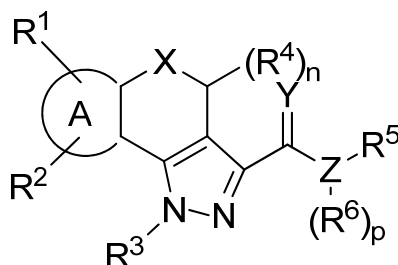


CLAIMS

1. A compound of formula I,



I

or a pharmaceutically acceptable salt thereof, wherein:

X is O;

Y is O;

Z is O, or N; wherein when Z is O, then p is 0;

each R is independently hydrogen, C₁₋₆ aliphatic, C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or

two R groups on the same atom are taken together with the atom to which they are attached to form a C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

Ring A is a fused C₃₋₁₀ aryl, a fused 3-8 membered saturated or partially unsaturated carbocyclic ring, a fused 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a fused 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R¹ is -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂;

R² is -R, halogen, -haloalkyl, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂;

R³ is a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

each R⁴ is independently -R, halogen, -haloalkyl, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂;

R⁵ is C₁₋₆ aliphatic, C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

R⁶ is hydrogen, C₁₋₆ aliphatic, C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

or R⁵ and R⁶, together with the atom to which each is attached, form a 3-8 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 3-8 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

n is 0, 1, or 2; and

p is 0 or 1.

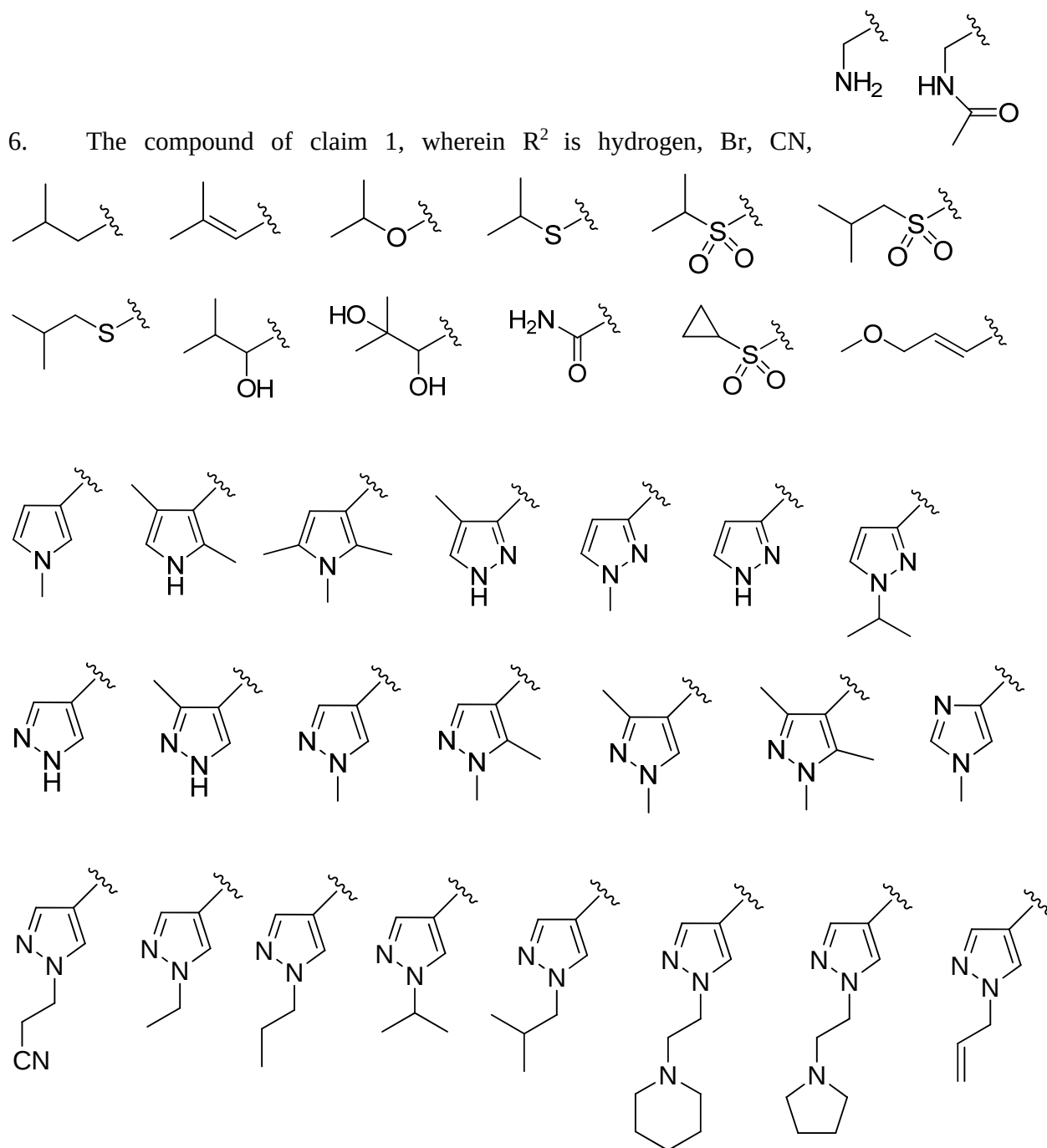
2. The compound of claim 1, wherein Y is O.

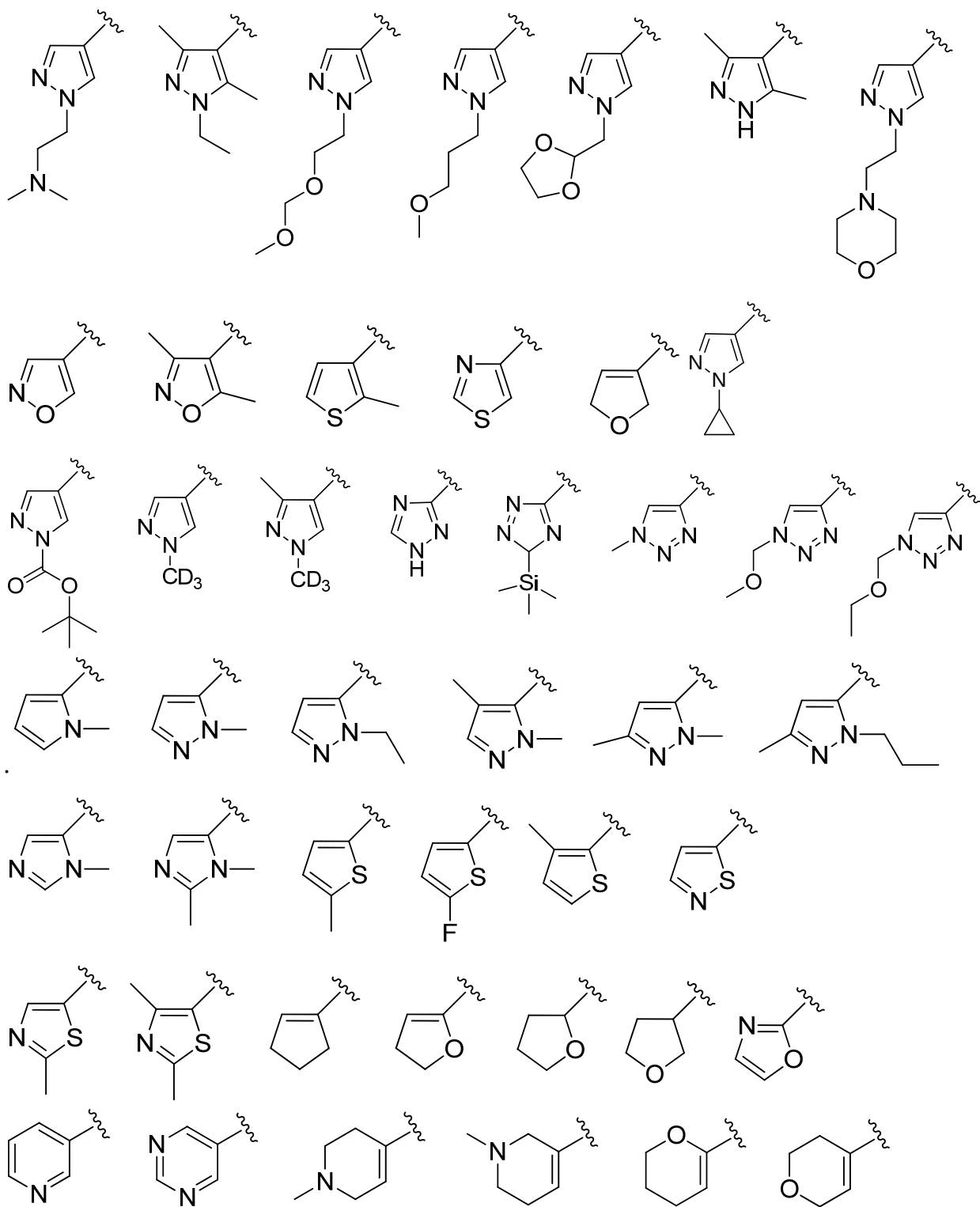
3. The compound of claim 1, wherein Z is N.

4. The compound of claim 1, wherein Ring A is phenyl.

5. The compound of claim 1, wherein R¹ is -OR, and R is C₁₋₆ aliphatic.

6. The compound of claim 1, wherein R² is hydrogen, Br, CN,

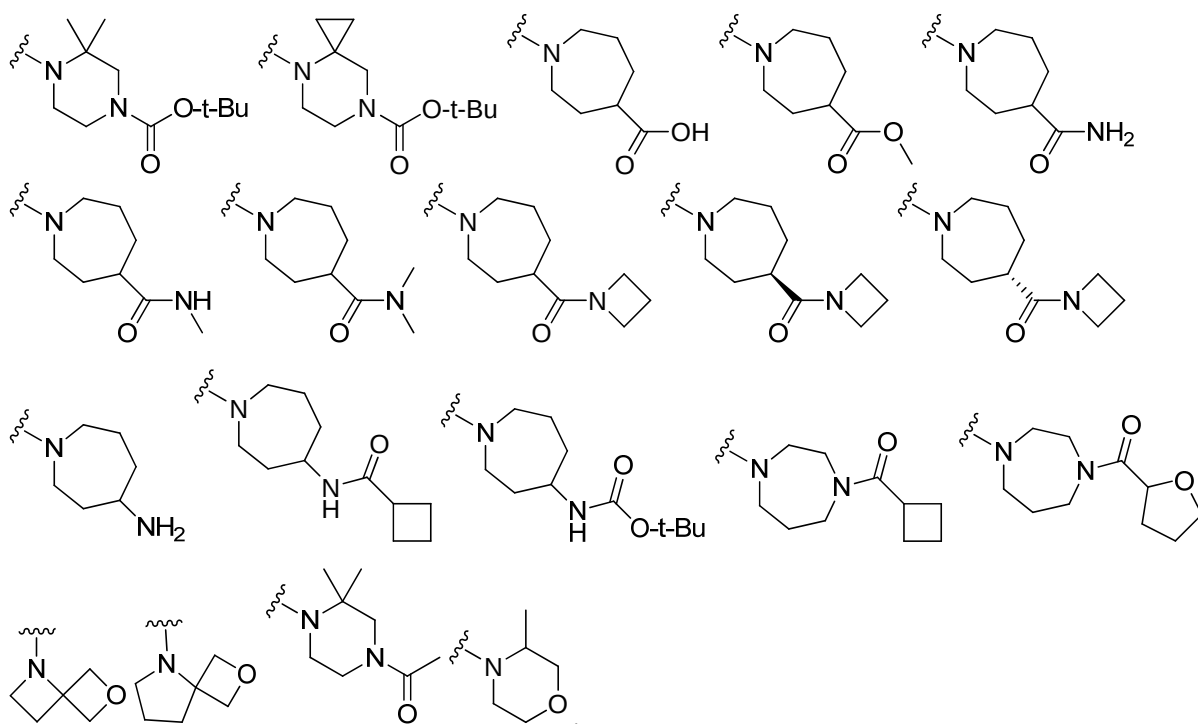




7. The compound of claim 1, wherein R^3 is

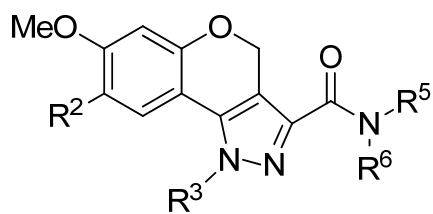
-
- This figure displays 120 chemical structures of small molecules, organized into four rows of 30 structures each. The molecules include various alcohols, ethers, amines, and carbocyclic compounds, many of which are substituted with a wavy line indicating a point of attachment to a polymer or surface. The structures are diverse, ranging from simple alcohols like 1-propanol to more complex molecules like 2-methyl-2-butanol and 2-methoxy-2-methylpropan-1-ol. Some structures feature functional groups like amides, carbamates, and carbocyclic rings (cyclopropane, cyclobutane, cyclopentane, cyclohexane).

