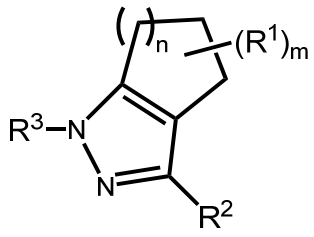
CLAIMS:

1. A compound, or a pharmaceutically acceptable salt thereof, having a structure according to Formula I:



(Formula I)

wherein:

n is 1 or 2;

m is 2, 3, 4, 5, 6, 7, or 8, provided that when n is 1, m is 2, 3, 4, 5, or 6;

each R^1 is independently selected from the group consisting of halo, -OH, and -O-(C_1-C_3 alkyl);

R^2 selected from the group consisting of -C_1-C_6 alkyl, -CN, and -$S(O)_2$-(C_1-C_3 alkyl), wherein the -C_1-C_6 alkyl and -$S(O)_2$-(C_1-C_3 alkyl) are substituted with 0-3 halo;

R^3 is selected from the group consisting of -C_1-C_2 alkyl substituted with 1-3 R^4, -C_3-C_6 alkyl, -C_3-C_8 cycloalkyl, -3- to 7-membered heterocycloalkyl having 1-3 heteroatom or heteroatom groups selected from N, O, S, S(=O), and $S(=O)_2$, -Y-(C_3-C_6 cycloalkyl), -Y-O-(C_3-C_6 cycloalkyl), -Y-(3- to 6-membered heterocycloalkyl) having 1-3 heteroatom or heteroatom groups selected from N, O, S, S(=O), and $S(=O)_2$, -X-(phenyl), and -Y-(5- to 6-membered heteroaryl) having 1-3 heteroatoms selected from N, O, and S, wherein the -C_3-C_6 alkyl, -C_3-C_6 cycloalkyl, -3- to 7-membered heterocycloalkyl, -Y-(C_3-C_6 cycloalkyl), -Y-O-(C_3-C_6 cycloalkyl), -Y-(3- to 6-membered heterocycloalkyl), -X-(phenyl), and -Y-(5- to 6-membered heteroaryl), are substituted with 0-3 R^4;

each R^4 is independently selected from halo, -C_1-C_6 alkyl, -CN, -C_1-C_6 haloalkyl, -OH, -O-(C_1-C_6 alkyl), -Y-O-(C_1-C_6 alkyl), -S-(C_1-C_6 alkyl), -S(O)-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl), wherein the -O-(C_1-C_6 alkyl), -Y-O-(C_1-C_6 alkyl), -S-(C_1-C_6 alkyl), -S(O)-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl) are substituted with 0-3 halo;

X is -C_2-C_3 alkylene-; and

Y is -C_1-C_3 alkylene-.

2. The compound, or a pharmaceutically acceptable salt thereof, according to claim 1 wherein:

n is 1 or 2;

m is 2, 3, 4, 5, 6, 7, or 8, provided that when n is 1, m is 2, 3, 4, 5 or 6;

each R^1 is independently selected from the group consisting of halo, -OH, and -O-(C_1-C_3 alkyl);

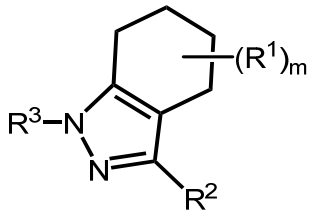
R^2 selected from the group consisting of -C_1-C_6 alkyl, -CN, and -$S(O)_2$-(C_1-C_3 alkyl), wherein the -C_1-C_6 alkyl and -$S(O)_2$-(C_1-C_3 alkyl) are substituted with 0-3 halo;

R^3 is selected from the group consisting of -C_1-C_2 alkyl substituted with 1-3 R^4, -C_3-C_6 alkyl, -C_3-C_6 cycloalkyl, -Y-(C_3-C_6 cycloalkyl), -Y-O-(C_3-C_6 cycloalkyl), -Y-(3- to 6-membered heterocycloalkyl) having 1-3 heteroatom or heteroatom groups selected from N, O, S, S(=O), $S(=O)_2$, and -Y-(5- to 6-membered heteroaryl) having 1-3 heteroatoms selected from N, O, and S, wherein the -C_3-C_6 alkyl, -C_3-C_6 cycloalkyl, -Y-(C_3-C_6 cycloalkyl), -Y-O-(C_3-C_6 cycloalkyl), -Y-(3- to 6-membered heterocycloalkyl), and -Y-(5- to 6-membered heteroaryl) are substituted with 0-3 R^4;

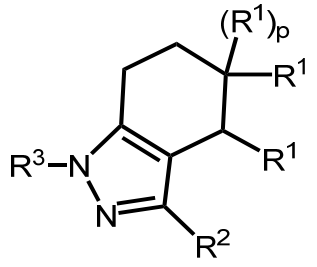
each R^4 is independently selected from halo, -C_1-C_6 alkyl, -CN, -C_1-C_6 haloalkyl, -OH, -O-(C_1-C_6 alkyl), -S-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl), wherein the -O-(C_1-C_6 alkyl), -S-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl) are substituted with 0-3 halo; and

Y is -C_1-C_3 alkylene-.

3. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound of Formula I has a structure according to Formula II:



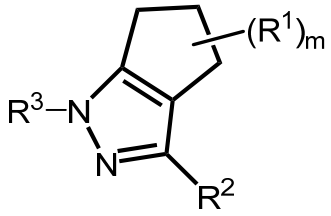
(Formula II), optionally wherein the compound of Formula II has a structure according to Formula IIa:



(Formula IIa)

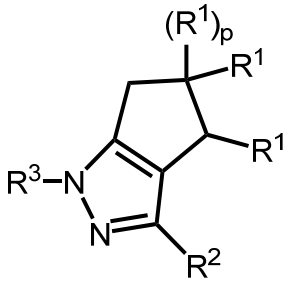
wherein p is 0 or 1.

4. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound of Formula I has a structure according to Formula III:



(Formula III), optionally wherein the compound of Formula III has a structure according to:

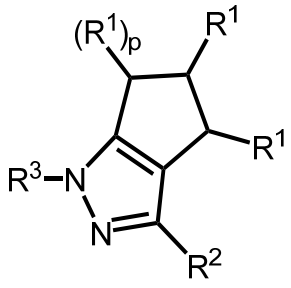
(i) Formula IIIa:



(Formula IIIa)

wherein p is 0 or 1;

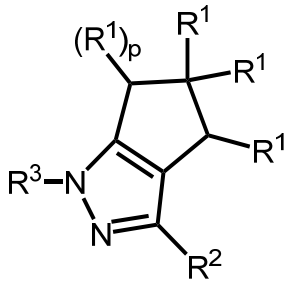
(ii) Formula IIIc:



(Formula IIIc)

wherein p is 0 or 1; or

(iii) Formula IIIe:



(Formula IIIe)

wherein p is 0 or 1.

5. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1, 3 and 4, wherein:

each R^1 is independently halo or -OH;

R^2 is -C_1-C_6 alkyl substituted with 0-3 halo;

R^3 is -C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, tetrahydropyranyl, or -Y-(C_3-C_6 cycloalkyl), each of which is substituted with 1-3 R^4;

each R^4 is independently halo, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), -Y-O-(C_1-C_6 alkyl), -S-(C_1-C_6 alkyl), or -$S(O)_2$-(C_1-C_6 alkyl), wherein the -O-(C_1-C_6 alkyl), -Y-O-(C_1-C_6 alkyl), -S-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl) are substituted with 0-3 halo; and

Y is -C_1-C_3 alkylene-.

6. The compound, or pharmaceutically acceptable salt thereof, according to claim 5, wherein each R^4 is independently selected from the group consisting of halo, -CN, -O-(C_1-C_3 alkyl), -S-(C_1-C_3 alkyl), and -$S(O)_2$-(C_1-C_3 alkyl), wherein the -O-(C_1-C_3 alkyl), -S-(C_1-C_3 alkyl), and -$S(O)_2$-(C_1-C_3 alkyl) are substituted with 0-3 halo, optionally wherein each R^4 is independently selected from -F, -CN, -OCH_3, -OCF_2H, -OCF_3, -SCF_3, and -$S(O)_2CF_3$.

7. The compound, or pharmaceutically acceptable salt thereof, according to claim 5, wherein each R^4 is independently halo, -C_1-C_6 haloalkyl, -O-(C_1-C_6 alkyl), or -Y-O-(C_1-C_6 alkyl), wherein the -O-(C_1-C_6 alkyl), or -Y-O-(C_1-C_6 alkyl) are substituted with 0-3 halo, optionally wherein each R^4 is independently -F, -CF_3, -OCH_3, -OCF_3, or -$CH(CH_3)$-O-CF_3.

8. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 4, wherein:

each R^1 is independently halo or -OH;

R^2 is -C_1-C_6 alkyl substituted with 0-3 halo, or -$S(O)_2$-(C_1-C_3 alkyl);

R^3 is -C_1-C_6 alkyl substituted with 1-3 R^4, -C_3-C_6 cycloalkyl, -6 to 7-membered heterocycloalkyl having one heteroatom or heteroatom group selected from O and $S(=O)_2$, -C_1-C_2 alkylene-(C_3-C_4 cycloalkyl), -C_1-C_2 alkylene-(4- to 5-membered heterocycloalkyl) having 1 heteroatom or heteroatom group selected from O and $S(=O)_2$, -C_2-C_3 alkylene-(phenyl), and -C_1-C_2 alkylene-(5-membered heteroaryl) having 1-2 heteroatoms selected from N, O, and S, wherein the -C_3-C_6 cycloalkyl, -6 to 7-membered heterocycloalkyl, -C_1-C_2 alkylene-(C_3-C_4 cycloalkyl), -C_1-C_2 alkylene-(4- to 5-membered heterocycloalkyl), -C_2-C_3 alkylene-(phenyl), and -C_1-C_2 alkylene-(5-membered heteroaryl) are substituted with 0-3 R^4;

each R^4 is independently selected from halo, -CN, -C_1-C_6 haloalkyl, -OH, -O-(C_1-C_6 alkyl), -(C_1-C_2 alkylene)-O-(C_1-C_6 alkyl), -S(O)-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl), wherein the -O-(C_1-C_6 alkyl), -(C_1-C_2 alkylene)-O-(C_1-C_6 alkyl), -S(O)-(C_1-C_6 alkyl), and -$S(O)_2$-(C_1-C_6 alkyl) are substituted with 0-3 halo.

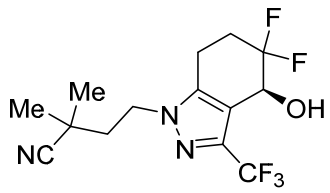
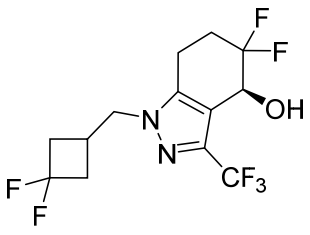
9. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein:

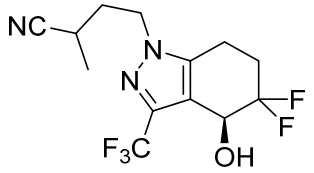
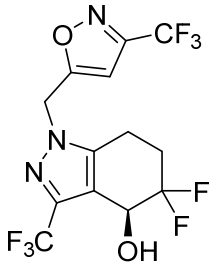
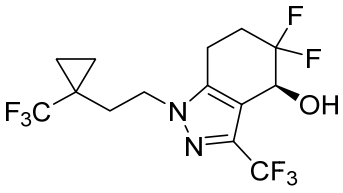
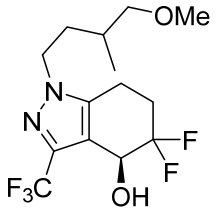
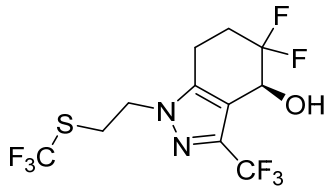
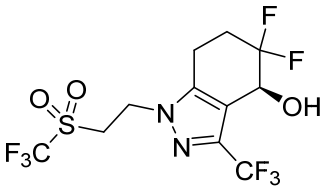
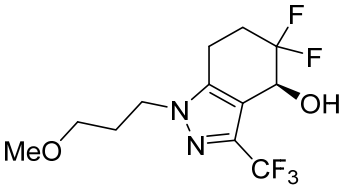
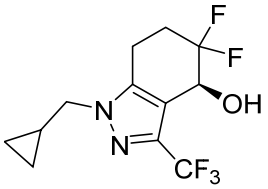
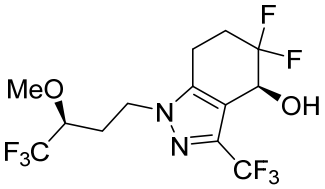
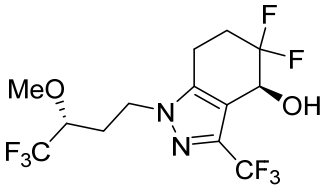
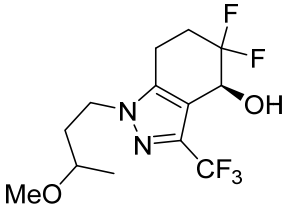
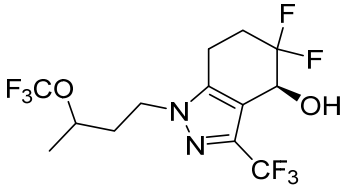
(i) R^2 is -CF_3; and/or

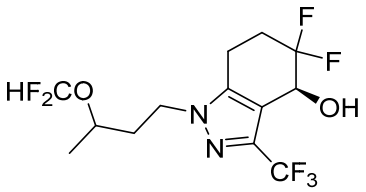
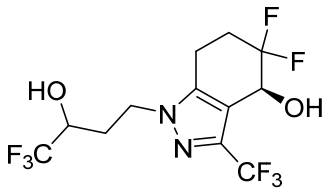
(ii) at least one R^1 is -F; and/or

(iii) at least one R^1 is -OH.

