Slide 7: KPT-9274

Initial Task: HIA

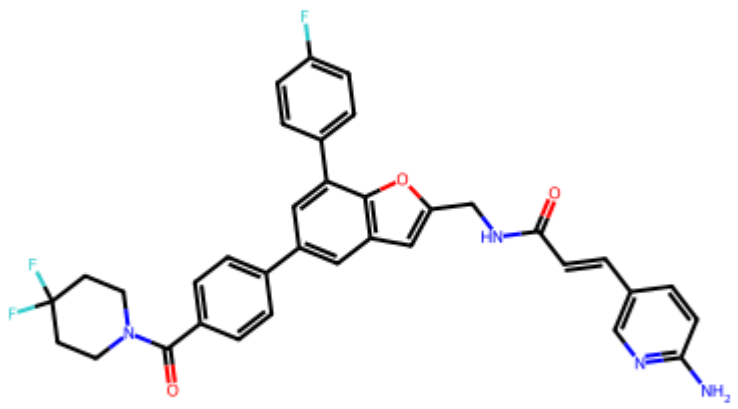
SMILES: `C1=CC(=NC=C1/C=C/C(=O)NCC2=CC3=C(C(=CC(=C3)C4=CC=C(C=C4)C(=O)N5CCC(CC5)(F)F)C6=CC=C(C=C6)F)O2)N`

KPT-9274 - Optimization Results

🔗 Optimization Path

📊 Overall Comparison - Initial → Final

Initial Molecule `C1=CC(=NC=C1/C=C/C(=O)NCC2=CC3=C(C(=CC(=C3)C4=CC=C(C=C4)C(=O)N5CCC(CC5)(F)F)C6=CC=C(C=C6)F)O2)N`

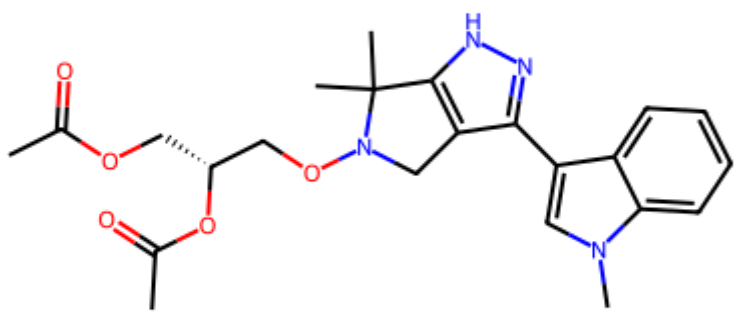


QED (Drug-likeness): 0.1918 **Number of Blocks:** 4

▶ ***Show ADMET Scores***

Task	Score
AMES	0.438620
BBBP	0.999970
CYP3A4	0.046397
DILI	0.750240
HIA	0.988937
PGP	0.653441

Final Optimized `CC(=O)OC[C@H](CON1Cc2c(-c3cn(C)c4ccccc34)n[nH]c2C1(C)C)OC(C)=O`



QED (Drug-likeness): 0.5639 (+0.3721) ✅ **Number of Blocks:** 2 (-2) ↓
Total Block Changes: 16

▶ ***Show ADMET Scores***

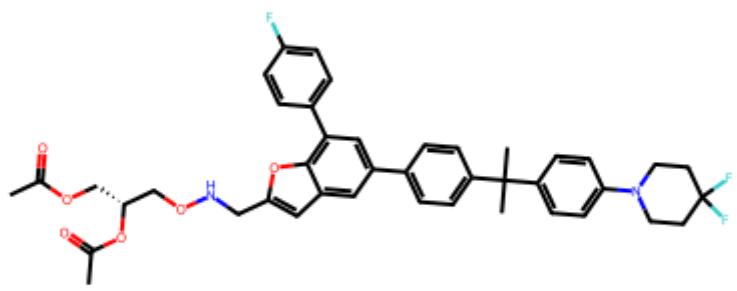
Task	Score	Change	Rel. Improvement	% Change
AMES ✅	0.381034	-0.057586	+0.1313	-13.13%
BBBP ✅	1.000000	+0.000030	+0.0000	+0.00%
CYP3A4 ✅	0.011194	-0.035203	+0.7587	-75.87%
DILI ✅	0.458021	-0.292219	+0.3895	-38.95%
HIA ✅	0.995235	+0.006298	+0.0064	+0.64%
PGP ✅	0.630667	-0.022773	+0.0349	-3.49%

