

Fallen Angel Drugs - mCLM Analysis

Combined Report of 24 Drug Analyses

Fallen Angel Drugs - Optimization Summary

Generated: 2025-11-17 00:31:43

Total Drugs: 23 **Successful:** 23 **Errors:** 0

Successfully Processed

#	Drug	Task	Output File
1	Tarenflurbil (Flurizan)	BBBP	01 <i>Tarenflurbil</i> Flurizan.md
2	Gavestinel (GV-150,526)	BBBP	02 <i>Gavestinel</i> GV-150526.md
3	NXY-059 (Cerovive)	BBBP	03 <i>NXY-059</i> Cerovive.md
4	PF-03758309 (PF-3758309)	HIA	04 <i>PF-03758309</i> PF-3758309.md
5	Olcegepant (BIBN-4096BS)	HIA	05 <i>Olcegepant</i> BIBN-4096BS.md
6	EPI-506 (ralaniten acetate / prodrug of EPI-002)	HIA	06 <i>EPI-506</i> ralaniten acetate prodrug of_EPI-002.md
7	KPT-9274	HIA	07_KPT-9274.md
8	Valeresol	HIA	08_Valeresol.md
9	Fialuridine (FIAU)	DILI	09 <i>Fialuridine</i> FIAU.md
10	Ximelagatran (Exanta / oral direct thrombin inhibitor)	DILI	10 <i>Ximelagatran</i> Exanta _oral direct thrombin inhibitor.md
11	Fasiglifam (TAK-875)	DILI	11 <i>Fasiglifam</i> TAK-875.md
12	Lapaquinstat acetate (TAK-475)	DILI	12 <i>Lapaquinstat acetate</i> _TAK-475.md
13	Danuglipron (Pfizer)	DILI	13 <i>Danuglipron</i> Pfizer.md
14	Rosiglitazone	BBBP	14_Rosiglitazone.md
15	Paclitaxel / other taxanes	BBBP	15 <i>Paclitaxel</i> other taxanes.md
16	Mibepradil (Posicor)	CYP3A4	16 <i>Mibepradil</i> Posicor.md
17	Nefazodone (Serzone)	CYP3A4	17 <i>Nefazodone</i> Serzone.md
18	GSK1059615	HIA	18_GSK1059615.md
19	Neflamapimod (VX-745)	HIA	19 <i>Neflamapimod</i> VX-745.md
20	SAR260301	CYP3A4	20_SAR260301.md
21	Taranabant (MK-0364)	DILI	21 <i>Taranabant</i> MK-0364.md
22	NYX-059	BBBP	22_NYX-059.md
23	AZD-3514	HIA	23_AZD-3514.md

Errors

None

Configuration

- **Number of beams:** 12
- **Depth:** 3
- **CSV source:** /shared/nas2/knguye71/mCLM_nov/fallenangel.csv

Features Included

Each slide includes: - ADMET score predictions (6 tasks: ames, bbbp, cyp3a4, dili, hia, pgp) - QED (drug-likeness) analysis with change tracking - **Molecular block count and changes** (shows structural modifications) - Step-by-step optimization path with before/after comparisons - Safety threshold analysis - Overall improvement statistics

Slide 1: Tarenflurbil (Flurizan)

Initial Task: BBBP

SMILES: C[C@H](C1=CC(=C(C=C1)C2=CC=CC=C2)F)C(=O)O

✖ Optimization Failed for Tarenflurbil (Flurizan)

No valid paths found. The optimization could not generate any improved molecules.

Initial Molecule Scores

Input SMILES: C[C@H](C1=CC(=C(C=C1)C2=CC=CC=C2)F)C(=O)O

- Molecules Generated: 7
- Valid Paths: 0

Reason: All generated molecules had worse scores than the initial molecule.

Recommendations

1. **Increase beams:** Try `num_beams=7` or `num_beams=10` for more diversity
2. **Change initial task:** Try a different task as the starting point
3. **Reduce depth:** Start with `depth=1` to see if single-step improvements work
4. **Check initial molecule:** It may already be highly optimized

Slide 2: Gavestinel (GV-150,526)

Initial Task: BBBP

SMILES: C1=CC=C(C=C1)NC(=O)/C=C/C2=C(C(=O)O)NC3=C2C(=CC(=C3)Cl)Cl

✖ Optimization Failed for Gavestinel (GV-150,526)

No valid paths found. The optimization could not generate any improved molecules.

Initial Molecule Scores

Input SMILES: C1=CC=C(C=C1)NC(=O)/C=C/C2=C(C(=O)O)NC3=C2C(=CC(=C3)Cl)Cl

- **Molecules Generated:** 7
- **Valid Paths:** 0

Reason: All generated molecules had worse scores than the initial molecule.

Recommendations

1. **Increase beams:** Try `num_beams=7` or `num_beams=10` for more diversity
2. **Change initial task:** Try a different task as the starting point
3. **Reduce depth:** Start with `depth=1` to see if single-step improvements work
4. **Check initial molecule:** It may already be highly optimized

Slide 3: NX-059 (Cerovive)

Initial Task: BBBP

SMILES: CC(C)(C)/[N+](=C/C1=CC=C(C=C1S(=O)(=O)OC)S(=O)(=O)OC)/[O-]

✖ Optimization Failed for NX-059 (Cerovive)

No valid paths found. The optimization could not generate any improved molecules.

Initial Molecule Scores

Input SMILES: CC(C)(C)/[N+](=C/C1=CC=C(C=C1S(=O)(=O)OC)S(=O)(=O)OC)/[O-]

- **Molecules Generated:** 73
- **Valid Paths:** 0

Reason: All generated molecules had worse scores than the initial molecule.

Recommendations

1. **Increase beams:** Try `num_beams=7` or `num_beams=10` for more diversity
2. **Change initial task:** Try a different task as the starting point
3. **Reduce depth:** Start with `depth=1` to see if single-step improvements work
4. **Check initial molecule:** It may already be highly optimized

Slide 4: PF-03758309 (PF-3758309)

Initial Task: HIA

SMILES: CC1=NC2=C(C(=N1)NC3=NNC4=C3CN(C(=O)N[C@H](CN(C)C)C5=CC=CC=C5)C4(C)C)SC=C2

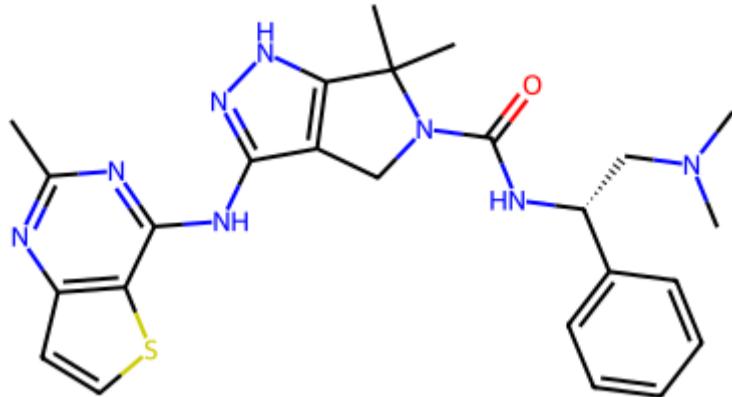
PF-03758309 (PF-3758309) - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule

`CC1=NC2=C(C(=N1)NC3=NNC4=C3CN(C(=O)N[C@H](CN(C)C)C5=CC=CC=C5)C4(C)C)SC=C2`



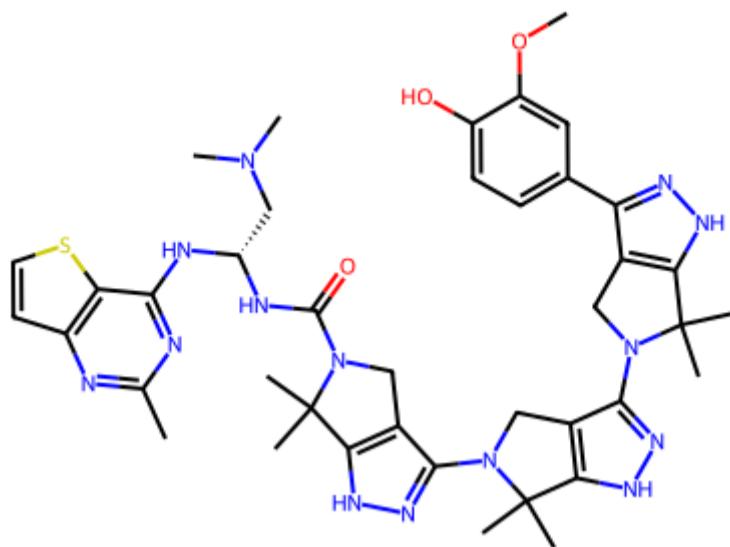
QED (Drug-likeness): 0.3671 **Number of Blocks:** 4

► Show ADMET Scores

Task	Score
AMES	0.419049
BBBP	0.778013
CYP3A4	0.011948
DILI	0.793920
HIA	0.984575
PGP	0.499705

Final Optimized `COc1cc(-

c2n[nH]c3c2CN(c2n[nH]c4c2CN(c2n[nH]c5c2CN(C(=O)N[C@@H](CN(C)C)Nc2nc(C)nc6ccsc26)C5(C)C)C4(C)C)C3(C)C)ccc1O`



QED (Drug-likeness): 0.0961 (-0.2710) ✗ **Number of Blocks:** 6 (+2) ↑

Total Block Changes: 13

► Show ADMET Scores

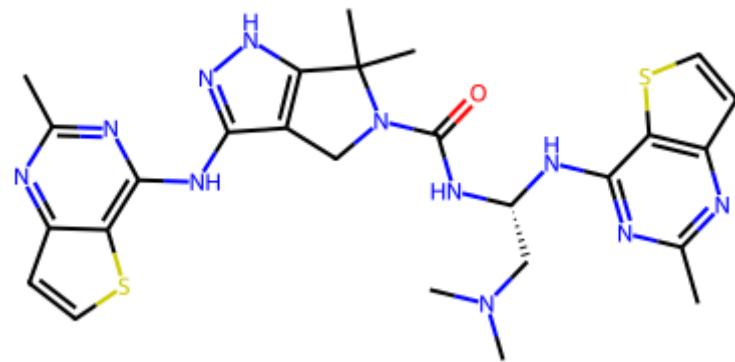
Task	Score	Change	Rel. Improvement	% Change
AMES ✗	0.686654	+0.267605	-0.6386	+63.86%
BBBP ✗	0.000213	-0.777801	-0.9997	-99.97%
CYP3A4 ✓	0.000889	-0.011059	+0.9256	-92.56%
DILI ✓	0.659112	-0.134808	+0.1698	-16.98%
HIA ✓	0.997891	+0.013316	+0.0135	+1.35%
PGP ✗	0.556859	+0.057154	-0.1144	+11.44%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

Cc1nc(Nc2n[nH]c3c2CN(C(=O)N[C@@H](CN(C)C)Nc2nc(C)nc4ccsc24)C3(C)C)c2sccc2n1



QED: 0.2053 (-0.1618) X

Number of Blocks: 4 (+0) →

Block Changes: 6 (+3, -3)

HIA Score: 0.984575 → 0.995240 (+0.010665)

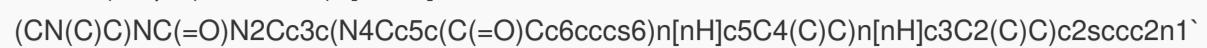
DETAILS *PLACEHOLDER 3*

► Step 2: PGP (+0.0081 ↓) →

****Before (Step 1)****



****After (Step 2)**** `Cc1nc(N[C@H]



****QED:**** 0.2053 ****Number of Blocks:**** 4

► All ADMET Scores

Task	Score	Direction
AMES	0.717762	↓ lower
BBBP	0.000191	↑ higher
CYP3A4	0.003685	↓ lower
DILI	0.691250	↓ lower
HIA	0.995240	↑ higher
PGP	0.564487	↓ lower

QED: 0.1259 (-0.0794) X

Number of Blocks: 5 (+1) ↑

Block Changes: 3 (+2, -1)

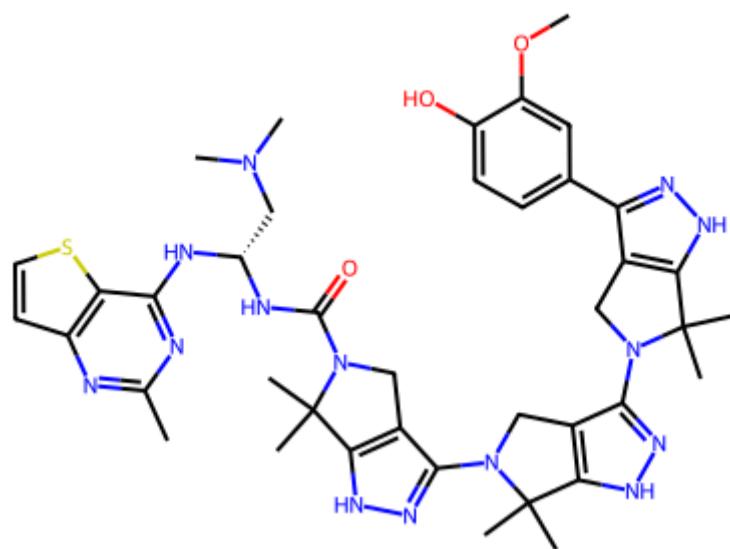
PGP Score: 0.564487 → 0.572543 (+0.008057)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

C0c1cc(-c2n[nH]c3c2CN(c2n[nH]c4c2CN(c2n[nH]c5c2CN(C(=O)N[C@@H](C)C)Nc2nc(C)nc6ccsc26)C5(C)C)C4(C)C)C3(C)C)ccc10



QED: 0.0961 (-0.0299) X

Number of Blocks: 6 (+1) ↑

Block Changes: 4 (+2, -2)

CYP3A4 Score: 0.004173 → 0.000889 (-0.003285)

DETAILS PLACEHOLDER 7

Step Details

Step 1: HIA ✓

Original	New	Change
0.984575	0.995240	+0.010665 ↑

```
Cc1nc(Nc2n[nH]c3c2CN(C(=O)N[C@H](CN(C)C)Nc2nc(C)nc4ccsc24)C3(C)C)c2sccc2n1
```

Step 2: PGP ⚠

Original	New	Change
0.564487	0.572543	+0.008057 ↓

```
Cc1nc(N[C@H](CN(C)C)NC(=O)N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)c2sccc2n1
```

Step 3: CYP3A4 ✓

Original	New	Change
0.004173	0.000889	-0.003285 ↓

```
C0c1cc(-c2n[nH]c3c2CN(c2n[nH]c4c2CN(c2n[nH]c5c2CN(C(=O)N[C@H](CN(C)C)Nc2nc(C)nc6ccsc26)C5(C)C)c4(C)C)c3(C)C)ccc10
```

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.419049	0.686654	+0.267605	-0.6386	+63.86%	X Declined
BBBP	↑ higher	0.778013	0.000213	-0.777801	-0.9997	-99.97%	X Declined
CYP3A4	↓ lower	0.011948	0.000889	-0.011059	+0.9256	-92.56%	✓ Improved
DILI	↓ lower	0.793920	0.659112	-0.134808	+0.1698	-16.98%	✓ Improved
HIA	↑ higher	0.984575	0.997891	+0.013316	+0.0135	+1.35%	✓ Improved
PGP	↓ lower	0.499705	0.556859	+0.057154	-0.1144	+11.44%	X Declined

Improved: 3/6 (50.0%) | **Molecules:** 139 | **Paths:** 2743

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠ **Below threshold:** 4

Task	Score	Threshold	Gap
BBBP	0.0002	↑ 0.5	0.4998
AMES	0.6867	↓ 0.3	0.3867
DILI	0.6591	↓ 0.4	0.2591
PGP	0.5569	↓ 0.3	0.2569

✓ **Passing:** 2

Task	Score	Threshold
CYP3A4	0.0009	↓ 0.55
HIA	0.9979	↑ 0.2

Slide 5: Olcegepant (BIBN-4096BS)

Initial Task: HIA

SMILES: C1=CC2=C(C=C1)NC(=O)N(C2)C3CCN(CC3)C(=O)N[C@H](CC4=CC(=C(C(=C4)Br)O)Br)C(=O)N[C@@H](CCCCN)C(=O)N5CCN(CC5)C6=CC=NC=C6

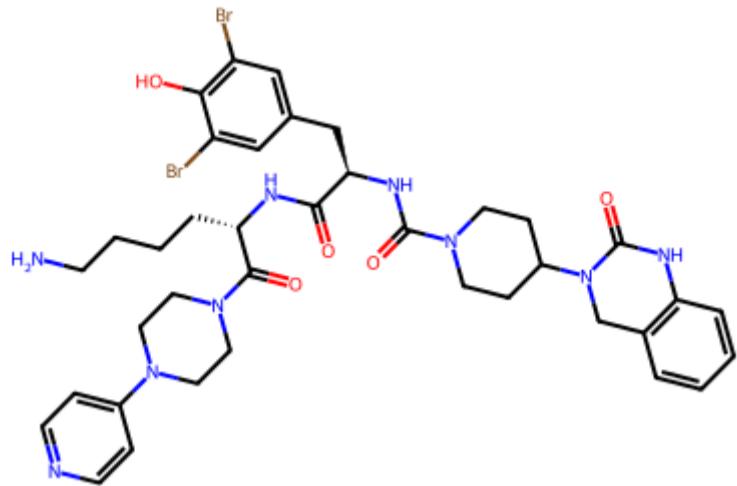
Olcegepant (BIBN-4096BS) - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule

`C1=CC2=C(C=C1)NC(=O)N(C2)C3CCN(CC3)C(=O)N[C@H]
(CC4=CC(=C(C(=C4)Br)O)Br)C(=O)N[C@@H]
(CCCCN)C(=O)N5CCN(CC5)C6=CC=NC=C6`



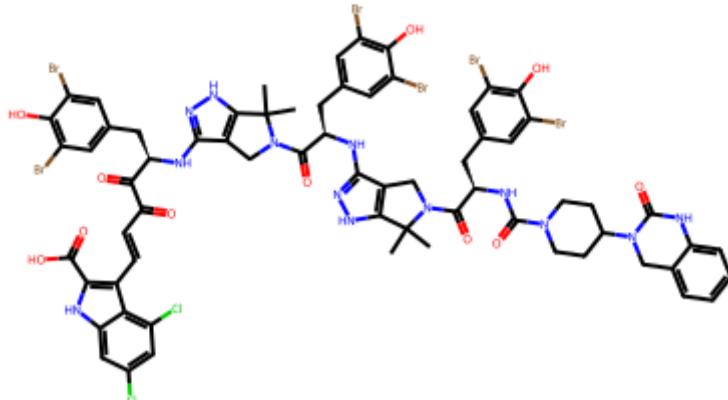
QED (Drug-likeness): 0.1666 **Number of Blocks:** 5

► Show ADMET Scores

Task	Score
AMES	0.721609
BBBP	0.000066
CYP3A4	0.009376
DILI	0.714050
HIA	0.989571
PGP	0.702944

Final Optimized `CC1(C)c2[nH]nc(N[C@H]

(Cc3cc(Br)c(O)c(Br)c3)C(=O)N3Cc4c(N[C@H]
(Cc5cc(Br)c(O)c(Br)c5)C(=O)C(=O)/C=C/c5c(C(=O)O)
[nH]c6cc(Cl)cc(Cl)c56)n[nH]c4C3(C)C)c2CN1C(=O)[C@@H]
(Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N2Cc3cccc3NC2=O)CC1`



QED (Drug-likeness): 0.0265 (-0.1401) ✗ **Number of Blocks:** 7 (+2) ↑

Total Block Changes: 16

► Show ADMET Scores

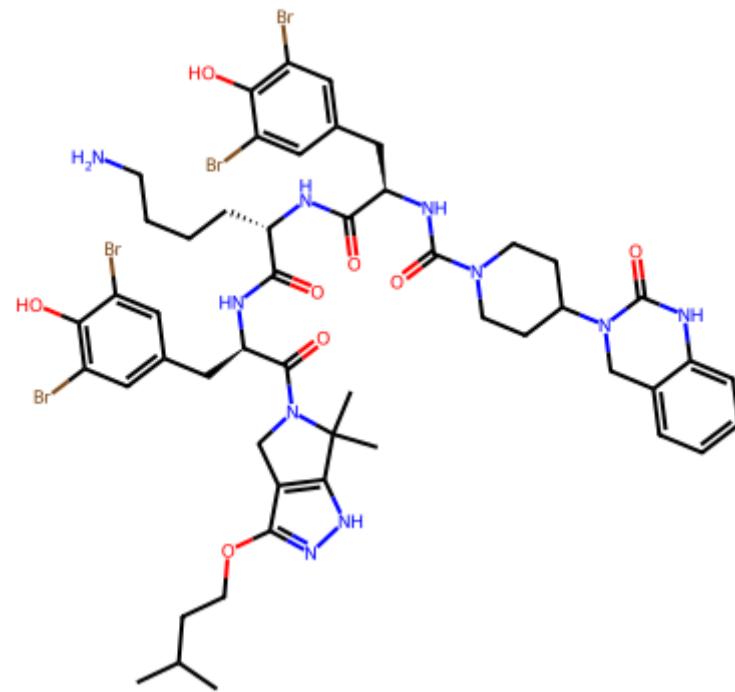
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.528857	-0.192753	+0.2671	-26.71%
BBBP ✓	0.000205	+0.000139	+2.1037	+210.37%
CYP3A4 ✓	0.000009	-0.009367	+0.9991	-99.91%
DILI ✓	0.525996	-0.188054	+0.2634	-26.34%
HIA ✓	0.999984	+0.010413	+0.0105	+1.05%
PGP ✗	0.824368	+0.121425	-0.1727	+17.27%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CC(C)CCOc1n[nH]c2c1CN(C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4cccc4NC3=O)CC1)C2(C)C



QED: 0.0420 (-0.1246) ✗

Number of Blocks: 6 (+1) ↑

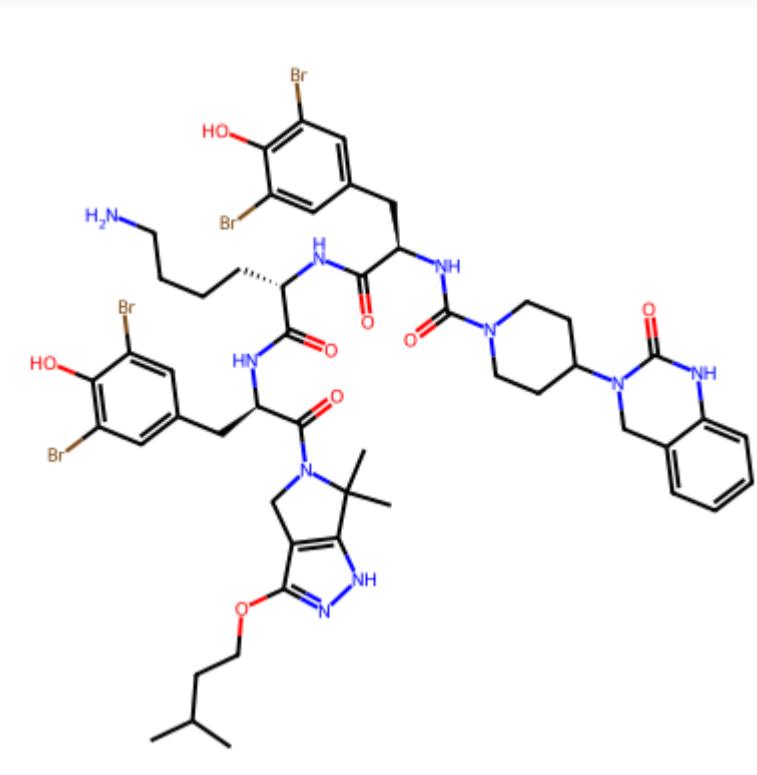
Block Changes: 8 (+4, -4)

HIA Score: 0.989571 → 0.999710 (+0.010140)

