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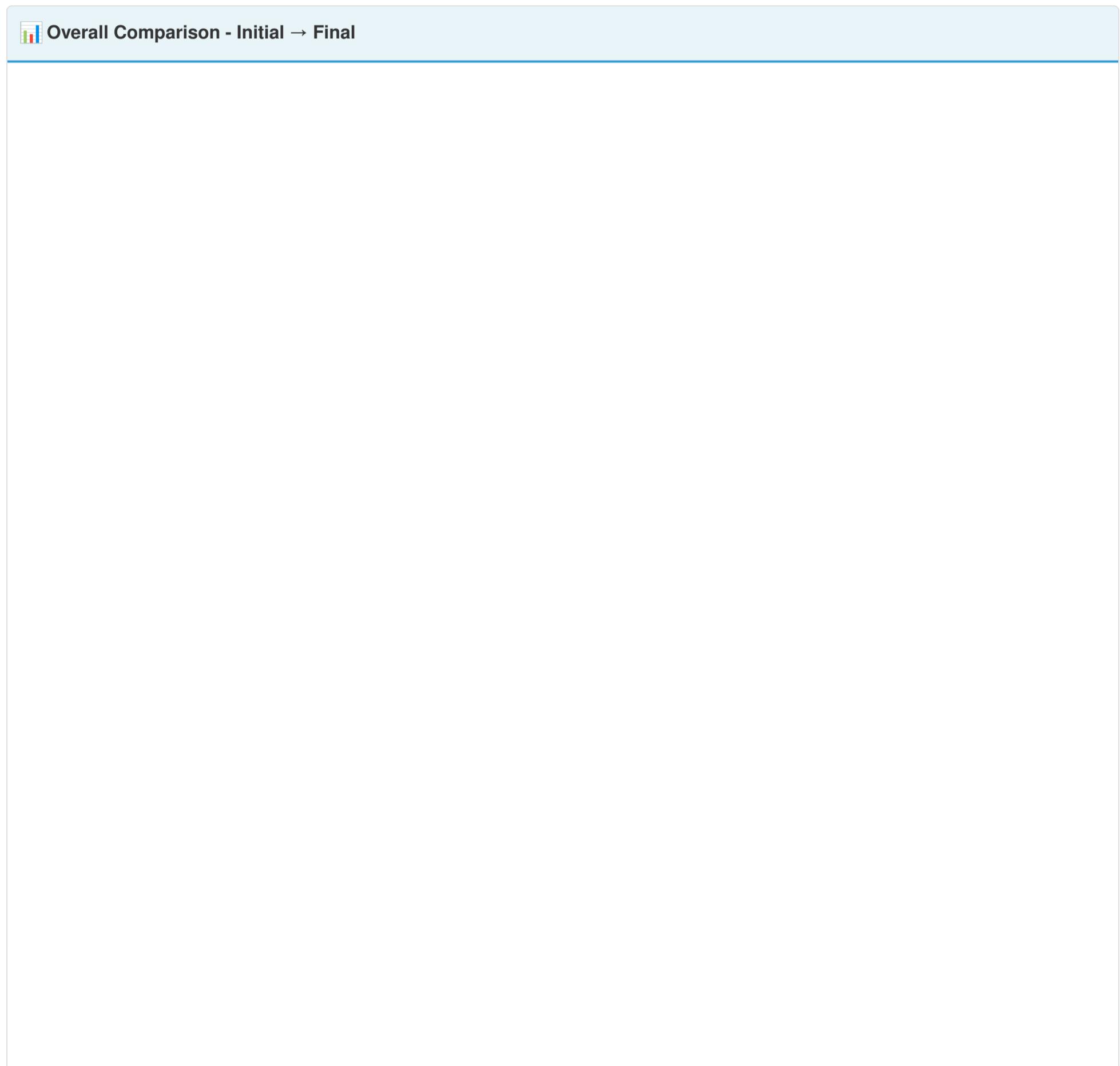
Initial Task: DILI