- [illegible]



10. The compound of claim 1, wherein R^6 is hydrogen, methyl, t-butyl, or $-CD_3$.

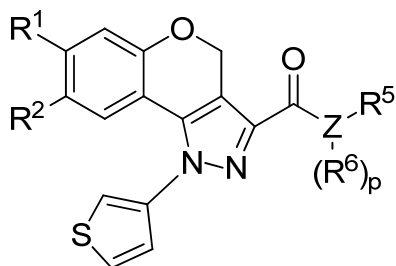
11. The compound of claim 1, of formula **I-f**:



I-f;

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, of formula **I-h**:

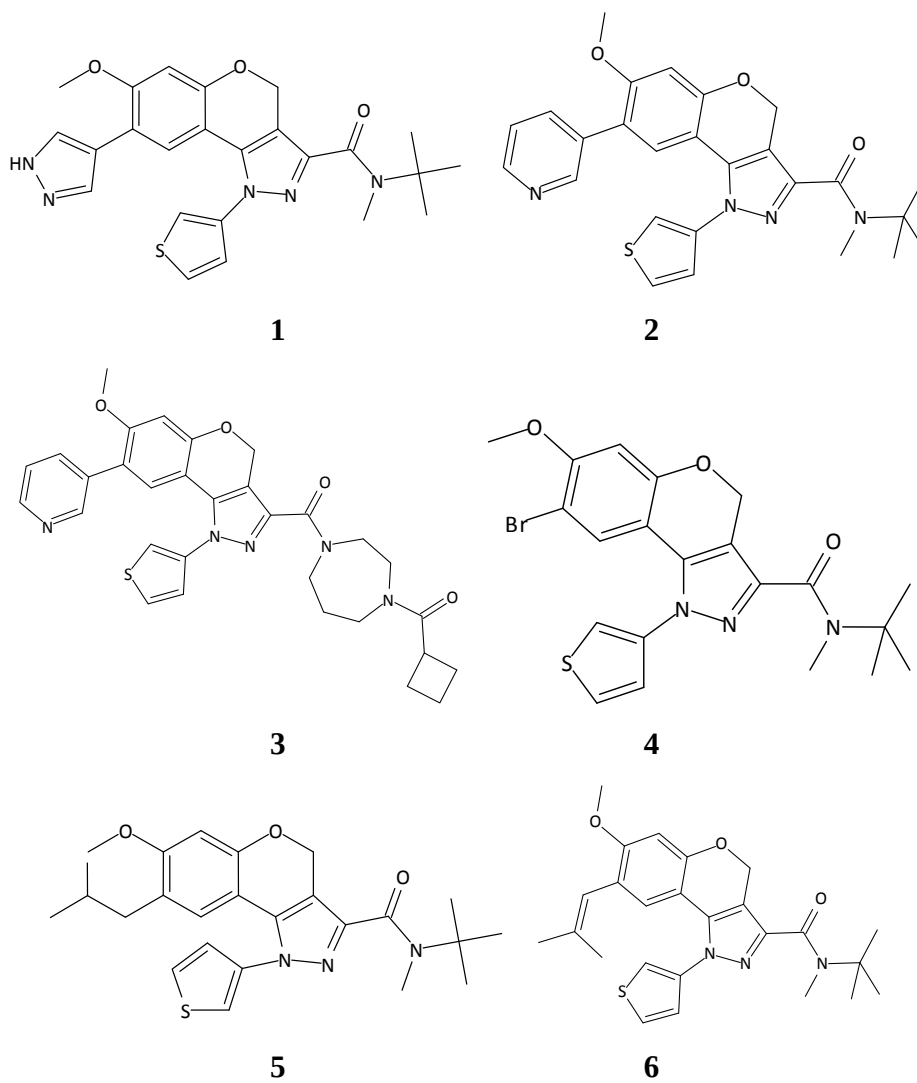


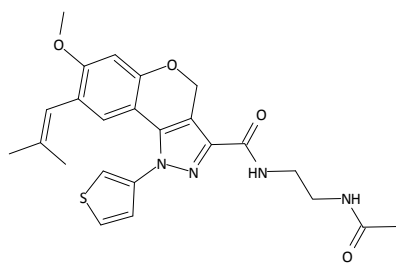
I-h;

or a pharmaceutically acceptable salt thereof.

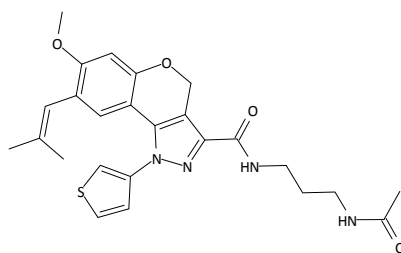
13. The compound of claim 1, selected from Table 1