10. The compound, or pharmaceutically acceptable salt thereof, according to claim 1, selected from the group consisting of:

Example 1	Example 2
	

Example 3 	Example 4 
Example 5 	Example 6 
Example 7 	Example 8 
Example 9 	Example 10 
Example 11 	Example 12 
Example 13 	Example 14 

Example 15	Example 16
	
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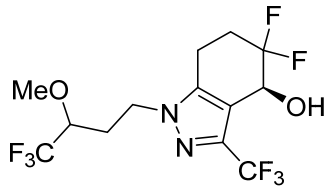	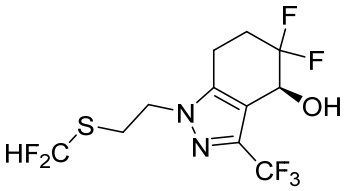
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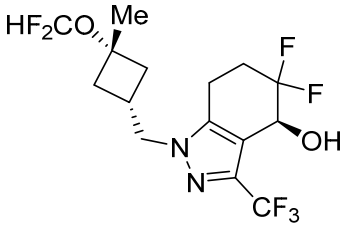	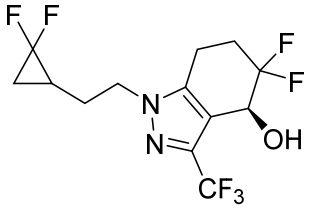
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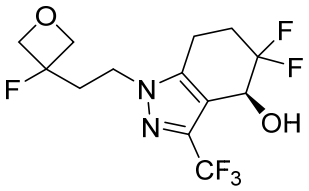	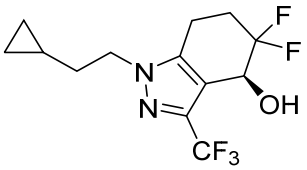
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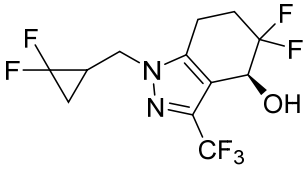
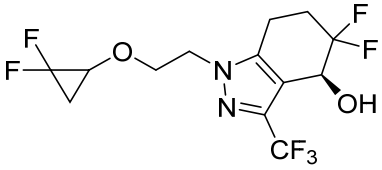
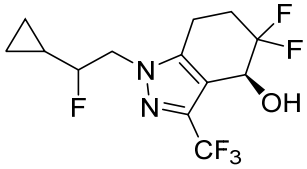
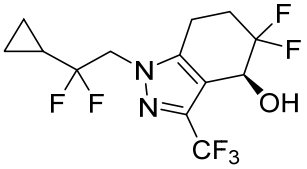
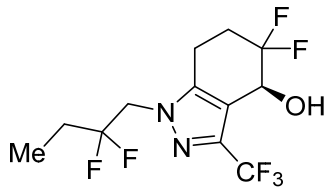
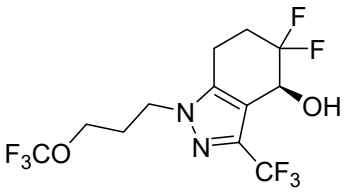
	
