

Slide 5: Olcegepant (BIBN-4096BS)

Initial Task: HIA

SMILES: C1=CC2=C(C=C1)NC(=O)N(C2)C3CCN(CC3)C(=O)N[C@H](CC4=CC(=C(C(=C4)Br)O)Br)C(=O)N[C@@H](CCCCN)C(=O)N5CCN(CC5)C6=CC=NC=C6

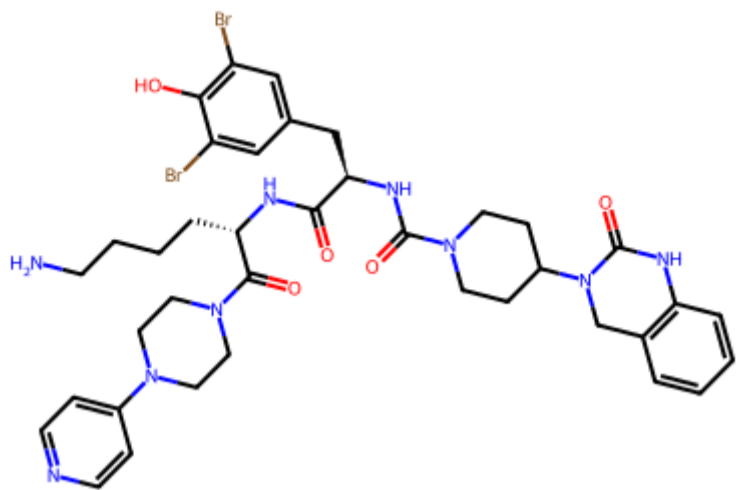
Olcegepant (BIBN-4096BS) - Optimization Results

Optimization Path

Overall Comparison - Initial → Final

****Initial Molecule****

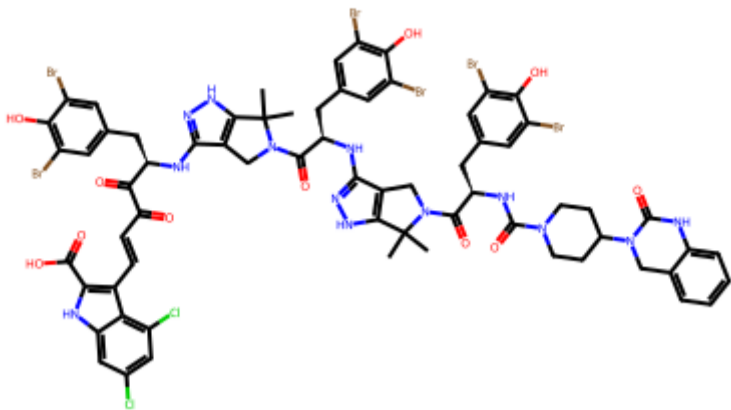
`C1=CC2=C(C=C1)NC(=O)N(C2)C3CCN(CC3)C(=O)N[C@H](CC4=CC(=C(C(=C4)Br)O)Br)C(=O)N[C@@H](CCCCN)C(=O)N5CCN(CC5)C6=CC=NC=C6`



****QED (Drug-likeness):**** 0.1666 ****Number of Blocks:**** 5

► <i>Show ADMET Scores</i>	
Task	Score
AMES	0.721609
BBBP	0.000066
CYP3A4	0.009376
DILI	0.714050
HIA	0.989571
PGP	0.702944

****Final Optimized**** `CC1(C)c2[nH]nc(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)N3Cc4c(N[C@H](Cc5cc(Br)c(O)c(Br)c5)C(=O)C(=O)/C=C/c5c(C(=O)O)[nH]c6cc(Cl)cc(Cl)c56)n[nH]c4C3(C)C)c2CN1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N2Cc3ccccc3NC2=O)CC1`



