# Slide 11: Fasiglifam (TAK-875)

**Initial Task:** DILI

**SMILES:** `CC1=C(C(=CC(=C1)OCCCS(=O)(=O)C)C)C2=CC(=CC=C2)COC3=CC=C4[C@@H](CC(=O)O)COC4=C3`

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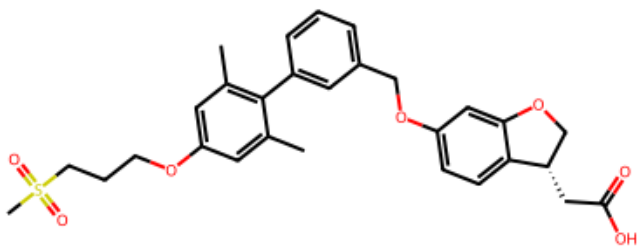
# Fasiglifam (TAK-875) - Optimization Results

## 🔗 Optimization Path

### 📊 Overall Comparison - Initial → Final

**Initial Molecule** `CC1=C(C(=CC(=C1)OCCCS(=O)(=O)C)C)C2=CC(=CC=C2)COC3=CC=C4[C@@H](CC(=O)O)COC4=C3`

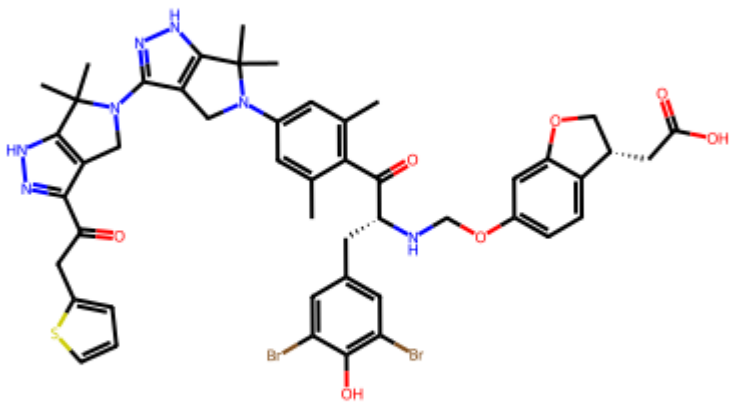


**QED (Drug-likeness):** 0.3393 **Number of Blocks:** 4

▶ ***Show ADMET Scores***

| Task | Score |
|---|---|
| AMES | 0.459273 |
| BBBP | 0.999996 |
| CYP3A4 | 0.082408 |
| DILI | 0.605552 |
| HIA | 0.659498 |
| PGP | 0.636196 |

**Final Optimized** `Cc1cc(N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`



**QED (Drug-likeness):** 0.0486 (-0.2907) ❌ **Number of Blocks:** 5 (+1) ↑ **Total Block Changes:** 11

▶ ***Show ADMET Scores***

| Task | Score | Change | Rel. Improvement | % Change |
|---|---|---|---|---|
| AMES ✅ | 0.259236 | -0.200037 | +0.4356 | -43.56% |
| BBBP ❌ | 0.999966 | -0.000030 | -0.0000 | -0.00% |
| CYP3A4 ✅ | 0.001861 | -0.080547 | +0.9774 | -97.74% |
| DILI ✅ | 0.380775 | -0.224777 | +0.3712 | -37.12% |
| HIA ✅ | 0.996015 | +0.336517 | +0.5103 | +51.03% |
| PGP ❌ | 0.755818 | +0.119622 | -0.1880 | +18.80% |

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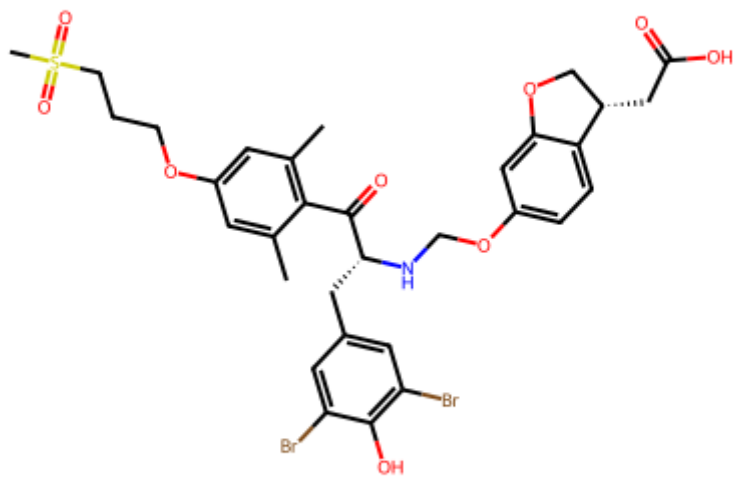
**Optimization Steps:**

