Slide 12: Lapaquistat acetate (TAK-475)

Initial Task: DILI

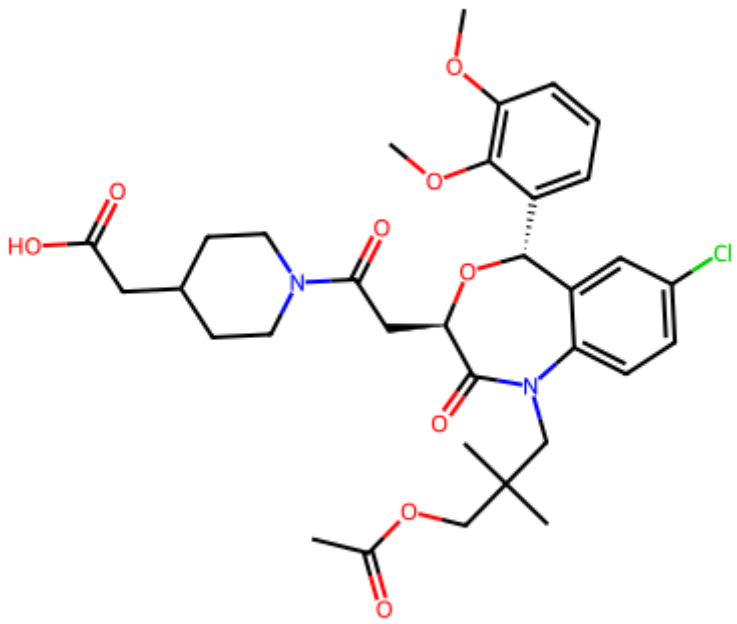
SMILES: `CC(=O)OCC(C)(C)CN1C2=CC=C(C=C2[C@@H](C3=CC=CC(=C3OC)OC)O[C@H](CC(=O)N4CCC(CC4)CC(=O)O)C1=O)Cl`

Lapaquistat acetate (TAK-475) - Optimization Results

🔗 Optimization Path

📊 Overall Comparison - Initial → Final

Initial Molecule `CC(=O)OCC(C)(C)CN1C2=CC=C(C=C2[C@@H](C3=CC=CC(=C3OC)OC)O[C@H](CC(=O)N4CCC(CC4)CC(=O)O)C1=O)Cl`

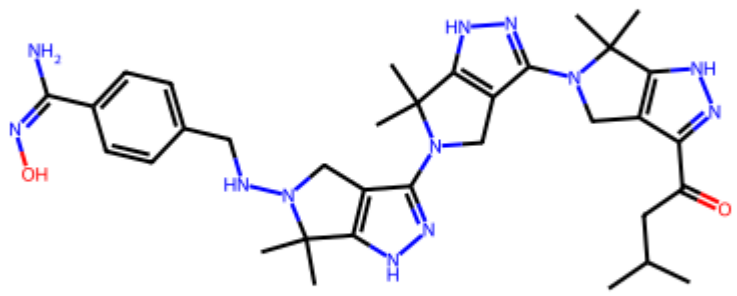


QED (Drug-likeness): 0.3403 **Number of Blocks:** 3

▶ ***Show ADMET Scores***

Task	Score
AMES	0.419620
BBBP	0.999985
CYP3A4	0.035988
DILI	0.602326
HIA	0.980337
PGP	0.662407

Final Optimized `CC(C)CC(=O)c1n[nH]c2c1CN(c1n[nH]c3c1CN(c1n[nH]c4c1CN(NCc1ccc(/C(N)=N\O)cc1)C4(C)C)C3(C)C)C2(C)C`



QED (Drug-likeness): 0.0496 (-0.2907) ❌ **Number of Blocks:** 4 (+1) ↑ **Total Block Changes:** 13

▶ ***Show ADMET Scores***

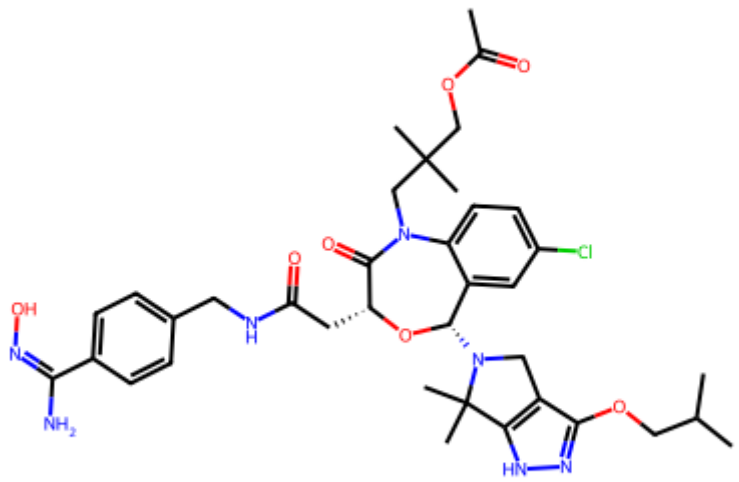
Task	Score	Change	Rel. Improvement	% Change
AMES ❌	0.683061	+0.263441	-0.6278	+62.78%
BBBP ❌	0.000186	-0.999799	-0.9998	-99.98%
CYP3A4 ✅	0.001016	-0.034972	+0.9718	-97.18%
DILI ❌	0.619393	+0.017067	-0.0283	+2.83%
HIA ✅	0.987780	+0.007443	+0.0076	+0.76%
PGP ✅	0.592538	-0.069869	+0.1055	-10.55%