Table 1

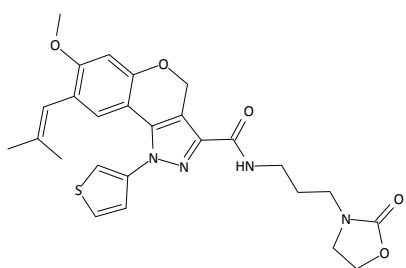




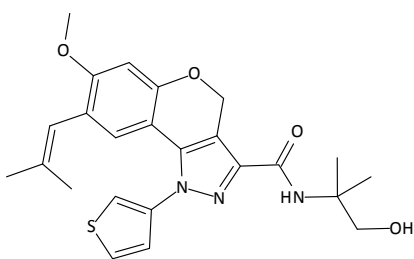
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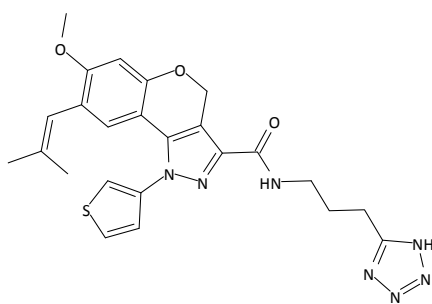
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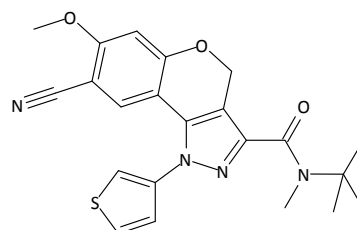
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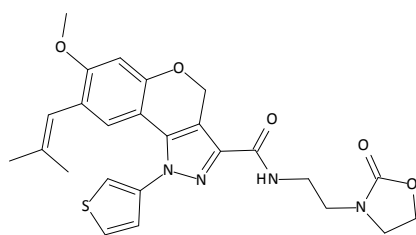
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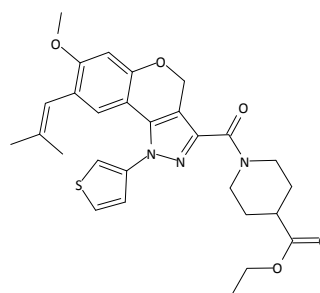
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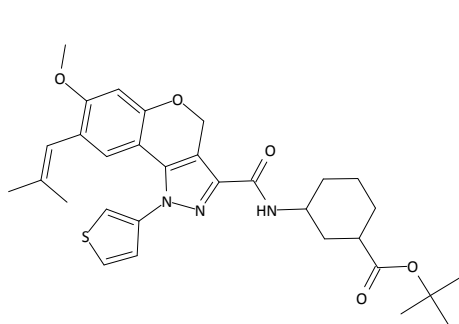
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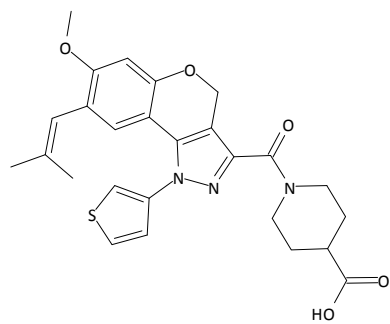
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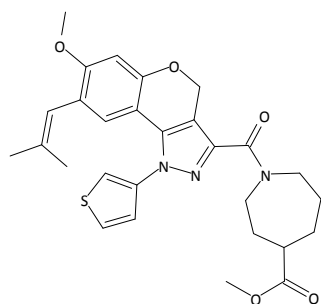
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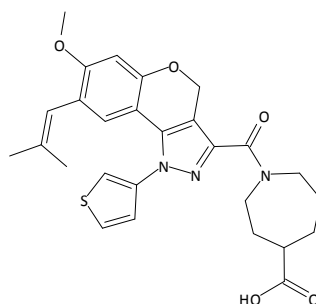
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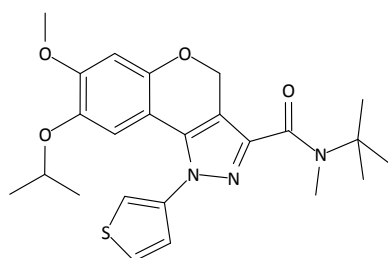
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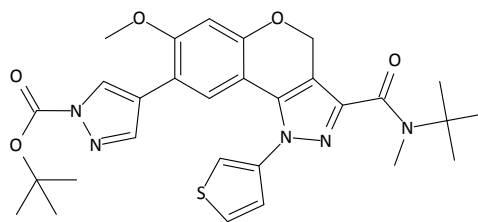
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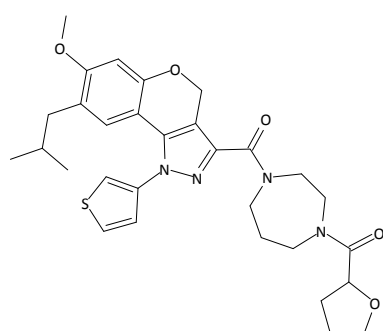
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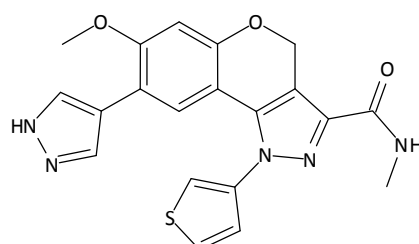
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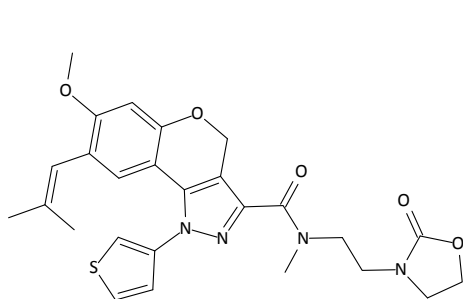
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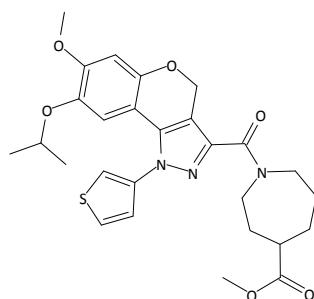
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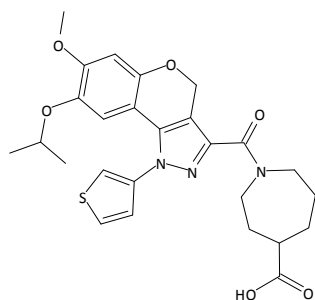
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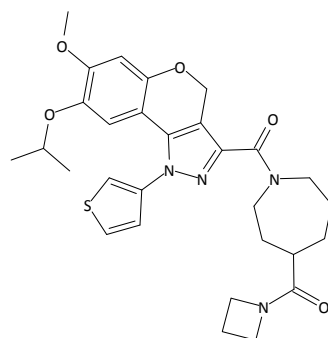
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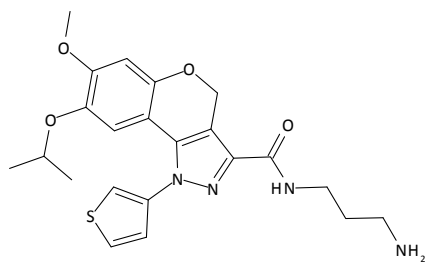
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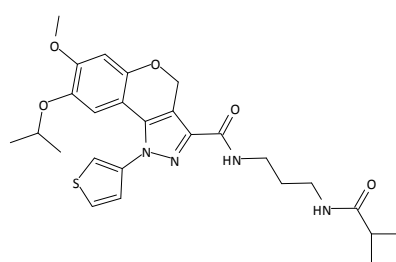
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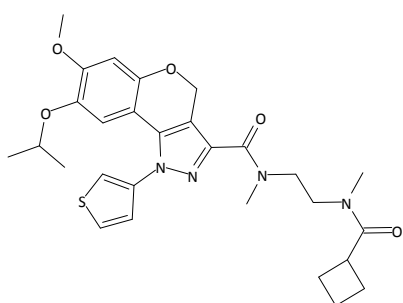
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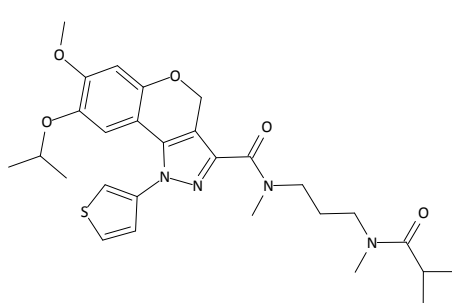
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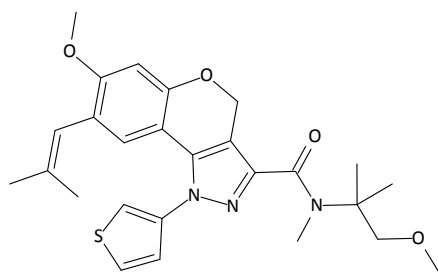
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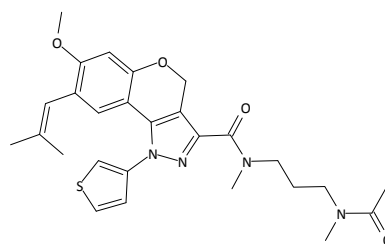
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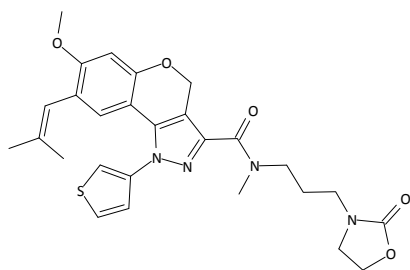
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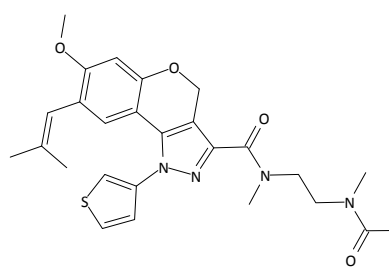
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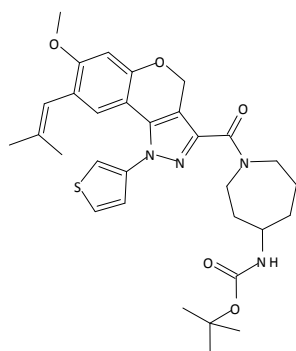
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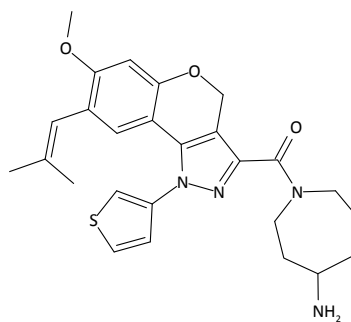
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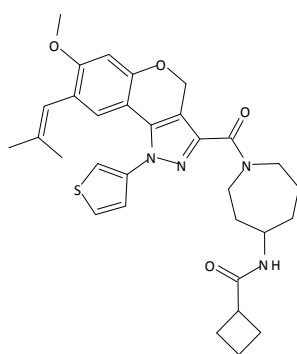
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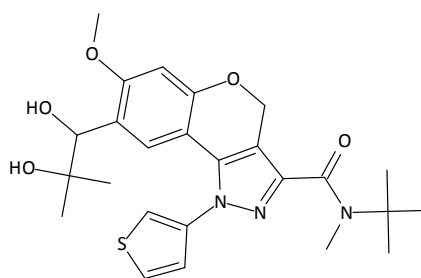
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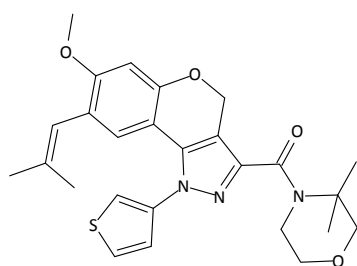
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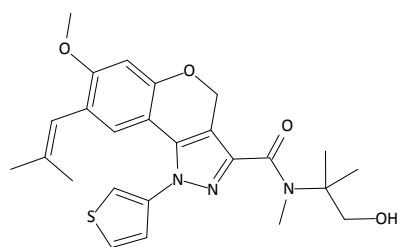
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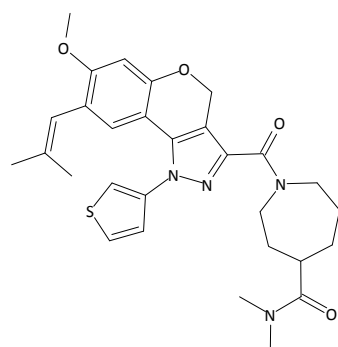
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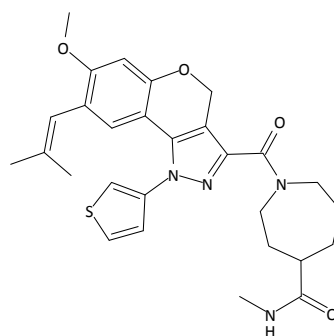
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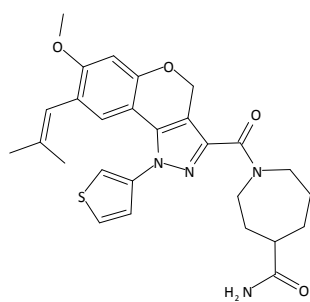
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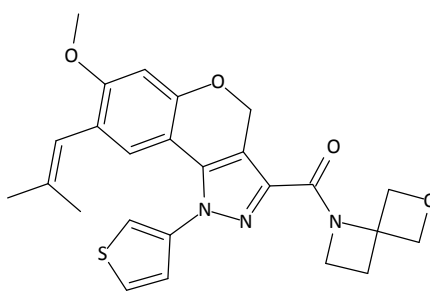
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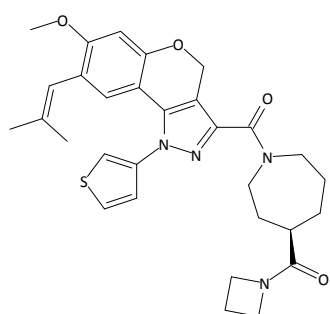
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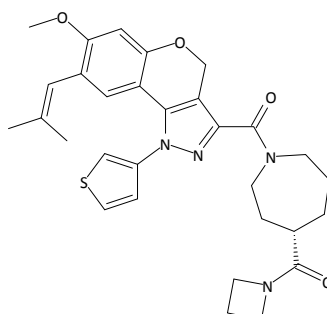
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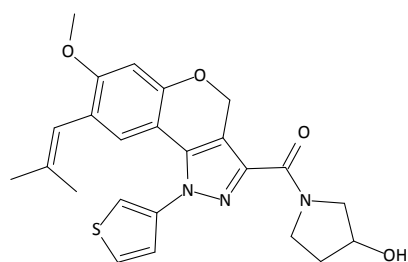
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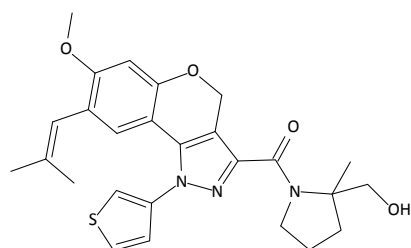
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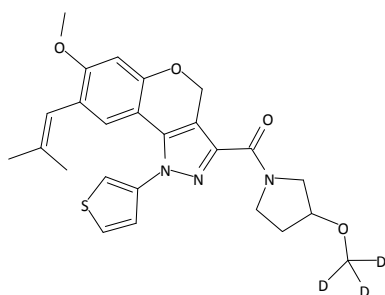
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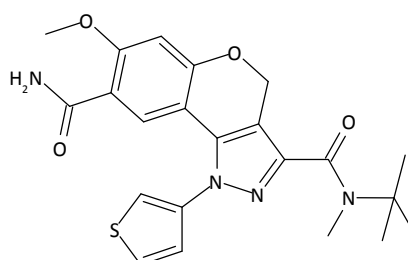
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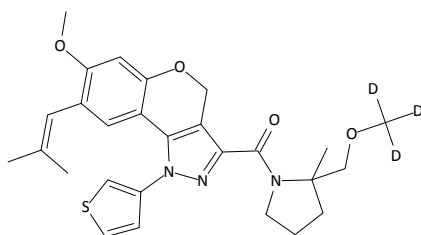
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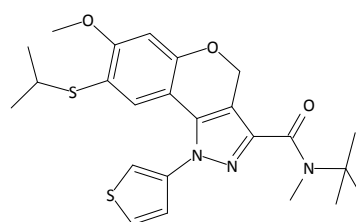
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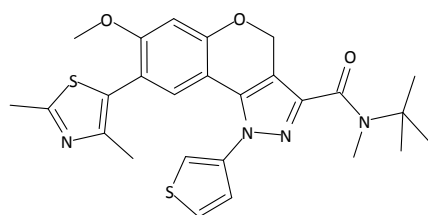
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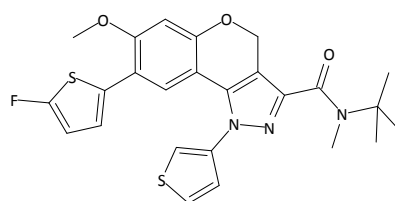
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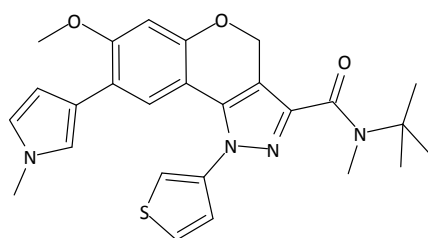
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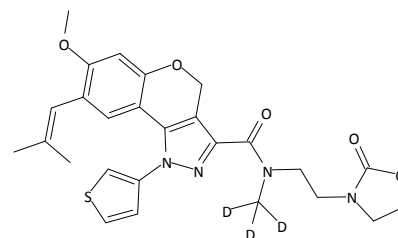
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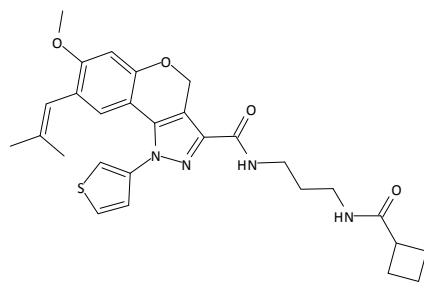
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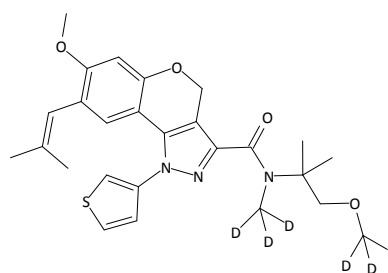
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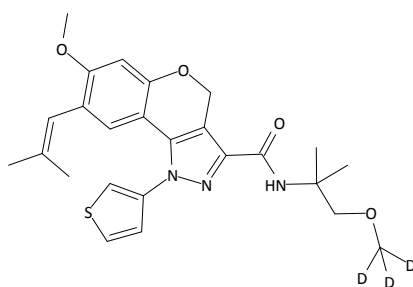
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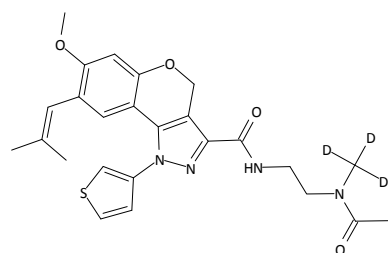
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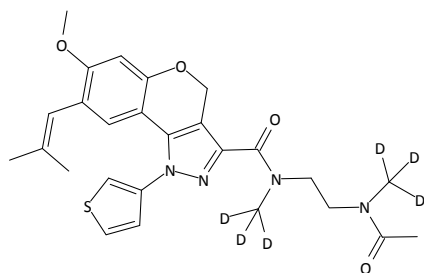
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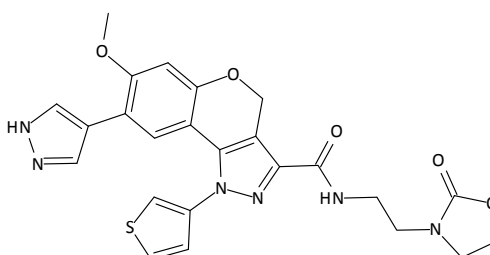
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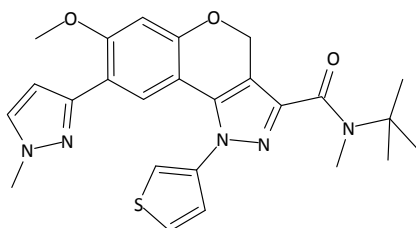
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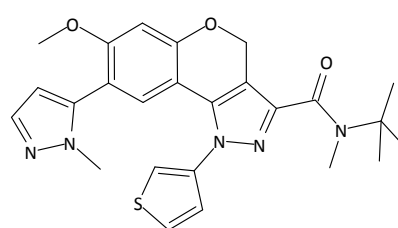
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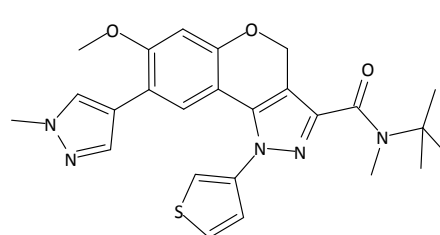
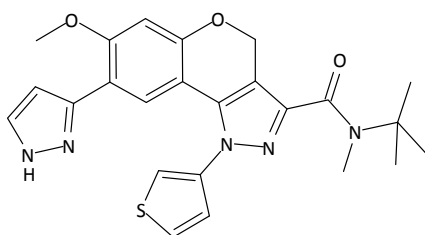
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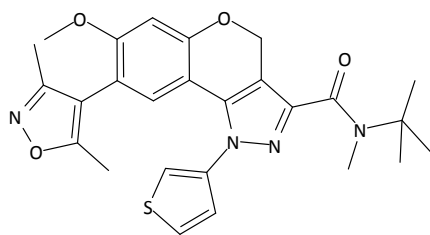


