Slide 9: Fialuridine (FIAU)

Initial Task: DILI

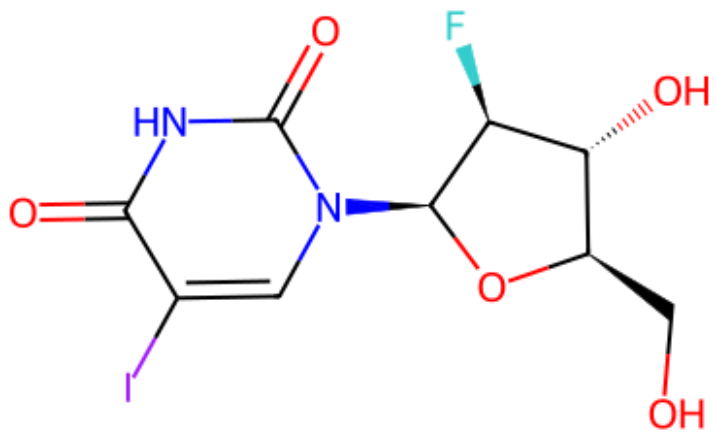
SMILES: `C1=C(C(=O)NC(=O)N1[C@H]2[C@H]([C@@H]([C@@H](CO)O2)O)F)I`

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)I`

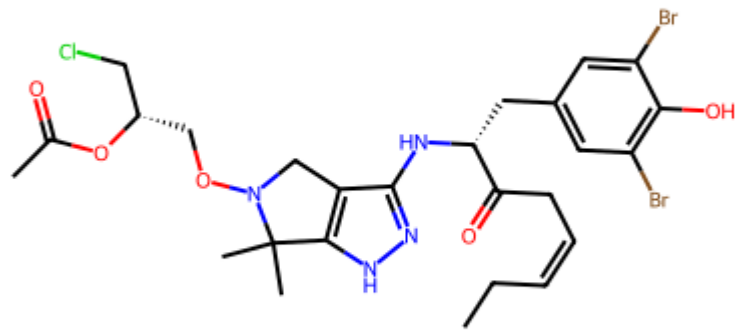


QED (Drug-likeness): 0.5621 **Number of Blocks:** 1

▶ ***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***

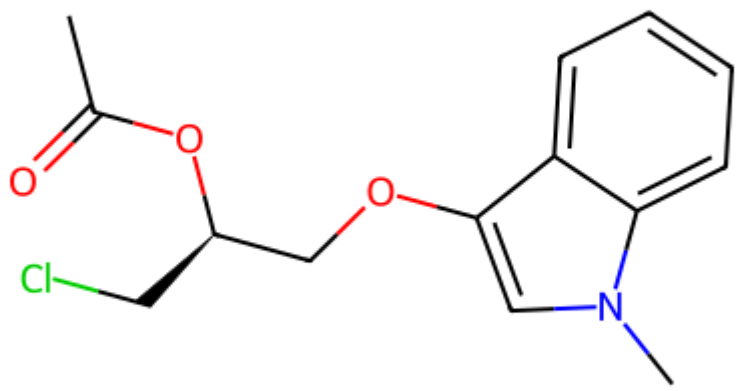
Task	Score	Change	Rel. Improvement	% Change
AMES ❌	0.266793	+0.152631	-1.3370	+133.70%
BBBP ❌	1.000000	+0.000000	+0.0000	+0.00%
CYP3A4 ❌	0.000067	+0.000067	-5806.1212	+580612.12%
DILI ❌	0.259323	+0.113579	-0.7793	+77.93%
HIA ❌	0.999987	-0.000013	-0.0000	-0.00%
PGP ✅	0.866124	-0.074351	+0.0791	-7.91%

Optimization Steps:

DETAILS*PLACEHOLDER2*

After (Step 1)

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



QED: 0.6249 (+0.0629) ✅

Number of Blocks: 2 (+1) ↑

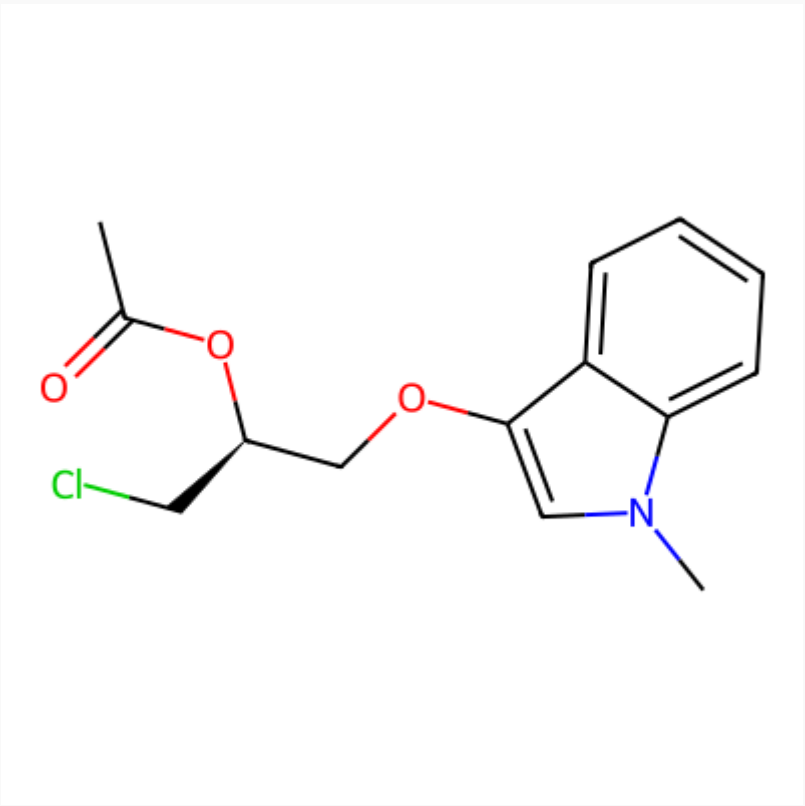
Block Changes: 3 (+2, -1)