Example 26 and 27	Example 28
	
Example 29	Example 30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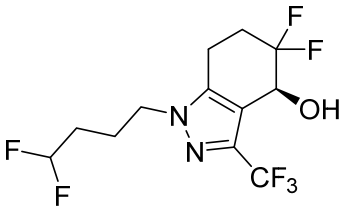	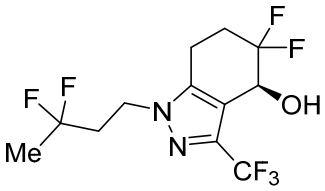
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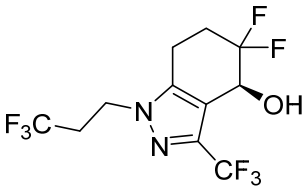	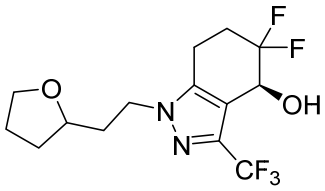
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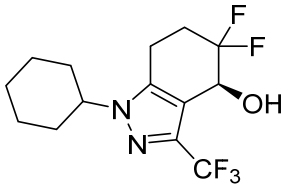	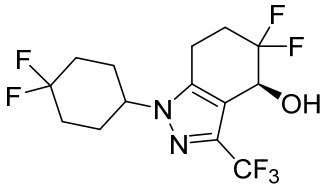
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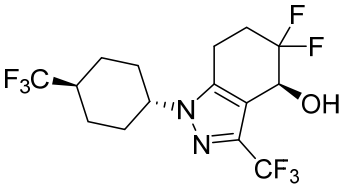	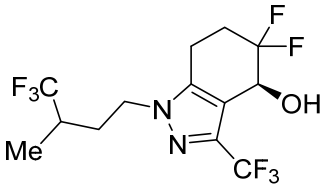
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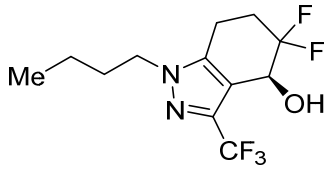	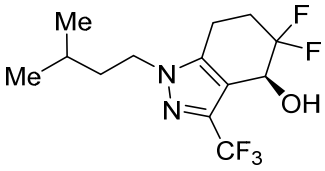
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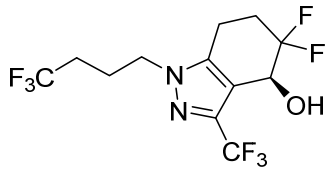	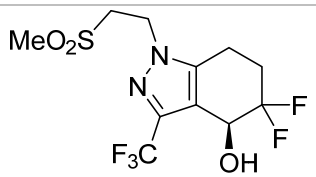
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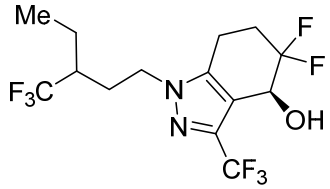	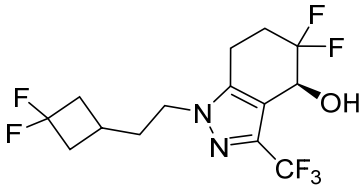
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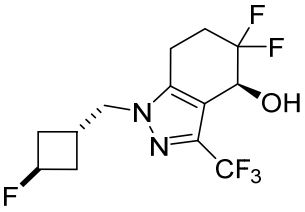	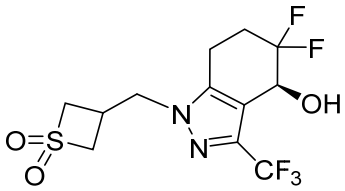
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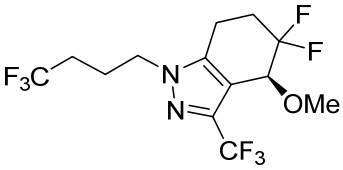	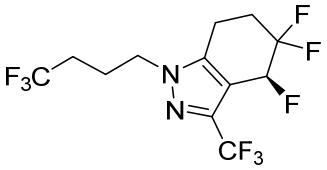
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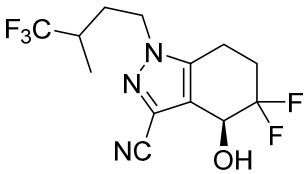	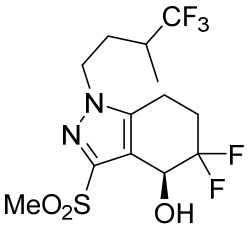
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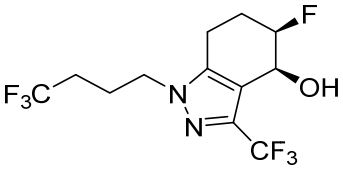	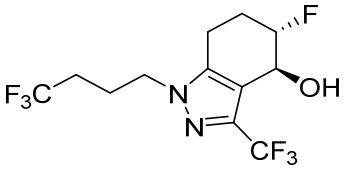
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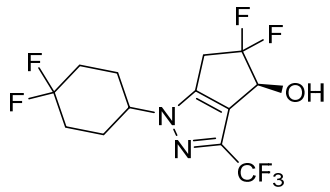	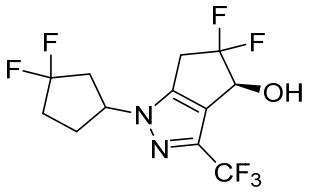
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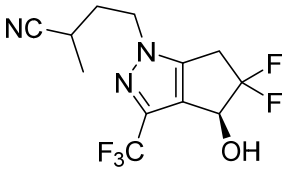	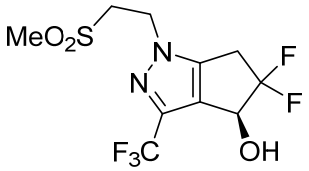
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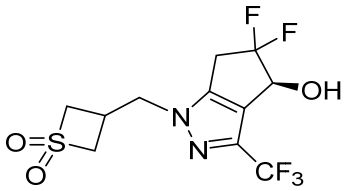	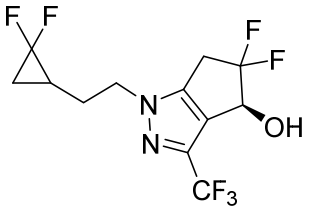
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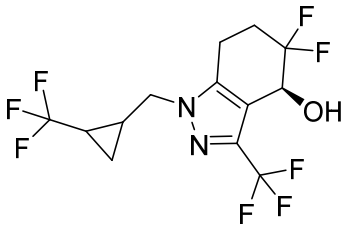	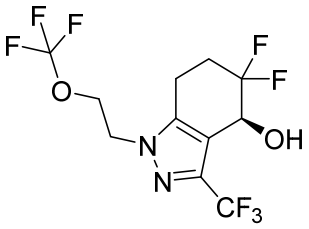
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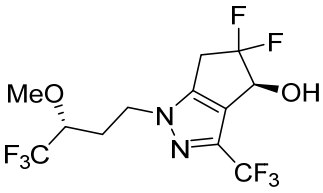	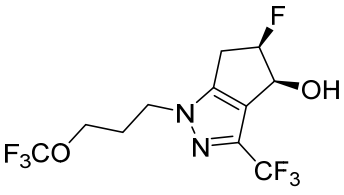 ,
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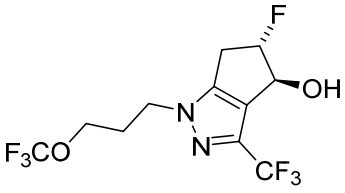 .	

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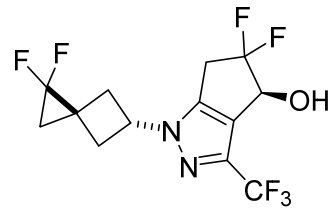	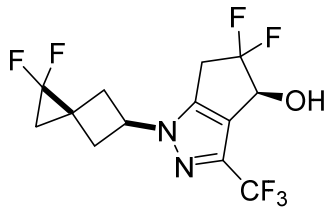
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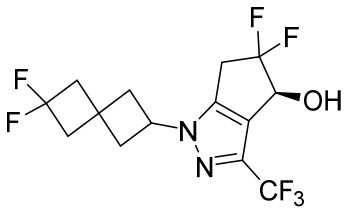	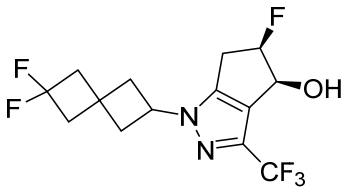
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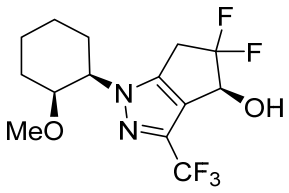	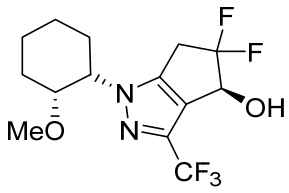
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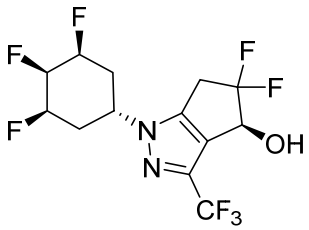	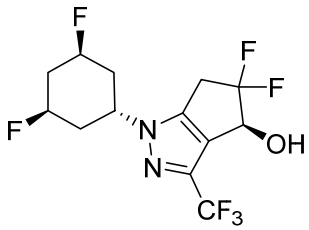
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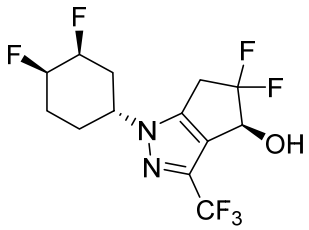	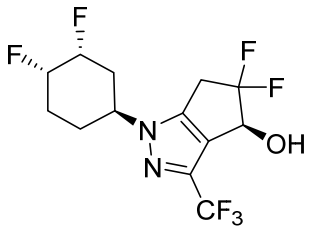
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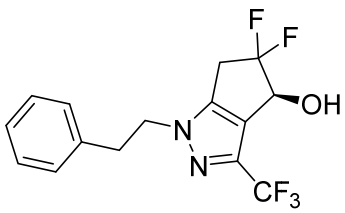	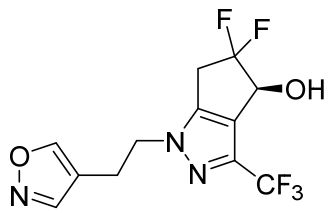

