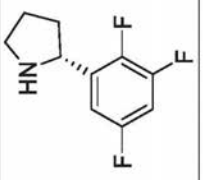
Cmpd	氨基醇	胺	实施例
81			1
82			1
83			1
84			22
85			1

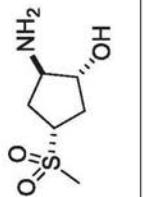
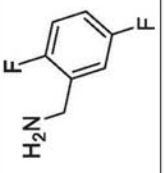
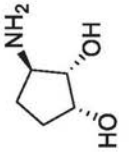
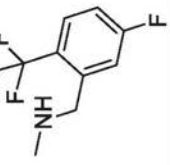
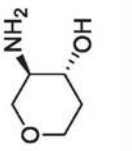
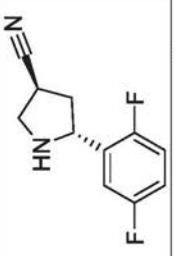
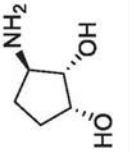
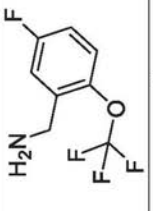
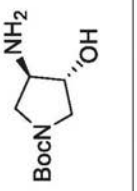
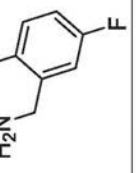
[0654]

Cmpd	氨基醇	胺	实施例
76			3
77			1
78			1
79			1
80			1

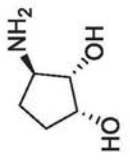
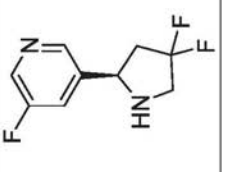
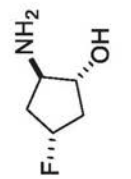
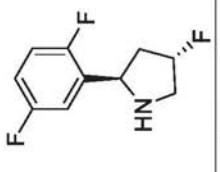
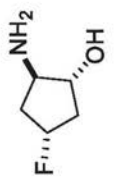
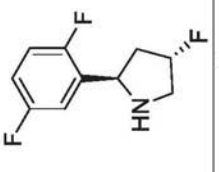
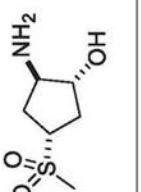
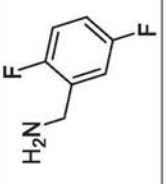
Cmpd	氨基醇	胺	实施例
90			2
91			2
92			1
93			1

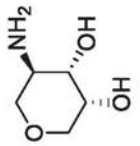
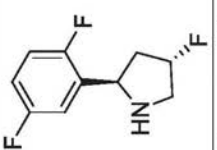
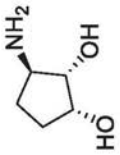
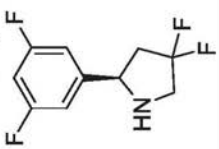
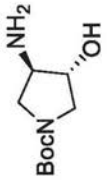
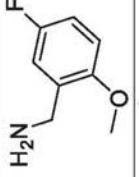
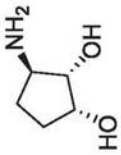
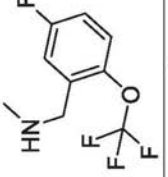
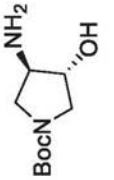
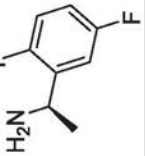
[0655]

Cmpd	氨基醇	胺	实施例
86			2
87			2
88			1
89			1

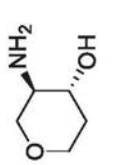
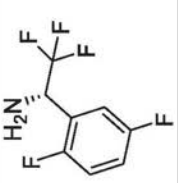
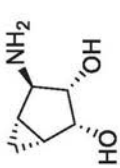
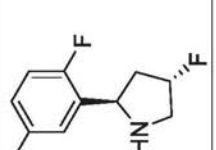
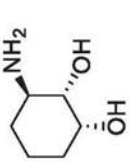
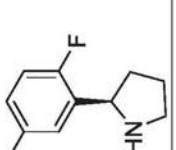
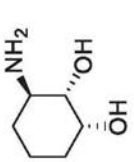
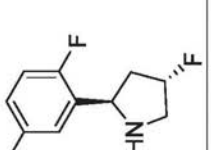
Cmpd	氨基醇	胺	实施例
98			2
99			1
100			1
101			1
102			23

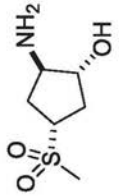
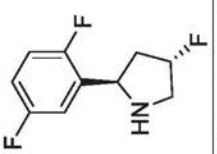
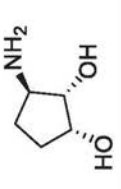
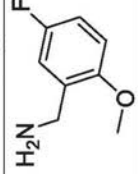
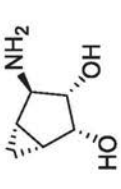
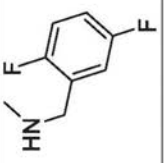
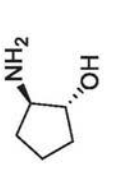
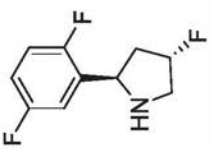
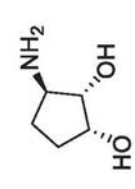
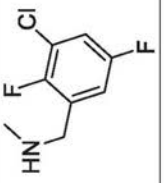
[0656]

Cmpd	氨基醇	胺	实施例
94			1
95			3
96			3
97			2

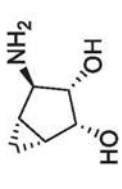
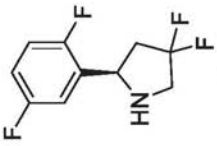
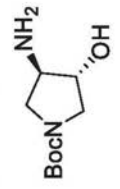
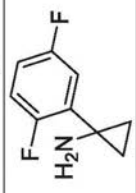
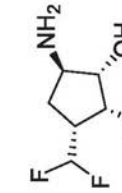
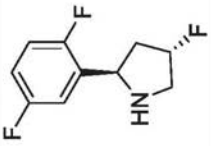
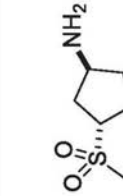
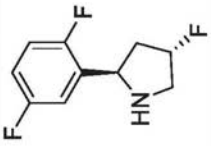
Cmpd	氨基醇	胺	实施例
107			1
108			1
109			23
110			1
111			23

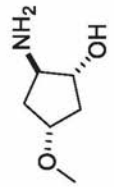
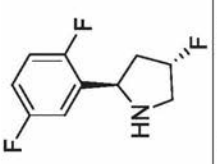
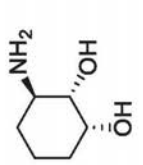
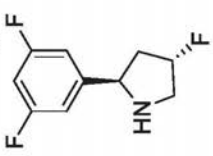
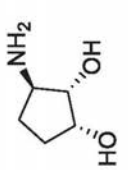
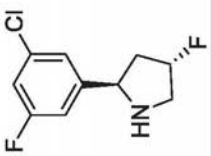
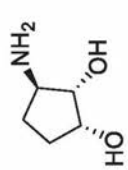
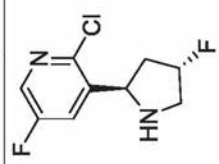
[0657]

Cmpd	氨基醇	胺	实施例
103			1
104			1
105			1
106			1

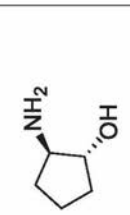
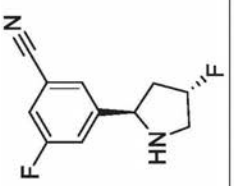
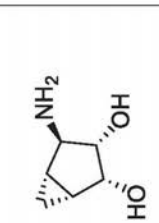
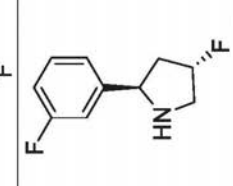
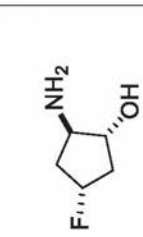
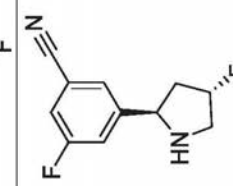
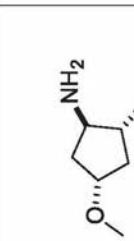
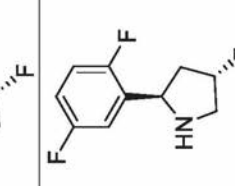
Cmpd	氨基醇	胺	实施例
116			2
117			1
118			1
119			1
120			1

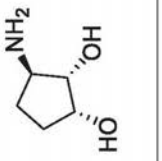
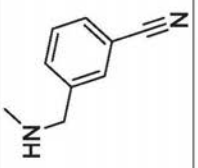
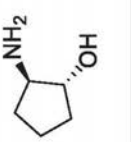
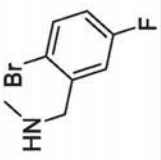
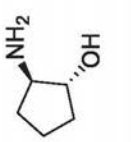
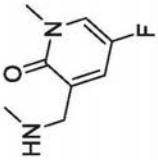
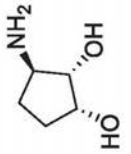
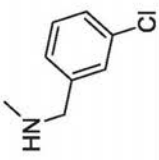
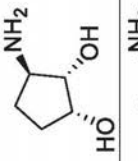
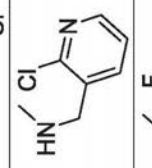
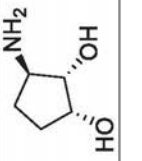
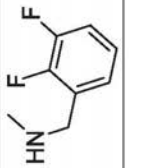
[0658]

Cmpd	氨基醇	胺	实施例
112			1
113			23
114			1
115			2

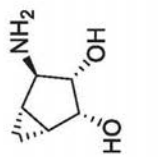
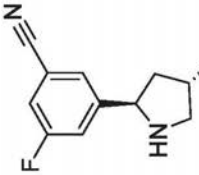
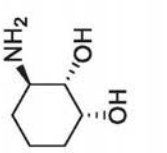
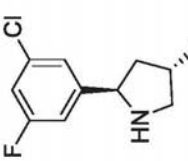
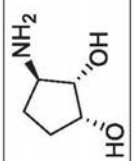
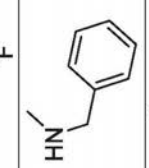
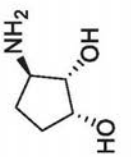
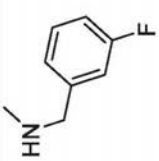
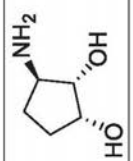
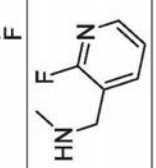
Cmpd	氨基醇	胺	实施例
125			2
126			1
127			1
128			1

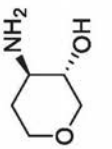
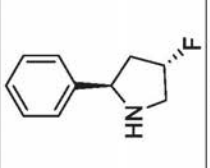
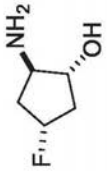
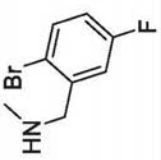
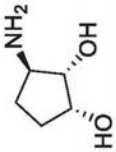
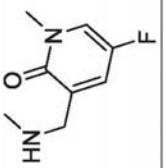
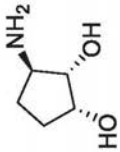
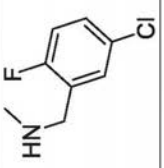
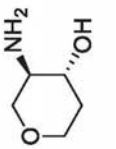
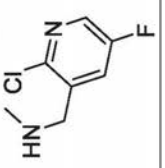
[0659]

Cmpd	氨基醇	胺	实施例
121			1
122			1
123			3
124			2

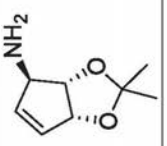
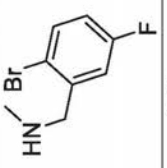
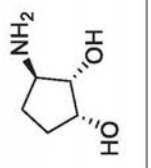
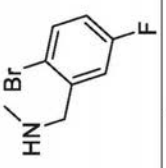
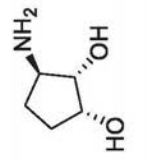
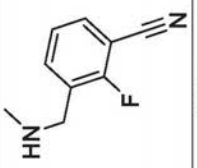
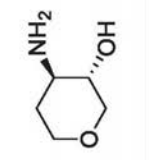
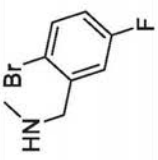
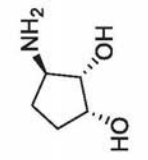
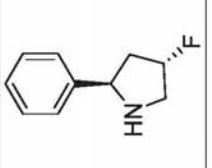
Cmpd	氨基醇	胺	实施例
134			1
135			24
136			1
137			1
138			1
139			1

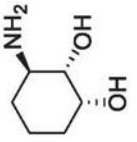
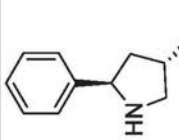
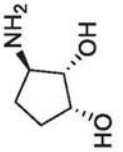
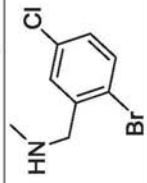
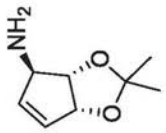
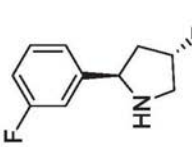
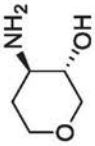
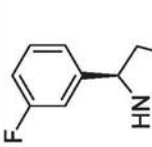
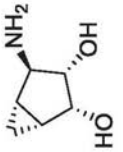
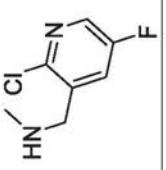
[0660]

Cmpd	氨基醇	胺	实施例
129			1
130			1
131			1
132			1
133			1

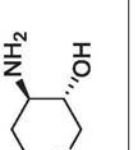
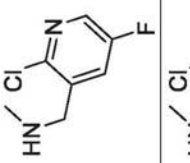
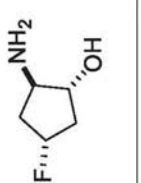
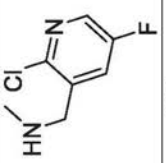
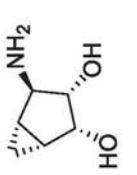
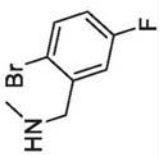
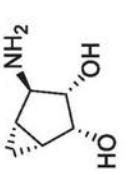
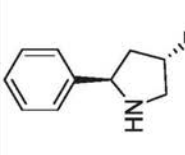
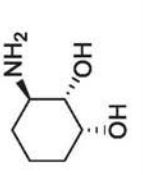
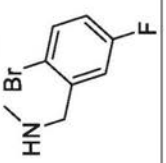
Cmpd	氨基醇	胺	实施例
145			1
146			24
147			1
148			1
149			1

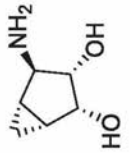
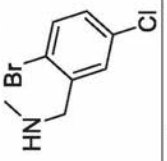
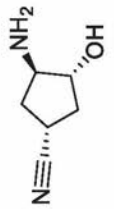
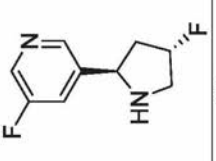
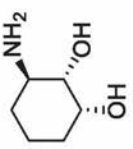
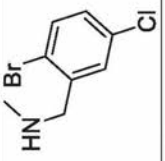
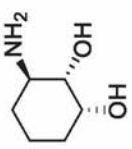
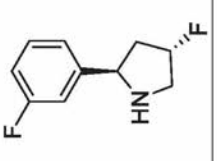
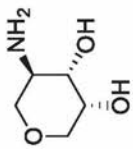
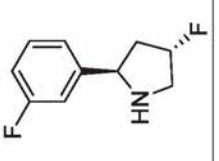
[0661]

Cmpd	氨基醇	胺	实施例
140			24
141			24
142			1
143			24
144			1

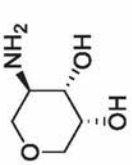
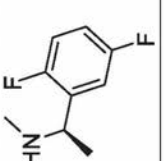
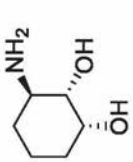
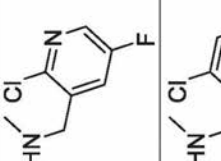
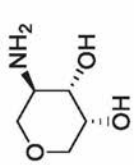
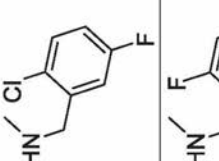
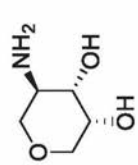
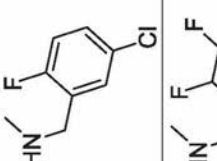
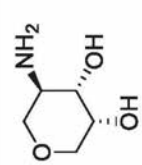
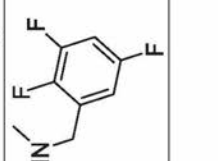
Cmpd	氨基醇	胺	实施例
155			1
156			24
157			1
158			1
159			1

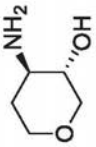
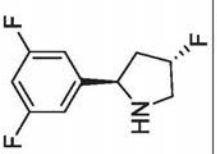
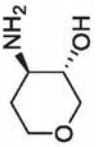
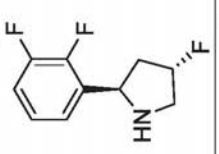
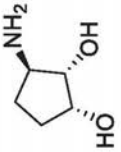
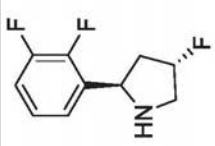
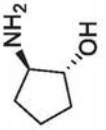
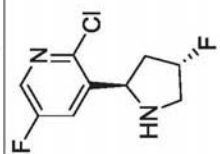
[0662]

Cmpd	氨基醇	胺	实施例
150			1
151			3
152			24
153			1
154			24

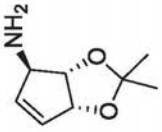
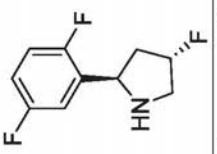
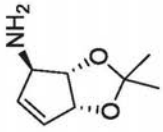
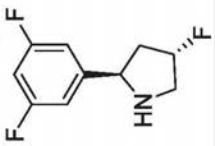
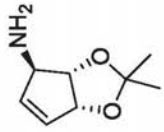
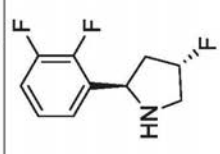
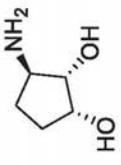
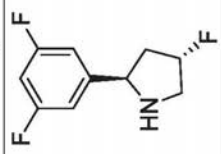
Cmpd	氨基醇	胺	实施例
165			24
166			1
167			24
168			1
169			1

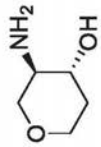
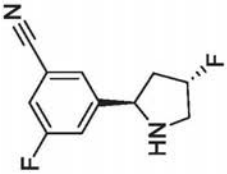
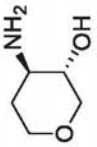
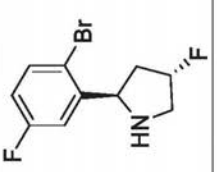
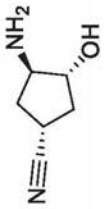
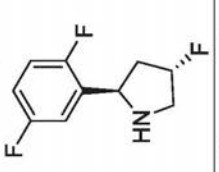
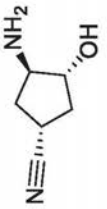
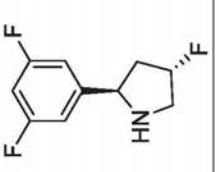
[0663]

Cmpd	氨基醇	胺	实施例
160			1
161			1
162			1
163			1
164			1

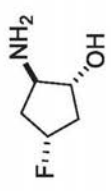
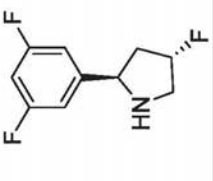
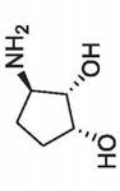
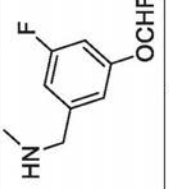
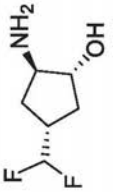
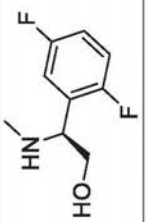
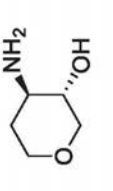
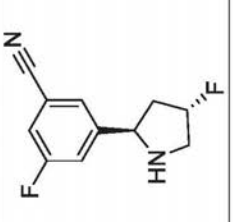
Cmpd	氨基醇	胺	实施例
174			1
175			1
176			1
177			1

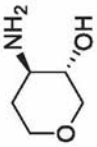
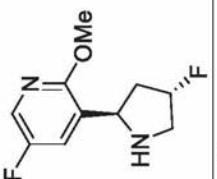
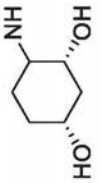
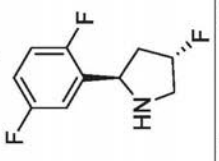
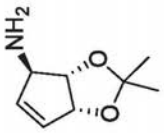
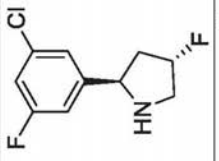
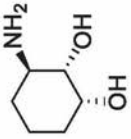
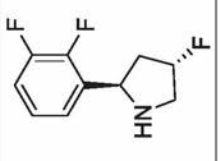
[0664]

Cmpd	氨基醇	胺	实施例
170			1
171			1
172			1
173			1

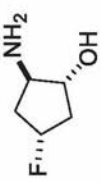
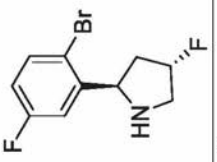
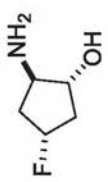
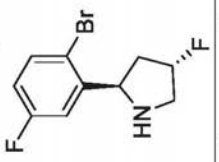
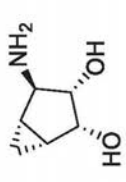
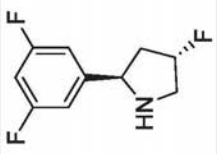
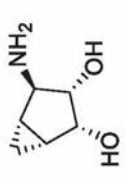
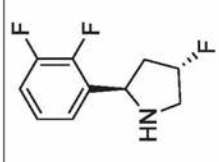
Cmpd	氨基醇	胺	实施例
182			1
183			24
184			1
185			1

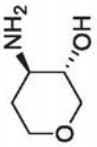
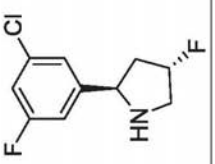
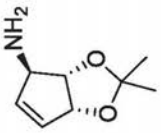
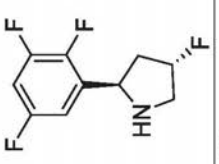
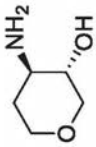
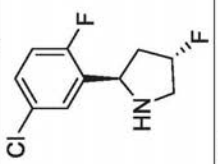
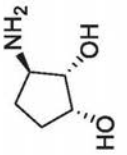
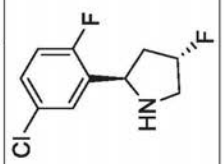
[0665]

Cmpd	氨基醇	胺	实施例
178			3
179			1
180			1
181			1

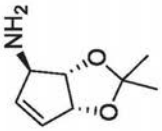
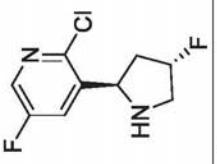
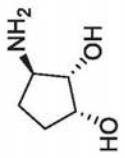
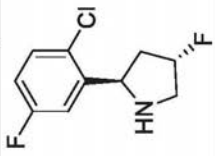
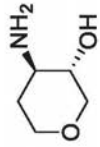
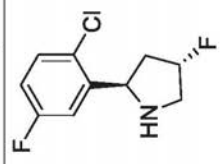
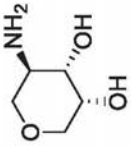
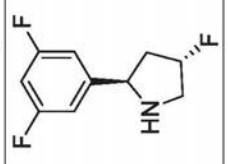
Cmpd	氨基醇	胺	实施例
190			1
191			1
192			1
193			1

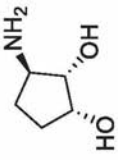
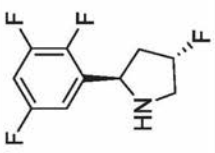
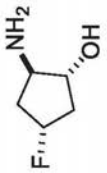
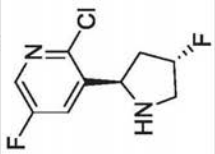
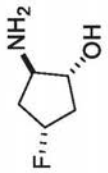
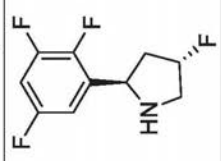
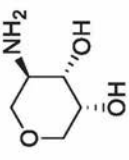
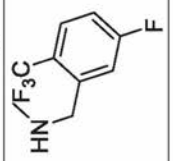
[0666]

Cmpd	氨基醇	胺	实施例
186			3
187			3
188			1
189			1

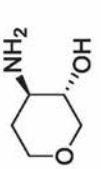
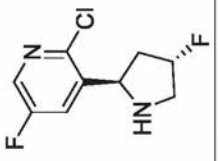
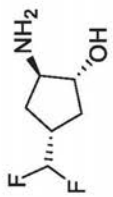
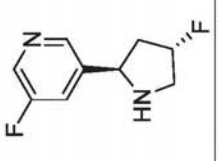
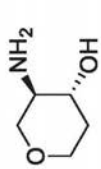
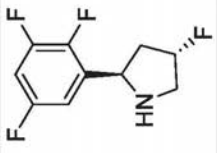
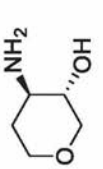
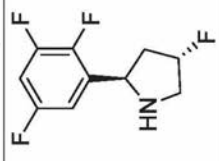
Cmpd	氨基醇	胺	实施例
198			1
199			1
200			1
201			1

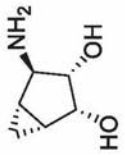
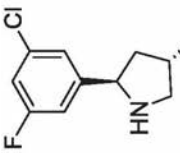
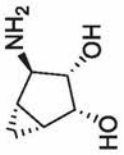
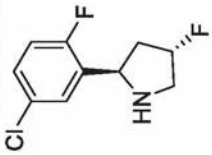
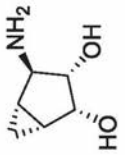
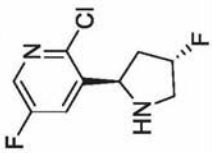
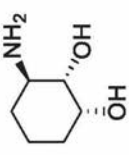
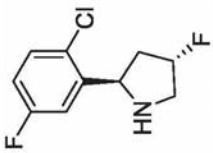
[0667]

Cmpd	氨基醇	胺	实施例
194			1
195			1
196			1
197			1

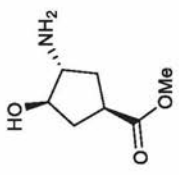
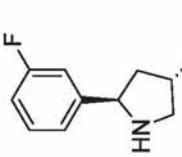
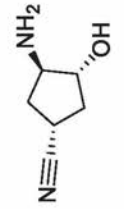
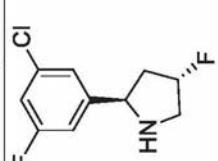
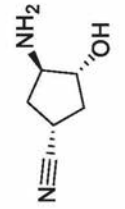
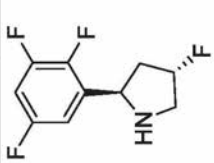
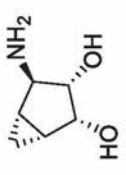
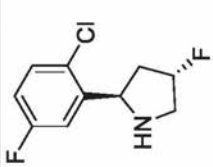
Cmpd	氨基醇	胺	实施例
206			1
207			3
208			3
209			1

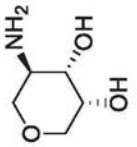
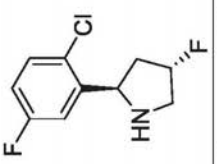
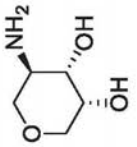
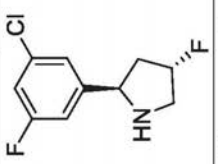
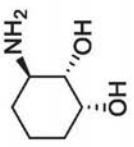
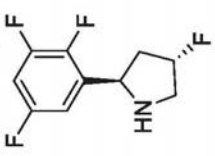
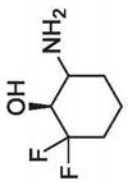
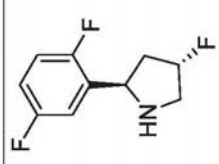
[0668]

Cmpd	氨基醇	胺	实施例
202			1
203			1
204			1
205			1

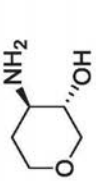
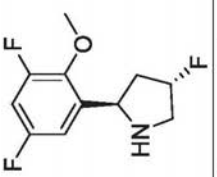
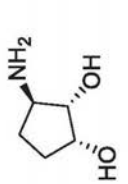
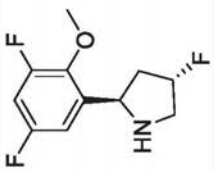
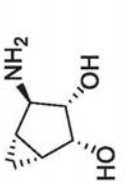
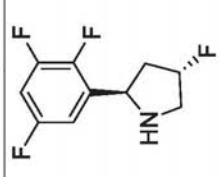
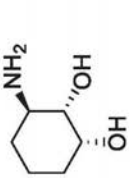
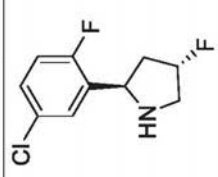
Cmpd	氨基醇	胺	实施例
214			1
215			1
216			1
217			1

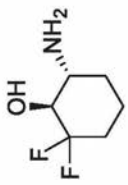
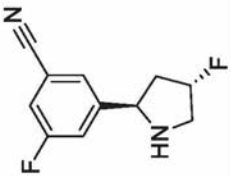
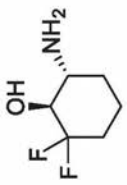
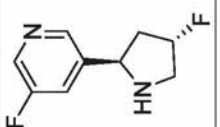
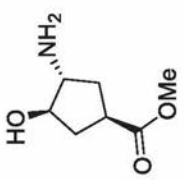
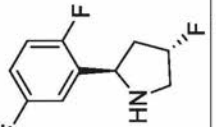
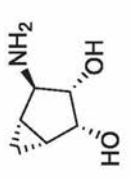
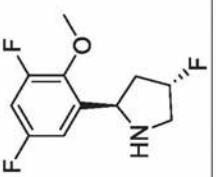
[0669]

Cmpd	氨基醇	胺	实施例
210			22
211			1
212			1
213			1

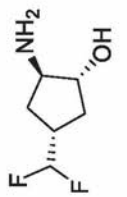
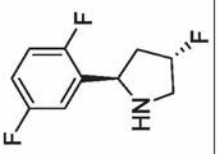
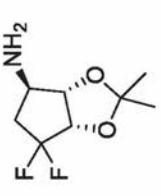
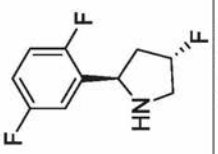
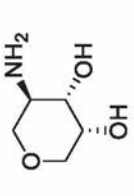
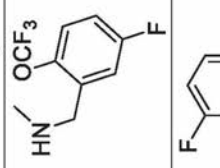
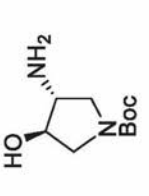
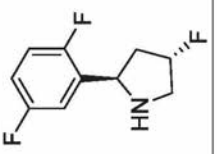
Cmpd	氨基醇	胺	实施例
222			1
223			1
224			1
225			1

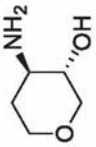
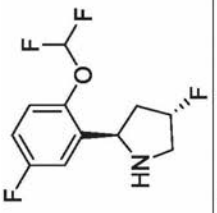
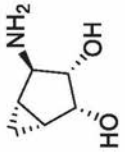
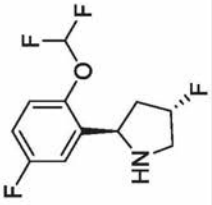
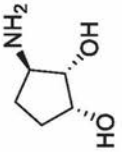
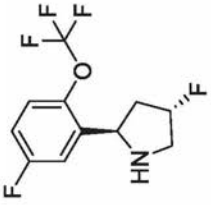
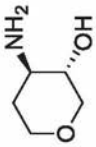
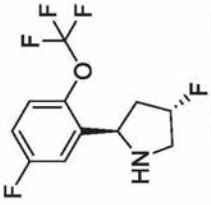
[0670]

Cmpd	氨基醇	胺	实施例
218			1
219			1
220			1
221			1

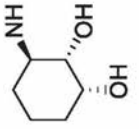
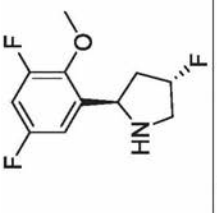
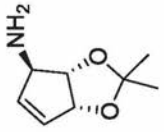
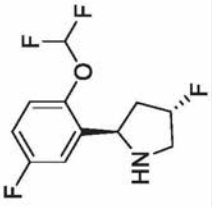
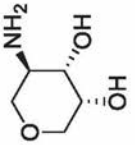
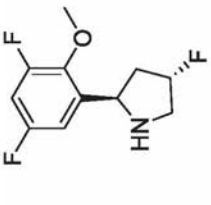
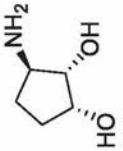
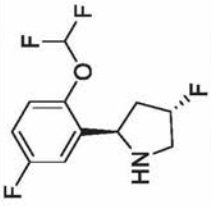
Cmpd	氨基醇	胺	实施例
230			1
231			1
232			22
233			1

[0671]

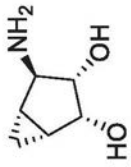
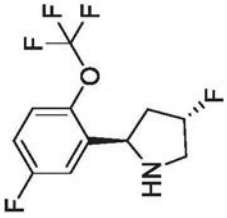
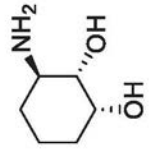
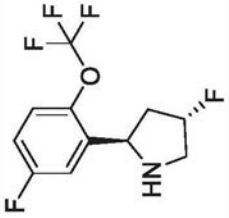
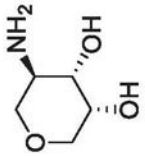
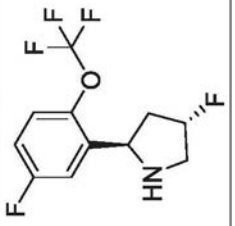
Cmpd	氨基醇	胺	实施例
226			27
227			1
228			1
229			23

Cmpd	氨基醇	胺	实施例
238			1
239			1
240			1
241			1

[0672]

Cmpd	氨基醇	胺	实施例
234			1
235			1
236			1
237			1

[0673]

Cmpd	氨基醇	胺	实施例
242			1
243			1
244			1

[0674] 对于本文公开的化合物所获得的NMR和LC MS数据示出在图1中。

[0675] 实施例29.测定

[0676] 1mM ATP处的NTRK1野生型测定

[0677] 在384孔板的每个孔中,在25℃下,在一系列剂量浓度的化合物(1%DMSO最终浓度)存在或不存在下,将1nM-1.5nM野生型NTRK1酶(BPS Bioscience;40280)在总共12.5μL缓冲液(100mM HEPES pH 7.5,0.015%Brij 35,10mM $MgCl_2$,1mM DTT)中与1-2μM CSKtide(Tuft's University or Anaspec;FITC-AHA-KKKKD DIYFFFG-NH2)和1mM ATP一起孵育60分钟。通过添加70μL终止缓冲液(100mM HEPES pH 7.5,0.015%Brij 35,35mM EDTA和0.2%涂布试剂3(Caliper Lifesciences))来终止反应。然后,将板在Caliper EZReader 2(方案设置:-1.7psi,上游电压-500,下游电压-3000,采样后sip 35s)上读取。数据归一化至0%和100%抑制对照并且IC_{50}使用CORE LIMS中的4-参数拟合计算。

[0678] NTRK野生型和G595R突变型细胞测定方案

[0679] 具有TPM3-NTRK1融合蛋白质的KM12野生型结肠癌细胞系从国家癌症学会(NCI)获得。此细胞系先前证明依赖于来自NTRK融合蛋白质的NTRK活性以便生长和存活。KM12 Cliff(G595R)细胞系通过用DNA甲基化剂诱变野生型KM12细胞系并且随后选择对于长期暴露于高浓度已知NTRK抑制剂(克唑替尼)有抗性的克隆来产生。将细胞首先在384孔板中以1000个细胞/孔涂覆于完全培养基(10%FBS和1%pen/strep)中并且在37℃下孵育过夜。然后,使用Bravo液体处置系统给予细胞不同浓度的测试样品。浓度范围为25uM直至9.5pM(4倍稀释,总共10个浓度)。每种化合物以每个板重复运行两次。DMSO和十字孢碱(25uM)作为

