Slide 14: Rosiglitazone

Initial Task: BBBP

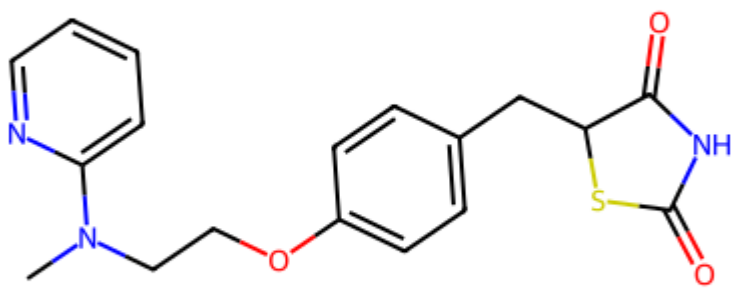
SMILES: `CN(CCOC1=CC=C(C=C1)CC2C(=O)NC(=O)S2)C3=CC=CC=N3`

Rosiglitazone - Optimization Results

🔗 Optimization Path

📊 Overall Comparison - Initial → Final

Initial Molecule
`CN(CCOC1=CC=C(C=C1)CC2C(=O)NC(=O)S2)C3=CC=CC=N3`

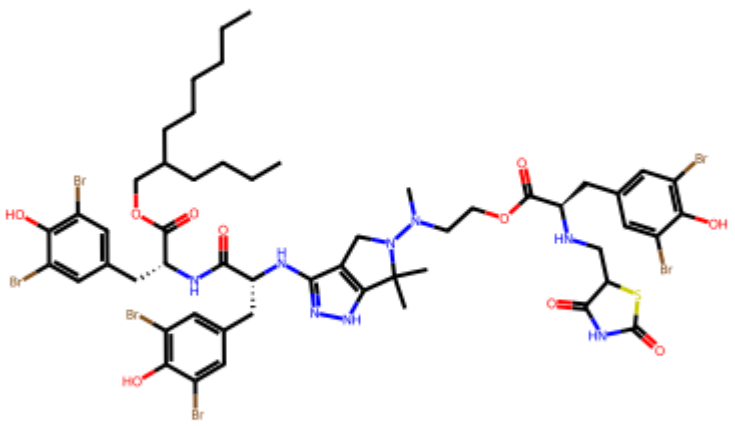


QED (Drug-likeness): 0.8209 **Number of Blocks:** 4

▶ ***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](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 (Drug-likeness): 0.0186 (-0.8023) ❌ **Number of Blocks:** 6 (+2) ↑
Total Block Changes: 15

▶ ***Show ADMET Scores***

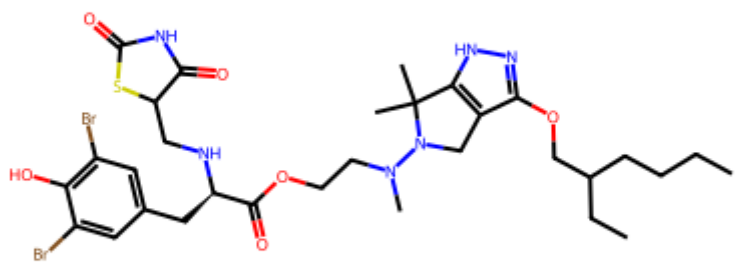
Task	Score	Change	Rel. Improvement	% Change
AMES ✅	0.155246	-0.253299	+0.6200	-62.00%
BBBP ✅	1.000000	+0.353944	+0.5479	+54.79%
CYP3A4 ✅	0.000001	-0.080224	+1.0000	-100.00%
DILI ✅	0.306504	-0.497774	+0.6189	-61.89%
HIA ✅	1.000000	+0.001626	+0.0016	+0.16%
PGP ❌	0.882034	+0.343167	-0.6368	+63.68%

Optimization Steps:

DETAILS*PLACEHOLDER2*

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) ❌

Number of Blocks: 4 (+0) ➡️

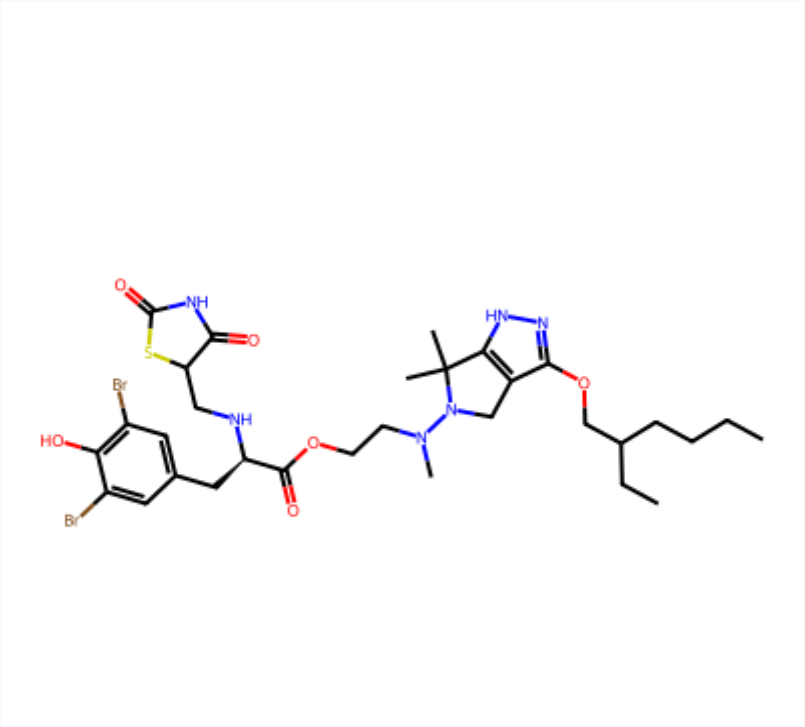
Block Changes: 8 (+4, -4)

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`

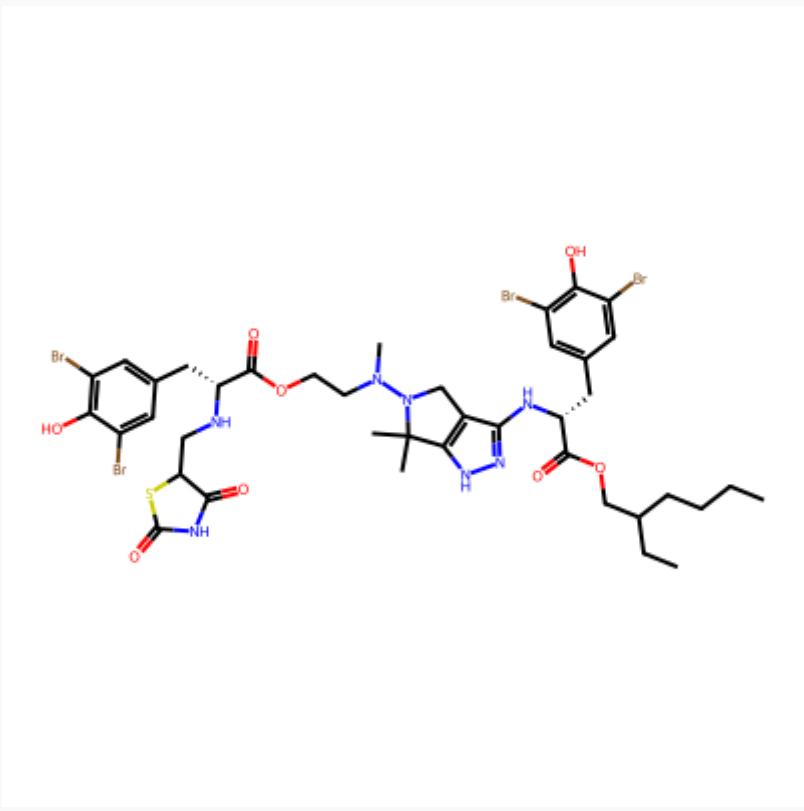


QED: 0.1564 **Number of Blocks:** 4

▶ ***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

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: 0.0569 (-0.0995) ❌

Number of Blocks: 5 (+1) ↑

Block Changes: 5 (+3, -2)

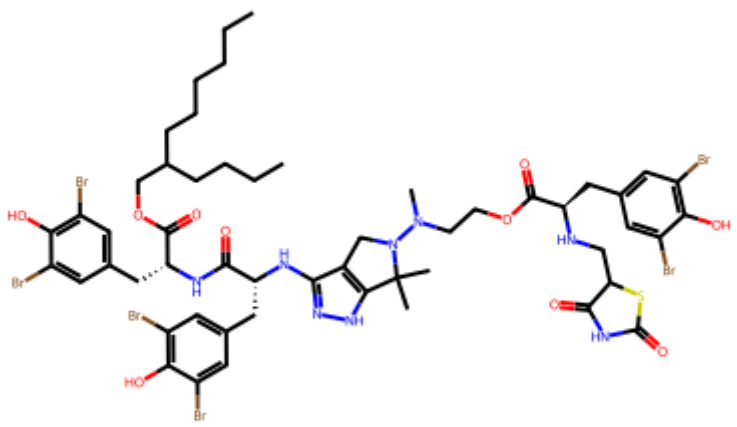
AMES Score: 0.587563 → 0.499352 (-0.088211)

DETAILS*PLACEHOLDER5*

DETAILS*PLACEHOLDER6*

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*PLACEHOLDER7*

📊 Step Details

Step 1: BBBP ⚠️

Original	New	Change
0.646056	0.000386	-0.645670 ↑

```
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
```

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]c2c1CN(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 ↓

```
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(B
```

📊 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