

# Slide 5: Olcegepant (BIBN-4096BS)

Initial Task: HIA

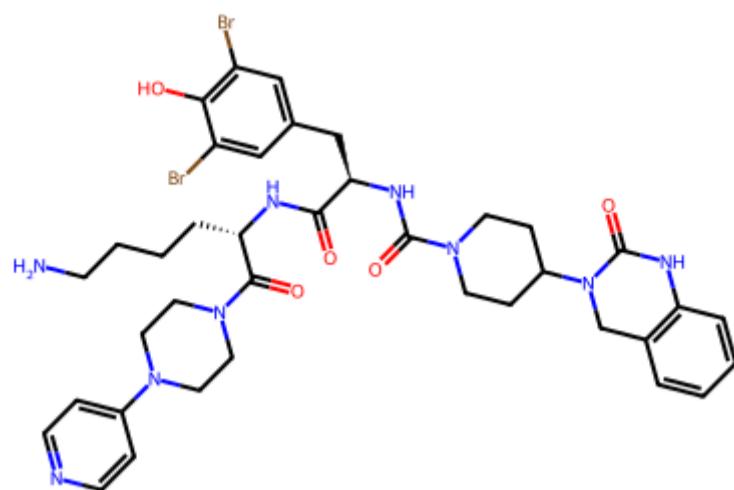
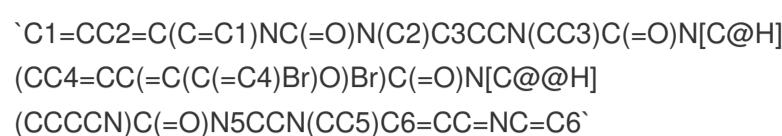
**SMILES:** C1=CC2=C(C=C1)NC(=O)N(C2)C3CCN(CC3)C(=O)N[C@H](CC4=CC(=C(C(=C4)Br)O)Br)C(=O)N[C@@H](CCCCN)C(=O)N5CCN(CC5)C6=CC=NC=C6

## Olcegepant (BIBN-4096BS) - Optimization Results

### Optimization Path

 Overall Comparison - Initial → Final

**\*\*Initial Molecule\*\***

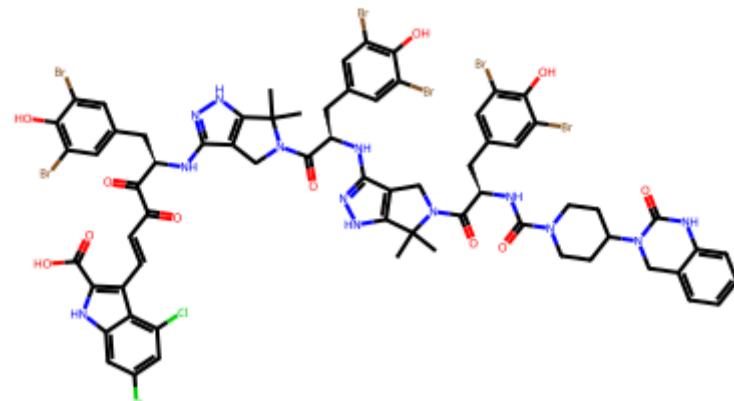
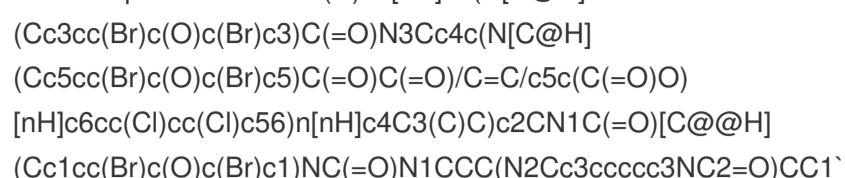