生长抑制的阴性和阳性对照包括于每个板上。在给药之后72h,测定板使用CellTiter-Glo(Promega)显影并且所得荧光在Envision板阅读器上读取。IC_{50}确定值使用4-参数曲线拟合算法来计算。

[0680] 下表总结如上所述生物测定的结果。以下表示法用于指示每个测定中的IC_{50}:A＜10.00nM;B＝10.01-100.0nM;C＝100.01-1000.0nM;和D＞1000.1nM;“ND”＝未确定。

[0681]

化合物编号	Enz NTRK1	KM12 (WT)	KM12 (G595R)
1	B	B	B
2	C	C	C
3	D	D	D
4	C	D	D
5	C	C	C
6	A	B	B
7	B	B	B
8	B	B	C
9	B	B	C
10	C	C	D
11	C	C	C
12	C	C	D
13	B	B	C
14	C	C	C
15	C	C	D
16	C	D	D
17	B	B	C
18	C	C	D
19	D	D	D
20	B	B	C
21	C	C	D
22	C	D	D
23	A	B	B
24	B	C	C
25	B	B	C
26	B	B	C
27	A	B	B
28	A	B	B
29	A	B	B
30	C	B	C
31	C	C	C
32	B	C	C
33	B	B	B
34	B	B	C
35	C	C	D
36	B	C	C
37	B	C	C
38	C	C	C
39	A	B	B
40	B	C	C
41	B	C	C
42	C	D	D
43	B	B	C

化合物编号	Enz NTRK1	KM12 (WT)	KM12 (G595R)
44	B	B	C
45	A	A	A
46	A	A	A
47	C	C	C
48	B	B	C
49	A	B	B
50	B	B	C
51	C	C	C
52	B	B	B
53	B	B	C
54	B	C	C
55	B	B	B
56	B	C	C
57	A	A	B
58	A	B	B
59	C	C	C
60	B	B	B
61	C	C	D
62	B	B	C
63	A	B	B
64	C	C	C
65	C	ND	ND
66	D	D	D
67	D	D	D
68	A	A	A
69	A	B	B
70	A	B	B
71	B	B	C
72	A	B	B
73	A	A	B
74	A	B	B
75	B	C	D
76	A	B	B
77	A	B	B
78	A	A	B
79	A	A	B
80	B	C	C
81	B	C	C
82	B	C	C
83	B	C	C
84	A	B	B
85	A	B	B
86	A	A	A

[0682]

化合物编号	Enz NTRK1	KM12 (WT)	KM12 (G595R)
87	A	B	B
88	A	A	A
89	A	B	A
90	D	D	D
91	B	B	C
92	A	A	A
93	A	A	A
94	C	C	D
95	A	A	A
96	B	B	C
97	A	B	C
98	C	D	D
99	A	A	A
100	B	B	C
101	C	C	C
102	A	B	B
103	D	D	D
104	A	A	A
105	A	B	B
106	A	A	A
107	A	B	B
108	B	C	C
109	A	B	C
110	A	B	B
111	A	B	B
112	B	B	C
113	A	B	B
114	A	A	A
115	A	B	B
116	A	A	A
117	C	C	D
118	A	A	A
119	A	A	A
120	B	B	B
121	A	A	A
122	A	A	A
123	A	B	B
124	A	ND	ND
125	A	ND	ND
126	A	A	A
127	A	A	A
128	A	A	A
129	A	B	B

化合物编号	Enz NTRK1	KM12 (WT)	KM12 (G595R)
130	A	A	A
131	C	C	C
132	B	B	C
133	C	C	C
134	C	C	C
135	A	A	A
136	A	B	B
137	B	B	B
138	C	C	C
139	B	B	B
140	A	B	A
141	A	B	A
142	B	B	C
143	B	B	B
144	B	B	C
145	C	B	C
146	A	B	B
147	B	C	C
148	A	A	A
149	A	B	B
150	B	B	B
151	B	B	B
152	A	B	A
153	B	B	B
154	A	B	B
155	B	B	B
156	B	B	A
157	A	B	B
158	A	B	B
159	A	B	B
160	A	B	B
161	B	B	B
162	A	B	B
163	A	B	B
164	B	B	B
165	A	A	A
166	A	C	C
167	A	A	A
168	A	A	A
169	B	B	B
170	A	A	A
171	B	B	B
172	A	B	B

[0683]

化合物编号	Enz NTRK1	KM12 (WT)	KM12 (G595R)
173	A	A	A
174	A	A	A
175	A	B	B
176	A	B	B
177	A	A	A
178	A	B	B
179	B	B	C
180	A	A	A
181	A	B	B
182	A	A	B
183	A	A	A
184	A	A	A
185	A	A	A
186	A	A	A
187	A	B	B
188	A	A	A
189	A	A	B
190	A	B	B
191	A	B	B
192	A	B	B
193	A	B	B
194	B	B	B
195	A	A	A
196	A	A	A
197	A	B	B
198	A	A	A
199	B	A	A
200	A	B	B
201	A	A	A
202	A	B	B
203	A	A	A
204	A	A	A
205	A	A	A
206	A	A	A
207	B	B	B
208	A	A	A
209	A	B	B
210	A	A	A
211	A	A	A
212	A	A	A
213	A	A	A
214	A	A	A
215	A	A	A

化合物编号	Enz NTRK1	KM12 (WT)	KM12 (G595R)
216	A	A	A
217	A	A	A
218	A	A	A
219	A	A	A
220	A	A	A
221	A	A	A
222	A	B	B
223	A	B	B
224	A	A	A
225	A	B	B
226	A	A	A
227	A	A	A
228	B	B	B
229	A	A	A
230	A	B	B
231	B	B	C
232	A	A	A
233	A	A	A
234	A	A	A
235	A	B	B
236	A	A	B
237	A	B	B
238	ND	B	B
239	A	A	B
240	A	A	A
241	A	A	A
242	A	A	A
243	A	A	A
244	A	A	A

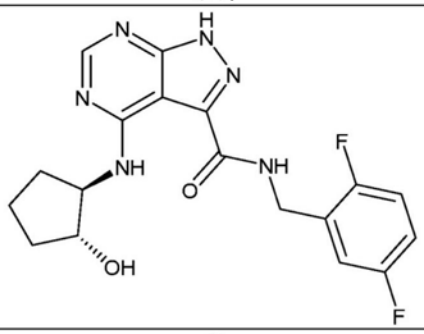
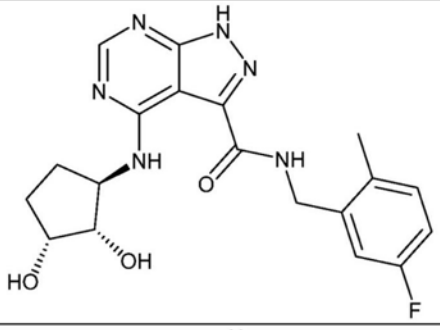
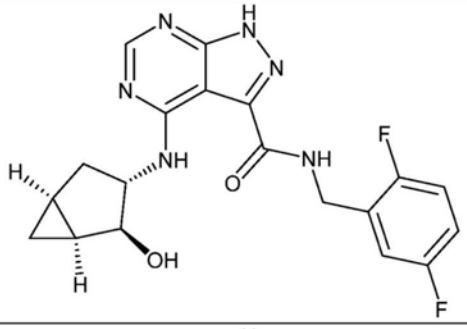
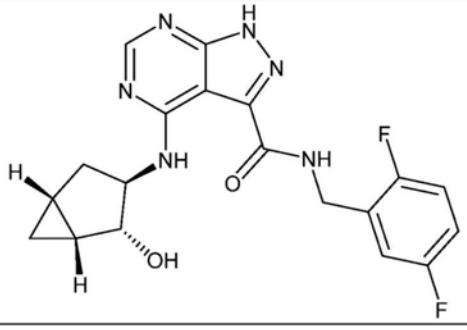
[0684] 以引用的方式并入

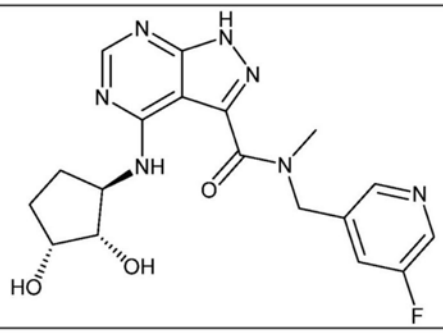
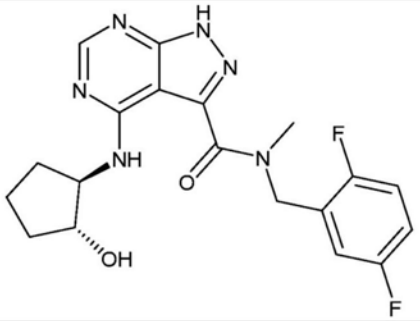
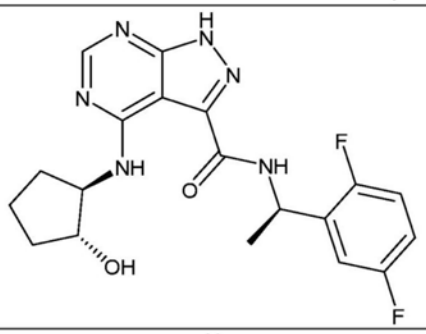
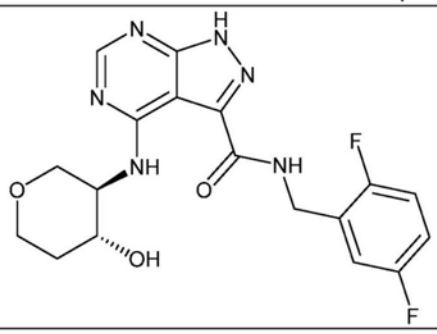
[0685] 本文提及的所有公布和专利均据此以全文引用的方式并入本文中,其引用程度就

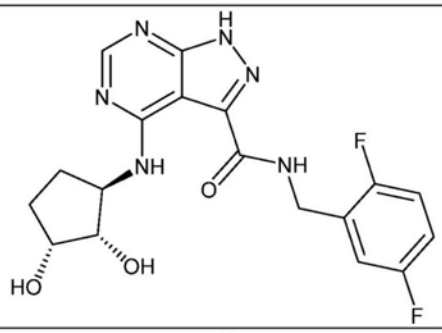
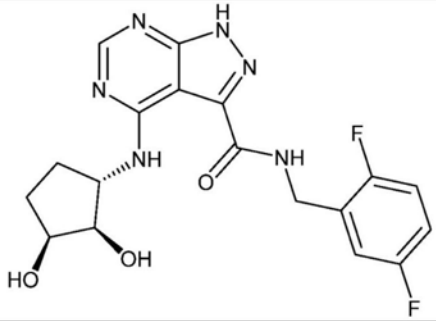
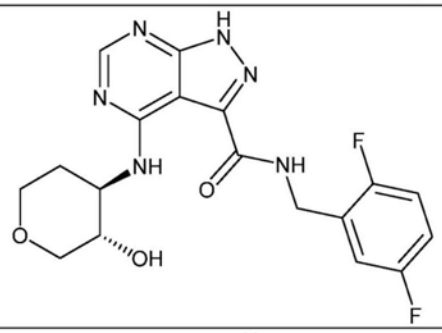
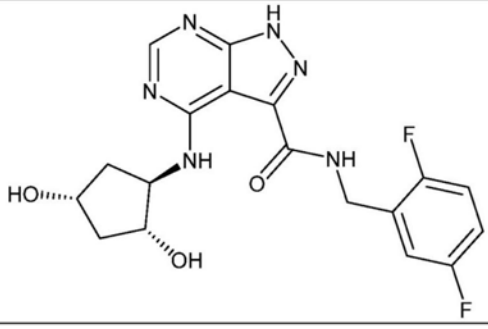
如同已明确并且个别地指示将各个别公布或专利以引用的方式并入本文中一般。

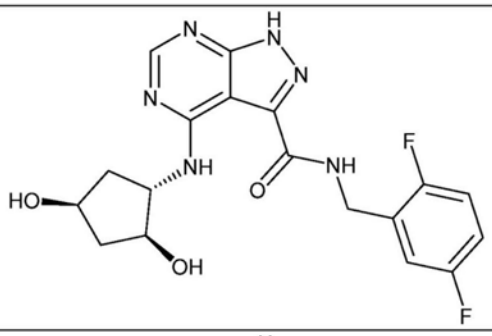
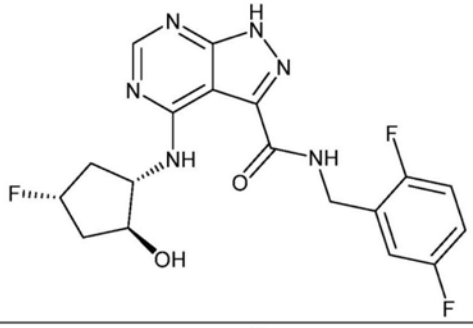
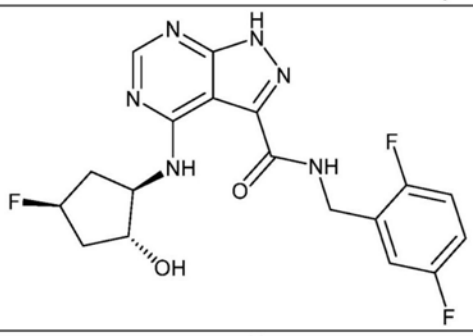
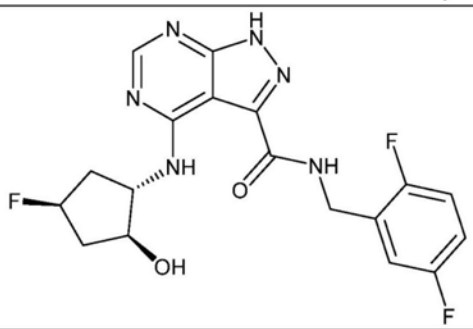
[0686] 等效物

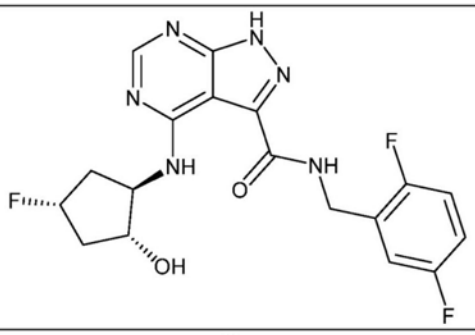
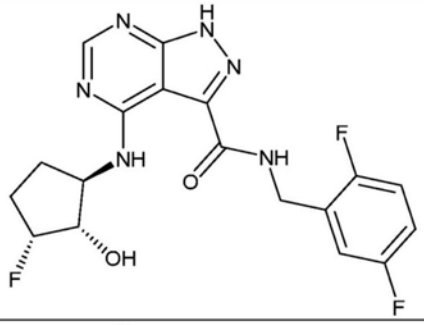
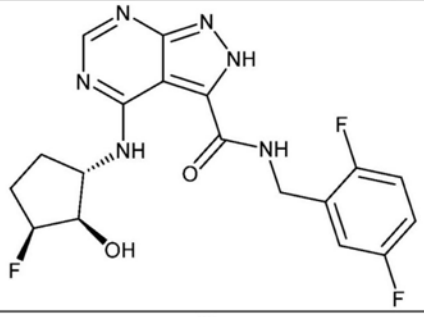
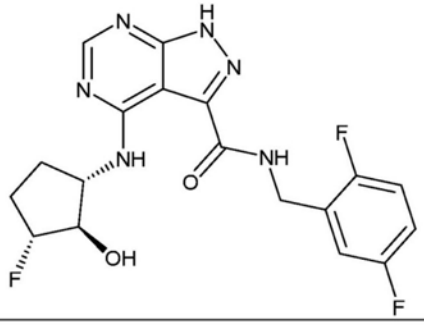
[0687] 本领域技术人员将仅使用不超过常规实验即会认识到或能够确定本文所述的本发明的特定实施方案的许多等效物。这些等效物旨在由以下权利要求书涵盖。

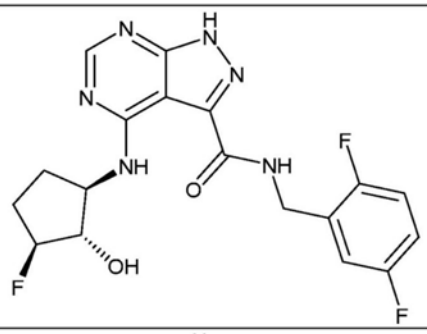
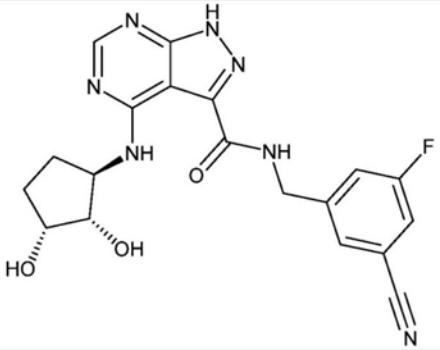
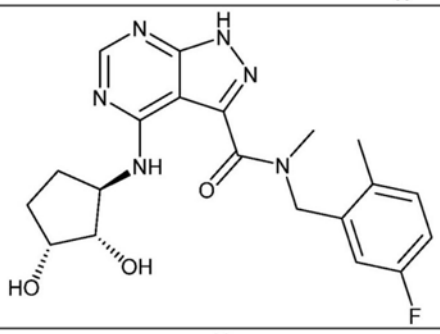
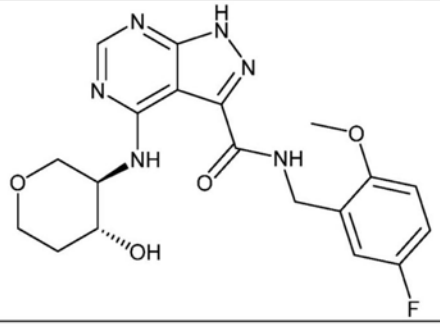
#	结构	NMR; LCMS
1		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.13-7.02 (m, 3H), 4.66 (s, 2H), 4.17 (d, 2H, J = 3.2 Hz), 2.32-2.29 (m, 1H), 2.11-2.08 (m, 1H), 1.91-1.87 (m, 2H), 1.86-1.74 (m, 2H).; LCMS: 389.1
2		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.319-7.15 (m, 1H), 7.02-7.01 (m, 1H), 6.99-6.88 (m, 1H), 4.61 (s, 2H), 4.38-4.31 (m, 1H), 4.13-4.11 (m, 1H), 4.03-4.02 (m, 1H), 2.44-2.41 (m, 1H), 2.34 (s, 3H), 2.16-2.13 (m, 1H), 1.79-1.70 (m, 2H).; LCMS: 401.1
3		1H-NMR (400 MHz, CD3OD) δ ppm 8.21 (s, 1H), 7.15-7.09 (m, 2H), 7.08-7.01 (m, 1H), 4.65 (s, 2H), 4.41-4.38 (m, 1H), 4.03-3.96 (m, 1H), 2.41-2.36 (m, 1H), 1.90-1.89 (m, 1H), 1.58-1.56 (m, 1H), 1.44-1.41 (m, 1H), 0.76-0.73 (m, 1H), 0.50-0.47 (m, 1H).; LCMS: 401.1
4		1H-NMR (400 MHz, CD3OD) δ ppm 8.12 (s, 1H), 7.06-6.99 (m, 2H), 6.93-6.92 (m, 1H), 4.56 (s, 2H), 4.32-4.29 (m, 1H), 3.93-3.87 (m, 1H), 2.32-2.25 (m, 1H), 1.81-1.80 (m, 1H), 1.49-1.47 (m, 1H), 1.35-1.33 (m, 1H), 0.67-0.64 (m, 1H), 0.41-0.40 (m, 1H).; LCMS: 401.1

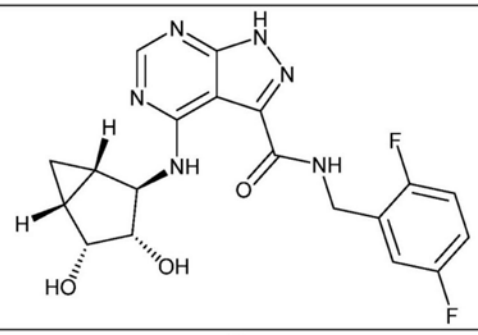
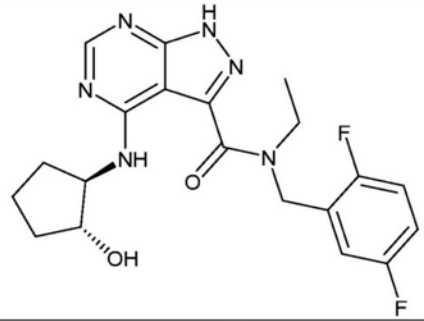
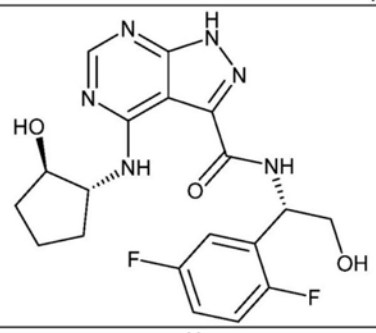
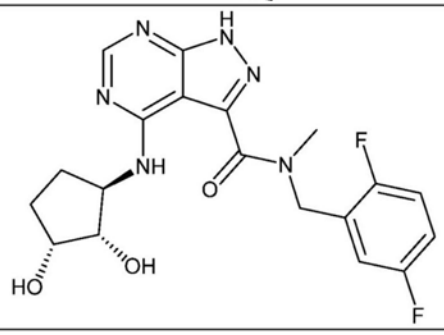
5		1H-NMR (400 MHz, CD3OD) δ ppm 8.51-8.47 (m, 2H), 8.38 (d, 1H, J = 2.0 Hz), 7.74 (d, 1H, J = 9.2 Hz), 5.50 (s, 1H), 4.94 (s, 1H), 4.39-4.34 (m, 1H), 4.15-4.13 (m, 1H), 4.07-4.01 (m, 1H), 3.70 (s, 1.5H), 3.20 (s, 1.5H), 2.47-2.44 (m, 1H), 2.19-2.16 (m, 1H), 1.84-1.71 (m, 2H).; LCMS: 402.1
6		1H-NMR (400 MHz, CD3OD) δ ppm 8.40 (d, 1H, J = 4.0 Hz), 7.22-7.07 (m, 3H), 5.51 (s, 1H), 4.26-4.17 (m, 2H), 3.70 (s, 1.5H), 3.21 (s, 1.5H), 2.38-2.36 (m, 1H), 2.17-2.06 (m, 1H), 1.96-1.76 (m, 4H).; LCMS: 403.1
7		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.22-7.21 (m, 1H), 7.13-7.11 (m, 1H), 7.04-7.02 (m, 1H), 5.56-5.51 (m, 1H), 4.16-4.13 (m, 2H), 2.32-2.29 (m, 1H), 2.09-2.08 (m, 1H), 1.90-1.70 (m, 4H), 1.59 (d, 3H, J = 7.2 Hz).; LCMS: 403.1
8		1H-NMR (400 MHz, CD3OD) δ ppm 8.32 (s, 1H), 7.15-7.09 (m, 2H), 7.05-7.03 (m, 1H), 4.67 (s, 2H), 4.15-4.11 (m, 1H), 4.05-4.04 (m, 1H), 3.98-3.95 (m, 1H), 3.85-3.84 (m, 1H), 3.56 (t, 1H, J = 10.8 Hz), 3.43 (t, 1H, J = 10.8 Hz), 2.10-2.07 (m, 1H), 1.76-1.68 (m, 1H).; LCMS: 405.0

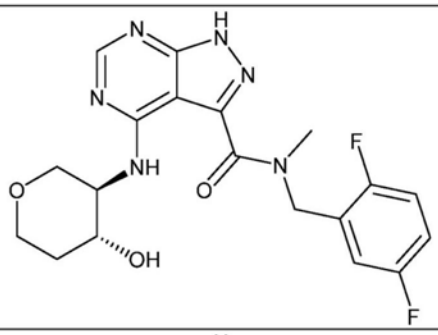
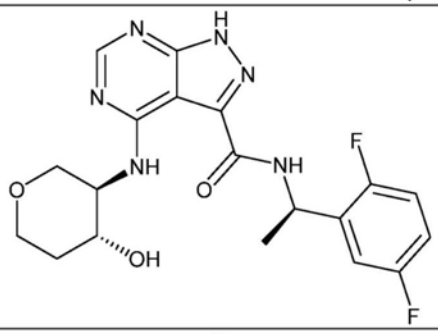
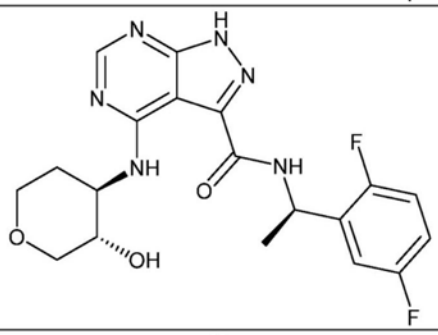
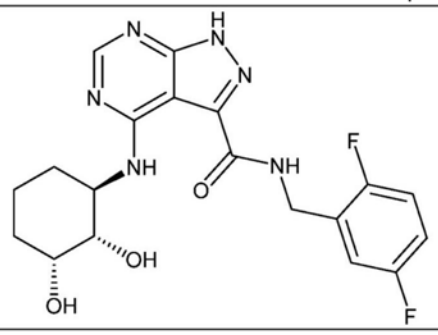
9		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (s, 1H), 7.16-7.03 (m, 3H), 4.68 (s, 2H), 4.37 (q, 1H, J = 8.4 Hz), 4.12 (d, 1H, J = 4.4 Hz), 4.02 (dd, 1H, J = 8.4, 4.4 Hz), 2.45-2.42 (m, 1H), 2.17-2.14 (m, 1H), 1.82-1.71 (m, 2H).; LCMS: 405.1
10		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (s, 1H), 7.16-7.03 (m, 3H), 4.68 (s, 2H), 4.40-4.36 (m, 1H), 4.12 (d, 1H, J = 4.0 Hz), 4.02 (dd, 1H, J = 8.4, 4.4 Hz), 2.45-2.42 (m, 1H), 2.17-2.13 (m, 1H), 1.81-1.70 (m, 2H).; LCMS: 405.1
11		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.16-7.10 (m, 2H), 704-7.03 (m, 1H), 4.68 (s, 2H), 4.07-4.01 (m, 1H), 4.00-3.97 (m, 2H), 3.67-3.65 (m, 1H), 3.52-3.51 (m, 1H), 3.27-3.24 (m, 1H), 2.19-2.15 (m, 1H), 1.83-1.79 (m, 1H).; LCMS: 405.1
12		1H-NMR (400 MHz, CD3OD) δ ppm 8.17 (s, 1H), 7.05-7.00 (m, 2H), 6.93-6.92 (m, 1H), 4.60-4.56 (m, 2H), 4.42-4.38 (m, 1H), 4.28-4.26 (m, 1H), 4.03-3.97 (m, 1H), 2.41-2.36 (m, 1H), 2.17-2.14 (m, 1H), 1.90-1.85 (m, 1H), 1.60-1.57 (m, 1H).; LCMS: 405.1

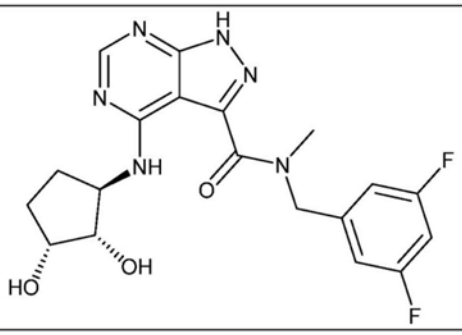
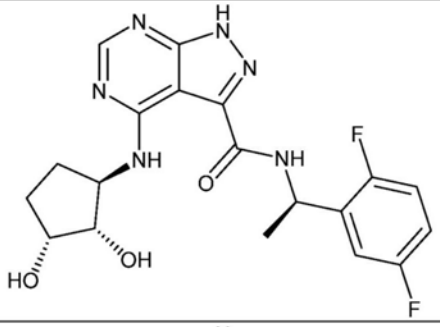
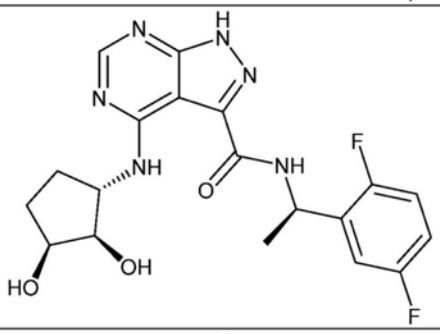
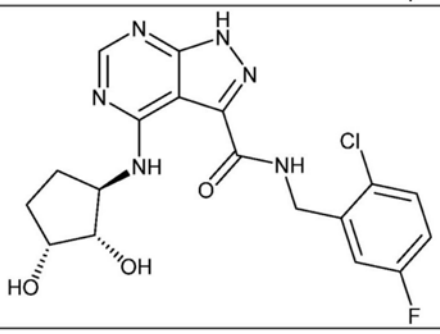
13		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.15-7.09 (m, 2H), 7.03-7.02 (m, 1H), 4.65 (s, 2H), 4.53-4.49 (m, 1H), 4.39-4.35 (m, 1H), 4.12-4.07 (m, 1H), 2.50-2.45 (m, 1H), 2.26-2.25 (m, 1H), 1.99-1.92 (m, 1H), 1.70-1.66 (m, 1H).; LCMS: 405.1
14		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.16-7.09 (m, 2H), 7.02-7.01(m, 1H), 5.27-5.13 (m, 1H), 4.65 (s, 2H), 4.38-4.33 (m, 2H), 2.79-2.70 (m, 1H), 2.37-2.35 (m, 1H), 1.99-1.88 (m, 2H).; LCMS: 407.1
15		1H-NMR (400 MHz, CDCl3) δ ppm 9.76 (s, 1H), 8.35 (s, 1H), 7.57 (t, 1H, J = 5.6 Hz), 7.05-6.90 (m, 3H), 5.16 (d, 1H, J = 52.4 Hz), 4.68-4.62 (m, 2H), 4.39-4.34 (m, 1H), 4.15-4.12 (m, 1H), 2.78-2.70 (m, 1H), 2.48-2.40 (m, 1H), 2.18-2.08 (m, 1H), 1.93-1.81 (m, 1H).; LCMS: 407.1
16		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.12-7.07 (m, 2H), 7.02-7.00 (m, 1H), 5.15 (d, 1H, J = 53.6 Hz), 4.64 (s, 2H), 4.58-4.52 (m, 1H), 4.17 (dd, 1H, J = 12.8, 6.4 Hz), 2.59-2.51 (m, 2H), 1.99-1.87 (m, 2H).; LCMS: 407.1

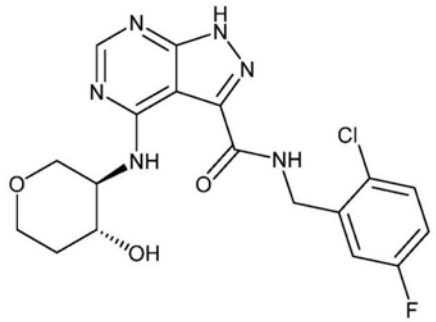
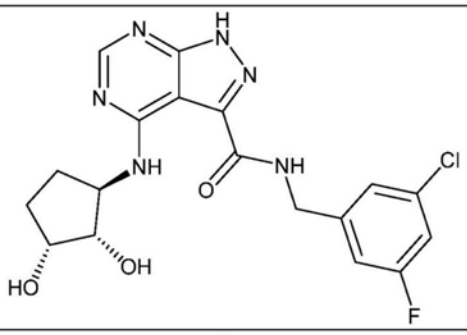
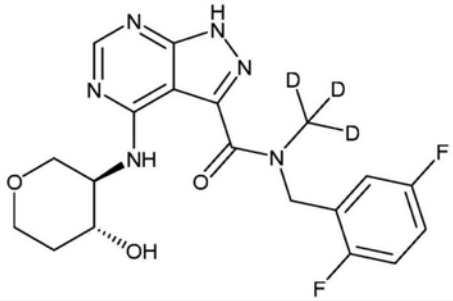
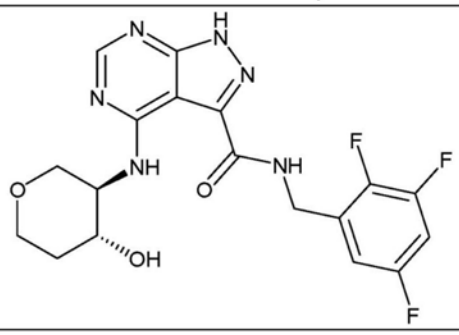
17		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.14-7.08 (m, 2H), 7.02-7.00 (m, 1H), 5.13 (d, 1H, J = 53.2 Hz), 4.64 (s, 2H), 4.57-4.52 (m, 1H), 4.19-4.16 (m, 1H), 2.59-2.51 (m, 2H), 1.99-1.90 (m, 2H).; LCMS: 407.1
18		1H-NMR (400 MHz, CD3OD) δ ppm 8.14 (s, 1H), 7.04-6.97 (m, 2H), 6.91-6.90 (m, 1H), 4.89-4.88 (m, 1H), 4.55 (s, 2H), 4.53-4.46 (m, 1H), 3.98-3.89 (m, 1H), 2.38-2.3 (m, 1H), 2.18-2.00 (m, 1H), 1.90-1.83 (m, 1H), 1.56-1.52 (m, 1H).; LCMS: 407.1
19		1H-NMR (400 MHz, CD3OD) δ ppm 8.13 (s, 1H), 7.05-6.98 (m, 2H), 6.91-6.90 (m, 1H), 4.89-4.87 (m, 1H), 4.55 (s, 2H), 4.50-4.46 (m, 1H), 3.98-3.89 (m, 1H), 2.37-2.32 (m, 1H), 2.19-2.00 (m, 1H), 1.90-1.83 (m, 1H), 1.56-1.51 (m, 1H).; LCMS: 407.1
20		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.15-7.01 (m, 3H), 4.94-4.92 (m, 1H), 4.66 (s, 2H), 4.32-4.28 (m, 1H), 4.17-4.10 (m, 1H), 2.34-1.88 (m, 4H).; LCMS: 407.2