DETAILS*PLACEHOLDER2*

**After (Step 1)**

```
Cc1cc(OCCCS(C)(=O)=O)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O
```




**QED:** 0.0997 (-0.2396) ❌

**Number of Blocks:** 3 (-1) ↓

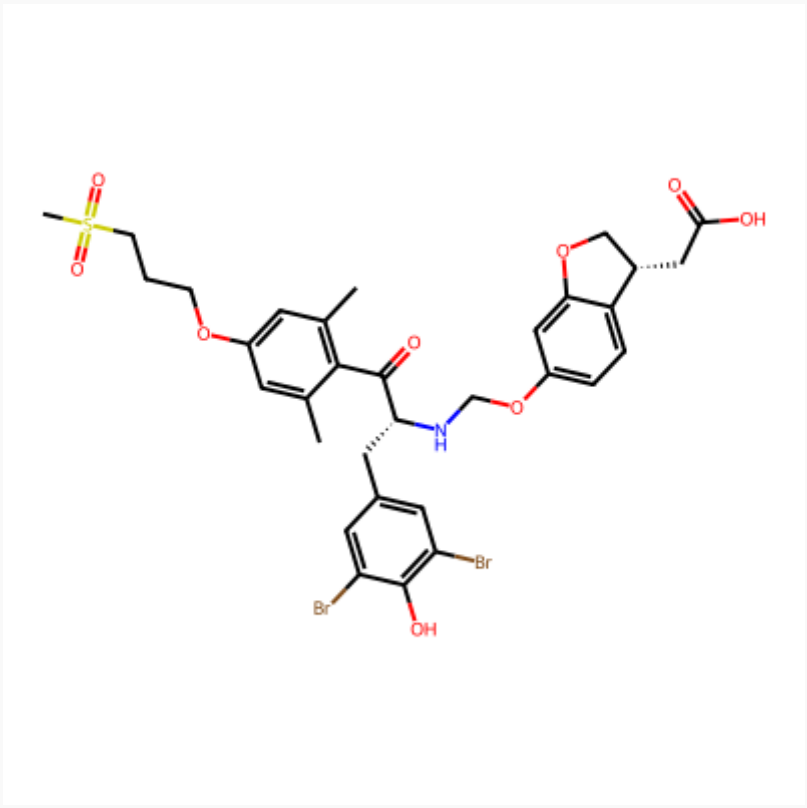
**Block Changes:** 5 (+2, -3)

**DILI Score:** 0.605552 → 0.424327 (-0.181224)

DETAILS*PLACEHOLDER3*

**▶ Step 2: BBBP (+0.0000 ↑) ✅**

**Before (Step 1)** `Cc1cc(OCCCS(C)(=O)=O)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`

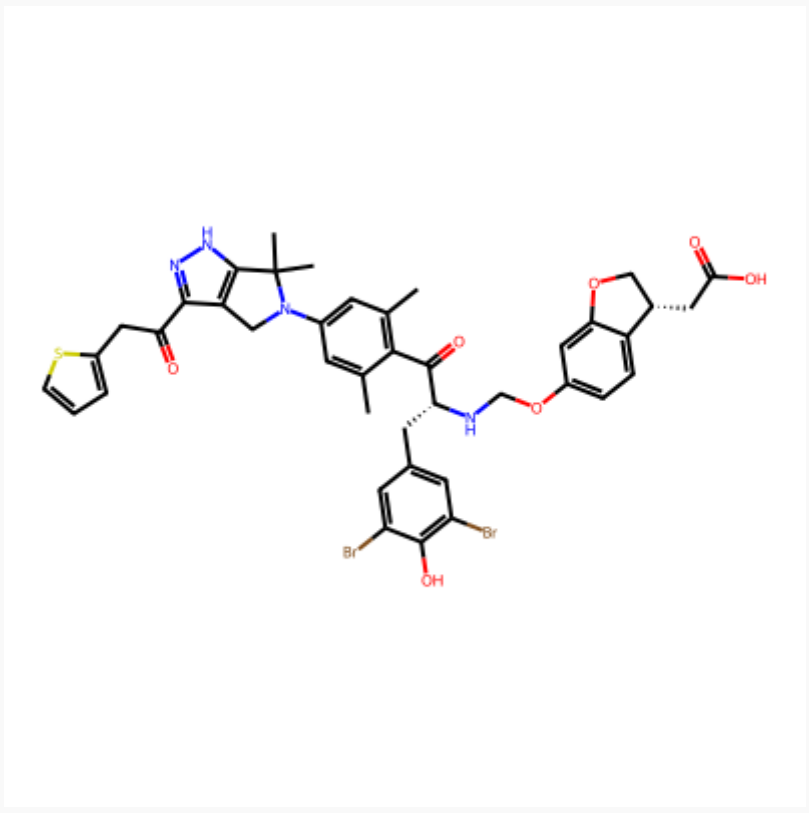


**QED:** 0.0997 **Number of Blocks:** 3

▶ ***All ADMET Scores***

| Task | Score | Direction |
|---|---|---|
| AMES | 0.265935 | ↓ lower |
| BBBP | 0.999996 | ↑ higher |
| CYP3A4 | 0.000436 | ↓ lower |
| DILI | 0.424327 | ↓ lower |
| HIA | 0.999337 | ↑ higher |
| PGP | 0.816133 | ↓ lower |