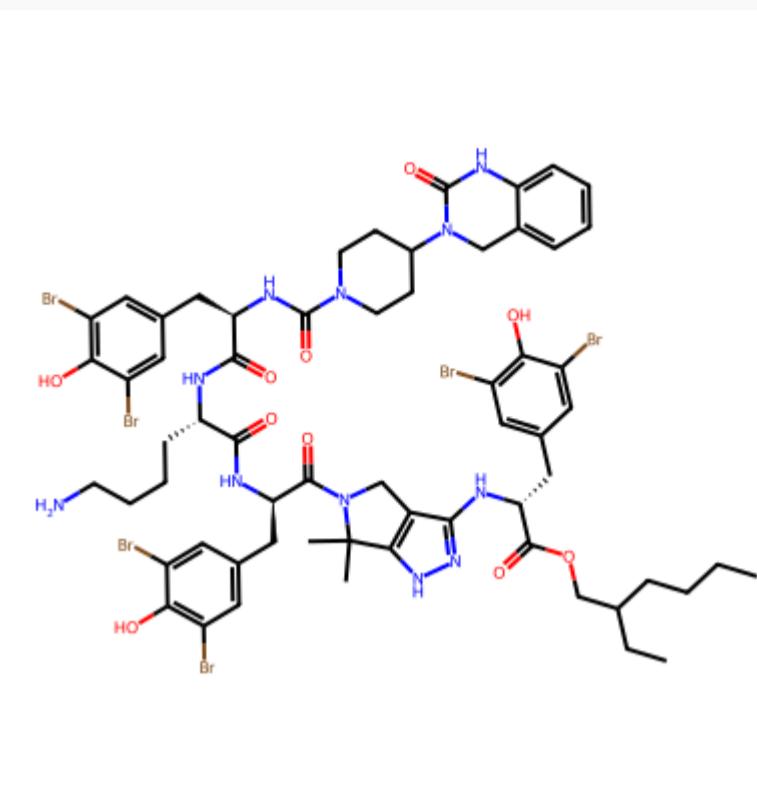
DETAILS PLACEHOLDER 3

► Step 2: AMES (-0.0478 ↓) ✓

Before (Step 1) `CC(C)CCOc1n[nH]c2c1CN(C(=O)[C@@H]
 (Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H]
 (Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4cccc4NC3=O)CC1)C2(C)C`



After (Step 2) `CCCCC(CC)COC(=O)[C@@H]
 (Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(C(=O)[C@@H]
 (Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H]
 (Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4cccc4NC3=O)CC1)C2(C)C`



QED: 0.0420 **Number of Blocks:** 6

► All ADMET Scores

Task	Score	Direction
AMES	0.612386	↓ lower
BBBP	0.000221	↑ higher
CYP3A4	0.000178	↓ lower
DILI	0.505321	↓ lower
HIA	0.999710	↑ higher
PGP	0.820831	↓ lower

QED: 0.0182 (-0.0238) ✗

Number of Blocks: 7 (+1) ↑

Block Changes: 3 (+2, -1)

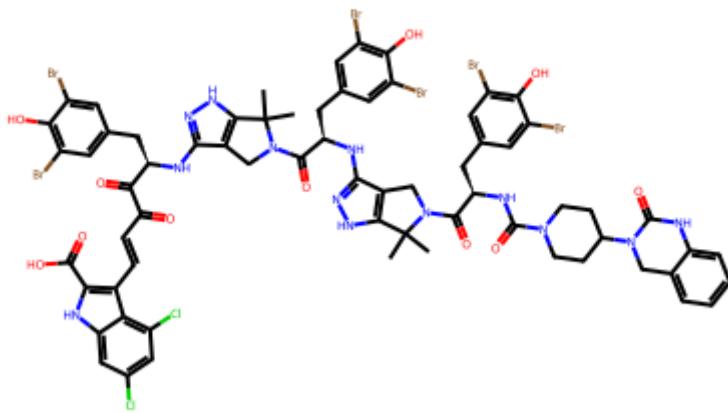
AMES Score: 0.612386 → 0.564568 (-0.047817)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC1(C)c2[nH]nc(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)N3Cc4c(N[C@H](Cc5cc(Br)c(O)c(Br)c5)C(=O)C(=O)/C=C/c5c(C(=O)O)[nH]c6cc(Cl)cc(Cl)c56)n[nH]c4C3(C)C)c2CN1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N2Cc3cccc3NC2=O)CC1



QED: 0.0265 (+0.0083) ✓

Number of Blocks: 7 (+0) ➡

Block Changes: 5 (+2, -3)

CYP3A4 Score: 0.000019 → 0.000009 (-0.000011)

DETAILS PLACEHOLDER 7

Step Details

Step 1: HIA ✓

Original	New	Change
0.989571	0.999710	+0.010140 ↑

CC(C)CCOc1n[nH]c2c1CN(C(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4cccc4NC

Step 2: AMES ✓

Original	New	Change
0.612386	0.564568	-0.047817 ↓

CCCCC(CC)COC(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(C(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@H](Cc1cc(Br)

Step 3: CYP3A4 ✓

Original	New	Change
0.000019	0.000009	-0.000011 ↓

CC1(C)c2[nH]nc(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)N3Cc4c(N[C@H](Cc5cc(Br)c(O)c(Br)c5)C(=O)C(=O)/C=C/c5c(C(=O)O)[nH]c6cc(Cl)cc(Cl)c56)n

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.721609	0.528857	-0.192753	+0.2671	-26.71%	✓ Improved
BBBP	↑ higher	0.000066	0.000205	+0.000139	+2.1037	+210.37%	✓ Improved
CYP3A4	↓ lower	0.009376	0.000009	-0.009367	+0.9991	-99.91%	✓ Improved
DILI	↓ lower	0.714050	0.525996	-0.188054	+0.2634	-26.34%	✓ Improved
HIA	↑ higher	0.989571	0.999984	+0.010413	+0.0105	+1.05%	✓ Improved
PGP	↓ lower	0.702944	0.824368	+0.121425	-0.1727	+17.27%	✗ Declined

Improved: 5/6 (83.3%) | **Molecules:** 637 | **Paths:** 5011

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠️ Below threshold: 4

Task	Score	Threshold	Gap
PGP	0.8244	↓ 0.3	0.5244
BBBP	0.0002	↑ 0.5	0.4998
AMES	0.5289	↓ 0.3	0.2289
DILI	0.5260	↓ 0.4	0.1260

✓ Passing: 2

Task	Score	Threshold
CYP3A4	0.0000	↓ 0.55
HIA	1.0000	↑ 0.2

Slide 6: EPI-506 (ralaniten acetate / prodrug of EPI-002)

Initial Task: HIA

SMILES: CC(=O)OC[C@H](COC1=CC=C(C=C1)C(C)(C)C2=CC=C(C=C2)OC[C@H](CC1)OC(=O)C)OC(=O)C

✖ Optimization Failed for EPI-506 (ralaniten acetate / prodrug of EPI-002)

No valid paths found. The optimization could not generate any improved molecules.

Initial Molecule Scores

Input SMILES: CC(=O)OC[C@H](COC1=CC=C(C=C1)C(C)(C)C2=CC=C(C=C2)OC[C@H](CC1)OC(=O)C)OC(=O)C

- Molecules Generated: 85
- Valid Paths: 0

Reason: All generated molecules had worse scores than the initial molecule.

Recommendations

1. Increase beams: Try `num_beams=7` or `num_beams=10` for more diversity
2. Change initial task: Try a different task as the starting point
3. Reduce depth: Start with `depth=1` to see if single-step improvements work
4. Check initial molecule: It may already be highly optimized

Slide 7: KPT-9274

Initial Task: HIA

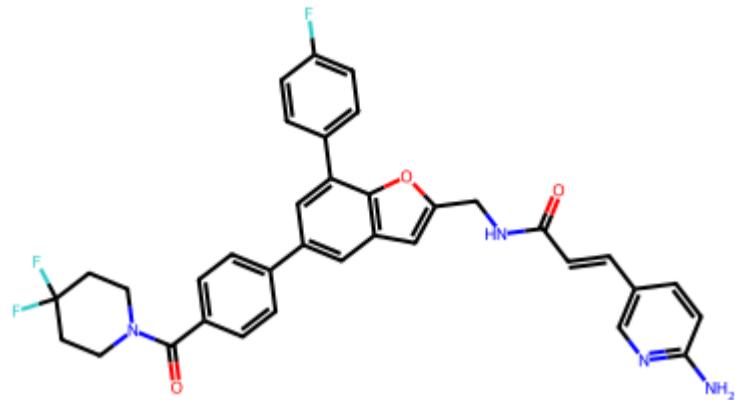
SMILES: C1=CC(=NC=C1/C=C/C(=O)NCC2=CC3=C(C(=CC(=C3)C4=CC=C(C=C4)C(=O)N5CCC(CC5)(F)F)C6=CC=C(C=C6)F)O2)N

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`

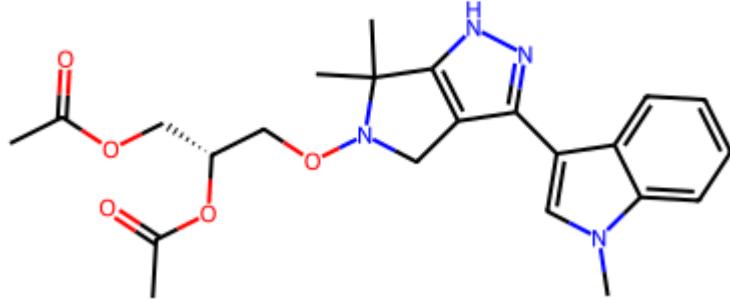


QED (Drug-likeness): 0.1918 **Number of Blocks:** 4

► 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](CONCc1cc2cc(-c3ccc(C(C)(C)c4ccc(N5CCC(F)(F)CC5)cc4)cc3)cc(-c3ccc(F)cc3)c2o1)OC(=O)`



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

► Show ADMET Scores

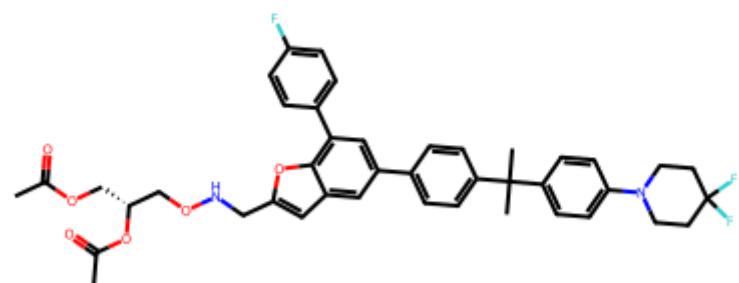
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.381034	-0.057586	+0.1313	-13.13%
BBBP ✓	1.000000	+0.000030	+0.0000	+0.00%
CYP3A4 ✓	0.011194	-0.035203	+0.7587	-75.87%
DILI ✓	0.458021	-0.292219	+0.3895	-38.95%
HIA ✓	0.995235	+0.006298	+0.0064	+0.64%
PGP ✓	0.630667	-0.022773	+0.0349	-3.49%

Optimization Steps:

DETAILS PLACEHOLDER 2

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(=O)



QED: 0.0731 (-0.1188) X

Number of Blocks: 4 (+0)

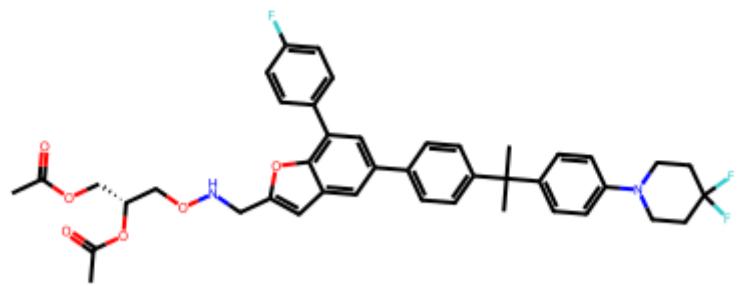
Block Changes: 6 (+3, -3)

HIA Score: 0.988937 → 0.941353 (-0.047584)

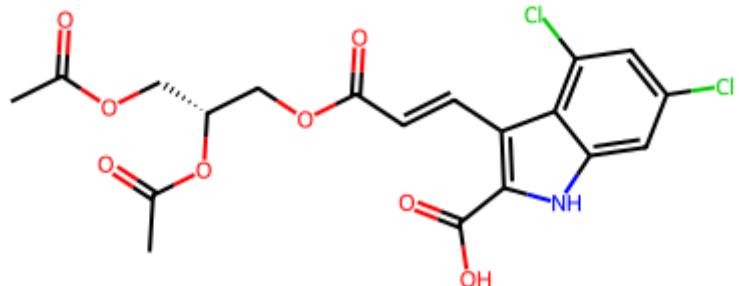
DETAILS PLACEHOLDER 3

► 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`



****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:**** 0.0731 ****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

QED: 0.3503 (+0.2772) ✓

Number of Blocks: 2 (-2) ↓

Block Changes: 6 (+2, -4)

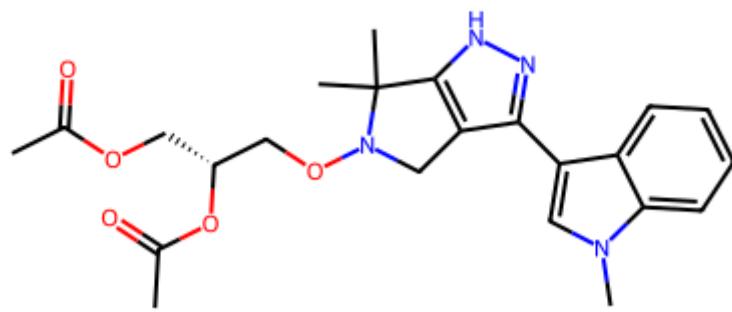
AMES Score: 0.432780 → 0.408373 (-0.024407)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC(=O)OC[C@H](CON1Cc2c(-c3cn(C)c4cccc34)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 PLACEHOLDER 7