**\*\*QED (Drug-likeness):\*\* 0.1666 \*\*Number of Blocks:\*\* 5**

► Show ADMET Scores

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]**



**\*\*QED (Drug-likeness):\*\* 0.0265 (-0.1401) ✗ \*\*Number of Blocks:\*\* 7 (+2) ↑**

**\*\*Total Block Changes:\*\* 16**

► Show ADMET Scores

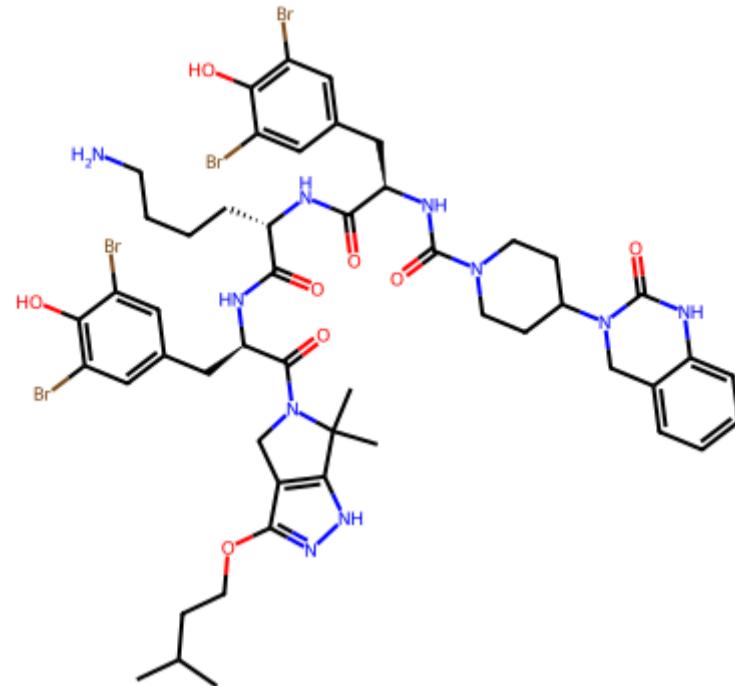
Task	Score	Change	Rel. Improvement	% Change
AMES <span style="color: green;">✓</span>	0.528857	-0.192753	+0.2671	-26.71%
BBBP <span style="color: green;">✓</span>	0.000205	+0.000139	+2.1037	+210.37%
CYP3A4 <span style="color: green;">✓</span>	0.000009	-0.009367	+0.9991	-99.91%
DILI <span style="color: green;">✓</span>	0.525996	-0.188054	+0.2634	-26.34%
HIA <span style="color: green;">✓</span>	0.999984	+0.010413	+0.0105	+1.05%
PGP <span style="color: red;">✗</span>	0.824368	+0.121425	-0.1727	+17.27%

**Optimization Steps:**

DETAILS PLACEHOLDER2

**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) X

**Number of Blocks:** 6 (+1) ↑

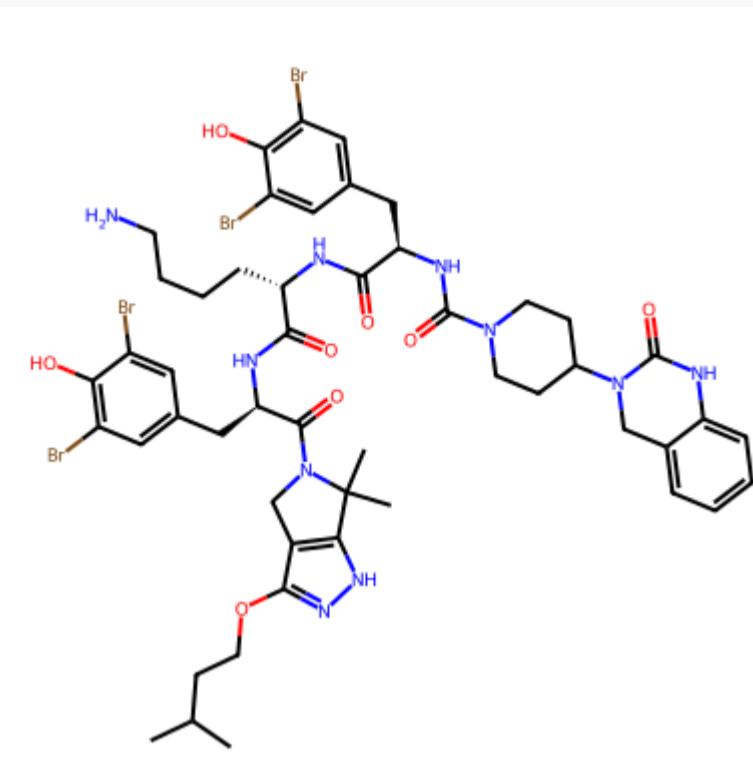
**Block Changes:** 8 (+4, -4)