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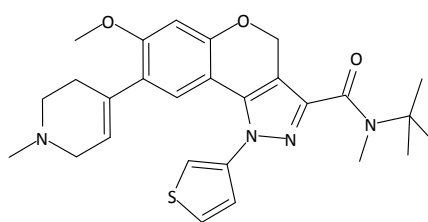


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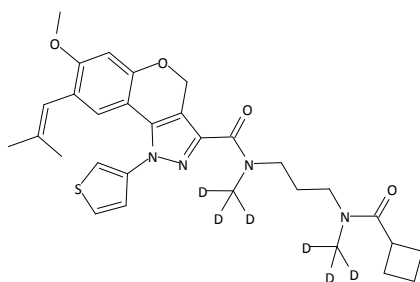
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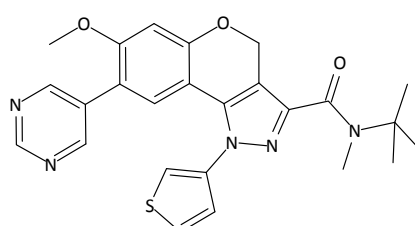
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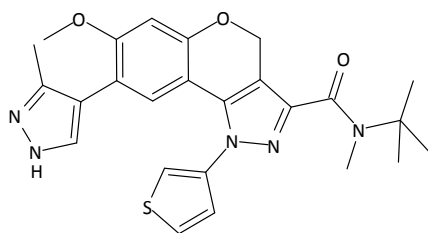
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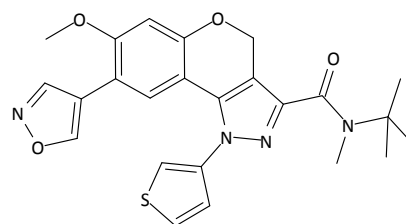
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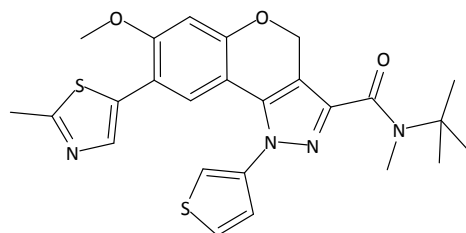
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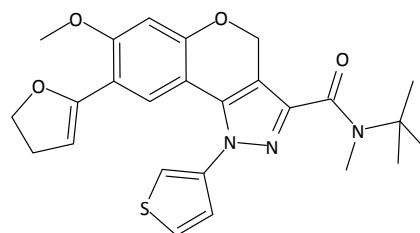
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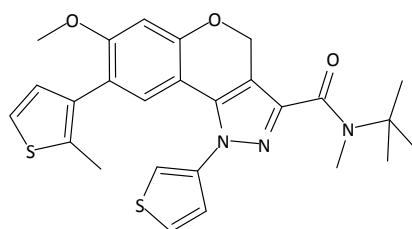
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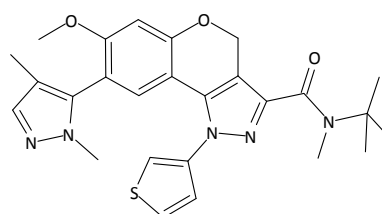
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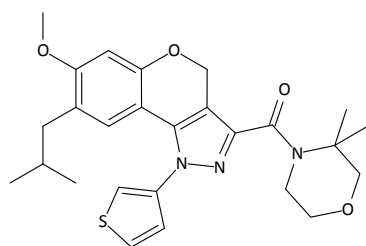
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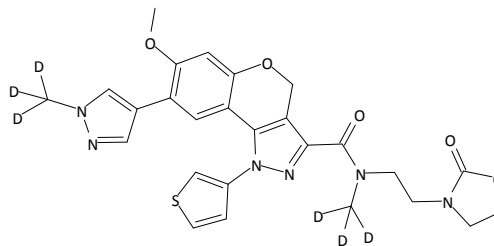
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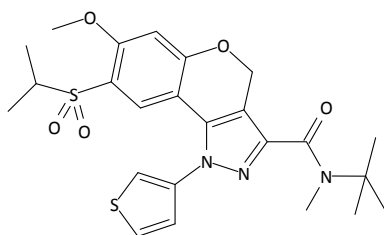
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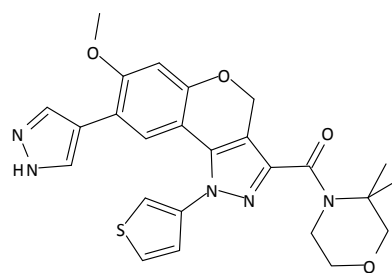
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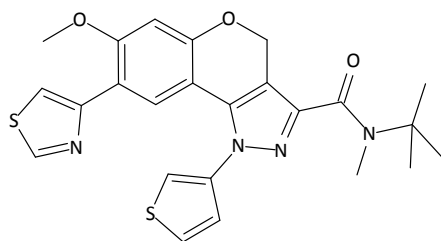
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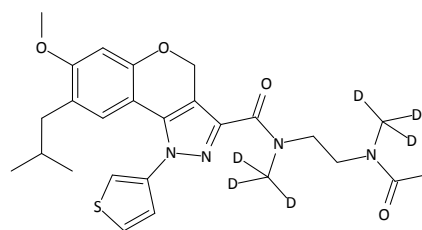
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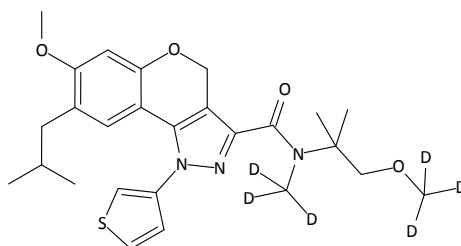
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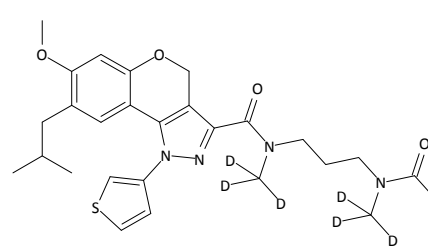
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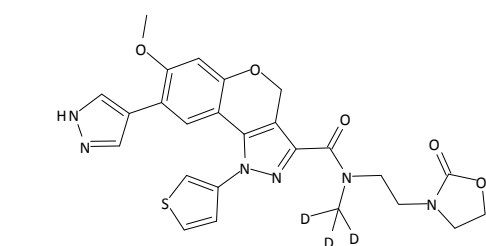
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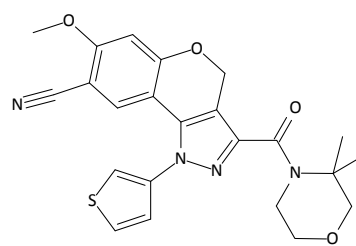
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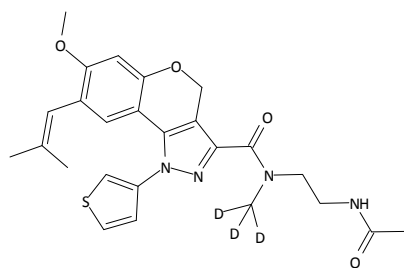
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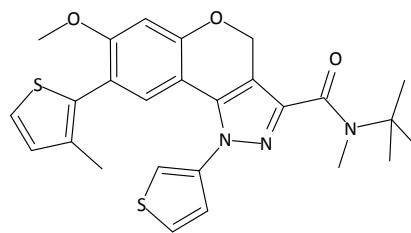
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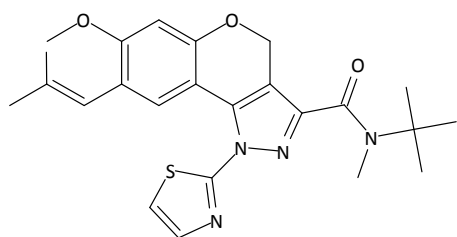
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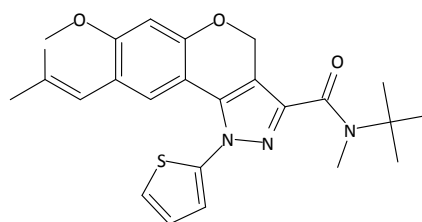
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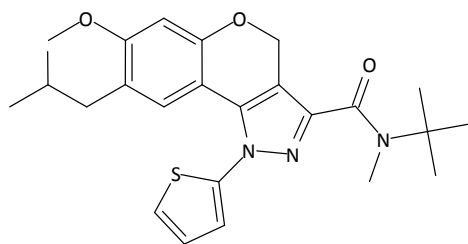
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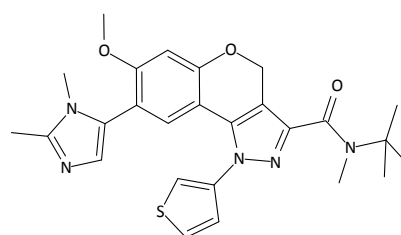
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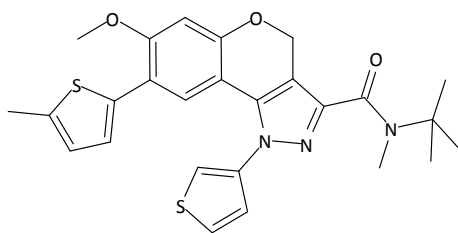
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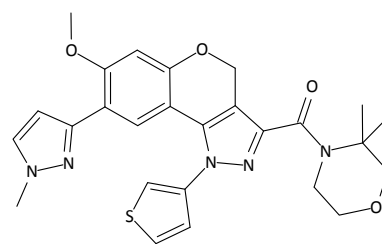
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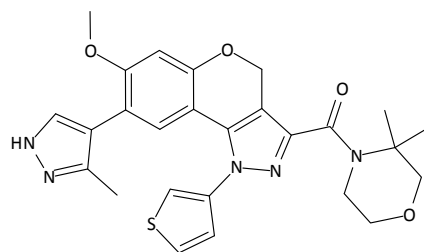
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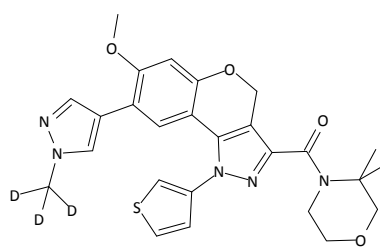
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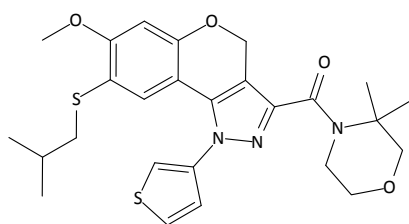
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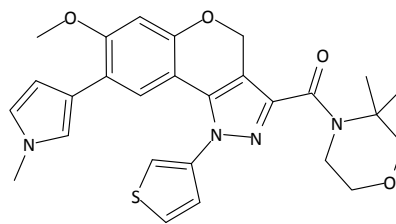
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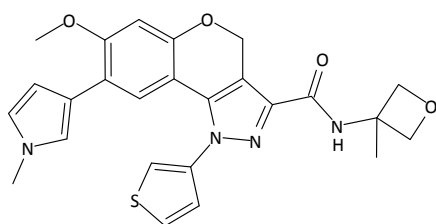
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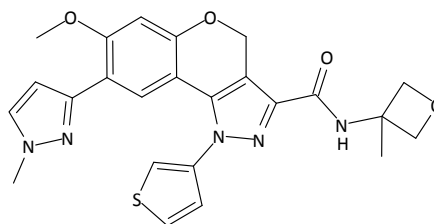
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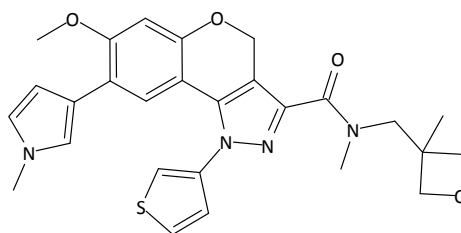
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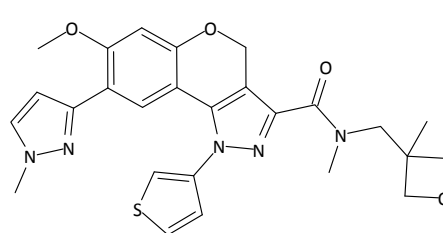
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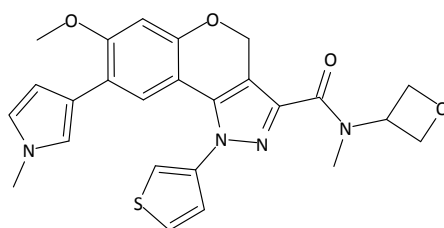
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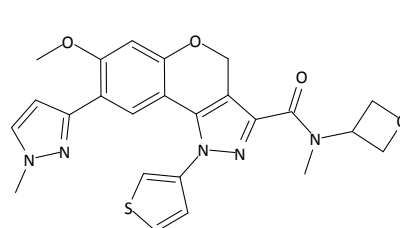
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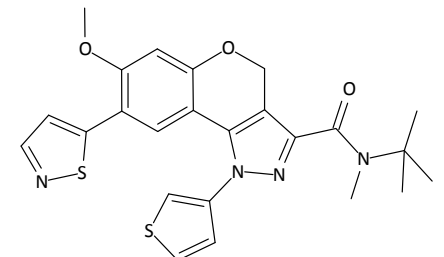
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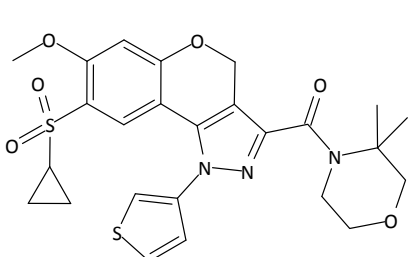
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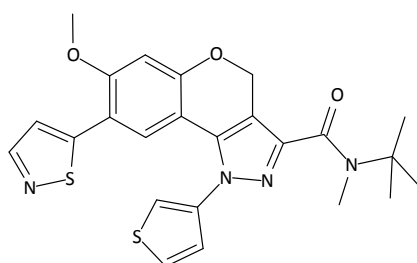
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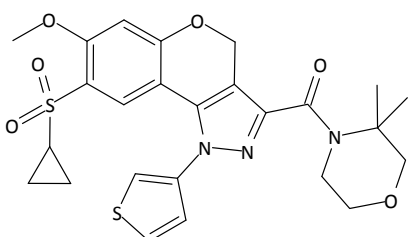
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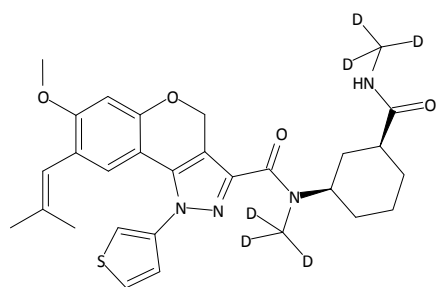