DILI Score: 0.145744 → 0.641619 (+0.495875)

DETAILS*PLACEHOLDER3*

▶ Step 2: CYP3A4 (-0.1500 ↓) ✅

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

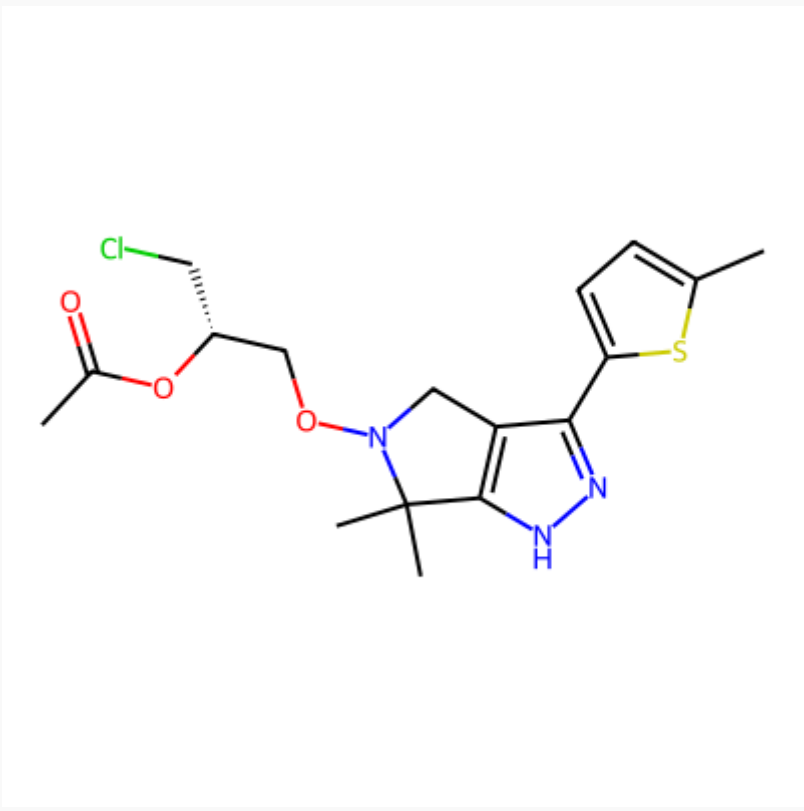


QED: 0.6249 **Number of Blocks:** 2

▶ ***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

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



QED: 0.6094 (-0.0155) ❌

Number of Blocks: 2 (+0) ➡️

Block Changes: 4 (+2, -2)

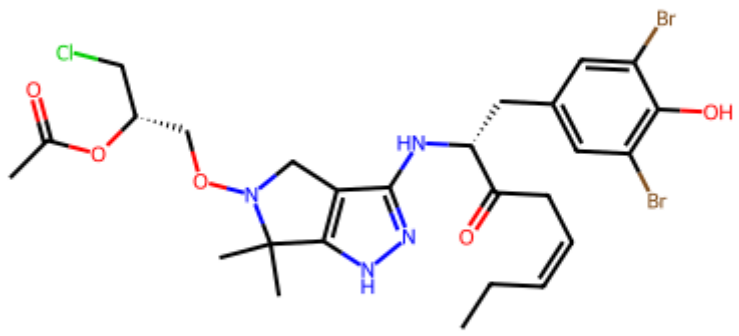
CYP3A4 Score: 0.159087 → 0.009106 (-0.149981)

DETAILS*PLACEHOLDER*5

DETAILS*PLACEHOLDER*6

After (Step 3)

```
CC/C=C\CC(=O)[C@@H](Cc1cc(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*PLACEHOLDER7*

📊 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%	❌ 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%	❌ Declined
DILI	↓ lower	0.145744	0.259323	+0.113579	-0.7793	+77.93%	❌ Declined
HIA	↑ higher	1.000000	0.999987	-0.000013	-0.0000	-0.00%	❌ 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