Slide 17: Nefazodone (Serzone)

Initial Task: CYP3A4

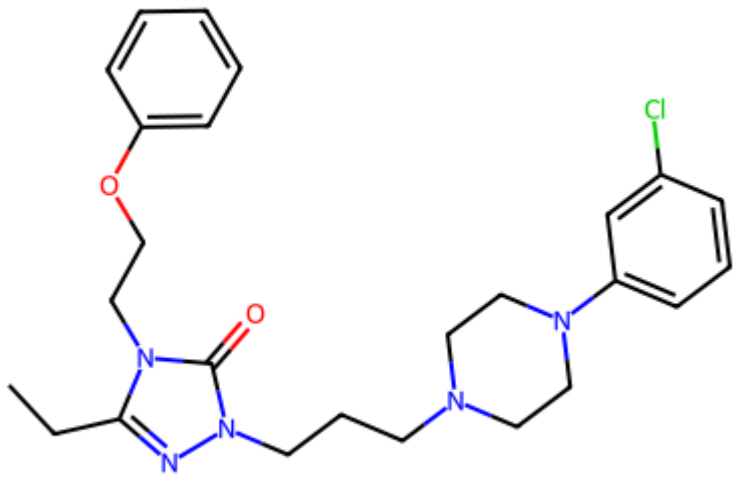
SMILES: `CCC1=NN(CCCN2CCN(CC2)C3=CC=CC(=C3)Cl)C(=O)N1CCOC4=CC=CC=C4`

Nefazodone (Serzone) - Optimization Results

🔗 Optimization Path

📊 Overall Comparison - Initial → Final

Initial Molecule
`CCC1=NN(CCCN2CCN(CC2)C3=CC=CC(=C3)Cl)C(=O)N1CCOC4=CC=CC=C4`

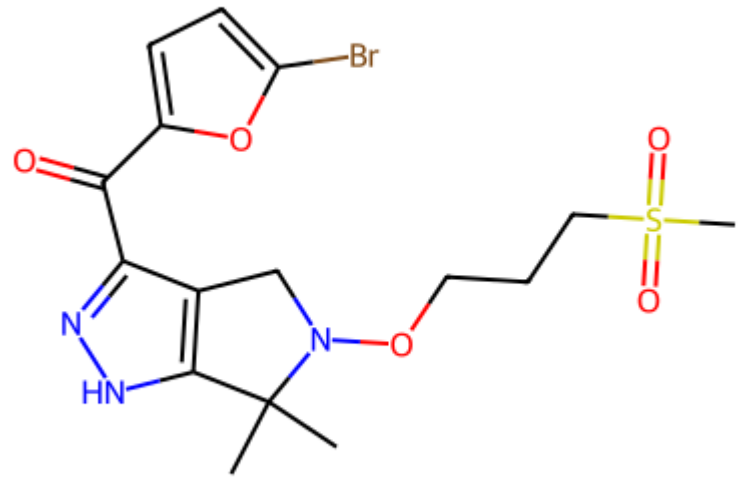


QED (Drug-likeness): 0.4542 **Number of Blocks:** 2

▶ ***Show ADMET Scores***

Task	Score
AMES	0.373806
BBBP	0.988244
CYP3A4	0.024539
DILI	0.803705
HIA	0.999946
PGP	0.605185

Final Optimized `CC1(C)c2[nH]nc(C(=O)c3ccc(Br)o3)c2CN1OCCCS(C)(=O)=O`



QED (Drug-likeness): 0.5145 (+0.0603) ✅ **Number of Blocks:** 1 (-1) ↓
Total Block Changes: 9

▶ ***Show ADMET Scores***

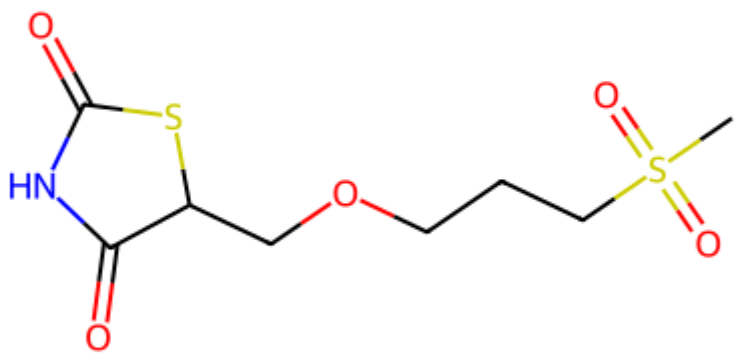
Task	Score	Change	Rel. Improvement	% Change
AMES ✅	0.284693	-0.089113	+0.2384	-23.84%
BBBP ✅	1.000000	+0.011756	+0.0119	+1.19%
CYP3A4 ✅	0.000204	-0.024335	+0.9917	-99.17%
DILI ✅	0.390386	-0.413319	+0.5143	-51.43%
HIA ❌	0.999757	-0.000189	-0.0002	-0.02%
PGP ❌	0.841080	+0.235895	-0.3898	+38.98%