Optimization Steps:

DETAILS*PLACEHOLDER2*

After (Step 1)

`CC(=O)OCC(C)(C)CN1C(=O)[C@@H](CC(=O)NCc2ccc(/C(N)=N\O)cc2)O[C@@H](N2Cc3c(OCC(C)C)n[nH]c3C2(C)C)c2cc(Cl)ccc21`



QED: 0.0614 (-0.2789) ❌

Number of Blocks: 2 (-1) ↓

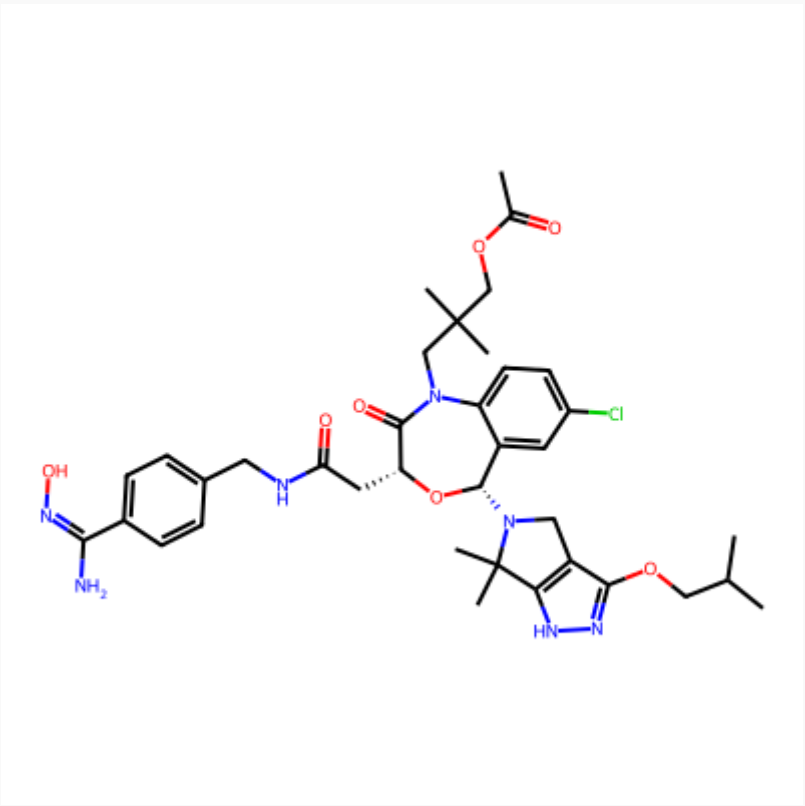
Block Changes: 5 (+2, -3)

DILI Score: 0.602326 → 0.416277 (-0.186049)

DETAILS*PLACEHOLDER3*

▶ Step 2: CYP3A4 (-0.0305 ↓) ✅

Before (Step 1) `CC(=O)OCC(C)(C)CN1C(=O)[C@@H](CC(=O)NCc2ccc(/C(N)=N\O)cc2)O[C@@H](N2Cc3c(OCC(C)C)n[nH]c3C2(C)C)c2cc(Cl)ccc21`