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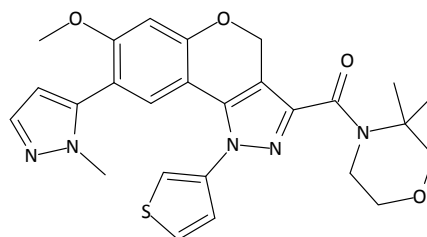


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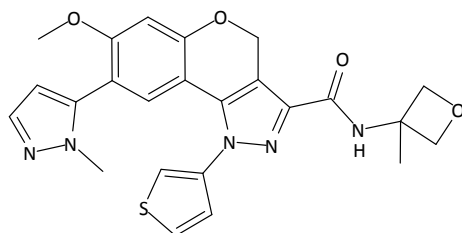




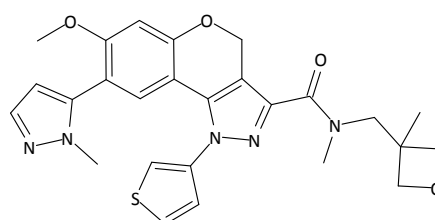
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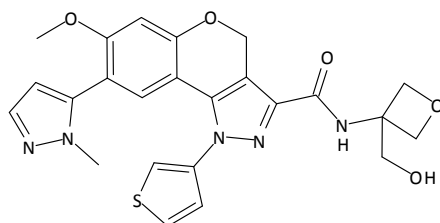
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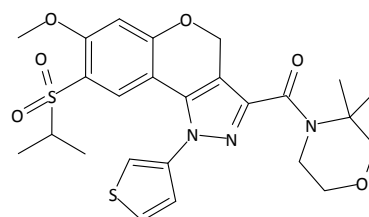
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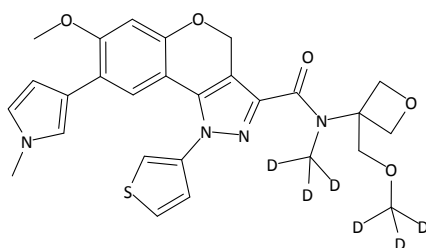
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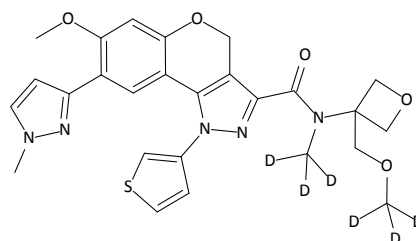
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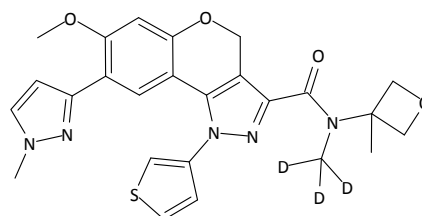
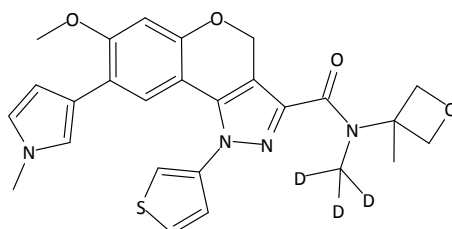
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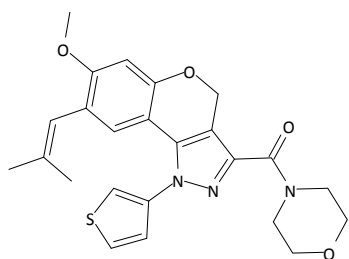


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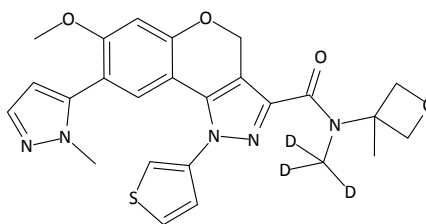


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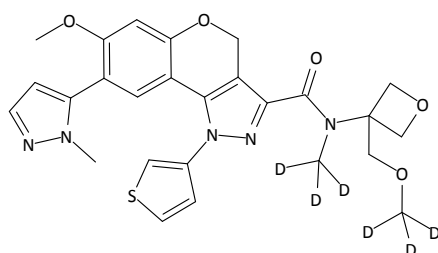
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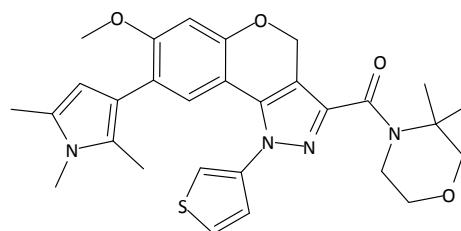
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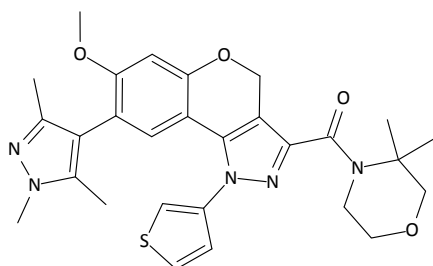
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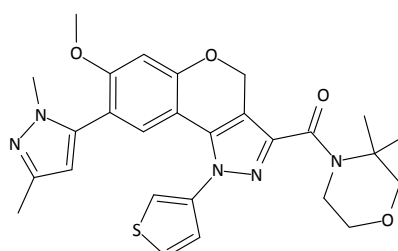
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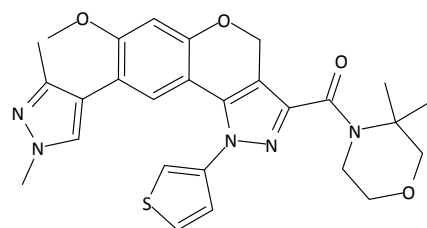
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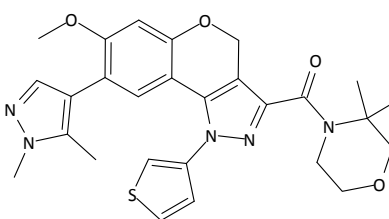
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121



