

# Slide 16: Mibepradil (Posicor)

Initial Task: CYP3A4

SMILES: CC(C)[C@H]1C2=CC=C(C=C2CC[C@H]1CCN(C)CCCC3=NC4=C(C=CC=C4)N3)OC(=O)COC)F

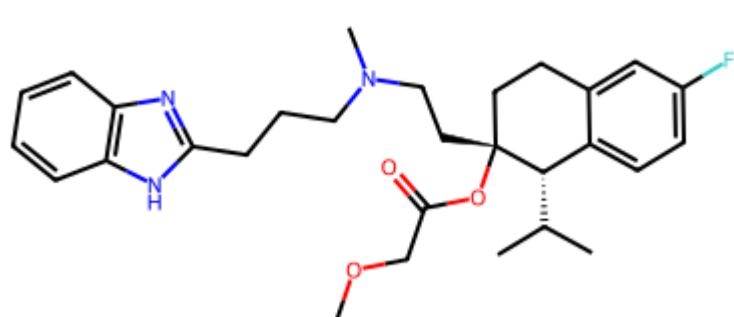
## Mibepradil (Posicor) - Optimization Results

### Optimization Path

 Overall Comparison - Initial → Final

\*\*Initial Molecule\*\* `CC(C)

[C@H]1C2=CC=C(C=C2CC[C@@]1(CCNC(=CCCC3=NC4=C(C=CC=C4)N3)OC(=O)CO)F`



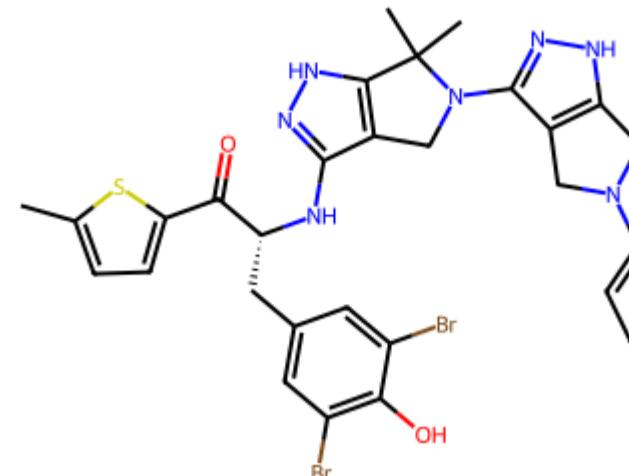
\*\*QED (Drug-likeness):\*\* 0.3672 \*\*Number of Blocks:\*\* 3

► Show ADMET Scores

Task	Score
AMES	0.456651
BBBP	0.999996
CYP3A4	0.020786
DILI	0.675483
HIA	0.994189
PGP	0.700888

\*\*Final Optimized\*\* `Cc1ccc(C(=O)[C@@H]

(Cc2cc(Br)c(O)c(Br)c2)Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#



\*\*QED (Drug-likeness):\*\* 0.1154 (-0.2518) ✗ \*\*Number of Blocks:\*\*

Changes:\*\* 11

► Show ADMET Scores

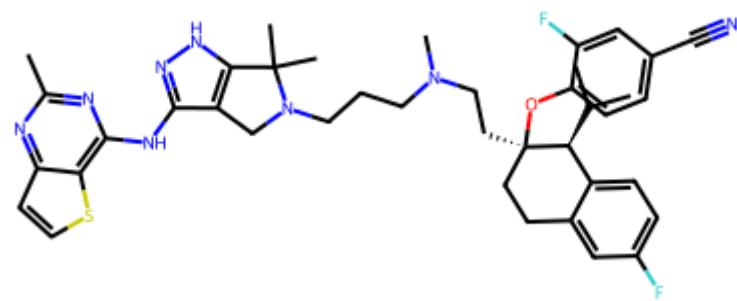
Task	Score	Change	Rel. Improvement
AMES ✗	0.665578	+0.208928	-0.4575
BBBP ✗	0.000031	-0.999965	-1.0000
CYP3A4 ✓	0.000141	-0.020645	+0.9932
DILI ✓	0.393913	-0.281570	+0.4168
HIA ✓	0.999665	+0.005475	+0.0055
PGP ✗	0.747508	+0.046620	-0.0665

### Optimization Steps:

DETAILS PLACEHOLDER2

### After (Step 1)

Cc1nc(Nc2n[nH]c3c2CN(CCCN(C)CC[C@@]2(0c4ccc(C#N)cc4F)CCc4cc(F)ccc4[C@@H]2C(C)C)C3(C)C)c2sc2n1



**QED:** 0.1319 (-0.2353) X

**Number of Blocks:** 3 (+0)  

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

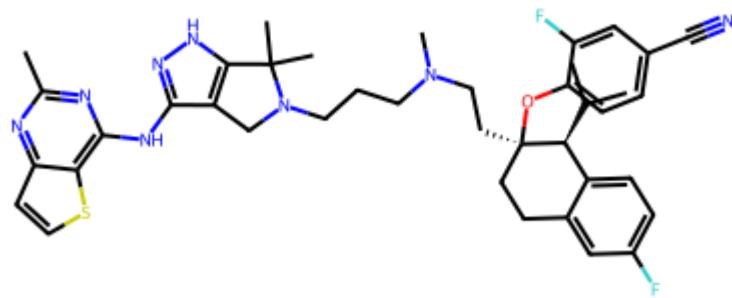
**CYP3A4 Score:** 0.020786 → 0.012962 (-0.007824)

