

Slide 23: AZD-3514

Initial Task: HIA

SMILES: CC(=O)N1CCN(CC1)CCOC2=CC=C(C=C2)C3CCN(CC3)C4=NN5C(=NN=C5C(F)(F)F)CC4

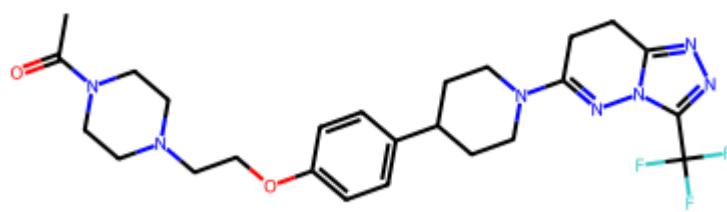
AZD-3514 - Optimization Results

Optimization Path

 Overall Comparison - Initial → Final

****Initial Molecule****

`CC(=O)N1CCN(CC1)CCOC2=CC=C(C=C2)C3CCN(CC3)C4=NN5C(=NN=C5C(F)(F)F)CC4`

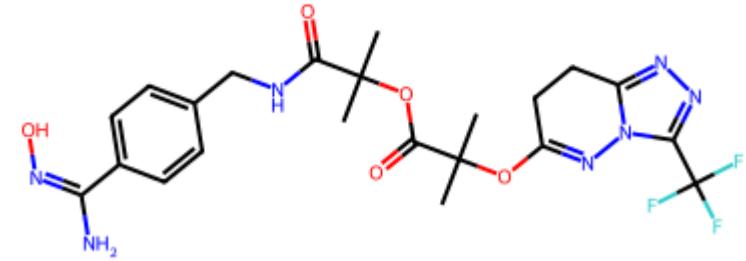


****QED (Drug-likeness):**** 0.6048 ****Number of Blocks:**** 4

► Show ADMET Scores

Task	Score
AMES	0.382188
BBBP	0.998411
CYP3A4	0.030133
DILI	0.747011
HIA	0.999712
PGP	0.644132

****Final Optimized**** `CC(C)(OC(=O)C(C)(C)OC1=Nn2c(nnc2C(F)(F)F)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1`



****QED (Drug-likeness):**** 0.1621 (-0.4427) **X** ****Number of Blocks:**** 3 (-1) ↓
****Total Block Changes:**** 9

► Show ADMET Scores

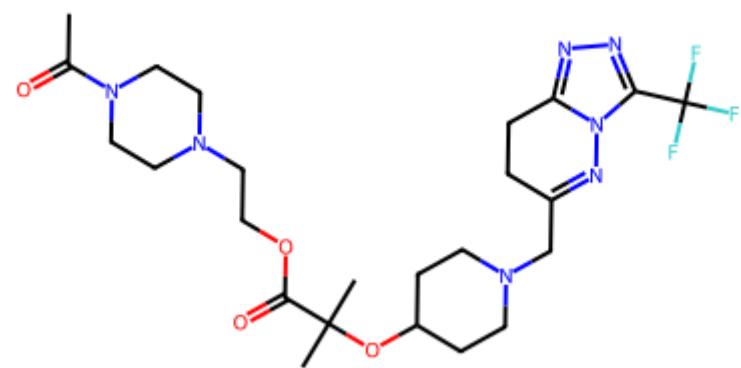
Task	Score	Change	Rel. Improvement	% Change
AMES X	0.641817	+0.259629	-0.6793	+67.93%
BBBP X	0.000596	-0.997815	-0.9994	-99.94%
CYP3A4 ✓	0.019928	-0.010205	+0.3387	-33.87%
DILI ✓	0.551265	-0.195746	+0.2620	-26.20%
HIA X	0.938515	-0.061197	-0.0612	-6.12%
PGP ✓	0.620027	-0.024105	+0.0374	-3.74%

Optimization Steps:

DETAILS PLACEHOLDER2

After (Step 1)

CC(=O)N1CCN(CC1)CCOC(=O)C(C)(C)OC2CCN(CC3=Nn4c(nnc4C(F)(F)F)CC3)CC2)CC1



QED: 0.4537 (-0.1511) X

Number of Blocks: 3 (-1) ↓

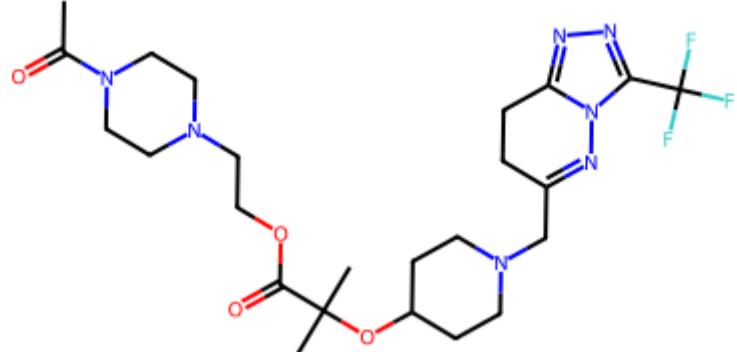
Block Changes: 3 (+1, -2)

HIA Score: 0.999712 → 0.999154 (-0.000558)