SMILES: CCOC(=O)CN[C@H](C1CCCCC1)C(=O)N2CC[C@H]2C(=O)NCC3=CC=C(C=C3)/C(=N\O)/N
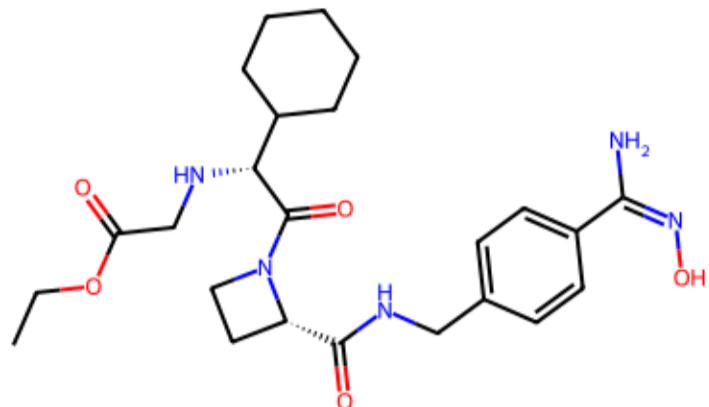
Ximelagatran (Exanta / oral direct thrombin inhibitor) - Optimization Results

🔗 **Optimization Path**

📊 **Overall Comparison - Initial → Final**

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

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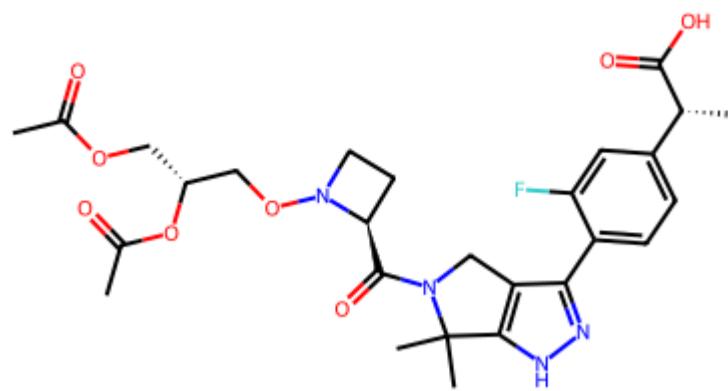
QED (Drug-likeness): 0.1308 **Number of Blocks:** 3

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

▶ *Show ADMET Scores*

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

▶ *Show ADMET Scores*

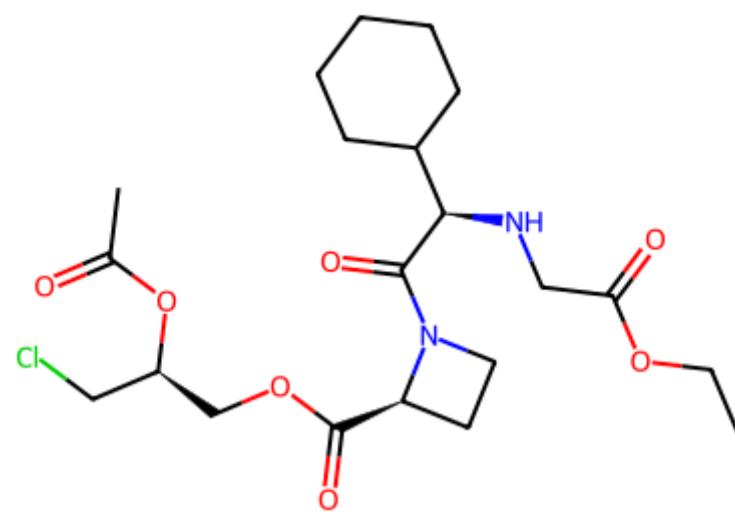| Task	Score	Change	Rel. Improvement	% Change
AMES ✅	0.404659	-0.315416	+0.4380	-43.80%
BBBP ✅	0.999947	+0.999867	+12529.0183	+1252901.83%
CYP3A4 ❌	0.020061	+0.002053	-0.1140	+11.40%
DILI ✅	0.408363	-0.241285	+0.3714	-37.14%
HIA ❌	0.991177	-0.006638	-0.0067	-0.67%
PGP ❌	0.659510	+0.004374	-0.0067	+0.67%