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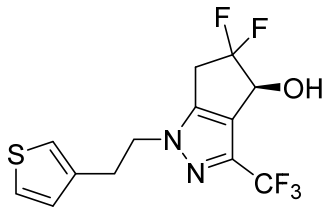	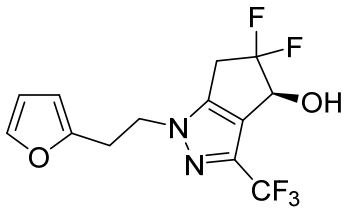
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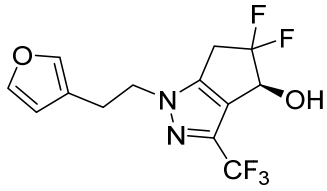	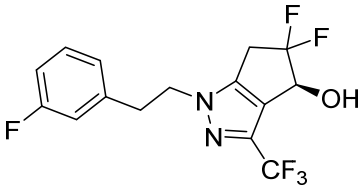
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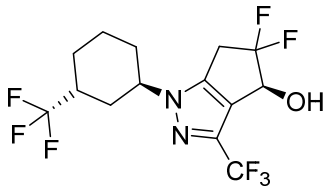	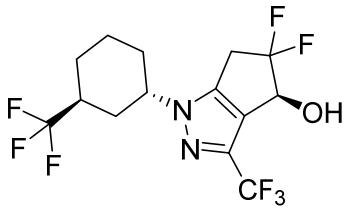
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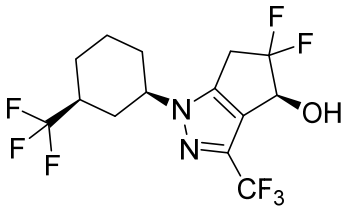	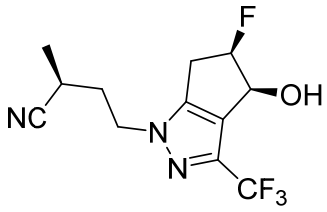
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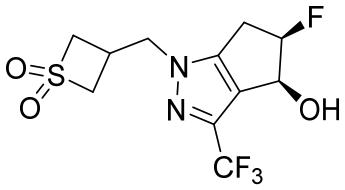	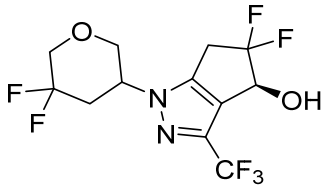
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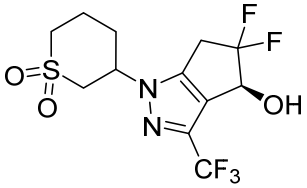	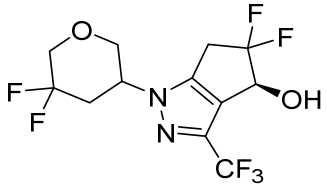
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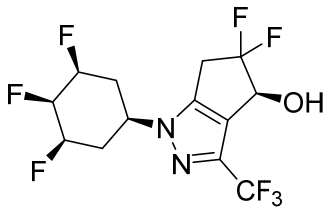	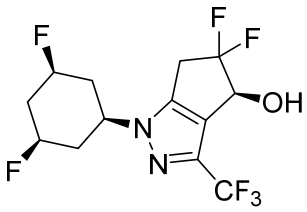
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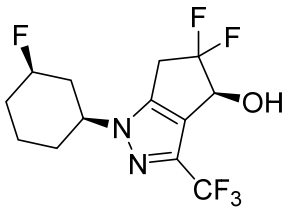	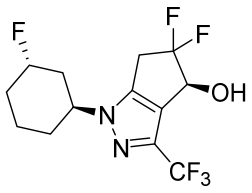
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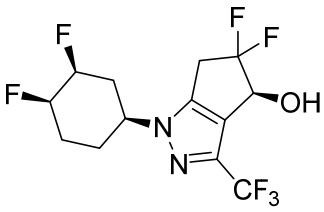	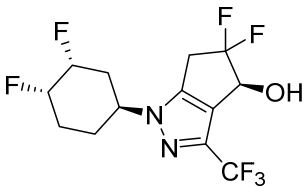
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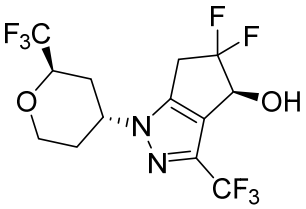
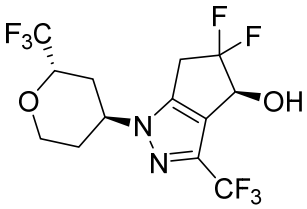
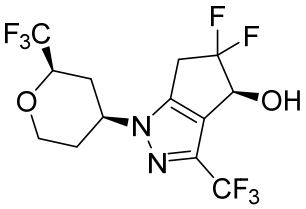
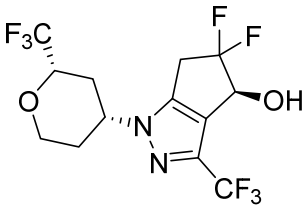
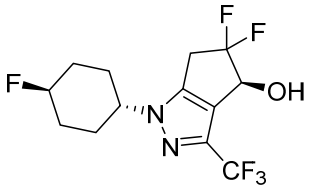
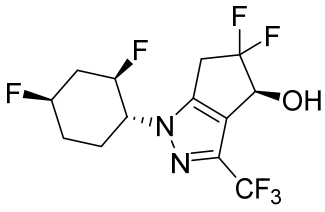
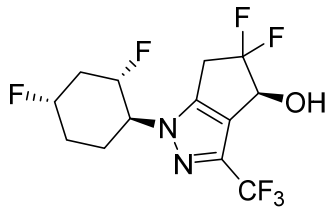
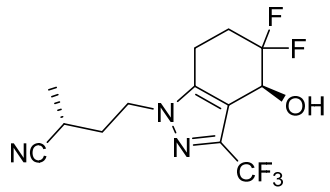
	
