Slide 20: SAR260301

Initial Task: CYP3A4
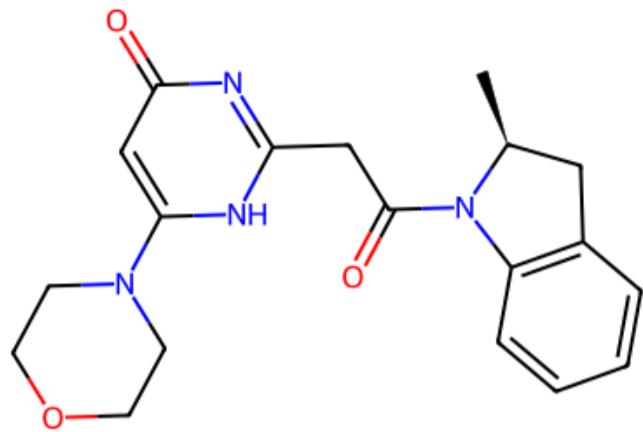
SMILES: `O=C1N=C(CC(N2[C@@H](C)CC3=C2C=CC=C3)=O)NC(N4CCOCC4)=C1`

SAR260301 - Optimization Results

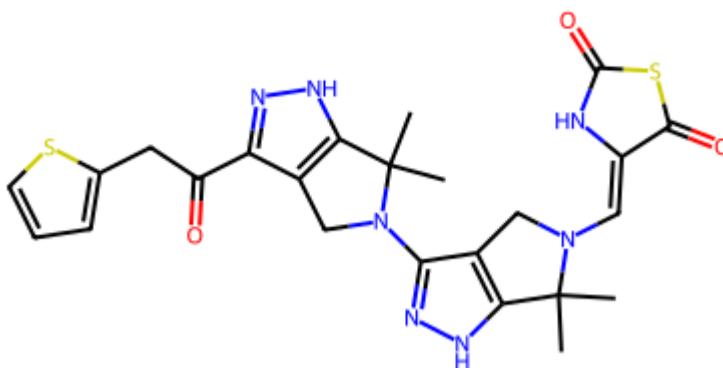### 🔗 Optimization Path

📊 **Overall Comparison - Initial → Final**

Initial Molecule `O=C1N=C(CC(N2[C@@H](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*

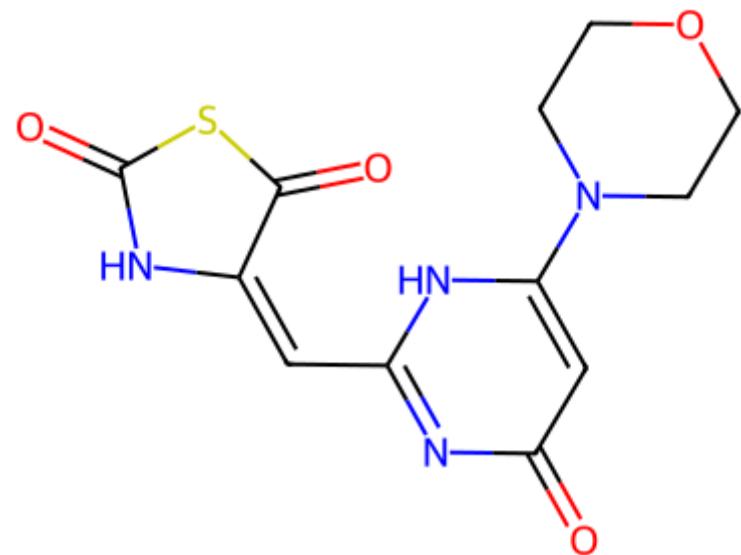| Task	Score	Change	Rel. Improvement	% Change
AMES ✅	0.314900	-0.162003	+0.3397	-33.97%
BBBP ❌	0.999992	-0.000006	-0.0000	-0.00%
CYP3A4 ✅	0.006490	-0.031599	+0.8296	-82.96%
DILI ✅	0.495032	-0.272661	+0.3552	-35.52%
HIA ❌	0.999245	-0.000155	-0.0002	-0.02%
PGP ✅	0.627767	-0.052867	+0.0777	-7.77%

Optimization Steps:

DETAILS_PLACEHOLDER_2

After (Step 1)