****QED (Drug-likeness):**** 0.0265 (-0.1401) ❌ ****Number of Blocks:**** 7 (+2) ↑
****Total Block Changes:**** 16

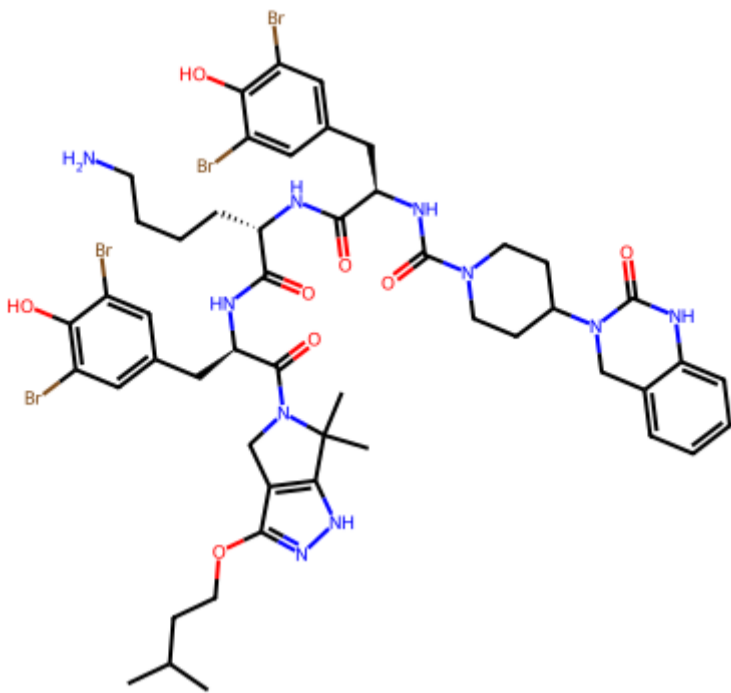
► <i>Show ADMET Scores</i>				
Task	Score	Change	Rel. Improvement	% Change
AMES ✓	0.528857	-0.192753	+0.2671	-26.71%
BBBP ✓	0.000205	+0.000139	+2.1037	+210.37%
CYP3A4 ✓	0.000009	-0.009367	+0.9991	-99.91%
DILI ✓	0.525996	-0.188054	+0.2634	-26.34%
HIA ✓	0.999984	+0.010413	+0.0105	+1.05%
PGP ❌	0.824368	+0.121425	-0.1727	+17.27%

Optimization Steps:

DETAILSPLACEHOLDER2

After (Step 1)

CC(C)CCOc1n[nH]c2c1CN(C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4cccc4NC3=O)CC1)C2(C)C



QED: 0.0420 (-0.1246) ❌

Number of Blocks: 6 (+1) ↑

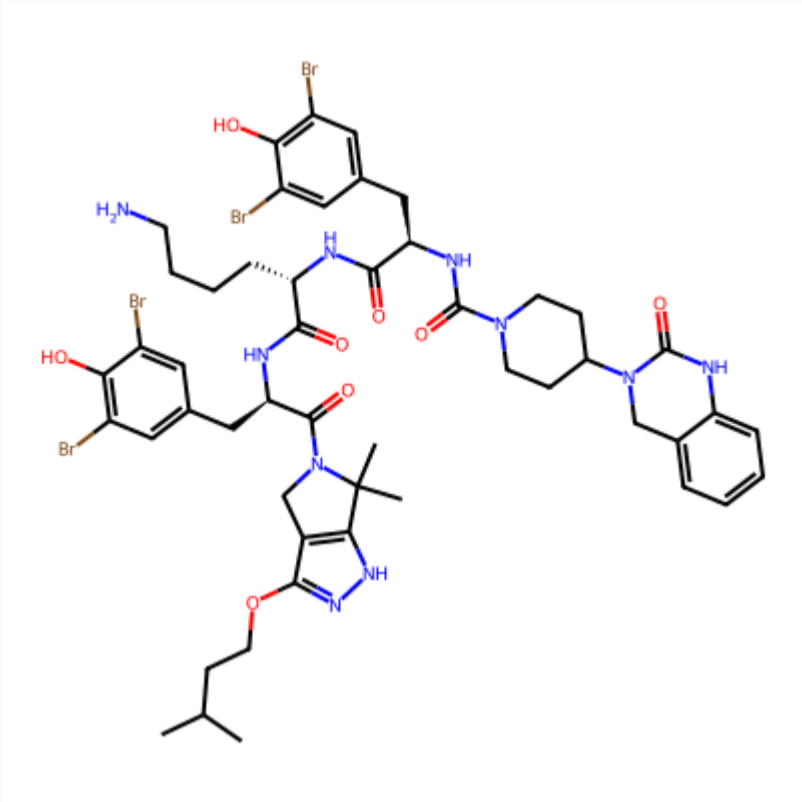
Block Changes: 8 (+4, -4)