📊 Step Details

Step 1: HIA ⚠

Original	New	Change
0.988937	0.941353	-0.047584 ↑

```
CC(=O)OC[C@H](COCc1cc2cc(-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)c4cccc34)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

Slide 8: Valeresol

Initial Task: HIA

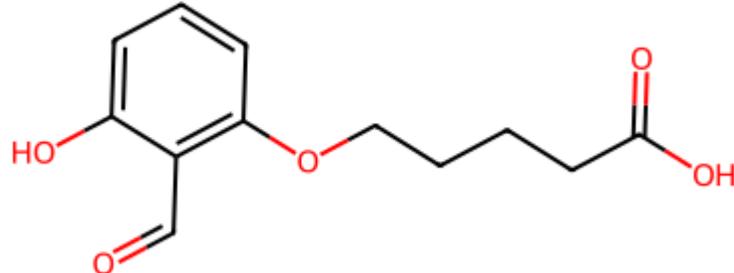
SMILES: c1ccoc1=C(C=O)C(=CC=C1)O)CC(=O)O

Valeresol - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule `C(CCOC1=C(C=O)C(=CC=C1)O)CC(=O)O`



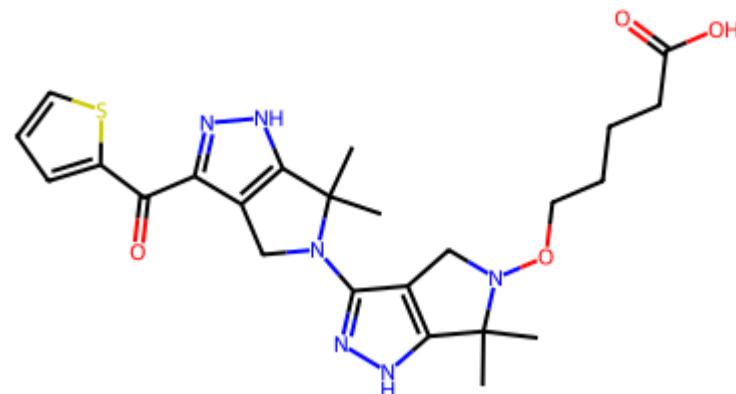
QED (Drug-likeness): 0.5590 **Number of Blocks:** 2

► Show ADMET Scores

Task	Score
AMES	0.687406
BBBP	0.001264
CYP3A4	0.022560
DILI	0.623776
HIA	0.984511
PGP	0.615759

Final Optimized

`CC1(C)c2[nH]nc(N3Cc4c(C(=O)c5cccs5)n[nH]c4C3(C)C)c2CN1OCCCCCC(=O)O`



QED (Drug-likeness): 0.2992 (-0.2597) ✗ **Number of Blocks:** 2 (+0) ➔

Total Block Changes: 8

► Show ADMET Scores

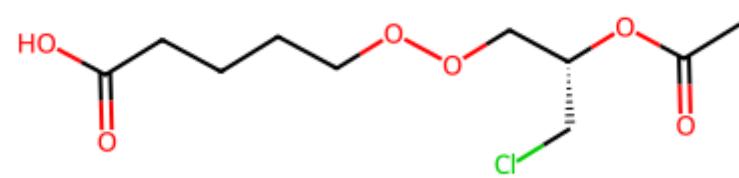
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.368299	-0.319107	+0.4642	-46.42%
BBBP ✓	0.898326	+0.897062	+709.5506	+70955.06%
CYP3A4 ✓	0.005592	-0.016969	+0.7521	-75.21%
DILI ✗	0.676924	+0.053148	-0.0852	+8.52%
HIA ✗	0.980476	-0.004035	-0.0041	-0.41%
PGP ✓	0.498713	-0.117046	+0.1901	-19.01%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CC(=O)O[C@H](CCl)COOCCCCCC(=O)O



QED: 0.2118 (-0.3472) ✘

Number of Blocks: 1 (-1) ↓

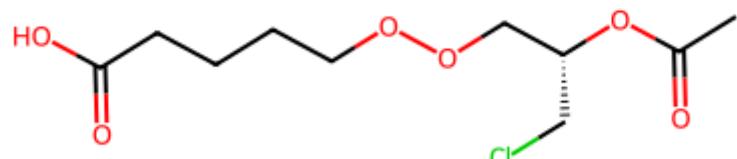
Block Changes: 3 (+1, -2)

HIA Score: 0.984511 → 0.999700 (+0.015189)

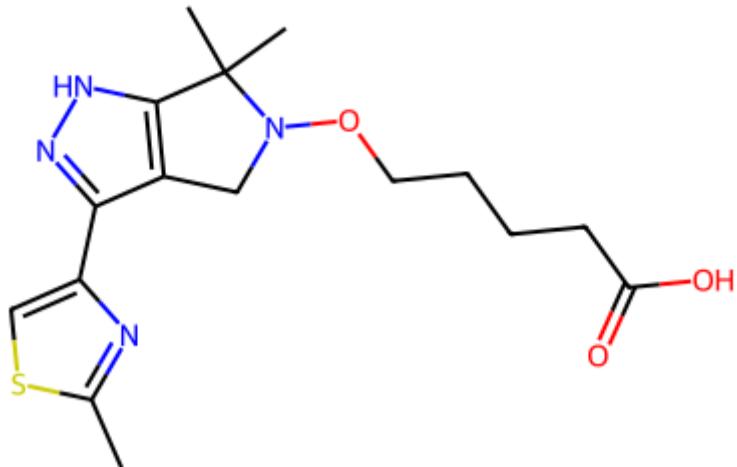
DETAILS PLACEHOLDER 3

► Step 2: AMES (+0.3483 ↓) ➔

****Before (Step 1)**** `CC(=O)O[C@H](CCl)COOCCCCC(=O)O`



****After (Step 2)**** `Cc1nc(-c2n[nH]c3c2CN(OCCCCCC(=O)O)C3(C)C)cs1`



****QED:**** 0.2118 ****Number of Blocks:**** 1

► All ADMET Scores

Task	Score	Direction
AMES	0.428290	↓ lower
BBBP	1.000000	↑ higher
CYP3A4	0.063673	↓ lower
DILI	0.424375	↓ lower
HIA	0.999700	↑ higher
PGP	0.791106	↓ lower

QED: 0.7458 (+0.5340)

Number of Blocks: 2 (+1) ↑

Block Changes: 3 (+2, -1)

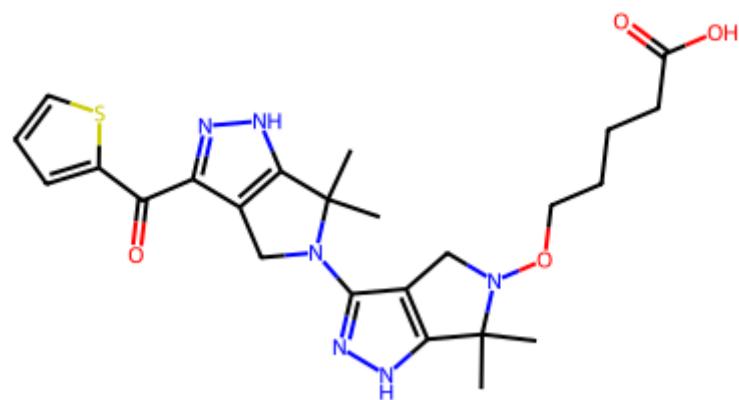
AMES Score: 0.428290 → 0.776573 (+0.348283)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC1(C)c2[nH]nc(N3Cc4c(C(=O)c5cccs5)n[nH]c4C3(C)C)c2CN10CCCCCC(=O)O



QED: 0.2992 (-0.4465) X

Number of Blocks: 2 (+0) →

Block Changes: 2 (+1, -1)

PGP Score: 0.609776 → 0.498713 (-0.111063)

DETAILS PLACEHOLDER 7

Step Details

Step 1: HIA ✓

Original	New	Change
0.984511	0.999700	+0.015189 ↑

CC(=O)O[C@H](CCl)COOCCCCC(=O)O

Step 2: AMES ⚠

Original	New	Change
0.428290	0.776573	+0.348283 ↓

Cc1nc(-c2n[nH]c3c2CN(OCCCCCC(=O)O)C3(C)C)cs1

Step 3: PGP ✓

Original	New	Change
0.609776	0.498713	-0.111063 ↓

CC1(C)c2[nH]nc(N3Cc4c(C(=O)c5cccs5)n[nH]c4C3(C)C)c2CN1OCCCCCC(=O)O

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.687406	0.368299	-0.319107	+0.4642	-46.42%	✓ Improved
BBBP	↑ higher	0.001264	0.898326	+0.897062	+709.5506	+70955.06%	✓ Improved
CYP3A4	↓ lower	0.022560	0.005592	-0.016969	+0.7521	-75.21%	✓ Improved
DILI	↓ lower	0.623776	0.676924	+0.053148	-0.0852	+8.52%	✗ Declined
HIA	↑ higher	0.984511	0.980476	-0.004035	-0.0041	-0.41%	✗ Declined
PGP	↓ lower	0.615759	0.498713	-0.117046	+0.1901	-19.01%	✓ Improved

Improved: 4/6 (66.7%) | **Molecules:** 85 | **Paths:** 1719

🔍 Safety Threshold Analysis

Status: 3/6 meet thresholds

⚠ Below threshold: 3

Task	Score	Threshold	Gap
DILI	0.6769	↓ 0.4	0.2769
PGP	0.4987	↓ 0.3	0.1987
AMES	0.3683	↓ 0.3	0.0683

✓ Passing: 3

Task	Score	Threshold
BBBP	0.8983	↑ 0.5
CYP3A4	0.0056	↓ 0.55
HIA	0.9805	↑ 0.2

Slide 9: Fialuridine (FIAU)

Initial Task: DILI

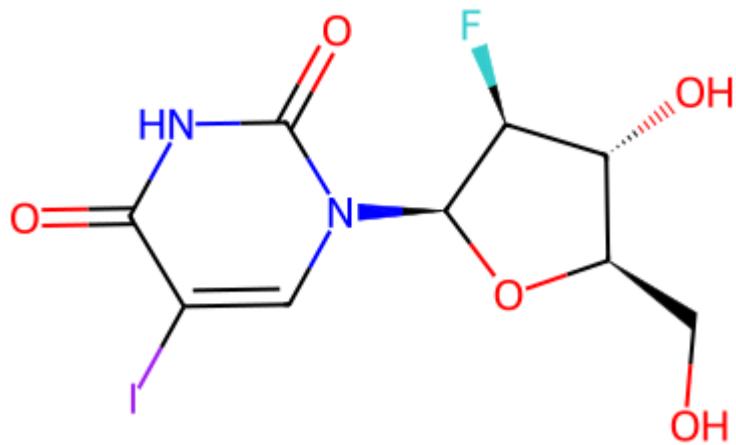
SMILES: C1=C(C(=O)NC(=O)N1[C@H]2[C@H](C[C@@H]([C@@H](CO)O2)O)F)I

Fialuridine (FIAU) - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule `C1=C(C(=O)NC(=O)N1[C@H]2[C@H]
([C@@H])([C@@H](CO)O2)O)F`

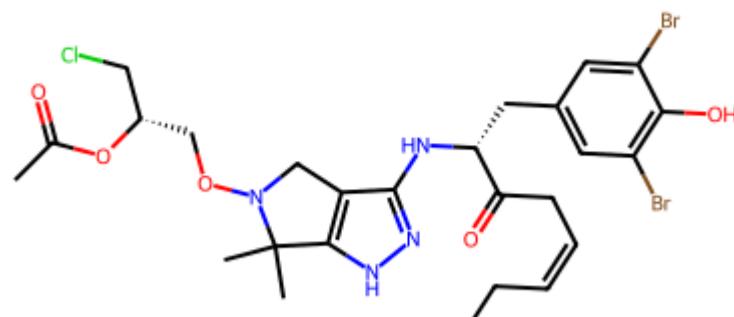


QED (Drug-likeness): 0.5621 **Number of Blocks:** 1

► Show ADMET Scores

Task	Score
AMES	0.114162
BBBP	1.000000
CYP3A4	0.000000
DILI	0.145744
HIA	1.000000
PGP	0.940474

Final Optimized `CC/C=C\CC(=O)[C@@H]
(Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(OC[C@H](CCl)OC(C)=O)C2(C)C`



QED (Drug-likeness): 0.1398 (-0.4222) ✗ **Number of Blocks:** 3 (+2) ↑
Total Block Changes: 10

► Show ADMET Scores

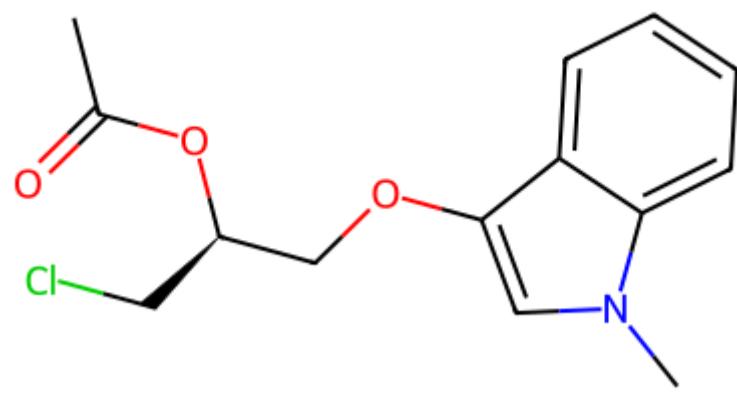
Task	Score	Change	Rel. Improvement	% Change
AMES ✗	0.266793	+0.152631	-1.3370	+133.70%
BBBP ✗	1.000000	+0.000000	+0.0000	+0.00%
CYP3A4 ✗	0.000067	+0.000067	-5806.1212	+580612.12%
DILI ✗	0.259323	+0.113579	-0.7793	+77.93%
HIA ✗	0.999987	-0.000013	-0.0000	-0.00%
PGP ✓	0.866124	-0.074351	+0.0791	-7.91%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CC(=O)O[C@H](CCl)COc1cn(C)c2ccccc12



QED: 0.6249 (+0.0629)

Number of Blocks: 2 (+1) ↑

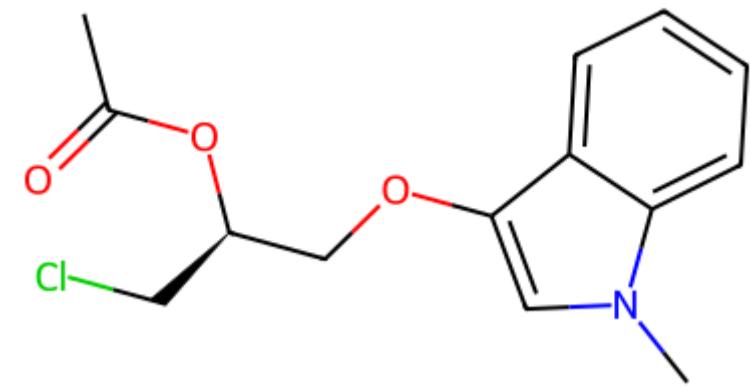
Block Changes: 3 (+2, -1)

DILI Score: 0.145744 → 0.641619 (+0.495875)

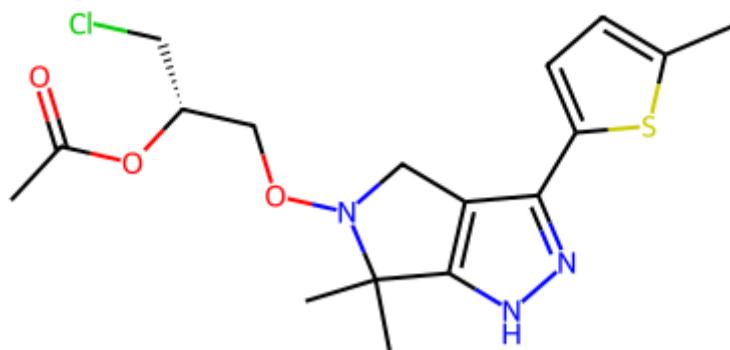
DETAILS *PLACEHOLDER 3*

► Step 2: CYP3A4 (-0.1500 ↓)

****Before (Step 1)**** `CC(=O)O[C@H](CCl)COc1cn(C)c2ccccc12`



****After (Step 2)**** `CC(=O)O[C@H](CCl)CON1Cc2c(-c3ccc(C)s3)n[nH]c2C1(C)C`



****QED:**** 0.6249 ****Number of Blocks:**** 2

► All ADMET Scores

Task	Score	Direction
AMES	0.376149	↓ lower
BBBP	0.999958	↑ higher
CYP3A4	0.159087	↓ lower
DILI	0.641619	↓ lower
HIA	0.976337	↑ higher
PGP	0.594567	↓ lower

QED: 0.6094 (-0.0155) X

Number of Blocks: 2 (+0) ➡

Block Changes: 4 (+2, -2)

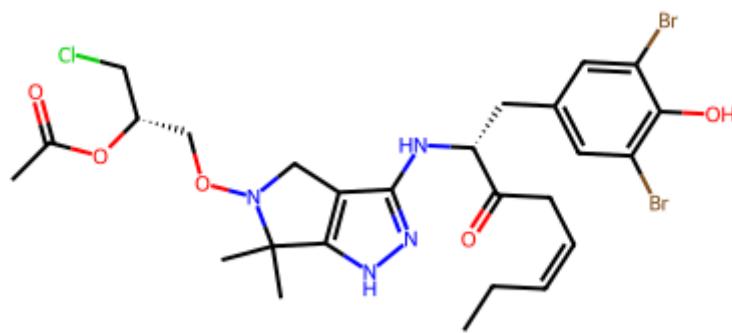
CYP3A4 Score: 0.159087 → 0.009106 (-0.149981)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC/C=C\CC(=O)[C@@H](CCl)C(Oc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(OC[C@@H](CCl)OC(C)=O)C2(C)C



QED: 0.1398 (-0.4696) ✗

Number of Blocks: 3 (+1) ↑

Block Changes: 3 (+2, -1)

DILI Score: 0.576163 → 0.259323 (-0.316840)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: DILI ⚠

Original	New	Change
0.145744	0.641619	+0.495875 ↓

CC(=O)O[C@H](CCl)COC1CN(C)C2CCCCC12

Step 2: CYP3A4 ✓

Original	New	Change
0.159087	0.009106	-0.149981 ↓

CC(=O)O[C@H](CCl)CON1Cc2c(-c3ccc(C)s3)n[nH]c2C1(C)C

Step 3: DILI ✓

Original	New	Change
0.576163	0.259323	-0.316840 ↓

CC/C=C\CC(=O)[C@@H](CC1CC(Br)C(O)C(Br)C1)Nc1n[nH]c2c1CN(OC[C@@H](CCl)OC(C)=O)C2(C)C

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.114162	0.266793	+0.152631	-1.3370	+133.70%	X Declined
BBBP	↑ higher	1.000000	1.000000	+0.000000	+0.0000	+0.00%	→ Unchanged
CYP3A4	↓ lower	0.000000	0.000067	+0.000067	-5806.1212	+580612.12%	X Declined
DILI	↓ lower	0.145744	0.259323	+0.113579	-0.7793	+77.93%	X Declined
HIA	↑ higher	1.000000	0.999987	-0.000013	-0.0000	-0.00%	X Declined
PGP	↓ lower	0.940474	0.866124	-0.074351	+0.0791	-7.91%	✓ Improved