Example 94/95	Example 94/95
	
Example 96	Example 97/98
	
Example 97/98	Example 99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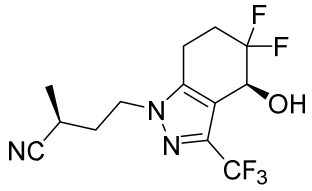	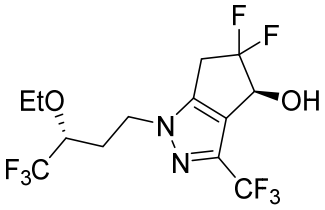
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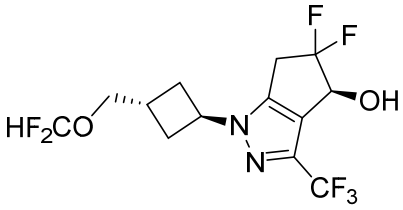	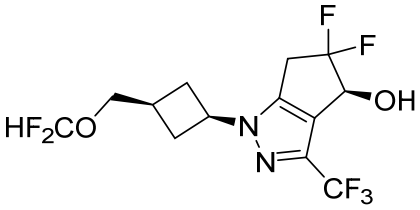
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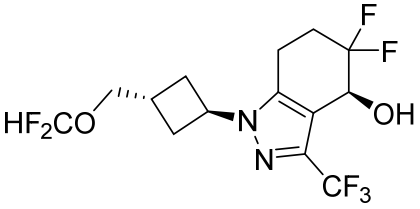
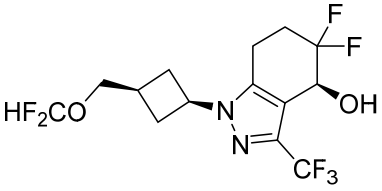
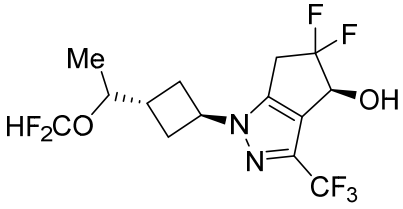
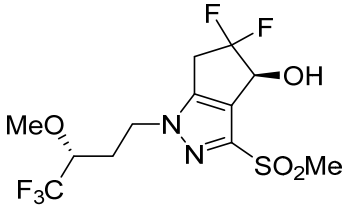
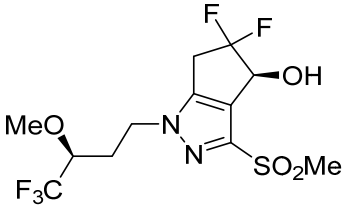
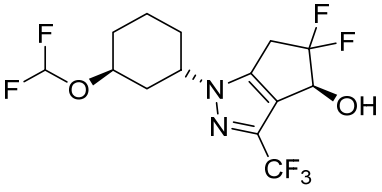
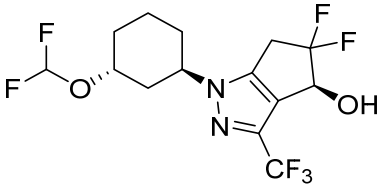
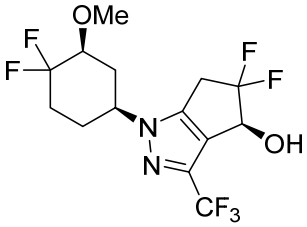
	
Example 106	Example 107a
	
Example 107b	Example 108a
	
Example 108b	Example 109a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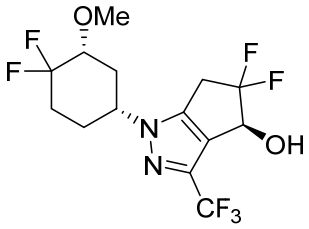	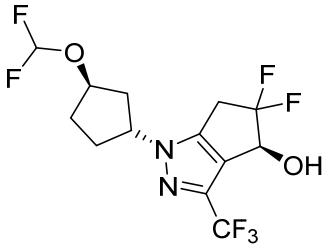
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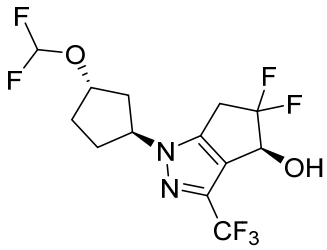	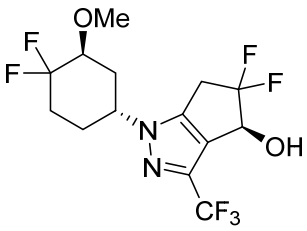
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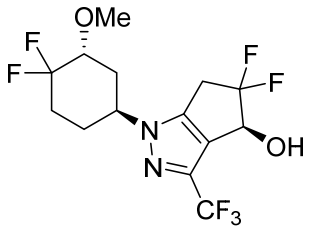	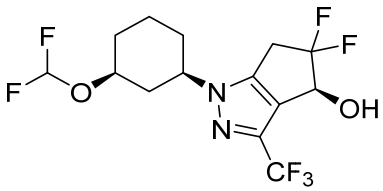
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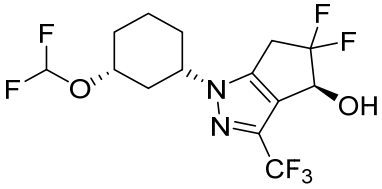	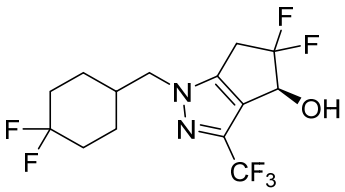
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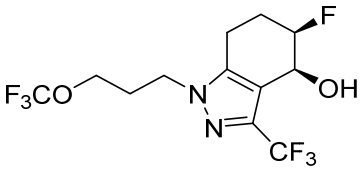	