Optimization Steps:

DETAILS*PLACEHOLDER2*

After (Step 1)

`CS(=O)(=O)CCCOCC1SC(=O)NC1=O`



QED: 0.6697 (+0.2155) ✅

Number of Blocks: 1 (-1) ↓

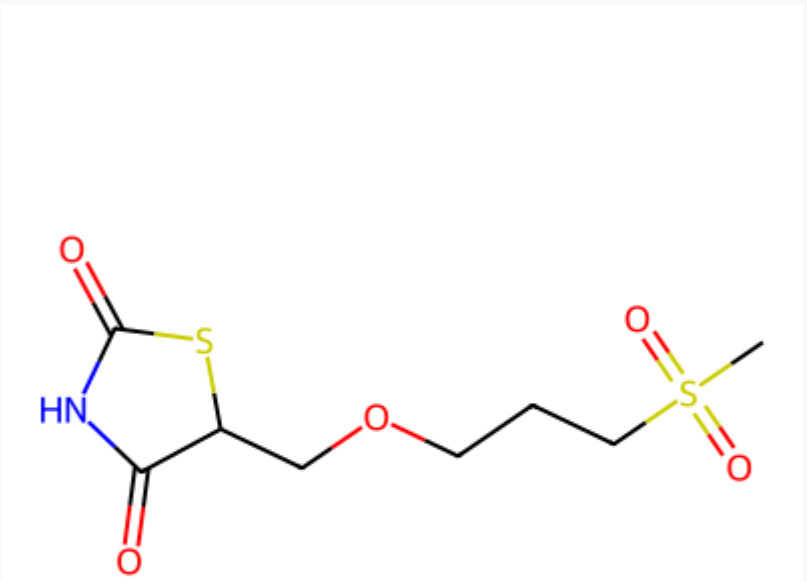
Block Changes: 3 (+1, -2)

CYP3A4 Score: 0.024539 → 0.001181 (-0.023358)

DETAILS*PLACEHOLDER3*

▶ Step 2: AMES (+0.4434 ↓) ➡️

Before (Step 1) `CS(=O)(=O)CCCOCC1SC(=O)NC1=O`

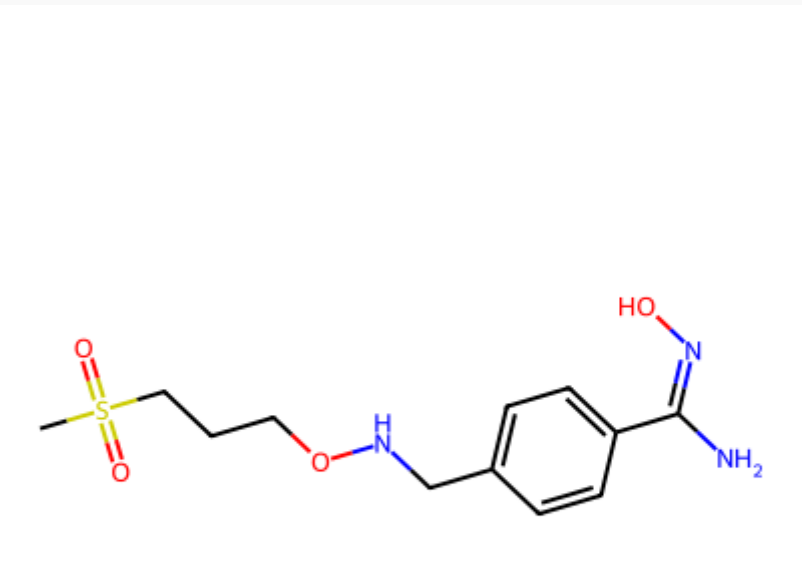


QED: 0.6697 **Number of Blocks:** 1

▶ ***All ADMET Scores***

Task	Score	Direction
AMES	0.243126	↓ lower
BBBP	0.992016	↑ higher
CYP3A4	0.001181	↓ lower
DILI	0.562681	↓ lower
HIA	0.999992	↑ higher
PGP	0.719436	↓ lower