DETAILS *PLACEHOLDER3*

► Step 2: AMES (+0.0112 ↓)

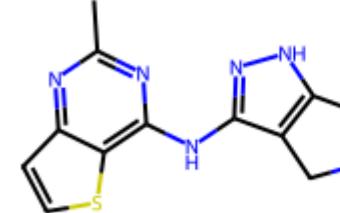
**\*\*Before (Step 1)\*\***

`Cc1nc(Nc2n[nH]c3c2CN(CCCN(C)CC[C@@]2(Oc4ccc(C#N)cc4F)CCc4cc(F)ccc4[C@@H]2C(C)C)C3(C)C)c2sccc2n1`



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

`Cc1nc(Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)s1`



**\*\*QED:\*\*** 0.1319 **\*\*Number of Blocks:\*\*** 3

**QED:** 0.2579 (+0.1260) ✓

**Number of Blocks:** 4 (+1) ↑

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

**AMES Score:** 0.735399 → 0.746586 (+0.01117)

DETAILSPLACEHOLDER5

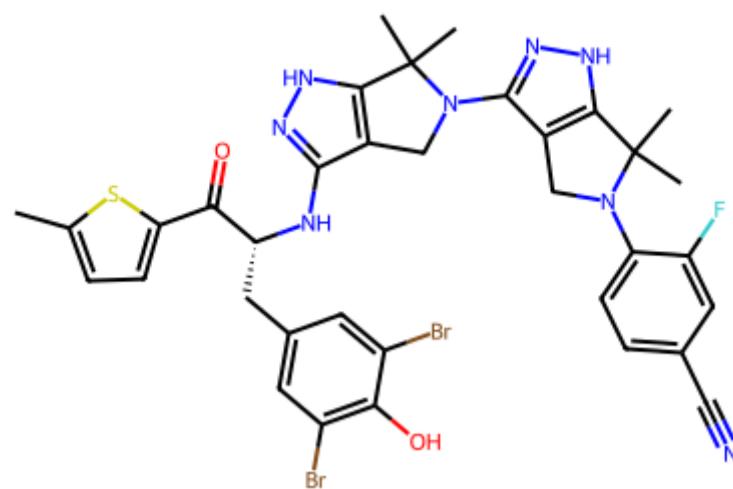
► All ADMET Scores

Task	Score	Direction
AMES	0.735399	↓ lower
BBBP	0.000129	↑ higher
CYP3A4	0.012962	↓ lower
DILI	0.669453	↓ lower
HIA	0.865108	↑ higher
PGP	0.575484	↓ lower

DETAILSPLACEHOLDER6

**After (Step 3)**

Cc1ccc(C(=O)[C@H](Cc2cc(Br)c(O)c(Br)c2)Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)s1



**QED:** 0.1154 (-0.1425) X

**Number of Blocks:** 5 (+1) ↑

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

**CYP3A4 Score:** 0.000895 → 0.000141 (-0.000755)

DETAILSPLACEHOLDER7

## Step Details

### Step 1: CYP3A4 ✓

Original	New	Change
0.020786	0.012962	-0.007824 ↓

```
Cc1nc(Nc2n[nH]c3c2CN(CCCN(C)CC[C@H]2(Oc4ccc(C#N)cc4F)CCc4cc(F)ccc4[C@H]2C(C)C)C3(C)C)c2scCc2n1
```

### Step 2: AMES ⚠

Original	New	Change
0.735399	0.746586	+0.011187 ↓

```
Cc1nc(Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)c2scCc2n1
```

### Step 3: CYP3A4 ✓

Original	New	Change
0.000895	0.000141	-0.000755 ↓

```
Cc1ccc(C(=O)[C@H](Cc2cc(Br)c(O)c(Br)c2)Nc2n[nH]c3c2CN(c2n[nH]c4c2CN(c2ccc(C#N)cc2F)C4(C)C)C3(C)C)s1
```

## ADMET Comparison

Task	Direction	Initial	Final	Change	Rel. Improvement	% Change	Status
AMES	↓ lower	0.456651	0.665578	+0.208928	-0.4575	+45.75%	✗ Declined
BBBP	↑ higher	0.999996	0.000031	-0.999965	-1.0000	-100.00%	✗ Declined
CYP3A4	↓ lower	0.020786	0.000141	-0.020645	+0.9932	-99.32%	✓ Improved
DILI	↓ lower	0.675483	0.393913	-0.281570	+0.4168	-41.68%	✓ Improved
HIA	↑ higher	0.994189	0.999665	+0.005475	+0.0055	+0.55%	✓ Improved
PGP	↓ lower	0.700888	0.747508	+0.046620	-0.0665	+6.65%	✗ Declined

**Improved:** 3/6 (50.0%) | **Molecules:** 283 | **Paths:** 5578

## 🔍 Safety Threshold Analysis

**Status:** 3/6 meet thresholds

⚠️ **Below threshold:** 3

Task	Score	Threshold	Gap
BBBP	0.0000	↑ 0.5	0.5000
PGP	0.7475	↓ 0.3	0.4475
AMES	0.6656	↓ 0.3	0.3656

✓ **Passing:** 3

Task	Score	Threshold
CYP3A4	0.0001	↓ 0.55
DILI	0.3939	↓ 0.4
HIA	0.9997	↑ 0.2