122



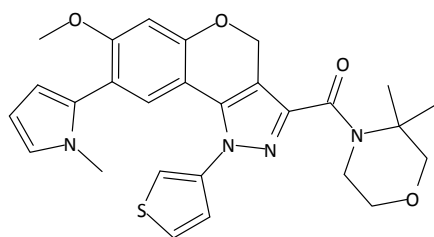
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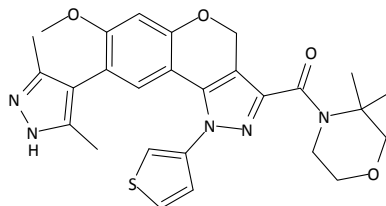
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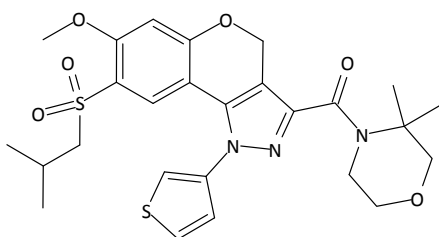
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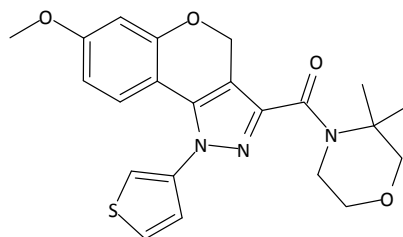
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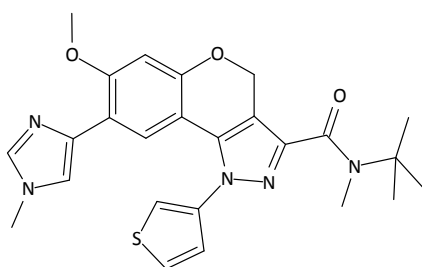
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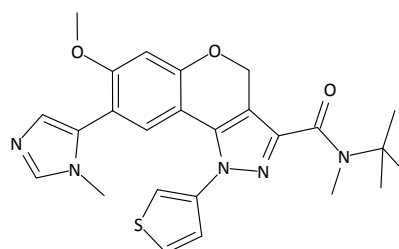
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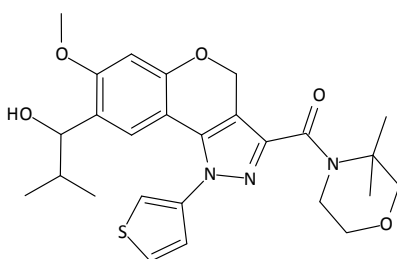
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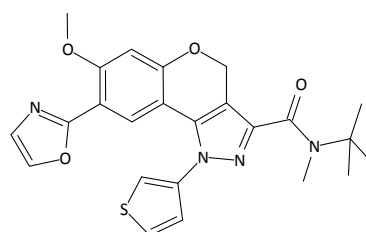
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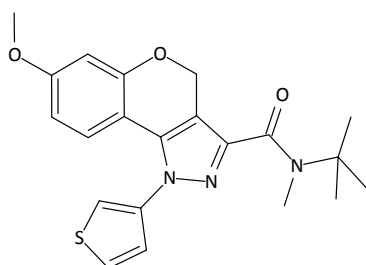
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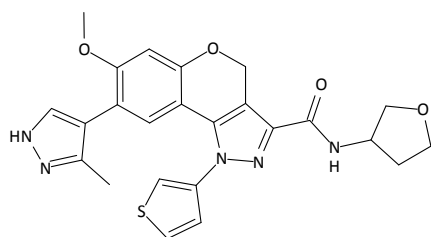


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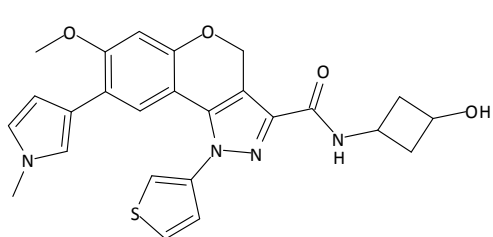


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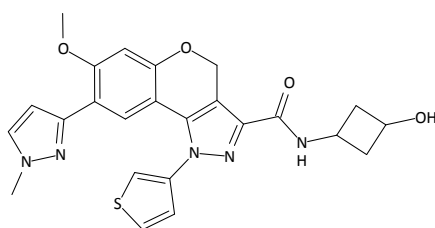
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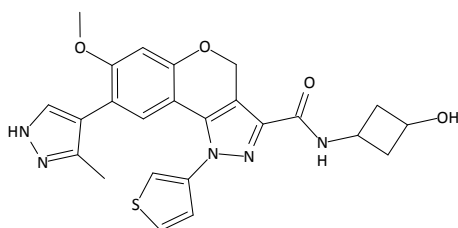
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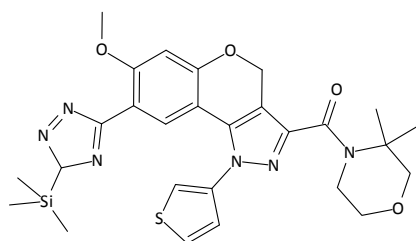
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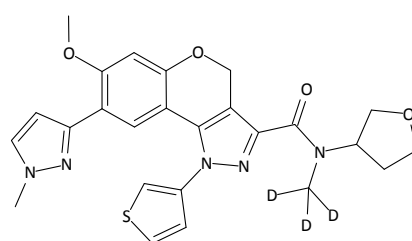
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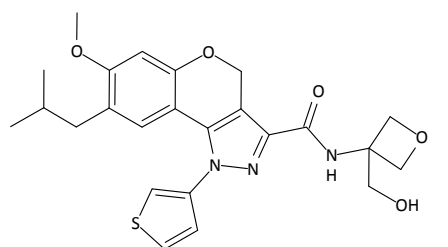
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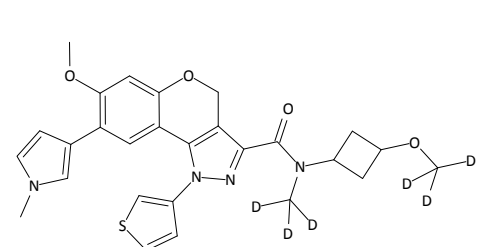
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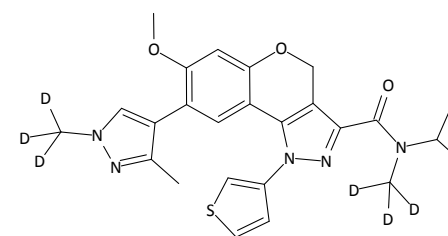
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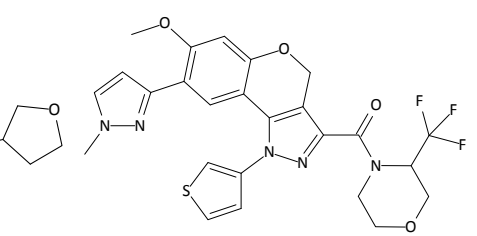
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141



142

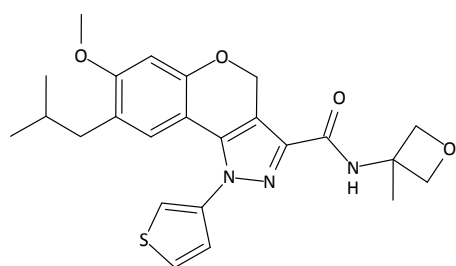


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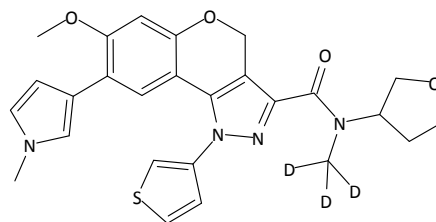


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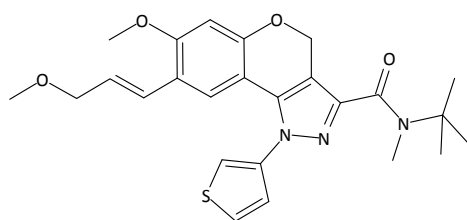




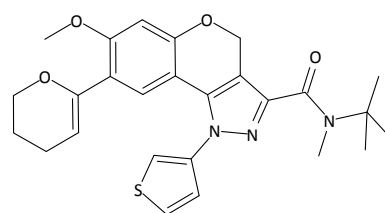
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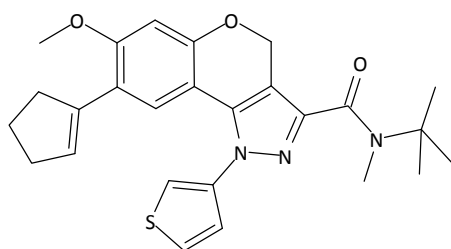
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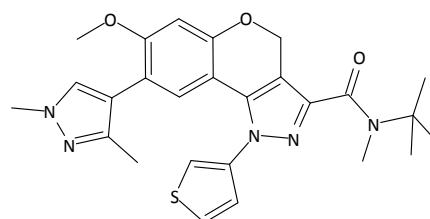
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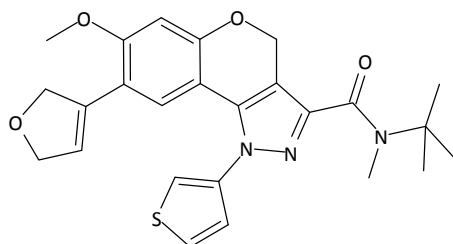
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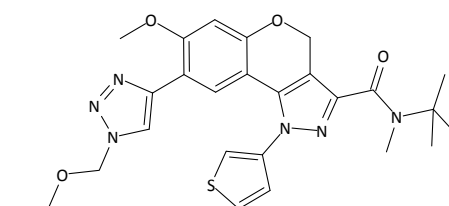
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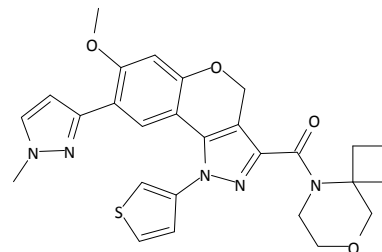
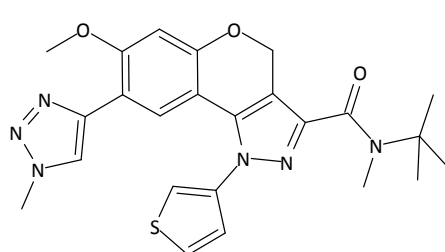
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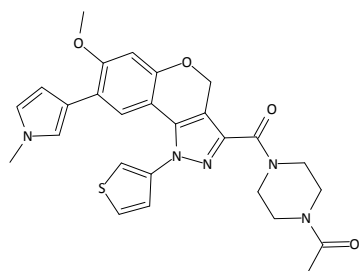
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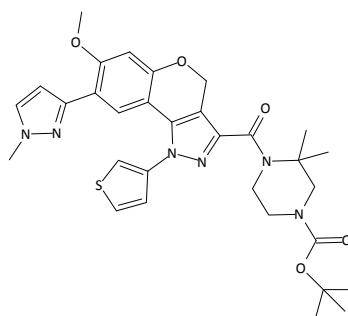
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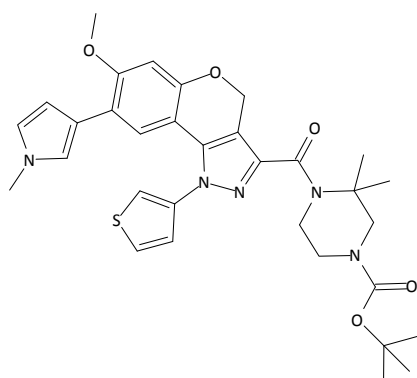
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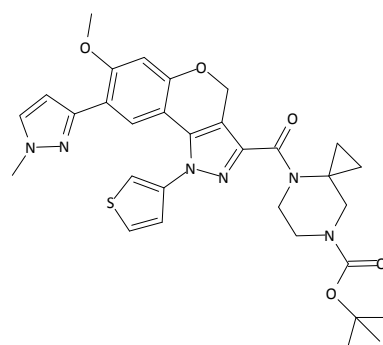
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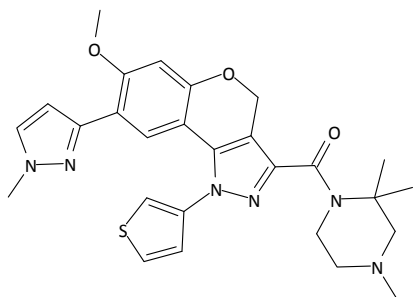
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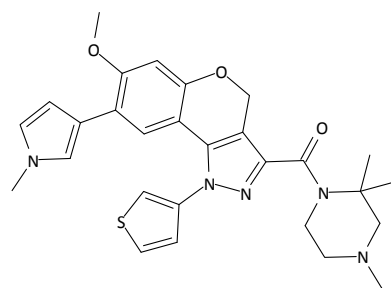
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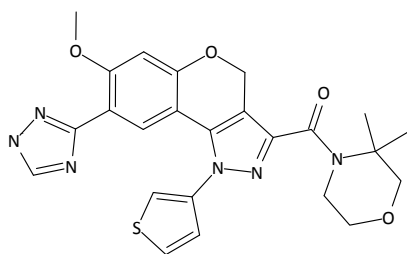
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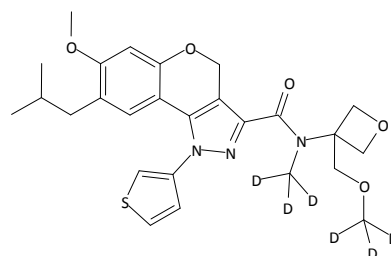
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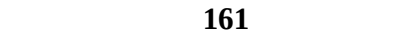
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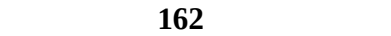
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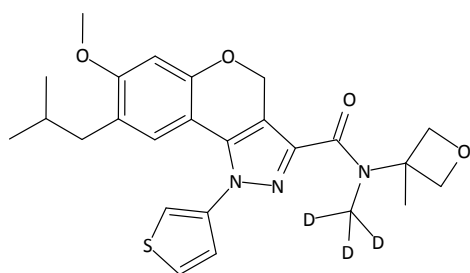
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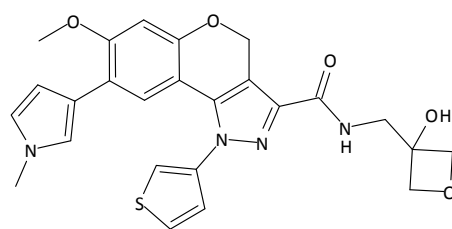
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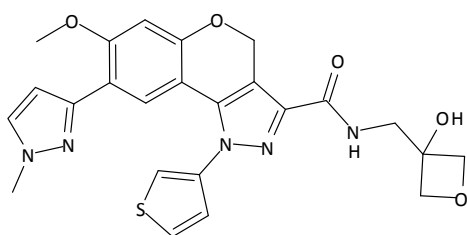
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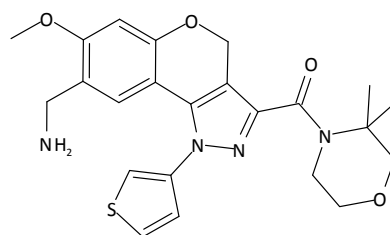
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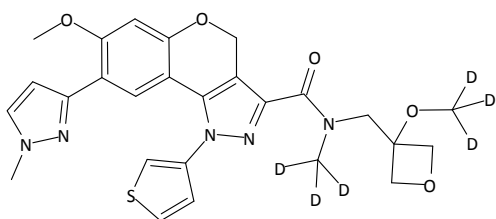
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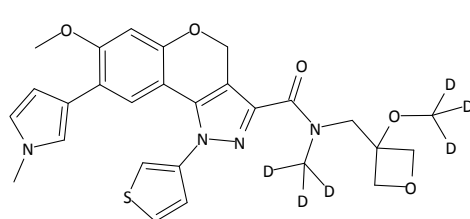
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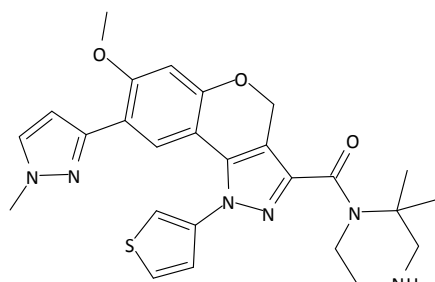
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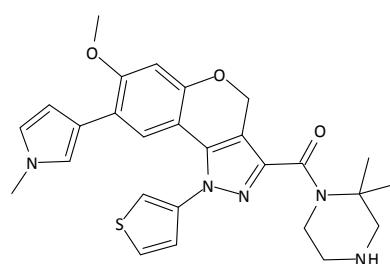
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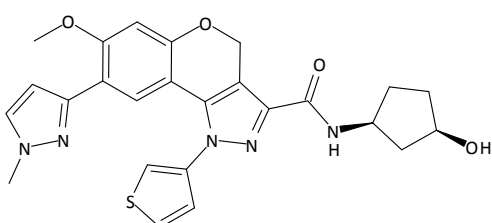
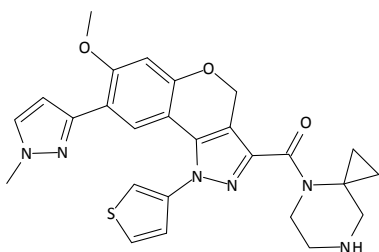
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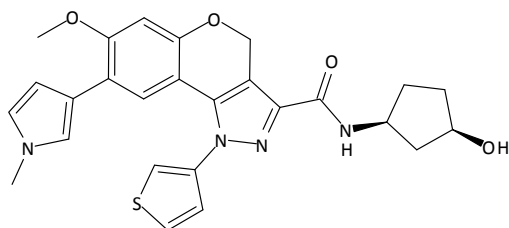


