

# Reaction Report for *LEI\_401*, Priority 1

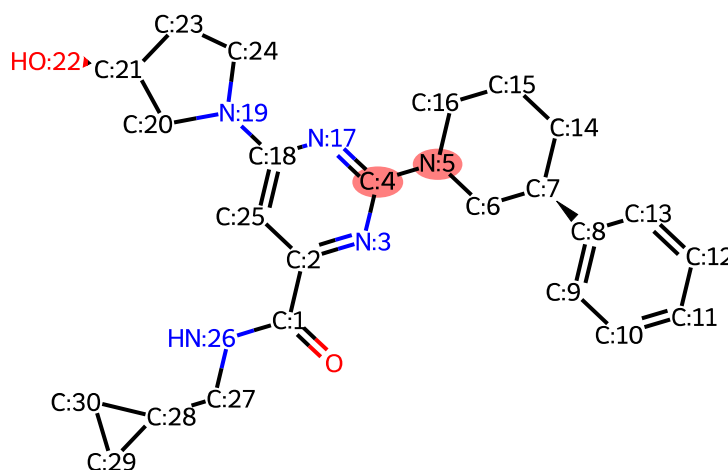
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**Selected Position:** C:4 N:5

**Selected Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine

## Product

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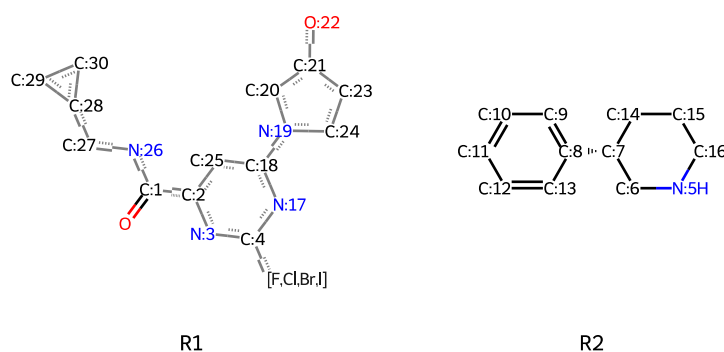
Reaction site highlighted at position C:4 N:5

**Product SMILES:** O=[C:1]([c:2]1[n:3][c:4]([N:5]2[CH2:6][C@H:7]([c:8]3[cH:9][cH:10][cH:11][cH:12][cH:13]3)[CH2:14][CH2:15][CH2:16]2)[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1

# Proposed Transitions

## Transition 1

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Is Chemically Valid:** True
- **Is Template-based:** True
- **Reasoning:** This is the general template for N-arylation using a heteroaryl halide. The leaving group at position C:4 is a member of the class.
- **Is Smiles Valid:** False
- **Reactant 1:** O=[C:1]([c:2]1[n:3][c:4]([F,Cl,Br,I])[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1
- **Reactant 2:** [NH:5]1[CH2:6][C@H:7]([c:8]2[cH:9][cH:10][cH:11][cH:12][cH:13]2)[CH2:14][CH2:15][CH2:16]1

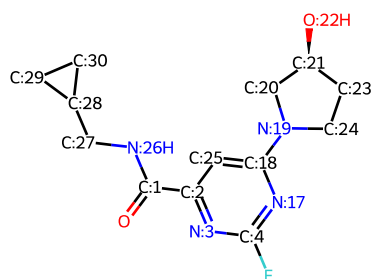


Reactants for Transition 1

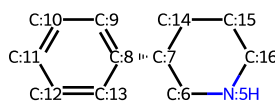
## Transition 2

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Both reactants are stable. The reaction is plausible, although aryl fluorides are the least reactive halides for this transformation and often require forcing conditions or specialized catalysts. The primary challenge is chemoselectivity, as the secondary amine at N:19 is a competing nucleophile. The secondary amide at NH:26 is significantly less reactive and unlikely to interfere. The stereocenters at C:7 and C:21 are unaffected by the reaction.
- **Is Smiles Valid:** True

- **Reactant 1:** O=[C:1]([c:2]1[n:3][c:4](F)[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1
- **Reactant 2:** [NH:5]1[CH2:6][C@H:7]([c:8]2[cH:9][cH:10][cH:11][cH:12][cH:13]2)[CH2:14][CH2:15][CH2:16]1



