

Slide 19: Neflamapimod (VX-745)

Initial Task: HIA

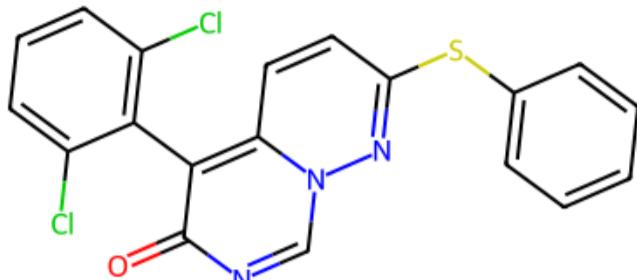
SMILES: O=c1ncn2nc(Sc3cccc3)ccc2c1-c1c(Cl)cccc1Cl

Neflamapimod (VX-745) - Optimization Results

Optimization Path

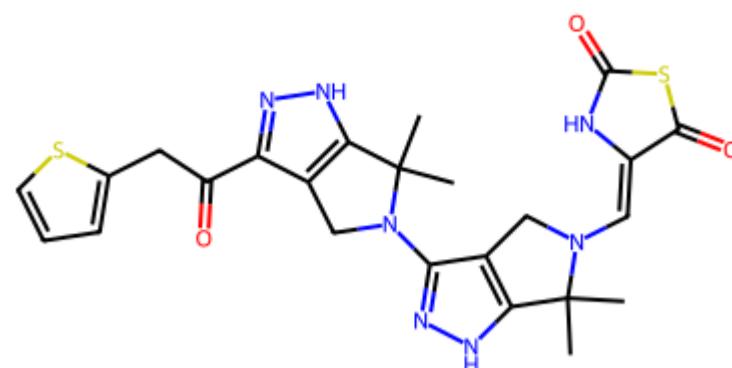
 Overall Comparison - Initial → Final

****Initial Molecule**** `O=c1ncn2nc(Sc3cccc3)ccc2c1-c1c(Cl)cccc1Cl`



****Final Optimized****

`CC1(C)c2[nH]nc(N3Cc4c(C(=O)Cc5cccs5)n[nH]c4C3(C)C)c2CN1C=C1NC(=O)SC1=O`



****QED (Drug-likeness):**** 0.4735 ****Number of Blocks:****

2

► Show ADMET Scores

Task	Score
AMES	0.675174
BBBP	0.000046
CYP3A4	0.002328
DILI	0.771123
HIA	0.988214
PGP	0.672094

****QED (Drug-likeness):**** 0.3409 (-0.1326) **✗** ****Number of Blocks:**** 4 (+2) ↑ ****Total Block Changes:**** 10

► Show ADMET Scores

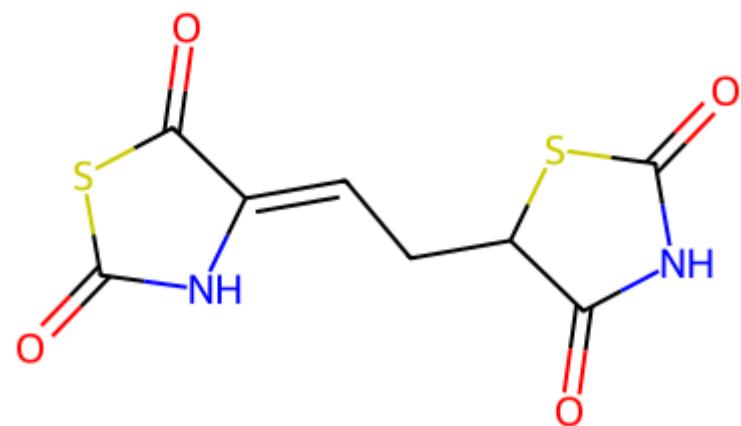
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.314901	-0.360274	+0.5336	-53.36%
BBBP ✓	0.999992	+0.999947	+21894.4005	+2189440.05%
CYP3A4 ✗	0.006490	+0.004162	-1.7876	+178.76%
DILI ✓	0.495032	-0.276091	+0.3580	-35.80%
HIA ✓	0.999245	+0.011031	+0.0112	+1.12%
PGP ✓	0.627767	-0.044327	+0.0660	-6.60%

Optimization Steps:

DETAILS PLACEHOLDER2

After (Step 1)

0=C1NC(=CCC2SC(=O)NC2=O)C(=O)S1



QED: 0.7044 (+0.2309) ✓

Number of Blocks: 2 (+0) →

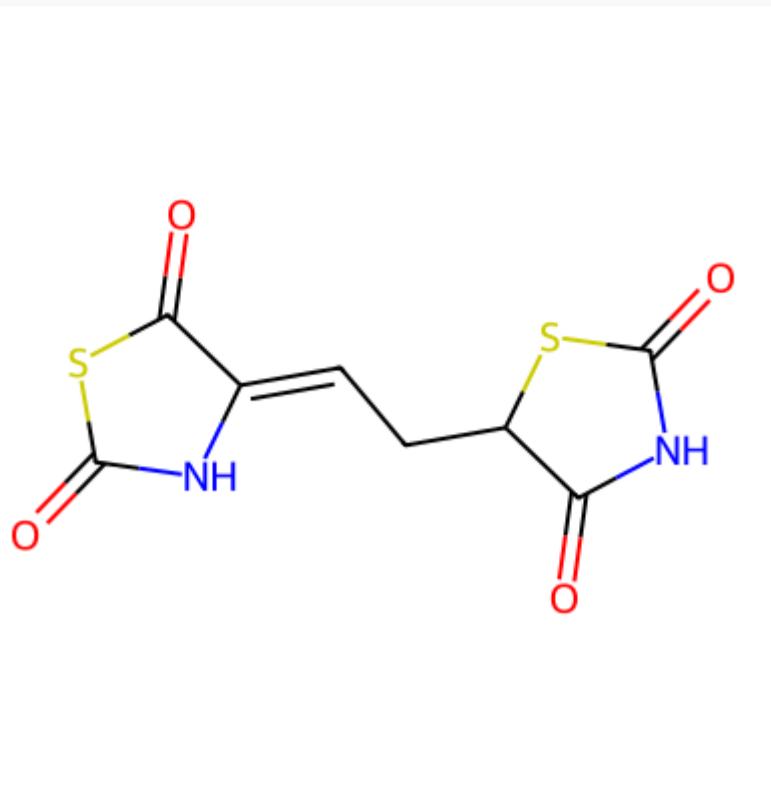
Block Changes: 4 (+2, -2)