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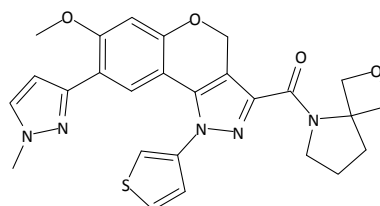


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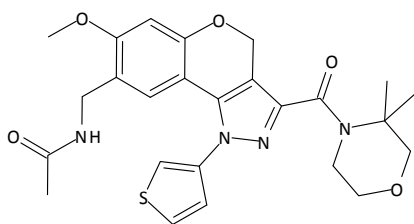
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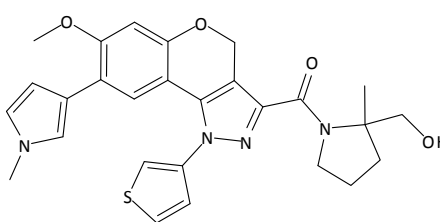
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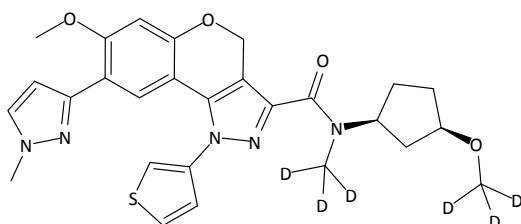
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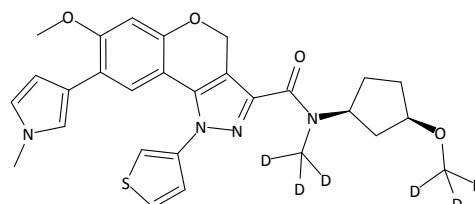
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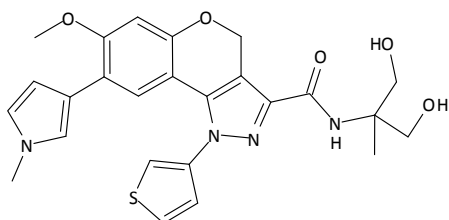
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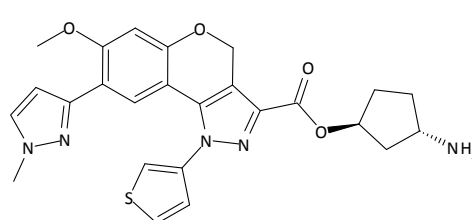
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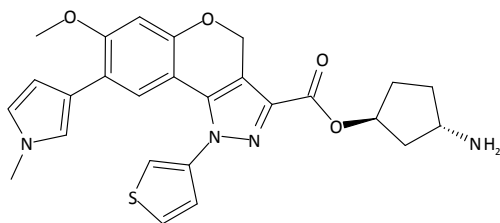
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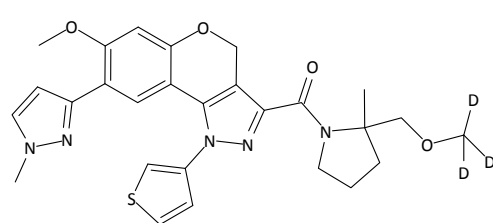
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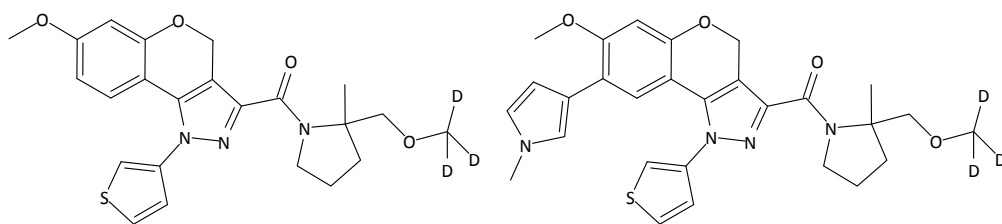


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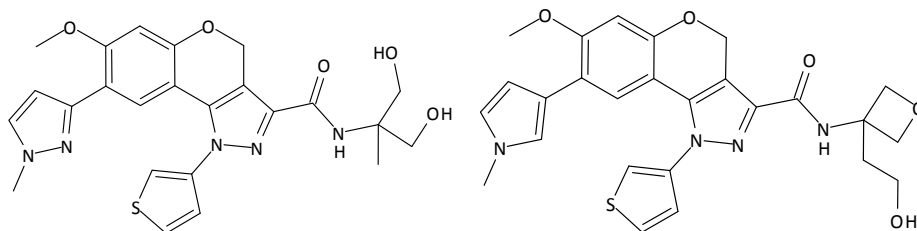
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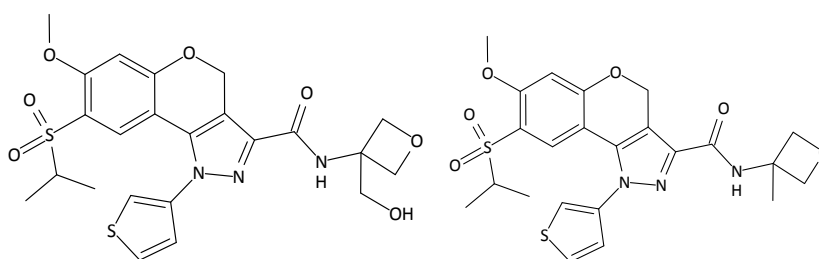
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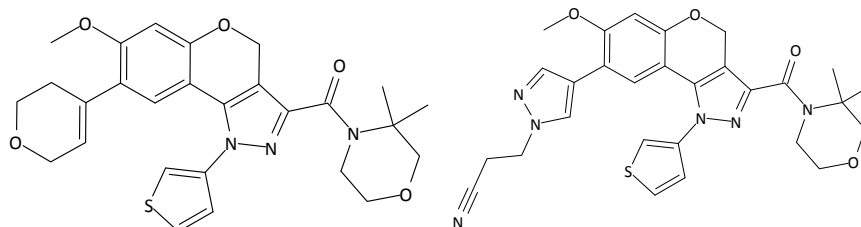
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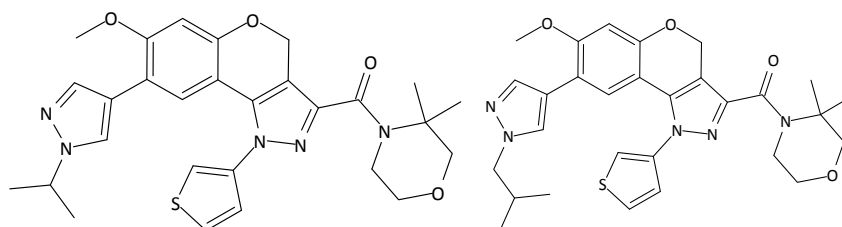
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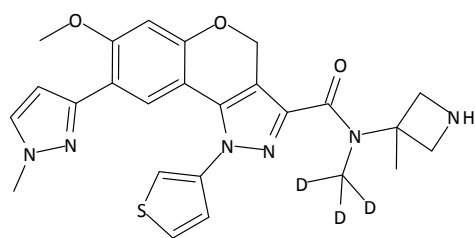
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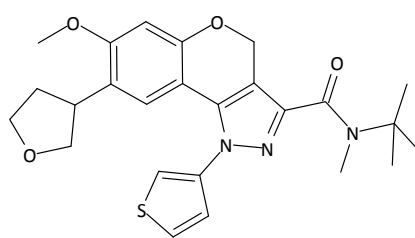
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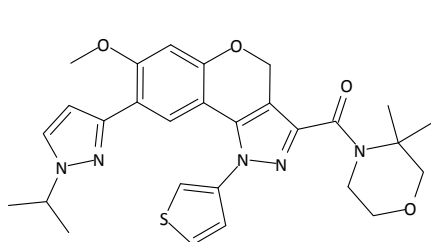
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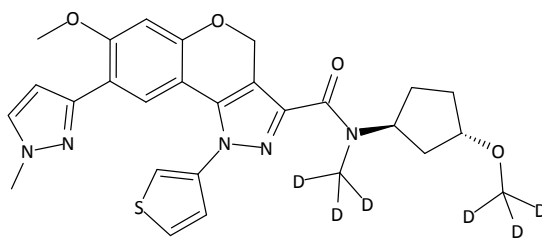
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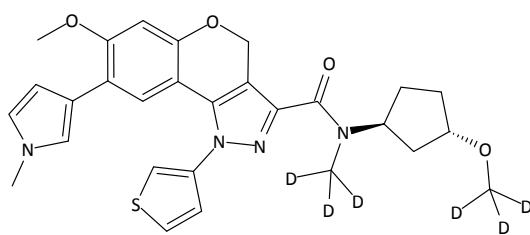
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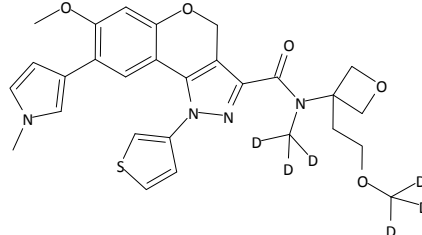
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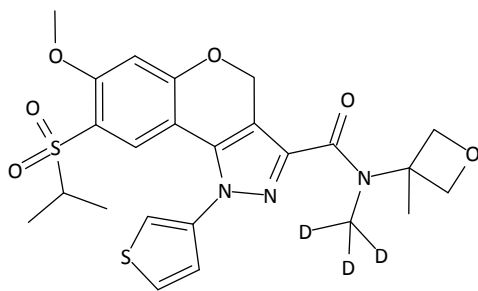
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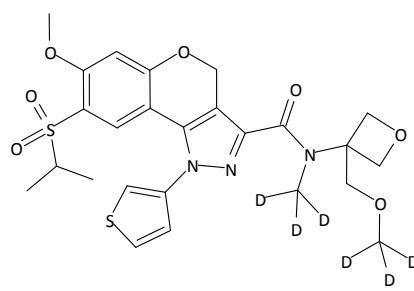
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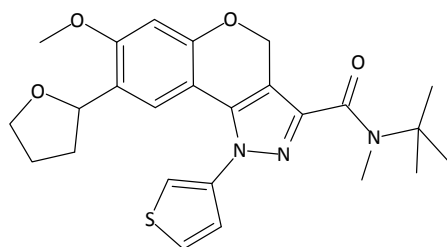
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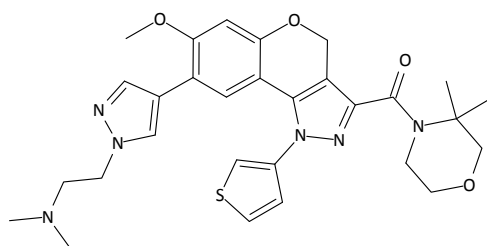