Improved: 1/6 (16.7%) | Molecules: 271 | Paths: 19870

🔍 Safety Threshold Analysis

Status: 5/6 meet thresholds

⚠ Below threshold: 1

Task	Score	Threshold	Gap
PGP	0.8661	↓ 0.3	0.5661

✓ Passing: 5

Task	Score	Threshold
AMES	0.2668	↓ 0.3
BBBP	1.0000	↑ 0.5
CYP3A4	0.0001	↓ 0.55
DILI	0.2593	↓ 0.4
HIA	1.0000	↑ 0.2

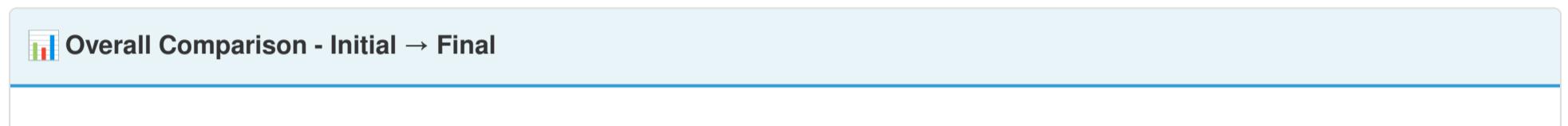
Slide 10: Ximelagatran (Exanta / oral direct thrombin inhibitor)

Initial Task: DILI

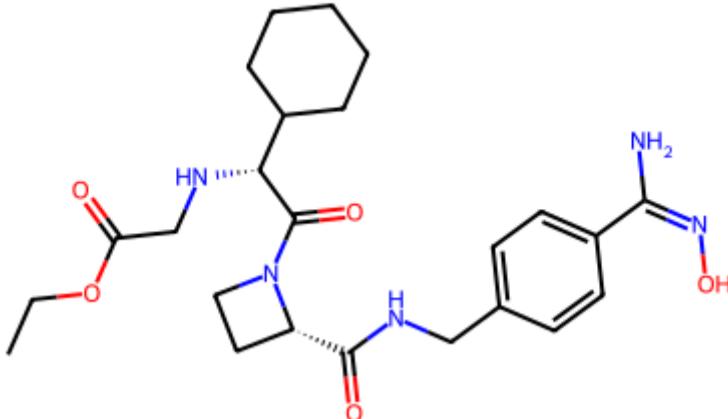
SMILES: CCOC(=O)CN[C@H](C1CCCCC1)C(=O)N2CC[C@H]2C(=O)NCC3=CC=C(C=C3)/C(=N\O)/N

Ximelagatran (Exanta / oral direct thrombin inhibitor) - Optimization Results

Optimization Path



Initial Molecule `CCOC(=O)CN[C@H]
(C1CCCCC1)C(=O)N2CC[C@H]2C(=O)NCC3=CC=C(C=C3)/
C(=N\O)/N`

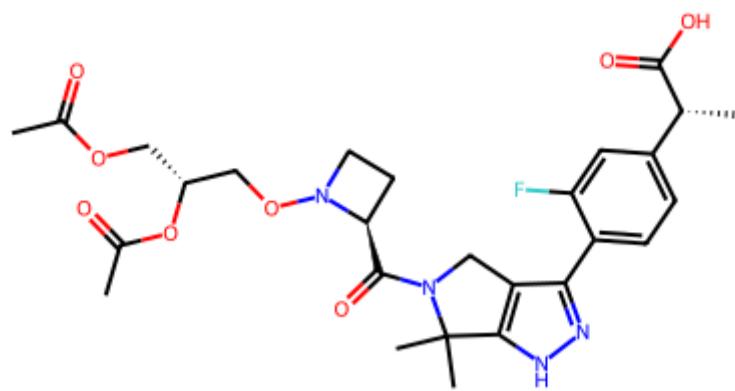


QED (Drug-likeness): 0.1308 **Number of Blocks:** 3

► Show ADMET Scores

Task	Score
AMES	0.720076
BBBP	0.000080
CYP3A4	0.018008
DILI	0.649647
HIA	0.997815
PGP	0.655136

Final Optimized `CC(=O)OC[C@H](CON1CC[C@H]1C(=O)N1Cc2c(-
c3ccc([C@@H](C)C(=O)O)cc3F)n[nH]c2C1(C)C)OC(C)=O`



QED (Drug-likeness): 0.4148 (+0.2840) ✓ **Number of Blocks:** 3 (+0) ➡
Total Block Changes: 10

► Show ADMET Scores

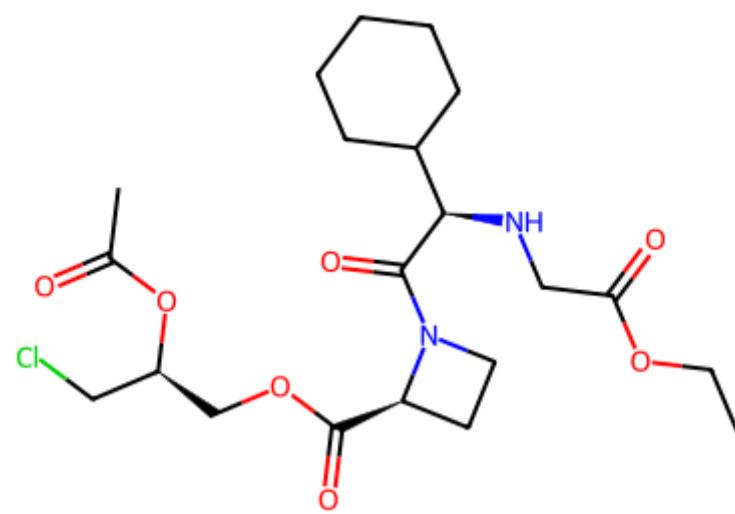
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.404659	-0.315416	+0.4380	-43.80%
BBBP ✓	0.999947	+0.999867	+12529.0183	+1252901.83%
CYP3A4 ✗	0.020061	+0.002053	-0.1140	+11.40%
DILI ✓	0.408363	-0.241285	+0.3714	-37.14%
HIA ✗	0.991177	-0.006638	-0.0067	-0.67%
PGP ✗	0.659510	+0.004374	-0.0067	+0.67%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CCOC(=O)CN[C@H](C(=O)N1CC[C@H]1C(=O)OC[C@H](CCl)OC(C)=O)C1CCCCC1



QED: 0.2796 (+0.1488) ✓

Number of Blocks: 3 (+0) →

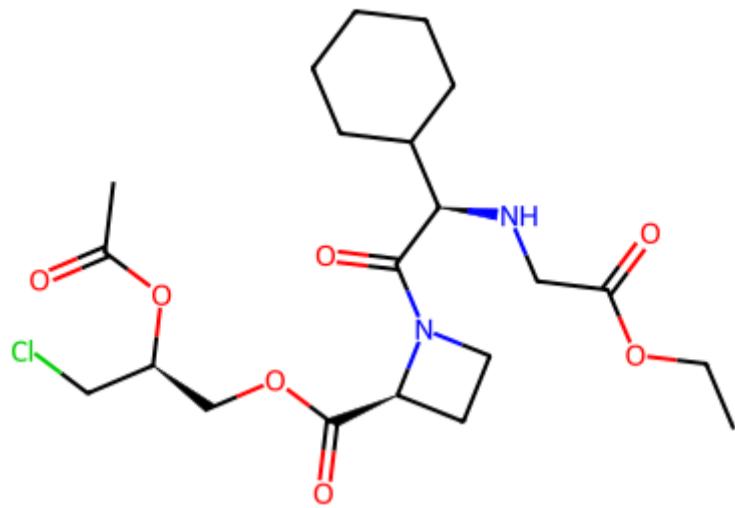
Block Changes: 2 (+1, -1)

DILI Score: 0.649647 → 0.419199 (-0.230448)

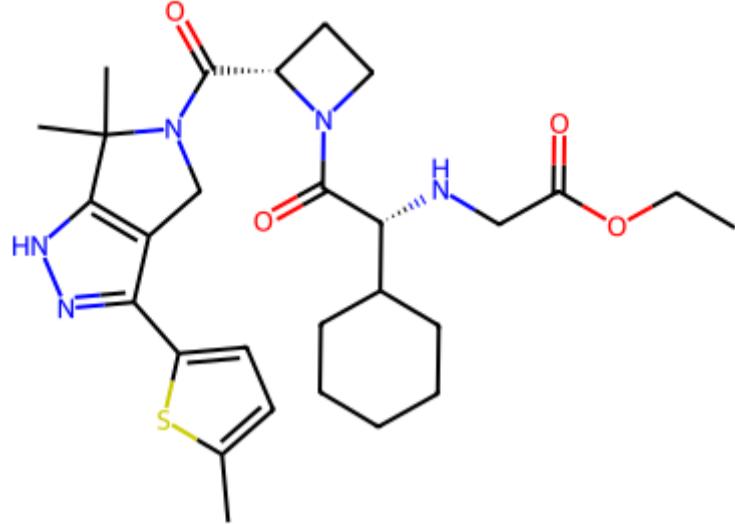
DETAILS *PLACEHOLDER 3*

► Step 2: AMES (+0.3920 ↓) →

****Before (Step 1)**** `CCOC(=O)CN[C@@H]
(C(=O)N1CC[C@H]1C(=O)OC[C@@H](CCl)OC(C)=O)C1CCCCC1`



****After (Step 2)**** `CCOC(=O)CN[C@@H]
(C(=O)N1CC[C@H]1C(=O)N1Cc2c(-c3ccc(C)s3)n[nH]c2C1(C)C)C1CCCCC1`



****QED:**** 0.2796 ****Number of Blocks:**** 3

► All ADMET Scores

Task	Score	Direction
AMES	0.340648	↓ lower
BBBP	0.999998	↑ higher
CYP3A4	0.025386	↓ lower
DILI	0.419199	↓ lower
HIA	0.999903	↑ higher
PGP	0.814016	↓ lower

QED: 0.4934 (+0.2138)

Number of Blocks: 4 (+1) ↑

Block Changes: 3 (+2, -1)

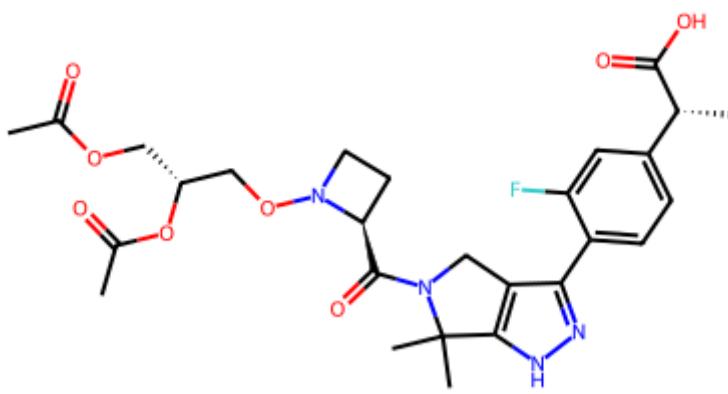
AMES Score: 0.340648 → 0.732660 (+0.392012)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC(=O)OC[C@H](CON1CC[C@H]1C(=O)N1Cc2c(-c3ccc([C@@H](C)C(=O)O)cc3F)n[nH]c2C1(C)C)OC(C)=O



QED: 0.4148 (-0.0787) ✗

Number of Blocks: 3 (-1) ↓

Block Changes: 5 (+2, -3)

AMES Score: 0.732660 → 0.404659 (-0.328000)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: DILI ✓

Original	New	Change
0.649647	0.419199	-0.230448 ↓

CCOC(=O)CN[C@H](C(=O)N1CC[C@H]1C(=O)OC[C@H](CCl)OC(C)=O)C1CCCC1

Step 2: AMES !

Original	New	Change
0.340648	0.732660	+0.392012 ↓

CCOC(=O)CN[C@H](C(=O)N1CC[C@H]1C(=O)N1Cc2c(-c3ccc(C)s3)n[nH]c2C1(C)C)C1CCCC1

Step 3: AMES ✓

Original	New	Change
0.732660	0.404659	-0.328000 ↓

CC(=O)OC[C@H](CON1CC[C@H]1C(=O)N1Cc2c(-c3ccc([C@H](C)C(=O)O)cc3F)n[nH]c2C1(C)C)OC(C)=O

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.720076	0.404659	-0.315416	+0.4380	-43.80%	✓ Improved
BBBP	↑ higher	0.000080	0.999947	+0.999867	+12529.0183	+1252901.83%	✓ Improved
CYP3A4	↓ lower	0.018008	0.020061	+0.002053	-0.1140	+11.40%	✗ Declined
DILI	↓ lower	0.649647	0.408363	-0.241285	+0.3714	-37.14%	✓ Improved
HIA	↑ higher	0.997815	0.991177	-0.006638	-0.0067	-0.67%	✗ Declined
PGP	↓ lower	0.655136	0.659510	+0.004374	-0.0067	+0.67%	✗ Declined

Improved: 3/6 (50.0%) | **Molecules:** 283 | **Paths:** 3915

🔍 Safety Threshold Analysis

Status: 3/6 meet thresholds

⚠ Below threshold: 3

Task	Score	Threshold	Gap
PGP	0.6595	↓ 0.3	0.3595
AMES	0.4047	↓ 0.3	0.1047
DILI	0.4084	↓ 0.4	0.0084

✓ Passing: 3

Task	Score	Threshold
BBBP	0.9999	↑ 0.5
CYP3A4	0.0201	↓ 0.55
HIA	0.9912	↑ 0.2

Slide 11: Fasiglifam (TAK-875)

Initial Task: DILI

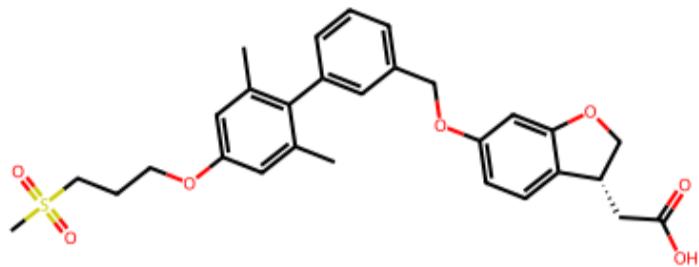
SMILES: CC1=C(C(=CC(=C1)OCCCS(=O)(=O)C)C)C2=CC(=CC=C2)COC3=CC=C4[C@@H](CC(=O)O)COC4=C3

Fasiglifam (TAK-875) - Optimization Results

Optimization Path

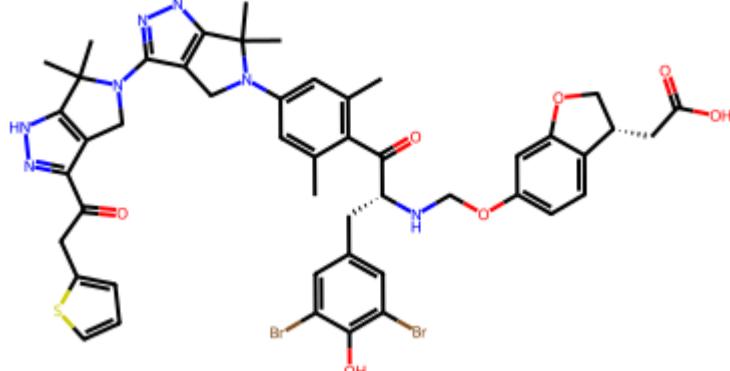
 Overall Comparison - Initial → Final

Initial Molecule `CC1=C(C(=CC=C1)OCCCS(=O)(=O)C)C2=CC(=CC=C2)COC3=CC=C4[C@@H](CC(=O)O)CO



Final Optimized

`Cc1cc(N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`



QED (Drug-likeness): 0.3393 **Number of Blocks:** 4

► Show ADMET Scores

Task	Score
AMES	0.459273
BBBP	0.999996
CYP3A4	0.082408
DILI	0.605552
HIA	0.659498
PGP	0.636196

QED (Drug-likeness): 0.0486 (-0.2907) ✗ **Number of Blocks:** 5 (+1) ↑ **Total Block Changes:** 11

► Show ADMET Scores

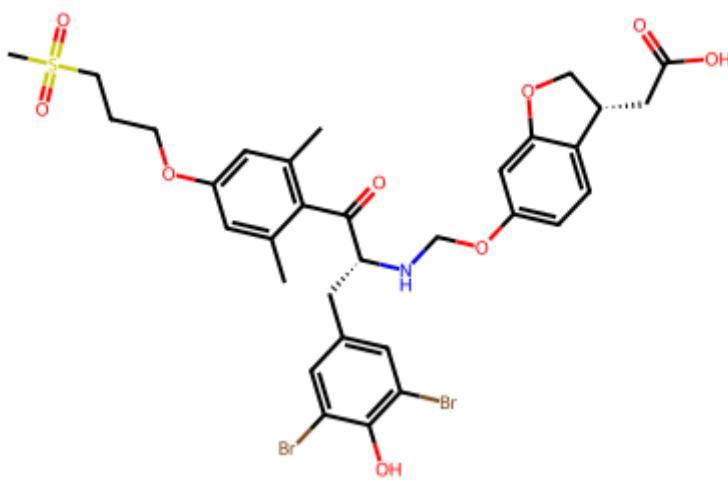
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.259236	-0.200037	+0.4356	-43.56%
BBBP ✗	0.999966	-0.000030	-0.0000	-0.00%
CYP3A4 ✓	0.001861	-0.080547	+0.9774	-97.74%
DILI ✓	0.380775	-0.224777	+0.3712	-37.12%
HIA ✓	0.996015	+0.336517	+0.5103	+51.03%
PGP ✗	0.755818	+0.119622	-0.1880	+18.80%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

Cc1cc(OCCCS(C)(=O)=O)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O



QED: 0.0997 (-0.2396) ✗

Number of Blocks: 3 (-1) ↓

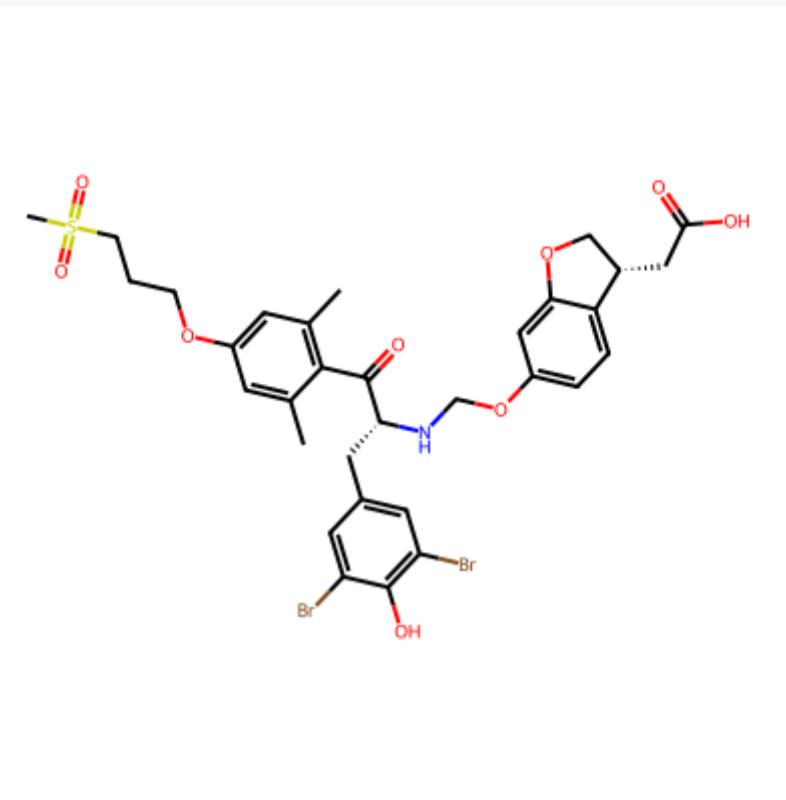
Block Changes: 5 (+2, -3)

DILI Score: 0.605552 → 0.424327 (-0.181224)

DETAILS PLACEHOLDER 3

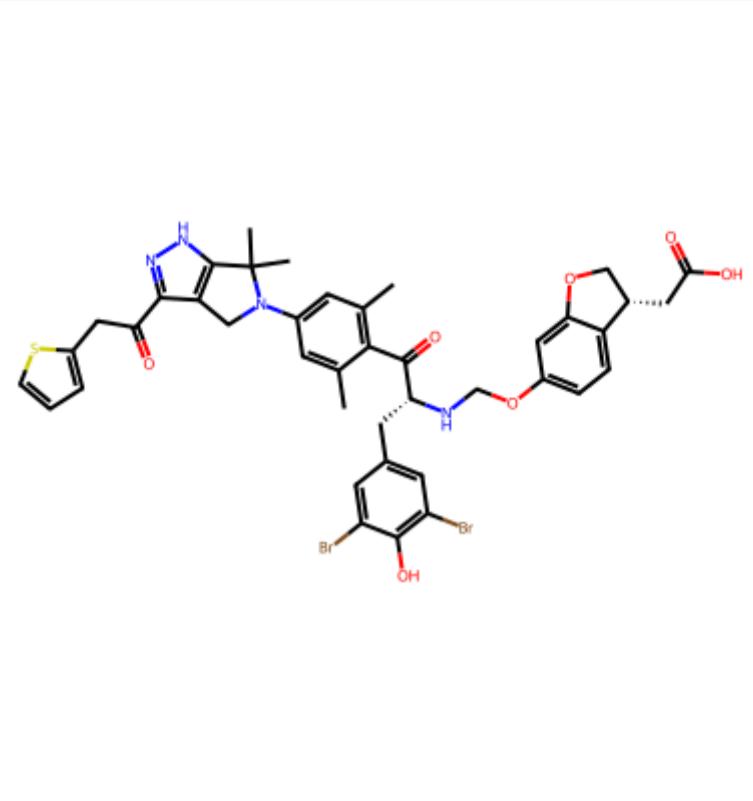
► Step 2: BBBP (+0.0000 ↑) ✓

****Before (Step 1)**** `Cc1cc(OCCCS(C)(=O)=O)cc(C)c1C(=O)[C@@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`



****After (Step 2)****

`Cc1cc(N2Cc3c(C(=O)Cc4cccs4)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`



****QED:**** 0.0997 ****Number of Blocks:**** 3

► All ADMET Scores

Task	Score	Direction
AMES	0.265935	↓ lower
BBBP	0.999996	↑ higher
CYP3A4	0.000436	↓ lower
DILI	0.424327	↓ lower
HIA	0.999337	↑ higher
PGP	0.816133	↓ lower

QED: 0.0632 (-0.0365) ✗

Number of Blocks: 4 (+1) ↑

Block Changes: 5 (+3, -2)

BBBP Score: 0.999996 → 1.000000 (+0.000004)

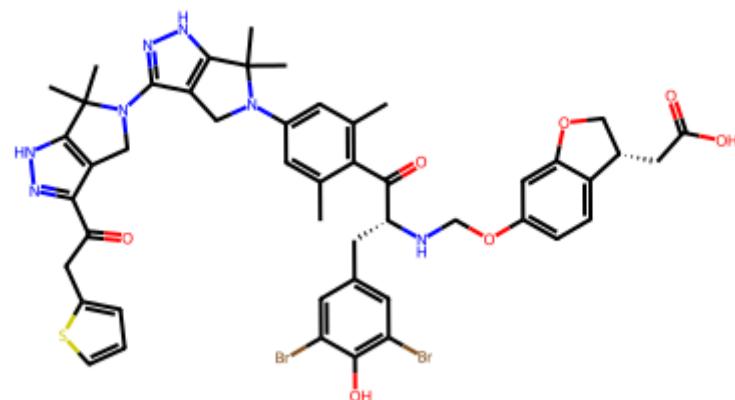
DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

Cc1cc(N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H]

(Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O



QED: 0.0486 (-0.0146) ✗

Number of Blocks: 5 (+1) ↑

Block Changes: 1 (+1, -0)

PGP Score: 0.798334 → 0.755818 (-0.042516)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: DILI ✓

Original	New	Change
0.605552	0.424327	-0.181224 ↓