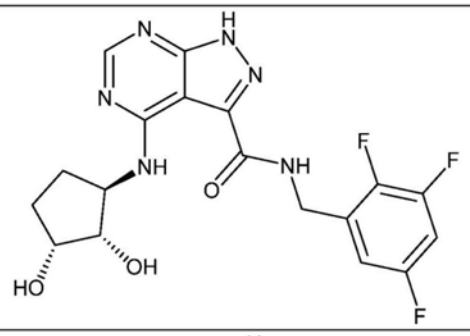
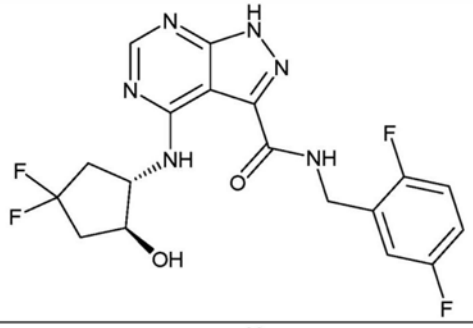
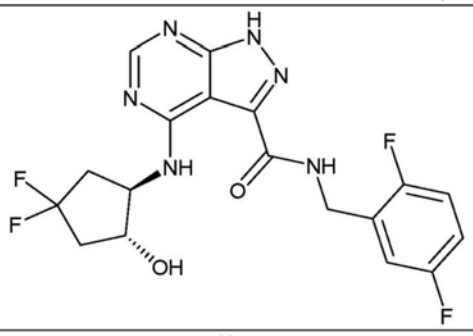
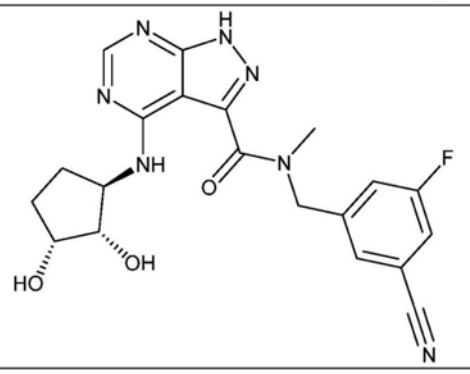
21		1H-NMR (400 MHz, CD3OD) δ ppm 8.17 (s, 1H), 7.05-6.92 (m, 3H), 4.86-4.83 (m, 1H), 4.56 (s, 2H), 4.23-4.21 (m, 1H), 4.08-4.02 (m, 1H), 2.24-1.78 (m, 4H).; LCMS: 407.2
22		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (s, 1H), 7.58 (s, 1H), 7.47 (s, 2H), 4.67 (s, 2H), 4.39-4.37 (m, 1H), 4.13 (s, 1H), 4.02 (s, 1H), 2.44 (br.s, 1H), 2.16-2.15 (m, 1H), 1.79-1.69 (m, 2H).; LCMS: 412.1
23		1H-NMR (400 MHz, CD3OD) δ ppm 8.37, 8.34 (s, 1H), 7.25-7.18 (m, 1H), 6.93-6.82 (m, 2H), 5.40 (s, 1H), 4.42-4.35 (m, 1H), 4.16-3.99 (m, 2H), 3.61 (s, 1.5H), 3.22 (s, 1.5H), 2.47-2.43 (m, 1H), 2.31 (s, 1.5H), 2.28 (s, 1.5H), 2.18-2.12 (m, 1H), 1.83-1.75 (m, 2H).; LCMS: 415.1
24		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.07 (s, 1H), 9.45 (d, J = 7.7 Hz, 1H), 9.26 (t, J = 6.4 Hz, 1H), 8.27 (s, 1H), 7.11 – 6.81 (m, 3H), 6.51 (s, 0H), 5.10 (d, J = 4.8 Hz, 1H), 4.47 (d, J = 6.3 Hz, 2H), 4.04 (dd, J = 7.8, 4.0 Hz, 1H), 3.96 (dd, J = 11.2, 3.9 Hz, 1H), 3.82 (s, 3H), 3.81 – 3.71 (m, 1H), 3.65 (s, 1H), 3.43 (t, J = 9.3 Hz, 1H), 3.18 (dd, J = 11.2, 7.6 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.53 – 1.43 (m, 1H); LCMS: 417

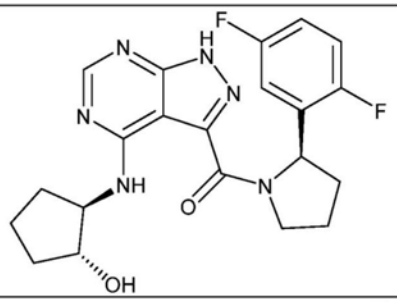
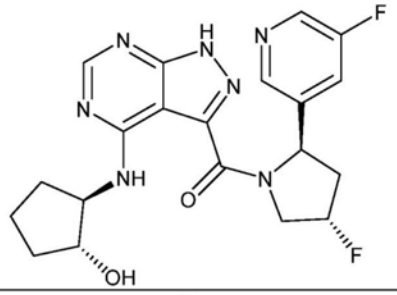
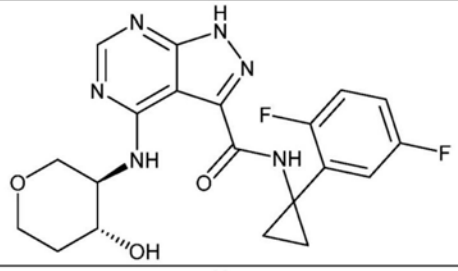
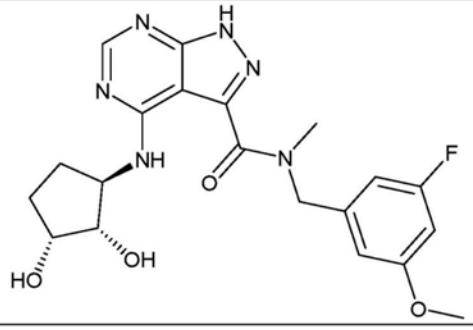
25		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.09 (s, 1H), 9.48 – 9.31 (m, 2H), 8.30 (s, 1H), 7.25 (td, *J* = 9.4, 4.5 Hz, 1H), 7.15 (td, *J* = 7.5, 6.7, 4.1 Hz, 2H), 4.81 (d, *J* = 4.1 Hz, 1H), 4.55 (d, *J* = 6.2 Hz, 2H), 4.40 (d, *J* = 7.1 Hz, 1H), 4.35 (d, *J* = 7.7 Hz, 2H), 3.64 (t, *J* = 5.1 Hz, 1H), 1.56 (dq, *J* = 8.7, 4.2 Hz, 1H), 1.32 (p, *J* = 4.6 Hz, 1H), 1.07 (q, *J* = 4.1 Hz, 1H), 0.43 (td, *J* = 8.3, 4.6 Hz, 1H); LCMS: 417
26		1H-NMR (400 MHz, CD3OD) δ ppm 8.37-8.36 (m, 1H), 7.17-7.07 (m, 3H), 4.81 (s, 2H), 4.16-4.13 (m, 2H), 3.66-3.60 (m, 2H), 2.40-2.27 (m, 1H), 2.20-2.03 (m, 1H), 1.91-1.72 (m, 4H), 1.40-1.24 (m, 3H).; LCMS: 417.1
27		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.06 (s, 1H), 9.24 (d, *J* = 7.2 Hz, 1H), 9.11 (d, *J* = 8.6 Hz, 1H), 8.20 (s, 1H), 7.35 (ddd, *J* = 9.1, 5.7, 3.2 Hz, 1H), 7.20 (td, *J* = 9.3, 4.6 Hz, 1H), 7.10 (ddt, *J* = 9.0, 7.3, 3.6 Hz, 1H), 5.44 – 5.32 (m, 1H), 5.11 (t, *J* = 5.9 Hz, 1H), 5.02 – 4.91 (m, 1H), 4.16 (p, *J* = 6.6 Hz, 1H), 3.86 (ddt, *J* = 9.1, 6.2, 3.6 Hz, 1H), 3.77 – 3.60 (m, 2H), 2.15 – 2.02 (m, 1H), 1.78 (m, 1H), 1.64 (m, 2H), 1.42 (m, 2H); LCMS: 419
28		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.08 (br s, 1H), 9.30 (m, 1H), 8.28 (s, 1H), 7.31 (m, 1H), 7.20 (m, 2H), 5.36 (d, *J* = 2.4 Hz, 1H), 4.90 – 4.76 (m, 1H), 4.40 (q, *J* = 7.5 Hz, 1H), 3.94 (dtd, *J* = 11.7, 5.6, 5.1, 3.4 Hz, 1H), 3.72 (ddd, *J* = 22.6, 7.5, 4.5 Hz, 2H), 3.60 (br s, 1H), 3.07 (s, 3H), 2.32 – 2.19 (m, 1H), 1.94 (m, 1H), 1.58 (m, 1H), 1.41 – 1.26 (m, 1H); LCMS: 419

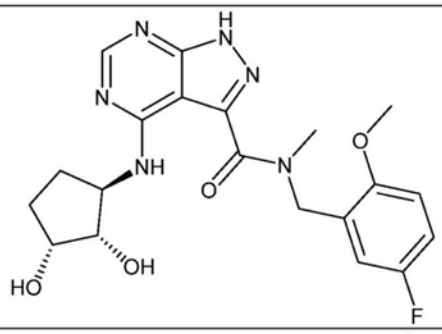
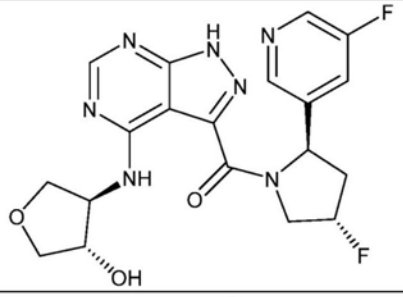
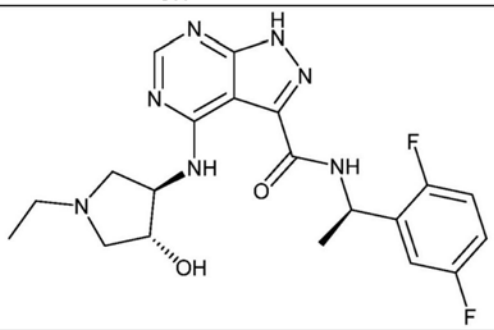
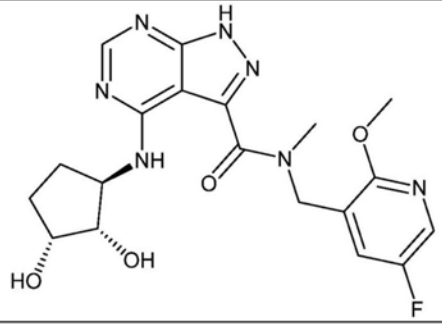
29		1H-NMR (400 MHz, CDCl3) δ ppm 10.62-10.49 (m, 1H), 8.39 (d, 1H, J = 5.6 Hz), 7.10-6.97 (m, 3H), 5.47-5.34 (m, 1H), 4.83 (s, 1H), 4.26-4.16 (m, 2H), 4.02-3.89 (m, 2H), 3.60-3.45 (m, 3.5H), 3.13 (s,1.5H), 2.17-2.13 (m, 1H), 1.81 (br.s, 1H).; LCMS: 419.1
30		1H-NMR (400 MHz, CDCl3) δ ppm 13.68 (br.s, 1H), 9.40 (d, 1H, J = 6.8 Hz), 8.33 (s, 1H), 7.61 (d, 1H, J = 9.2 Hz), 7.03-6.88 (m, 3H), 5.40 (t, 1H, J = 7.6 Hz), 4.13-4.09 (m, 2H), 3.95-3.92 (m, 1H), 3.78-3.76 (m, 1H), 3.42-3.34 (m, 2H), 2.04 (dd, 1H, J = 10.8, 2.0 Hz), 1.73-1.70 (m, 1H), 1.57 (d, 3H, J = 7.2 Hz).; LCMS: 419.1
31		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.23-7.21 (m, 1H), 7.13-7.10 (m, 1H), 7.04-7.01 (m, 1H), 5.58-5.52 (m, 1H), 4.03-3.94 (m, 3H), 3.62-3.61 (m, 1H), 3.52-3.49 (m, 1H), 3.27-3.22 (m, 1H), 2.17-2.13 (m, 1H), 1.86-1.80 (m, 1H), 1.60 (d, 3H, J = 7.2 Hz).; LCMS: 419.1
32		1H-NMR (400 MHz, CD3OD) δ ppm 8.21 (s, 1H), 7.14-7.10 (m, 2H), 7.03-7.01 (m, 1H), 4.66 (s, 2H), 4.51-4.45 (m, 1H), 4.00 (s, 1H), 3.70-3.63 (m, 1H), 2.09-2.07 (m, 1H), 1.85-1.78 (m, 2H), 1.61-1.56 (m, 2H), 1.45-1.36 (m, 1H).; LCMS: 419.1

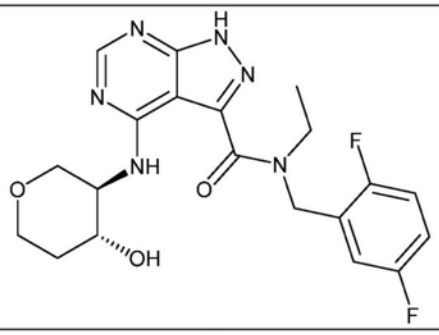
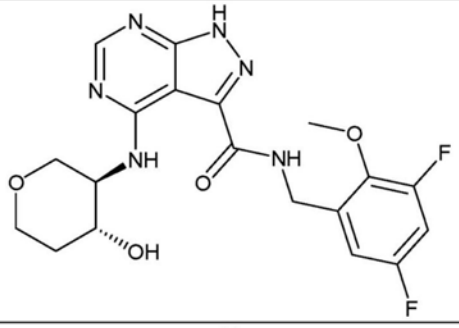
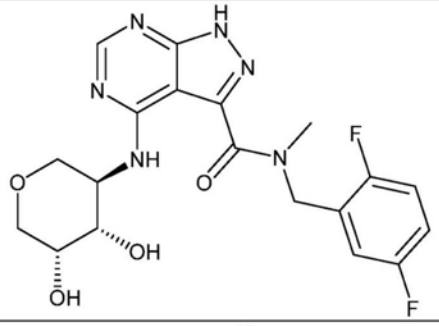
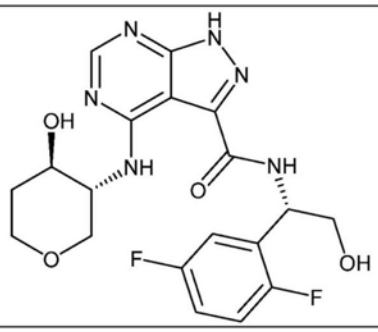
33		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 5.6 Hz), 6.99-6.96 (m, 2H), 6.92-6.88 (m, 1H), 5.43 (s, 1H), 4.90 (s, 1H), 4.43-4.37 (m, 1H), 4.15-4.13 (m, 1H), 4.05-4.01 (m, 1H), 3.64 (s, 1.5H), 3.16 (s, 1.5H), 2.46-2.43 (m, 1H), 2.19-2.15 (m, 1H), 1.82-1.65 (m, 2H).; LCMS: 419.1
34		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.21 (br.s, 1H), 7.11-7.09 (m, 1H), 7.01 (br.s, 1H), 5.54 (d, 1H, J = 7.2 Hz), 4.39-4.32 (m, 1H), 4.10 (br.s, 1H), 3.99-3.96 (m, 1H), 2.43-2.40 (m, 1H), 2.14-2.12 (m, 1H), 1.78-1.74 (m, 1H), 1.69 (br.s, 1H), 1.59 (d, 3H, J = 6.8 Hz).; LCMS: 419.2
35		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.21 (br.s, 1H), 7.13-7.09 (m, 1H), 7.03-7.01 (m, 1H), 5.55-5.51 (m, 1H), 4.37-4.31 (m, 1H), 4.11 (s, 1H), 4.02-3.99 (m, 1H), 2.42-2.38 (m, 1H), 2.15-2.11 (m, 1H), 1.78-1.76 (m, 1H), 1.67-1.64 (m, 1H), 1.59 (d, 3H, J = 6.8 Hz).; LCMS: 419.2
36		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.10 (s, 1H), 9.49 (m, 1H), 9.37 (d, J = 7.3 Hz, 1H), 8.27 (s, 1H), 7.53 (dd, J = 8.8, 5.1 Hz, 1H), 7.18 (td, J = 8.4, 2.9 Hz, 1H), 7.12 (dd, J = 9.4, 3.5 Hz, 1H), 5.68 (d, J = 7.4 Hz, 1H), 4.87 (m, 1H), 4.56 (m, 1H), 4.48 (m, 1H), 4.39 (p, J = 7.6 Hz, 2H), 3.90 (m, 1H), 3.70 (m, 1H), 2.22 (m, 1H), 1.91 (m, 1H), 1.60 – 1.47 (m, 1H), 1.31 (m, 1H); LCMS: 421

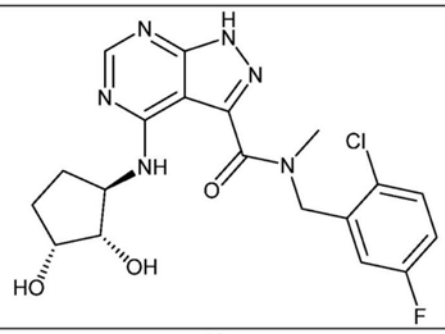
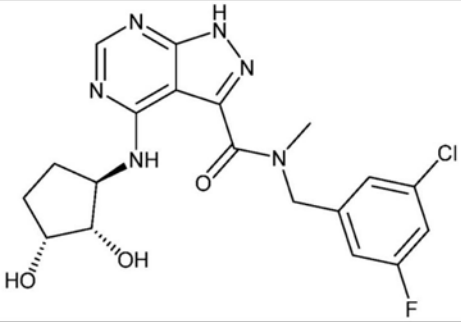
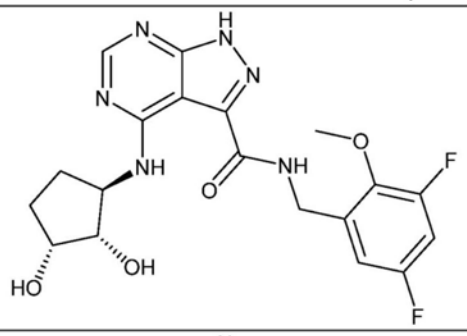
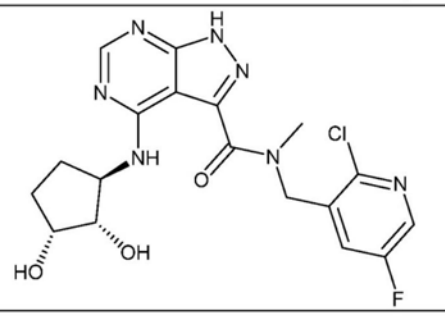
37		^{1}H NMR (400 MHz, DMSO-d_6) δ 13.80 (s, 1H), 9.43 (t, J = 6.2 Hz, 1H), 9.31 (d, J = 7.8 Hz, 1H), 8.22 (s, 1H), 7.47 (dd, J = 8.8, 5.1 Hz, 1H), 7.13 (td, J = 8.4, 3.1 Hz, 1H), 7.06 (dd, J = 9.6, 3.1 Hz, 1H), 5.06 (d, J = 4.8 Hz, 1H), 4.51 (d, J = 6.2 Hz, 2H), 3.99 (qd, J = 7.7, 3.8 Hz, 1H), 3.91 (dd, J = 11.1, 4.0 Hz, 1H), 3.72 (dt, J = 11.3, 4.6 Hz, 1H), 3.59 (tt, J = 8.5, 4.5 Hz, 1H), 3.38 (ddd, J = 11.7, 9.0, 3.1 Hz, 1H), 3.12 (dd, J = 11.1, 7.7 Hz, 1H), 1.84 (ddt, J = 9.2, 7.6, 3.6 Hz, 1H), 1.43 (dtd, J = 13.0, 8.7, 4.0 Hz, 1H); LCMS: 421
38		1H-NMR (400 MHz, CD3OD) δ ppm 8.24 (s, 1H), 7.23 (s, 1H), 7.08 (d, 2H, J = 8.8 Hz), 4.60 (s, 2H), 4.51-4.46 (m, 1H), 4.13 (br.s, 1H), 3.94-3.90 (m, 1H), 2.46-2.40 (m, 1H), 2.11-2.06 (m, 1H), 1.78-1.74 (m, 1H), 1.62-1.58 (m, 1H).; LCMS: 421.2
39		^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (d, J = 145.0 Hz, 1H), 8.08 (d, J = 31.1 Hz, 1H), 7.37 – 7.02 (m, 3H), 5.58 (s, 1H), 5.18 (s, 1H), 4.78 (s, 1H), 4.08 – 3.90 (m, 2H), 3.78 (s, 1H), 3.63 (s, 1H), 3.43 (d, J = 11.5 Hz, 1H), 3.17 (dd, J = 11.2, 7.4 Hz, 1H), 1.92 (s, 2H), 1.48 (s, 1H); LCMS: 422
40		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.19 (s, 1H), 9.51 (t, J = 6.3 Hz, 2H), 7.57 – 7.35 (m, 1H), 7.11 – 6.94 (m, 1H), 4.60 (d, J = 6.1 Hz, 2H), 4.04 (dt, J = 11.7, 5.8 Hz, 1H), 3.97 (dd, J = 11.1, 4.0 Hz, 1H), 3.78 (dd, J = 11.3, 5.1 Hz, 1H), 3.60 (tt, J = 6.6, 3.4 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.19 (dd, J = 11.1, 7.7 Hz, 1H), 3.12 (qd, J = 7.3, 4.2 Hz, 2H), 1.91 (d, J = 13.1 Hz, 1H), 1.50 (dq, J = 8.7, 4.6 Hz, 1H); LCMS: 423

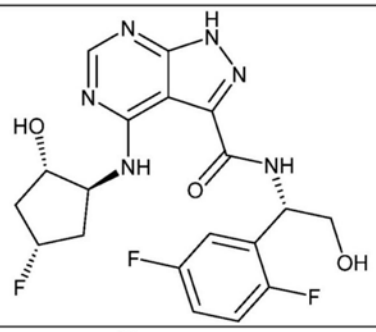
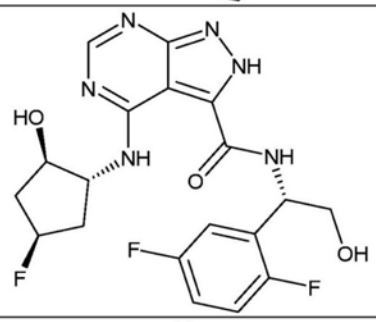
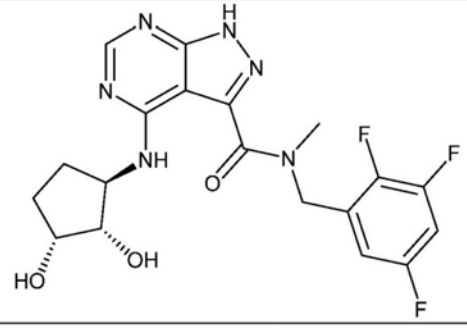
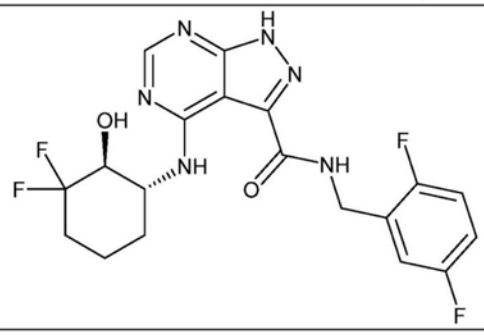
41		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.09-6.98 (m, 2H), 4.71 (s, 2H), 4.41-4.34 (m, 1H), 4.13 (br.s, 1H), 4.04-4.02 (m, 1H), 2.45-2.43 (m, 1H), 2.17-2.13 (m, 1H), 1.82-1.69 (m, 2H).; LCMS: 423.1
42		1H-NMR (400 MHz, CD3OD) δ ppm 8.33 (s, 1H), 7.14-6.99 (m, 3H), 4.65 (s, 2H), 4.49-4.43 (m, 1H), 4.35-4.32 (m, 1H), 2.85-2.80 (m, 1H), 2.67-2.58 (m, 1H), 2.26-2.16 (m, 2H).; LCMS: 425.1
43		1H-NMR (400 MHz, CD3OD) δ ppm 8.28 (s, 1H), 7.13-6.99 (m, 3H), 4.65 (s, 2H), 4.52-4.46 (m, 1H), 4.33-4.28 (m, 1H), 2.87-2.79 (m, 1H), 2.64-2.59 (m, 1H), 2.22-2.14 (m, 2H).; LCMS: 425.1
44		1H-NMR (400 MHz, CD3OD) δ ppm 8.33 (d, 1H, J = 6.0 Hz), 7.60 (d, 1H, J = 9.2 Hz), 7.52-7.49 (m, 2H), 5.43 (d, 1H, J = 3.6 Hz), 4.90 (d, 1H, J = 3.2 Hz), 4.43-4.38 (m, 1H), 4.13 (br.s, 1H), 4.03-3.96 (m, 1H), 3.65 (s, 1.5H), 3.17 (s, 1.5H), 2.48-2.44 (m, 1H), 2.17-2.13 (m, 1H), 1.83-1.66 (m, 2H).; LCMS: 426.1

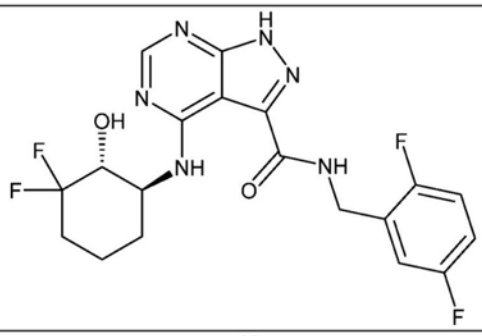
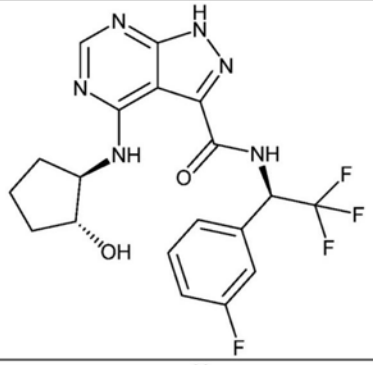
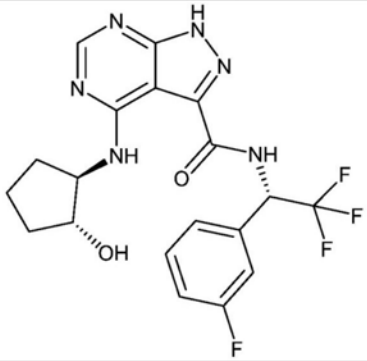
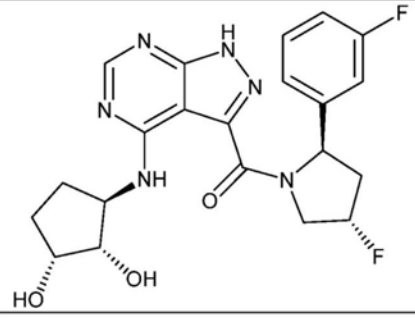
45		1H-NMR (400 MHz, CDCl3) δ ppm 11.58-11.21 (m, 1H), 8.47 (br.s, 0.5H), 6.98-6.55 (m, 3.5H), 6.33 (d, 0.5H, J = 8.0 Hz), 5.51-5.49 (m, 0.5H), 4.38-3.83 (m, 4H), 2.37-2.32 (m, 2H), 2.05-1.64 (m, 8H).; LCMS: 429.1
46		1H-NMR (400 MHz, CD3OD) δ ppm 8.50 (br.s, 1H), 8.40 (br.s, 1H), 8.38 (s, 1H), 7.72 (d, 1H, J = 9.2 Hz), 5.54-5.41 (m, 2H), 4.97-4.92 (m, 1H), 4.59-4.45 ((m, 1H), 4.09-4.04 (m, 2H), 2.91-2.84 (m, 1H), 2.29-2.26 (m, 2H), 1.79-1.66 (m, 5H).; LCMS: 430.1
47		1H-NMR (400 MHz, CD3OD) δ ppm 9.57 (s, 1H), 8.34 (s, 1H), 7.38-7.37 (m, 1H), 7.06-6.96 (m, 2H), 4.13-4.09 (m, 1H), 4.00-3.96 (m, 2H), 3.87-3.76 (m, 1H), 3.58-3.47(m, 1H), 3.45-3.44 (m, 1H), 2.11-2.07 (m, 1H), 1.75-1.66 (m, 1H), 1.37 (s, 4H).; LCMS: 431.1
48		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 4.8 Hz), 6.73 (d, 1H, J = 12.0 Hz), 6.69-6.63 (m, 2H), 5.40 (s, 1H), 4.82 (s, 1H), 4.39-4.36 (m, 1H), 4.15-4.12 (m, 1H), 4.06-4.02 (m, 1H), 3.78 (d, 3H, J = 6.4 Hz), 3.62 (s, 1.5H), 3.14 (s, 1.5H), 2.47-2.44 (m, 1H), 2.18-2.15 (m, 1H), 1.82-1.70 (m, 2H).; LCMS: 431.1

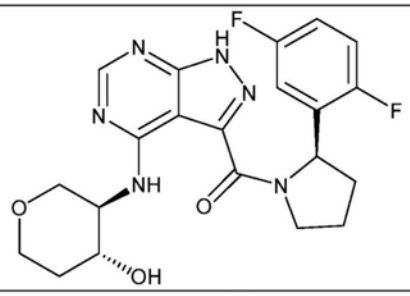
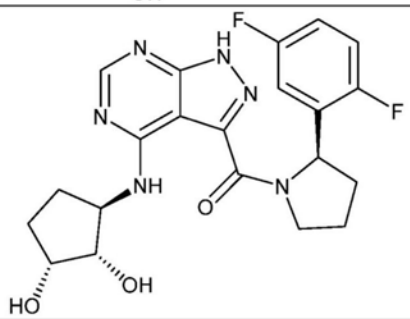
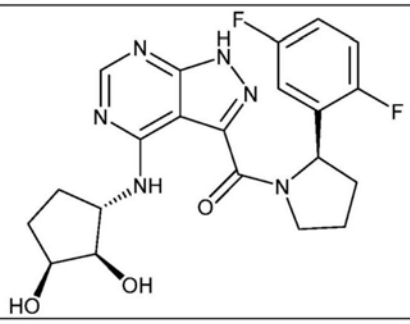
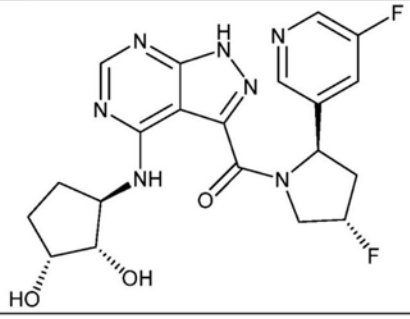
49		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (d, 1H, J = 3.6 Hz), 7.01-6.93 (m, 1H), 5.44-5.33 (m, 1H), 4.83 (s, 1H), 4.40-4.35 (m, 1H), 4.14-4.12 (m, 1H), 4.05-4.01 (m, 1H), 3.86 (s, 1.5H), 3.75 (s, 1.5H), 3.63 (s, 1.5H), 3.12 (s, 1.5H), 2.46-2.43 (m, 1H), 2.17-2.15 (m, 1H), 1.82-1.63 (m, 2H).; LCMS: 431.1
50		1H-NMR (400 MHz, CD3OD) δ ppm 8.60 (br.s, 1H), 8.50 (br.s, 1H), 8.43 (s, 1H), 7.89 (d, 1H, J = 9.2 Hz), 5.57-5.35 (m, 2H), 4.58-4.38 (m, 3H), 4.25-4.13 (m, 2H), 4.00-3.93 (m, 1H), 3.84-3.71 (m, 2H), 2.90-2.82 (m, 1H), 2.34-2.21 (m, 1H).; LCMS: 432.1
51		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (s, 1H), 7.22-7.19 (m, 1H), 7.12-7.11 (m, 1H), 7.02-7.01 (m, 1H), 5.52-5.50 (m, 1H), 5.04-5.02 (m, 1H), 4.78-4.76 (m, 2H), 4.30-3.89 (m, 1H), 3.80-3.75 (m, 2H), 3.36-3.34 (m, 2H), 1.59 (d, 3H, J = 6.8 Hz), 1.50-1.34 (m, 3H).; LCMS: 432.2
52		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (d, 1H, J = 6.0 Hz), 7.94 (dd, 1H, J = 9.2, 2.4 Hz), 7.47-7.41 (m, 1H), 5.31 (s, 1H), 4.78 (s, 1H), 4.41-4.35 (m, 1H), 4.14-4.11 (m, 1H), 4.04-4.02 (m, 1H), 3.97 (s, 1.5H), 3.89 (s, 1.5H), 3.70 (s, 1.5H), 3.17 (s, 1.5H), 2.47-2.40 (m, 1H), 2.18-2.14 (m, 1H), 1.81-1.64 (m, 2H).; LCMS: 432.2

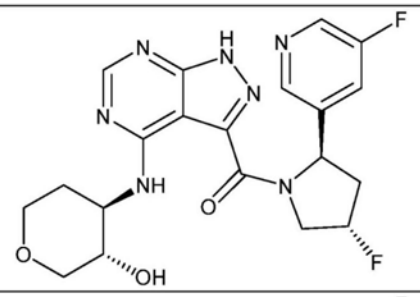
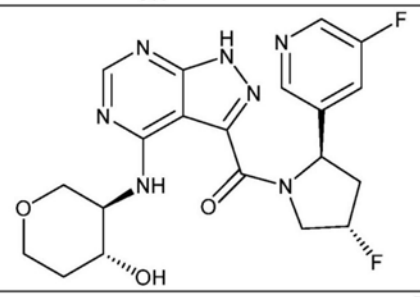
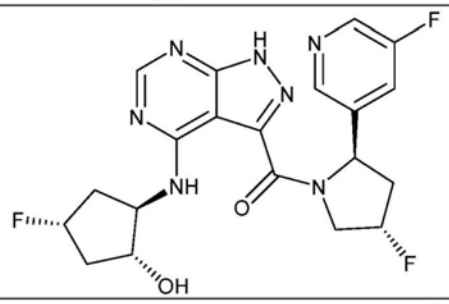
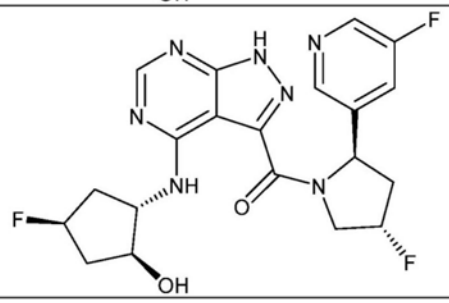
53		1H-NMR (400 MHz, CD3OD) δ ppm 8.38 (d, 1H, J = 5.2 Hz), 7.20-7.05 (m, 3H), 4.87 (s, 2H), 4.17-4.11 (m, 2H), 4.00-3.97 (m, 3H), 3.64-3.44 (m, 3H), 2.13-2.06 (m, 1H), 1.76-1.70 (m, 1H), 1.39-1.18 (m, 3H).; LCMS: 433.1
54		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.19 (s, 1H), 9.51 (t, J = 6.3 Hz, 2H), 7.57 – 7.35 (m, 1H), 7.11 – 6.94 (m, 1H), 4.60 (d, J = 6.1 Hz, 2H), 4.04 (dt, J = 11.7, 5.8 Hz, 1H), 3.97 (dd, J = 11.1, 4.0 Hz, 1H), 3.78 (dd, J = 11.3, 5.1 Hz, 1H), 3.60 (tt, J = 6.6, 3.4 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.19 (dd, J = 11.1, 7.7 Hz, 1H), 3.12 (qd, J = 7.3, 4.2 Hz, 2H), 1.91 (d, J = 13.1 Hz, 1H), 1.50 (dq, J = 8.7, 4.6 Hz, 1H); LCMS: 435
55		LCMS: 435
56		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.23-7.21 (m, 1H), 7.13-7.12 (m, 1H), 7.11-7.03 (m, 1H), 5.57-5.54 (m, 1H), 4.14-4.01 (m, 1H), 4.00-3.92 (m, 4H), 3.91-3.90 (m, 1H), 3.61-3.44 (m, 2H), 2.05-2.02 (m, 1H), 1.72-1.68 (m, 1H).; LCMS: 435.1

