Slide 18: GSK1059615

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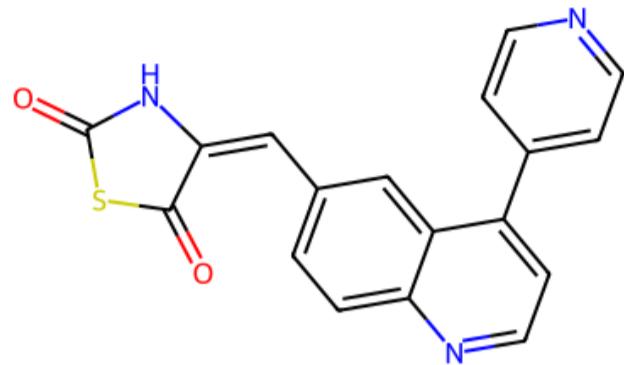
SMILES: `O=C(N/C1=C/C2=CC=C3N=CC=C(C4=CC=NC=C4)C3=C2)SC1=O`

GSK1059615 - Optimization Results

🔗 Optimization Path

📊 **Overall Comparison - Initial → Final**

Initial Molecule `O=C(N/C1=C/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*

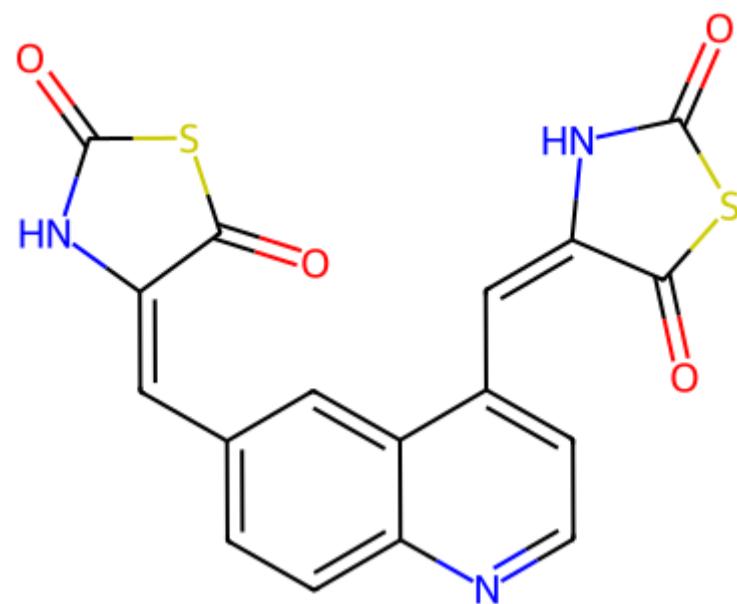| Task	Score	Change	Rel. Improvement	% Change
AMES ✅	0.701288	-0.028402	+0.0389	-3.89%
BBBP ❌	0.000159	-0.000957	-0.8576	-85.76%
CYP3A4 ✅	0.003058	-0.014888	+0.8296	-82.96%
DILI ✅	0.648698	-0.236948	+0.2675	-26.75%
HIA ✅	0.974224	+0.088808	+0.1003	+10.03%
PGP ❌	0.561292	+0.018458	-0.0340	+3.40%

Optimization Steps:

DETAILS_PLACEHOLDER_2

After (Step 1)