R1

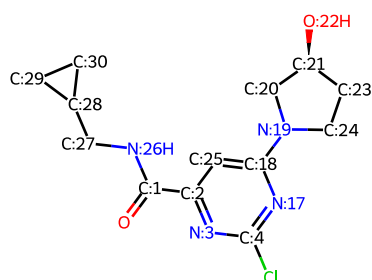


R2

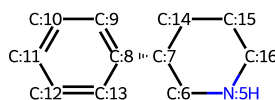
Reactants for Transition 2

## Transition 3

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Reactants are stable. Heteroaryl chlorides are common substrates for N-arylation. The reaction is plausible, but chemoselectivity is a significant concern due to the presence of a competing secondary amine at N:19. The secondary amide at NH:26 is unlikely to compete. The stereocenters at C:7 and C:21 are unaffected.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([c:2]1[n:3][c:4](Cl)[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1
- **Reactant 2:** [NH:5]1[CH2:6][C@H:7]([c:8]2[cH:9][cH:10][cH:11][cH:12][cH:13]2)[CH2:14][CH2:15][CH2:16]1



R1

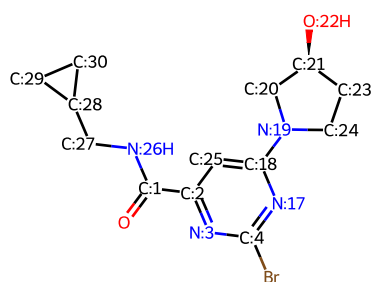


R2

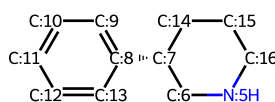
Reactants for Transition 3

## Transition 4

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Both reactants are stable. Heteroaryl bromides are highly effective substrates for N-arylation, often showing better reactivity than chlorides. The main challenge remains achieving chemoselectivity over the secondary amine at N:19. The stereocenters at C:7 and C:21 are preserved.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([c:2]1[n:3][c:4](Br)[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1
- **Reactant 2:** [NH:5]1[CH2:6][C@H:7]([c:8]2[cH:9][cH:10][cH:11][cH:12][cH:13]2)[CH2:14][CH2:15][CH2:16]1



R1

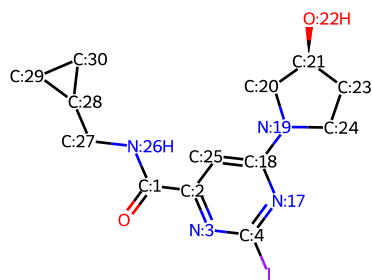


R2

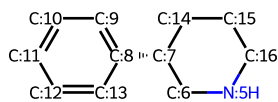
Reactants for Transition 4

## Transition 5

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Reactants are stable. Heteroaryl iodides are the most reactive halides, which may allow for milder reaction conditions that could potentially improve chemoselectivity. Nevertheless, competition from the secondary amine at N:19 is a major consideration. The stereocenters at C:7 and C:21 are not involved in the reaction.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([c:2]1[n:3][c:4](I)[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1
- **Reactant 2:** [NH:5]1[CH2:6][C@H:7]([c:8]2[cH:9][cH:10][cH:11][cH:12][cH:13]2)[CH2:14][CH2:15][CH2:16]1



R1

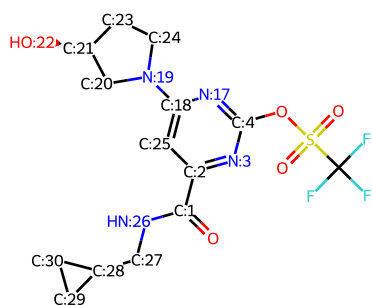


R2

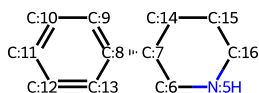
Reactants for Transition 5

## Transition 6

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This option is valid. Both reactants are stable. Heteroaryl triflates are excellent electrophiles for N-arylation, with reactivity comparable to bromides or iodides. The synthesis of the triflate precursor from the corresponding pyrazinone would be required. The key challenge remains the chemoselective reaction at the desired amine in the presence of the competing amine at N:19. The stereocenters are preserved.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([c:2]1[n:3][c:4](OS(=O)(=O)C(F)(F)F)[n:17][c:18]([N:19]2[CH2:20][C@@H:21]([OH:22])[CH2:23][CH2:24]2)[cH:25]1)[NH:26][CH2:27][CH:28]1[CH2:29][CH2:30]1
- **Reactant 2:** [NH:5]1[CH2:6][C@H:7]([c:8]2[cH:9][cH:10][cH:11][cH:12][cH:13]2)[CH2:14][CH2:15][CH2:16]1



R1



R2

Reactants for Transition 6