	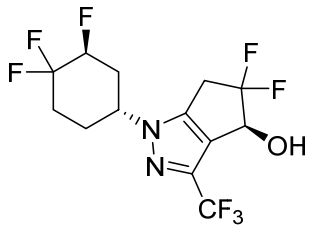
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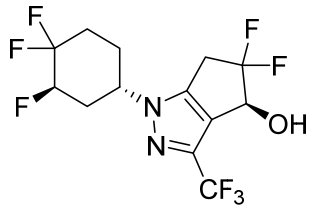	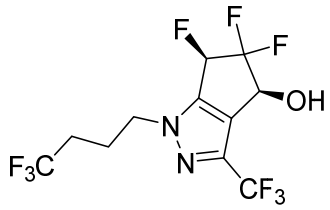
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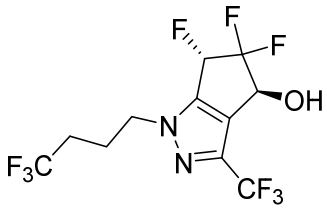
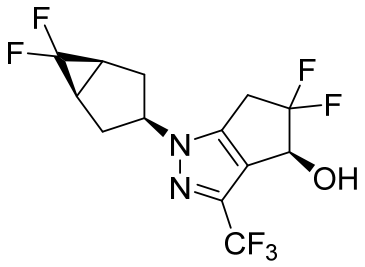
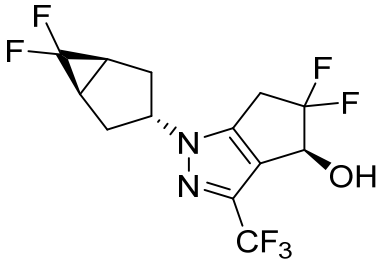
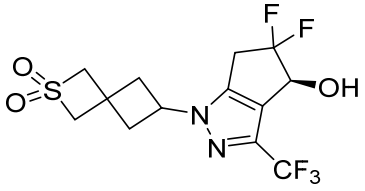
	
Example 125/126	Example 127
	
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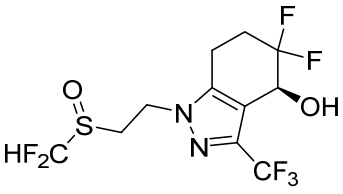
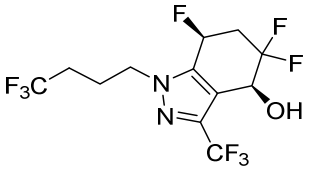
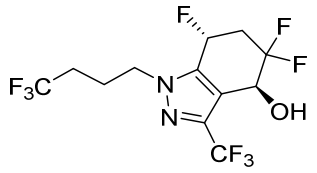
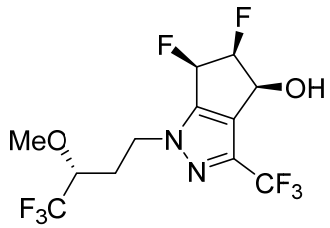
	
Example 129/130	Example 131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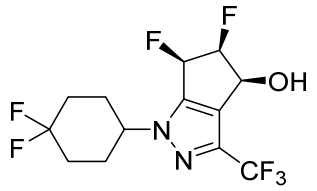	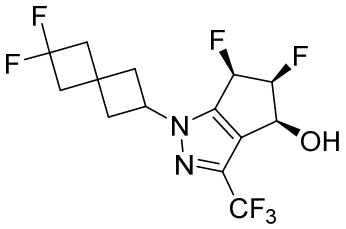
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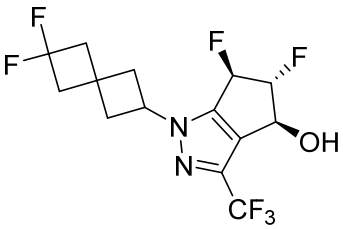
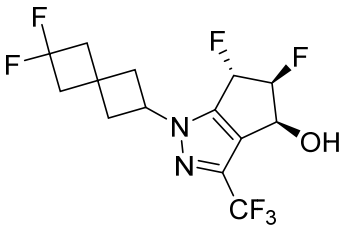
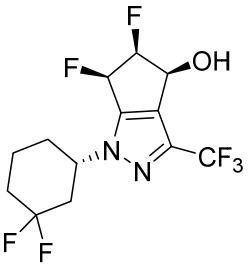
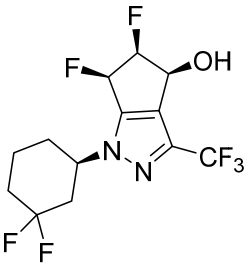
	