```
Cc1cc(OCCCS(=O)(=O)C=C1)c1c(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)c1ccc2c(c1)OC[C@H]2CC(=O)O
```

Step 2: BBBP ✓

Original	New	Change
0.999996	1.000000	+0.000004 ↑

```
Cc1cc(N2Cc3c(C(=O)Cc4cccc4)n[nH]c3C2(C)C)cc(C)c1c(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)c1ccc2c(c1)OC[C@H]2CC(=O)O
```

Step 3: PGP ✓

Original	New	Change
0.798334	0.755818	-0.042516 ↓

```
Cc1cc(N2Cc3c(N4Cc5c(C(=O)Cc6cccc6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1c(=O)[C@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)c1ccc2c(c1)OC[C@H]2CC(=O)O
```

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.459273	0.259236	-0.200037	+0.4356	-43.56%	✓ Improved
BBBP	↑ higher	0.999996	0.999966	-0.000030	-0.0000	-0.00%	✗ Declined
CYP3A4	↓ lower	0.082408	0.001861	-0.080547	+0.9774	-97.74%	✓ Improved
DILI	↓ lower	0.605552	0.380775	-0.224777	+0.3712	-37.12%	✓ Improved
HIA	↑ higher	0.659498	0.996015	+0.336517	+0.5103	+51.03%	✓ Improved
PGP	↓ lower	0.636196	0.755818	+0.119622	-0.1880	+18.80%	✗ Declined

Improved: 4/6 (66.7%) | **Molecules:** 175 | **Paths:** 2055

🔍 Safety Threshold Analysis

Status: 5/6 meet thresholds

⚠️ Below threshold: 1

Task	Score	Threshold	Gap
PGP	0.7558	↓ 0.3	0.4558

✓ Passing: 5

Task	Score	Threshold
AMES	0.2592	↓ 0.3
BBBP	1.0000	↑ 0.5
CYP3A4	0.0019	↓ 0.55
DILI	0.3808	↓ 0.4
HIA	0.9960	↑ 0.2

Slide 12: Lapaquistat acetate (TAK-475)

Initial Task: DILI

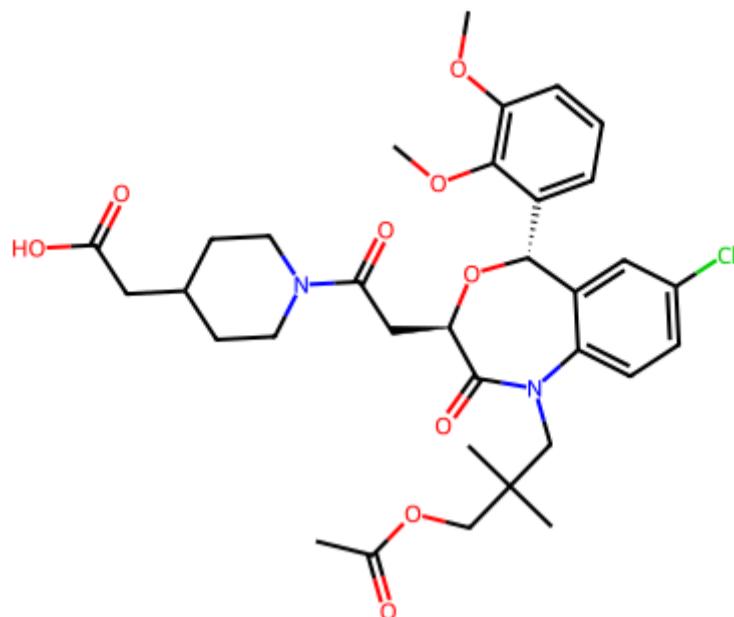
SMILES: CC(=O)OCC(C)(C)CN1C2=CC=C(C=C2[C@H](C3=CC=CC(=C3OC)OC)O[C@H](CC(=O)N4CCC(CC4)CC(=O)O)C1=O)Cl

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`



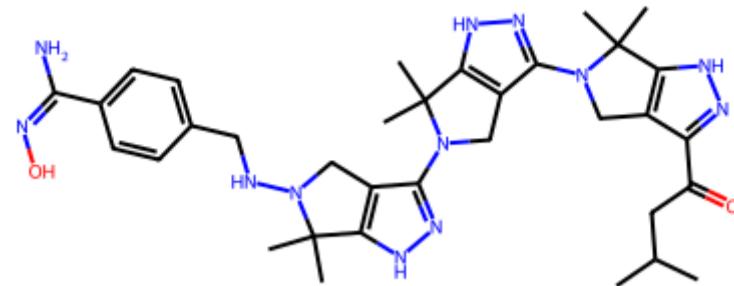
QED (Drug-likeness): 0.3403 **Number of Blocks:** 3

► 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

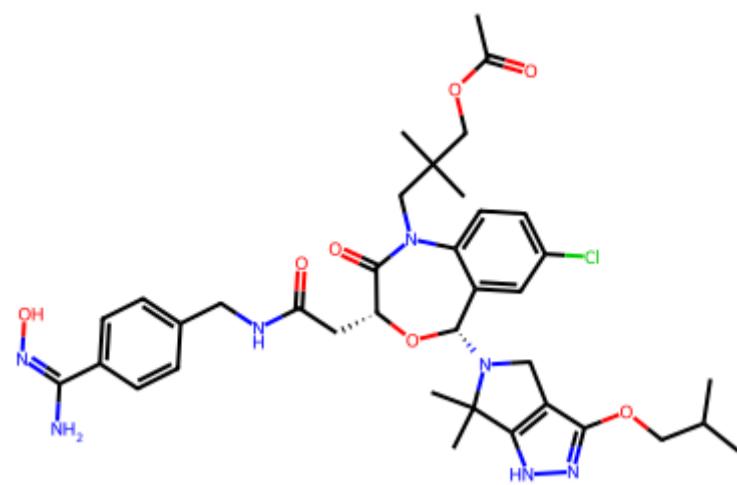
Task	Score	Change	Rel. Improvement	% Change
AMES ✗	0.683061	+0.263441	-0.6278	+62.78%
BBBP ✗	0.000186	-0.999799	-0.9998	-99.98%
CYP3A4 ✓	0.001016	-0.034972	+0.9718	-97.18%
DILI ✗	0.619393	+0.017067	-0.0283	+2.83%
HIA ✓	0.987780	+0.007443	+0.0076	+0.76%
PGP ✓	0.592538	-0.069869	+0.1055	-10.55%

Optimization Steps:

DETAILS PLACEHOLDER 2

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) ↓

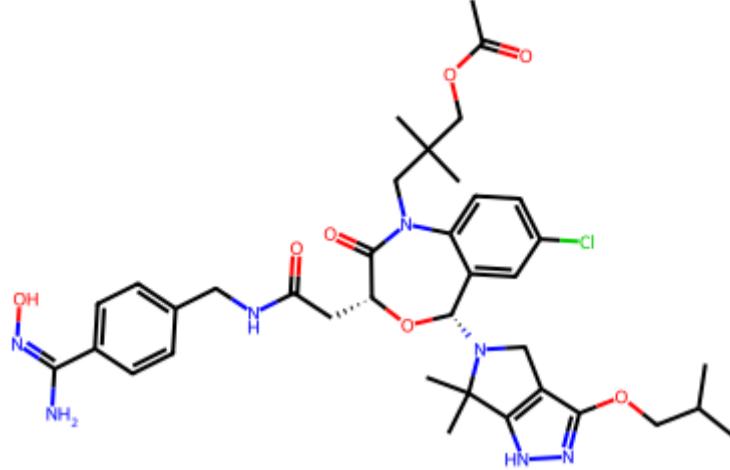
Block Changes: 5 (+2, -3)

DILI Score: 0.602326 → 0.416277 (-0.186049)

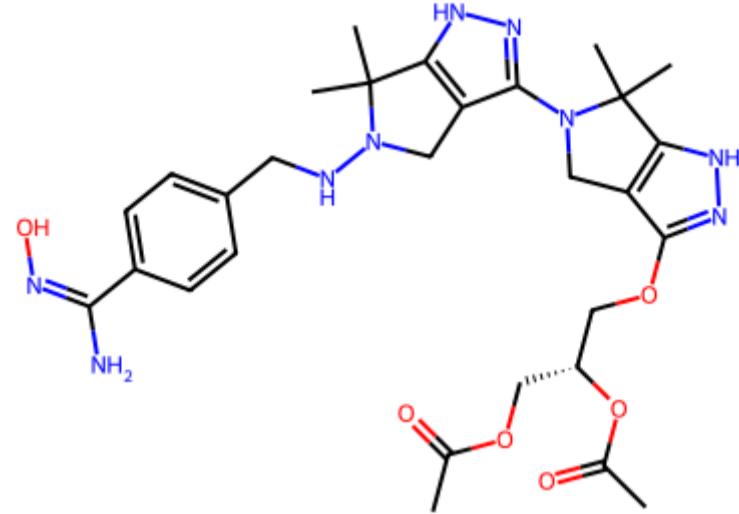
DETAILS PLACEHOLDER 3

► 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`



****After (Step 2)**** `CC(=O)OC[C@H]
 (COc1n[nH]c2c1CN(c1n[nH]c3c1CN(NCc1ccc(/C(N)=N\O)cc1)C4(C)C)c3(C)C)C2(C)C)OC(C)=O`



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

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

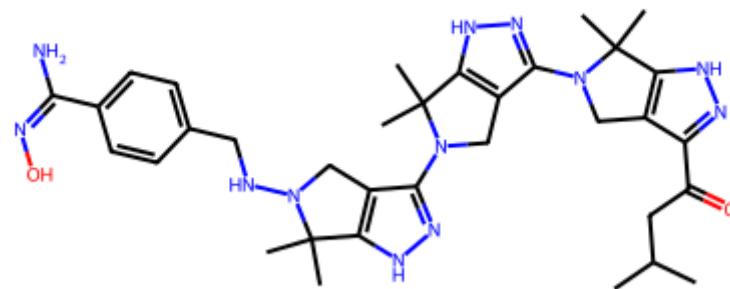
► All ADMET Scores

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

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) X

Number of Blocks: 4 (+0) →

Block Changes: 2 (+1, -1)

CYP3A4 Score: 0.020237 → 0.001016 (-0.019221)

DETAILS PLACEHOLDER 7

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%	X Declined
BBBP	↑ higher	0.999985	0.000186	-0.999799	-0.9998	-99.98%	X 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%	X 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

Slide 13: Danuglipron (Pfizer)

Initial Task: DILI

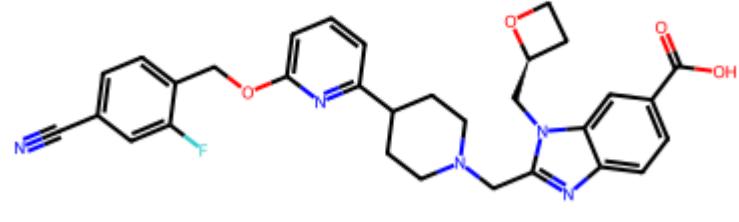
SMILES: C1=CC(=NC(=C1)OCC2=CC=C(C=C2F)C#N)C3CCN(CC3)CC4=NC5=CC=C(C=C5N4C[C@H]6CCO6)C(=O)O

Danuglipron (Pfizer) - Optimization Results

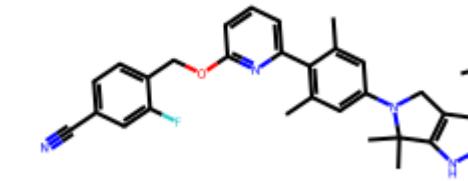
Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule



Final Optimized `Cc1cc(N2Cc3c(N4Cc5c(-c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)n[n]c1cccc(OCc2ccc(C#N)cc2F)n1`



QED (Drug-likeness): 0.3107 **Number of Blocks:** 4

► Show ADMET Scores

Task	Score
AMES	0.755845
BBBP	0.000238
CYP3A4	0.009860
DILI	0.804817
HIA	0.993762
PGP	0.573991

QED (Drug-likeness): 0.1314 (-0.1793) X **

Block Changes:** 16

► Show ADMET Scores

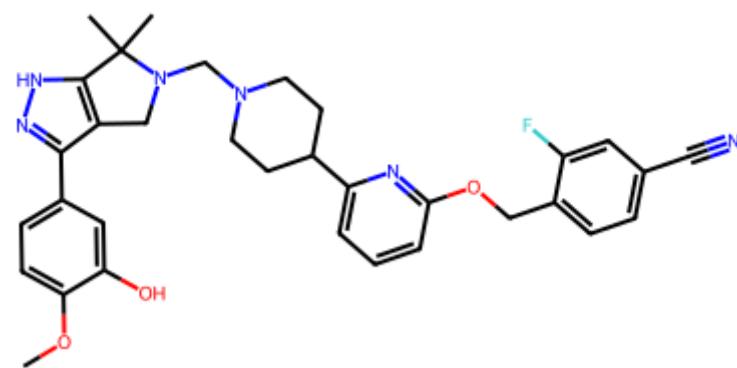
Task	Score	Change
AMES ✓	0.648178	-0.107668
BBBP ✓	0.000290	+0.000053
CYP3A4 ✓	0.001107	-0.008752
DILI ✓	0.550500	-0.254317
HIA X	0.966419	-0.027343
PGP ✓	0.571472	-0.002519

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

C0c1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(OCc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc10



QED: 0.2738 (-0.0369) X

Number of Blocks: 4 (+0) →

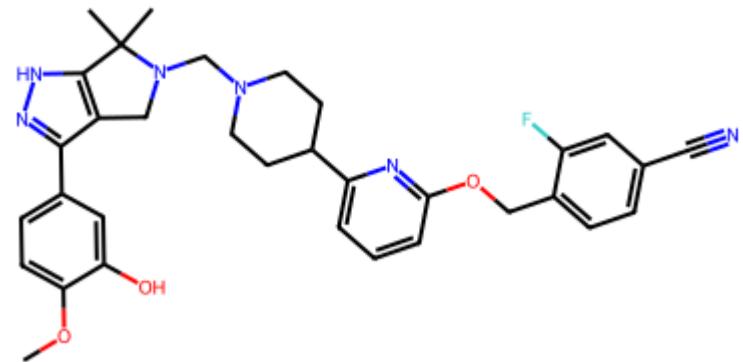
Block Changes: 6 (+3, -3)

DILI Score: 0.804817 → 0.721803 (-0.083013)

DETAILS *PLACEHOLDER 3*

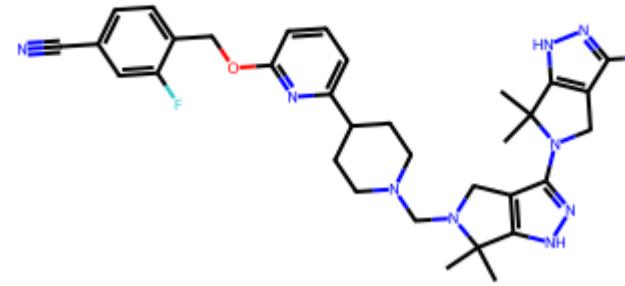
► Step 2: PGP (-0.0441 ↓) ✓

Before (Step 1) `COc1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(OCCc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc1O`



After (Step 2)

`CC1(C)c2[nH]nc(N3Cc4c(NC56CC7CC(CC(C7)C5)C6)n[nH]c4C3(C)C)c2CN1CN1`



QED: 0.2738 **Number of Blocks:** 4

► All ADMET Scores

Task	Score	Direction
AMES	0.713190	↓ lower
BBBP	0.000162	↑ higher
CYP3A4	0.018157	↓ lower
DILI	0.721803	↓ lower
HIA	0.971368	↑ higher
PGP	0.598865	↓ lower

QED: 0.1586 (-0.1151) ✗

Number of Blocks: 5 (+1) ↑

Block Changes: 7 (+4, -3)

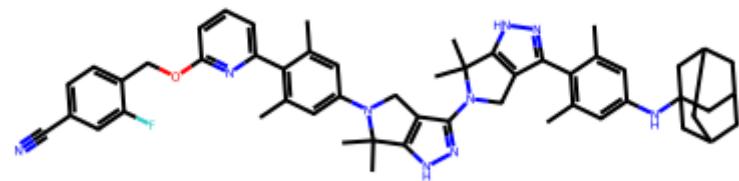
PGP Score: 0.598865 → 0.554803 (-0.044061)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

Cc1cc(N2Cc3c(N4Cc5c(-c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1-c1cccc(OCC2CCC(C#N)CC2F)n1



QED: 0.1314 (-0.0272) ✗

Number of Blocks: 7 (+2) ↑

Block Changes: 3 (+2, -1)

PGP Score: 0.554803 → 0.571472 (+0.016669)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: DILI ✓

Original	New	Change
0.804817	0.721803	-0.083013 ↓

C0c1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(0Cc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc10

Step 2: PGP ✓

Original	New	Change
0.598865	0.554803	-0.044061 ↓

CC1(C)c2[nH]nc(N3Cc4c(NC56CC7CC(CC(C7)C5)C6)n[nH]c4C3(C)C)c2CN1CN1CCC(c2cccc(0Cc3ccc(C#N)cc3F)n2)CC1

Step 3: PGP !

Original	New	Change
0.554803	0.571472	+0.016669 ↓

Cc1cc(N2Cc3c(N4Cc5c(-c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1-c1cccc(0Cc2ccc(C#N)cc2F)n1

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.755845	0.648178	-0.107668	+0.1424	-14.24%	✓ Improved
BBBP	↑ higher	0.000238	0.000290	+0.000053	+0.2221	+22.21%	✓ Improved
CYP3A4	↓ lower	0.009860	0.001107	-0.008752	+0.8877	-88.77%	✓ Improved
DILI	↓ lower	0.804817	0.550500	-0.254317	+0.3160	-31.60%	✓ Improved
HIA	↑ higher	0.993762	0.966419	-0.027343	-0.0275	-2.75%	✗ Declined
PGP	↓ lower	0.573991	0.571472	-0.002519	+0.0044	-0.44%	✓ Improved

Improved: 5/6 (83.3%) | **Molecules:** 385 | **Paths:** 5311

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠️ Below threshold: 4

Task	Score	Threshold	Gap
BBBP	0.0003	↑ 0.5	0.4997
AMES	0.6482	↓ 0.3	0.3482
PGP	0.5715	↓ 0.3	0.2715
DILI	0.5505	↓ 0.4	0.1505

✓ Passing: 2

Task	Score	Threshold
CYP3A4	0.0011	↓ 0.55
HIA	0.9664	↑ 0.2

Slide 14: Rosiglitazone

Initial Task: BBBP

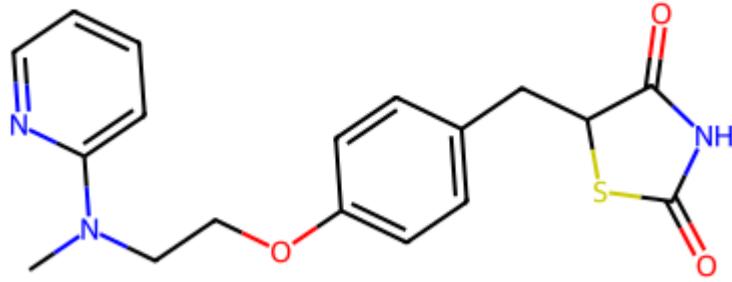
SMILES: CN(CCOC1=CC=C(C=C1)CC2C(=O)NC(=O)S2)C3=CC=CC=N3

Rosiglitazone - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule

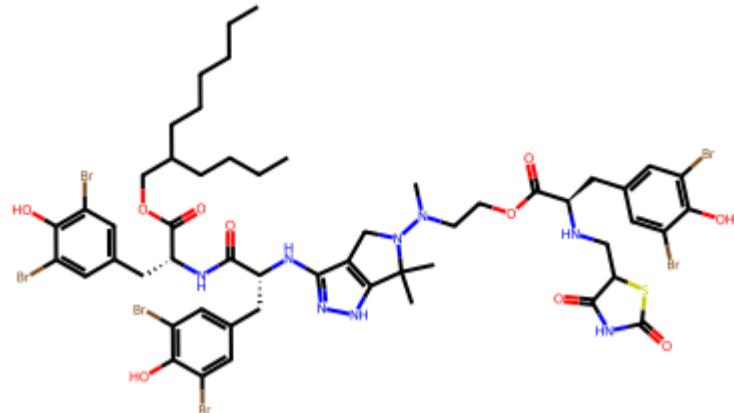
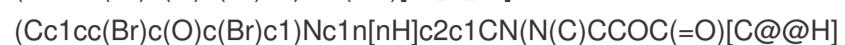
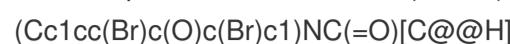


QED (Drug-likeness): 0.8209 **Number of Blocks:** 4

► Show ADMET Scores

Task	Score
AMES	0.408545
BBBP	0.646056
CYP3A4	0.080225
DILI	0.804278
HIA	0.998374
PGP	0.538867

Final Optimized `CCCCCCC(CCCC)COC(=O)[C@@H]



QED (Drug-likeness): 0.0186 (-0.8023) ✗ **Number of Blocks:** 6 (+2) ↑

Total Block Changes: 15

► Show ADMET Scores

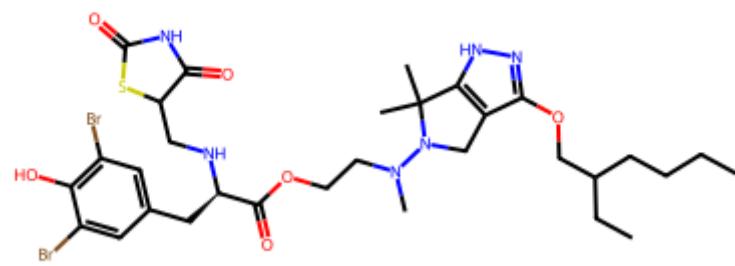
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.155246	-0.253299	+0.6200	-62.00%
BBBP ✓	1.000000	+0.353944	+0.5479	+54.79%
CYP3A4 ✓	0.000001	-0.080224	+1.0000	-100.00%
DILI ✓	0.306504	-0.497774	+0.6189	-61.89%
HIA ✓	1.000000	+0.001626	+0.0016	+0.16%
PGP ✗	0.882034	+0.343167	-0.6368	+63.68%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CCCCC(CC)COc1n[nH]c2c1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C



QED: 0.1564 (-0.6645) X

Number of Blocks: 4 (+0)

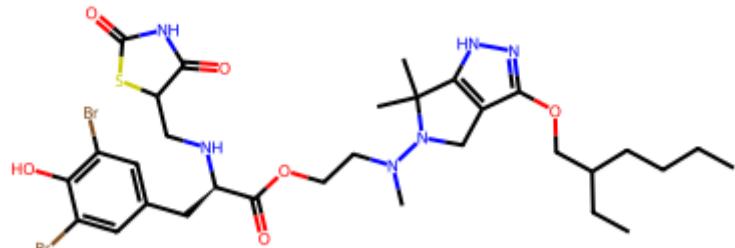
Block Changes: 8 (+4, -4)

BBBP Score: 0.646056 → 0.000386 (-0.645670)

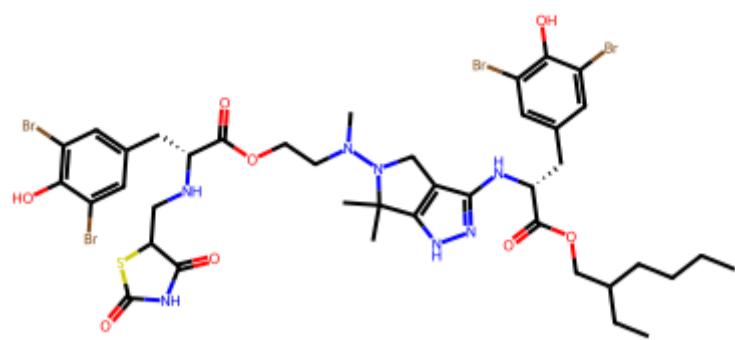
DETAILS *PLACEHOLDER 3*

► Step 2: AMES (-0.0882 ↓) ✓

****Before (Step 1)**** `CCCCC(CC)COc1n[nH]c2c1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C`



****After (Step 2)**** `CCCCC(CC)COC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C`



****QED:**** 0.1564 ****Number of Blocks:**** 4

► All ADMET Scores

Task	Score	Direction
AMES	0.587563	↓ lower
BBBP	0.000386	↑ higher
CYP3A4	0.000278	↓ lower
DILI	0.498078	↓ lower
HIA	0.999383	↑ higher
PGP	0.817270	↓ lower

QED: 0.0569 (-0.0995) X

Number of Blocks: 5 (+1) ↑

Block Changes: 5 (+3, -2)

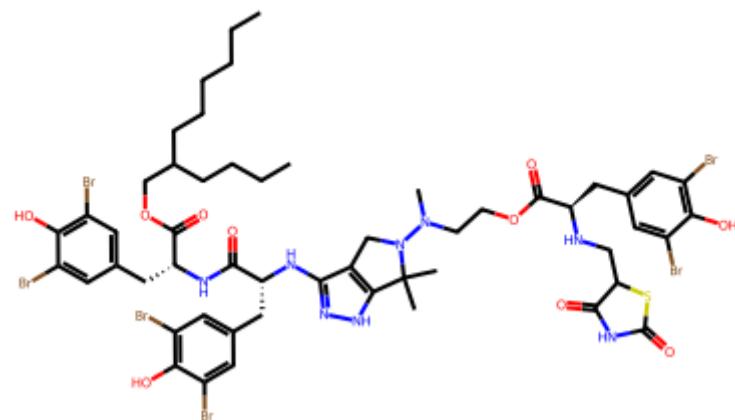
AMES Score: 0.587563 → 0.499352 (-0.088211)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CCCCCCC(CCCC)COC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C



QED: 0.0186 (-0.0383) ✗

Number of Blocks: 6 (+1) ↑

Block Changes: 2 (+1, -1)

CYP3A4 Score: 0.000004 → 0.000001 (-0.000004)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: BBBP ⚠

Original	New	Change
0.646056	0.000386	-0.645670 ↑