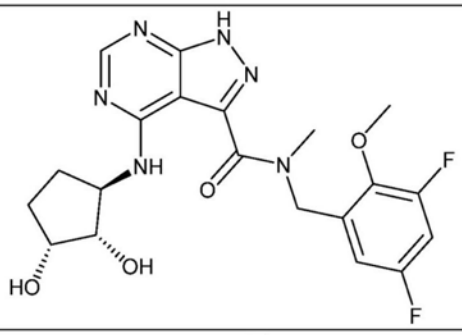
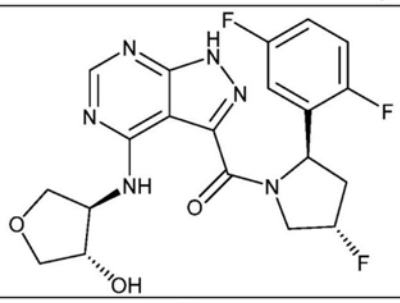
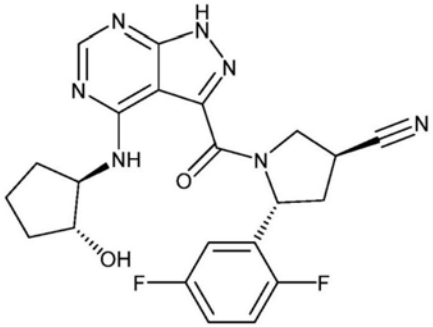
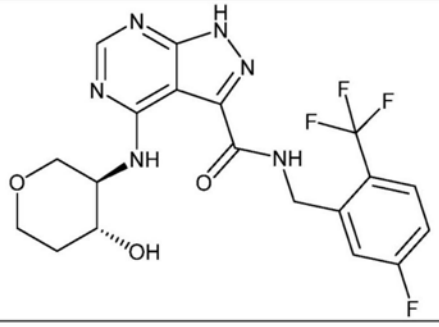
57		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 14.8 Hz), 7.50-7.45 (m, 1H), 7.09-7.04 (m, 2H), 5.46 (s, 1H), 4.96 (s, 1H), 4.40-4.35 (m, 1H), 4.16-3.97 (m, 2H), 3.67 (s, 1.5H), 3.22 (s, 1.5H), 2.47-2.45 (m ,1H), 2.20-2.16 (m, 1H), 1.87-1.77 (m, 2H).; LCMS: 435.1
58		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 5.2 Hz), 7.23 (d, 1H, J = 12.0 Hz), 7.16-7.09 (m, 2H), 5.42 (s, 1H), 4.85 (s, 1H), 4.40-4.36 (m, 1H), 4.15-4.13 (m, 1H), 4.06-4.02 (m, 1H), 3.64 (s, 1.5H), 3.16 (s, 1.5H), 2.47-2.44 (m, 1H), 2.19-2.15 (m, 1H), 1.84-1.72 (m, 2H).; LCMS: 435.1
59		1H-NMR (400 MHz, CD3OD) δ ppm 8.24 (s, 1H), 6.94-6.89 (m, 2H), 4.64 (s, 2H), 4.52-4.48 (m, 1H), 4.14-4.12 (m, 1H), 3.95 (s, 3H), 3.93-3.92 (m, 1H), 2.43-2.40 (m, 1H), 2.10-2.08 (m, 1H), 1.78-1.75 (m, 1H), 1.61-1.57 (m, 1H).; LCMS: 435.2
60		1H-NMR (400 MHz, CD3OD) δ ppm 8.26-8.22 (m, 2H), 7.64-7.59 (m, 1H), 5.34 (s, 1H), 4.89 (s, 1H), 4.51-4.47 (m, 1H), 4.15-4.09 (m, 1H), 3.95-3.86 (m, 1H), 3.68 (s, 1.2H), 3.22 (s, 1.8H), 2.46-2.40 (m, 1H), 2.11-2.09 (m, 1H), 1.80-1.49 (m, 2H).; LCMS: 436.2

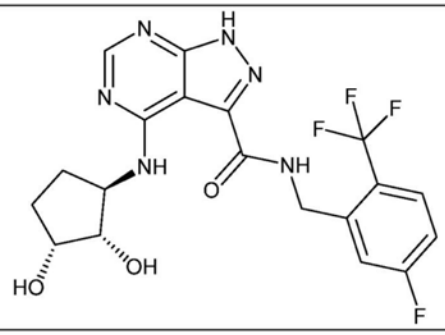
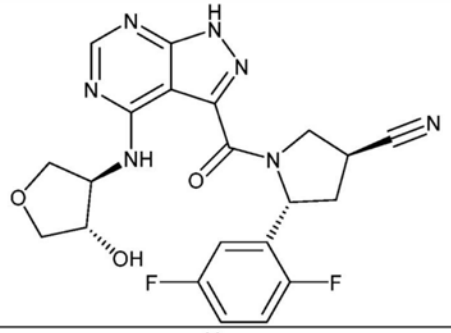
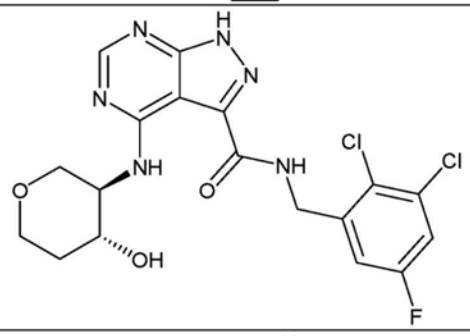
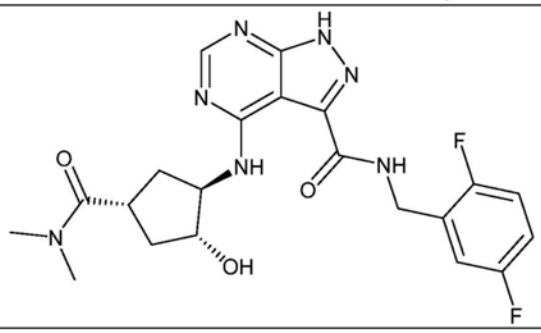
61		1H-NMR (400 MHz, CD3OD) δ ppm 8.30 (s, 1H), 7.25-7.15 (m, 2H), 7.08-7.07 (m, 1H), 5.55-5.52 (m, 1H), 5.15 (d, 1H, J = 53.6 Hz), 4.60-4.55 (m, 1H), 4.21-4.18 (m, 1H), 3.95-3.88 (m, 2H), 2.62-2.51 (m, 2H), 2.00-1.89 (m, 2H).; LCMS: 436.4
62		1H-NMR (400 MHz, CD3OD) δ ppm 8.30 (s, 1H), 7.25-7.15 (m, 2H), 7.08-7.07 (m, 1H), 5.55-5.52 (m, 1H), 5.16 (d, 1H, J = 53.6 Hz), 4.60-4.54 (m, 1H), 4.18-4.14 (m, 1H), 3.94-3.89 (m, 2H), 2.60-2.51 (m, 2H), 1.99-1.90 (m, 2H).; LCMS: 436.4
63		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.09 (br s, 1H), 9.25 (Abqd, 1H), 8.33 (d, J = 8.2 Hz, 1H), 7.67 – 7.47 (m, 1H), 7.14 (m, 1H), 5.46 (m, 1H), 4.96 (m, 1H), 4.59 (dd, J = 9.6, 4.0 Hz, 1H), 4.47 (q, J = 7.8 Hz, 1H), 4.00 (m, 1H), 3.84 – 3.71 (m, 1H), 3.58 (s, 1H), 3.40 (s, 3H), 2.42 – 2.26 (m, 1H), 2.08 – 1.92 (m, 1H), 1.72 – 1.57 (m, 1H), 1.37 (m, 1H); LCMS: 437
64		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.12 (s, 1H), 9.58 – 9.35 (m, 2H), 8.29 (s, 1H), 7.37 – 7.12 (m, 3H), 5.72 (d, J = 6.2 Hz, 1H), 4.67 – 4.49 (m, 2H), 4.29 (s, 1H), 3.76 (m, 1H), 2.04 (m, 2H), 1.99 – 1.79 (m, 1H), 1.71 (s, 1H), 1.47 (m, 2H); LCMS: 439

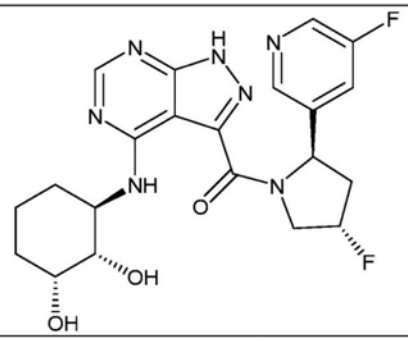
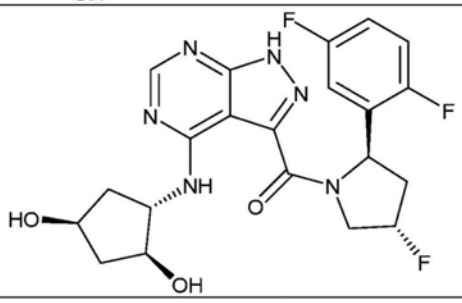
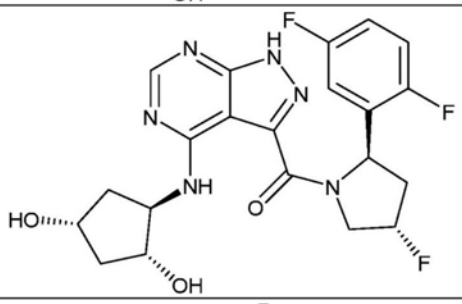
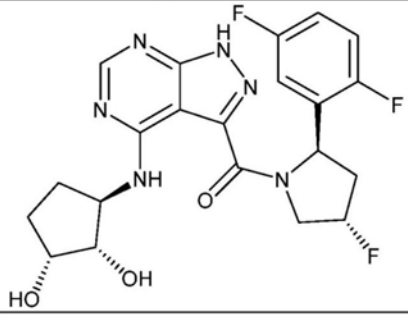
65		LCMS: 439
66		1H-NMR (400 MHz, CD3OD) δ ppm 8.17 (s, 1H), 7.38-7.34 (m, 3H), 7.10-7.06 (m, 1H), 6.01-5.95 (m, 1H), 4.17-4.12 (m, 1H), 4.07-4.03 (m, 1H), 2.19-2.17 (m, 1H), 1.96-1.94 (m, 1H), 1.76-1.73 (m, 2H), 1.60-1.57 (m, 2H).; LCMS: 439.2
67		1H-NMR (400 MHz, CD3OD) δ ppm 8.15 (s, 1H), 7.38-7.35 (m, 3H), 7.10-7.05 (m, 1H), 6.02-5.96 (m, 1H), 4.24-4.14 (m, 1H), 4.03-3.99 (m, 1H), 2.24-2.19 (m, 1H), 1.94-1.93 (m, 1H), 1.77-1.74 (m, 2H), 1.60-1.55 (m, 2H).; LCMS: 439.2
68		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.09 (s, 1H), 9.01 (d, J = 7.1 Hz, 1H), 8.19 (s, 1H), 7.31 (m, 1H), 7.16 – 7.10 (m, 2H), 7.00 (m, 1H), 5.43-5.30 (m, 2H), 4.79 (d, J = 5.6 Hz, 1H), 4.60 (m, 1H), 4.48 – 4.33 (m, 2H), 4.33 – 4.22 (m, 1H), 3.78 (m, 1H), 3.56 (m, 1H), 2.77 – 2.59 (m, 1H), 2.10 (m, 2H), 1.99 – 1.76 (m, 2H), 1.46 (m, 1H), 1.27 – 1.15 (m, 1H); LCMS: 445

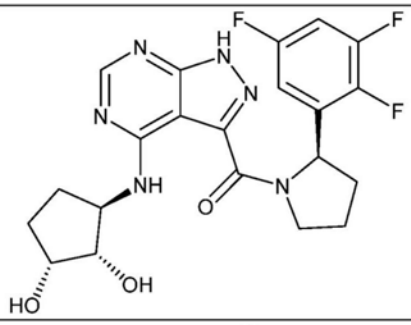
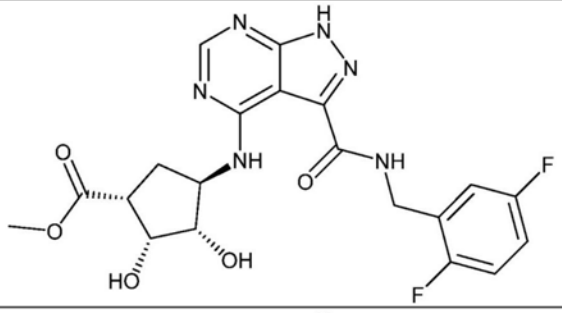
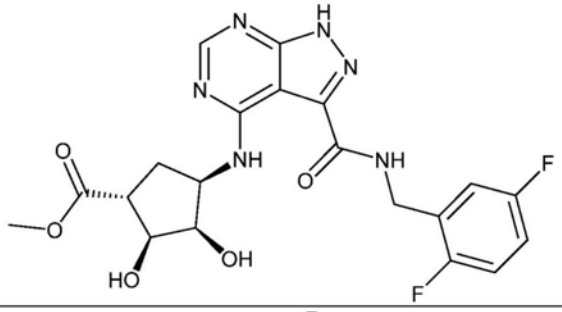
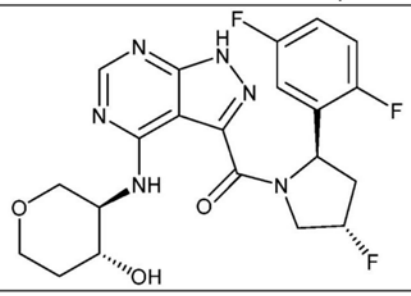
69		1H-NMR (400 MHz, CDCl3) δ ppm 11.87-11.48 (m, 1H), 8.50-8.46 (m, 1H), 7.06-6.65 (m, 3H), 6.40-6.39 (m, 0.5H), 5.62-5.59 (m, 0.5H), 4.46-3.95 (m, 6H), 3.55-3.51 (m, 2H), 2.42-2.11 (m, 1H), 2.04-1.76 (m, 5H).; LCMS: 445.1
70		1H-NMR (400 MHz, CD3OD) δ ppm 8.35, 8.28 (s, 1H), 7.14-6.80 (m, 3H), 6.43 (d, 0.5H, J = 7.6 Hz), 5.60 (dd, 0.5H, J = 7.6, 4.0 Hz), 4.52-4.31 (m, 2H), 4.05-3.89 (m, 3H), 2.48-2.41 (m, 2H), 2.12-2.06 (m, 4H), 1.94-1.61 (m, 2H).; LCMS: 445.1
71		1H-NMR (400 MHz, CD3OD) δ ppm 8.33, 8.27 (s, 1H), 7.14-6.92 (m, 3H), 6.43 (d, 0.5H, J = 8.0 Hz), 5.58 (dd, 0.5H, J = 8.0, 4.4 Hz), 4.39-4.31 (m, 2H), 4.15-4.08 (m, 2H), 394-3.91 (m, 1H), 2.48-2.43 (m, 2H), 2.12-2.06 (m, 3H), 1.76-1.51 (m, 3H).; LCMS: 445.1
72		1H-NMR (400 MHz, CD3OD) δ ppm 8.42 (br.s, 1H), 8.31 (br.s, 1H), 8.26 (s, 1H), 7.63-7.61 (m, 1H), 5.46-5.26 (m, 2H), 4.50-4.37 (m, 1H), 4.26-4.21 (m, 1H), 3.97 (br.s, 2H), 3.80-3.77 (m, 1H), 2.80-2.76 (m, 1H), 2.33-2.30 (m, 1H), 2.29-2.27 (m, 1H), 2.07-2.00 (m, 1H), 1.69-1.67 (m, 1H), 1.52-1.51 (m, 1H).; LCMS: 446.1

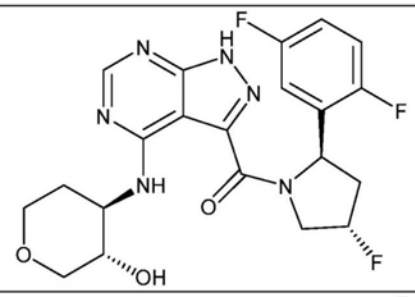
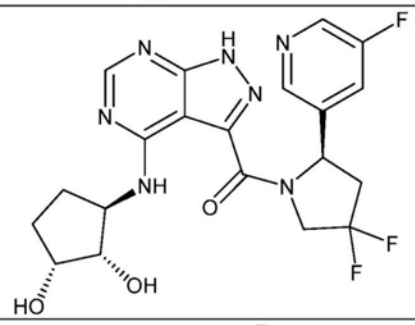
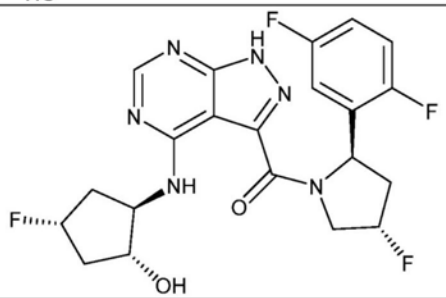
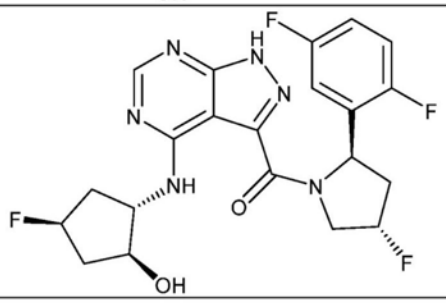
73		1H-NMR (400 MHz, CD3OD) δ ppm 8.52 (s, 1H), 8.41 (s, 1H), 8.35-8.29 (m, 1H), 7.76 (d, 1H, J = 9.2 Hz), 5.57-5.36 (m, 2H), 4.96-4.94 (m, 1H), 4.60-4.51 (m, 1H), 3.98-3.89 (m, 3H), 3.50-3.47 (m, 2H), 3.24-3.21 (m, 1H), 2.88-2.86 (m, 1H), 2.18-2.09 (m, 2H), 1.75-1.71 (m, 1H).; LCMS: 446.1
74		1H-NMR (400 MHz, CD3OD) δ ppm 8.60 (br.s, 2H), 8.35 (s, 1H), 7.75 (d, 1H, J = 9.2 Hz), 5.57-5.35 (m, 2H), 4.59-4.45 (m, 1H), 4.09-4.05 (m, 1H), 3.95-3.91 (m, 2H), 3.65-3.75 (m, 1H), 3.53-3.50 (m, 1H), 3.40-3.35 (m, 1H), 2.88-2.86 (m, 1H), 2.29-2.27 (m, 2H), 1.97-1.93 (m, 1H), 1.66-1.63 (m, 1H).; LCMS: 446.2
75		1H-NMR (400 MHz, CD3OD) δ ppm 8.89-8.87 (m, 0.5H), 8.52-8.43 (m, 1H), 8.39 (s, 1H), 8.13-8.10 (m, 0.5H), 7.77 (d, 1H, J = 9.2 Hz), 5.55-5.40 (m, 2H), 5.16-5.01 (m, 2H), 4.60-4.37 (m, 2H), 4.17-4.15 (m, 1H), 2.89-2.86 (m, 1H), 2.66-2.56 (m, 1H), 2.44-2.42 (m, 1H), 2.30-2.20 (m, 1H), 1.98-1.88 (m, 2H).; LCMS: 448.1
76		1H-NMR (400 MHz, CD3OD) δ ppm 8.87-8.86 (m, 0.5H), 8.67-8.50 (m, 1H), 8. 46 (s, 1H), 8.12-8.10 (m, 0.5H), 7.75-7.73 (m, 1H), 5.54-5.24 (m, 2H), 5.16-5.03 (m, 2H), 4.58-4.37 (m, 2H), 4.11-4.07 (m, 1H), 2.87-2.85 (m, 1H), 2.55-2.47 (m, 2H), 2.26-2.01 (m, 1H), 1.95-1.84 (m, 2H).; LCMS: 448.1

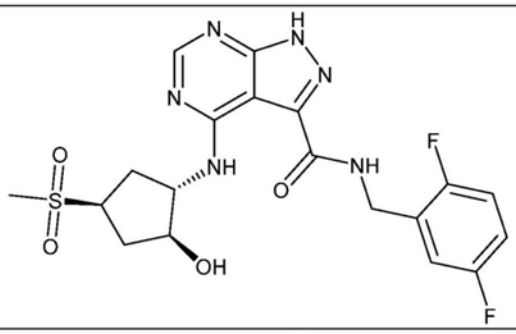
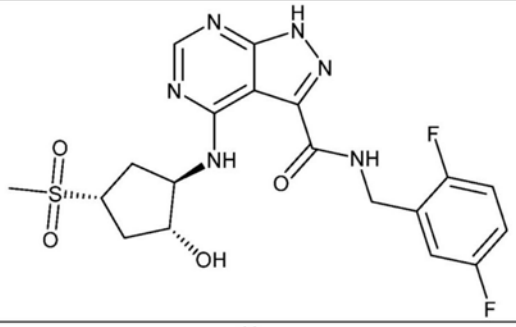
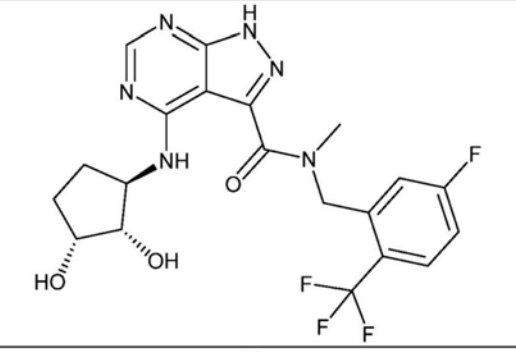
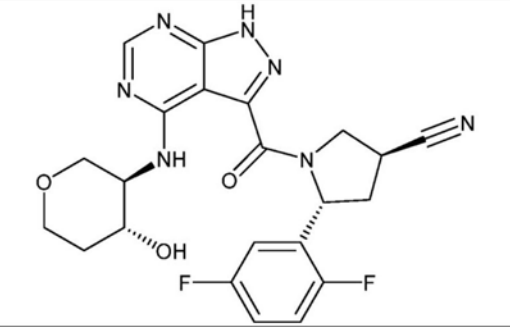
77		1H-NMR (400 MHz, CD3OD) δ ppm 8.43 (d, 1H, J = 5.2 Hz), 7.06-6.99 (m, 1H), 6.96-6.87 (m, 1H), 5.57-5.48 (m, 1H), 5.00 (s, 1H), 4.45-4.41 (m, 1H), 4.20-4.19 (m, 1H), 4.12-4.07 (m, 1H), 3.98 (s, 1.5H), 3.89 (s, 1.5H), 3.71 (s, 1.5H), 3.22 (s, 1.5H), 2.53-2.49 (m, 1H), 2.25-2.21 (m, 1H), 1.90-1.79 (m, 2H).; LCMS: 449.1
78		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.14-7.00 (m, 3H), 5.59-5.55 (m, 1H), 5.48-5.32 (m, 1H), 4.46-4.33 (m, 3H), 4.23-4.12 (m, 2H), 3.97-3.94 (m, 1H), 3.69-3.68 (m, 2H), 2.85-2.75 (m, 1H), 2.16-2.09 (m, 1H).; LCMS: 449.1
79		1H-NMR (400 MHz, CD3OD) δ ppm 8.41 (s, 1H), 8.35 (s, 1H), 7.20-7.16 (m, 1H), 7.07-7.01 (m, 2H), 5.76-5.73 (m, 1H), 4.84-4.75 (m, 1H), 4.25-4.08 (m, 3H), 3.64-3.61 (m, 1H), 2.81-2.78 (m, 1H), 2.41-2.38 (m, 2H), 2.00-1.68 (m, 5H).; LCMS: 453.5
80		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.35 (s, 1H), 9.60 (q, J = 7.8, 7.0 Hz, 1H), 8.33 (s, 1H), 7.84 (dd, J = 8.7, 5.4 Hz, 1H), 7.39 – 7.16 (m, 2H), 4.72 (d, J = 6.1 Hz, 2H), 4.04 (qd, J = 7.9, 4.0 Hz, 1H), 3.96 (dd, J = 11.1, 4.0 Hz, 1H), 3.78 (dt, J = 11.5, 4.5 Hz, 1H), 3.65 (td, J = 8.2, 4.3 Hz, 1H), 3.48 – 3.38 (m, 1H), 3.23 – 3.15 (m, 1H), 1.89 (dq, J = 12.7, 4.1 Hz, 1H), 1.49 (dtd, J = 13.2, 8.9, 4.0 Hz, 1H), 1.25 (dt, J = 13.3, 7.9 Hz, 1H); LCMS: 455

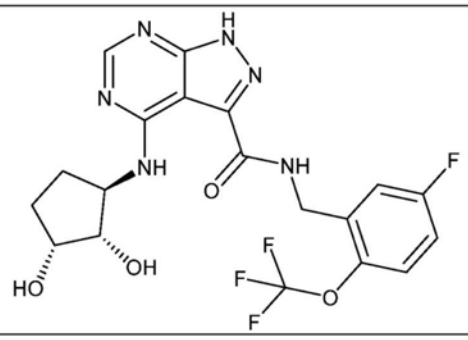
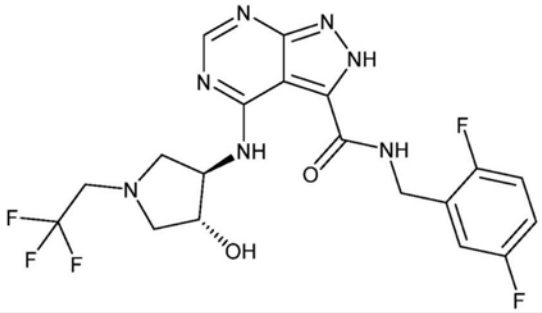
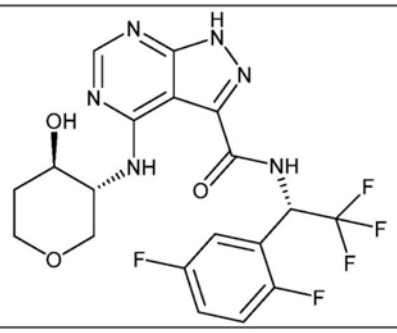
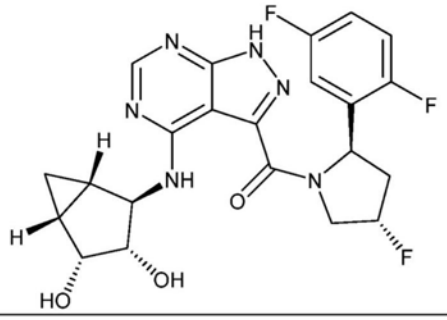
81		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.80-7.71 (m, 1H), 7.29-7.27 (m, 1H), 7.21-7.17 (m, 1H), 4.74-4.67 (m, 2H), 4.44-4.30 (m, 1H), 4.11 (s, 1H), 4.02-4.01 (m, 1H), 2.50-2.40 (m, 1H), 2.15-2.12 (m, 1H), 1.78-1.77 (m, 1H), 1.70-1.67 (m, 1H).; LCMS: 455.1
82		1H-NMR (400 MHz, CD3OD) δ ppm 8.39 (s, 1H), 8.33 (s, 1H), 7.22-6.90 (m, 3H), 5.74 (br.s, 1H), 4.83-4.73 (m, 1H), 4.51-4.42 (m, 2H), 4.26-4.17 (m, 2H), 3.98-3.95 (m, 1H), 3.82-3.71 (m, 3H), 2.87-2.75 (m, 1H), 2.53-2.50 (m, 1H).; LCMS: 455.4
83		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.12 (s, 1H), 9.51 (t, J = 6.2 Hz, 1H), 9.33 (d, J = 7.7 Hz, 1H), 8.28 (s, 1H), 7.64 (dd, J = 8.2, 3.0 Hz, 1H), 7.15 (dd, J = 9.2, 3.1 Hz, 1H), 5.09 (d, J = 4.9 Hz, 1H), 4.60 (d, J = 6.1 Hz, 2H), 4.05 (dd, J = 7.7, 4.1 Hz, 1H), 3.96 (dd, J = 11.2, 4.1 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.65 (d, J = 4.9 Hz, 1H), 3.43 (t, J = 9.4 Hz, 1H), 3.17 (dd, J = 11.2, 7.6 Hz, 1H), 1.89 (d, J = 12.9 Hz, 1H), 1.52 – 1.44 (m, 1H); LCMS: 456
84		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.11 (s, 1H), 9.60 – 9.39 (m, 2H), 8.28 (s, 1H), 7.32 – 7.24 (m, 1H), 7.17 (m, 1H), 5.21 (d, J = 5.2 Hz, 1H), 4.56 (d, J = 6.1 Hz, 2H), 4.29 (m, 1H), 3.96 (d, J = 6.7 Hz, 1H), 3.29 – 3.18 (m, 1H), 2.97 (s, 3H), 2.84 (s, 3H), 2.30 (m, 1H), 2.14 (m, 1H), 1.78 – 1.61 (m, 2H); LCMS: 460

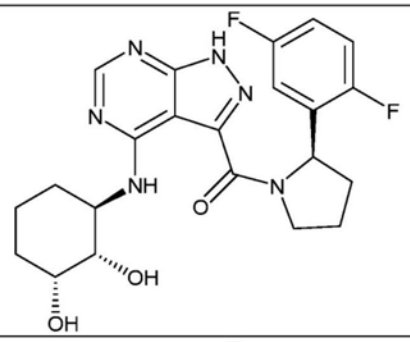
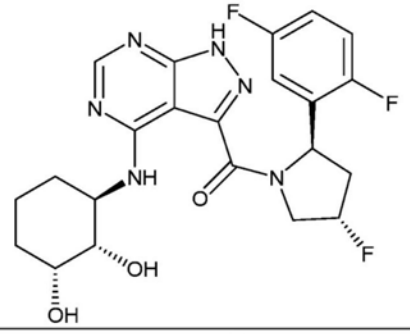
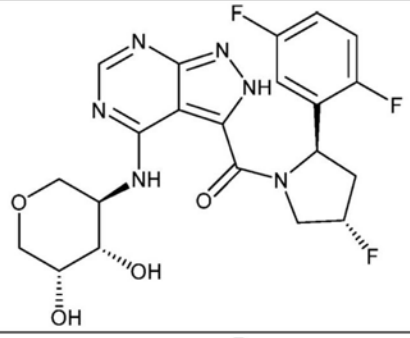
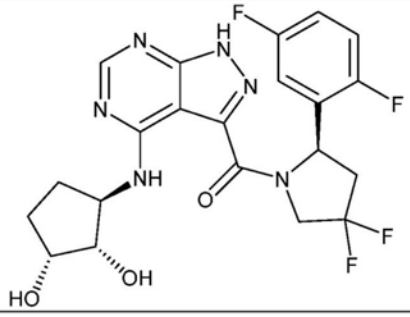
85		1H-NMR (400 MHz, CD3OD) δ ppm 8.51 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 7.76 (d, 1H, J = 9.2 Hz), 5.56-5.40 (m, 2H), 4.87-4.82 (m, 1H), 4.59-4.50 (m, 1H), 4.11-3.97 (m, 2H), 3.48-3.45 (m, 1H), 2.88-2.86 (m, 1H), 2.27-1.80 (m, 2H), 1.78-1.67 (m, 2H), 1.59-1.46 (m, 3H).; LCMS: 460.1
86		1H-NMR (400 MHz, CD3OD) δ ppm 8.25-8.19 (m, 1H), 7.14-6.85 (m, 3H), 5.63-5.59 (m, 1H), 5.42 (d, 1H, J = 52.4 Hz), 4.83 (br.s, 1H), 4.48-4.31 (m, 3H), 4.12-3.99 (m, 1H), 2.88-2.80 (m, 1H), 2.42-2.39 (m, 1H), 2.25-2.20 (m, 2H), 1.92-1.89 (m, 1H), 1.69-1.64 (m, 1H).; LCMS: 462.4
87		1H-NMR (400 MHz, CD3OD) δ ppm 8.26-8.19 (m, 1H), 7.15-6.86 (m, 3H), 5.63-5.59 (m, 1H), 5.42 (d, 1H, J = 52.0 Hz), 4.85-4.80 (m, 1H), 4.47-4.31 (m, 3H), 4.11-4.03 (m, 1H), 2.83-2.78 (m, 1H), 2.49-2.43 (m, 1H), 2.23-2.20 (m, 2H), 1.87-1.83 (m, 1H), 1.70-1.65 (m, 1H).; LCMS: 462.4
88		^{1}H-NMR (400 MHz, CD_3OD) δ ppm 8.25 (s, 1H), 7.17-7.03 (m, 3H), 5.62 (t, 1H, J = 8.8 Hz), 5.43 (d, 1H, J = 52.0 Hz), 4.86-4.81 (m, 1H), 4.50-4.40 (m, 2H), 4.12-4.08 (m, 1H), 3.93-3.84 (m, 1H), 2.89-2.79 (m, 1H), 2.41-2.38 (m, 1H), 2.12-2.05 (m, 2H), 1.76-1.75 (m, 1H), 1.56-1.55 (m, 1H); LCMS: 463

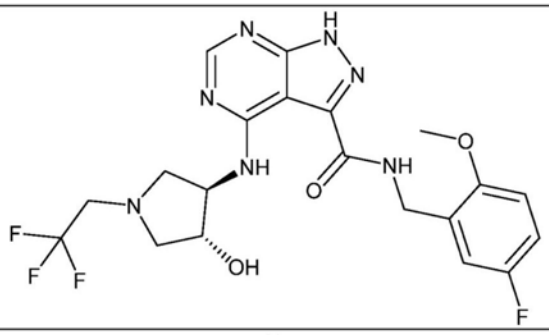
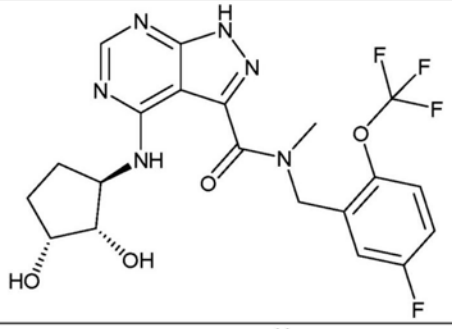
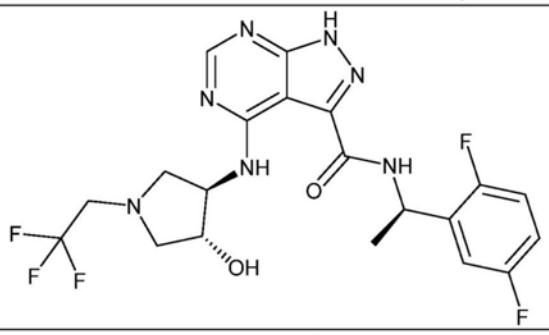
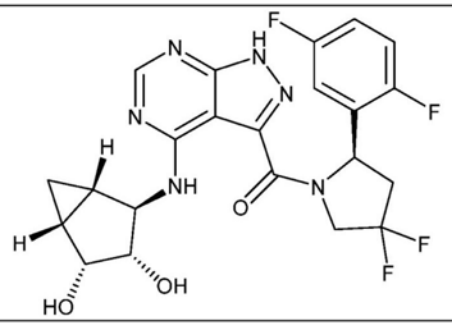
89		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.02 (s, 1H), 9.23 (d, J = 7.0 Hz, 1H), 8.24 (s, 1H), 7.41 (qd, J = 9.4, 4.9 Hz, 1H), 7.12 (ddt, J = 11.4, 7.6, 2.0 Hz, 1H), 5.48 (m, 1H), 4.90 (m, 1H), 4.46 (m, 1H), 4.36 (m, 2H), 4.09 (m, 1H), 3.89 – 3.83 (m, 1H), 3.59 (m, 1H), 2.49 – 2.38 (m, 1H), 2.30 – 2.10 (m, 2H), 1.97 – 1.79 (m, 3H), 1.54 (m, 2H), 1.37 – 1.24 (m, 2H); LCMS: 463
90		LCMS: 463
91		LCMS: 463
92		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.14-6.86 (m, 3H), 5.63-5.59 (m, 1H), 5.51-5.35 (m, 1H), 4.50-4.41 (m, 1H), 4.10-4.06 (m, 1H), 3.98-3.92 (m, 2H), 3.75-3.70 (m, 1H), 3.52-3.41 (m, 1H), 3.39-3.36 (m, 1H), 2.84-2.81 (m, 1H), 2.25-2.00 (m, 1H), 2.00-1.96 (m, 1H), 1.67-1.64 (m, 1H), 1.38-1.28 (m, 1H).; LCMS: 463.1