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

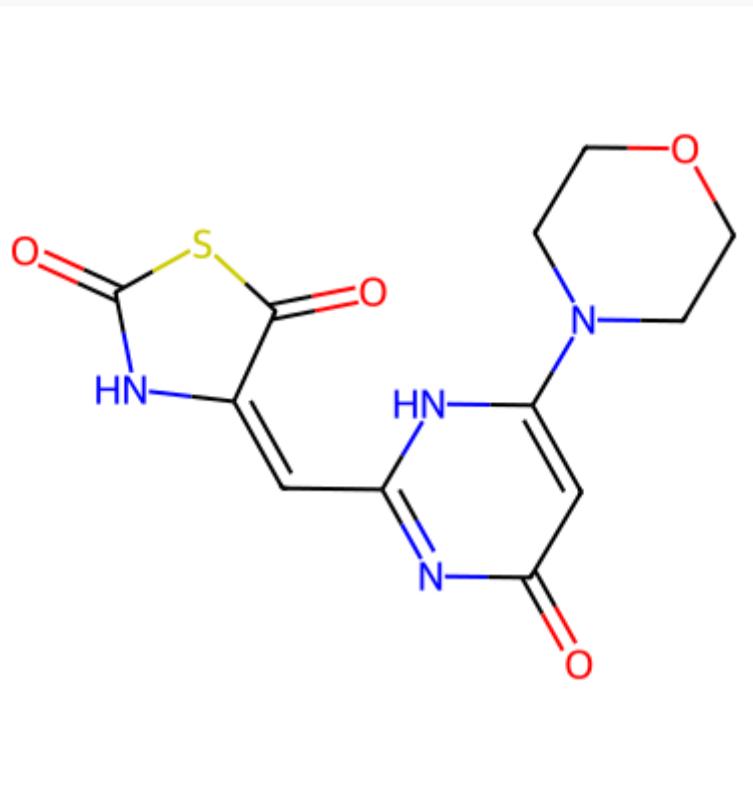**QED:** 0.7369 (-0.1570) ❌

Number of Blocks: 2 (+0) ➡️

Block Changes: 2 (+1, -1)

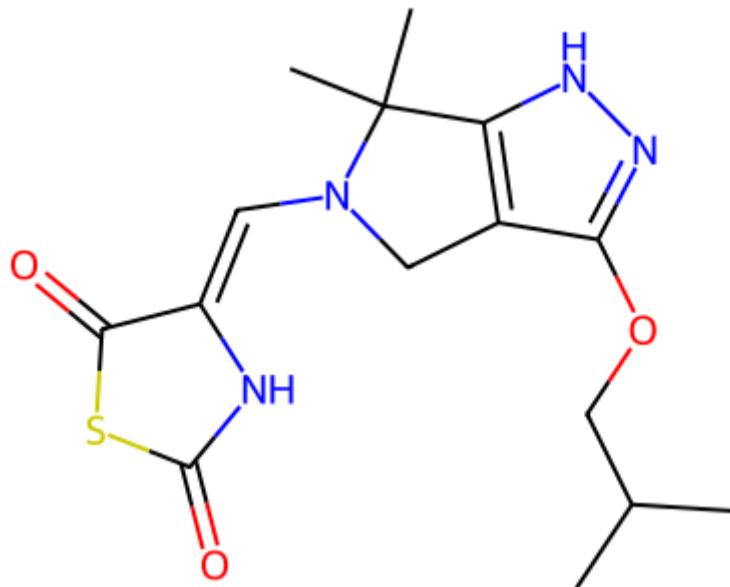**CYP3A4 Score:** 0.038089 → 0.034567 (-0.003522)

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

QED: 0.8206 (+0.0838) ✅

Number of Blocks: 2 (+0) ➡️
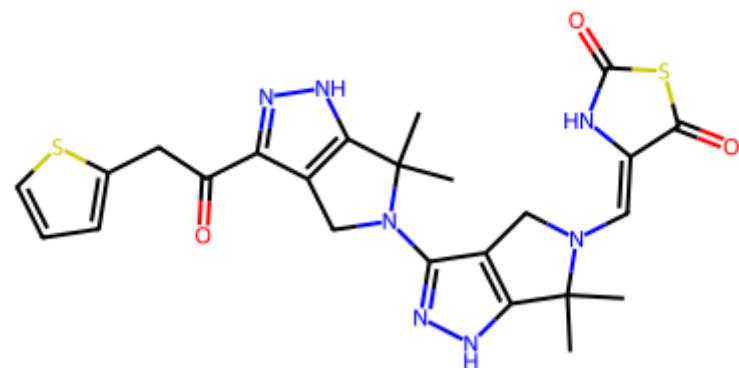
Block Changes: 2 (+1, -1)

PGP Score: 0.755234 → 0.621777 (-0.133457)

DETAILS*PLACEHOLDER*5

► *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

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*PLACEHOLDER7*

📊 Step Details

Step 1: CYP3A4 ✅

Original	New	Change
0.038089	0.034567	-0.003522 ↓

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

Step 2: PGP ✅

Original	New	Change
0.755234	0.621777	-0.133457 ↓

```
CC(C)COc1n[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