

# Slide 13: Danuglipron (Pfizer)

Initial Task: DILI

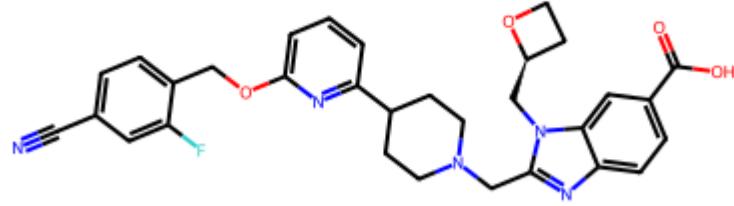
SMILES: C1=CC(=NC(=C1)OCC2=CC=C(C=C2F)C#N)C3CCN(CC3)CC4=NC5=CC=C(C=C5N4C[C@H]6CCO6)C(=O)O

## Danuglipron (Pfizer) - Optimization Results

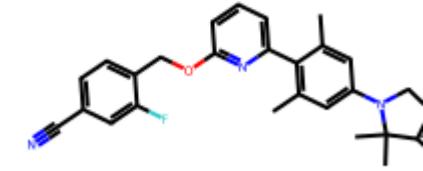
### Optimization Path

 Overall Comparison - Initial → Final

\*\*Initial Molecule\*\*



\*\*Final Optimized\*\* `Cc1cc(N2Cc3c(N4Cc5c(c6c(C)cc(NC78CC9CC(CC(C9)C7)C8)cc6C)c1cccc(OCc2ccc(C#N)cc2F)n1`



\*\*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

\*\*QED (Drug-likeness):\*\* 0.1314 (-0.1793) X

Block Changes:\*\* 16

► Show ADMET Scores

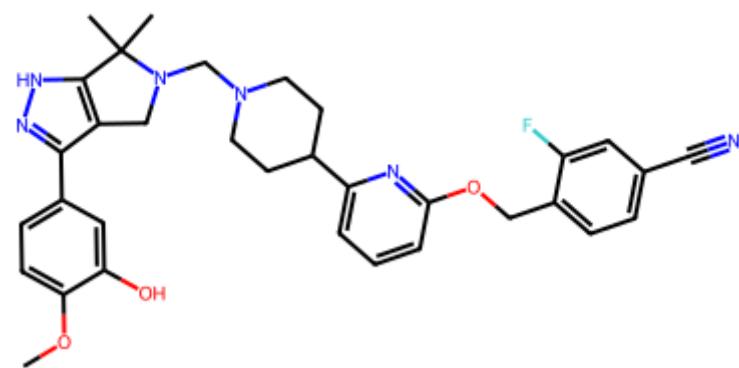
Task	Score	Change
AMES <span style="color:green">✓</span>	0.648178	-0.107668
BBBP <span style="color:green">✓</span>	0.000290	+0.000053
CYP3A4 <span style="color:green">✓</span>	0.001107	-0.008752
DILI <span style="color:green">✓</span>	0.550500	-0.254317
HIA <span style="color:red">X</span>	0.966419	-0.027343
PGP <span style="color:green">✓</span>	0.571472	-0.002519

Optimization Steps:

DETAILS PLACEHOLDER2

After (Step 1)

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



**QED:** 0.2738 (-0.0369) X

**Number of Blocks:** 4 (+0)  

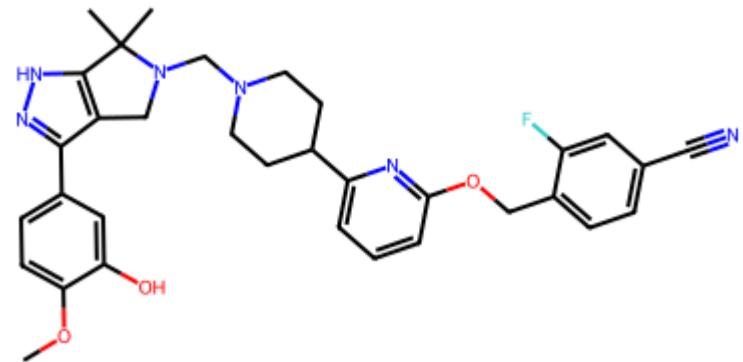
**Block Changes:** 6 (+3, -3)

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

DETAILS *PLACEHOLDER3*

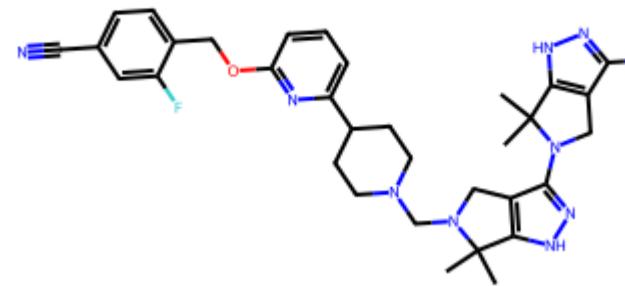
► Step 2: PGP (-0.0441 ↓) ✓

\*\*Before (Step 1)\*\* `COc1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(OCCc5ccc(C#N)cc5F)n4)CC2)C3(C)C)cc1O`



\*\*After (Step 2)\*\*

`CC1(C)c2[nH]nc(N3Cc4c(NC56CC7CC(CC(C7)C5)C6)n[nH]c4C3(C)C)c2CN1CN1`



\*\*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

**QED:** 0.1586 (-0.1151) ✗

**Number of Blocks:** 5 (+1) ↑

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

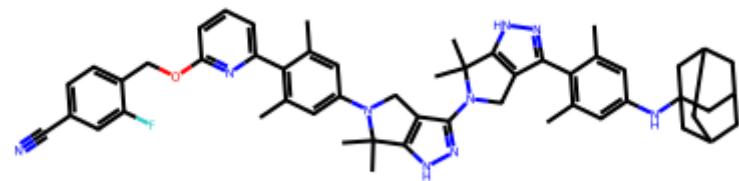
**PGP Score:** 0.598865 → 0.554803 (-0.044061)

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)

DETAILS PLACEHOLDER7

## 📊 Step Details

### Step 1: DILI ✓

Original	New	Change
0.804817	0.721803	-0.083013 ↓

```
C0c1ccc(-c2n[nH]c3c2CN(CN2CCC(c4cccc(0Cc5ccc(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(0Cc3ccc(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(0Cc2ccc(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