

## Slide 13: Danuglipron (Pfizer)

## Initial Task: DILI

**SMILES:** C1=CC(=NC(=C1)OCC2=CC=C(C=C2F)C#N)C3CCN(CC3)CC4=NC5=CC=C(C=C5N4C[C@H]6CCO6)C(=O)O

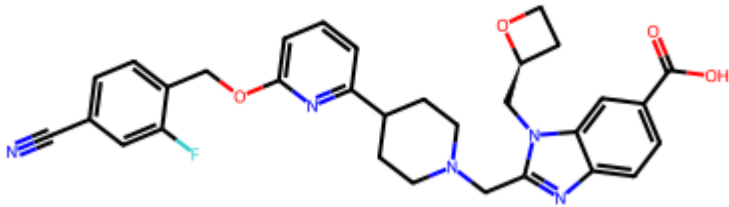
## Danuglipron (Pfizer) - Optimization Results

## Optimization Path

## Overall Comparison - Initial → Final

\*\*Initial Molecule\*\*

`C1=CC(=NC(=C1)OCC2=CC=C(C=C2F)C#N)C3CCN(CC3)CC4=NC5=CC=C(C=C5N4C[C@@H]6CCO6)C(=O)O`

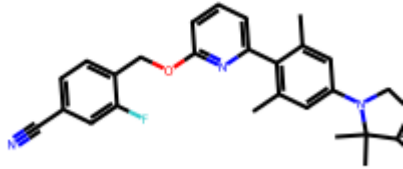


\*\*QED (Drug-likeness):\*\* 0.3107 \*\*Number of Blocks:\*\* 4

► **Show ADMET Scores**

Task	Score
AMES	0.755845
BBBP	0.000238
CYP3A4	0.009860
DILI	0.804817
HIA	0.993762
PGP	0.573991

\*\*Final Optimized\*\* `Cc1cc(N2Cc3c(N4Cc5c(-c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)n1cccc(OCc2ccc(C#N)cc2F)n1`



\*\*QED (Drug-likeness):\*\* 0.1314 (-0.1793) ✗  
Block Changes:\*\* 16

► **Show ADMET Scores**

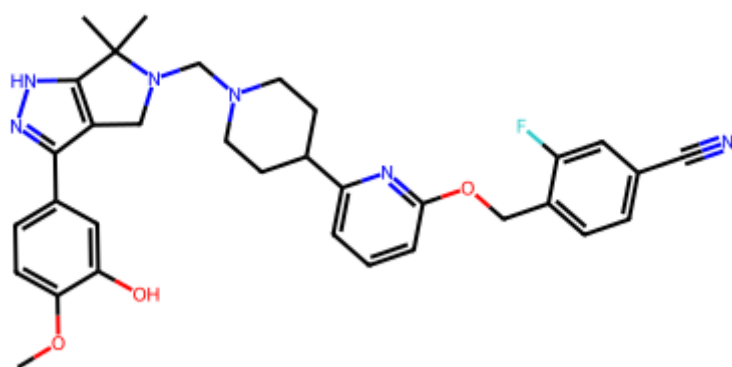
Task	Score	Change
AMES <span>✓</span>	0.648178	-0.107668
BBBP <span>✓</span>	0.000290	+0.000053
CYP3A4 <span>✓</span>	0.001107	-0.008752
DILI <span>✓</span>	0.550500	-0.254317
HIA <span>✗</span>	0.966419	-0.027343
PGP <span>✓</span>	0.571472	-0.002519

**Optimization Steps:**

DETAILSPLACEHOLDER2

**After (Step 1)**

C0c1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(OCc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc1O



**QED:** 0.2738 (-0.0369) ❌

**Number of Blocks:** 4 (+0) ➡

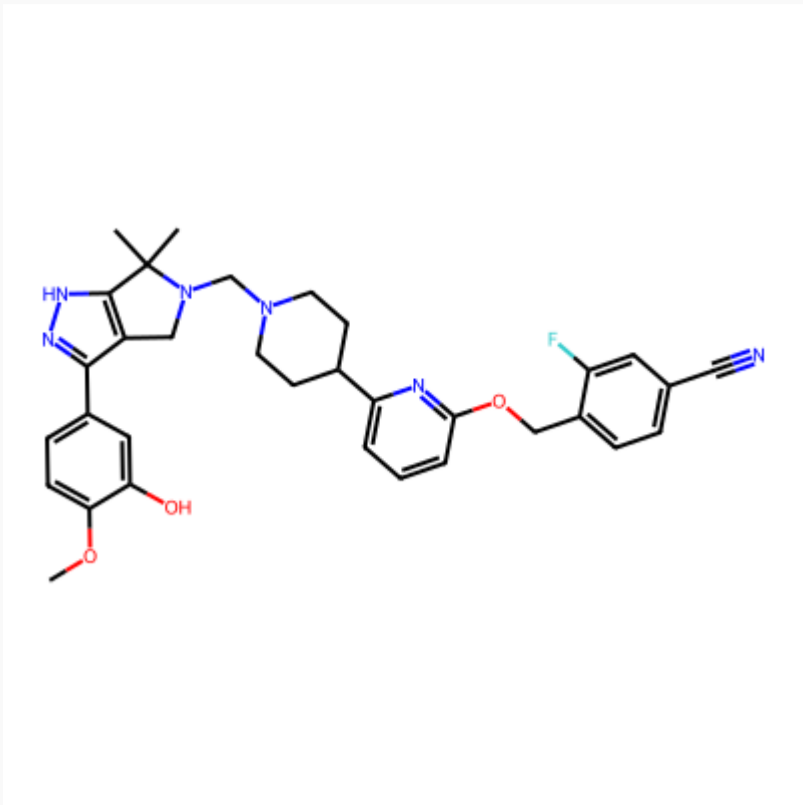
**Block Changes:** 6 (+3, -3)