Optimization Steps:

DETAILS*PLACEHOLDER2*

After (Step 1)

```
CC(=O)OC[C@H](CONCc1cc2cc(-c3ccc(C(C)(C)c4ccc(N5CCC(F)(F)CC5)cc4)cc3)cc(-c3ccc(F)cc3)c2o1)OC(C)=O
```



QED: 0.0731 (-0.1188) ❌

Number of Blocks: 4 (+0) ➡️

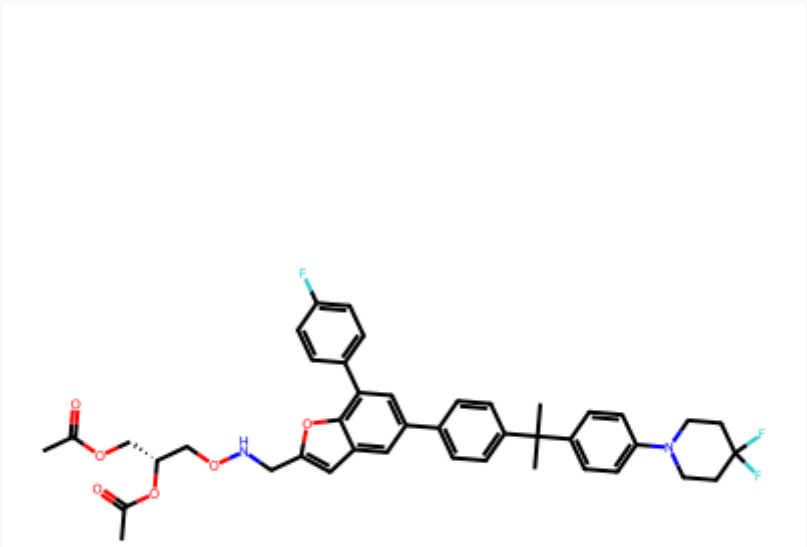
Block Changes: 6 (+3, -3)

HIA Score: 0.988937 → 0.941353 (-0.047584)

DETAILS*PLACEHOLDER*3

▶ Step 2: AMES (-0.0244 ↓) ✅

Before (Step 1) `CC(=O)OC[C@H](CONCc1cc2cc(-c3ccc(C(C)(C)c4ccc(N5CCC(F)(F)CC5)cc4)cc3)cc(-c3ccc(F)cc3)c2o1)OC(C)=O`

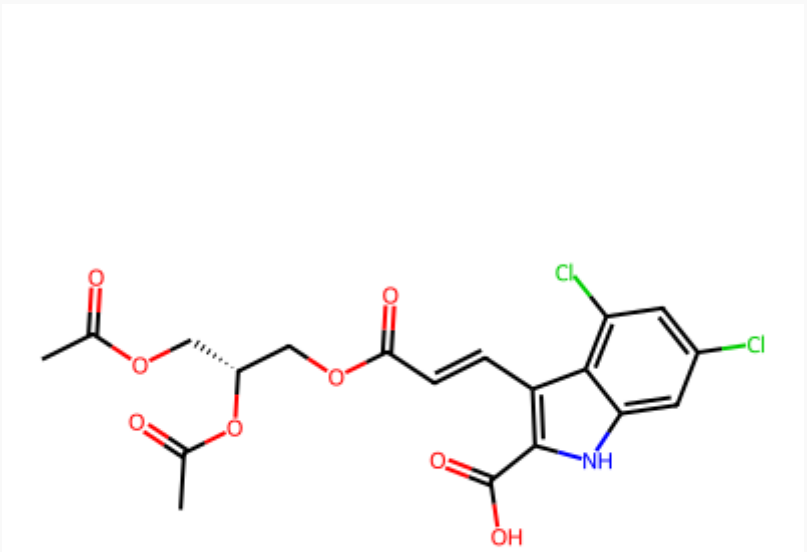


QED: 0.0731 **Number of Blocks:** 4

▶ ***All ADMET Scores***

Task	Score	Direction
AMES	0.432780	↓ lower
BBBP	1.000000	↑ higher
CYP3A4	0.063941	↓ lower
DILI	0.415682	↓ lower
HIA	0.941353	↑ higher
PGP	0.714547	↓ lower