```
CCCCC(CC)COC1N[nH]C2Cc1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C
```

Step 2: AMES ✓

Original	New	Change
0.587563	0.499352	-0.088211 ↓

```
CCCCC(CC)COC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2Cc1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C
```

Step 3: CYP3A4 ✓

Original	New	Change
0.000004	0.000001	-0.000004 ↓

```
CCCCCC(CCCC)COC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2Cc1CN(N(C)CCOC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCC1SC(=O)NC1=O)C2(C)C
```

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.408545	0.155246	-0.253299	+0.6200	-62.00%	✓ Improved
BBBP	↑ higher	0.646056	1.000000	+0.353944	+0.5479	+54.79%	✓ Improved
CYP3A4	↓ lower	0.080225	0.000001	-0.080224	+1.0000	-100.00%	✓ Improved
DILI	↓ lower	0.804278	0.306504	-0.497774	+0.6189	-61.89%	✓ Improved
HIA	↑ higher	0.998374	1.000000	+0.001626	+0.0016	+0.16%	✓ Improved
PGP	↓ lower	0.538867	0.882034	+0.343167	-0.6368	+63.68%	✗ Declined

Improved: 5/6 (83.3%) | **Molecules:** 373 | **Paths:** 7117

🔍 Safety Threshold Analysis

Status: 5/6 meet thresholds

⚠️ Below threshold: 1

Task	Score	Threshold	Gap
PGP	0.8820	↓ 0.3	0.5820

✓ Passing: 5

Task	Score	Threshold
AMES	0.1552	↓ 0.3
BBBP	1.0000	↑ 0.5
CYP3A4	0.0000	↓ 0.55
DILI	0.3065	↓ 0.4
HIA	1.0000	↑ 0.2

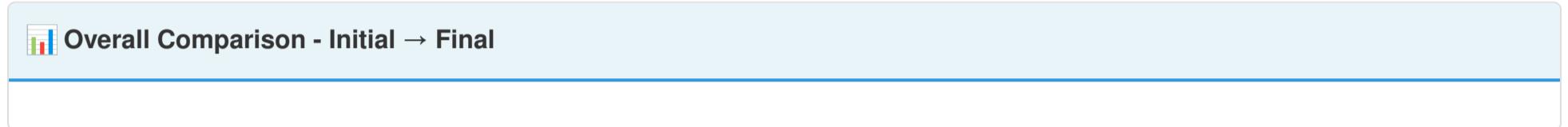
Slide 15: Paclitaxel / other taxanes

Initial Task: BBBP

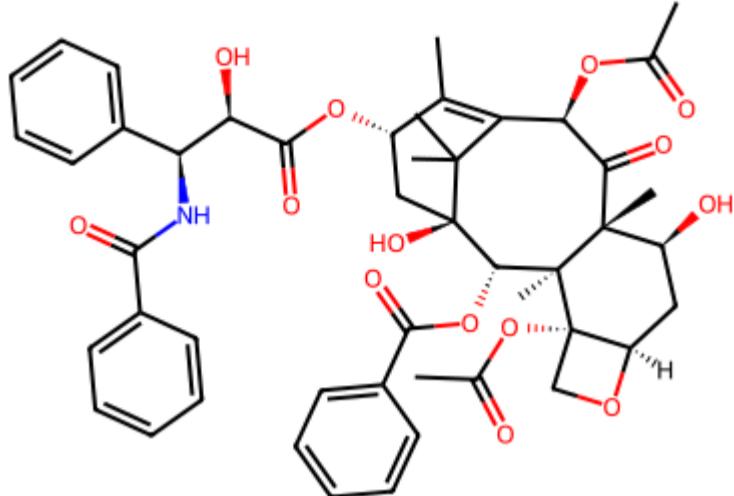
SMILES: CC1=C2[C@H](C(=O)[C@]3(C)[C@H](C[C@@H]4[C@@](C04)([C@@]3(C)[C@H]([C@](C[C@H]1OC(=O)[C@@H]([C@H](C5=CC=CC=C5)NC(=O)C6=CC=CC=C6)O)(C2(C)C)O)OC(=O)C7=CC=CC=C7)OC(=O)C)O)OC(=O)C

Paclitaxel / other taxanes - Optimization Results

Optimization Path



Initial Molecule `CC1=C2[C@H](C(=O)[C@]3(C)[C@H](C[C@@H]4[C@@](CO4)([C@@]3(C)[C@H](C[C@@H](COC(=O)C6=CC=CC=C6)OC(=O)C7=CC=CC=C7)OC(=O)C)OC(=O)C`

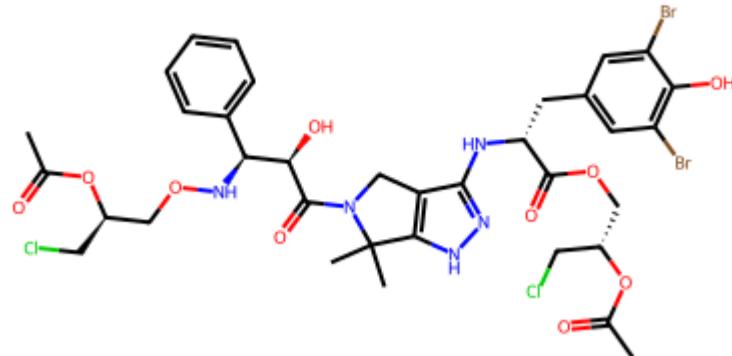


QED (Drug-likeness): 0.1280 **Number of Blocks:** 4

► Show ADMET Scores

Task	Score
AMES	0.766300
BBBP	0.000153
CYP3A4	0.009794
DILI	0.767576
HIA	0.750817
PGP	0.573305

Final Optimized `CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)O[C@H]1C[C@@]2(O)[C@@H](ON[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)OC(=O)n[nH]c2C1(C)C`



QED (Drug-likeness): 0.0507 (-0.0773) X **Number of Blocks:** 5 (+1) ↑
Total Block Changes: 18

► Show ADMET Scores

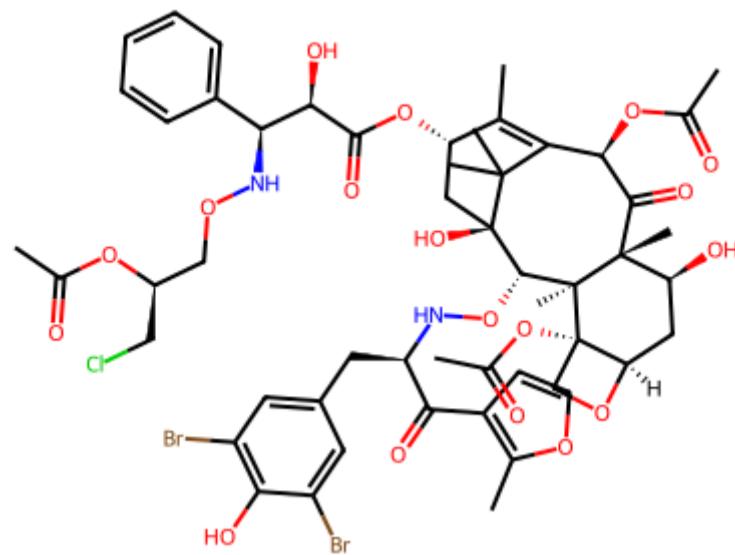
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.233688	-0.532611	+0.6950	-69.50%
BBBP ✓	1.000000	+0.999847	+6552.6969	+655269.69%
CYP3A4 ✓	0.001079	-0.008715	+0.8899	-88.99%
DILI ✓	0.459665	-0.307911	+0.4011	-40.11%
HIA ✓	0.999811	+0.248993	+0.3316	+33.16%
PGP X	0.862906	+0.289601	-0.5051	+50.51%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)O[C@H]1C[C@@]2(O)[C@@H](ON[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)OC(=O)n[nH]c2C1(C)C`



QED: 0.0210 (-0.1070) X

Number of Blocks: 4 (+0) →

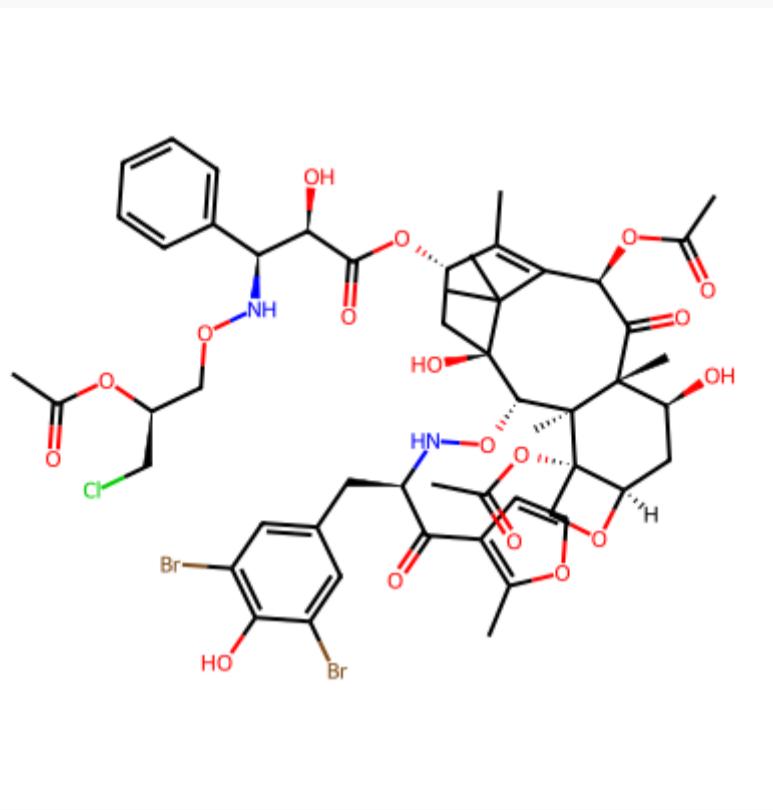
Block Changes: 7 (+4, -3)

BBBP Score: 0.000153 → 0.000113 (-0.000040)

DETAILS PLACEHOLDER 3

► Step 2: AMES (-0.1010 ↓) ✓

Before (Step 1) `CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)O[C@H]1C[C@@]2(O)[C@@H](ON[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)c3ccoc3C)[C@]3(C)[C@]4(OC(C)=O)CO[C@@H]4C[C@H](O)[C@@]3(C)C(=O)[C@H](OC(C)=O)C(=C1C)C2(C)C`



QED: 0.0210 **Number of Blocks:** 4

► All ADMET Scores

Task	Score	Direction
AMES	0.677737	↓ lower
BBBP	0.000113	↑ higher
CYP3A4	0.004253	↓ lower
DILI	0.616722	↓ lower
HIA	0.943954	↑ higher
PGP	0.731751	↓ lower

After (Step 2) `CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)N1Cc2c(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)c3ccoc3C)CC3SC(=O)NC3=O)n[nH]c2C1(C)C`



QED: 0.0672 (+0.0462) ✓

Number of Blocks: 5 (+1) ↑

Block Changes: 3 (+2, -1)

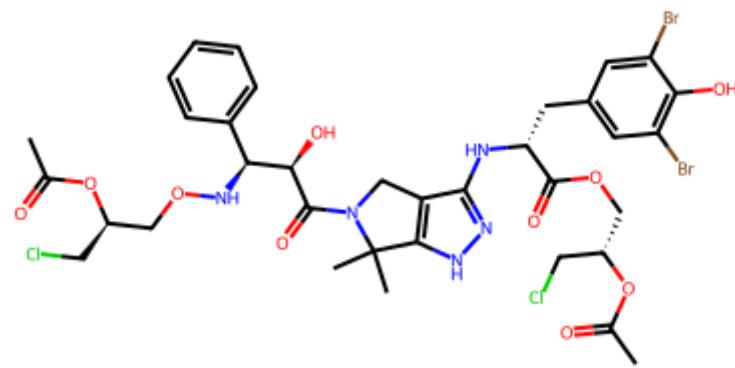
AMES Score: 0.677737 → 0.576776 (-0.100962)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)N1Cc2c(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)c3ccoc3C)CC3SC(=O)NC3=O)n[nH]c2C1(C)C



QED: 0.0507 (-0.0165) ✗

Number of Blocks: 5 (+0) ➔

Block Changes: 8 (+4, -4)

AMES Score: 0.576776 → 0.233688 (-0.343087)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: BBBP ⚠

Original	New	Change
0.000153	0.000113	-0.000040 ↑

CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)O[C@H]1C[C@@]2(O)[C@@H](ON[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)c3ccoc3C)[C@]3(C)[C@]4(O

Step 2: AMES ✓

Original	New	Change
0.677737	0.576776	-0.100962 ↓

CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)N1Cc2c(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)CC3SC(=O)NC3=O)n[nH]c2C1(C)C

Step 3: AMES ✓

Original	New	Change
0.576776	0.233688	-0.343087 ↓

CC(=O)O[C@H](CCl)CON[C@@H](c1ccccc1)[C@@H](O)C(=O)N1Cc2c(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)OC[C@@H](CCl)OC(C)=O)n[nH]c2C1(C)C

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.766300	0.233688	-0.532611	+0.6950	-69.50%	✓ Improved
BBBP	↑ higher	0.000153	1.000000	+0.999847	+6552.6969	+655269.69%	✓ Improved
CYP3A4	↓ lower	0.009794	0.001079	-0.008715	+0.8899	-88.99%	✓ Improved
DILI	↓ lower	0.767576	0.459665	-0.307911	+0.4011	-40.11%	✓ Improved
HIA	↑ higher	0.750817	0.999811	+0.248993	+0.3316	+33.16%	✓ Improved
PGP	↓ lower	0.573305	0.862906	+0.289601	-0.5051	+50.51%	✗ Declined

Improved: 5/6 (83.3%) | **Molecules:** 187 | **Paths:** 2468

🔍 Safety Threshold Analysis

Status: 4/6 meet thresholds

⚠️ Below threshold: 2

Task	Score	Threshold	Gap
PGP	0.8629	↓ 0.3	0.5629
DILI	0.4597	↓ 0.4	0.0597

✓ Passing: 4

Task	Score	Threshold
AMES	0.2337	↓ 0.3
BBBP	1.0000	↑ 0.5
CYP3A4	0.0011	↓ 0.55
HIA	0.9998	↑ 0.2

Slide 16: Mibepradil (Posicor)

Initial Task: CYP3A4

SMILES: CC(C)[C@H]1C2=CC=C(C=C2CC[C@H]1CCN(C)CCCC3=NC4=C(C=CC=C4)N3)OC(=O)COC)F

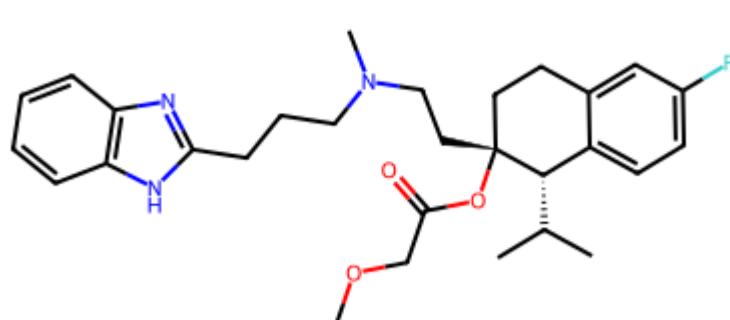
Mibepradil (Posicor) - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule `CC(C)

[C@H]1C2=CC=C(C=C2CC[C@@]1(CCN(C)CCCC3=NC4=C(C=CC=C4)N3)OC(=O)COC)F`



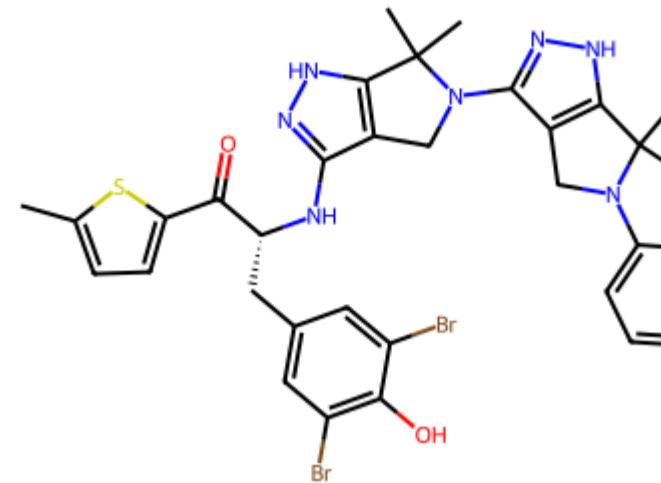
QED (Drug-likeness): 0.3672 **Number of Blocks:** 3

► Show ADMET Scores

Task	Score
AMES	0.456651
BBBP	0.999996
CYP3A4	0.020786
DILI	0.675483
HIA	0.994189
PGP	0.700888

Final Optimized `Cc1ccc(C(=O)[C@@H](C)c2cc(Br)c(O)c(Br)c2)Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)

(C)c2cc(C#N)c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)



QED (Drug-likeness): 0.1154 (-0.2518) ✗ **Number of Blocks:** 5

Changes:** 11

► Show ADMET Scores

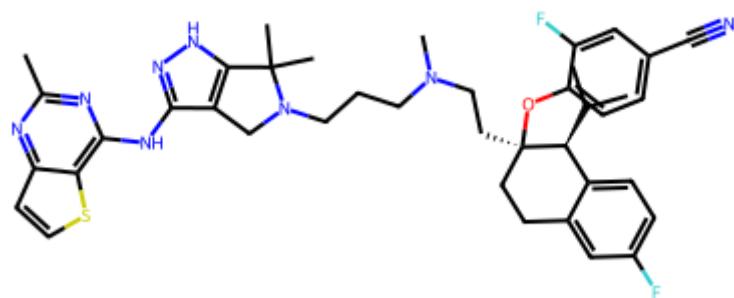
Task	Score	Change	Rel. Improvement
AMES ✗	0.665578	+0.208928	-0.4575
BBBP ✗	0.000031	-0.999965	-1.0000
CYP3A4 ✓	0.000141	-0.020645	+0.9932
DILI ✓	0.393913	-0.281570	+0.4168
HIA ✓	0.999665	+0.005475	+0.0055
PGP ✗	0.747508	+0.046620	-0.0665

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

Cc1nc(Nc2n[nH]c3c2CN(cccN(C)CC[C@H]2(OC4CCC(C#N)CC4F)CCc4cc(F)ccc4[C@H]2C(C)C)C3(C)C)c2scCc2n1



QED: 0.1319 (-0.2353) X

Number of Blocks: 3 (+0)

Block Changes: 6 (+3, -3)

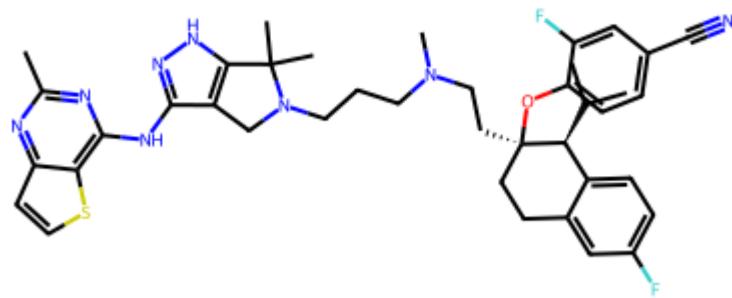
CYP3A4 Score: 0.020786 → 0.012962 (-0.007824)

DETAILS PLACEHOLDER 3

► Step 2: AMES (+0.0112 ↓)

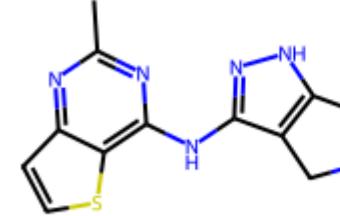
****Before (Step 1)****

`Cc1nc(Nc2n[nH]c3c2CN(CCCN(C)CC[C@@]2(Oc4ccc(C#N)cc4F)CCc4cc(F)ccc4[C@@H]2C(C)C)C3(C)C)c2sccc2n1`



****After (Step 2)****

`Cc1nc(Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)s1`



****QED:**** 0.1319 ****Number of Blocks:**** 3

QED: 0.2579 (+0.1260) ✓

Number of Blocks: 4 (+1) ↑

Block Changes: 2 (+1, -1)

AMES Score: 0.735399 → 0.746586 (+0.01117)

DETAILS PLACEHOLDER 5

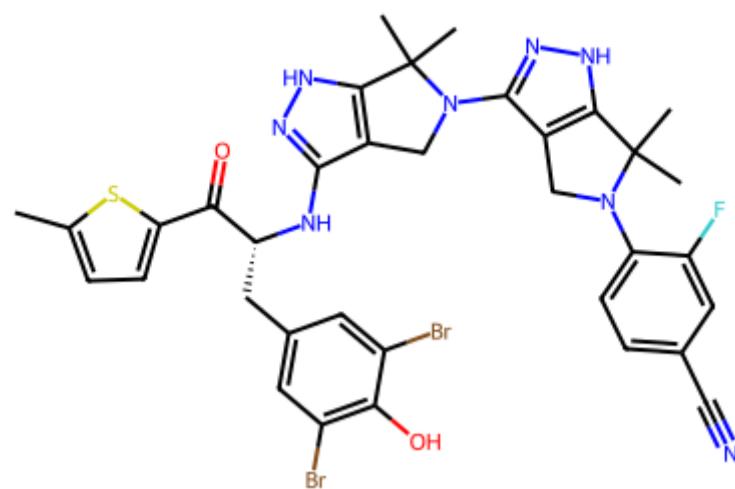
► All ADMET Scores

Task	Score	Direction
AMES	0.735399	↓ lower
BBBP	0.000129	↑ higher
CYP3A4	0.012962	↓ lower
DILI	0.669453	↓ lower
HIA	0.865108	↑ higher
PGP	0.575484	↓ lower

DETAILS PLACEHOLDER 6

After (Step 3)

Cc1ccc(C(=O)[C@H](Cc2cc(Br)c(O)c(Br)c2)Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)s1



QED: 0.1154 (-0.1425) X

Number of Blocks: 5 (+1) ↑

Block Changes: 3 (+2, -1)

CYP3A4 Score: 0.000895 → 0.000141 (-0.000755)

DETAILS PLACEHOLDER 7

Step Details

Step 1: CYP3A4 ✓

Original	New	Change
0.020786	0.012962	-0.007824 ↓