HIA Score: 0.989571 → 0.999710 (+0.010140)

DETAILSPLACEHOLDER3

► **Step 2: AMES (-0.0478 ↓)** ✅

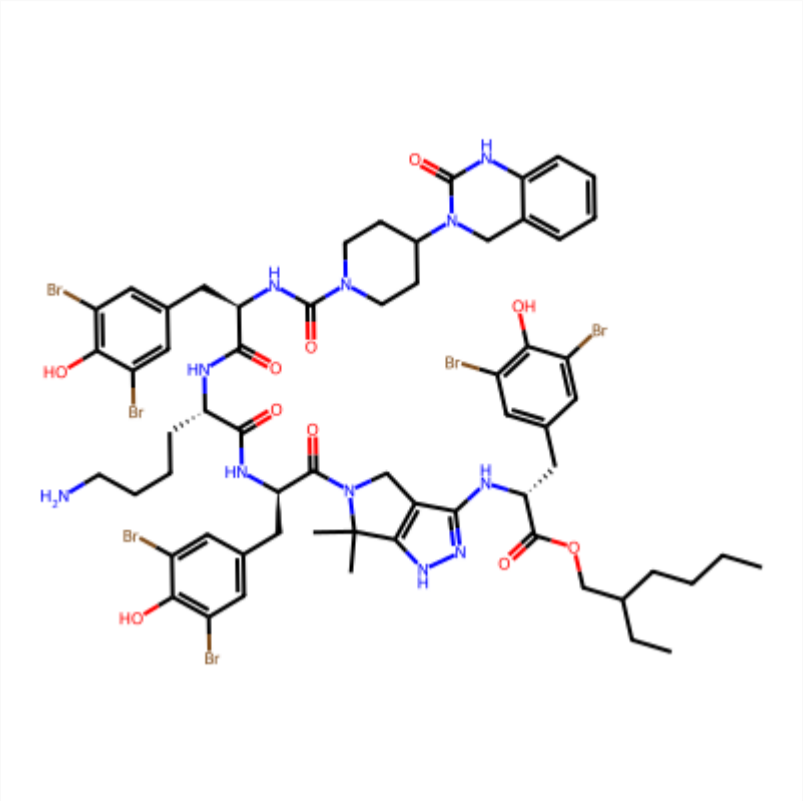
****Before (Step 1)**** `CC(C)CCOc1n[nH]c2c1CN(C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4ccccc4NC3=O)CC1)C2(C)C`



****QED:**** 0.0420 ****Number of Blocks:**** 6

► All ADMET Scores		
Task	Score	Direction
AMES	0.612386	↓ lower
BBBP	0.000221	↑ higher
CYP3A4	0.000178	↓ lower
DILI	0.505321	↓ lower
HIA	0.999710	↑ higher
PGP	0.820831	↓ lower

****After (Step 2)**** `CCCCC(CC)COC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4ccccc4NC3=O)CC1)C2(C)C`



QED: 0.0182 (-0.0238) ❌

Number of Blocks: 7 (+1) ↑

Block Changes: 3 (+2, -1)