After (Step 2) `CC(=O)OC[C@H](COC(=O)/C=C/c1c(C(=O)O)[nH]c2cc(Cl)cc(Cl)c12)OC(C)=O`



QED: 0.3503 (+0.2772) ✅

Number of Blocks: 2 (-2) ↓

Block Changes: 6 (+2, -4)

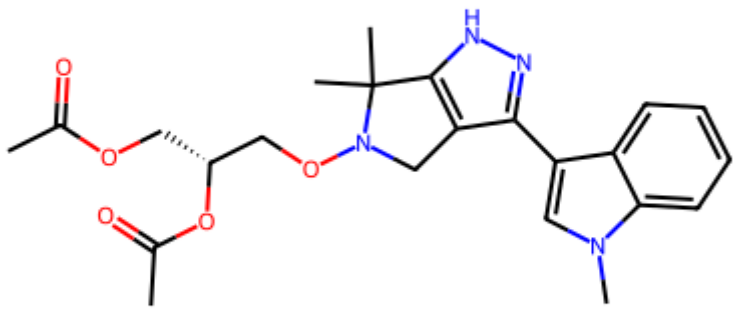
AMES Score: 0.432780 → 0.408373 (-0.024407)

DETAILS*PLACEHOLDER*5

DETAILS*PLACEHOLDER*6

After (Step 3)

`CC(=O)OC[C@H](CON1Cc2c(-c3cn(C)c4ccccc34)n[nH]c2C1(C)C)OC(C)=O`



QED: 0.5639 (+0.2137) ✅

Number of Blocks: 2 (+0) ➡️

Block Changes: 4 (+2, -2)

AMES Score: 0.408373 → 0.381034 (-0.027339)

DETAILS*PLACEHOLDER7*

📊 Step Details

Step 1: HIA ⚠️

Original	New	Change
0.988937	0.941353	-0.047584 ↑

```
CC(=O)OC[C@H](CONCc1cc2cc(-c3ccc(C(C)(C)c4ccc(N5CCC(F)(F)CC5)cc4)cc3)cc(-c3ccc(F)cc3)c2o1)OC(C)=O
```

Step 2: AMES ✅

Original	New	Change
0.432780	0.408373	-0.024407 ↓

```
CC(=O)OC[C@H](COC(=O)/C=C/c1c(C(=O)O)[nH]c2cc(Cl)cc(Cl)c12)OC(C)=O
```

Step 3: AMES ✅

Original	New	Change
0.408373	0.381034	-0.027339 ↓

```
CC(=O)OC[C@H](CON1Cc2c(-c3cn(C)c4ccccc34)n[nH]c2C1(C)C)OC(C)=O
```

📊 ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.438620	0.381034	-0.057586	+0.1313	-13.13%	✅ Improved
BBBP	↑ higher	0.999970	1.000000	+0.000030	+0.0000	+0.00%	✅ Improved
CYP3A4	↓ lower	0.046397	0.011194	-0.035203	+0.7587	-75.87%	✅ Improved
DILI	↓ lower	0.750240	0.458021	-0.292219	+0.3895	-38.95%	✅ Improved
HIA	↑ higher	0.988937	0.995235	+0.006298	+0.0064	+0.64%	✅ Improved
PGP	↓ lower	0.653441	0.630667	-0.022773	+0.0349	-3.49%	✅ Improved

Improved: 6/6 (100.0%) | **Molecules:** 175 | **Paths:** 1473

🔍 Safety Threshold Analysis

Status: 3/6 meet thresholds

⚠️ **Below threshold:** 3

Task	Score	Threshold	Gap
PGP	0.6307	↓ 0.3	0.3307
AMES	0.3810	↓ 0.3	0.0810
DILI	0.4580	↓ 0.4	0.0580

✅ **Passing:** 3

Task	Score	Threshold
BBBP	1.0000	↑ 0.5
CYP3A4	0.0112	↓ 0.55
HIA	0.9952	↑ 0.2