Example 136/137	Example 136/137
	
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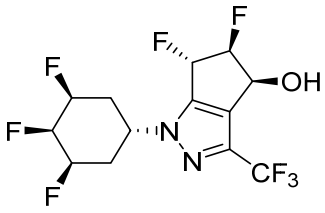
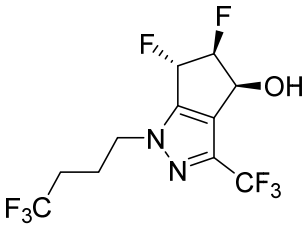
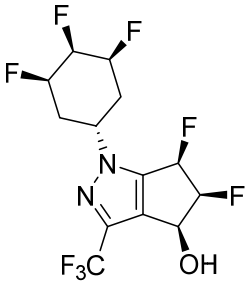
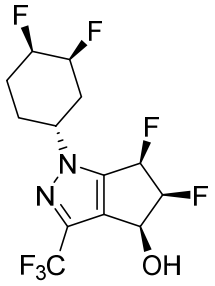
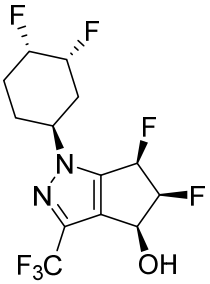
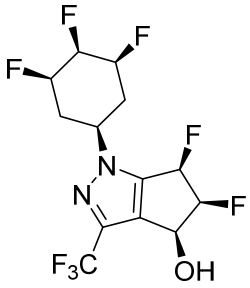
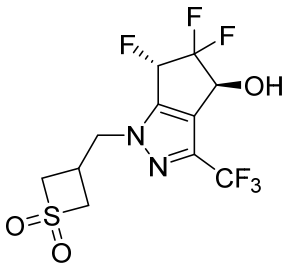
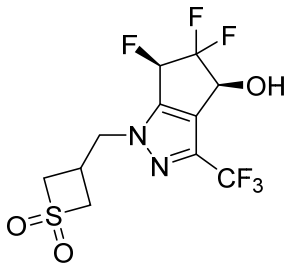
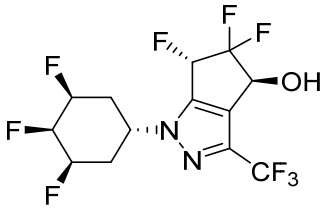
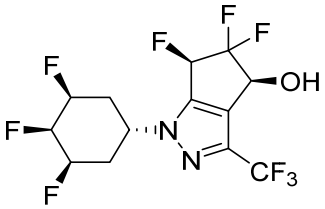
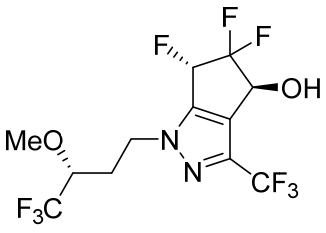
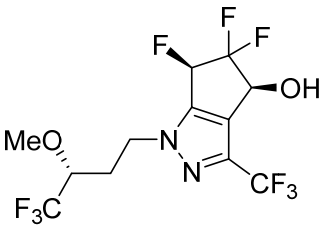
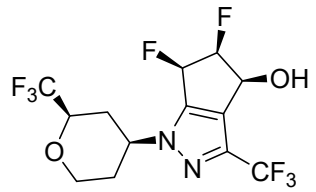
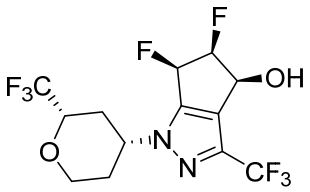
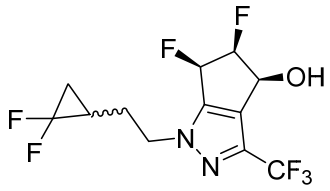
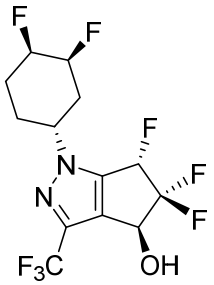
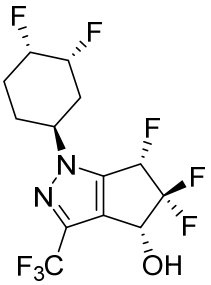
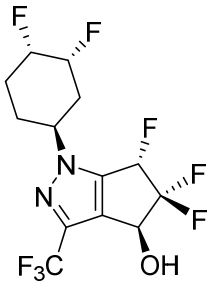
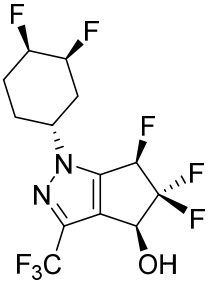
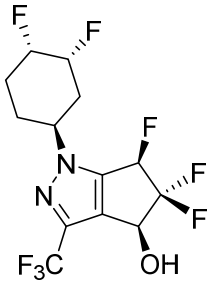
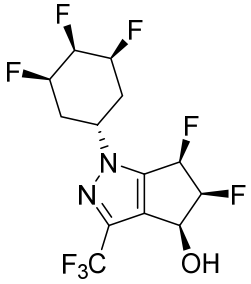
	
Example 140	Example 141/142

	
Example 141/142	Example 143
	
Example 144/145	Example 144/145
	
Example 146/147	Example 146/147
	
Example 148/149	Example 148/149
 ,	

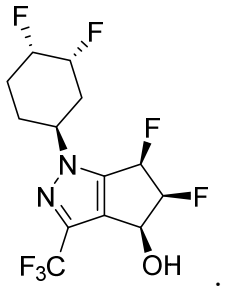
Example 150/151	Example 150/151

	
Example 152	Example 153
	
Example 154	Example 155
	
Example 156	Example 157
 , and	

11. The compound according to claim 1, which is:

 .

12. The compound according to claim 1, which is:



.

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

14. Use of a pharmaceucial composition comprising a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, in the manfacture of a medicament.

15. Use of a pharmaceucial composition comprising a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, in the manfacture of a medicament for treating a disease, disorder, or condition, mediated at least in part by HIF-2α, , wherein the disease, disorder, or condition is von Hippel-Lindau (VHL) disease, cancer, or an immune-related disease, disorder or condition.

16. The use according to claim 15, wherein:

(i) the disease, disorder, or condition is von Hippel-Lindau (VHL) disease and the von Hippel-Lindau (VHL) disease is associated with renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET); or

(ii) the disease, disorder, or condition is cancer and the cancer is a cancer of the prostate, colon, rectum, pancreas, cervix, stomach, endometrium, uterus, brain, liver, bladder, ovary, testis, head, neck, skin (including melanoma and basal carcinoma), mesothelial lining, white blood cell (including lymphoma and leukemia), esophagus, breast, muscle, connective

tissue, intestine, lung (including small-cell lung carcinoma and non-small-cell lung carcinoma), adrenal gland, thyroid, kidney, or bone; or is glioblastoma, mesothelioma, renal cell carcinoma, gastric carcinoma, sarcoma (including Kaposi's sarcoma), choriocarcinoma, cutaneous basocellular carcinoma, or testicular seminoma, optionally wherein the cancer is selected from the group consisting of melanoma, colorectal cancer, pancreatic cancer, liver cancer, breast cancer, prostate cancer, lung cancer, leukemia, a brain tumor, lymphoma, ovarian cancer, Kaposi's sarcoma, renal cell carcinoma, head and neck cancer, esophageal cancer, and urothelieal carcinoma;

(iii) the disease, disorder, or condition the immune-related disesease and the immune-related disease, disorder, or condition is selected from the group consisting of rheumatoid arthritis, kidney failure, lupus, asthma, psoriasis, colitis, pancreatitis, allergies, fibrosis, anemia fibromyalgia, Alzheimer's disease, congestive heart failure, stroke, aortic valve stenosis, arteriosclerosis, osteoporosis, Parkinson's disease, infections, Crohn's disease, ulcerative colitis, allergic contact dermatitis and other eczemas, systemic sclerosis, and multiple sclerosis.

17. The use according to claim 15 or claim 16, further comprising administering one or more additional therapeutic agents.

18. Use of a pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combinatorial therapy, wherein said medicament is to be administered in combination with at least one additional therapeutic agent.

19. The use according to claim 17 or claim 18, wherein the one or more additional therapeutic agents comprise one or more agents selected from the group consisting of a tyrosine kinase inhibitor, a cytokine therapy, an antiangiogenic agent, an mTOR inhibitor, an immune checkpoint inhibitor, an inhibitor of CDK-4 and/or CDK-6, an agent that targets the extracellular production of adenosine, radiation therapy, and a chemotherapeutic agent, optionally wherein:

(i) the immune checkpoint inhibitor comprises an immune checkpoint inhibitor that blocks the activity of at least one of PD-1, PD-L1, BTLA, LAG-3, a B7 family member, TIM-3, TIGIT or CTLA-4; and/or

(ii) the tyrosine kinase inhibitor is cabozantinib, foretinib gilteritinib, glesatinib, merestinib, rebastinib, or sitravatinib; and/or

(iii) the anti-angiogenic agent is axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, or tivozanib.