

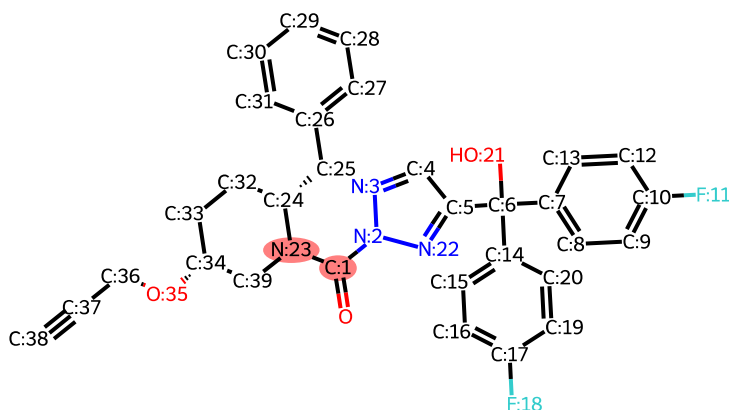
# Reaction Report for *DH\_376*, Priority 2

**Selected Position:** C:1 N:23

**Selected Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and  
Analog\_N

## Product

Reaction site highlighted at position C:1 N:23

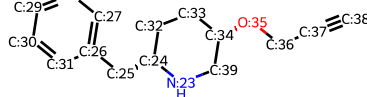


**Product SMILES:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)[N:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([O:35][CH2:36][C:37]#[CH:38])[CH2:39]1

## Transition 1

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R1



R2

Reactants for Transition 1

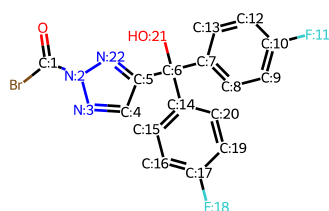
## Transition 2

- **Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs\_N
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This is a standard and common method for forming this type of carbamoyl linkage. Both reactants are synthetically accessible. The primary concern is chemoselectivity; the free tertiary alcohol ([OH:21]) on the electrophile could compete with the amine nucleophile, potentially requiring a protection strategy for the alcohol to achieve a good yield.
- **Is Smiles Valid:** True

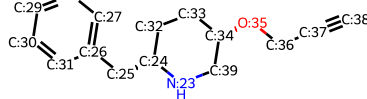


## Transition 4

- **Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs\_N
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** Carbamoyl bromides are more reactive than chlorides. This increased reactivity would likely exacerbate the potential side reaction with the tertiary alcohol ([OH:21]), making chemoselectivity a significant challenge. While chemically possible, it is less practical than using the corresponding chloride or fluoride.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1](Br)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1
- **Reactant 2:** [NH:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([O:35][CH2:36][C:37]#[CH:38])[CH2:39]1



R1

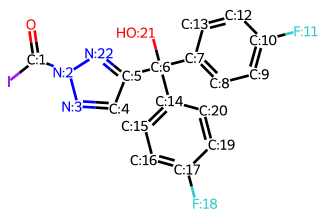


R2

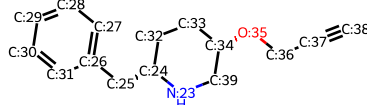
## Transition 5

- **Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs\_N
- **Is Chemically Valid:** False
- **Is Template-based:** False
- **Reasoning:** Carbamoyl iodides are highly reactive and generally unstable, making them impractical for this transformation. The high reactivity would lead to very poor chemoselectivity with the unprotected alcohol ([OH:21]). This route is considered invalid due to the instability of the electrophile.
- **Is Smiles Valid:** True

- **Reactant 1:** O=[C:1](I)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1
- **Reactant 2:** [NH:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([O:35][CH2:36][C:37]#[CH:38])[CH2:39]1



R1

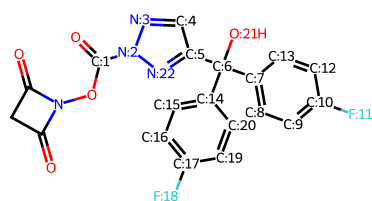


R2

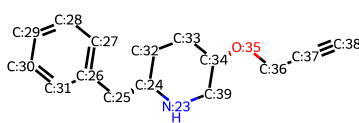
Reactants for Transition 5

## Transition 6

- **Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs\_N
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This disconnection proposes using an N-hydroxysuccinimide (NHS) activated ester as the electrophile. NHS esters are stable, isolable solids that react cleanly and selectively with amines, even in the presence of alcohols like [OH:21]. This is a very common and robust strategy, making it a highly valid option.
- **Is Smiles Valid:** True
- **Reactant 1:** O=C1CC(=O)N10[C:1](=O)[n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1
- **Reactant 2:** [NH:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([O:35][CH2:36][C:37]#[CH:38])[CH2:39]1



R1

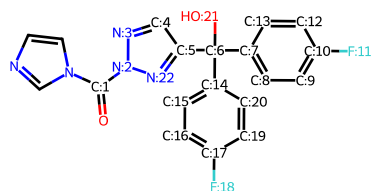


R2

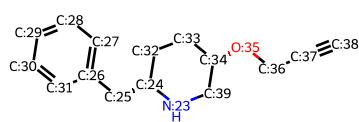
Reactants for Transition 6

## Transition 7

- **Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs\_N
- **Is Chemically Valid:** True
- **Is Template-based:** False
- **Reasoning:** This disconnection proposes using an N-acylimidazole as the activated electrophile. This reagent is typically prepared from a precursor and carbonyldiimidazole (CDI). It is an excellent, mild method for this transformation, known for high chemoselectivity that favors amine nucleophiles over alcohols like [OH:21]. This is a highly plausible and synthetically useful option.
- **Is Smiles Valid:** True
- **Reactant 1:** O=[C:1]([n:2]1[n:3][cH:4][c:5]([C:6]([c:7]2[cH:8][cH:9][c:10]([F:11])[cH:12][cH:13]2)[c:14]2[cH:15][cH:16][c:17]([F:18])[cH:19][cH:20]2)[OH:21])[n:22]1)n1cncc1
- **Reactant 2:** [NH:23]1[C@@H:24]([CH2:25][c:26]2[cH:27][cH:28][cH:29][cH:30][cH:31]2)[CH2:32][CH2:33][C@@H:34]([O:35][CH2:36][C:37]#[CH:38])[CH2:39]1



R1



R2

Reactants for Transition 7