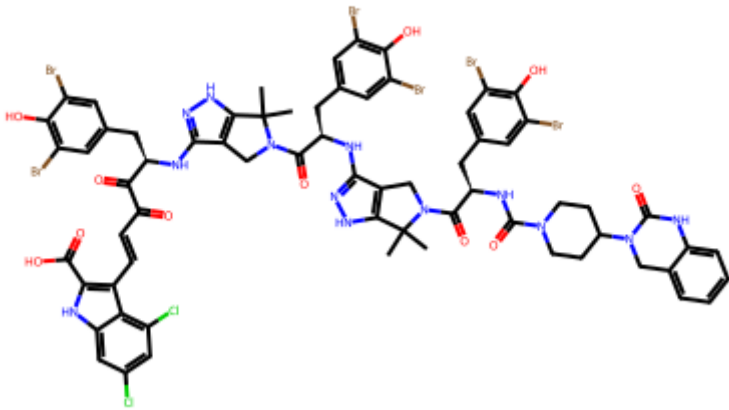
AMES Score: 0.612386 → 0.564568 (-0.047817)

DETAILSPLACEHOLDER5

DETAILSPLACEHOLDER6

After (Step 3)

CC1(C)c2[nH]nc(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)N3Cc4c(N[C@H](Cc5cc(Br)c(O)c(Br)c5)C(=O)C(=O)/C=C/c5c(C(=O)O)[nH]c6cc(Cl)cc(Cl)c56)n[nH]c4C3(C)C)c2CN1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N2Cc3ccccc3NC2=O)CC1



QED: 0.0265 (+0.0083) ✔

Number of Blocks: 7 (+0) ➡

Block Changes: 5 (+2, -3)

CYP3A4 Score: 0.000019 → 0.000009 (-0.000011)

DETAILSPLACEHOLDER7

Step Details

Step 1: HIA ✔

Original	New	Change
0.989571	0.999710	+0.010140 ↑

CC(C)CC0c1n[nH]c2c1CN(C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4ccccc4NC(=O)N3)C1=O

Step 2: AMES ✔

Original	New	Change
0.612386	0.564568	-0.047817 ↓

CCCCC(CC)COC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)Nc1n[nH]c2c1CN(C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)[C@H](CCCCN)NC(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NC(=O)N1CCC(N3Cc4ccccc4NC(=O)N3)C1=O

Step 3: CYP3A4 ✔

Original	New	Change
0.000019	0.000009	-0.000011 ↓

CC1(C)c2[nH]nc(N[C@H](Cc3cc(Br)c(O)c(Br)c3)C(=O)N3Cc4c(N[C@H](Cc5cc(Br)c(O)c(Br)c5)C(=O)C(=O)/C=C/c5c(C(=O)O)[nH]c6cc(Cl)cc(Cl)c56)n3)C2=O

 ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.721609	0.528857	-0.192753	+0.2671	-26.71%	✔ Improved
BBBP	↑ higher	0.000066	0.000205	+0.000139	+2.1037	+210.37%	✔ Improved
CYP3A4	↓ lower	0.009376	0.000009	-0.009367	+0.9991	-99.91%	✔ Improved
DILI	↓ lower	0.714050	0.525996	-0.188054	+0.2634	-26.34%	✔ Improved
HIA	↑ higher	0.989571	0.999984	+0.010413	+0.0105	+1.05%	✔ Improved
PGP	↓ lower	0.702944	0.824368	+0.121425	-0.1727	+17.27%	✘ Declined

Improved: 5/6 (83.3%) | Molecules: 637 | Paths: 5011

 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠ Below threshold: 4

Task	Score	Threshold	Gap
PGP	0.8244	↓ 0.3	0.5244
BBBP	0.0002	↑ 0.5	0.4998
AMES	0.5289	↓ 0.3	0.2289
DILI	0.5260	↓ 0.4	0.1260

✔ Passing: 2

Task	Score	Threshold
CYP3A4	0.0000	↓ 0.55
HIA	1.0000	↑ 0.2