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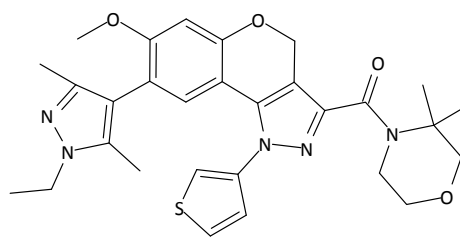


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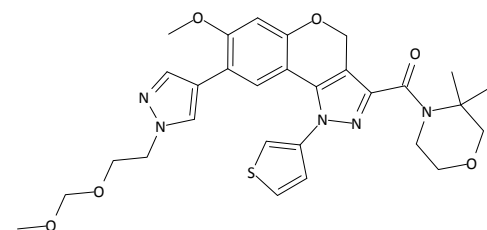
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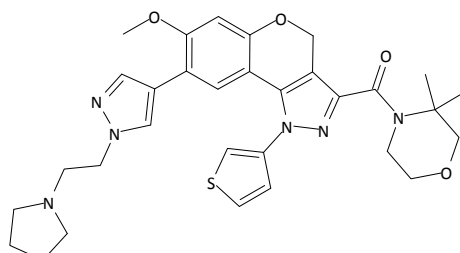
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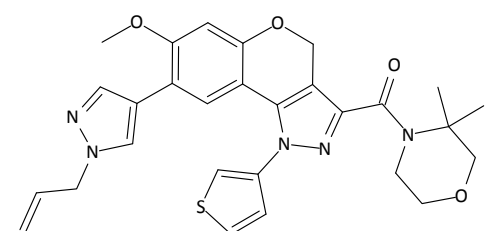
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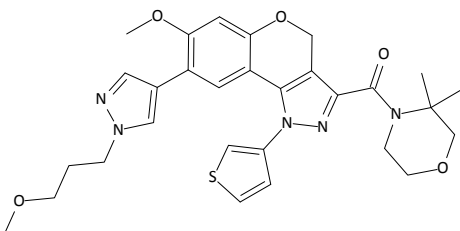
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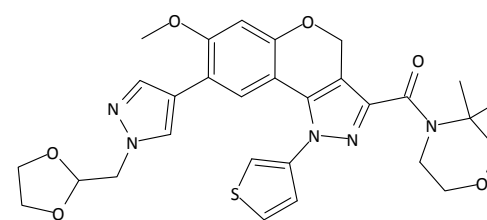
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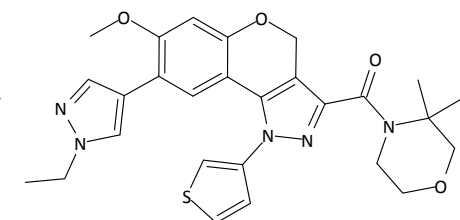
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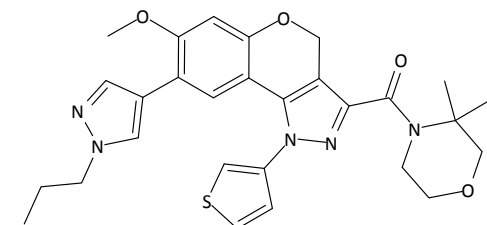
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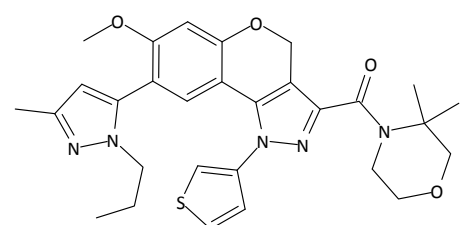
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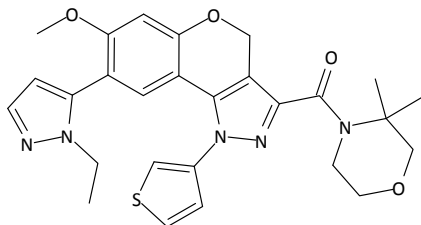
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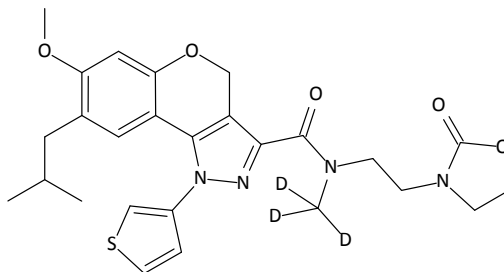
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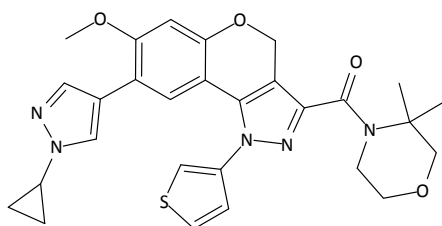
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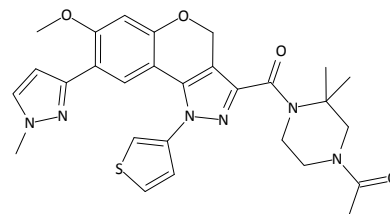
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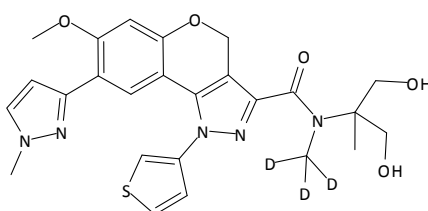
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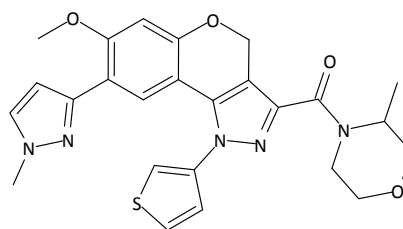
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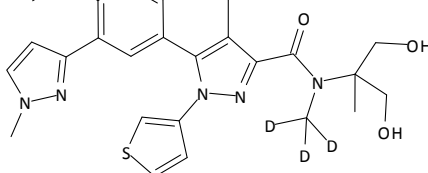
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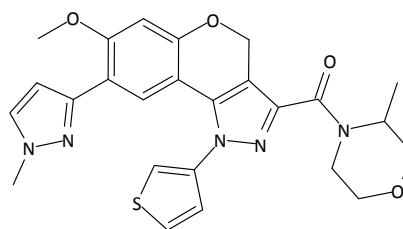
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218.



14. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

15. Compound of claim 1 for use in modulating FSHR, or a mutant thereof, activity in a patient or in a biological sample, comprising the step of administering to said patient or contacting said biological sample with a compound of claim 1 or a physiologically acceptable salt thereof.

16. Compound of claim 1 for use in treating a FSHR-mediated disorder including but are not limited to, hypogonadotropic hypogonadism, Isolated idiopathic hypogonadotropic

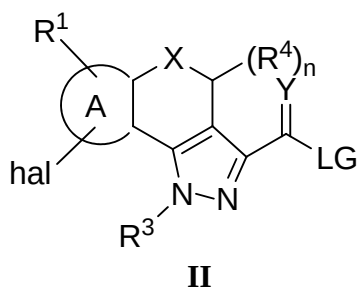
hypogonadism, Kallmann syndrome, Idiopathic hypogonadotropic hypogonadism, Craniopharyngiomas, Combined pituitary hormone deficiency, Fertile eunuch syndrome, Abnormal beta subunit of LH, Abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), Infiltrative lesions, Hemochromatosis, sarcoidosis, histiocytosis, lymphoma, Lymphocytic hypophysitis, Infections, Meningitis, Pituitary apoplexy, Hyperprolactinemia, hypothyroidism, Intentional (iatrogenic) secondary hypogonadism, Empty sella, Pituitary infarction, Sheehan syndrome, Anorexia nervosa, Congenital adrenal hyperplasia, and disorders related to GnRH deficiency in a patient in need thereof, comprising the step of administering to said patient a compound of claim 1.

17. Use of compound of claim 1 for treating fertility disorders in a subject, comprising the step of administering to said subject a compound of claim 1 or a physiologically acceptable salt thereof.

18. Use of a compound according to claim 1 or physiologically acceptable salts thereof, for the production of a medicament for the prophylactic or therapeutic treatment of a FSHR-mediated disorder, including but are not limited to, hypogonadotropic hypogonadism, Isolated idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, Idiopathic hypogonadotropic hypogonadism, Craniopharyngiomas, Combined pituitary hormone deficiency, Fertile eunuch syndrome, Abnormal beta subunit of LH, Abnormal beta subunit of FSH, mass lesions, pituitary adenomas, cysts, metastatic cancer to the sella (breast in women, lung and prostate in men), Infiltrative lesions, Hemochromatosis, sarcoidosis, histiocytosis, lymphoma, Lymphocytic hypophysitis, Infections, Meningitis, Pituitary apoplexy, Hyperprolactinemia, hypothyroidism, Intentional (iatrogenic) secondary hypogonadism, Empty sella, Pituitary infarction, Sheehan syndrome, Anorexia nervosa, Congenital adrenal hyperplasia, and disorders related to GnRH deficiency in a patient in need thereof, comprising the step of administering to said patient a compound of claim 1.

19. A process for manufacturing a compound of formula I according to claim 1, comprising the steps of:

reacting a compound of formula (II)

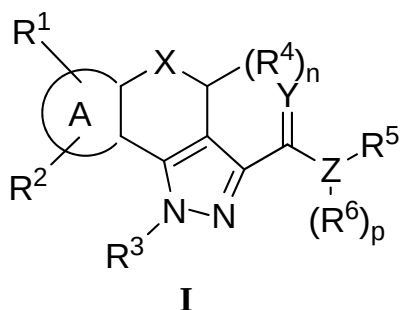


wherein X, Y, R¹, R³, R⁴, and n are as defined in claim 1, and LG is a leaving group;

with a compound of formula ZH(R⁵)(R⁶)_p

wherein Z, R⁵, R⁶, and p are as defined in claim 1;

to yield a compound of formula I:



wherein X, Y, Z, R¹, R², R³, R⁴, R⁵, R⁶, n, and p, are as defined in claim 1.