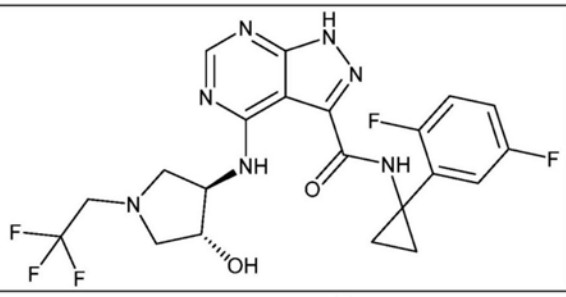
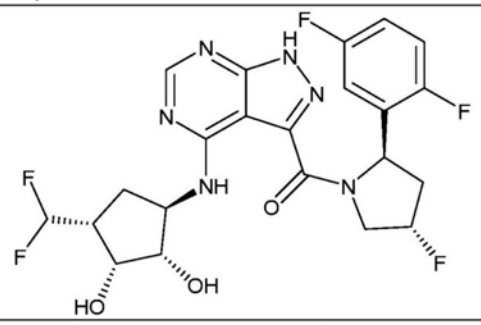
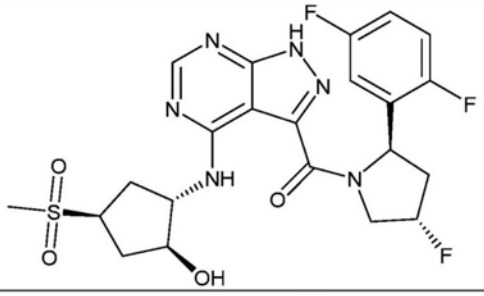
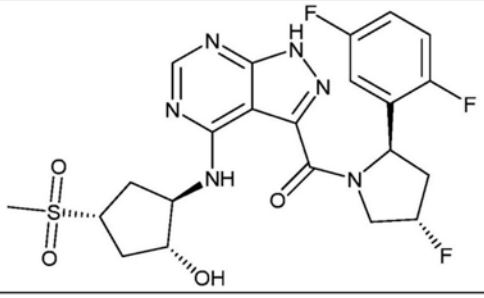
93		1H-NMR (400 MHz, CD3OD) δ ppm 8.14-8.04 (m, 1H), 7.02-6.74 (m, 3H), 5.73-5.48 (m, 1H), 5.37-5.24 (m, 1H), 4.36-4.10 (m, 2H), 3.87-3.76 (m, 2H), 3.44-3.38 (m, 2H), 3.18-3.10 (m, 1H), 2.76-2.72 (m, 1H), 2.10-1.88 (m, 2H), 1.52 (br.s, 1H), 1.33-1.17 (m, 1H).; LCMS: 463.1
94		1H-NMR (400 MHz, CD3OD) δ ppm 8.53 (s, 1H), 8.46-8.43 (m, 1H), 8.29-8.24 (m, 1H), 7.81-7.66 (m, 1H), 5.81-5.78 (m, 1H), 4.89-4.85 (m, 1H), 4.57-4.52 (m, 2H), 4.50-4.48 (m, 1H), 4.13-4.11 (m, 1H), 3.88-3.85 (m, 1H), 3.12-3.11 (m, 1H), 2.62-2.59 (m, 1H), 2.44-2.42 (m, 1H), 2.08-2.05 (m, 1H), 1.82-1.77 (m, 1H), 1.55-1.53 (m, 1H).; LCMS: 464.1
95		1H-NMR (400 MHz, CD3OD) δ ppm 8.15-8.09 (m, 1H), 7.03-6.74 (m, 3H), 5.52-5.47 (m, 1H), 5.31 (d, 1H, J = 52.0 Hz), 5.06-4.92 (m, 2H), 4.44-4.38 (m, 2H), 3.99-3.96 (m, 1H), 2.72-2.70 (m, 1H), 2.45-2.32 (m, 2H), 1.84-1.75 (m, 3H).; LCMS: 465.1
96		1H-NMR (400 MHz, CD3OD) δ ppm 8.22-8.10 (m, 1H), 7.05-6.75 (m, 3H), 5.51-5.47 (m, 1H), 5.31 (d, 1H, J = 52.0 Hz), 4.99 (d, 1H, J = 54.0 Hz), 4.44-4.29 (m, 2H), 4.02-3.99 (m, 1H), 2.90-2.72 (m, 1H), 2.47-2.35 (m, 2H), 2.12-1.64 (m, 3H).; LCMS: 465.1

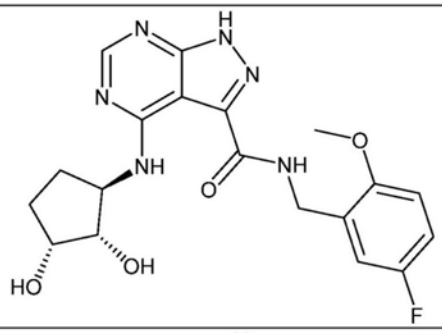
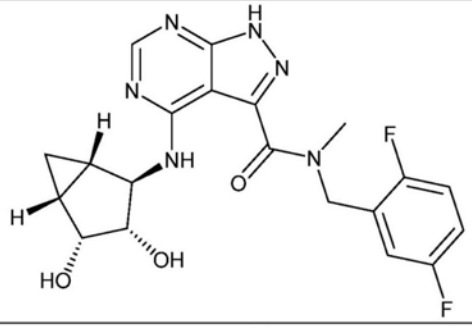
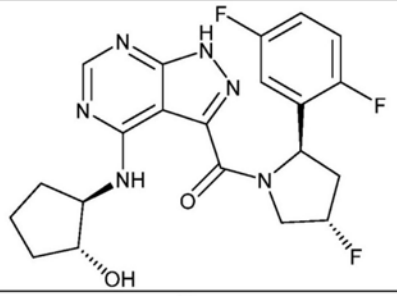
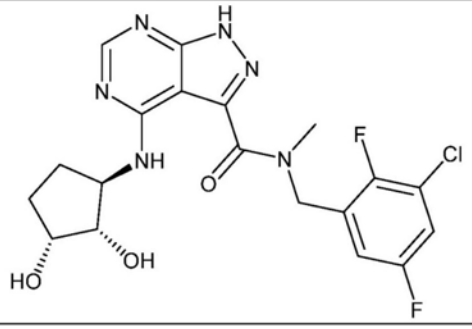
97		1H-NMR (400 MHz, CD3OD) δ ppm 8.28 (s, 1H), 7.15-7.11 (m, 2H), 7.04-7.02 (m, 1H), 4.66 (s, 2H), 4.51-4.45 (m, 1H), 4.28-4.23 (m, 1H), 3.84-3.80 (m, 1H), 2.96 (s, 3H), 2.75-2.70 (m, 1H), 2.53-2.50 (m, 1H), 2.15-2.06 (m, 2H).; LCMS: 467.1
98		1H-NMR (400 MHz, CD3OD) δ ppm 8.28 (s, 1H), 7.15-7.11 (m, 2H), 7.09-7.02 (m, 1H), 4.66 (s, 2H), 4.51-4.45 (m, 1H), 4.28-4.25 (m, 1H), 3.84-3.80 (m, 1H), 2.96 (s, 3H), 2.75-2.70 (m, 1H), 2.54-2.52 (m, 1H), 2.13-2.06 (m, 2H).; LCMS: 467.1
99		1H-NMR (400 MHz, CD3OD) δ ppm 8.40, 8.36 (d, 1H, J = 11.6 Hz), 7.85-7.80 (m, 1H), 7.25-7.17 (m, 2H), 5.60 (s, 1H), 5.57 (s, 1H), 4.40-4.35 (m, 1H), 4.16-3.98 (m, 2H), 3.69 (s, 1.5H), 3.23 (s, 1.5H), 2.49-2.43 (m, 1H), 2.21-2.20 (m, 1H), 1.85-1.64 (m, 2H).; LCMS: 469.1
100		1H-NMR (400 MHz, CD3OD) δ ppm 8.28-8.22 (m, 1H), 7.19-6.90 (m, 3H), 5.78-5.76 (m, 1H), 4.85-4.80 (m, 1H), 4.71-4.69 (m, 1H), 4.19-4.17 (m, 2H), 4.09-4.08 (m, 2H), 3.75-3.74 (m, 1H), 3.59-3.48 (m, 2H), 2.86-2.76 (m, 1H), 2.51-2.35 (m, 1H), 2.13-1.96 (m, 1H), 1.71-1.60 (m, 1H).; LCMS: 469.4

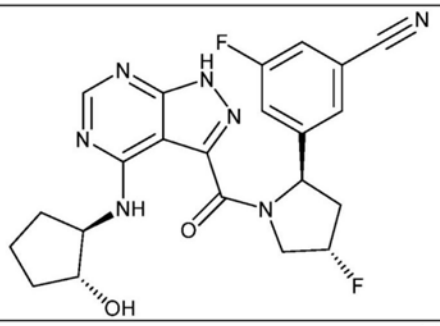
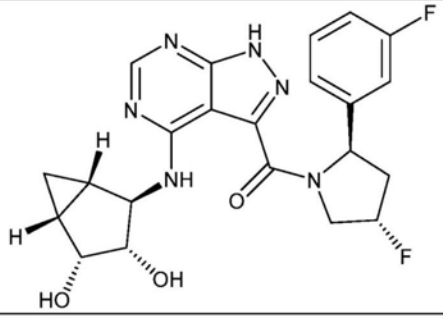
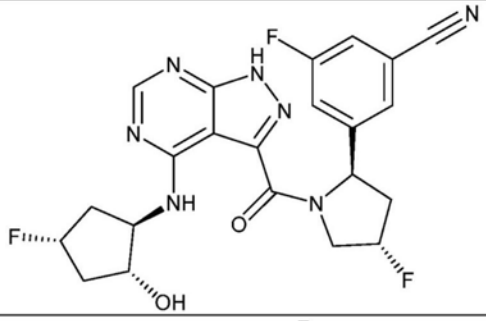
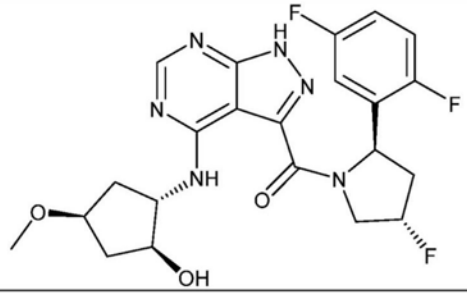
101		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.35 (br.s, 1H), 7.20 (d, 1H, J = 6.8 Hz), 7.13 (t, 1H, J = 8.0 Hz), 4.71 (s, 2H), 4.41-4.35 (m, 1H), 4.12 (br.s, 1H), 4.01-3.99 (m, 1H), 2.45-2.40 (m, 1H), 2.15-2.11 (m, 1H), 1.80-1.68 (m, 2H).; LCMS: 471.1
102		1H-NMR (400 MHz, CDCl3) δ ppm 11.11 (d, 1H, J = 6.0 Hz), 8.67 (s, 1H), 7.84-7.82 (m, 1H), 7.04-6.92 (m, 3H), 4.64 (d, 2H, J = 6.4 Hz), 4.41 (br.s, 1H), 4.29 (br.s, 1H), 3.42-3.38 (m, 2H), 3.25-3.22 (m, 2H), 3.09-3.07 (m, 1H), 2.79-2.77 (m, 1H).; LCMS: 472.2
103		^{1}H NMR (400 MHz, DMSO-d_6) δ 14.32 (s, 1H), 10.13 (d, *J* = 9.9 Hz, 1H), 8.99 (d, *J* = 7.6 Hz, 1H), 8.30 (s, 1H), 8.14 – 8.03 (m, 1H), 7.41 (m, 2H), 6.40 (m, 1H), 5.11 (s, 1H), 4.03 (m, 3H), 3.80 (m, 1H), 3.67 (m, 1H), 3.54 – 3.42 (m, 1H), 3.21 (m, 1H), 1.90 (dq, *J* = 12.7, 4.3 Hz, 1H), 1.50 (dq, *J* = 13.7, 5.1 Hz, 1H); LCMS: 473
104		LCMS: 475

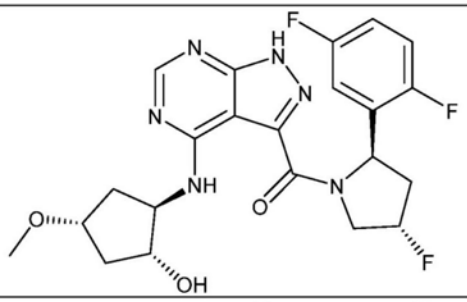
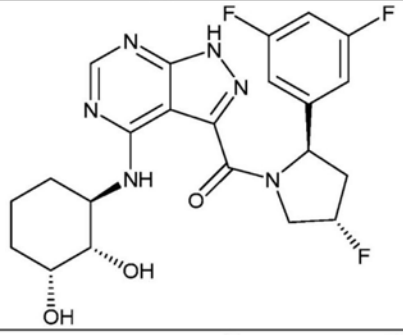
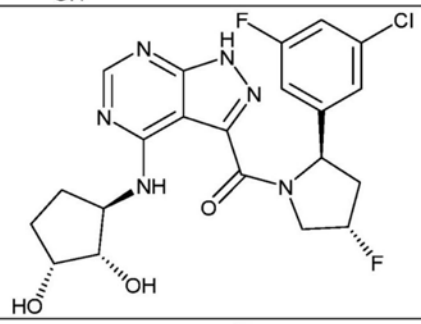
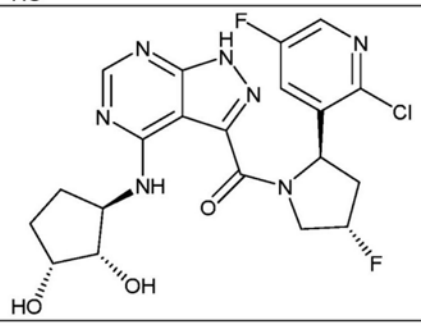
105		1H-NMR (400 MHz, CD3OD) δ ppm 8.32-8.25 (m, 1H), 7.15-6.87 (m, 3H), 5.62-5.58 (m, 1H), 5.51-5.38 (m, 1H), 4.94-4.90 (m, 1H), 4.51-4.47 (m, 1H), 4.14-4.07 (m, 1H), 4.02 (br.s, 1H), 3.52-3.49 (m, 1H), 2.83-2.79 (m, 1H), 2.27-2.24 (m, 1H), 2.14-2.05 (m, 1H), 1.88-1.80 (m, 2H), 1.60-1.48 (m, 3H).; LCMS: 477.1
106		1H-NMR (400 MHz, CD3OD) δ ppm 8.32-8.25 (m, 1H), 7.15-6.87 (m, 3H), 5.62-5.58 (m, 1H), 5.51-5.38 (m, 1H), 4.94-4.90 (m, 1H), 4.51-4.47 (m, 1H), 4.14-4.07 (m, 1H), 4.02 (br.s, 1H), 3.52-3.49 (m, 1H), 2.83-2.79 (m, 1H), 2.27-2.24 (m, 1H), 2.14-2.05 (m, 1H), 1.88-1.80 (m, 2H), 1.60-1.48 (m, 3H).; LCMS: 477.1
107		1H-NMR (400 MHz, CD3OD) δ ppm 8.35-8.27 (m, 1H), 7.16-7.01 (m, 3H), 5.63-5.59 (m, 1H), 5.44 (d, 1H, J = 52.0 Hz), 4.51-4.32 (m, 2H), 4.04-3.75 (m, 5H), 3.60-3.57 (m, 1H), 3.39-3.38 (m, 1H), 2.86-2.80 (m, 1H), 2.27-2.13 (m, 1H); LCMS: 479
108		1H-NMR (400 MHz, CD3OD) δ ppm 8.22-8.16 (m, 1H), 7.15-7.11 (m, 1H), 7.05-7.01 (m, 1H), 6.94-6.92 (m, 1H), 5.79-5.75 (m, 1H), 4.82-4.75 (m, 1H), 4.46-4.41 (m, 1H), 4.04-4.02 (m, 1H), 3.82-3.79 (m, 1H), 2.98-2.94 (m, 1H), 2.52-2.36 (m, 2H), 2.01-1.92 (m, 1H), 1.71-1.60 (m, 1H), 1.32-1.29 (m, 1H), 1.23-1.19 (m, 1H).; LCMS: 481.1

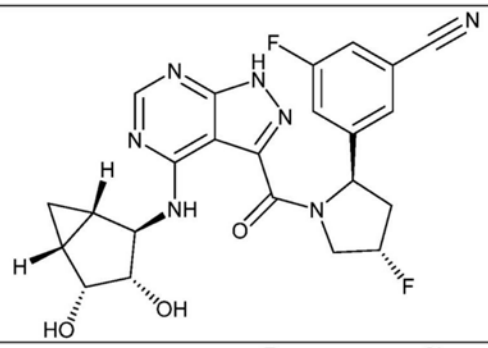
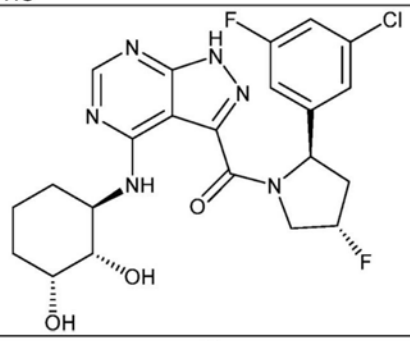
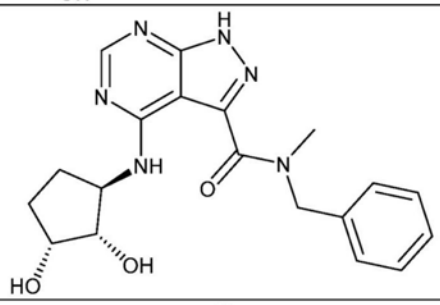
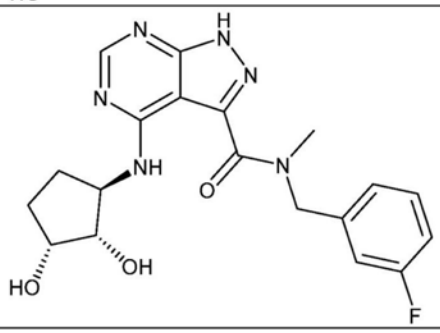
109		1H-NMR (400 MHz, CDCl3) δ ppm 11.26 (d, 1H, J = 6.0 Hz), 8.67 (s, 1H), 7.94-7.91 (m, 1H), 7.00-6.76 (m, 3H), 4.55 (d, 2H, J = 6.0 Hz), 4.39 (br.s, 1H), 4.28 (br.s, 1H), 3.82 (s, 3H), 3.39-3.35 (m, 2H), 3.25-3.22 (m, 2H), 3.09-3.08 (m, 1H), 2.79-2.78 (m, 1H).; LCMS: 484.2
110		1H-NMR (400 MHz, CD3OD) δ ppm 8.40, 8.35 (s, 1H), 7.40 (br.s, 1H), 7.20-7.14 (m, 2H), 5.51 (s, 1H), 4.94 (d, 1H, J = 9.6 Hz), 4.41-4.36 (m, 1H), 4.15-3.97 (m, 2H), 3.65 (s, 1.5H), 3.18 (s, 1.5H), 2.48-2.42 (m, 1H), 2.19-2.14 (m, 1H), 1.82-1.65 (m, 2H).; LCMS: 485.1
111		1H-NMR (400 MHz, CDCl3) δ ppm 8.77 (br.s, 1H), 7.83 (d, 1H, J = 8.4 Hz), 7.10-6.97 (m, 3H), 5.45-5.41 (m, 1H), 4.44 (br.s, 1H), 4.35 (br.s, 1H), 3.51-3.43 (m, 2H), 3.36-3.33 (m, 2H), 3.21 (d, 1H, J = 8.0 Hz), 2.85 (d, 1H, J = 2.0 Hz), 1.67 (d, 1H, J = 6.8 Hz).; LCMS: 486.2
112		1H-NMR (400 MHz, CD3OD) δ ppm 8.38-8.32 (m, 1H), 7.17-6.67 (m, 3H), 5.77 (dd, 1H, J = 9.2, 6.0 Hz), 4.83-4.77 (m, 1H), 4.40-4.37 (m, 1H), 4.30-4.26 (m, 1H), 3.94-3.76 (m, 1H), 3.05-2.99 (m, 1H), 2.57-2.50 (m, 1H), 1.70-1.65 (m, 1H), 1.48-1.46 (m, 1H), 1.25-1.23 (m, 1H), 0.64-0.61 (m, 1H).; LCMS: 493.1

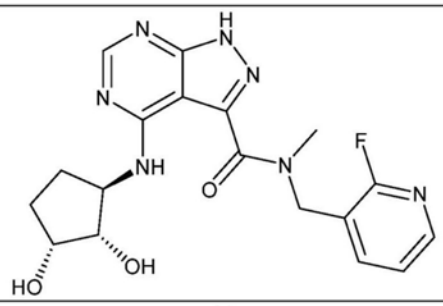
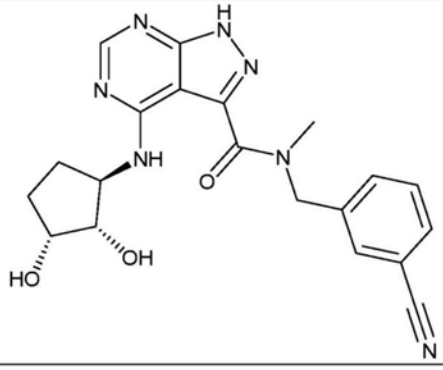
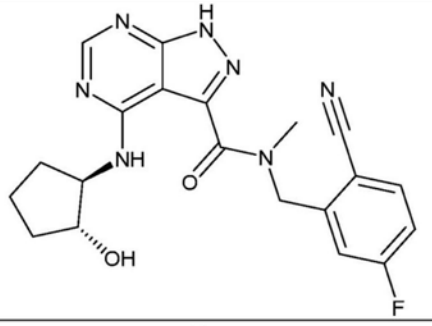
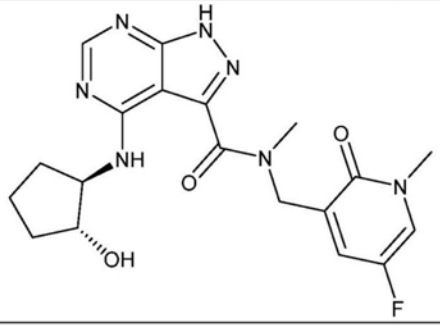
113		1H-NMR (400 MHz, CDCl3) δ ppm 11.10 (d, 1H, J = 6.0 Hz), 8.69 (s, 1H), 7.80 (s, 1H), 7.28-7.26 (m, 1H), 6.92-6.87 (m, 2H), 4.33 (br.s, 1H), 4.26 (br.s, 1H), 3.46-3.44 (m, 1H), 3.31-3.25 (m, 1H), 3.12-3.10 (m, 1H), 2.73-2.72 (m, 1H), 1.32-1.24 (m, 4H).; LCMS: 498.2
114		LCMS: 513
115		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.15-7.01 (m, 3H), 5.62-5.57 (m, 1H), 5.49-5.36 (m, 1H), 4.44-4.41 (m, 2H), 4.17-4.12 (m, 1H), 3.75-3.68 (m, 1H), 2.96 (s, 3H), 2.80-2.70 (m, 1H), 2.68-2.64 (m, 1H), 2.41-2.39 (m, 1H), 2.10-2.00 (m, 4H).; LCMS: 525.1
116		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.15-7.01 (m, 3H), 5.61-5.57 (m, 1H), 5.49-5.36 (m, 1H), 4.44-4.41 (m, 2H), 4.17-4.12 (m, 1H), 3.75-3.68 (m, 1H), 2.96 (s, 3H), 2.80-2.70 (m, 1H), 2.68-2.64 (m, 1H), 2.41-2.39 (m, 1H), 2.10-2.00 (m, 4H).; LCMS: 525.1

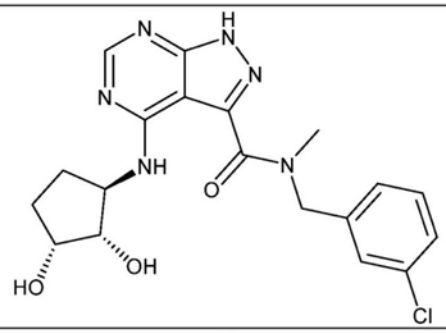
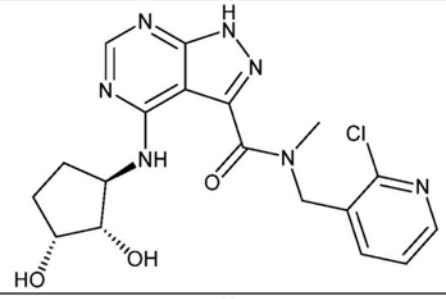
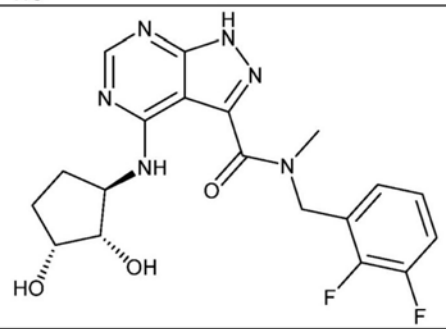
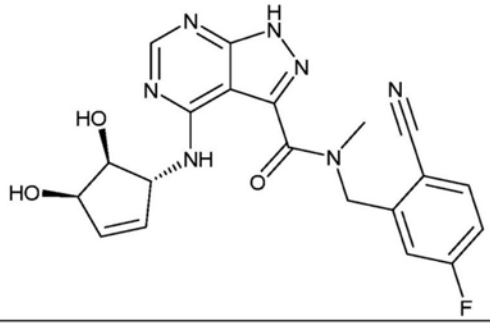
117		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (s, 1H), 7.01-6.96 (m, 3H), 4.62 (s, 2H), 4.37-4.31 (m, 1H), 4.13 (br.s, 1H), 4.04-4.01 (m, 1H), 3.88 (s, 3H), 2.26-2.24 (m, 1H), 2.46-2.39 (m, 1H), 2.16-2.14 (m, 1H), 1.82-1.72 (m, 2H).; LCMS:ND
118		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.01 (d, J = 41.7 Hz, 1H), 9.31 (d, J = 7.6 Hz, 1H), 8.98 (d, J = 7.5 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 7.36 – 7.07 (m, 3H), 5.33 (s, 1H), 4.81 (dd, J = 9.2, 5.0 Hz, 2H), 4.48 – 4.23 (m, 3H), 3.72 – 3.55 (m, 1H), 3.49 (s, 2H), 3.05 (s, 1H), 1.56 (dt, J = 29.6, 6.3 Hz, 1H), 1.38 – 1.20 (m, 1H), 1.08 (dq, J = 8.5, 4.1 Hz, 1H)
119		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.18-7.04 (m, 3H), 5.61 (t, 1H, J = 8.4 Hz), 5.47 (d, 1H, J = 51.6 Hz), 4.51-4.38 (m, 1H), 4.14-4.08 (m, 2H), 2.89-2.81 (m, 1H), 2.33-1.69 (m, 8H); LCMS: 447
120		1H-NMR (400 MHz, CD3OD) δ ppm 8.28 (s, 0.2H), 8.26 (s, 0.8H), 7.24-7.20 (m, 1H), 7.11-7.09 (m, 1H), 5.77-5.67 (m, 1H), 5.04-4.95 (m, 1H), 4.33-4.27 (m, 1H), 4.05-4.04 (m, 1H), 3.93-3.89 (m, 1H), 3.43 (s, 1.8H), 2.92 (s, 1.2H), 2.40-2.35 (m, 1H), 2.08-2.07 (m, 1H), 1.72-1.71 (m, 1H), 1.62-1.59 (m, 1H); LCMS: 453

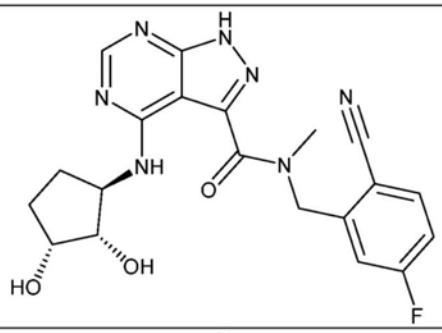
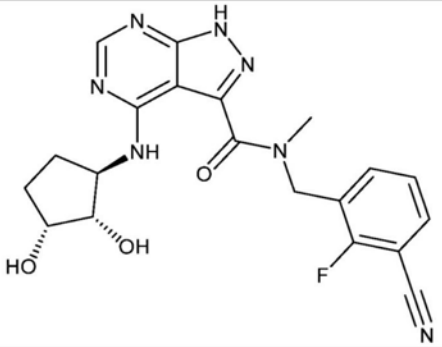
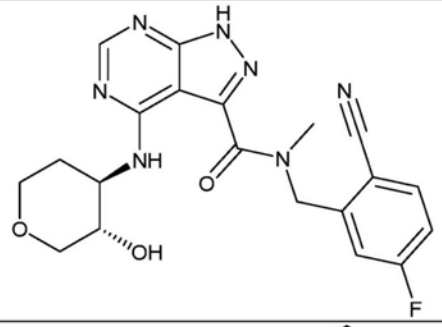
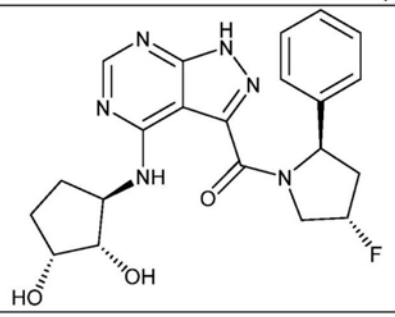
121		^{1}H NMR (500 MHz, DMSO-d_6) δ 14.14 (s, 1H), 9.01 (d, J = 7.2 Hz, 1H), 8.38 – 8.05 (m, 1H), 7.78 (t, J = 1.5 Hz, 1H), 7.74 – 7.62 (m, 2H), 5.44 – 5.31 (m, 2H), 4.92 (d, J = 4.0 Hz, 1H), 4.77 (dd, J = 21.4, 14.1 Hz, 1H), 4.46 (dd, J = 39.9, 14.0 Hz, 1H), 4.18 (d, J = 4.8 Hz, 1H), 3.79 (t, J = 4.7 Hz, 1H), 2.73 (dt, J = 16.8, 8.4 Hz, 1H), 2.20 – 1.99 (m, 2H), 1.78 – 1.60 (m, 3H), 1.56 – 1.32 (m, 2H)
122		1H-NMR (400 MHz, CD3OD) δ ppm 8.23-8.15 (m, 1H), 7.36-7.31 (m, 1H), 7.15-7.14 (m, 1H), 7.06 (d, 1H, J = 9.6 Hz), 6.96-6.94 (m, 1H), 5.41 (br.s, 1H), 5.37 (d, 1H, J = 50.4 Hz), 4.60-4.33 (m, 4H), 4.81-4.70 (m, 1H), 2.83-2.74 (m, 1H), 2.20-2.15 (m, 1H), 1.75-1.63 (m, 1H), 1.46-1.40 (m, 1H), 1.38-1.17 (m, 2H), 0.54-0.51 (m, 1H); LCMS: 457
123		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.60 (s, 1H), 7.48-7.43 (m, 2H), 5.48-5.45 (m, 1H), 5.43-5.33 (m, 1H), 5.16-5.02 (m, 1H), 4.80-4.75 (m, 1H), 4.55-4.48 (m, 2H), 4.06-4.03 (m, 1H), 2.83-2.81 (m, 1H), 2.55-2.43 (m, 2H), 1.93-1.85 (m, 3H).; LCMS: 472.1
124		1H-NMR (400 MHz, CD3OD) δ ppm 8.24-8.17 (m, 1H), 7.15-7.01 (m, 3H), 5.61-5.57 (m, 1H), 5.41 (d, 1H, J = 51.6 Hz), 4.88-4.86 (m, 1H), 4.43-4.37 (m, 2H), 4.09-4.00 (m, 1H), 3.87-3.85 (m, 1H), 3.28 (s, 3H), 2.82-2.80 (m, 1H), 2.45-2.24 (m, 3H), 1.78-1.69 (m, 2H); LCMS: 477

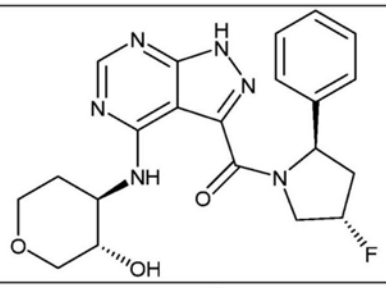
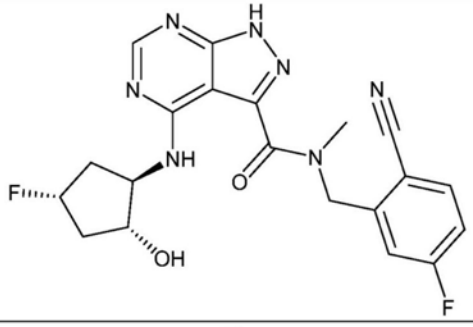
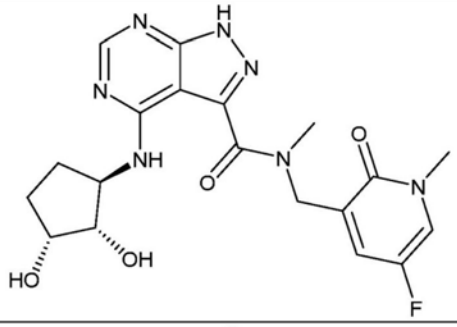
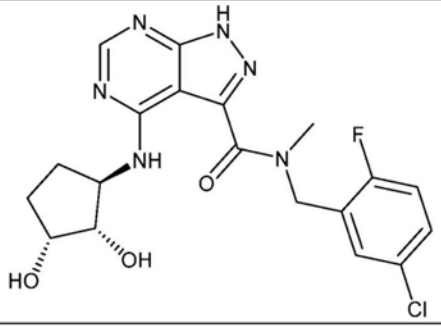
125		1H-NMR (400 MHz, CD3OD) δ ppm 8.24-8.17 (m, 1H), 7.14-6.84 (m, 3H), 5.61-5.57 (m, 1H), 5.41 (d, 1H, J = 51.6 Hz), 4.89-4.86 (m, 1H), 4.46-4.36 (m, 2H), 4.00-3.96 (m, 1H), 3.88-3.86 (m, 1H), 3.29 (s, 3H), 2.82-2.75 (m, 1H), 2.38-2.25 (m, 3H), 1.86-1.80 (m, 1H), 1.67-1.64 (m, 1H); LCMS:477
126		1H-NMR (400 MHz, CD3OD) δ ppm 8.19 (s, 1H), 6.96-6.94 (m, 2H), 6.80-6.77 (m, 1H), 5.44-5.30 (m, 2H), 4.79-4.76 (m, 1H), 4.48-4.38 (m, 2H), 3.87 (br.s, 1H), 3.65-3.53 (m, 1H), 2.84-2.74 (m, 1H), 2.05-2.00 (m, 2H), 1.78-1.72 (m, 2H), 1.53-1.35 (m, 3H).; LCMS: 477.1
127		1H-NMR (400 MHz, CD3OD) δ ppm 8.23-8.16 (m, 1H), 7.21 (s, 1H), 7.08-7.05 (m, 2H), 5.44-5.31 (m, 2H), 4.80-4.79 (m, 1H), 4.50-4.41 (m, 2H), 4.06-4.04 (m, 1H), 3.85-3.82 (m, 1H), 2.83-2.77 (m, 1H), 2.38-2.36 (m, 1H), 2.07-2.00 (m, 2H), 1.74-1.71 (m, 1H), 1.52-1.49 (m, 1H).; LCMS: 479
128		1H-NMR (400 MHz, CD3OD) δ ppm 8.23-8.20 (m, 2H), 7.59 (dd, 1H, J = 8.8, 3.2 Hz), 5.67-5.62 (m, 1H), 5.40 (d, 1H, J = 52.8 Hz), 4.63-4.40 (m, 3H), 4.03-4.01 (m, 1H), 3.80 (dd, 1H, J = 7.2, 4.4 Hz), 2.95-2.87 (m, 1H), 2.37-2.35 (m, 1H), 2.06-1.99 (m, 2H), 1.71-1.68 (m, 1H), 1.49-1.46 (m, 1H). ; LCMS: 480