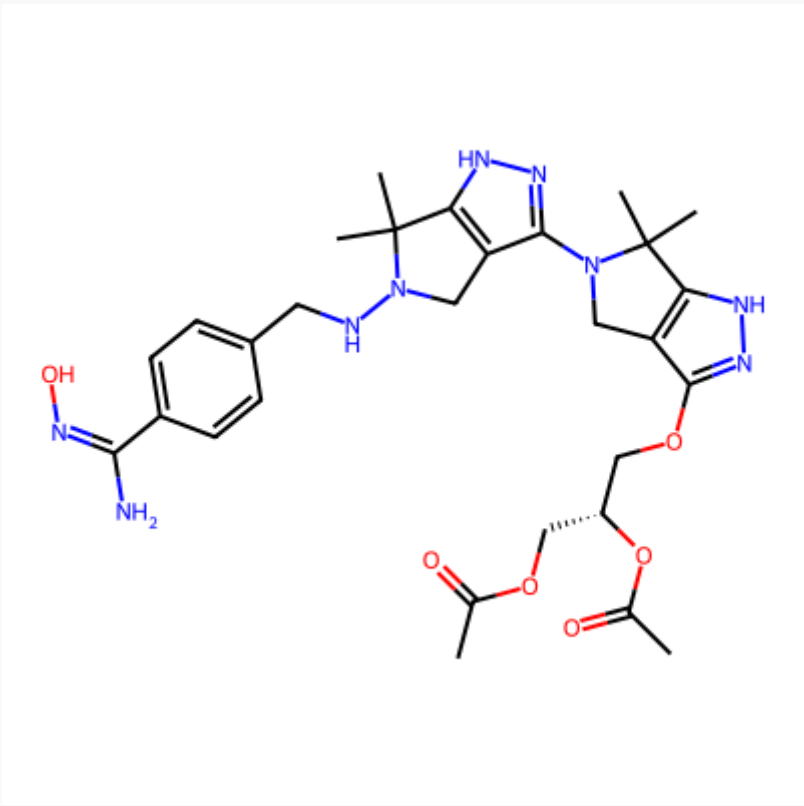


QED: 0.0614 **Number of Blocks:** 2

▶ ***All ADMET Scores***

Task	Score	Direction
AMES	0.400792	↓ lower
BBBP	1.000000	↑ higher
CYP3A4	0.050735	↓ lower
DILI	0.416277	↓ lower
HIA	0.974486	↑ higher
PGP	0.692923	↓ lower

After (Step 2) `CC(=O)OC[C@H](COc1n[nH]c2c1CN(c1n[nH]c3c1CN(NCc1ccc(/C(N)=N\O)cc1)C3(C)C)C2(C)C)OC(C)=O`



QED: 0.0699 (+0.0085) ✅

Number of Blocks: 4 (+2) ↑

Block Changes: 6 (+4, -2)

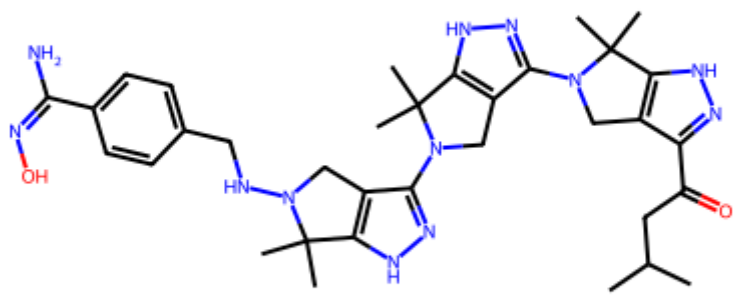
CYP3A4 Score: 0.050735 → 0.020237 (-0.030498)

DETAILS*PLACEHOLDER*5

DETAILS*PLACEHOLDER*6

After (Step 3)

```
CC(C)CC(=O)c1n[nH]c2c1CN(c1n[nH]c3c1CN(c1n[nH]c4c1CN(NCc1ccc(/C(N)=N\O)cc1)C4(C)C)C3(C)C)C2(C)C
```



QED: 0.0496 (-0.0203) ❌

Number of Blocks: 4 (+0) ➡️

Block Changes: 2 (+1, -1)

CYP3A4 Score: 0.020237 → 0.001016 (-0.019221)

DETAILS*PLACEHOLDER7*

📊 Step Details

Step 1: DILI ✅

Original	New	Change
0.602326	0.416277	-0.186049 ↓

```
CC(=O)OCC(C)(C)CN1C(=O)[C@@H](CC(=O)NCc2ccc(/C(N)=N\O)cc2)O[C@@H](N2Cc3c(OCC(C)C)n[nH]c3C2(C)C)c2cc(Cl)ccc21
```

Step 2: CYP3A4 ✅

Original	New	Change
0.050735	0.020237	-0.030498 ↓

```
CC(=O)OC[C@H](COc1n[nH]c2c1CN(c1n[nH]c3c1CN(NCc1ccc(/C(N)=N\O)cc1)C3(C)C)C2(C)C)OC(C)=O
```

Step 3: CYP3A4 ✅

Original	New	Change
0.020237	0.001016	-0.019221 ↓

```
CC(C)CC(=O)c1n[nH]c2c1CN(c1n[nH]c3c1CN(c1n[nH]c4c1CN(NCc1ccc(/C(N)=N\O)cc1)C4(C)C)C3(C)C)C2(C)C
```

📊 ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.419620	0.683061	+0.263441	-0.6278	+62.78%	❌ Declined
BBBP	↑ higher	0.999985	0.000186	-0.999799	-0.9998	-99.98%	❌ Declined
CYP3A4	↓ lower	0.035988	0.001016	-0.034972	+0.9718	-97.18%	✅ Improved
DILI	↓ lower	0.602326	0.619393	+0.017067	-0.0283	+2.83%	❌ Declined
HIA	↑ higher	0.980337	0.987780	+0.007443	+0.0076	+0.76%	✅ Improved
PGP	↓ lower	0.662407	0.592538	-0.069869	+0.1055	-10.55%	✅ Improved

Improved: 3/6 (50.0%) | **Molecules:** 415 | **Paths:** 7886

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠️ **Below threshold:** 4

Task	Score	Threshold	Gap
BBBP	0.0002	↑ 0.5	0.4998
AMES	0.6831	↓ 0.3	0.3831
PGP	0.5925	↓ 0.3	0.2925
DILI	0.6194	↓ 0.4	0.2194

✅ **Passing:** 2

Task	Score	Threshold
CYP3A4	0.0010	↓ 0.55
HIA	0.9878	↑ 0.2