

# Slide 4: PF-03758309 (PF-3758309)

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Initial Task: HIA

SMILES: CC1=NC2=C(C(=N1)NC3=NNC4=C3CN(C(=O)N[C@H](CN(C)C)C5=CC=CC=C5)C4(C)C)SC=C2

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## PF-03758309 (PF-3758309) - Optimization Results

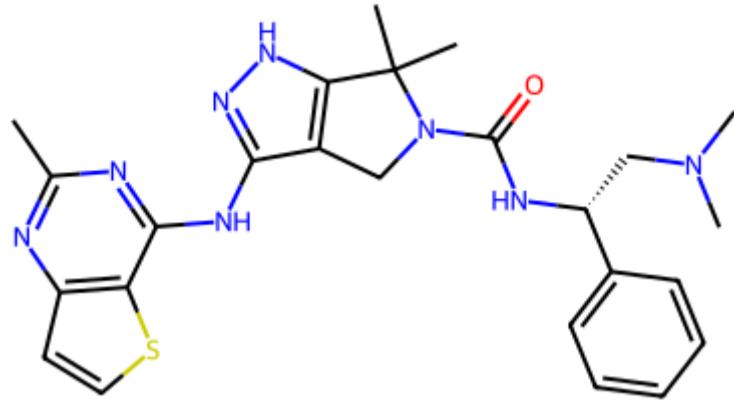
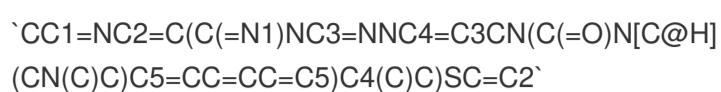
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### Optimization Path

 Overall Comparison - Initial → Final

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\*\*Initial Molecule\*\*

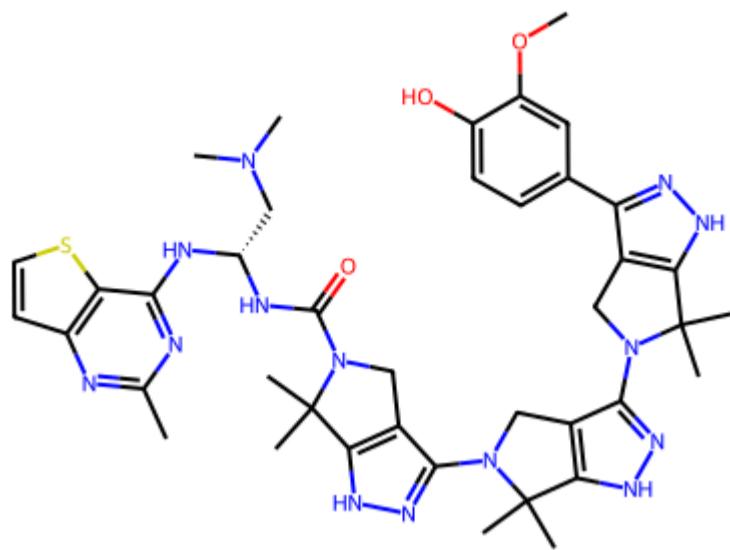


\*\*QED (Drug-likeness):\*\* 0.3671 \*\*Number of Blocks:\*\* 4

► Show ADMET Scores

Task	Score
AMES	0.419049
BBBP	0.778013
CYP3A4	0.011948
DILI	0.793920
HIA	0.984575
PGP	0.499705

\*\*Final Optimized\*\* `COc1cc(-c2n[nH]c3c2CN(c2n[nH]c4c2CN(c2n[nH]c5c2CN(C(=O)N[C@@H](CN(C)C)Nc2nc(C)nc6ccsc26)C5(C)C)C4(C)C)C3(C)C)ccc1O`



\*\*QED (Drug-likeness):\*\* 0.0961 (-0.2710) ✗ \*\*Number of Blocks:\*\* 6 (+2) ↑