```
Cc1nc(Nc2n[nH]c3c2CN(CCCN(C)CC[C@H]2(Oc4ccc(C#N)cc4F)CCc4cc(F)ccc4[C@H]2C(C)C)C3(C)C)c2scCc2n1
```

Step 2: AMES ⚠

Original	New	Change
0.735399	0.746586	+0.011187 ↓

```
Cc1nc(Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)c2scCc2n1
```

Step 3: CYP3A4 ✓

Original	New	Change
0.000895	0.000141	-0.000755 ↓

```
Cc1ccc(C(=O)[C@H](Cc2cc(Br)c(O)c(Br)c2)Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)s1
```

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.456651	0.665578	+0.208928	-0.4575	+45.75%	✗ Declined
BBBP	↑ higher	0.999996	0.000031	-0.999965	-1.0000	-100.00%	✗ Declined
CYP3A4	↓ lower	0.020786	0.000141	-0.020645	+0.9932	-99.32%	✓ Improved
DILI	↓ lower	0.675483	0.393913	-0.281570	+0.4168	-41.68%	✓ Improved
HIA	↑ higher	0.994189	0.999665	+0.005475	+0.0055	+0.55%	✓ Improved
PGP	↓ lower	0.700888	0.747508	+0.046620	-0.0665	+6.65%	✗ Declined

Improved: 3/6 (50.0%) | **Molecules:** 283 | **Paths:** 5578

🔍 Safety Threshold Analysis

Status: 3/6 meet thresholds

⚠️ **Below threshold:** 3

Task	Score	Threshold	Gap
BBBP	0.0000	↑ 0.5	0.5000
PGP	0.7475	↓ 0.3	0.4475
AMES	0.6656	↓ 0.3	0.3656

✓ **Passing:** 3

Task	Score	Threshold
CYP3A4	0.0001	↓ 0.55
DILI	0.3939	↓ 0.4
HIA	0.9997	↑ 0.2

Slide 17: Nefazodone (Serzone)

Initial Task: CYP3A4

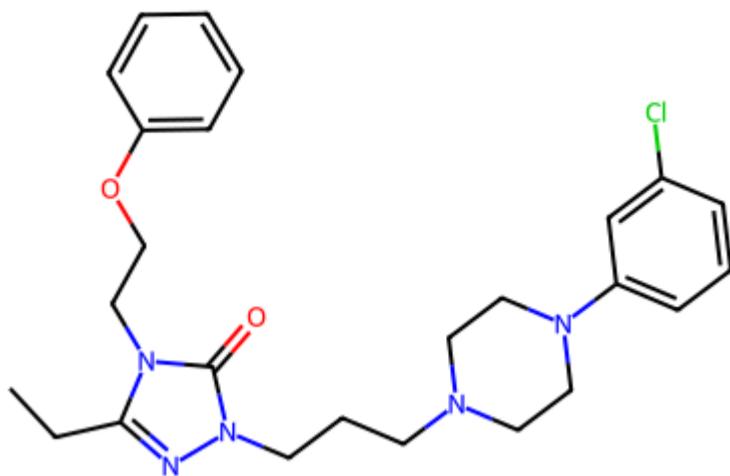
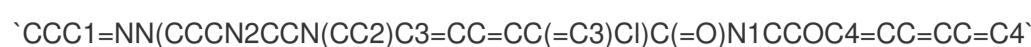
SMILES: CCC1=NN(CCCN2CCN(CC2)C3=CC=CC(=C3)C1)C(=O)N1CCOC4=CC=CC=C4

Nefazodone (Serzone) - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule

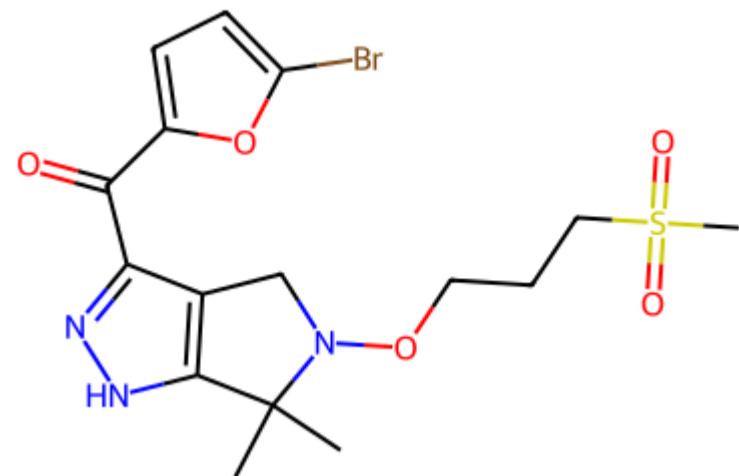


QED (Drug-likeness): 0.4542 **Number of Blocks:** 2

► Show ADMET Scores

Task	Score
AMES	0.373806
BBBP	0.988244
CYP3A4	0.024539
DILI	0.803705
HIA	0.999946
PGP	0.605185

Final Optimized `CC1(C)c2[nH]nc(C(=O)c3ccc(Br)o3)c2CN1OCCCS(C)(=O)=O`



QED (Drug-likeness): 0.5145 (+0.0603) ✓ **Number of Blocks:** 1 (-1) ↓
Total Block Changes: 9

► Show ADMET Scores

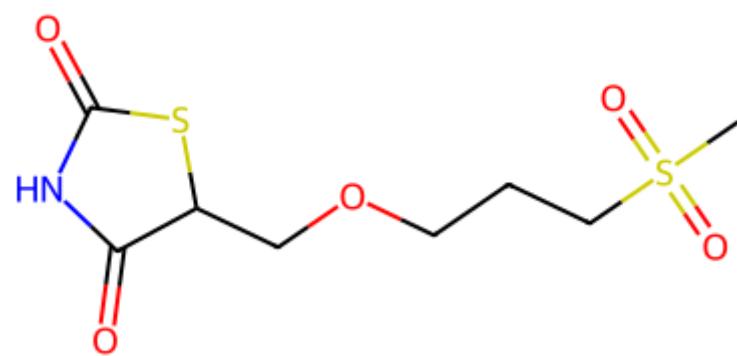
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.284693	-0.089113	+0.2384	-23.84%
BBBP ✓	1.000000	+0.011756	+0.0119	+1.19%
CYP3A4 ✓	0.000204	-0.024335	+0.9917	-99.17%
DILI ✗	0.390386	-0.413319	+0.5143	-51.43%
HIA ✗	0.999757	-0.000189	-0.0002	-0.02%
PGP ✗	0.841080	+0.235895	-0.3898	+38.98%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CS(=O)(=O)CCCOCC1SC(=O)NC1=O



QED: 0.6697 (+0.2155)

Number of Blocks: 1 (-1) ↓

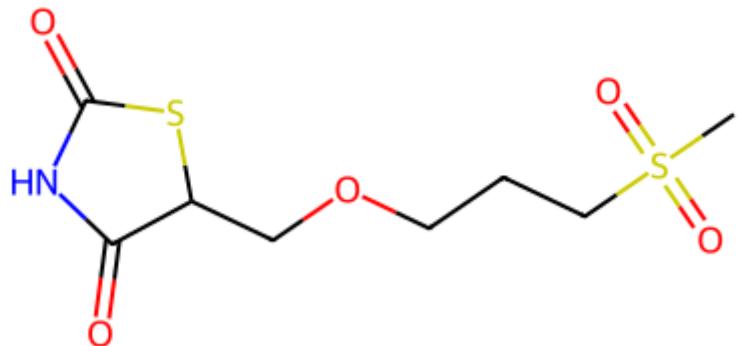
Block Changes: 3 (+1, -2)

CYP3A4 Score: 0.024539 → 0.001181 (-0.023358)

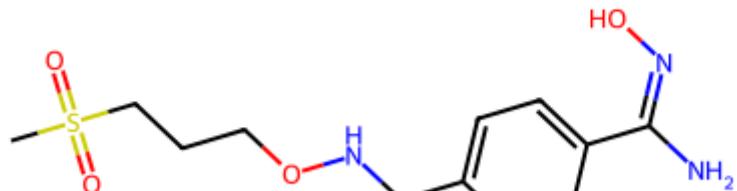
DETAILS *PLACEHOLDER 3*

► Step 2: AMES (+0.4434 ↓)

****Before (Step 1)**** `CS(=O)(=O)CCCOCC1SC(=O)NC1=O`



****After (Step 2)**** `CS(=O)(=O)CCCONCc1ccc(/C(N)=N\O)cc1`



****QED:**** 0.6697 ****Number of Blocks:**** 1

► All ADMET Scores

Task	Score	Direction
AMES	0.243126	↓ lower
BBBP	0.992016	↑ higher
CYP3A4	0.001181	↓ lower
DILI	0.562681	↓ lower
HIA	0.999992	↑ higher
PGP	0.719436	↓ lower

QED: 0.2082 (-0.4615) X

Number of Blocks: 2 (+1) ↑

Block Changes: 3 (+2, -1)

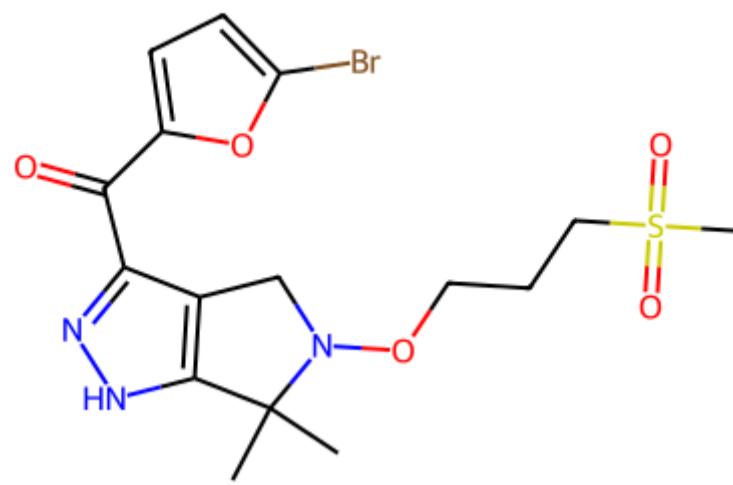
AMES Score: 0.243126 → 0.686480 (+0.443354)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC1(C)c2[nH]nc(C(=O)c3ccc(Br)o3)c2CN10CCCS(C)(=O)=O



QED: 0.5145 (+0.3062) ✓

Number of Blocks: 1 (-1) ↓

Block Changes: 3 (+1, -2)

PGP Score: 0.675115 → 0.841080 (+0.165965)

DETAILS PLACEHOLDER 7

Step Details

Step 1: CYP3A4 ✓

Original	New	Change
0.024539	0.001181	-0.023358 ↓

CS(=O)(=O)CCCOCC1SC(=O)NC1=O

Step 2: AMES ⚠

Original	New	Change
0.243126	0.686480	+0.443354 ↓

CS(=O)(=O)CCONCc1ccc(/C(N)=N\O)cc1

Step 3: PGP ⚠

Original	New	Change
0.675115	0.841080	+0.165965 ↓

CC1(C)c2[nH]nc(C(=O)c3ccc(Br)o3)c2CN1OCCCS(C)(=O)=O

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.373806	0.284693	-0.089113	+0.2384	-23.84%	✓ Improved
BBBP	↑ higher	0.988244	1.000000	+0.011756	+0.0119	+1.19%	✓ Improved
CYP3A4	↓ lower	0.024539	0.000204	-0.024335	+0.9917	-99.17%	✓ Improved
DILI	↓ lower	0.803705	0.390386	-0.413319	+0.5143	-51.43%	✓ Improved
HIA	↑ higher	0.999946	0.999757	-0.000189	-0.0002	-0.02%	✗ Declined
PGP	↓ lower	0.605185	0.841080	+0.235895	-0.3898	+38.98%	✗ Declined

Improved: 4/6 (66.7%) | **Molecules:** 301 | **Paths:** 7666

🔍 Safety Threshold Analysis

Status: 5/6 meet thresholds

⚠️ Below threshold: 1

Task	Score	Threshold	Gap
PGP	0.8411	↓ 0.3	0.5411

✓ Passing: 5

Task	Score	Threshold
AMES	0.2847	↓ 0.3
BBBP	1.0000	↑ 0.5
CYP3A4	0.0002	↓ 0.55
DILI	0.3904	↓ 0.4
HIA	0.9998	↑ 0.2

Slide 18: GSK1059615

Initial Task: HIA

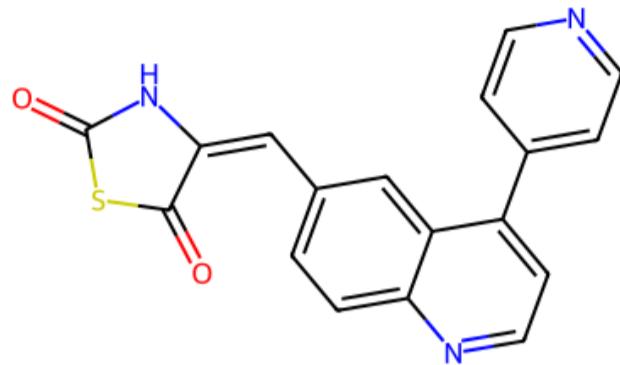
SMILES: O=C(N/C1=C/C2=CC=C3N=CC=C(C4=CC=NC=C4)C3=C2)SC1=O

GSK1059615 - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule `O=C(N/C1=C/C
C2=CC=C3N=CC=C(C4=CC=NC=C4)C3=C2)SC1=O`



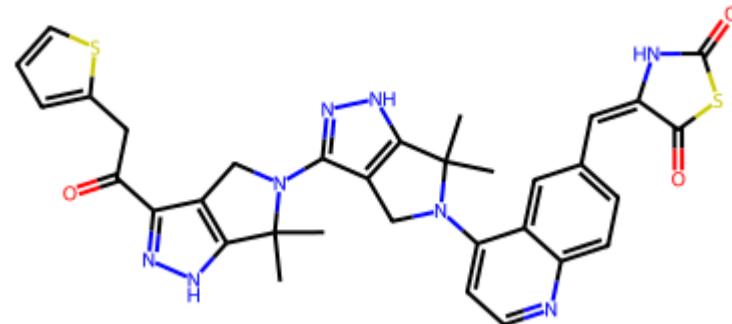
QED (Drug-likeness): 0.7253 **Number of Blocks:** 3

► Show ADMET Scores

Task	Score
AMES	0.729690
BBBP	0.001116
CYP3A4	0.017947
DILI	0.885647
HIA	0.885416
PGP	0.542834

Final Optimized

`CC1(C)c2[nH]nc(C(=O)Cc3cccs3)c2CN1c1n[nH]c2c1CN(c1ccnc3ccc(C=C4NC(=O)SC4=O)cc13)C2(C)C`



QED (Drug-likeness): 0.1491 (-0.5762) ✗ **Number of Blocks:** 5 (+2) ↑ **Total Block Changes:** 6

► Show ADMET Scores

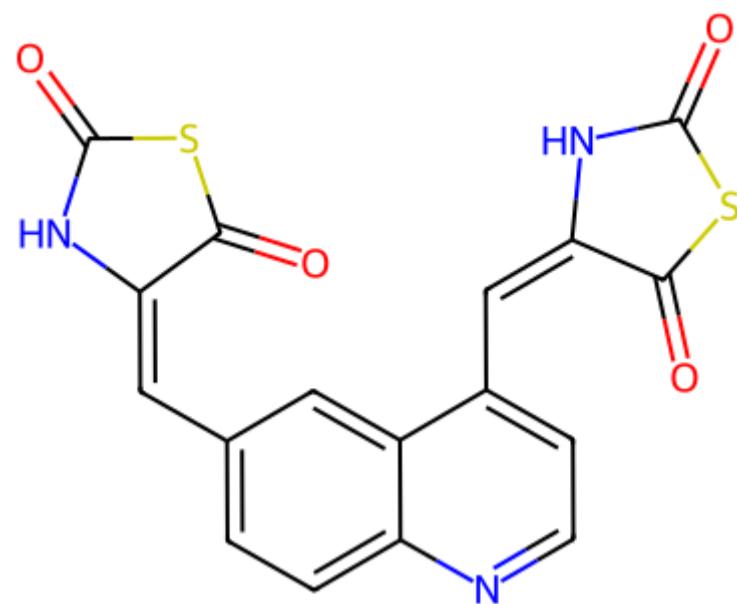
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.701288	-0.028402	+0.0389	-3.89%
BBBP ✗	0.000159	-0.000957	-0.8576	-85.76%
CYP3A4 ✓	0.003058	-0.014888	+0.8296	-82.96%
DILI ✓	0.648698	-0.236948	+0.2675	-26.75%
HIA ✓	0.974224	+0.088808	+0.1003	+10.03%
PGP ✗	0.561292	+0.018458	-0.0340	+3.40%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

0=C1NC(=Cc2cccc3nccc(C=C4NC(=O)SC4=O)c3c2)C(=O)S1



QED: 0.7683 (+0.0430)

Number of Blocks: 3 (+0)

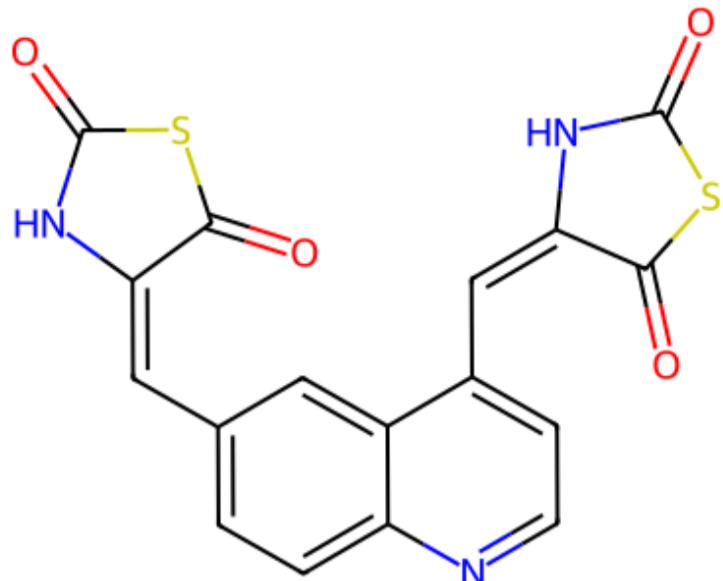
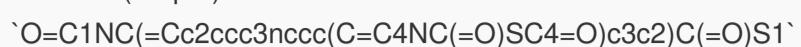
Block Changes: 3 (+1, -2)

HIA Score: 0.885416 → 0.992403 (+0.106986)

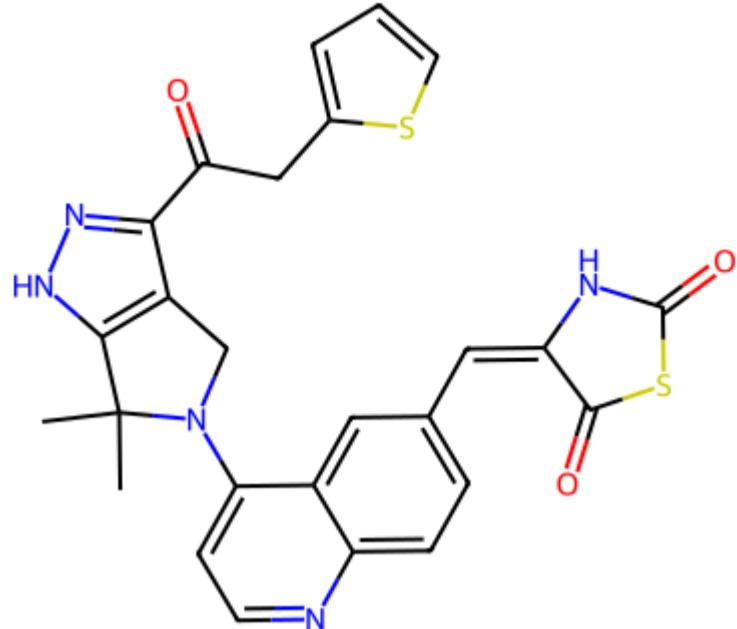
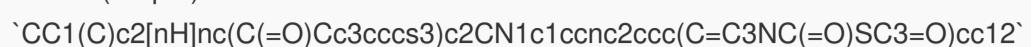
DETAILS *PLACEHOLDER 3*

► Step 2: PGP (-0.0781 ↓)

****Before (Step 1)****



****After (Step 2)****



****QED:** 0.7683 **Number of Blocks:** 3**

► All ADMET Scores

Task	Score	Direction
AMES	0.649793	↓ lower
BBBP	0.000285	↑ higher
CYP3A4	0.009557	↓ lower
DILI	0.704362	↓ lower
HIA	0.992403	↑ higher
PGP	0.675779	↓ lower

QED: 0.2837 (-0.4847) ✗

Number of Blocks: 4 (+1) ↑

Block Changes: 2 (+2, -0)

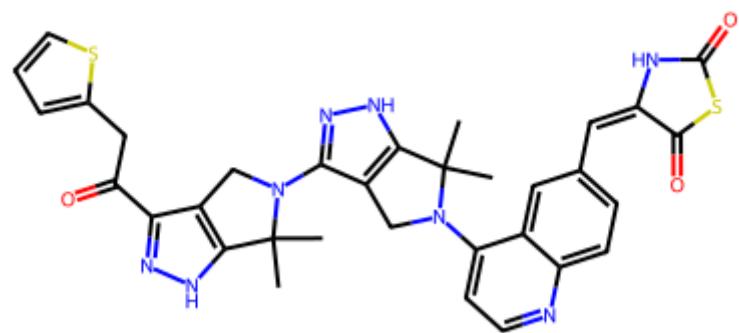
PGP Score: 0.675779 → 0.597692 (-0.078087)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)





QED: 0.1491 (-0.1346) ✗

Number of Blocks: 5 (+1) ↑

Block Changes: 1 (+1, -0)

PGP Score: 0.597692 → 0.561292 (-0.036400)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: HIA ✓

Original	New	Change
0.885416	0.992403	+0.106986 ↑

0=C1NC(=Cc2ccc3nccc(C=C4NC(=O)SC4=O)c3c2)C(=O)S1

Step 2: PGP ✓

Original	New	Change
0.675779	0.597692	-0.078087 ↓

CC1(C)c2[nH]nc(C(=O)Cc3cccs3)c2CN1c1ccnc2ccc(C=C3NC(=O)SC3=O)cc12

Step 3: PGP ✓

Original	New	Change
0.597692	0.561292	-0.036400 ↓

CC1(C)c2[nH]nc(C(=O)Cc3cccs3)c2CN1c1n[nH]c2c1CN(c1ccnc3ccc(C=C4NC(=O)SC4=O)cc13)c2(C)C

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.729690	0.701288	-0.028402	+0.0389	-3.89%	✓ Improved
BBBP	↑ higher	0.001116	0.000159	-0.000957	-0.8576	-85.76%	✗ Declined
CYP3A4	↓ lower	0.017947	0.003058	-0.014888	+0.8296	-82.96%	✓ Improved
DILI	↓ lower	0.885647	0.648698	-0.236948	+0.2675	-26.75%	✓ Improved
HIA	↑ higher	0.885416	0.974224	+0.088808	+0.1003	+10.03%	✓ Improved
PGP	↓ lower	0.542834	0.561292	+0.018458	-0.0340	+3.40%	✗ Declined

Improved: 4/6 (66.7%) | **Molecules:** 67 | **Paths:** 88

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠️ Below threshold: 4

Task	Score	Threshold	Gap
BBBP	0.0002	↑ 0.5	0.4998
AMES	0.7013	↓ 0.3	0.4013
PGP	0.5613	↓ 0.3	0.2613
DILI	0.6487	↓ 0.4	0.2487

✓ Passing: 2

Task	Score	Threshold
CYP3A4	0.0031	↓ 0.55
HIA	0.9742	↑ 0.2

Slide 19: Neflamapimod (VX-745)

Initial Task: HIA

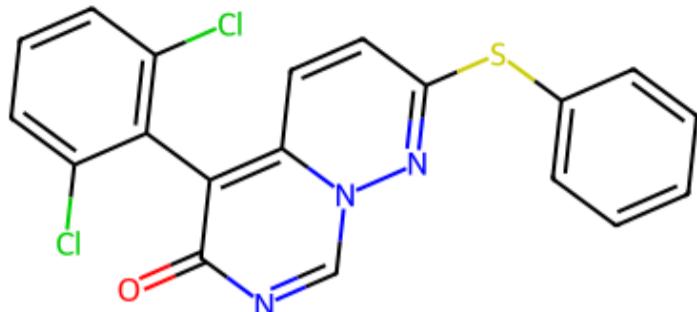
SMILES: `O=c1ncn2nc(Sc3cccc3)ccc2c1-c1c(Cl)cccc1Cl`

Neflamapimod (VX-745) - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule `O=c1ncn2nc(Sc3cccc3)ccc2c1-c1c(Cl)cccc1Cl`



QED (Drug-likeness): 0.4735 **Number of Blocks:** 2

► Show ADMET Scores

Task	Score
AMES	0.675174
BBBP	0.000046
CYP3A4	0.002328
DILI	0.771123
HIA	0.988214
PGP	0.672094

Final Optimized

`CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O`



QED (Drug-likeness): 0.3409 (-0.1326) ✗ **Number of Blocks:** 4 (+2) ↑ **Total Block Changes:** 10

► Show ADMET Scores

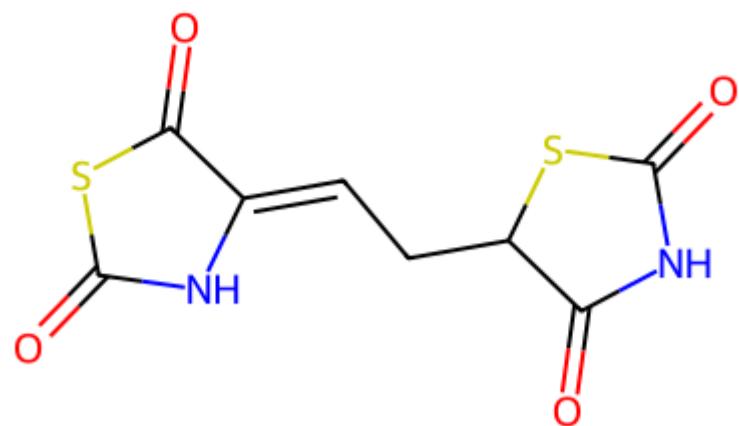
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.314901	-0.360274	+0.5336	-53.36%
BBBP ✓	0.999992	+0.999947	+21894.4005	+2189440.05%
CYP3A4 ✗	0.006490	+0.004162	-1.7876	+178.76%
DILI ✓	0.495032	-0.276091	+0.3580	-35.80%
HIA ✓	0.999245	+0.011031	+0.0112	+1.12%
PGP ✓	0.627767	-0.044327	+0.0660	-6.60%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

0=C1NC(=CCC2SC(=O)NC2=O)C(=O)S1



QED: 0.7044 (+0.2309)

Number of Blocks: 2 (+0)

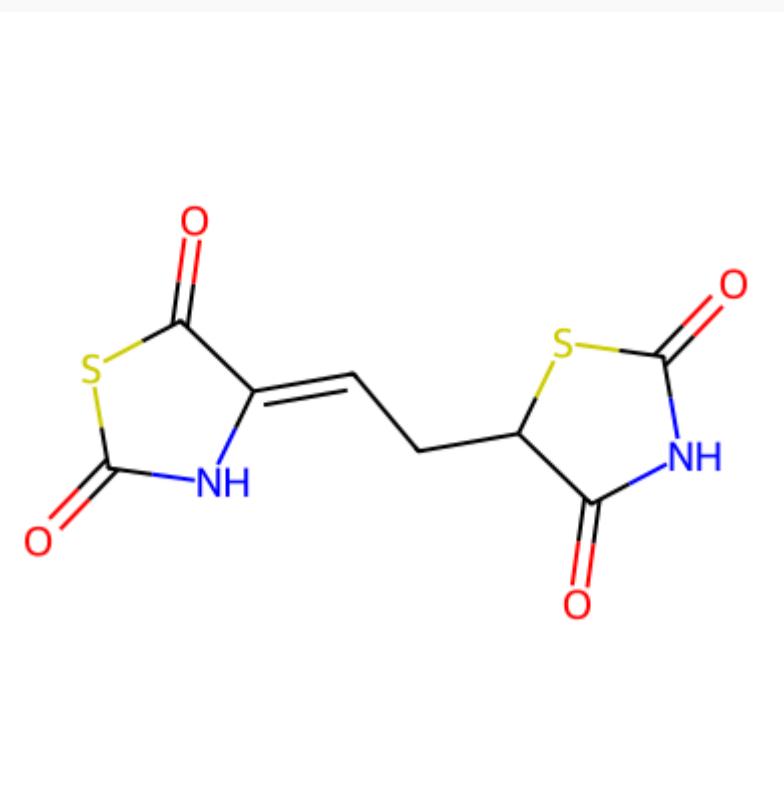
Block Changes: 4 (+2, -2)

HIA Score: 0.988214 → 1.000000 (+0.011786)

DETAILS *PLACEHOLDER 3*

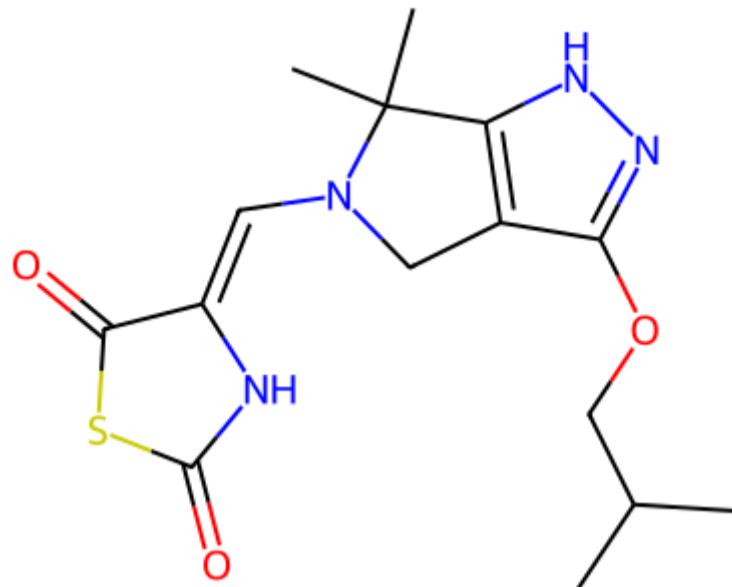
► Step 2: PGP (-0.0538 ↓)

****Before (Step 1)**** `O=C1NC(=CCC2SC(=O)NC2=O)C(=O)S1`



****After (Step 2)****

`CC(C)COc1n[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C`



****QED:**** 0.7044 ****Number of Blocks:**** 2

► All ADMET Scores

Task	Score	Direction
AMES	0.276939	↓ lower
BBBP	0.989504	↑ higher
CYP3A4	0.000312	↓ lower
DILI	0.575363	↓ lower
HIA	1.000000	↑ higher
PGP	0.675575	↓ lower

QED: 0.8206 (+0.1163)

Number of Blocks: 2 (+0)

Block Changes: 2 (+1, -1)

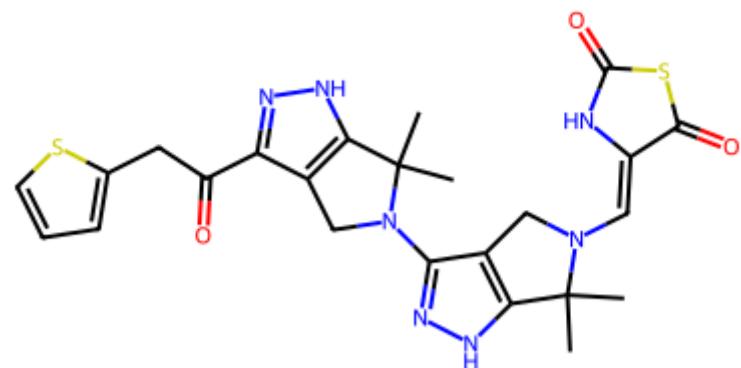
PGP Score: 0.675575 → 0.621777 (-0.053797)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O



QED: 0.3409 (-0.4797) ✗

Number of Blocks: 4 (+2) ↑

Block Changes: 4 (+3, -1)

PGP Score: 0.621777 → 0.627767 (+0.005990)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: HIA ✓

Original	New	Change
0.988214	1.000000	+0.011786 ↑

0=C1NC(=CCC2SC(=O)NC2=O)C(=O)S1

Step 2: PGP ✓

Original	New	Change
0.675575	0.621777	-0.053797 ↓

CC(C)COc1[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C

Step 3: PGP !

Original	New	Change
0.621777	0.627767	+0.005990 ↓

CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.675174	0.314901	-0.360274	+0.5336	-53.36%	✓ Improved
BBBP	↑ higher	0.000046	0.999992	+0.999947	+21894.4005	+2189440.05%	✓ Improved
CYP3A4	↓ lower	0.002328	0.006490	+0.004162	-1.7876	+178.76%	✗ Declined
DILI	↓ lower	0.771123	0.495032	-0.276091	+0.3580	-35.80%	✓ Improved
HIA	↑ higher	0.988214	0.999245	+0.011031	+0.0112	+1.12%	✓ Improved
PGP	↓ lower	0.672094	0.627767	-0.044327	+0.0660	-6.60%	✓ Improved

Improved: 5/6 (83.3%) | **Molecules:** 49 | **Paths:** 127

🔍 Safety Threshold Analysis

Status: 3/6 meet thresholds

⚠ Below threshold: 3

Task	Score	Threshold	Gap
PGP	0.6278	↓ 0.3	0.3278
DILI	0.4950	↓ 0.4	0.0950
AMES	0.3149	↓ 0.3	0.0149

✓ Passing: 3

Task	Score	Threshold
BBBP	1.0000	↑ 0.5
CYP3A4	0.0065	↓ 0.55
HIA	0.9992	↑ 0.2

Slide 20: SAR260301