**After (Step 2)** `Cc1cc(N2Cc3c(C(=O)Cc4cccs4)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`



**QED:** 0.0632 (-0.0365) ❌

**Number of Blocks:** 4 (+1) ↑

**Block Changes:** 5 (+3, -2)

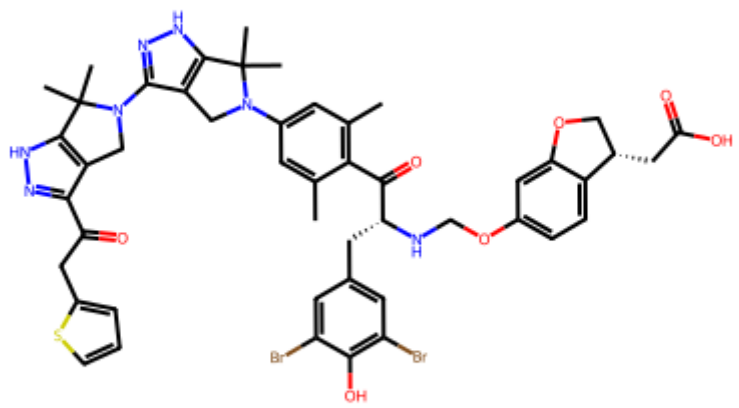
**BBBP Score:** 0.999996 → 1.000000 (+0.000004)

DETAILS*PLACEHOLDER*5

DETAILS*PLACEHOLDER*6

**After (Step 3)**

`Cc1cc(N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O`



**QED:** 0.0486 (-0.0146) ❌

**Number of Blocks:** 5 (+1) ↑

**Block Changes:** 1 (+1, -0)

**PGP Score:** 0.798334 → 0.755818 (-0.042516)

DETAILS*PLACEHOLDER7*

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## 📊 Step Details

**Step 1: DILI** ✅

| Original | New | Change |
|---|---|---|
| 0.605552 | 0.424327 | -0.181224 ↓ |

```
Cc1cc(OCCCS(C)(=O)=O)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O
```

**Step 2: BBBP** ✅

| Original | New | Change |
|---|---|---|
| 0.999996 | 1.000000 | +0.000004 ↑ |

```
Cc1cc(N2Cc3c(C(=O)Cc4cccs4)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O
```

**Step 3: PGP** ✅

| Original | New | Change |
|---|---|---|
| 0.798334 | 0.755818 | -0.042516 ↓ |

```
Cc1cc(N2Cc3c(N4Cc5c(C(=O)Cc6cccs6)n[nH]c5C4(C)C)n[nH]c3C2(C)C)cc(C)c1C(=O)[C@@H](Cc1cc(Br)c(O)c(Br)c1)NCOc1ccc2c(c1)OC[C@@H]2CC(=O)O
```

## 📊 ADMET Comparison

| Task | Direction | Initial | Final | Change | Rel. Improvement | % Change | Status |
|---|---|---|---|---|---|---|---|
| AMES | ↓ lower | 0.459273 | 0.259236 | -0.200037 | +0.4356 | -43.56% | ✅ Improved |
| BBBP | ↑ higher | 0.999996 | 0.999966 | -0.000030 | -0.0000 | -0.00% | ❌ Declined |
| CYP3A4 | ↓ lower | 0.082408 | 0.001861 | -0.080547 | +0.9774 | -97.74% | ✅ Improved |
| DILI | ↓ lower | 0.605552 | 0.380775 | -0.224777 | +0.3712 | -37.12% | ✅ Improved |
| HIA | ↑ higher | 0.659498 | 0.996015 | +0.336517 | +0.5103 | +51.03% | ✅ Improved |
| PGP | ↓ lower | 0.636196 | 0.755818 | +0.119622 | -0.1880 | +18.80% | ❌ Declined |

**Improved:** 4/6 (66.7%) | **Molecules:** 175 | **Paths:** 2055

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## 🔍 Safety Threshold Analysis

**Status:** 5/6 meet thresholds

⚠️ **Below threshold:** 1

| Task | Score | Threshold | Gap |
|---|---|---|---|
| PGP | 0.7558 | ↓ 0.3 | 0.4558 |

✅ **Passing:** 5

| Task | Score | Threshold |
|---|---|---|
| AMES | 0.2592 | ↓ 0.3 |
| BBBP | 1.0000 | ↑ 0.5 |
| CYP3A4 | 0.0019 | ↓ 0.55 |
| DILI | 0.3808 | ↓ 0.4 |
| HIA | 0.9960 | ↑ 0.2 |