\*\*Total Block Changes:\*\* 13

► Show ADMET Scores

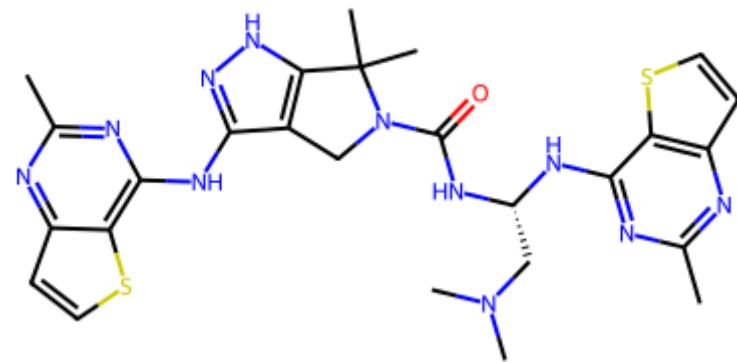
Task	Score	Change	Rel. Improvement	% Change
AMES ✗	0.686654	+0.267605	-0.6386	+63.86%
BBBP ✗	0.000213	-0.777801	-0.9997	-99.97%
CYP3A4 ✓	0.000889	-0.011059	+0.9256	-92.56%
DILI ✓	0.659112	-0.134808	+0.1698	-16.98%
HIA ✓	0.997891	+0.013316	+0.0135	+1.35%
PGP ✗	0.556859	+0.057154	-0.1144	+11.44%

### Optimization Steps:

DETAILS PLACEHOLDER2

### After (Step 1)

Cc1nc(Nc2n[nH]c3c2CN(C(=O)N[C@@H](CN(C)C)Nc2nc(C)nc4ccsc24)C3(C)C)c2scCc2n1



**QED:** 0.2053 (-0.1618) X

**Number of Blocks:** 4 (+0) →

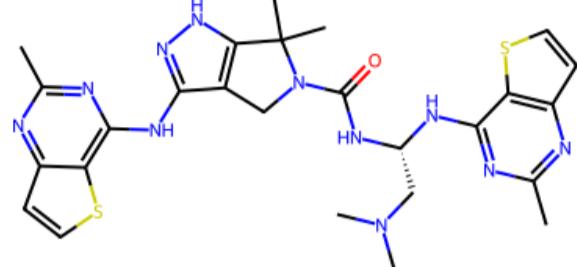
**Block Changes:** 6 (+3, -3)

**HIA Score:** 0.984575 → 0.995240 (+0.010665)

DETAILS *PLACEHOLDER3*

► Step 2: PGP (+0.0081 ↓) →

**\*\*Before (Step 1)\*\***

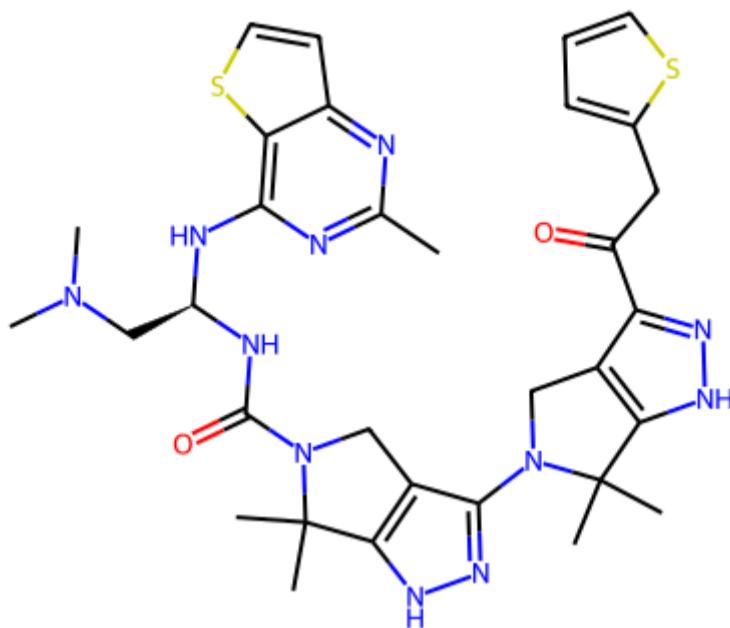


**\*\*QED:\*\*** 0.2053 **\*\*Number of Blocks:\*\*** 4

► All ADMET Scores

Task	Score	Direction
AMES	0.717762	↓ lower
BBBP	0.000191	↑ higher
CYP3A4	0.003685	↓ lower
DILI	0.691250	↓ lower
HIA	0.995240	↑ higher
PGP	0.564487	↓ lower