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

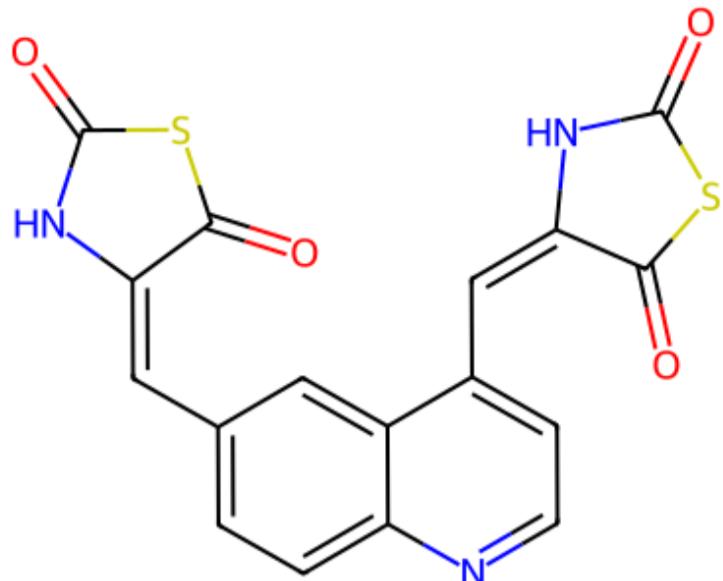**QED:** 0.7683 (+0.0430) ✅

Number of Blocks: 3 (+0) ➡️

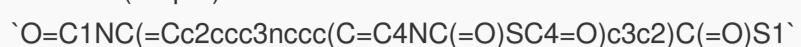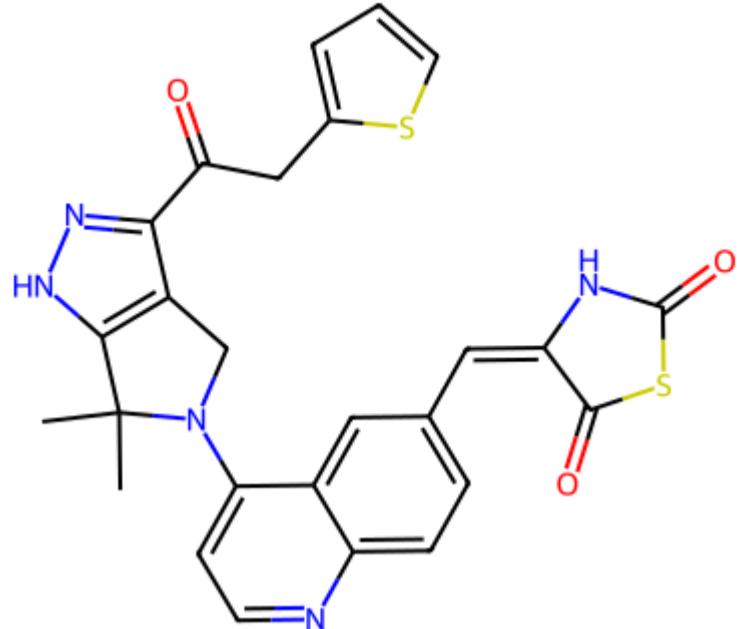**Block Changes:** 3 (+1, -2)
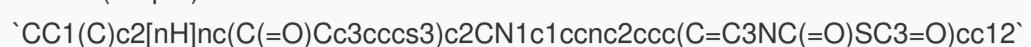
HIA Score: 0.885416 → 0.992403 (+0.106986)

DETAILS*PLACEHOLDER*3

▶ **Step 2: PGP (-0.0781 ↓)** ✅

Before (Step 1)

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

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

After (Step 2)

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

QED: 0.2837 (-0.4847) ❌

Number of Blocks: 4 (+1) ↑

Block Changes: 2 (+2, -0)
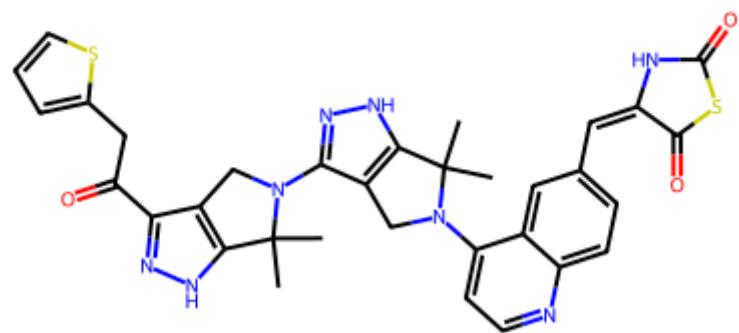
PGP Score: 0.675779 → 0.597692 (-0.078087)

DETAILS*PLACEHOLDER*5

DETAILS*PLACEHOLDER*6

After (Step 3)

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

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 ↑

```
O=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