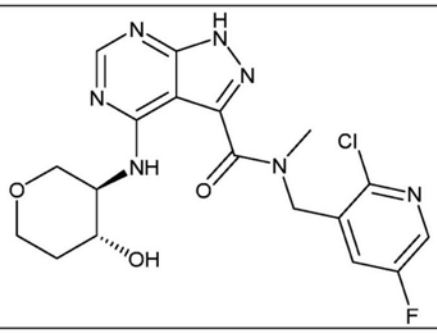
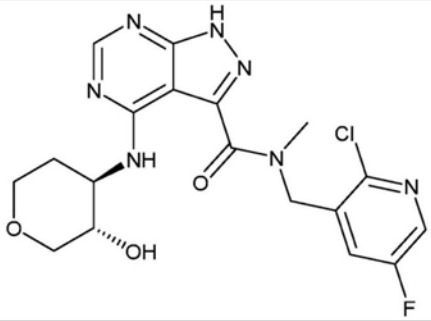
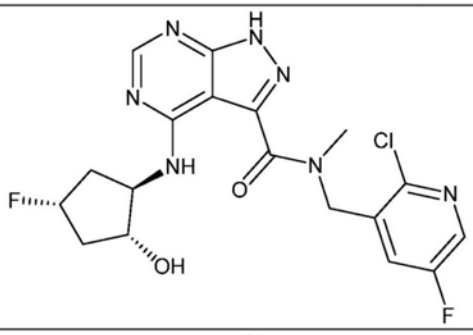
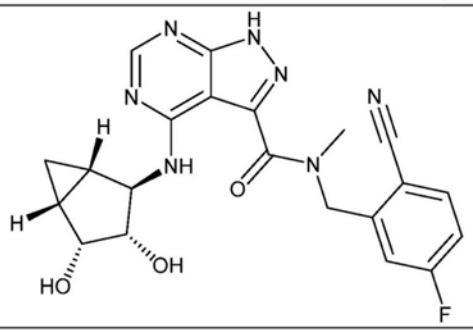
129		ND
130		1H-NMR (400 MHz, CD3OD) δ ppm 8.19-8.12 (m, 1H), 7.20 (s, 1H), 7.05 (d, 2H, J = 8.8 Hz), 5.43-5.30 (m, 2H), 4.77-4.76 (m, 1H), 4.49-4.39 (m, 2H), 3.87 (br.s, 1H), 3.56-3.53 (m, 1H), 2.81-2.75 (m, 1H), 2.15-2.13 (m, 1H), 1.81-1.73 (m, 2H), 1.58-1.35 (m, 4H).; LCMS: 493.1
131		1H-NMR (400 MHz, CDCl3) δ ppm 8.38 (br.s, 1H), 7.32-7.22 (m, 5H), 5.42-5.28 (m, 1H), 4.84-4.69 (m, 1H), 4.55 (br.s, 1H), 4.22 (br.s, 1H), 4.04 (br.s, 1H), 3.51 (s, 1.5H), 3.07 (s, 1.5H), 2.42 (br.s, 1H), 2.13 (br.s, 1H), 1.87 (br.s, 1H),1.71 (br.s, 1H).; LCMS: 383.2
132		1H-NMR (400 MHz, CDCl3) δ ppm 9.80 (s, 0.5H), 9.64 (s, 0.5H), 8.38 (d, 1H, J = 5.2 Hz), 7.35-7.27 (m, 1H), 7.13-7.02 (m, 3H), 5.40 (s, 1H), 4.82 (d, 1H, J = 4.8 Hz), 4.38 (br.s, 1H), 4.22 (s, 1H), 3.95 (s, 1H), 3.57 (s, 1.5H), 3.09 (s, 1.5H), 2.52 (br.s, 1H), 2.10-2.05 (m, 1H), 1.96 (m, 1H), 1.89-1.82 (m, 1H).; LCMS: 401.1

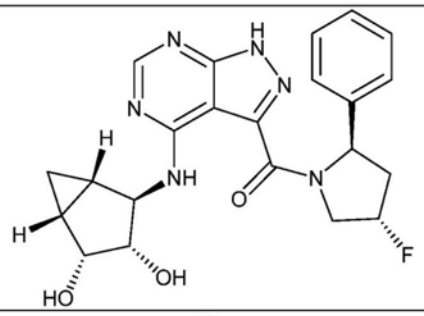
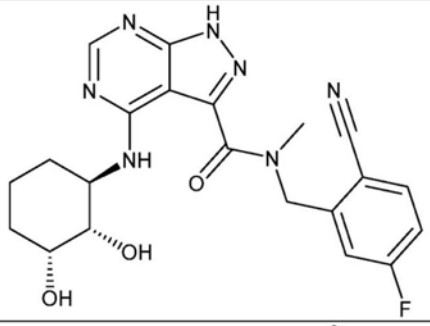
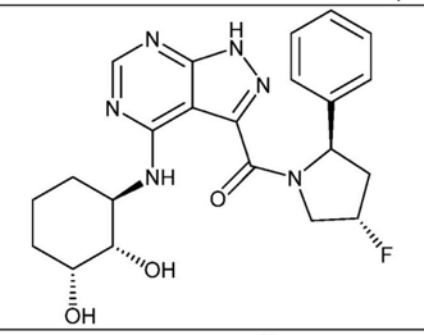
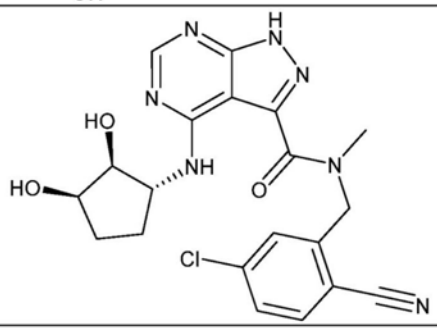
133		1H-NMR (400 MHz, CD3OD) δ ppm 8.35-8.33 (m, 1H), 8.16-8.12 (m, 1H), 7.97-7.88 (m, 1H), 7.34-7.30 (m, 1H), 5.47 (s, 1H), 4.85 (s, 1H), 4.38 (br.s, 1H), 4.15-4.12 (m, 1H), 4.03-3.98 (m, 1H), 3.70 (s, 1.5H), 3.35-3.25 (m, 1H), 3.22 (s, 1.5H), 2.48-2.40 (m, 1H), 2.14 (br.s, 1H), 1.81-1.75 (m, 1H).; LCMS: 402.1
134		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 4.8 Hz), 7.76-7.67 (m, 3H), 7.58-7.56 (m, 1H), 5.47 (d, 1H, J = 2.4 Hz), 4.91 (s, 1H), 4.42-4.37 (m, 1H), 4.15-4.14 (m, 1H), 4.04-3.99 (m, 1H), 3.65 (s, 1.5H), 3.16 (s, 1.5H), 2.48-2.45 (m, 1H), 1.84-1.81 (m, 1H), 1.71-1.66 (m, 2H).; LCMS: 408.1
135		1H NMR (400 MHz, DMSO-d6) δ 13.98 (s, 1H), 9.26 (m, 1H), 8.26 (d, J = 11.5 Hz, 1H), 7.99 (m, 1H), 7.45 – 7.28 (m, 2H), 5.47 (m, 1H), 5.02 (m, 1H), 4.25 (m, 1H), 3.94 (m, 1H), 3.56 (s, 1H), 3.30 (s, 3H), 3.09 (s, 1H), 2.22 – 2.03 (m, 1H), 1.91 (m, 1H), 1.84 – 1.64 (m, 2H), 1.64 – 1.34 (m, 2H).; LCMS: 410.2
136		1H NMR (400 MHz, DMSO-d6) δ 13.89 (s, 1H), 9.10 (ABqd, 1H), 8.21 (d, J = 10.6 Hz, 1H), 7.87 (ddd, J = 8.3, 4.7, 3.3 Hz, 1H), 7.33 (ddd, J = 9.4, 7.9, 3.2 Hz, 1H), 4.97 (m, 2H), 4.46 (s, 1H), 4.27 – 4.12 (m, 1H), 3.99 – 3.81 (m, 1H), 3.39 (d, J = 6.3 Hz, 3H), 3.29 (s, 3H), 2.18 – 2.01 (m, 1H), 1.86 – 1.35 (m, 5H).; LCMS: 416.1

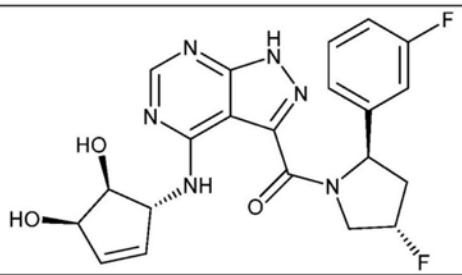
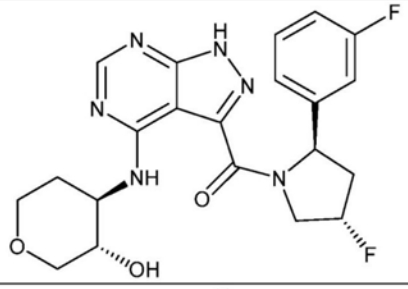
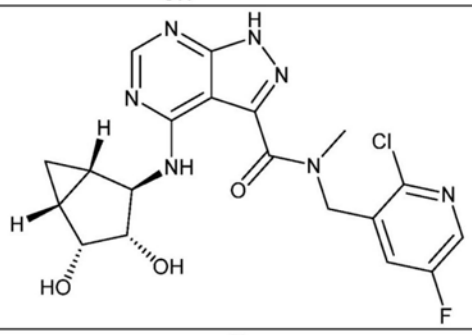
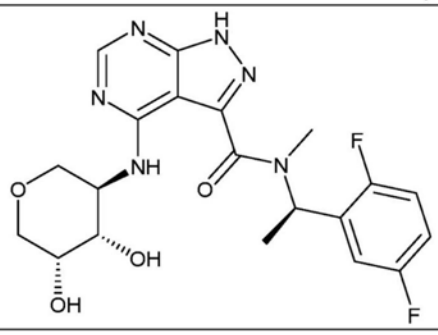
137		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (s, 1H), 7.52-7.41 (m, 4H), 5.49 (s, 1H), 4.91 (s, 1H), 4.63-4.60 (m, 1H), 4.27 (br.s, 1H), 4.04 (b.s, 1H), 3.67 (s, 1.7H), 3.21 (s, 1.3H), 2.56-2.55 (m, 1H), 2.23 (br.s, 1H), 1.90 (br.s, 1H), 1.71 (br.s, 1H).; LCMS: 417.1
138		1H-NMR (400 MHz, CD3OD) δ ppm 8.36-8.30 (m, 2H), 7.79-7.74 (m, 1H), 7.42-7.38 (m, 1H), 5.44 (s, 1H), 4.96 (s, 1H), 4.41-4.34 (m, 1H), 4.15-3.97 (m, 2H), 3.97 (s, 1H), 3.25 (s, 2H), 2.47-2.42 (m, 1H), 2.17-2.15 (m, 1H), 1.82-1.74 (m, 2H).; LCMS: 418.0
139		1H-NMR (400 MHz, CD3OD) δ ppm 8.25 (d, 1H, J = 5.2 Hz), 7.23-7.14 (m, 3H), 5.51 (s, 1H), 4.94 (s, 1H), 4.51-4.47 (m, 1H), 4.15-4.13 (m, 1H), 3.94-3.89 (m, 1H), 3.89 (s, 1.5H), 3.15 (s, 1.5H), 2.45-2.41 (m, 1H), 2.12-2.04 (m, 1H), 1.80-1.77 (m, 1H), 1.60-1.58 (m, 1H), 1.38-1.29 (m, 1H).; LCMS: 419.1
140		1H-NMR (400 MHz, CD3OD) δ ppm 8.40 (d, 1H, J = 8.8 Hz), 7.85 (dd, 1H, J = 7.6, 5.6 Hz), 7.31-7.22 (m, 2H), 6.22-6.17 (m, 1H), 6.09-6.04 (m, 1H), 5.61 (s, 1H), 5.05 (s, 1H), 5.02-5.01 (m, 1H), 4.61 (dd, 1H, J = 14.8, 2.8 Hz), 4.12 (td, 1H, J = 18.4, 5.6 Hz), 3.69 (s, 1.5H), 3.21 (s, 1.5H).; LCMS: 424.1

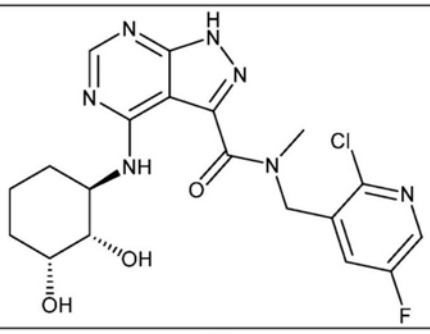
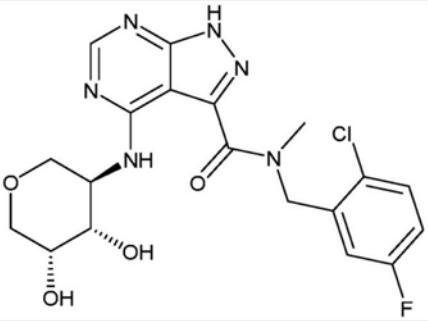
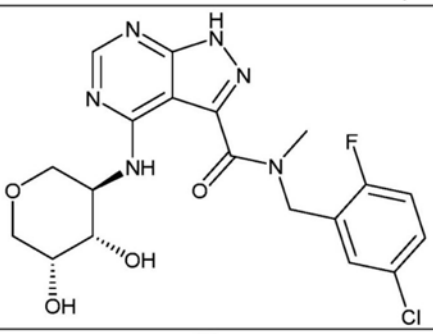
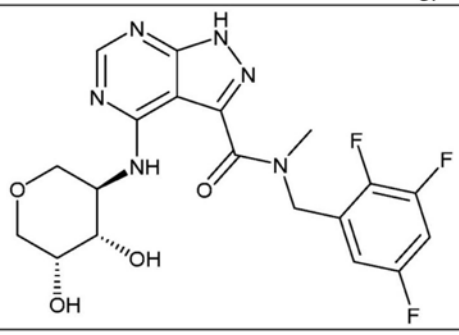
141		1H-NMR (400 MHz, CDCl3) δ ppm 8.38 (br.s, 1H), 7.68-7.65 (m, 1H), 7.10-7.03 (m, 2H), 5.55-5.46 (m, 1H), 4.94-4.83 (m, 1H), 4.56 (br.s, 1H), 4.21 (br.s, 1H), 4.09-4.02 (m, 1H), 3.58 (s, 1.5H), 3.11 (s, 1.5H), 2.42 (br.s, 1H), 2.10 (br.s, 1H), 1.85 (br.s, 1H), 1.69 (s, 1H).; LCMS: 426.1
142		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (d, 1H, J = 5.6 Hz), 7.75-7.65 (m, 2H), 7.37-7.34 (m, 1H), 5.53 (s, 1H), 4.95 (s, 1H), 4.38-4.33 (m, 1H), 4.13-4.11 (m, 1H), 4.04-3.96 (m, 1H), 3.68 (s, 1.5H), 3.20 (s, 1.5H), 2.45-2.42 (m, 1H), 2.17-2.13 (m, 1H), 1.80-1.69 (m, 2H).; LCMS: 426.1
143		1H-NMR (400 MHz, CD3OD) δ ppm 8.32 (d, 1H, J = 8.4 Hz), 7.87-7.82 (m, 1H), 7.33-7.23 (m, 2H), 5.66-5.55 (m, 1H), 5.11-5.02 (m, 1H), 4.06-3.95 (m, 3H), 3.68 (s, 1.5H), 3.67-3.58 (m, 1H), 3.52-3.49 (m, 1 H), 3.25-3.23 (m, 1H), 3.22 (s, 1.5H), 2.20-2.11 (m, 1H), 1.82-1.74 (m, 1H).; LCMS: 426.1
144		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.32-7.25 (m, 3H), 7.24-7.19 (m, 2H), 5.47-5.35 (m, 2H), 4.84-4.83 (m, 1H), 4.53-4.29 (m, 2H), 4.05-3.97 (m, 1H), 3.90-3.87 (m, 1H), 2.89-2.78 (m, 1H), 2.38-2.35 (m, 1H), 2.18-2.06 (m, 2H), 1.77-1.61 (m, 2H).; LCMS: 427.1

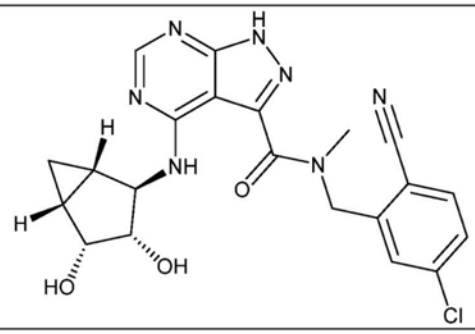
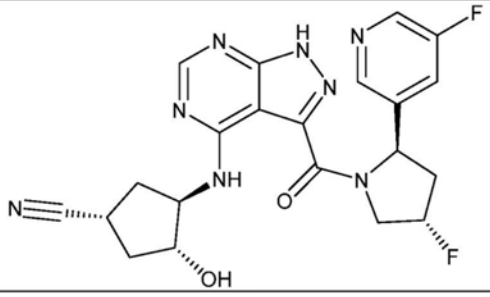
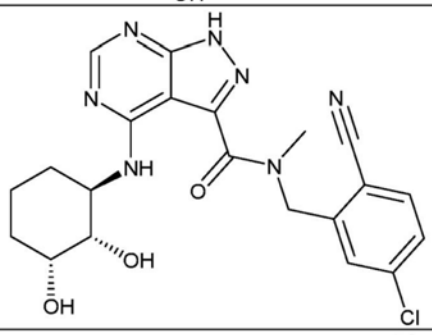
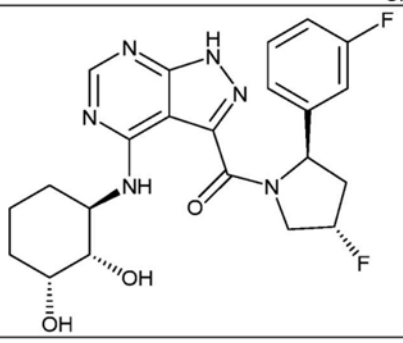
145		1H-NMR (400 MHz, CD3OD) δ ppm 8.33 (s, 1H), 7.34-7.19 (m, 5H), 5.48-5.36 (m, 2H), 4.93 (br.s, 1H), 4.53-4.44 (m, 1H), 3.98-3.91 (m, 3H), 3.50-3.46 (m, 2H), 3.23-3.20 (m, 1H), 2.80-2.79 (m, 1H), 2.13-2.07 (m, 2H), 1.77-1.74 (m, 1H).; LCMS: 427.2
146		1H-NMR (400 MHz, CD3OD) δ ppm 8.17 (d, 1H, J = 8.4 Hz), 7.78-7.72 (m, 1H), 7.21-7.11 (m, 2H), 5.52 (s, 1H), 5.48-4.98 (m, 1H), 4.95 (s, 1H), 4.50-4.44 (m, 1H), 4.10-4.03 (m, 1H), 3.56 (s, 1.5H), 3.10 (s, 1.5H), 2.52-2.41 (m, 2H), 1.88-1.81 (m, 2H).; LCMS: 428.1
147		1H NMR (400 MHz, DMSO-d6) δ 13.92 (br d, 1H), 9.19 (ABqd, 1H), 9.05 (d, J = 7.2 Hz, 0H), 8.20 (d, J = 9.9 Hz, 1H), 7.87 (m, 1H), 7.33 (m, 1H), 4.97 (d, J = 3.8 Hz, 1H), 4.87 (dd, J = 14.6, 5.5 Hz, 1H), 4.51 – 4.42 (m, 2H), 4.34 (m, 1H), 3.88 (m, 1H), 3.65 (ddt, J = 26.8, 7.3, 5.1 Hz, 1H), 3.40 (d, J = 6.3 Hz, 3H), 3.29 (s, 3H), 2.20 (m, 1H), 1.87 (m, 1H), 1.52 (m, 1H), 1.36 – 1.15 (m, 1H).; LCMS: 432.1
148		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (d, 1H, J = 4.4 Hz), 7.42 (d, 1H, J = 2.4 Hz), 7.41-7.32 (m, 1H), 7.18-7.14 (m, 1H), 5.48 (s, 1H), 4.91-4.89 (m, 1H), 4.40-4.36 (m, 1H), 4.15-4.13 (m, 1H), 4.05-3.99 (m, 1H), 3.66 (s, 1.5H), 3.17 (s, 1.5H), 3.47-2.44 (m, 1H), 2.18-2.14 (m, 1H), 1.82-1.80 (m, 1H), 1.71-1.65 (m, 1H).; LCMS: 435.1

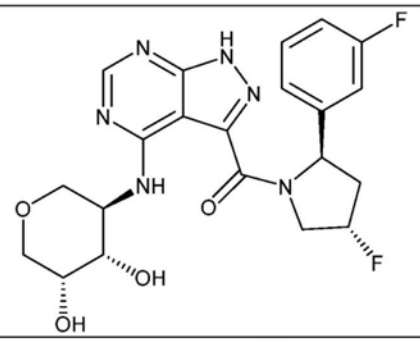
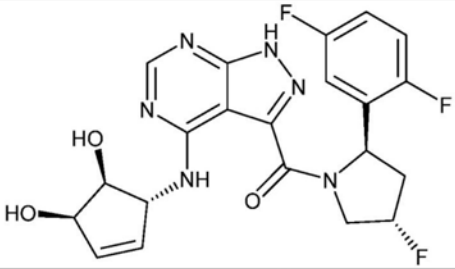
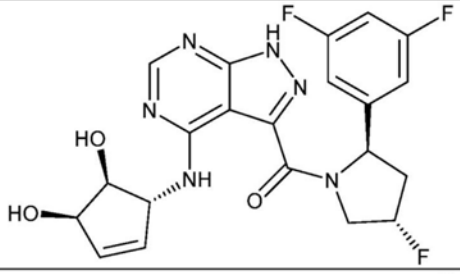
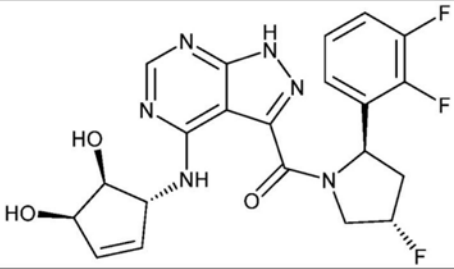
149		1H-NMR (400 MHz, CD3OD) δ ppm 8.35 (d, 1H, J = 12.4 Hz), 8.25 (d, 1H, J = 8.8 Hz), 7.64-7.59 (m, 1H), 5.38 (s, 1H), 4.92 (s, 1H), 4.16-3.88 (m, 4H), 3.72 (s, 1H), 3.59-3.39 (m, 2H), 3.26 (s, 2H), 2.13-2.00 (m, 1H), 1.78-1.68 (m, 1H).; LCMS: 436.1
150		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (dd, 1H, J = 12.8, 2.0 Hz), 8.25 (dd, 1H, J = 9.2, 2.0 Hz), 7.64-7.59 (m, 1H), 5.38 (s, 1H), 4.02-3.94 (m, 3H), 3.72 (s, 1H), 3.68-3.48 (m, 2H), 3.24 (s, 2H), 3.23-3.22 (m, 1H), 2.19-2.10 (m, 1H), 1.88-1.75 (m, 1H).; LCMS: 436.1
151		1H-NMR (400 MHz, CD3OD) δ ppm 8.27-8.23 (m, 2H), 7.61-7.57 (m, 1H), 5.32 (s, 1H), 5.24-5.10 (m, 1H), 4.94 (s, 1H), 4.58-4.49 (m, 1H), 4.18-4.08 (m, 1H), 3.67 (s, 1H), 3.20 (s, 2H), 2.65-2.48 (m, 2H), 1.99-1.82 (m, 2H).; LCMS: 438.1
152		1H-NMR (400 MHz, CD3OD) δ ppm 8.40 (d, 1H, J = 6.0 Hz), 7.88-7.84 (m, 1H), 7.36-7.24 (m, 2H), 5.62 (d, 1H, J = 4.0 Hz), 5.07 (d, 1H, J = 5.6 Hz), 4.61 (dt, 1H, J = 32.0, 5.6 Hz), 4.30 (d, 1H, J = 10.4 Hz), 3.94 (dd, 1H, J = 20.8, 6.0 Hz), 3.72 (s, 1.5H), 3.23 (s, 1.5H), 1.84-1.78 (m, 1H), 1.59-1.53 (m, 1H), 1.32-1.28 (m, 1H), 0.71-0.66 (m, 1H).; LCMS: 438.1

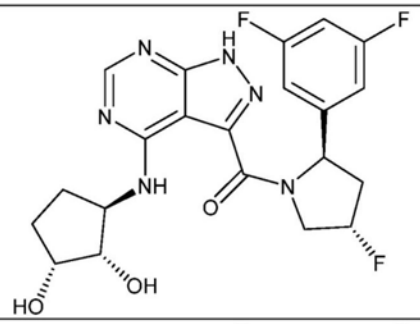
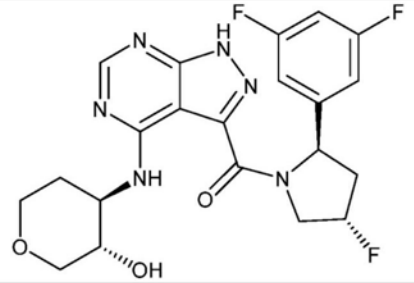
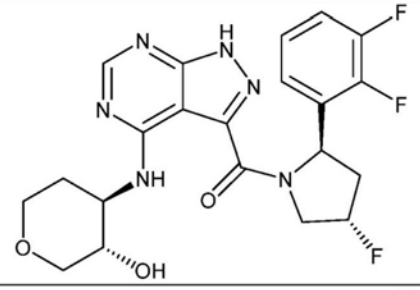
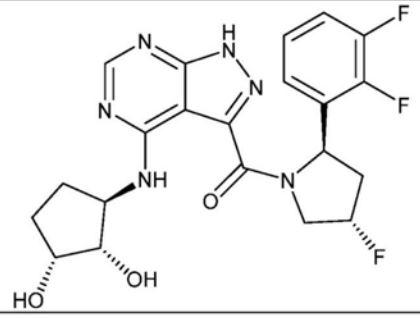
153		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.32 (m, 1H), 7.32-7.18 (m, 6H), 5.48-5.35 (m, 2H), 4.92-4.90 (m, 1H), 4.49-4.45 (m, 1H), 4.39-4.36 (m, 1H), 4.24-4.20 (m, 1H), 3.74-3.73 (m, 1H), 2.83-2.75 (m, 1H), 2.24-2.10 (m, 1H), 1.70-1.67 (m, 1H), 1.48-1.46 (m, 1H), 1.28-1.20 (m, 1H), 0.65-0.59 (m, 1H).; LCMS: 439.1
154		1H-NMR (400 MHz, CD3OD) δ ppm 8.13 (br.s, 1H), 7.81 (br.s, 1H), 7.29 (br.s, 1H), 7.20 (br.s, 1H), 5.61 (br.s, 1H), 5.02-4.99 (m, 1H), 4.42 (br.s, 1H), 4.02-3.97 (m, 1H), 3.62 (s, 2H), 3.14 (s, 1H), 2.06 (s, 1H), 1.82-1.40 (m, 5H). ; LCMS: 440.3
155		1H-NMR (400 MHz, CD3OD) δ ppm 8.31 (s, 1H), 7.32-7.25 (m, 3H), 7.24-7.20 (m, 2H), 5.47-5.35 (m, 2H), 4.53-4.43 (m, 1H), 4.10-3.97 (m, 3H), 3.49-3.46 (m, 1H), 2.81-2.79 (m, 1H), 2.17-2.03 (m, 2H), 1.88-1.83 (m, 2H), 1.59-1.49 (m, 3H).; LCMS: 441.1
156		1H-NMR (400 MHz, CD3OD) δ ppm 8.33 (d, 1H, J = 8.0 Hz), 7.80-7.77 (m, 1H), 7.58-7.50 (m, 2H), 5.61-5.60 (m, 1H), 5.05 (d, 1H, J = 4.8 Hz), 4.42-4.37 (m, 1H), 4.15-4.11 (m, 1H), 4.04-3.97 (m, 1H), 3.69 (s, 1.5H), 3.22 (s, 1.5H), 2.47-2.41 (m, 1H), 2.16-2.13 (m, 1H), 1.81-1.69 (m, 2H).; LCMS: 442.1

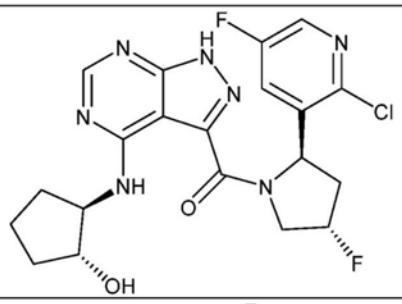
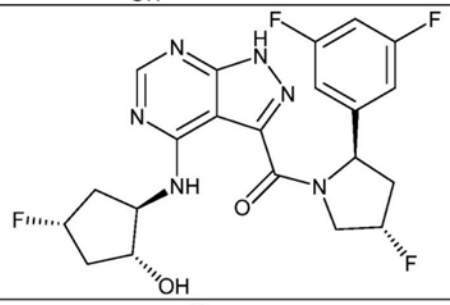
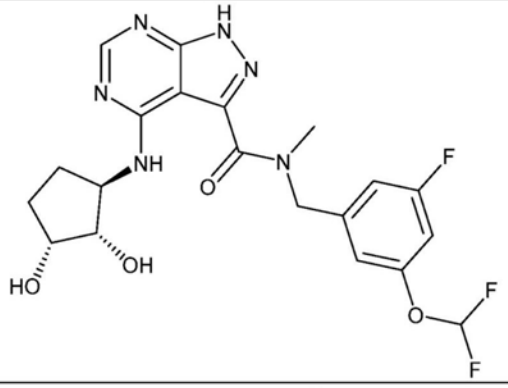
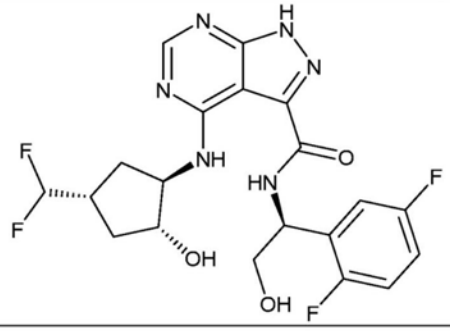
157		1H-NMR (400 MHz, CD3OD) δ ppm 8.32-8.24 (m, 1H), 7.35-7.31 (m, 1H), 7.14-6.93 (m, 3H), 6.10-5.96 (m, 2H), 5.47-5.03 (m, 2H), 4.83-4.87 (m, 1H), 4.52-4.38 (m, 2H), 4.07-3.94 (m, 1H), 2.83-2.67 (m, 1H), 2.17-2.01 (m, 1H).; LCMS: 443.1
158		1H-NMR (400 MHz, CD3OD) δ ppm 8.39-8.32 (m, 1H), 7.39-6.97 (m, 4H), 5.51-5.35 (m, 2H), 4.96-4.91 (m, 1H), 4.49-4.46 (m, 1H), 4.06-3.92 (m, 3H), 3.55-3.49 (m, 2H), 3.26-3.24 (m, 1H), 2.85-2.83 (m, 1H), 2.21-2.11 (m, 2H), 1.78-1.72 (m, 1H).; LCMS: 445.2
159		1H-NMR (400 MHz, CD3OD) δ ppm 8.40 (s, 0.5H), 8.37 (s, 0.5H), 8.23 (dd, 1H, J = 8.8, 2.8 Hz), 7.64-7.59 (m, 1H), 5.36 (s, 1H), 4.89 (s, 1H), 4.57 (td, 1H, J = 49.2, 4.2 Hz), 4.29 (s, 0.5H), 4.26 (s, 0.5H), 3.90 (dd, 1H, J = 26.4, 6.0 Hz), 3.70 (s, 1.5H), 3.25 (s, 1.5H), 1.82-1.81 (m, 1H), 1.56-1.48 (m, 1H), 1.30-1.27 (m, 1H), 1.68-1.62 (m, 1H).; LCMS: 448.1
160		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (d, 1H, J = 4.4 Hz), 7.31-7.29 (m, 1H), 7.13-7.06 (m, 2H), 6.24-6.19 (m, 1H), 4.37-4.35 (m, 1H), 4.12-4.09 (m, 1H), 3.95 (s, 1H), 3.90-3.87 (m, 2H), 3.67-3.65 (m, 1H), 3.47-3.44 (m, 1H), 3.33 (s, 1.5H), 2.86 (s, 1.5H), 1.79 (d, 1.5H, J = 6.8 Hz), 1.66 (d, 1.5H, J = 6.4 Hz).; LCMS: 449.1

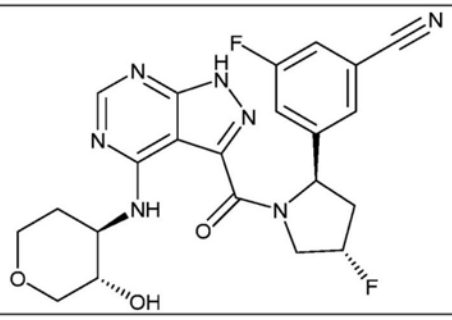
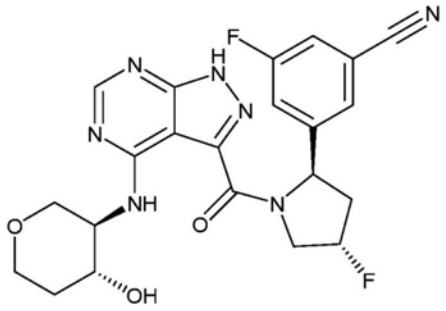
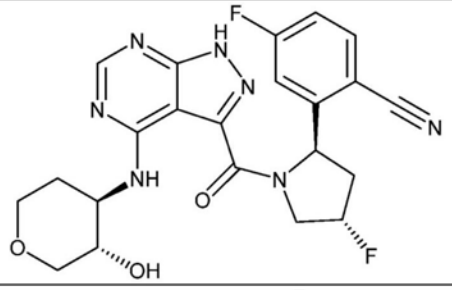
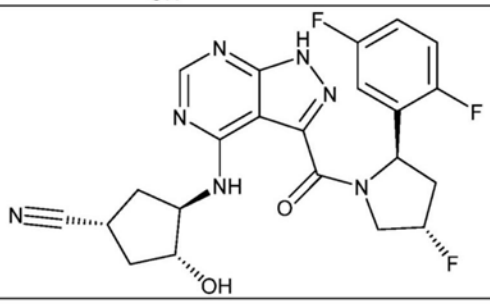
161		1H-NMR (400 MHz, CD3OD) δ ppm 8.25-8.19 (m, 2H), 7.16 (s, 1H), 5.33 (s, 1H), 4.94-4.88 (m, 1H), 4.54-4.46 (m, 1H), 4.03-3.95 (m, 1H), 3.66 (s, 1.5H), 3.60-3.58 (m, 1H), 3.21 (s, 1.5H), 2.20-2.00 (m, 1H), 1.85-1.81 (m, 2H), 1.60-1.35 (m, 3H).; LCMS: 450.1
162		1H-NMR (400 MHz, CD3OD) δ ppm 8.40-8.37 (m, 1H), 7.49-7.44 (m, 1H), 7.10-7.03 (m, 2H), 5.46 (s, 2H), 4.36-4.35 (m, 1H), 4.11-4.10 (m, 1H), 3.97-3.85 (m, 3H), 3.67-3.65 (m, 2.5H), 3.49-3.40 (m, 1H), 3.22 (s, 1.5H).; LCMS: 451
163		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 4.0 Hz), 7.43-7.30 (m, 2H), 7.17-7.12 (m, 1H), 5.45 (s, 1H), 4.88-4.86 (m, 1H), 4.41-4.37 (m, 1H), 4.16-4.11 (m, 1H), 3.97-3.95 (m, 1H), 3.89-3.86 (m, 2H), 3.69-3.65 (m, 1H), 3.64 (s, 1.5H), 3.47-3.45 (m, 1H), 3.16 (s, 1.5H).; LCMS: 451.1
164		1H-NMR (400 MHz, CD3OD) δ ppm 8.30 (d, 1H, J = 5.6 Hz), 7.11-6.96 (m, 2H), 5.48 (s, 1H), 4.93 (s, 1H), 4.46 (d, 1H, J = 7.6 Hz), 4.12-4.09 (m, 1H), 3.95-3.80 (m, 3H), 3.66-3.64 (m, 2.5H), 3.44-3.41 (m, 1H), 3.18 (s, 1.5H).; LCMS: 453.1