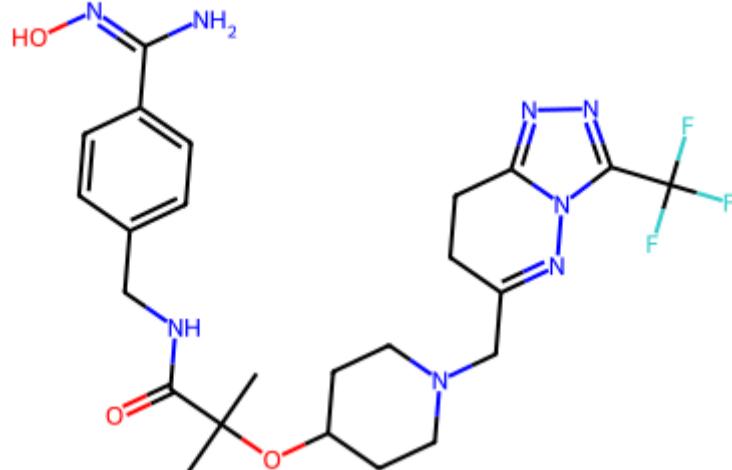
DETAILS *PLACEHOLDER3*

► Step 2: AMES (+0.3347 ↓)

****Before (Step 1)**** `CC(=O)N1CCN(CCOC(=O)C(C)(C)OC2CCN(CC3=Nn4c(nnc4C(F)(F)F)CC3)CC2)CC1`



****After (Step 2)**** `CC(C)(OC1CCN(CC2=Nn3c(nnc3C(F)(F)F)CC2)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1`



****QED:**** 0.4537 ****Number of Blocks:**** 3

► All ADMET Scores

Task	Score	Direction
AMES	0.396480	↓ lower
BBBP	0.999983	↑ higher
CYP3A4	0.051562	↓ lower
DILI	0.619876	↓ lower
HIA	0.999154	↑ higher
PGP	0.694290	↓ lower

QED: 0.2030 (-0.2507) X

Number of Blocks: 3 (+0) ➡

Block Changes: 2 (+1, -1)

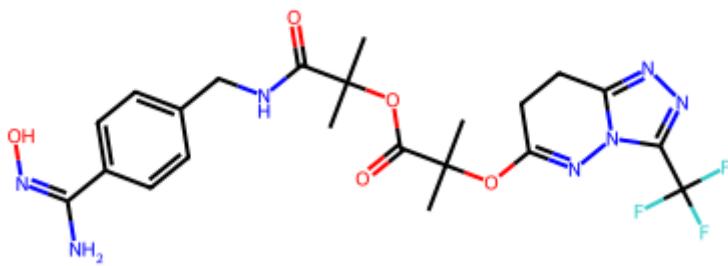
AMES Score: 0.396480 → 0.731145 (+0.334666)

DETAILSPLACEHOLDER5

DETAILSPLACEHOLDER6

After (Step 3)

CC(C)(OC(=O)C(C)(C)OC1=Nn2c(nnc2C(F)(F)F)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1



QED: 0.1621 (-0.0408) X

Number of Blocks: 3 (+0) →

Block Changes: 4 (+2, -2)

AMES Score: 0.731145 → 0.641817 (-0.089329)

DETAILSPLACEHOLDER7

Step Details

Step 1: HIA ⚠

Original	New	Change
0.999712	0.999154	-0.000558 ↑

CC(=O)N1CCN(CCOC(=O)C(C)(C)OC2CCN(CC3=Nn4c(nnc4C(F)(F)F)CC3)CC2)CC1

Step 2: AMES ⚠

Original	New	Change
0.396480	0.731145	+0.334666 ↓

CC(C)(OC1CCN(CC2=Nn3c(nnc3C(F)(F)F)CC2)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1

Step 3: AMES ✓

Original	New	Change
0.731145	0.641817	-0.089329 ↓

CC(C)(OC(=O)C(C)(C)OC1=Nn2c(nnc2C(F)(F)F)CC1)C(=O)NCc1ccc(/C(N)=N\O)cc1

ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.382188	0.641817	+0.259629	-0.6793	+67.93%	X Declined
BBBP	↑ higher	0.998411	0.000596	-0.997815	-0.9994	-99.94%	X Declined
CYP3A4	↓ lower	0.030133	0.019928	-0.010205	+0.3387	-33.87%	✓ Improved
DILI	↓ lower	0.747011	0.551265	-0.195746	+0.2620	-26.20%	✓ Improved
HIA	↑ higher	0.999712	0.938515	-0.061197	-0.0612	-6.12%	X Declined
PGP	↓ lower	0.644132	0.620027	-0.024105	+0.0374	-3.74%	✓ Improved

Improved: 3/6 (50.0%) | **Molecules:** 31 | **Paths:** 102

Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠ **Below threshold:** 4

Task	Score	Threshold	Gap
BBBP	0.0006	↑ 0.5	0.4994
AMES	0.6418	↓ 0.3	0.3418
PGP	0.6200	↓ 0.3	0.3200
DILI	0.5513	↓ 0.4	0.1513

✓ **Passing:** 2

Task	Score	Threshold
CYP3A4	0.0199	↓ 0.55
HIA	0.9385	↑ 0.2