**\*\*After (Step 2)\*\*** `Cc1nc(N[C@H](C)C)NC(=O)N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)c2sccc2n1`



**QED:** 0.1259 (-0.0794) ✗

**Number of Blocks:** 5 (+1) ↑

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

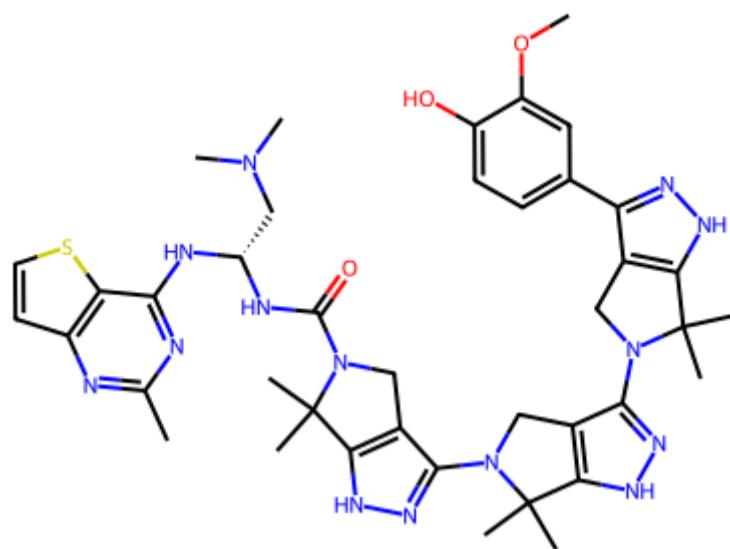
**PGP Score:** 0.564487 → 0.572543 (+0.008057)

DETAILSPLACEHOLDER5

DETAILSPLACEHOLDER6

**After (Step 3)**

C0c1cc(-c2n[nH]c3c2CN(c2n[nH]c4c2CN(c2n[nH]c5c2CN(C(=O)N[C@@H](C)C)Nc2nc(C)nc6ccsc26)C5(C)C)C4(C)C)C3(C)C)ccc10



**QED:** 0.0961 (-0.0299) X

**Number of Blocks:** 6 (+1) ↑

**Block Changes:** 4 (+2, -2)

**CYP3A4 Score:** 0.004173 → 0.000889 (-0.003285)

DETAILSPLACEHOLDER7

## Step Details

### Step 1: HIA ✓

Original	New	Change
0.984575	0.995240	+0.010665 ↑

```
Cc1nc(Nc2n[nH]c3c2CN(C(=O)N[C@H](CN(C)C)Nc2nc(C)nc4ccsc24)C3(C)C)c2sccc2n1
```

### Step 2: PGP ⚠

Original	New	Change
0.564487	0.572543	+0.008057 ↓

```
Cc1nc(N[C@H](CN(C)C)NC(=O)N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)c2sccc2n1
```

### Step 3: CYP3A4 ✓

Original	New	Change
0.004173	0.000889	-0.003285 ↓

```
C0c1cc(-c2n[nH]c3c2CN(c2n[nH]c4c2CN(c2n[nH]c5c2CN(C(=O)N[C@H](CN(C)C)Nc2nc(C)nc6ccsc26)C5(C)C)c4(C)C)c3(C)C)ccc10
```

## ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.419049	0.686654	+0.267605	-0.6386	+63.86%	<span style="color:red;">X</span> Declined
BBBP	↑ higher	0.778013	0.000213	-0.777801	-0.9997	-99.97%	<span style="color:red;">X</span> Declined
CYP3A4	↓ lower	0.011948	0.000889	-0.011059	+0.9256	-92.56%	<span style="color:green;">✓</span> Improved
DILI	↓ lower	0.793920	0.659112	-0.134808	+0.1698	-16.98%	<span style="color:green;">✓</span> Improved
HIA	↑ higher	0.984575	0.997891	+0.013316	+0.0135	+1.35%	<span style="color:green;">✓</span> Improved
PGP	↓ lower	0.499705	0.556859	+0.057154	-0.1144	+11.44%	<span style="color:red;">X</span> Declined

**Improved:** 3/6 (50.0%) | **Molecules:** 139 | **Paths:** 2743

## 🔍 Safety Threshold Analysis

**Status:** 2/6 meet thresholds

⚠ **Below threshold:** 4

Task	Score	Threshold	Gap
BBBP	0.0002	↑ 0.5	0.4998
AMES	0.6867	↓ 0.3	0.3867
DILI	0.6591	↓ 0.4	0.2591
PGP	0.5569	↓ 0.3	0.2569

✓ **Passing:** 2

Task	Score	Threshold
CYP3A4	0.0009	↓ 0.55
HIA	0.9979	↑ 0.2