**DILI Score:** 0.804817 → 0.721803 (-0.083013)

DETAILS *PLACEHOLDER3*

► **Step 2: PGP** (-0.0441 ↓) ✅

**\*\*Before (Step 1)\*\*** `COc1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(OCc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc1O`



**\*\*QED:\*\*** 0.2738 **\*\*Number of Blocks:\*\*** 4

► All ADMET Scores		
Task	Score	Direction
AMES	0.713190	↓ lower
BBBP	0.000162	↑ higher
CYP3A4	0.018157	↓ lower
DILI	0.721803	↓ lower
HIA	0.971368	↑ higher
PGP	0.598865	↓ lower

**\*\*After (Step 2)\*\*** `CC1(C)c2[nH]nc(N3Cc4c(NC56CC7CC(CC(C7)C5)C6)n[nH]c4C3(C)C)c2CN1CN1`



**QED:** 0.1586 (-0.1151) ❌

**Number of Blocks:** 5 (+1) ↑

**Block Changes:** 7 (+4, -3)

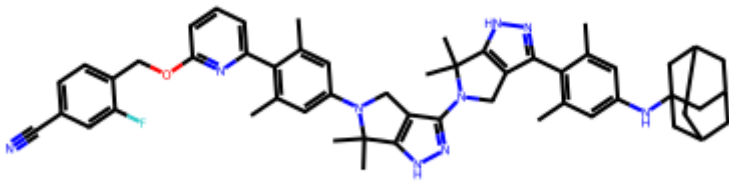
**PGP Score:** 0.598865 → 0.554803 (-0.044061)

DETAILSPLACEHOLDER5

DETAILSPLACEHOLDER6

After (Step 3)

Cc1cc(N2Cc3c(N4Cc5c(-c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1-c1cccc(OCc2ccc(C#N)cc2F)n1



QED: 0.1314 (-0.0272) ❌

Number of Blocks: 7 (+2) ↑

Block Changes: 3 (+2, -1)

PGP Score: 0.554803 → 0.571472 (+0.016669)

DETAILSPLACEHOLDER7

### Step Details

Step 1: DILI ✅

Original	New	Change
0.804817	0.721803	-0.083013 ↓

C0c1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(OCc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc10

Step 2: PGP ✅

Original	New	Change
0.598865	0.554803	-0.044061 ↓

CC1(C)c2[nH]nc(N3Cc4c(NC56CC7CC(CC(C7)C5)C6)n[nH]c4C3(C)C)c2CN1CN1CCC(c2cccc(OCc3ccc(C#N)cc3F)n2)CC1

Step 3: PGP ⚠️

Original	New	Change
0.554803	0.571472	+0.016669 ↓

Cc1cc(N2Cc3c(N4Cc5c(-c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1-c1cccc(OCc2ccc(C#N)cc2F)n1

 ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.755845	0.648178	-0.107668	+0.1424	-14.24%	✔ Improved
BBBP	↑ higher	0.000238	0.000290	+0.000053	+0.2221	+22.21%	✔ Improved
CYP3A4	↓ lower	0.009860	0.001107	-0.008752	+0.8877	-88.77%	✔ Improved
DILI	↓ lower	0.804817	0.550500	-0.254317	+0.3160	-31.60%	✔ Improved
HIA	↑ higher	0.993762	0.966419	-0.027343	-0.0275	-2.75%	✖ Declined
PGP	↓ lower	0.573991	0.571472	-0.002519	+0.0044	-0.44%	✔ Improved

Improved: 5/6 (83.3%) | Molecules: 385 | Paths: 5311

 Safety Threshold Analysis

Status: 2/6 meet thresholds

⚠ Below threshold: 4

Task	Score	Threshold	Gap
BBBP	0.0003	↑ 0.5	0.4997
AMES	0.6482	↓ 0.3	0.3482
PGP	0.5715	↓ 0.3	0.2715
DILI	0.5505	↓ 0.4	0.1505

✔ Passing: 2

Task	Score	Threshold
CYP3A4	0.0011	↓ 0.55
HIA	0.9664	↑ 0.2