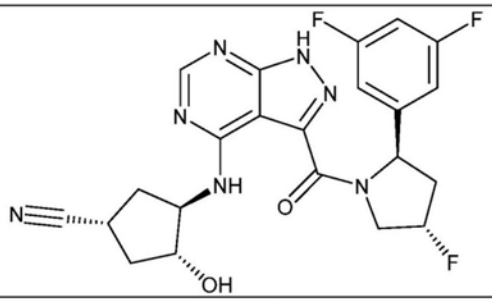
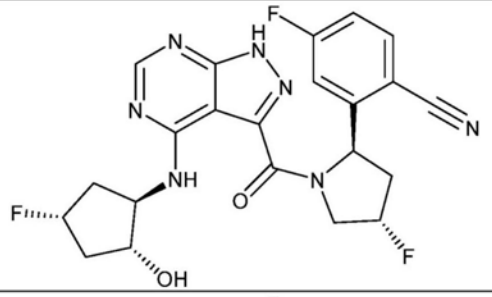
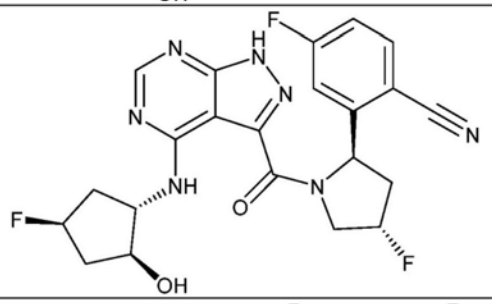
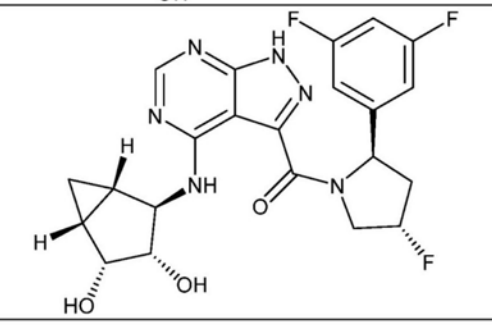
165		1H-NMR (400 MHz, CD3OD) δ ppm 8.33 (d, 1H, J = 6.4 Hz), 7.79-7.76 (m, 1H), 7.60-7.53 (m, 2H), 5.58 (d, 1H, J = 5.2 Hz), 5.03 (d, 1H, J = 5.2 Hz), 4.64-4.57 (m, 1H), 4.36-4.33 (m, 1H), 3.93-3.87 (dd, 1H, J = 17.2, 6.4 Hz), 3.69 (s, 1.5H), 3.02 (s, 1.5H), 1.80-1.76 (m, 1H), 1.55-1.51 (m, 1H), 1.29-1.25 (m, 1H), 0.67-0.62 (m, 1H). ; LCMS: 454.1
166		1H-NMR (400 MHz, CD3OD) δ ppm 8.47 (s, 1H), 8.38-8.23 (m, 2H), 7.70 (d, 1H, J = 9.6 Hz), 5.52-5.38 (m, 2H), 4.93-4.89 (m, 1H), 4.56-4.43 (m, 1H), 4.34-4.32 (m, 1H), 4.11-4.07 (m, 1H), 3.18-3.14 (m, 1H), 2.86-2.82 (m, 1H), 2.56-2.52 (m, 1H), 2.51-2.38 (m, 1H), 2.19-2.16 (m, 2H), 1.94-1.91 (m, 1H).; LCMS: 455.1
167		1H-NMR (400 MHz, CD3OD) δ ppm 8.32 (s, 0.5H), 8.30 (s, 0.5H), 7.80-7.77 (m, 1H), 7.58-7.52 (m, 2H), 5.66-5.55 (m, 1H), 5.10-5.00 (m, 1H), 4.20-4.07 (m, 2H), 3.70 (s, 1.5 H), 3.66-3.59 (m, 1H), 3.22 (s, 1.5H), 2.14-2.07 (m, 1H), 1.90-1.82 (m, 2H), 1.64-1.55 (m, 3H). ; LCMS: 456.1
168		1H-NMR (400 MHz, CD3OD) δ ppm 8.31-8.23 (m, 1H), 7.37-7.33 (m, 1H), 7.15 (d, 1H, J = 8.0 Hz), 7.06 (d, 1H, J = 10.0 Hz), 7.00-6.96 (m, 1H), 5.48-5.35 (m, 2H), 4.54-4.44 (m, 1H), 4.13-4.01 (m, 2H), 3.51-3.48 (m, 1H), 2.84-2.80 (m, 1H), 2.32-2.04 (m, 2H), 1.84-1.79 (m, 2H), 1.59-1.50 (m, 3H).; LCMS: 459.2

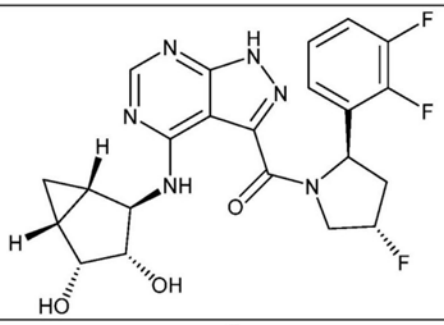
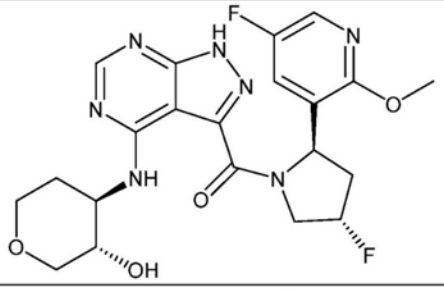
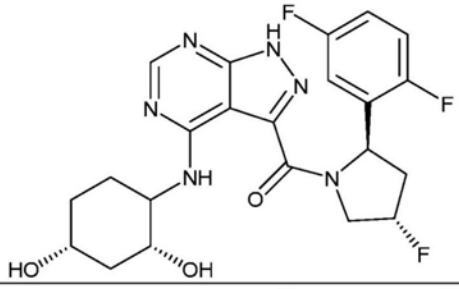
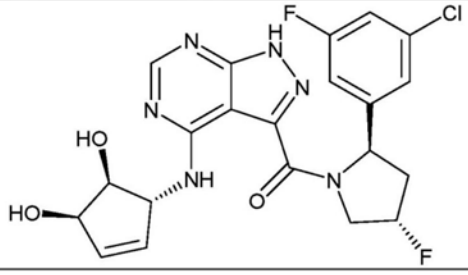
169		1H-NMR (400 MHz, CD3OD) δ ppm 8.37-8.29 (m, 1H), 7.44-6.96 (m, 4H), 5.46 (br.s, 1H), 5.40 (d, 1H, J = 52.0 Hz), 4.87-4.82 (m, 1H), 4.47 (dd, 1H, J = 38.4, 14.8 Hz), 4.30 (br.s, 1H), 4.05-3.83 (m, 2H), 3.75-3.58 (m, 2H), 3.55-3.36 (m, 2H), 3.09-2.81 (m, 1H), 2.21-2.08 (m, 1H).; LCMS: 461.1
170		1H-NMR (400 MHz, CD3OD) δ ppm 8.29 (s, 1H), 7.16-7.02 (m, 3H), 6.08-6.00 (m, 2H), 5.62-5.58 (m, 1H), 5.42 (d, 1H, J = 52.4 Hz), 5.16 (br.s, 1H), 4.66-4.58 (m, 2H), 4.49-4.36 (m, 1H), 4.07-3.94 (m, 1H), 2.88-2.78 (m, 1H), 2.25-2.09 (m, 1H).; LCMS: 461.1
171		1H-NMR (400 MHz, CD3OD) δ ppm 8.35-8.28 (m, 1H), 6.96-6.94 (m, 1H), 6.85-6.78 (m, 2H), 6.23-6.04 (m, 2H), 5.46-5.33 (m, 2H), 5.04 (br.s, 1H), 4.56-4.40 (m, 2H), 4.11-3.97 (m, 1H), 2.86-2.76 (m, 1H), 2.19-2.03 (m, 1H).; LCMS: 461.1
172		1H-NMR (400 MHz, CD3OD) δ ppm 8.32-8.23 (m, 1H), 7.16-7.09 (m, 3H), 6.10-5.98 (m, 2H), 5.66-5.61 (m, 1H), 5.43 (d, 1H, J = 52.0 Hz), 5.06-5.05 (m, 1H), 4.55-4.39 (m, 3H), 3.96-3.93 (m, 1H), 2.87-2.77 (m, 1H), 2.26-2.12 (m, 1H). ; LCMS: 461.1

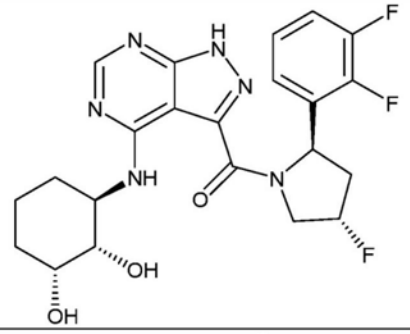
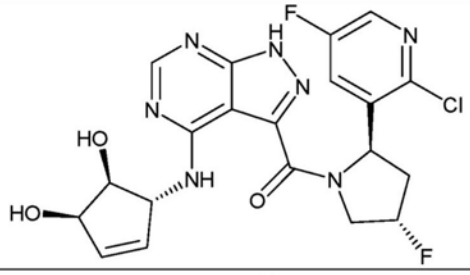
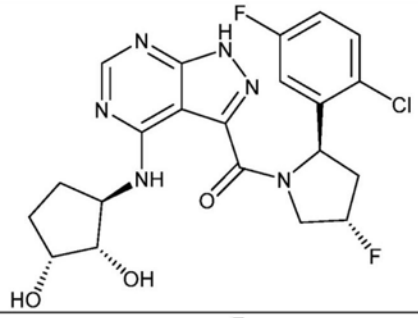
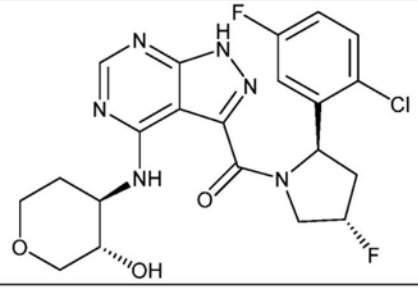
173		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 6.95 (d, 2H, J = 6.8 Hz), 6.87-6.67 (m, 1H), 5.46-5.33 (m, 2H), 4.91-4.89 (m, 1H), 4.53-4.50 (m, 1H), 4.34-4.30 (m, 1H), 4.05-4.04 (m, 1H), 3.91-3.88 (m, 1H), 2.84-2.78 (m, 1H), 2.38-2.37 (m, 1H), 2.10-2.06 (m, 2H), 1.74-1.61 (m, 2H).; LCMS: 463.1
174		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.26 (m, 1H), 6.98 (d, 1H, J = 6.4 Hz), 6.88-6.70 (m, 2H), 5.48-5.35 (m, 2H), 4.55-4.52 (m, 1H), 4.01-3.90 (m, 3H), 3.55-3.48 (m, 2H), 3.25-3.19 (m, 1H), 2.84-2.78 (m, 1H), 2.18-2.09 (m, 2H), 1.76-1.66 (m, 2H).; LCMS: 463.1
175		1H-NMR (400 MHz, CD3OD) δ ppm 8.32-8.24 (m, 1H), 7.17-6.96 (m, 3H), 5.69-5.65 (m, 1H), 5.46 (d, 1H, J = 52.0 Hz), 4.94-4.89 (m, 1H), 4.57-4.37 (m, 1H), 4.03-3.88 (m, 3H), 3.52-3.48 (m, 2H), 3.24-3.22 (m, 1H), 2.87-2.81 (m, 1H), 2.16-2.10 (m, 2H), 1.74-1.71 (m, 1H). ; LCMS: 463.1
176		1H-NMR (400 MHz, CD3OD) δ ppm 8.24-8.16 (m, 1H), 7.16-6.92 (m, 3H), 5.68-5.64 (m, 1H), 5.42 (d, 1H, J = 52.0 Hz), 4.91-4.89 (m, 1H), 4.48-4.41 (m, 2H), 4.06-4.04 (m, 1H), 3.84-3.81 (m, 1H), 2.86-2.80 (m, 1H), 2.40-2.35 (m, 1H), 2.09-2.01 (m, 2H), 1.74-1.72 (m, 1H), 1.53-1.51 (m, 1H). ; LCMS: 463.1

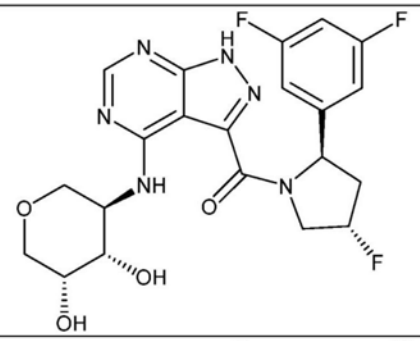
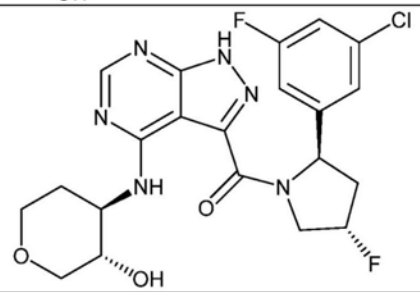
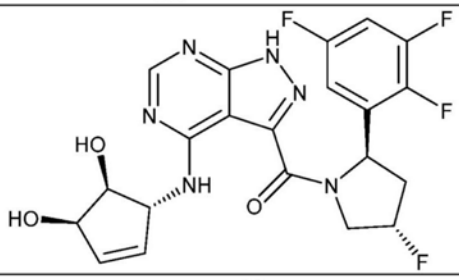
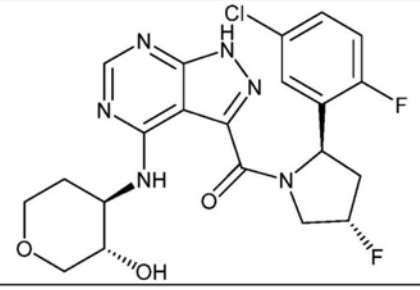
177		1H NMR (400 MHz, DMSO-d6) δ 14.17 (s, 1H), 8.99 (d, J = 7.2 Hz, 1H), 8.38 (d, J = 2.9 Hz, 1H), 8.26 (s, 1H), 7.87 (dd, J = 8.9, 3.0 Hz, 1H), 5.67 – 5.34 (m, 3H), 4.92 (d, J = 3.9 Hz, 1H), 4.80 (dd, J = 21.4, 14.0 Hz, 1H), 4.59 – 4.34 (m, 1H), 4.18 (s, 1H), 3.85 – 3.75 (m, 1H), 2.87 – 2.71 (m, 1H), 2.26 – 2.00 (m, 2H), 1.66 (dq, J = 13.1, 5.5 Hz, 2H), 1.58 – 1.34 (m, 2H).; LCMS: 464
178		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 6.97-6.95 (m, 2H), 6.84-6.79 (m, 1H), 5.47-5.41 (m, 1H), 5.10 (d, 1H, J = 53.6 Hz), 4.82 (s, 1H), 4.54-4.41 (m, 2H), 4.14-4.11 (m, 1H), 2.83-2.60 (m, 1H), 2.54-2.47 (m, 2H), 2.07-1.84 (m, 3H).; LCMS: 465.1
179		1H-NMR (400 MHz, CD3OD) δ ppm 8.42 (br.s, 1H), 7.13-7.03 (m, 2H), 6.97-6.74 (m, 2H), 5.48 (d, 1H, J = 1.6 Hz), 4.91 (s, 1H), 4.47-4.43 (m, 1H), 4.20-4.19 (m, 1H), 4.09-4.03 (m, 1H), 3.69 (s, 1.5H), 3.21 (s, 1.5H), 2.53-2.49 (m, 1H), 2.23-2.20 (m, 1H), 1.87-1.69 (m, 2H).; LCMS: 467.1
180		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.22-7.04 (m, 3H), 5.85 (td, 1H, J = 57.2, 4.4 Hz), 5.54-5.51 (m, 1H), 4.25-4.16 (m, 2H), 3.90-3.83 (m, 2H), 3.35-3.33 (m, 1H), 2.31-2.19 (m, 2H), 1.92-1.85 (m, 1H), 69-1.66 (m, 1H).; LCMS: 469.1

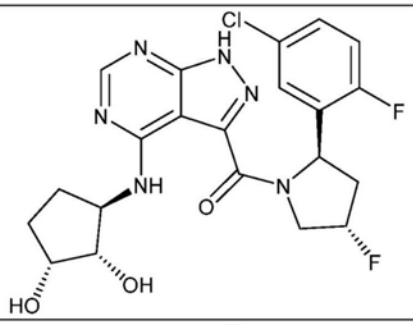
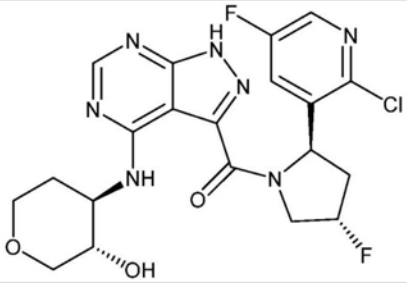
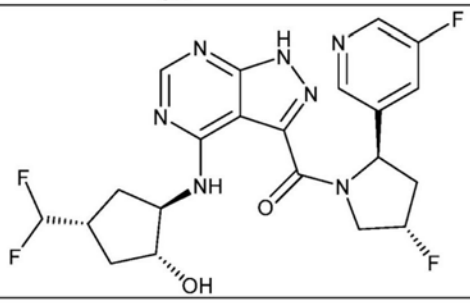
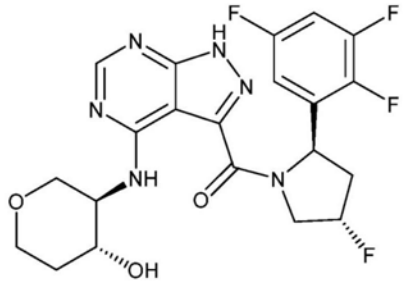
181		1H NMR (400 MHz, DMSO-d6) δ 14.18 (s, 1H), 9.10 (d, J = 7.3 Hz, 1H), 8.25 (s, 1H), 7.78 (s, 1H), 7.74 – 7.59 (m, 2H), 5.57 – 5.35 (m, 2H), 5.06 (d, J = 5.4 Hz, 1H), 4.76 – 4.63 (m, 1H), 4.50 (dd, J = 39.8, 14.4 Hz, 1H), 4.09 (s, 2H), 3.69 (dd, J = 11.3, 4.5 Hz, 2H), 3.42 – 3.37 (m, 1H), 3.09 (dd, J = 11.4, 8.7 Hz, 1H), 2.73 (dd, J = 33.7, 20.2 Hz, 1H), 2.09 (q, J = 13.8, 11.9 Hz, 2H), 1.50 – 1.33 (m, 1H).; LCMS: 470
182		1H NMR (400 MHz, DMSO-d6) δ 14.17 (s, 1H), 9.11 (d, J = 7.8 Hz, 1H), 8.26 (s, 1H), 7.88 – 7.55 (m, 3H), 5.52 (s, 1H), 5.45 – 5.35 (m, 1H), 5.02 (d, J = 4.7 Hz, 1H), 4.73 (dd, J = 21.9, 13.9 Hz, 1H), 4.48 (dd, J = 39.7, 13.0 Hz, 1H), 4.03 (dd, J = 7.5, 3.7 Hz, 1H), 3.92 (dd, J = 11.1, 3.7 Hz, 1H), 3.73 (dd, J = 11.0, 5.7 Hz, 1H), 3.56 – 3.46 (m, 1H), 3.43 – 3.34 (m, 1H), 3.18 (dd, J = 11.3, 6.5 Hz, 1H), 2.83 – 2.63 (m, 1H), 2.19 – 1.95 (m, 1H), 1.81 – 1.65 (m, 1H), 1.42 (d, J = 4.4 Hz, 1H).; LCMS: 470
183		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.26 (m, 1H), 7.84-7.81 (m, 1H), 7.36 (dd, 1H, J = 9.2, 2.0 Hz), 7.24-7.19 (m, 1H), 5.66 (dd, 1H, J = 10.4, 8.0 Hz), 5.49 (d, 1H, J = 52.0 Hz), 4.95-4.89 (m, 1H), 4.65-4.56 (m, 1H), 3.97-3.89 (m, 3H), 3.51-3.48 (m, 2H), 3.25-3.22 (m, 1H), 2.90-2.86 (m, 1H), 2.28-2.11 (m, 2H), 1.74-1.70 (m, 1H).; LCMS: 470.1
184		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.26 (m, 1H), 7.13-7.07 (m, 3H), 5.60-5.55 (m, 1H), 5.43 (d, 1H, J = 52.0 Hz), 4.47-4.33 (m, 2H), 4.13-4.09 (m, 1H), 3.20-3.14 (m, 2H), 2.83-2.78 (m, 1H), 2.53-2.51 (m, 1H), 2.49-2.38 (m, 1H), 2.21-2.15 (m, 2H), 1.92-1.89 (m, 1H).; LCMS: 472.1

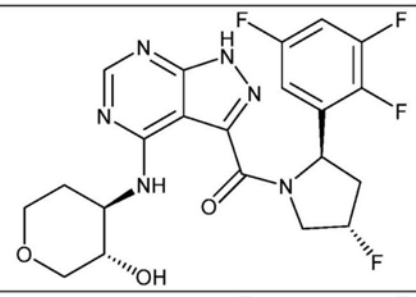
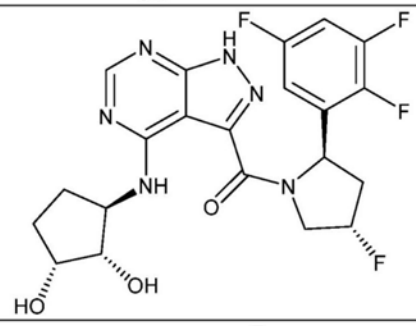
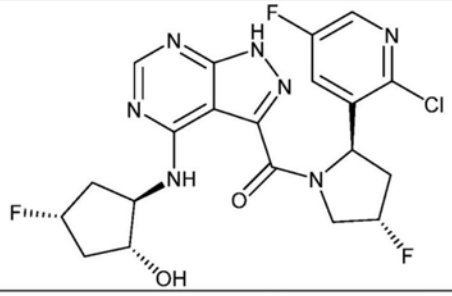
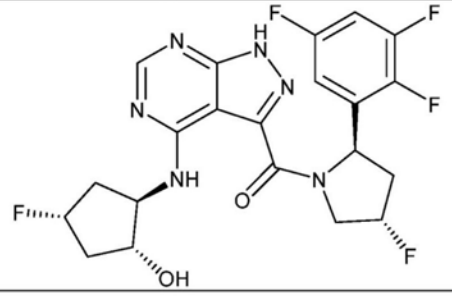
185		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.27 (m, 1H), 6.97 (d, 2H, J = 6.0 Hz), 6.85-6.80 (m, 1H), 5.48-5.34 (m, 2H), 4.92-4.86 (m, 1H), 4.72-4.61 (m, 1H), 4.42-4.36 (m, 2H), 4.13-4.12 (m, 1H), 3.17-3.13 (m, 1H), 2.85-2.80 (m, 1H), 2.54-2.51 (m, 1H), 2.44-2.40 (m, 1H), 2.21-2.16 (m, 1H), 1.94-1.90 (m, 1H).; LCMS: 472.1
186		1H-NMR (400 MHz, CD3OD) δ ppm 8.24 (s, 1H), 7.82-7.79 (m, 1H), 7.34-7.31 (m, 1H), 7.21-7.03 (m, 1H), 5.65-5.61 (m, 1H), 5.45 (d, 1H, J = 52.0 Hz), 5.10 (d, 1H, J = 53.6 Hz), 4.89 (s, 1H), 4.61-4.47 (m, 2H), 4.06-4.01 (m, 1H), 2.87-2.85 (m, 1H), 2.53-2.46 (m, 2H), 2.44-2.41 (m, 1H), 1.92-1.84 (m, 2H).; LCMS: 472.1
187		1H-NMR (400 MHz, CD3OD) δ ppm 8.25 (s, 1H), 7.83-7.80 (m, 1H), 7.34-7.31 (m, 1H), 7.21-7.13 (m, 1H), 5.65-5.61 (m, 1H), 5.45 (d, 1H, J = 51.6 Hz), 5.08 (d, 1H, J = 54.0 Hz), 4.78 (s, 1H), 4.61-4.47 (m, 2H), 4.15-4.07 (m, 1H), 3.06-2.85 (m, 1H), 2.55-2.42 (m, 2H), 2.25-2.00 (m, 1H), 1.94-1.82 (m, 2H).; LCMS: 472.1
188		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.27 (m, 1H), 6.98 (d, 1H, J = 6.4 Hz), 6.85-6.69 (m, 2H), 5.48-5.35 (m, 2H), 4.64-4.42 (m, 3H), 4.29-4.25 (m, 1H), 3.78 (d, 1H, J = 5.6 Hz), 2.82 (br.s, 1H), 2.19-2.08 (m, 1H), 1.70-1.64 (m, 1H), 1.55-1.47 (m, 1H), 1.23 (s, 1H), 0.66-0.63 (m, 1H).; LCMS: 475.1

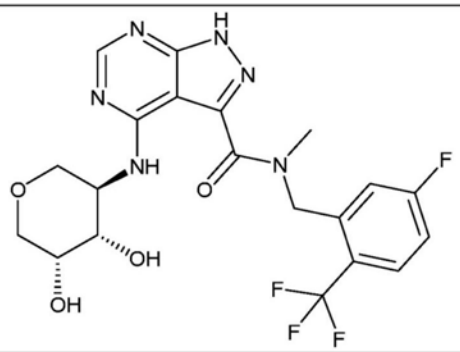
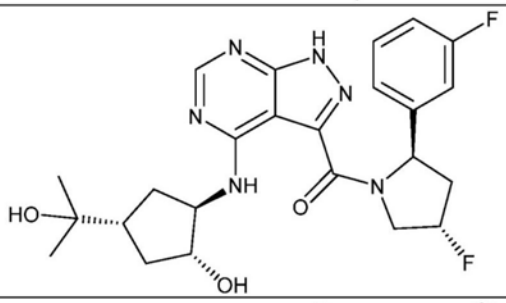
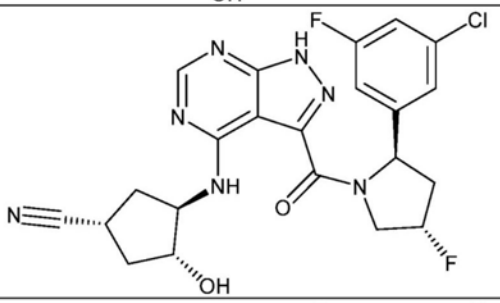
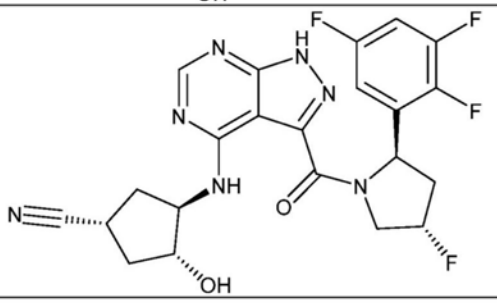
189		1H-NMR (400 MHz, CD3OD) δ ppm 8.31-8.23 (m, 1H), 7.18-6.95 (m, 3H), 5.66-5.62 (m, 1H), 5.45 (d, 1H, J = 52.0 Hz), 4.97-4.95 (m, 1H), 4.46-4.28 (m, 3H), 3.89-3.72 (m, 1H), 2.88-2.79 (m, 1H), 2.30-2.16 (m, 1H), 1.70-1.67 (m, 1H), 1.49-1.46 (m, 1H), 1.27-1.20 (m, 1H), 0.65-0.58 (m, 1H).; LCMS: 475.1
190		1H NMR (400 MHz, DMSO-d6) δ 14.16 (s, 1H), 9.15 (d, J = 7.4 Hz, 1H), 8.25 (s, 1H), 8.05 (d, J = 2.9 Hz, 1H), 7.54 (dd, J = 8.5, 3.1 Hz, 1H), 5.56 – 5.32 (m, 2H), 5.07 (d, J = 5.4 Hz, 1H), 4.79 – 4.62 (m, 1H), 4.53 – 4.27 (m, 1H), 4.09 (m, 1H), 3.91 (s,3H), 3.71 (m, 2H), 3.48 – 3.32 (m, 2H), 3.11 (m, 1H), 2.84 – 2.61 (m, 1H), 2.23 – 1.97 (m, 2H), 1.53 – 1.32 (m, 1H).; LCMS: 476.1
191		1H NMR (400 MHz, DMSO-d6) δ 14.11 (s, 1H), 8.90 (d, J = 7.4 Hz, 1H), 8.23 (s, 1H), 7.34 – 7.07 (m, 3H), 5.59 – 5.43 (m, 2H), 4.76 – 4.58 (m, 3H), 4.50 – 4.29 (m, 1H), 3.91 – 3.76 (m, 1H), 3.58 – 3.39 (m, 1H), 2.82 – 2.63 (m, 1H), 2.23 – 1.91 (m, 3H), 1.74 (d, J = 12.7 Hz, 1H), 1.32 – 1.05 (m, 2H).; LCMS: 477.1
192		1H-NMR (400 MHz, CD3OD) δ ppm 8.35-8.28 (m, 1H), 7.20 (s, 1H), 7.07-6.93 (m, 2H), 6.22-5.98 (m, 2H), 5.46-5.33 (m, 2H), 5.04-5.03 (m, 1H), 4.64-4.43 (m, 2H), 4.00-3.97 (m, 1H), 2.85-2.76 (m, 1H), 2.19-2.03 (m, 1H).; LCMS: 477.1

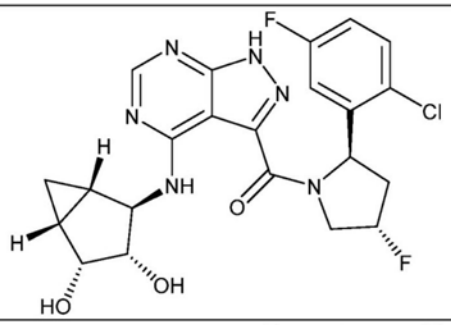
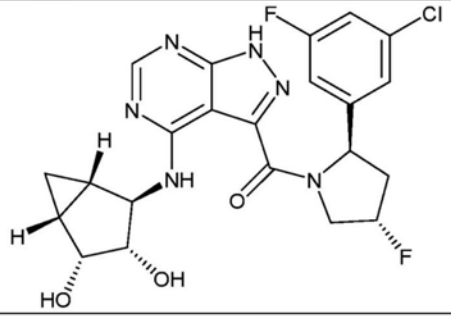
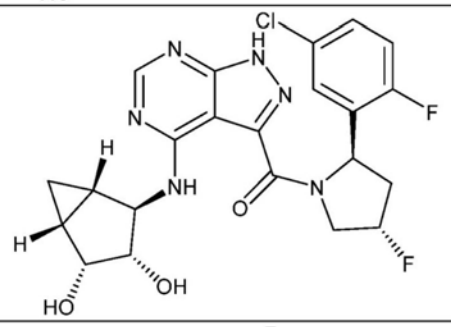
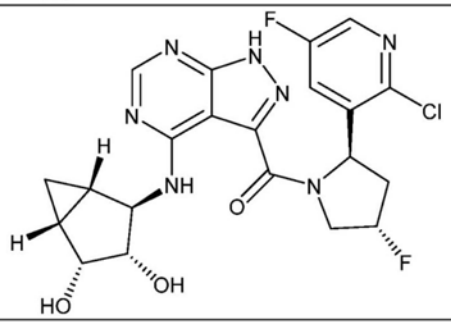
193		1H-NMR (400 MHz, CD3OD) δ ppm 8.30-8.22 (m, 1H), 7.17-6.95 (m, 3H), 5.67-5.63 (m, 1H), 5.44 (d, 1H, J = 52.0 Hz), 4.93-4.87 (m, 1H), 4.50-4.37 (m, 1H), 4.11-4.08 (m, 1H), 3.99 (s, 1H), 3.49-3.46 (m, 1H), 2.83-2.82 (m, 1H), 2.24-2.03 (m, 2H), 1.86-1.78 (m, 2H), 1.59-1.47 (m, 3H).; LCMS: 477.1
194		1H-NMR (400 MHz, CD3OD) δ ppm 8.32-8.25 (m, 1H), 8.21-8.09 (m, 1H), 7.61-7.48 (m, 1H), 6.10-6.08 (m, 1H), 5.98-5.96 (m, 1H), 5.65-5.61 (m, 1H), 5.48-5.35 (m, 1H), 5.04-5.03 (m, 1H), 4.55-4.51 (m, 2H), 4.08-3.92 (m, 1H), 2.96-2.87 (m, 1H), 2.19-2.04 (m, 1H).; LCMS: 478.1
195		1H-NMR (400 MHz, CD3OD) δ ppm 9.28 (br.s, 1H), 8.30-8.21 (m, 1H), 7.51 (br.s, 1H), 7.18-7.00 (m, 2H), 5.58-5.39 (m, 2H), 4.65-4.31 (m, 3H), 3.84-3.62 (m, 2H), 2.65 (br.s, 4H), 2.19-1.28 (m, 2H).; LCMS: 479.1
196		1H-NMR (400 MHz, CD3OD) δ ppm 8.36-8.28 (m, 1H), 7.46-7.42 (m, 1H), 7.09-6.91 (m, 2H), 5.75 (t, 1H, J = 8.8 Hz), 5.50-5.33 (m, 1H), 4.61-4.53 (m, 1H), 4.03-3.89 (m, 4H), 3.52-3.47 (m, 2H), 3.24-3.19 (m, 1H), 2.93-2.91 (m, 1H), 2.17-2.10 (m, 2H), 1.75-1.71 (m, 1H).; LCMS: 479.1

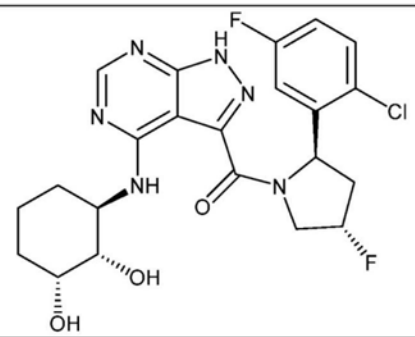
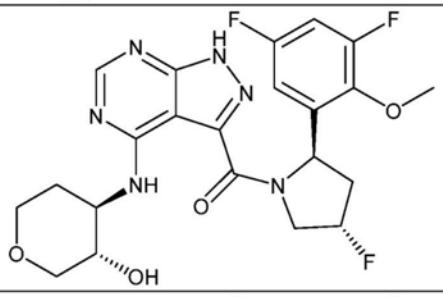
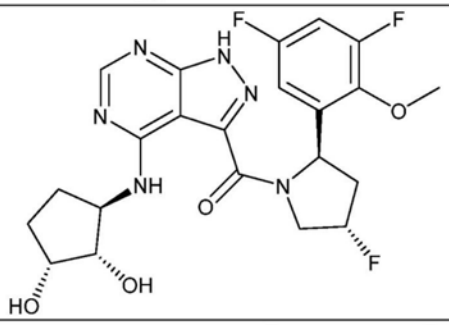
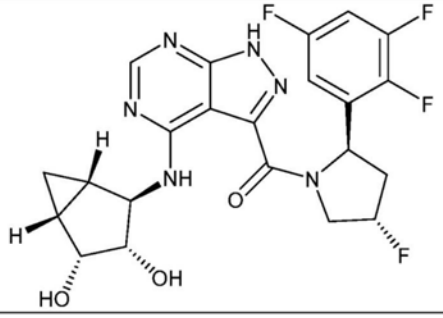
197		1H-NMR (400 MHz, CD3OD) δ ppm 8.35-8.28 (m, 1H), 6.97 (d, 1H, J = 6.4 Hz), 6.87-6.80 (m, 2H), 5.48-5.34 (m, 2H), 4.54-4.33 (m, 1H), 4.32-4.07 (m, 1H), 4.05-4.03 (m, 2H), 3.85-3.84 (m, 2H), 3.77-3.75 (m, 1H), 3.59-3.57 (m, 1H), 3.41-3.36 (m, 1H), 2.86-2.79 (m, 1H), 2.20-2.04 (m, 1H).; LCMS: 479.1
198		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.22 (s, 1H), 7.08 (d, 2H, J = 8.8 Hz), 5.47-5.34 (m, 2H), 4.86-4.82 (m, 1H), 4.55-4.50 (m, 1H), 3.97-3.90 (m, 3H), 3.54-3.46 (m, 2H), 3.23-3.21 (m, 1H), 2.83-2.81 (m, 1H), 2.17-2.07 (m, 2H), 1.76-1.73 (m, 1H).; LCMS: 479.1
199		1H-NMR (400 MHz, CD3OD) δ ppm 8.30-8.23 (m, 1H), 7.07-7.03 (m, 1H), 6.92-6.91 (m, 1H), 6.13-6.06 (m, 1H), 6.04-5.97 (m, 1H), 5.62-5.58 (m, 1H), 5.41 (d, 1H, J = 51.6 Hz), 5.08-5.07 (m, 1H), 4.55-4.35 (m, 2H), 4.05-3.93 (m, 1H), 2.86-2.76 (m, 1H), 2.24-2.08 (m, 1H).; LCMS: 479.1
200		1H-NMR (400 MHz, CD3OD) δ ppm 8.30-8.23 (m, 1H), 7.35-7.26 (m, 3H), 5.61-5.57 (m, 1H), 5.40 (d, 1H, J = 52.4 Hz), 4.52-4.36 (m, 1H), 4.03-3.87 (m, 4H), 3.53-3.47 (m, 2H), 3.24-3.21 (m, 1H), 2.80-2.80 (m, 1H), 2.24-2.10 (m, 2H), 1.69-1.67 (m, 1H).; LCMS: 479.1