After (Step 2) `CS(=O)(=O)CCCONCc1ccc(/C(N)=N\O)cc1`



QED: 0.2082 (-0.4615) ❌

Number of Blocks: 2 (+1) ↑

Block Changes: 3 (+2, -1)

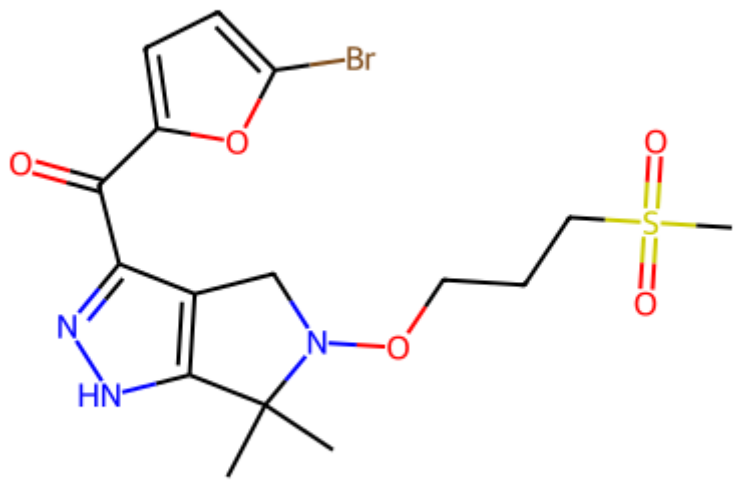
AMES Score: 0.243126 → 0.686480 (+0.443354)

DETAILS*PLACEHOLDER*5

DETAILS*PLACEHOLDER*6

After (Step 3)

```
CC1(C)c2[nH]nc(C(=O)c3ccc(Br)o3)c2CN1OCCCS(C)(=O)=O
```



QED: 0.5145 (+0.3062) ✅

Number of Blocks: 1 (-1) ↓

Block Changes: 3 (+1, -2)

PGP Score: 0.675115 → 0.841080 (+0.165965)

DETAILS*PLACEHOLDER7*

📊 Step Details

Step 1: CYP3A4 ✅

Original	New	Change
0.024539	0.001181	-0.023358 ↓

```
CS(=O)(=O)CCCOCC1SC(=O)NC1=O
```

Step 2: AMES ⚠️

Original	New	Change
0.243126	0.686480	+0.443354 ↓

```
CS(=O)(=O)CCCONCc1ccc(/C(N)=N\O)cc1
```

Step 3: PGP ⚠️

Original	New	Change
0.675115	0.841080	+0.165965 ↓

```
CC1(C)c2[nH]nc(C(=O)c3ccc(Br)o3)c2CN1OCCCS(C)(=O)=O
```

📊 ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.373806	0.284693	-0.089113	+0.2384	-23.84%	✅ Improved
BBBP	↑ higher	0.988244	1.000000	+0.011756	+0.0119	+1.19%	✅ Improved
CYP3A4	↓ lower	0.024539	0.000204	-0.024335	+0.9917	-99.17%	✅ Improved
DILI	↓ lower	0.803705	0.390386	-0.413319	+0.5143	-51.43%	✅ Improved
HIA	↑ higher	0.999946	0.999757	-0.000189	-0.0002	-0.02%	❌ Declined
PGP	↓ lower	0.605185	0.841080	+0.235895	-0.3898	+38.98%	❌ Declined

Improved: 4/6 (66.7%) | **Molecules:** 301 | **Paths:** 7666

🔍 Safety Threshold Analysis

Status: 5/6 meet thresholds

⚠️ **Below threshold:** 1

Task	Score	Threshold	Gap
PGP	0.8411	↓ 0.3	0.5411

✅ **Passing:** 5

Task	Score	Threshold
AMES	0.2847	↓ 0.3
BBBP	1.0000	↑ 0.5
CYP3A4	0.0002	↓ 0.55
DILI	0.3904	↓ 0.4
HIA	0.9998	↑ 0.2