**HIA Score:** 0.989571 → 0.999710 (+0.010140)

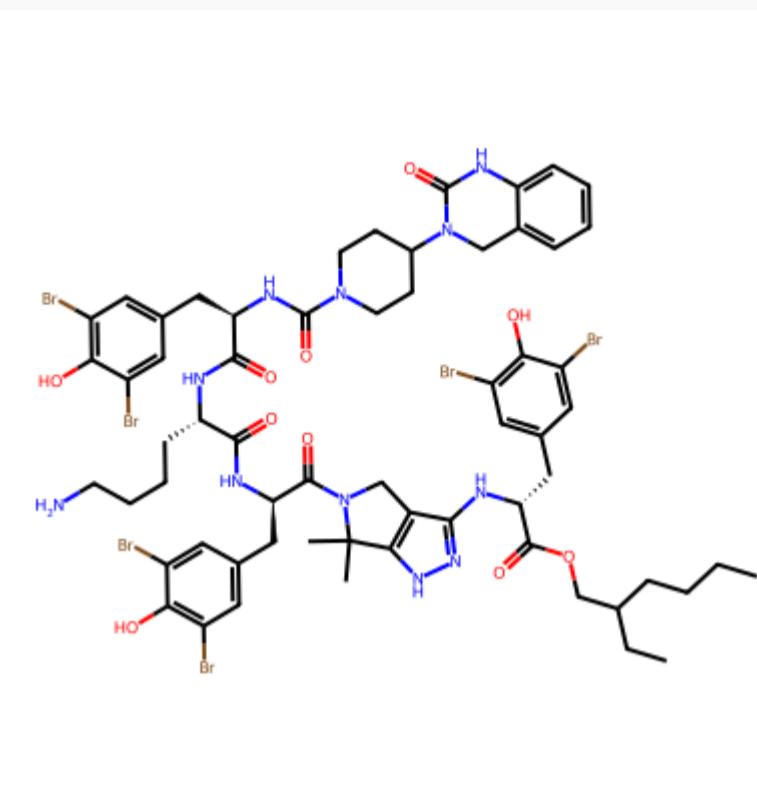
DETAILSPLACEHOLDER3

► 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(N3Cc4cccc4NC3=O)CC1)C2(C)C`



\*\*After (Step 2)\*\* `CCCCCC(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(N3Cc4cccc4NC3=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

**QED:** 0.0182 (-0.0238) ✗

**Number of Blocks:** 7 (+1) ↑

**Block Changes:** 3 (+2, -1)

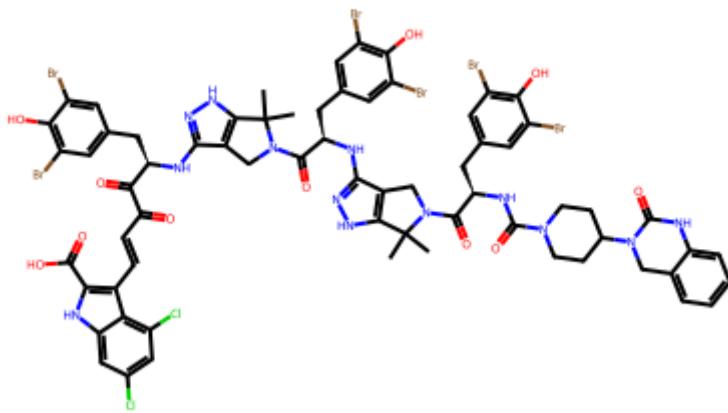
**AMES Score:** 0.612386 → 0.564568 (-0.047817)

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(N2Cc3cccc3NC2=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)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(N3Cc4cccc4NC

**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)

**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)n

## 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