HIA Score: 0.988214 → 1.000000 (+0.011786)

DETAILS *PLACEHOLDER3*

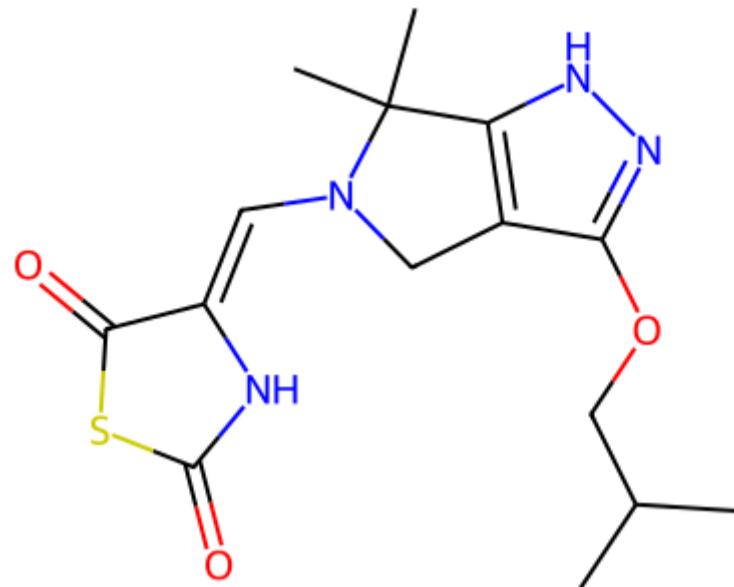
► Step 2: PGP (-0.0538 ↓) ✓

****Before (Step 1)**** `O=C1NC(=CCC2SC(=O)NC2=O)C(=O)S1`



****After (Step 2)****

`CC(C)COc1n[nH]c2c1CN(C=C1NC(=O)SC1=O)C2(C)C`



****QED:**** 0.7044 ****Number of Blocks:**** 2

► All ADMET Scores

Task	Score	Direction
AMES	0.276939	↓ lower
BBBP	0.989504	↑ higher
CYP3A4	0.000312	↓ lower
DILI	0.575363	↓ lower
HIA	1.000000	↑ higher
PGP	0.675575	↓ lower

QED: 0.8206 (+0.1163)

Number of Blocks: 2 (+0)

Block Changes: 2 (+1, -1)

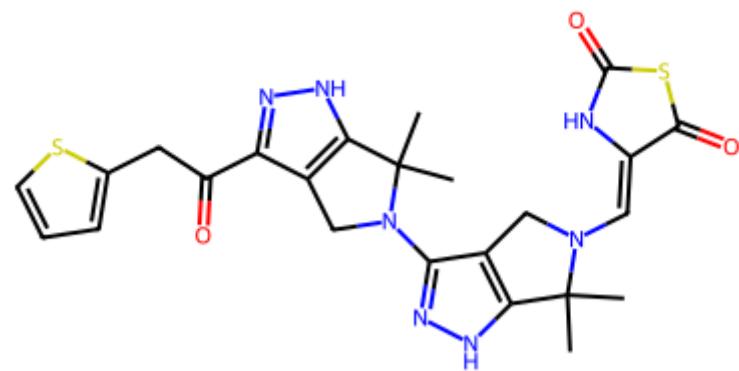
PGP Score: 0.675575 → 0.621777 (-0.053797)

DETAILSPLACEHOLDER5

DETAILSPLACEHOLDER6

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: HIA ✓

Original	New	Change
0.988214	1.000000	+0.011786 ↑

0=C1NC(=CCC2SC(=O)NC2=O)C(=O)S1

Step 2: PGP ✓

Original	New	Change
0.675575	0.621777	-0.053797 ↓

CC(C)COc1[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	0.675174	0.314901	-0.360274	+0.5336	-53.36%	✓ Improved
BBBP	↑ higher	0.000046	0.999992	+0.999947	+21894.4005	+2189440.05%	✓ Improved
CYP3A4	↓ lower	0.002328	0.006490	+0.004162	-1.7876	+178.76%	✗ Declined
DILI	↓ lower	0.771123	0.495032	-0.276091	+0.3580	-35.80%	✓ Improved
HIA	↑ higher	0.988214	0.999245	+0.011031	+0.0112	+1.12%	✓ Improved
PGP	↓ lower	0.672094	0.627767	-0.044327	+0.0660	-6.60%	✓ Improved

Improved: 5/6 (83.3%) | **Molecules:** 49 | **Paths:** 127

🔍 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