Initial Task: CYP3A4

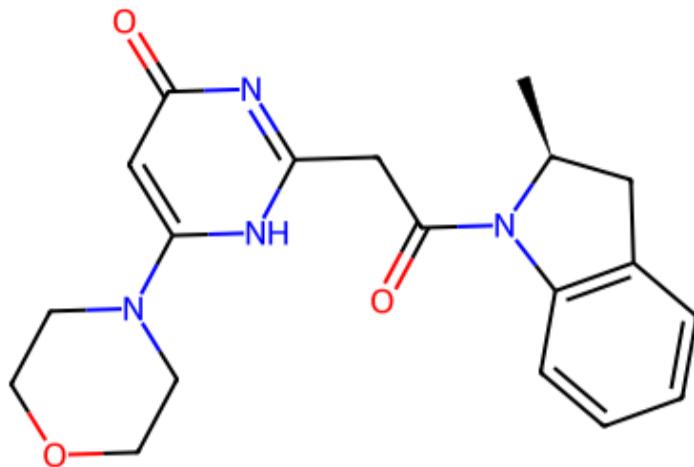
SMILES: O=C1N=C(CC(N2[C@H](C)CC3=C2C=CC=C3)=O)NC(N4CCOCC4)=C1

SAR260301 - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule `O=C1N=C(CC(N2C@@H)C(C)CC3=C2C=CC=C3)=O)NC(N4CCOCC4)=C1`



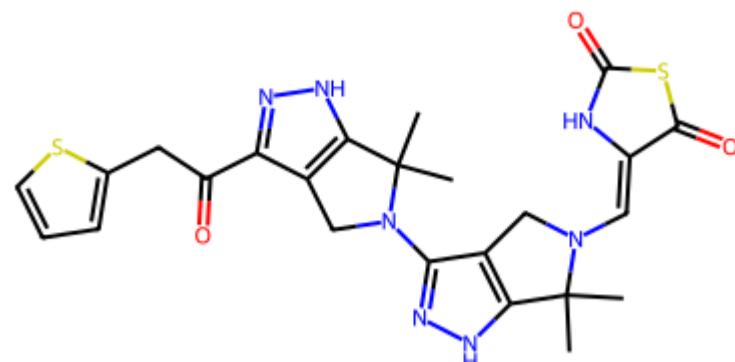
QED (Drug-likeness): 0.8939 **Number of Blocks:** 2

► Show ADMET Scores

Task	Score
AMES	0.476903
BBBP	0.999998
CYP3A4	0.038089
DILI	0.767693
HIA	0.999400
PGP	0.680634

Final Optimized

`CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O`



QED (Drug-likeness): 0.3409 (-0.5530) ✗ **Number of Blocks:** 4 (+2) ↑ **Total Block Changes:** 8

► Show ADMET Scores

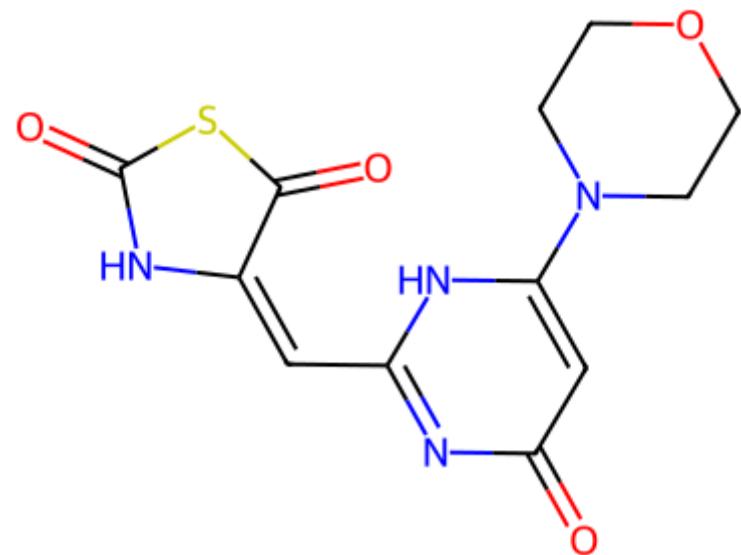
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.314900	-0.162003	+0.3397	-33.97%
BBBP ✗	0.999992	-0.000006	-0.0000	-0.00%
CYP3A4 ✓	0.006490	-0.031599	+0.8296	-82.96%
DILI ✓	0.495032	-0.272661	+0.3552	-35.52%
HIA ✗	0.999245	-0.000155	-0.0002	-0.02%
PGP ✓	0.627767	-0.052867	+0.0777	-7.77%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

0=C1NC(=Cc2nc(=O)cc(N3CCOCC3)[nH]2)C(=O)S1



QED: 0.7369 (-0.1570) X

Number of Blocks: 2 (+0) →

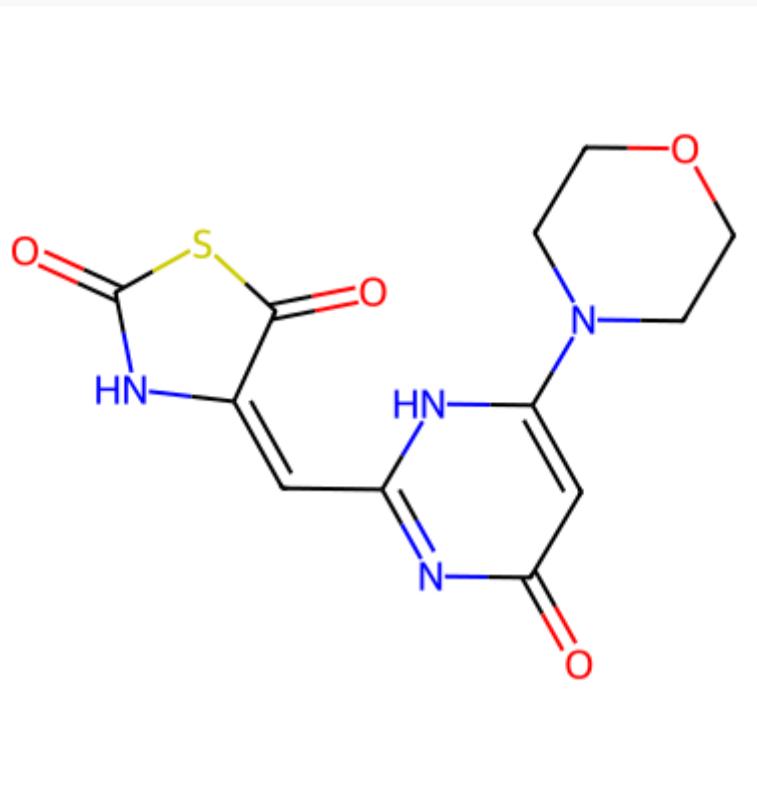
Block Changes: 2 (+1, -1)

CYP3A4 Score: 0.038089 → 0.034567 (-0.003522)

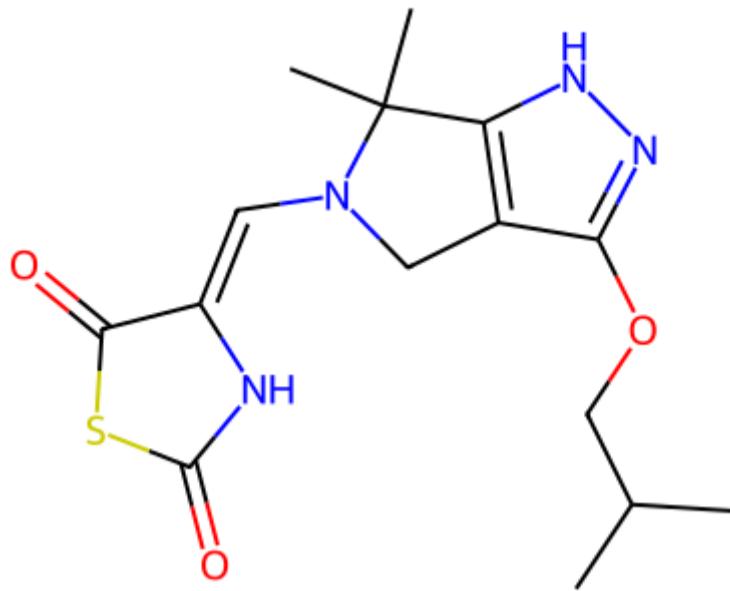
DETAILS PLACEHOLDER 3

► Step 2: PGP (-0.1335 ↓) ✓

Before (Step 1) `O=C1NC(=Cc2nc(=O)cc(N3CCOCC3)[nH]2)C(=O)S1`



After (Step 2) `CC(C)COc1n[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C`



QED: 0.7369 **Number of Blocks:** 2

► All ADMET Scores

Task	Score	Direction
AMES	0.396360	↓ lower
BBBP	1.000000	↑ higher
CYP3A4	0.034567	↓ lower
DILI	0.671969	↓ lower
HIA	0.999782	↑ higher
PGP	0.755234	↓ lower

QED: 0.8206 (+0.0838) ✓

Number of Blocks: 2 (+0) ➡

Block Changes: 2 (+1, -1)

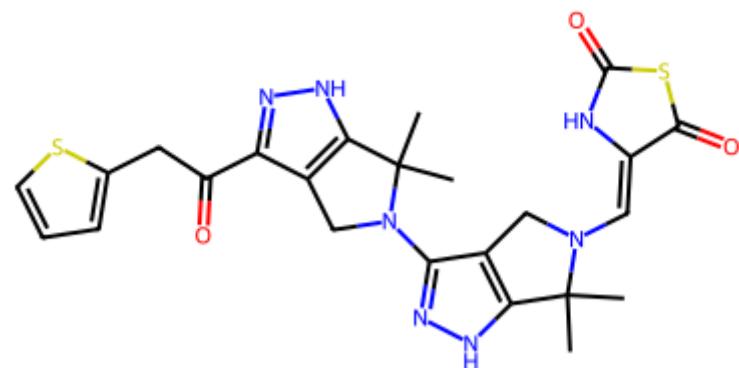
PGP Score: 0.755234 → 0.621777 (-0.133457)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O



QED: 0.3409 (-0.4797) ✗

Number of Blocks: 4 (+2) ↑

Block Changes: 4 (+3, -1)

PGP Score: 0.621777 → 0.627767 (+0.005990)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: CYP3A4 ✓

Original	New	Change
0.038089	0.034567	-0.003522 ↓

0=C1NC(=Cc2nc(=O)cc(N3CCOCC3)[nH]2)C(=O)S1

Step 2: PGP ✓

Original	New	Change
0.755234	0.621777	-0.133457 ↓

CC(C)COc1[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C

Step 3: PGP !

Original	New	Change
0.621777	0.627767	+0.005990 ↓

CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.476903	0.314900	-0.162003	+0.3397	-33.97%	✓ Improved
BBBP	↑ higher	0.999998	0.999992	-0.000006	-0.0000	-0.00%	✗ Declined
CYP3A4	↓ lower	0.038089	0.006490	-0.031599	+0.8296	-82.96%	✓ Improved
DILI	↓ lower	0.767693	0.495032	-0.272661	+0.3552	-35.52%	✓ Improved
HIA	↑ higher	0.999400	0.999245	-0.000155	-0.0002	-0.02%	✗ Declined
PGP	↓ lower	0.680634	0.627767	-0.052867	+0.0777	-7.77%	✓ Improved

Improved: 4/6 (66.7%) | **Molecules:** 55 | **Paths:** 94

🔍 Safety Threshold Analysis

Status: 3/6 meet thresholds

⚠️ **Below threshold:** 3

Task	Score	Threshold	Gap
PGP	0.6278	↓ 0.3	0.3278
DILI	0.4950	↓ 0.4	0.0950
AMES	0.3149	↓ 0.3	0.0149

✓ **Passing:** 3

Task	Score	Threshold
BBBP	1.0000	↑ 0.5
CYP3A4	0.0065	↓ 0.55
HIA	0.9992	↑ 0.2

Slide 21: Taranabant (MK-0364)

Initial Task: DILI

SMILES: C[C@H]([C@H](CC1=CC=C(C=C1)C1)C2=CC=CC(=C2)C#N)NC(=O)C(C)(C)OC3=NC=C(C=C3)C(F)(F)F

✖ Optimization Failed for Taranabant (MK-0364)

No valid paths found. The optimization could not generate any improved molecules.

Initial Molecule Scores

Input SMILES: C[C@H]([C@H](CC1=CC=C(C=C1)C1)C2=CC=CC(=C2)C#N)NC(=O)C(C)(C)OC3=NC=C(C=C3)C(F)(F)F

- **Molecules Generated:** 1
- **Valid Paths:** 0

Reason: All generated molecules had worse scores than the initial molecule.

Recommendations

1. **Increase beams:** Try `num_beams=7` or `num_beams=10` for more diversity
2. **Change initial task:** Try a different task as the starting point
3. **Reduce depth:** Start with `depth=1` to see if single-step improvements work
4. **Check initial molecule:** It may already be highly optimized

Slide 22: NYX-059

Initial Task: BBBP

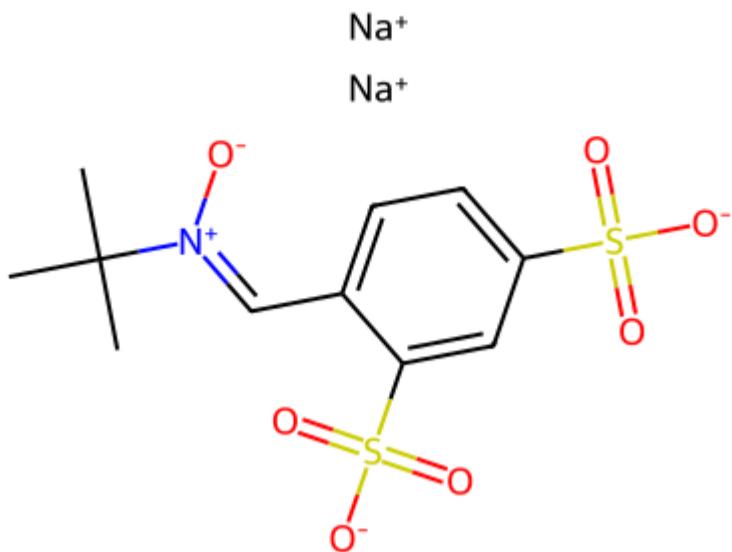
SMILES: CC(C)(C)[N+](=O)[O-]=Cc1ccc(cc1S(=O)(=O)[O-])S(=O)(=O)[O-].[Na+].[Na+]

NYX-059 - Optimization Results

Optimization Path

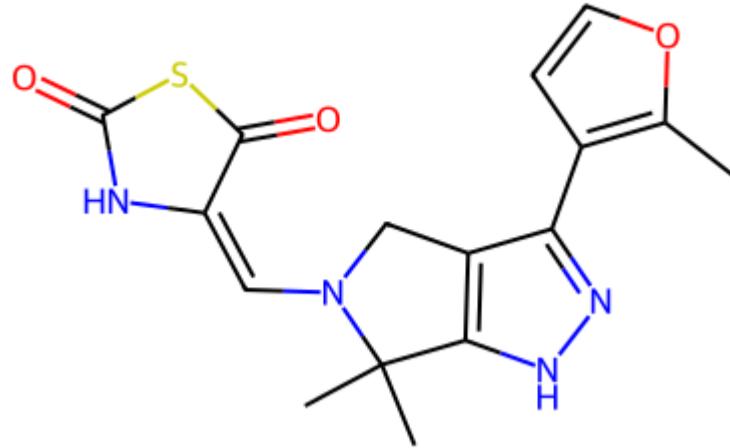
 Overall Comparison - Initial → Final

Initial Molecule `CC(C)(C)[N+](O-)=Cc1ccc(cc1S(=O)(=O)O-)[O-]S(=O)(=O)[O-].[Na+].[Na+]`



QED (Drug-likeness): 0.1268 **Number of Blocks:** 3

Final Optimized `Cc1occc1-c1n[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C`



QED (Drug-likeness): 0.8142 (+0.6874) ✓ **Number of Blocks:** 3 (+0) ➡
Total Block Changes: 7

► Show ADMET Scores

Task	Score
AMES	0.531967
BBBP	0.001933
CYP3A4	0.000120
DILI	0.483893
HIA	0.994940
PGP	0.765508

► Show ADMET Scores

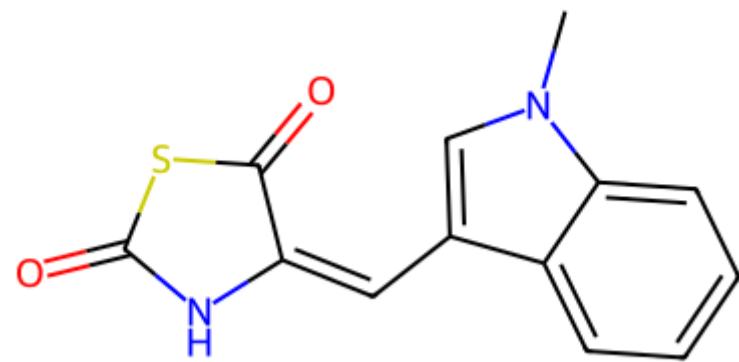
Task	Score	Change	Rel. Improvement	% Change
AMES ✗	0.609732	+0.077765	-0.1462	+14.62%
BBBP ✓	0.002764	+0.000832	+0.4304	+43.04%
CYP3A4 ✗	0.004026	+0.003907	-32.6844	+3268.44%
DILI ✗	0.741515	+0.257622	-0.5324	+53.24%
HIA ✓	0.996004	+0.001064	+0.0011	+0.11%
PGP ✓	0.583655	-0.181853	+0.2376	-23.76%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

Cn1cc(C=C2NC(=O)SC2=O)c2cccccc21



QED: 0.7995 (+0.6727)

Number of Blocks: 2 (-1) ↓

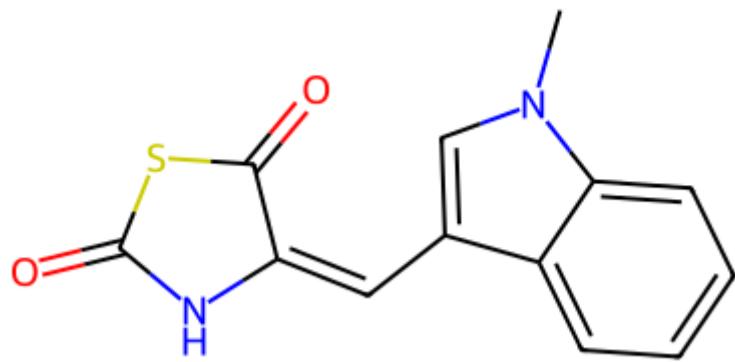
Block Changes: 4 (+2, -2)

BBBP Score: 0.001933 → 0.998710 (+0.996778)

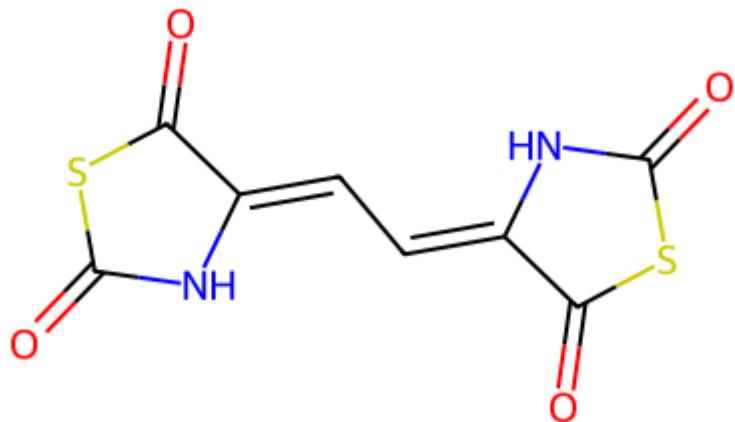
DETAILS *PLACEHOLDER 3*

► Step 2: AMES (-0.1157 ↓)

Before (Step 1) `Cn1cc(C=C2NC(=O)SC2=O)c2ccccc21`



After (Step 2) `O=C1NC(=CC=C2NC(=O)SC2=O)C(=O)S1`



QED: 0.7995 **Number of Blocks:** 2

► All ADMET Scores

Task	Score	Direction
AMES	0.324786	↓ lower
BBBP	0.998710	↑ higher
CYP3A4	0.007588	↓ lower
DILI	0.633693	↓ lower
HIA	0.999192	↑ higher
PGP	0.479166	↓ lower

QED: 0.6715 (-0.1280) ✗

Number of Blocks: 2 (+0) ➔

Block Changes: 1 (+0, -1)

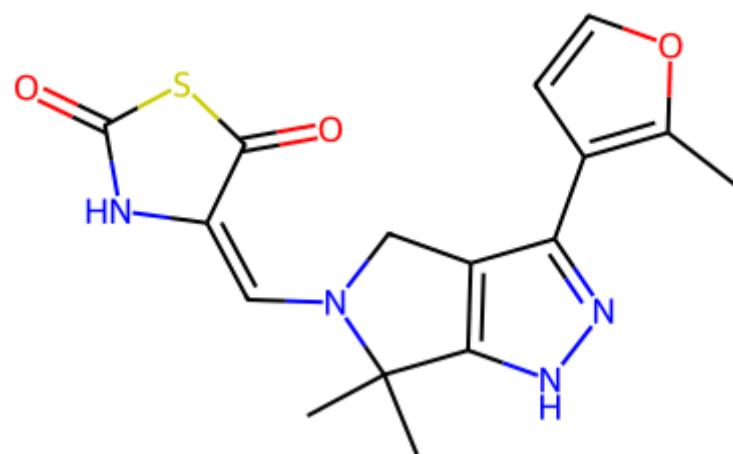
AMES Score: 0.324786 → 0.209113 (-0.115673)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

Cc1occc1-c1n[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C



QED: 0.8142 (+0.1427) ✓

Number of Blocks: 3 (+1) ↑

Block Changes: 2 (+2, -0)

PGP Score: 0.676219 → 0.583655 (-0.092563)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: BBBP ✓

Original	New	Change
0.001933	0.998710	+0.996778 ↑

Cn1cc(C=C2NC(=O)SC2=0)c2ccccc21

Step 2: AMES ✓

Original	New	Change
0.324786	0.209113	-0.115673 ↓

O=C1NC(=CC=C2NC(=O)SC2=0)C(=O)S1

Step 3: PGP ✓

Original	New	Change
0.676219	0.583655	-0.092563 ↓

Cc1occc1-c1n[nH]c2c1CN(C=C1NC(=O)SC1=0)C2(C)C

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.531967	0.609732	+0.077765	-0.1462	+14.62%	✗ Declined
BBBP	↑ higher	0.001933	0.002764	+0.000832	+0.4304	+43.04%	✓ Improved
CYP3A4	↓ lower	0.000120	0.004026	+0.003907	-32.6844	+3268.44%	✗ Declined
DILI	↓ lower	0.483893	0.741515	+0.257622	-0.5324	+53.24%	✗ Declined
HIA	↑ higher	0.994940	0.996004	+0.001064	+0.0011	+0.11%	✓ Improved
PGP	↓ lower	0.765508	0.583655	-0.181853	+0.2376	-23.76%	✓ Improved

Improved: 3/6 (50.0%) | **Molecules:** 133 | **Paths:** 300

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠️ Below threshold: 4

Task	Score	Threshold	Gap
BBBP	0.0028	↑ 0.5	0.4972
DILI	0.7415	↓ 0.4	0.3415
AMES	0.6097	↓ 0.3	0.3097
PGP	0.5837	↓ 0.3	0.2837

✓ Passing: 2

Task	Score	Threshold
CYP3A4	0.0040	↓ 0.55
HIA	0.9960	↑ 0.2

Slide 23: AZD-3514

Initial Task: HIA

SMILES: CC(=O)N1CCN(CC1)CCOC2=CC=C(C=C2)C3CCN(CC3)C4=NN5C(=NN=C5C(F)(F)F)CC4

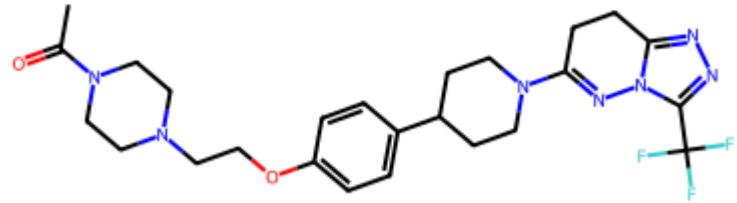
AZD-3514 - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

Initial Molecule

`CC(=O)N1CCN(CC1)CCOC2=CC=C(C=C2)C3CCN(CC3)C4=NN5C(=NN=C5C(F)(F)F)CC4`

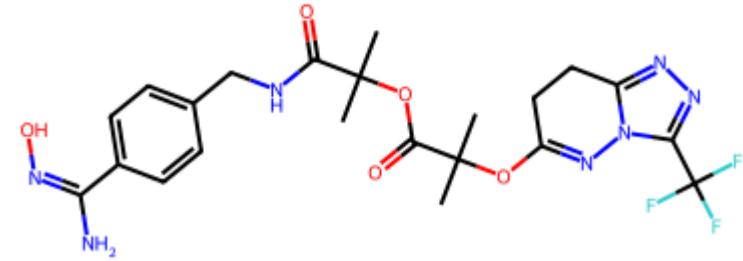


QED (Drug-likeness): 0.6048 **Number of Blocks:** 4

► Show ADMET Scores

Task	Score
AMES	0.382188
BBBP	0.998411
CYP3A4	0.030133
DILI	0.747011
HIA	0.999712
PGP	0.644132

Final Optimized `CC(C)(OC(=O)C(C)(C)OC1=Nn2c(nnc2C(F)(F)F)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1`



QED (Drug-likeness): 0.1621 (-0.4427) ✗ **Number of Blocks:** 3 (-1) ↓
Total Block Changes: 9

► Show ADMET Scores

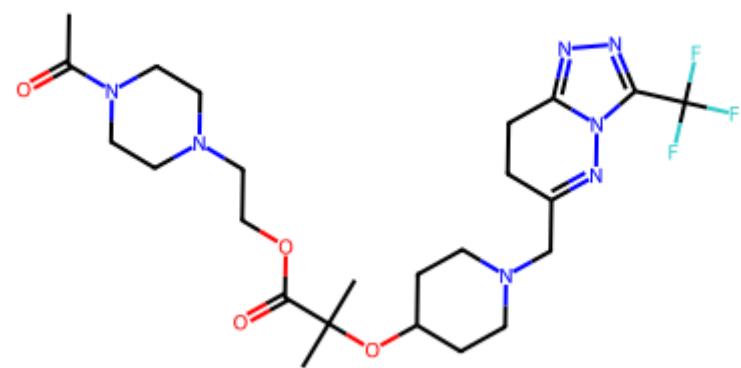
Task	Score	Change	Rel. Improvement	% Change
AMES ✗	0.641817	+0.259629	-0.6793	+67.93%
BBBP ✗	0.000596	-0.997815	-0.9994	-99.94%
CYP3A4 ✓	0.019928	-0.010205	+0.3387	-33.87%
DILI ✓	0.551265	-0.195746	+0.2620	-26.20%
HIA ✗	0.938515	-0.061197	-0.0612	-6.12%
PGP ✓	0.620027	-0.024105	+0.0374	-3.74%

Optimization Steps:

DETAILS PLACEHOLDER 2

After (Step 1)

CC(=O)N1CCN(CCOC(=O)C(C)(C)OC2CCN(CC3=Nn4c(nnc4C(F)(F)F)CC3)CC2)CC1



QED: 0.4537 (-0.1511) X

Number of Blocks: 3 (-1) ↓

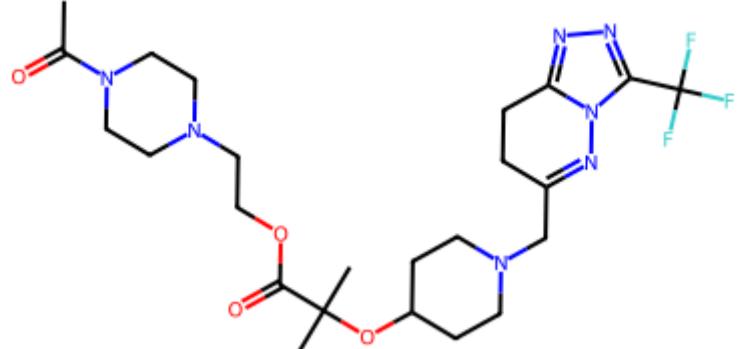
Block Changes: 3 (+1, -2)

HIA Score: 0.999712 → 0.999154 (-0.000558)

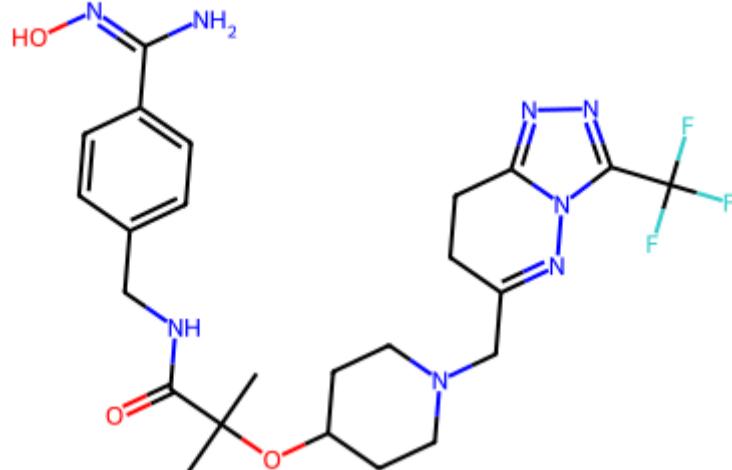
DETAILS *PLACEHOLDER 3*

► Step 2: AMES (+0.3347 ↓) →

****Before (Step 1)**** `CC(=O)N1CCN(CCOC(=O)C(C)(C)OC2CCN(CC3=Nn4c(nnc4C(F)(F)F)CC3)CC2)CC1`



****After (Step 2)**** `CC(C)(OC1CCN(CC2=Nn3c(nnc3C(F)(F)F)CC2)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1`



****QED:**** 0.4537 ****Number of Blocks:**** 3

► All ADMET Scores

Task	Score	Direction
AMES	0.396480	↓ lower
BBBP	0.999983	↑ higher
CYP3A4	0.051562	↓ lower
DILI	0.619876	↓ lower
HIA	0.999154	↑ higher
PGP	0.694290	↓ lower

QED: 0.2030 (-0.2507) X

Number of Blocks: 3 (+0) ➡

Block Changes: 2 (+1, -1)

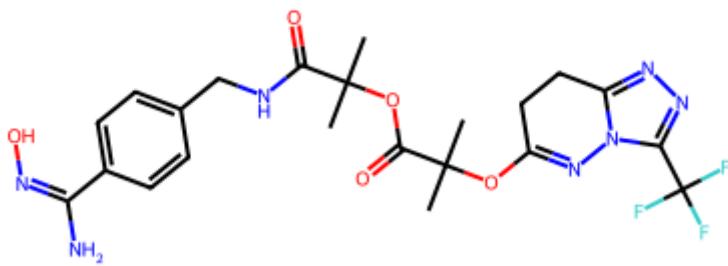
AMES Score: 0.396480 → 0.731145 (+0.334666)

DETAILS PLACEHOLDER 5

DETAILS PLACEHOLDER 6

After (Step 3)

CC(C)(OC(=O)C(C)(C)OC1=Nn2c(nnc2C(F)(F)F)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1



QED: 0.1621 (-0.0408) ✗

Number of Blocks: 3 (+0) ➔

Block Changes: 4 (+2, -2)

AMES Score: 0.731145 → 0.641817 (-0.089329)

DETAILS PLACEHOLDER 7

📊 Step Details

Step 1: HIA ⚠

Original	New	Change
0.999712	0.999154	-0.000558 ↑

CC(=O)N1CCN(CCOC(=O)C(C)(C)OC2CCN(CC3=Nn4c(nnc4C(F)(F)F)CC3)CC2)CC1

Step 2: AMES ⚠

Original	New	Change
0.396480	0.731145	+0.334666 ↓

CC(C)(OC1CCN(CC2=Nn3c(nnc3C(F)(F)F)CC2)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1

Step 3: AMES ✓

Original	New	Change
0.731145	0.641817	-0.089329 ↓

CC(C)(OC(=O)C(C)(C)OC1=Nn2c(nnc2C(F)(F)F)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.382188	0.641817	+0.259629	-0.6793	+67.93%	✗ Declined
BBBP	↑ higher	0.998411	0.000596	-0.997815	-0.9994	-99.94%	✗ Declined
CYP3A4	↓ lower	0.030133	0.019928	-0.010205	+0.3387	-33.87%	✓ Improved
DILI	↓ lower	0.747011	0.551265	-0.195746	+0.2620	-26.20%	✓ Improved
HIA	↑ higher	0.999712	0.938515	-0.061197	-0.0612	-6.12%	✗ Declined
PGP	↓ lower	0.644132	0.620027	-0.024105	+0.0374	-3.74%	✓ Improved

Improved: 3/6 (50.0%) | Molecules: 31 | Paths: 102

🔍 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠ Below threshold: 4

Task	Score	Threshold	Gap
BBBP	0.0006	↑ 0.5	0.4994
AMES	0.6418	↓ 0.3	0.3418
PGP	0.6200	↓ 0.3	0.3200
DILI	0.5513	↓ 0.4	0.1513

✓ Passing: 2

Task	Score	Threshold
CYP3A4	0.0199	↓ 0.55
HIA	0.9385	↑ 0.2