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

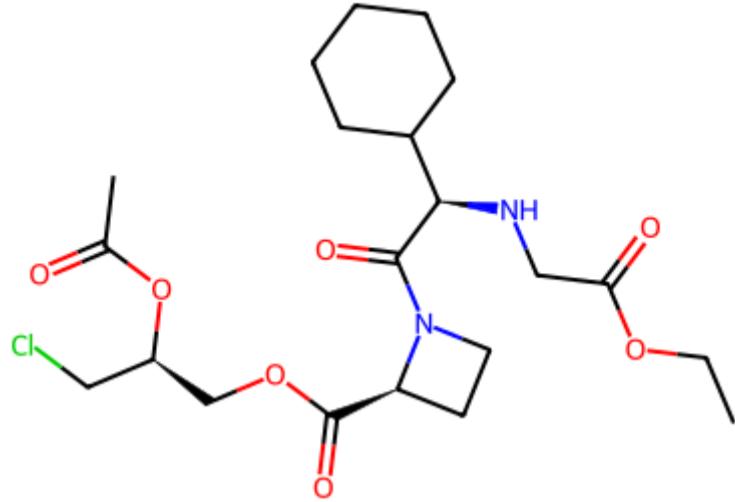**QED:** 0.2796 (+0.1488) ✅

Number of Blocks: 3 (+0) ➡️

Block Changes: 2 (+1, -1)

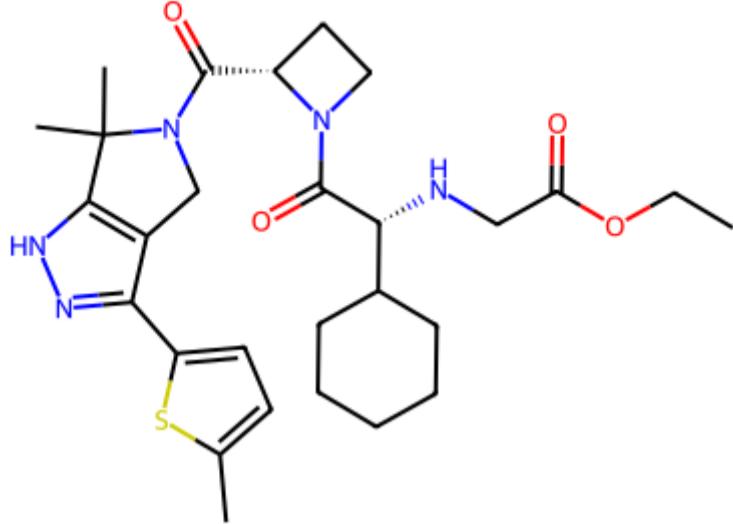**DILI Score:** 0.649647 → 0.419199 (-0.230448)

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`

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

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: 0.4934 (+0.2138) ✅

Number of Blocks: 4 (+1) ↑
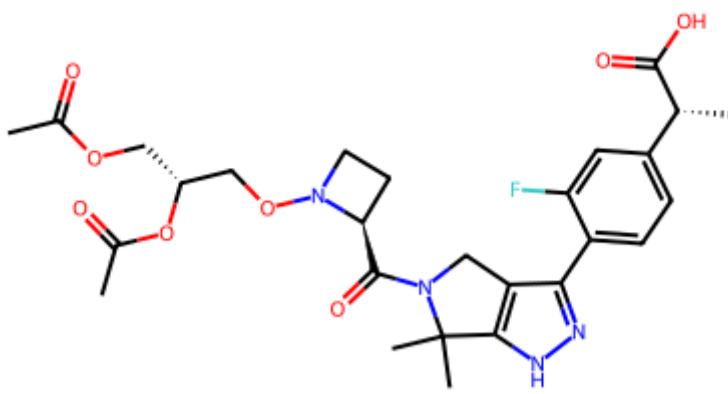
Block Changes: 3 (+2, -1)

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)C1CCCCC1
```

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)C1CCCCC1
```

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