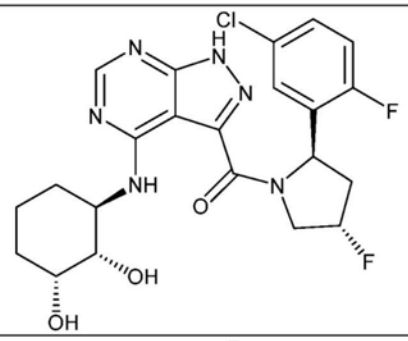
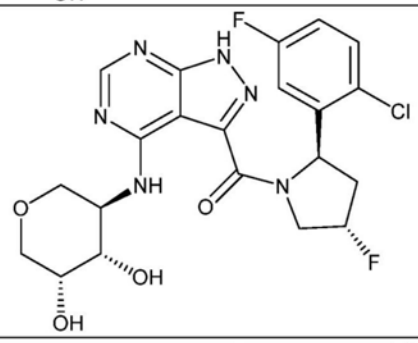
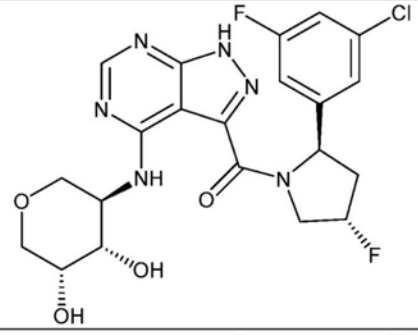
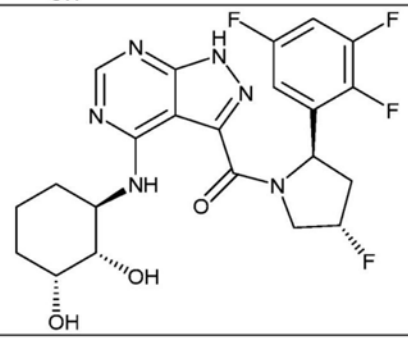
201		1H-NMR (400 MHz, CDCl3) δ ppm 8.37-8.29 (m, 1H), 7.35-7.10 (m, 3H), 5.60 (dd, 1H, J = 10.0, 8.4 Hz), 5.45 (d, 1H, J = 52.0 Hz)), 4.87-4.85 (m, 1H), 4.55-4.32 (m, 2H), 4.07-3.91 (m, 2H), 2.88-2.82 (m, 1H), 2.41-2.11 (m, 3H), 1.79-1.63 (m, 2H).; LCMS: 479.1
202		1H NMR (400 MHz, DMSO-d6) δ 14.20 (s, 1H), 9.07 (d, J = 7.4 Hz, 1H), 8.39 (d, J = 3.0 Hz, 1H), 8.25 (d, J = 6.0 Hz, 1H), 7.84 (dd, J = 8.8, 3.0 Hz, 1H), 5.60 – 5.42 (m, 2H), 5.05 (d, J = 5.3 Hz, 1H), 4.75 (dd, J = 21.3, 14.1 Hz, 1H), 4.51 (dd, J = 39.5, 15.0 Hz, 1H), 4.09 (s, 2H), 3.71 – 3.62 (m, 2H), 3.13 – 3.02 (m, 1H), 2.08 (s, 2H), 1.44 (dd, J = 27.0, 9.2 Hz, 2H), 1.21 (d, J = 13.5 Hz, 1H).; LCMS: 480
203		1H-NMR (400 MHz, CD3OD) δ ppm 8.49 (br.s, 1H), 8.38 (br.s, 1H), 8.33 (br.s, 1H), 7.69 (d, 1H, J = 9.2 Hz), 5.97-5.77 (m, 1H), 5.64-5.39 (m, 2H), 4.57-4.44 (m, 1H), 4.24-4.21 (m, 2H), 4.07 (d, 1H, J = 6.4 Hz), 2.89-2.85 (m, 1H), 2.46-2.44 (m, 1H), 2.27-2.25 (m, 1H), 2.15-2.12 (m, 1H), 1.92-1.81 (m, 2H), 1.66-1.62 (m, 1H).; LCMS: 480.1
204		1H NMR (400 MHz, DMSO-d6) δ 14.19 (s, 1H), 9.13 (d, J = 7.8 Hz, 1H), 8.26 (s, 1H), 7.47 – 7.34 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 5.59 – 5.48 (m, 2H), 4.80 – 4.60 (m, 1H), 4.41 (dd, J = 39.5, 14.0 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.92 (dd, J = 11.1, 3.7 Hz, 1H), 3.75 (dd, J = 12.0, 5.6 Hz, 1H), 3.47 (dtd, J = 59.1, 8.2, 7.8, 4.5 Hz, 2H), 3.19 (dd, J = 11.2, 6.9 Hz, 1H), 2.85 – 2.60 (m, 1H), 2.33 – 2.04 (m, 1H), 1.79 (dd, J = 11.3, 4.7 Hz, 1H), 1.53 – 1.33 (m, 1H).; LCMS: 481

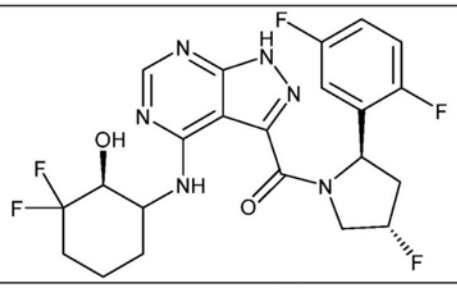
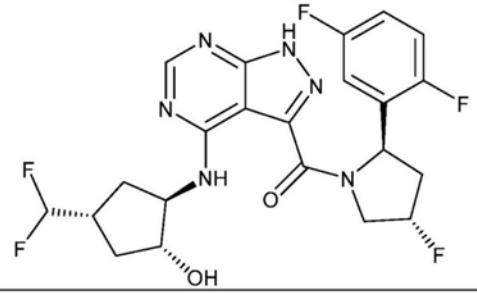
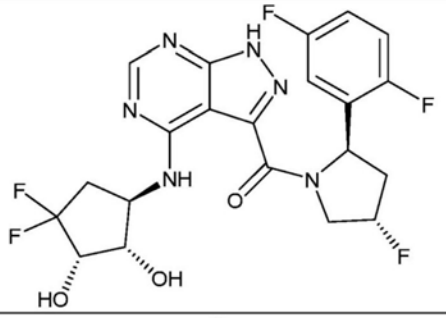
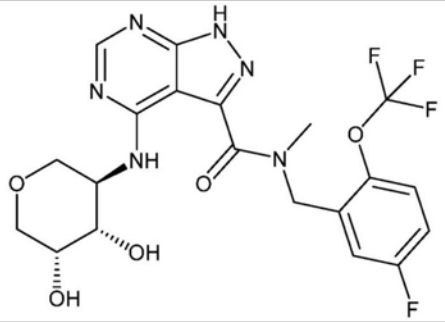
205		1H-NMR (400 MHz, CD3OD) δ ppm 8.37-9.30 (m, 1H), 7.08-6.98 (m, 2H), 5.68-5.63 (m, 1H), 5.53-5.36 (m, 1H), 4.53-4.40 (m, 1H), 4.02-3.91 (m, 4H), 3.55-3.46 (m, 2H), 3.26-3.21 (m, 1H), 2.86-2.82 (m, 1H), 2.30-2.12 (m, 2H), 1.78-1.70 (m, 1H).; LCMS: 481.1
206		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (s, 1H), 7.10-6.95 (m, 2H), 5.72-5.62 (m, 1H), 5.52-5.39 (m, 1H), 4.93-4.92 (m, 1H), 4.52-4.08 (m, 2H), 4.07-5.06 (m, 1H), 3.93-3.90 (m, 1H), 2.88-2.82 (m, 1H), 2.41-2.10 (m, 3H), 1.78-1.63 (m, 2H).; LCMS: 481.1
207		1H-NMR (400 MHz, CD3OD) δ ppm 8.25-8.20 (m, 2H), 7.61-7.58 (m, 1H), 5.66-5.62 (m, 1H), 5.25 (d, 1H, J = 52.0 Hz), 5.14-5.00 (m, 1H), 4.91-4.87 (m, 1H), 4.53-4.44 (m, 2H), 4.06-4.03 (m, 1H), 2.94-2.91 (m, 1H), 2.54-2.43 (m, 2H), 1.91-1.83 (m, 3H). ; LCMS: 482.1
208		1H-NMR (400 MHz, CD3OD) δ ppm 8.26-8.20 (m, 1H), 7.08-7.02 (m, 1H), 6.94-6.92 (m, 1H), 5.64-5.60 (m, 1H), 5.42 (d, 1H, J = 52.0 Hz), 5.10 (dt, 1H, J = 52.0, 6.0 Hz), 4.80 (s, 1H), 4.55-4.44 (m, 2H), 4.09-4.04 (m, 1H), 2.92-2.54 (m, 1H), 2.52-2.43 (m, 2H), 1.93-1.89 (m, 1H), 1.86-1.83 (m, 2H).; LCMS: 483.1

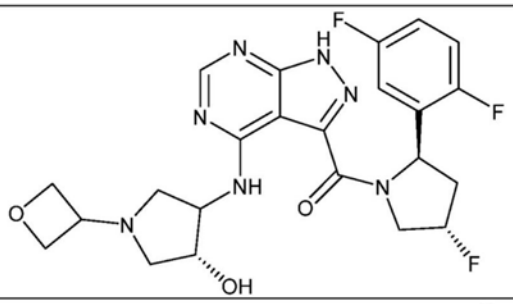
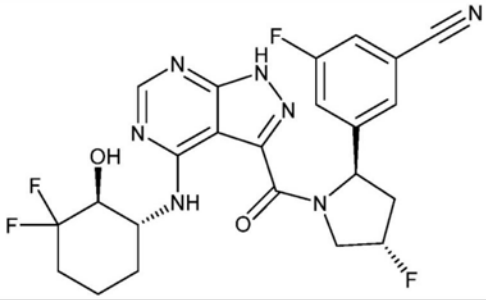
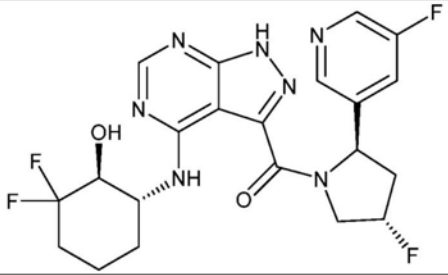
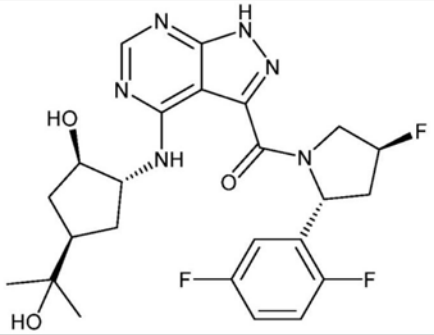
209		1H-NMR (400 MHz, CD3OD) δ ppm 8.38-8.35 (m, 1H), 7.84-7.80 (m, 1H), 7.24-7.15 (m, 2H), 5.58 (s, 1H), 5.07 (s, 1H), 4.40-4.39 (m, 1H), 4.11-4.10 (m, 1H), 3.98-3.90 (m, 3H), 3.68-3.61 (m, 2.5H), 3.48-3.41 (m, 1H), 3.22 (s, 1.5H).; LCMS: 485.1
210		1H-NMR (400 MHz, CD3OD) δ ppm 8.26 (s, 1H), 7.36-7.32 (m, 1H), 7.15 (d, 1H, J = 7.6 Hz), 7.07 (d, 1H, J = 9.6 Hz), 6.97-6.93 (m, 1H), 5.45-5.41 (m, 2H), 4.49-4.36 (m, 1H), 4.13-4.09 (m, 1H), 4.01-3.97 (m, 1H), 3.13-3.09 (m, 1H), 2.84-2.75 (m, 1H), 2.26-2.16 (m, 3H), 1.68-1.59 (m, 2H), 1.50-1.37 (m, 1H), 1.20-1.14 (m, 6H).; LCMS: 487.1
211		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.27 (m, 1H), 7.22 (s, 1H), 7.07 (d, 2H, J = 6.8 Hz), 5.47-5.34 (m, 2H), 4.88-4.87 (m, 1H), 4.79-4.77 (m, 1H), 4.42-4.37 (m, 2H), 4.13-4.12 (m, 1H), 3.17-3.13 (m, 1H), 2.83-2.80 (m, 1H), 2.54-2.51 (m, 1H), 2.44-2.40 (m, 1H), 2.21-2.17 (m, 1H), 1.94-1.91 (m, 1H).; LCMS: 488.1
212		1H-NMR (400 MHz, CD3OD) δ ppm 8.36-8.30 (m, 1H), 7.09-6.95 (m, 2H), 5.65-5.62 (m, 1H), 5.61-5.39 (m, 1H), 4.95-4.91 (m, 1H), 4.50-4.36 (m, 2H), 4.14-4.11 (m, 1H), 3.21-3.16 (m, 1H), 2.82-2.75 (m, 1H), 2.57-2.54 (m, 1H), 2.52-2.42 (m, 1H), 2.23-2.18 (m, 2H), 2.00-1.94 (m, 1H).; LCMS: 490.0

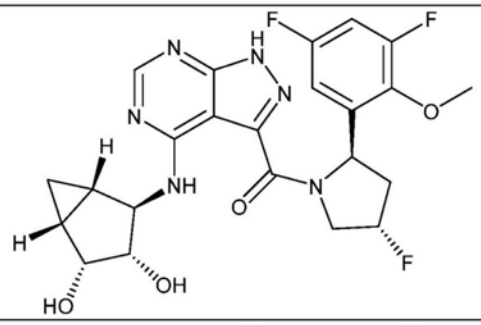
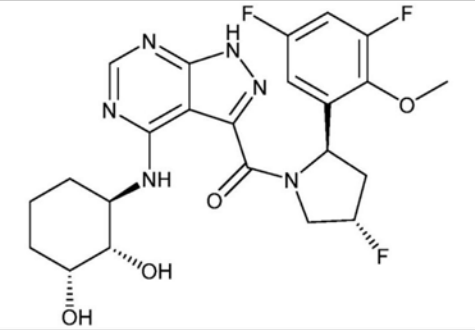
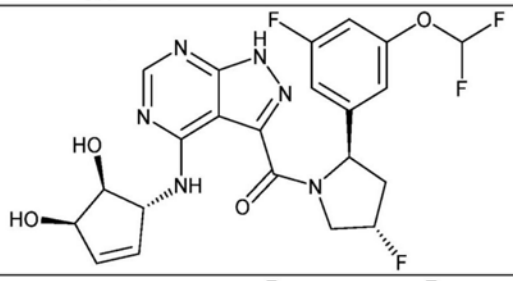
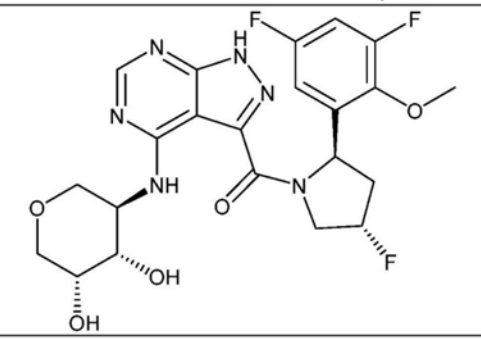
213		1H-NMR (400 MHz, CD3OD) δ ppm 7.49-7.46 (m, 1H), 7.12-7.06 (m, 2H), 5.76 (t, 1H, J = 8.4 Hz), 5.47 (d, 1H, J = 52.4 Hz), 4.46-4.28 (m, 3H), 4.00 (s, 1H), 3.79 (d, 1H, J = 6.4 Hz), 2.20-2.04 (m, 1H), 1.71 (br.s, 1H), 1.50 (br.s, 1H), 1.31-1.25 (m, 2H), 0.67-0.64 (m, 1H).; LCMS: 491.1
214		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.27 (m, 1H), 7.22 (s, 1H), 7.10-7.07 (m, 2H), 5.47-5.34 (m, 2H), 4.51-4.38 (m, 2H), 4.27-4.23 (m, 1H), 3.91-3.77 (m, 1H), 3.35-3.33 (m, 1H), 2.84-2.78 (m, 1H), 2.19-2.18 (m, 1H), 1.72-1.68 (m, 1H), 1.48-1.45 (m, 1H), 1.24-1.21 (m, 1H), 0.67-0.60 (m, 1H).; LCMS: 491.1
215		1H-NMR (400 MHz, CD3OD) δ ppm 8.41-8.28 (m, 1H), 7.36-6.33 (m, 3H), 5.58-5.54 (m, 1H), 5.51-5.38 (m, 1H), 4.98-4.96 (m, 1H), 4.52-3.76 (m, 4H), 2.97-2.74 (m, 1H), 2.30-2.15 (m, 1H), 1.73-1.48 (m, 2H), 1.26-1.22 (m, 1H), 0.66-0.61 (m, 1H).; LCMS: 491.1
216		1H NMR (400 MHz, DMSO-d6) δ 14.19 (s, 1H), 9.02 (d, J = 7.6 Hz, 1H), 8.39 (d, J = 2.8 Hz, 1H), 8.29 (s, 1H), 7.89 (dd, J = 9.0, 3.0 Hz, 1H), 5.64 – 5.37 (m, 3H), 4.92 – 4.71 (m, 2H), 4.43 (d, J = 9.1 Hz, 1H), 4.30 (dd, J = 13.2, 7.4 Hz, 2H), 4.14 (q, J = 6.0 Hz, 1H), 3.48 (t, J = 5.3 Hz, 1H), 2.79 (td, J = 16.6, 16.1, 7.2 Hz, 1H), 1.43 (dd, J = 8.9, 4.7 Hz, 1H), 1.24 (d, J = 16.9 Hz, 1H), 1.02 (q, J = 4.2 Hz, 1H), 0.48 – 0.33 (m, 1H).; LCMS: 492

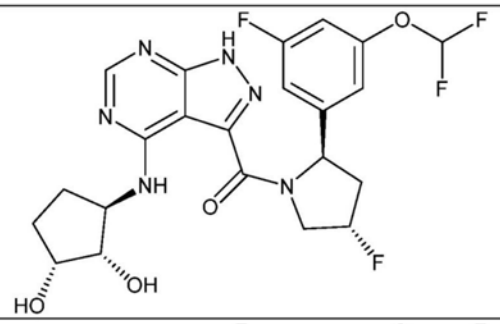
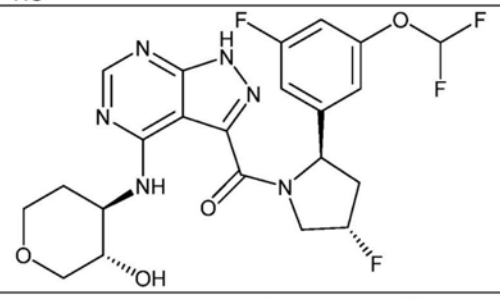
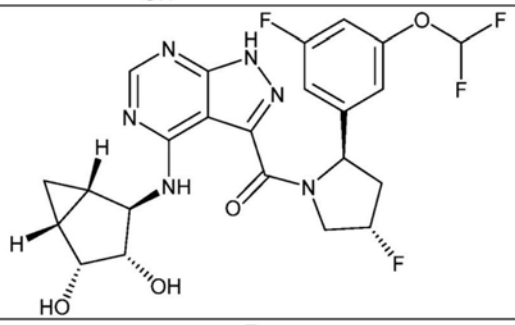
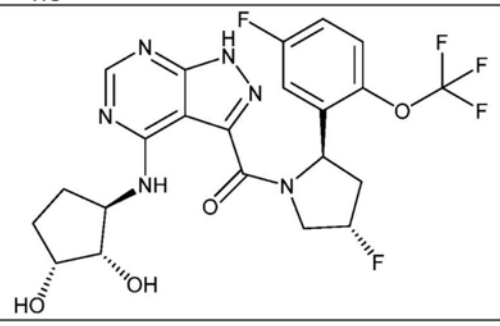
217		1H-NMR (400 MHz, CD3OD) δ ppm 8.39-8.30 (m, 1H), 7.51-7.48 (m, 1H), 7.11-6.95 (m, 2H), 5.79 (t, 1H, J = 9.2 Hz), 5.55-5.38 (m, 1H), 4.89 (br.s, 1H), 4.62-4.49 (m, 1H), 4.17-4.07 (m, 2H), 3.57-3.55 (m, 1H), 3.04-2.91 (m, 1H), 2.17-2.10 (m, 2H), 1.93-1.85 (m, 2H), 1.67-1.54 (m, 3H).; LCMS: 493.1
218		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.28 (m, 1H), 6.95-6.86 (m, 2H), 5.66 (t, 1H, J = 8.4 Hz), 5.50-5.37 (m, 1H), 4.52-4.43 (m, 1H), 4.03-3.91 (m, 7H), 3.54-3.49 (m, 2H), 3.26-3.21 (m, 1H), 2.86-2.75 (m, 1H), 2.24-2.11 (m, 2H), 1.76-1.71 (m, 1H).; LCMS: 493.1
219		1H-NMR (400 MHz, CD3OD) δ ppm 8.36-8.30 (m, 1H), 6.93-6.85 (m, 2H), 5.66 (t, 1H, J = 8.8 Hz), 5.50-5.37 (m, 1H), 4.52-4.31 (m, 2H), 4.07-4.04 (m, 2H), 3.98 (s, 3H), 3.93-3.90 (m, 1H), 2.79-2.75 (m, 1H), 2.43-2.39 (m, 1H), 2.20-2.07 (m, 2H), 1.79-1.77 (m, 1H), 1.64-1.62 (m, 1H).; LCMS: 493.1
220		1H-NMR (400 MHz, CD3OD) δ ppm 8.37 (s, 1H), 7.10-6.98 (m, 2H), 5.63 (t, 1H, J = 8.4 Hz), 5.54-5.36 (m, 1H), 4.98-4.95 (m, 1H), 4.50-4.37 (m, 2H), 4.29-4.25 (m, 1H), 3.80-3.78 (m, 1H), 2.89-2.79 (m, 1H), 2.31-2.15 (m, 1H), 1.78-1.72 (m, 1H), 1.56-1.50 (m, 1H), 1.30-1.25 (m, 1H), 0.68-0.62 (m, 1H).; LCMS: 493.1

221		1H-NMR (400 MHz, CD3OD) δ ppm 8.30-8.22 (m, 1H), 7.33-6.35 (m, 3H), 5.85-5.56 (m, 1H), 5.49-5.36 (m, 1H), 4.91-4.88 (m, 1H), 4.50-4.40 (m, 1H), 4.15-4.08 (m, 1H), 3.99 (br.s, 1H), 3.52-3.49 (m, 1H), 2.82-2.80 (m, 1H), 2.24-2.03 (m, 2H), 1.86-1.78 (m, 2H), 1.58-1.47 (m, 3H).; LCMS: 493.1
222		1H-NMR (400 MHz, CD3OD) δ ppm 8.38 (s, 1H), 7.49-7.45 (m, 1H), 7.10-7.03 (m, 2H), 5.77 (d, 1H, J = 8.4 Hz) 5.44 (d, 1H, J = 51.6 Hz), 4.59-4.49 (m, 1H), 4.38-4.36 (m, 1H), 4.09-3.61 (m, 6H), 3.42-3.39 (m, 1H), 2.99-2.90 (m, 0.5H), 2.16-2.01 (m, 0.5H).; LCMS: 495.1
223		1H-NMR (400 MHz, CD3OD) δ ppm 8.36-8.28 (m, 1H), 7.21 (s, 1H), 7.11-7.06 (m, 2H), 5.46-5.33 (m, 2H), 4.84-4.80 (m, 1H), 4.55-4.51 (m, 1H), 4.28-4.27 (m, 1H), 4.05-4.02 (m, 1H), 3.86-3.83 (m, 2H), 3.76-3.73 (m, 1H), 3.58-3.56 (m, 1H), 3.40-3.38 (m, 1H), 2.84-2.78 (m, 1H), 2.19-2.05 (m, 1H).; LCMS: 495.1
224		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.32 (m, 1H), 7.09-7.03 (m, 1H), 6.95-6.93 (m, 1H), 5.65-5.61 (m, 1H), 5.51-5.38 (m, 1H), 4.52-4.42 (m, 1H), 4.10-4.02 (m, 3H), 3.51-3.48 (m, 1H), 2.84-2.82 (m, 1H), 2.24-2.04 (m, 2H), 1.87-1.79 (m, 2H), 1.62-1.48 (m, 3H). ; LCMS: 495.2

225		N/A; LCMS: 497.1
226		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.27 (m, 1H), 7.15-7.02 (m, 3H), 5.99-5.62 (m, 1H), 5.60-5.58 (m, 1H), 5.51-5.38 (m, 1H), 4.96-4.90 (m, 1H), 4.49-4.40 (m, 1H), 4.23-4.18 (m, 1H), 4.12-4.09 (m, 1H), 2.87-2.79 (m, 1H), 2.58-2.50 (m, 1H), 2.30-2.23 (m, 2H), 2.15-2.11 (m, 1H), 1.87-1.77 (m, 1H), 1.67-1.64 (m, 1H).; LCMS: 497.1
227		N/A; LCMS: 499.1
228		1H-NMR (400 MHz, CD3OD) δ ppm 8.36 (d, 1H, J = 8.4 Hz), 7.40 (br.s, 1H), 7.20-7.14 (m, 2H), 5.50 (s, 1H), 4.94 (d, 1H, J = 7.2 Hz), 4.40-4.38 (m, 1H), 4.11-4.10 (m, 1H), 3.97-3.85 (m, 3H), 3.68-3.61 (m, 2.5H), 3.47-3.40 (m, 1H), 3.17 (s, 1.5H).; LCMS: 501.1

229		N/A; LCMS: 504.1
230		1H-NMR (400 MHz, CD3OD) δ ppm 8.19 (s, 1H), 7.59 (s, 1H), 7.48-7.41 (m, 2H), 5.47-5.30 (m, 2H), 4.78-4.75 (m, 1H), 4.53-4.43 (m, 1H), 4.34-4.30 (m, 1H), 3.75-3.70 (m, 1H), 2.84-2.79 (m, 1H), 2.18-2.07 (m, 3H), 1.75-1.49 (m, 4H).; LCMS: 504.1
231		1H-NMR (400 MHz, CD3OD) δ ppm 8.45 (s, 1H), 8.33 (d, 1H, J = 2.8 Hz), 8.21 (s, 1H), 7.64 (d, 1H, J = 9.6 Hz), 5.51-5.34 (m, 2H), 4.82-4.79 (m, 1H), 4.53-4.40 (m, 1H), 4.33 (br.s, 1H), 3.74-3.66 (m, 1H), 2.84-2.80 (m, 1H), 2.21-2.08 (m, 3H), 1.78-1.71 (m, 2H), 1.61-1.46 (m, 2H).; LCMS: 504.1
232		1H-NMR (400 MHz, CD3OD) δ ppm 8.22-8.15 (m, 1H), 7.13-6.83 (m, 3H), 5.61-5.56 (m, 1H), 5.41 (d, 1H, J = 52.0 Hz), 4.91-4.89 (m, 1H), 4.46-4.36 (m, 1H), 4.21-4.20 (m, 1H), 4.10-3.97 (m, 1H), 2.85-2.79 (m, 1H), 2.29-2.00 (m, 4H), 1.63-1.58 (m, 2H), 1.22-1.18 (m, 6H); LCMS: 505.2

233		1H-NMR (400 MHz, CD3OD) δ ppm 8.30-8.24 (m, 1H), 6.94-6.83 (m, 2H), 5.64 (t, 1H, J = 8.8 Hz), 5.41 (d, 1H, J = 52.0 Hz), 4.48-4.29 (m, 4H), 4.00 (s, 3H), 3.74 (d, 1H, J = 6.0 Hz), 2.79-2.71 (m, 1H), 2.20-2.06 (m, 2H), 1.65-1.60 (m, 1H), 1.47-1.45 (m, 1H), 1.23-1.20 (m, 1H), 0.61-0.55 (m, 1H).; LCMS: 505.3
234		1H-NMR (400 MHz, CD3OD) δ ppm 8.33-8.27 (m, 1H), 6.95-6.84 (m, 2H), 5.65 (t, 1H, J = 8.8 Hz), 5.50-5.31 (m, 1H), 4.52-4.39 (m, 1H), 4.11-4.08 (m, 1H), 4.03 (s, 1H), 3.98 (s, 3H), 3.73-3.50 (m, 2H), 2.84-2.74 (m, 1H), 2.20-2.06 (m, 2H), 1.86-1.81 (m, 2H), 1.61-1.47 (m, 3H).; LCMS: 507.1
235		1H-NMR (400 MHz, CD3OD) δ ppm 8.37-8.30 (m, 1H), 7.04-6.95 (m, 2H), 6.85-6.67 (m, 2H), 6.15-6.13 (m, 1H), 5.99-5.97 (m, 1H), 5.46-5.33 (m, 2H), 4.98 (d, 1H, J = 4.4 Hz), 4.80 (s, 1H), 4.53-4.42 (m, 2H), 4.00-3.97 (m, 1H), 2.85-2.75 (m, 1H), 2.19-2.02 (m, 1H).; LCMS: 509
236		1H-NMR (400 MHz, CD3OD) δ ppm 8.36-8.30 (m, 1H), 6.94-6.84 (m, 2H), 5.67 (t, 1H, J = 8.4 Hz), 5.50-5.31 (m, 1H), 4.52-4.42 (m, 1H), 4.31-4.30 (m, 1H), 4.07-3.89 (m, 5H), 3.83-3.76 (m, 3H), 3.58-3.40 (m, 2H), 2.81-2.75 (m, 1H), 2.22-2.03 (m, 1H).; LCMS: 509.1

237		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.27 (m, 1H), 7.05-6.96 (m, 2H), 6.86-6.68 (m, 2H), 5.47-5.34 (m, 2H), 4.81 (s, 1H), 4.54-4.49 (m, 1H), 4.31-4.29 (m, 1H), 4.06-4.04 (m, 1H), 3.91-3.88 (m, 1H), 2.86-2.83 (m, 1H), 2.40-2.36 (m, 1H), 2.17-2.06 (m, 2H), 1.76-1.62 (m, 2H).; LCMS: 511
238		1H-NMR (400 MHz, CD3OD) δ ppm 8.32 (s, 1H), 7.06-6.97 (m, 2H), 6.87-6.69 (m, 2H), 5.47-5.34 (m, 2H), 4.54-4.50 (m, 1H), 4.01-3.88 (m, 3H), 3.53-3.46 (m, 3H), 3.23-3.18 (m, 1H), 2.83-2.81 (m, 1H), 2.17-2.08 (m, 2H), 1.74-1.65 (m, 1H).; LCMS: 511.1
239		1H-NMR (400 MHz, CD3OD) δ ppm 8.34-8.27 (m, 1H), 7.05-6.97 (m, 2H), 6.87-6.68 (m, 2H), 5.47-5.34 (m, 2H), 4.89 (s, 1H), 4.62-4.47 (m, 1H), 4.40-4.37 (m, 1H), 4.27-4.23 (m, 1H), 3.77 (d, 1H, J = 6.0 Hz), 2.86-2.80 (m, 1H), 2.22-2.18 (m, 1H), 1.71-1.68 (m, 1H), 1.48-1.46 (m, 1H), 1.27-1.20 (m, 1H), 0.65-0.59 (m, 1H).; LCMS: 523
240		1H-NMR (400 MHz, CD3OD) δ ppm 8.23 (s, 1H), 7.36 (br.s, 1H), 7.16-7.08 (m, 2H), 5.65-5.61 (m, 1H), 5.41 (d, 1H, J = 52.0 Hz), 4.80 (s, 1H), 4.57-4.38 (m, 2H), 4.14-4.05 (m, 1H), 3.82-3.79 (m, 1H), 2.80-2.76 (m, 1H), 2.38-2.34 (m, 1H), 2.15-2.01 (m, 2H), 1.74-1.71 (m, 1H), 1.52-1.49 (m, 1H).; LCMS: 529.1

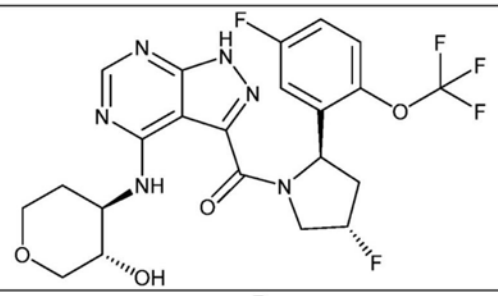
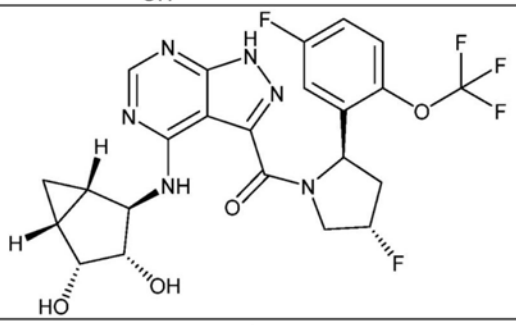
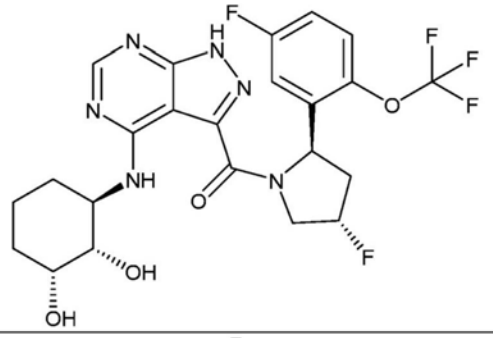
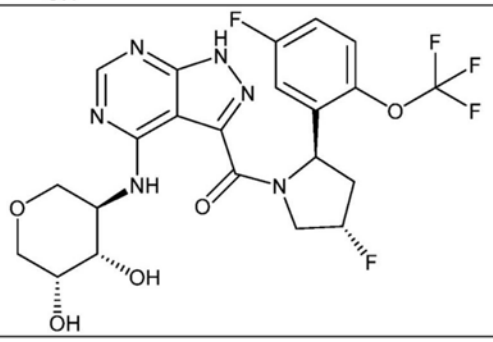
241		1H-NMR (400 MHz, CD3OD) δ ppm 8.22 (s, 1H), 7.36 (br.s, 1H), 7.17-7.15 (m, 1H), 7.11-7.08 (m, 1H), 5.67-5.62 (m, 1H), 5.41 (d, 1H, J = 52.0 Hz), 4.91 (s, 1H), 4.51-4.38 (m, 1H), 4.20 (br.s, 1H), 3.86-3.83 (m, 2H), 3.54-3.49 (m, 2H), 3.27-3.22 (m, 1H), 2.82-2.73 (m, 1H), 2.19-2.03 (m, 2H), 1.63-1.56 (m, 1H).; LCMS: 529.1
242		1H-NMR (400 MHz, CD3OD) δ ppm 8.34 (s, 1H), 7.38 (br.s, 1H), 7.18-7.10 (m, 2H), 5.65-5.61 (m, 1H), 5.46 (d, 1H, J = 52.0 Hz), 4.98-4.92 (m, 1H), 4.64-4.53 (m, 1H), 4.49-4.40 (m, 1H), 4.37-4.26 (m, 1H), 3.73 (d, 1H, J = 5.6 Hz), 2.82-2.73 (m, 1H), 2.24-2.07 (m, 1H), 1.67 (br.s, 1H), 1.47 (br.s, 1H), 1.29-1.23 (m, 1H), 0.68-0.59 (m, 1H).; LCMS: 541.2
243		1H-NMR (400 MHz, CD3OD) δ ppm 8.19 (s, 1H), 7.35-7.34 (m, 1H), 7.16-7.07 (m, 2H), 5.63-5.59 (m, 1H), 5.40 (d, 1H, J = 52.4 Hz), 4.86-4.80 (m, 1H), 4.49-4.41 (m, 2H), 3.81 (br.s, 1H), 3.56-3.54 (m, 1H), 2.81-2.75 (m, 1H), 2.15-1.97 (m, 2H), 1.77-1.71 (m, 2H), 1.52-1.47 (m, 2H), 1.47-1.27 (m, 1H).; LCMS: 543.1
244		1H-NMR (400 MHz, CD3OD) δ ppm 8.23 (s, 1H), 7.35 (br.s, 1H), 7.16-7.07 (m, 2H), 5.67-5.62 (m, 1H), 5.40 (d, 1H, J = 52.0 Hz), 4.77 (s, 1H), 4.54-4.40 (m, 2H), 4.01-3.86 (m, 2H), 3.79-3.72 (m, 3H), 3.57-3.54 (m, 1H), 2.82-2.72 (m, 1H), 2.22-2.12 (m, 1H).; LCMS: 545.1

图1