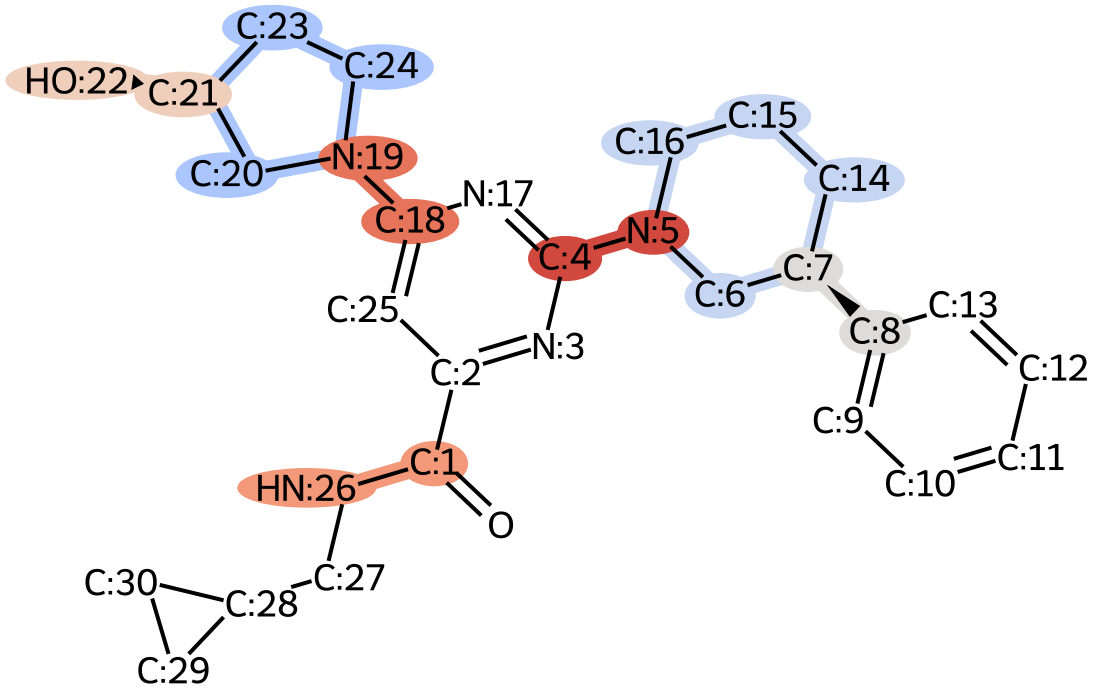
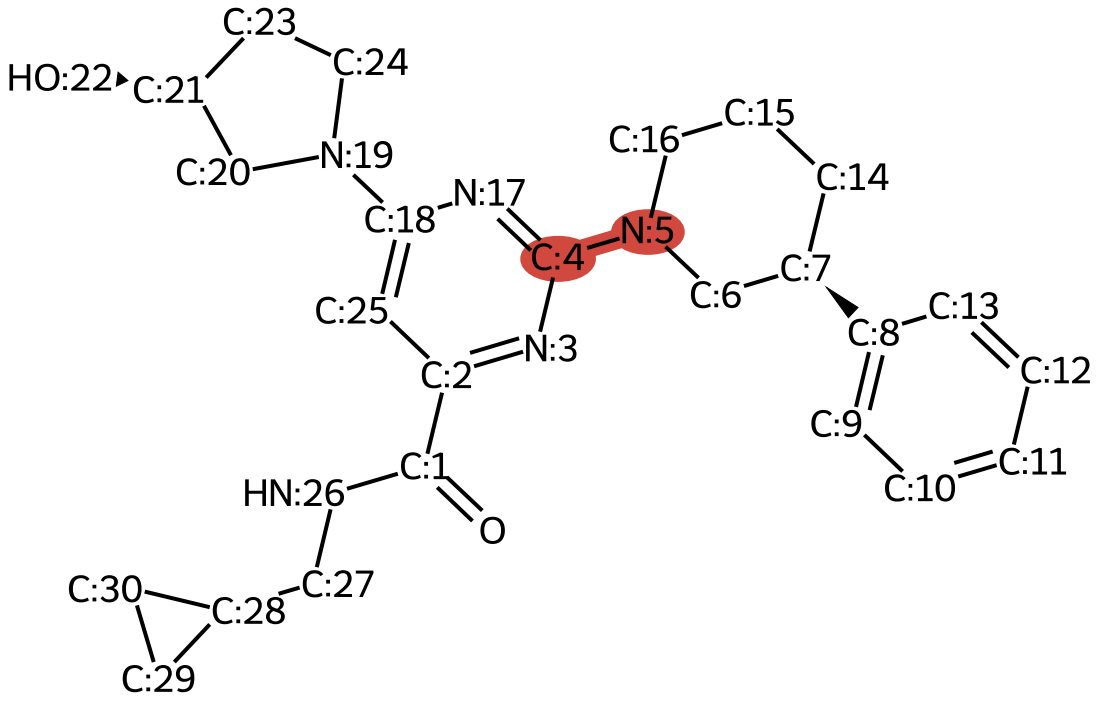
Disconnection Position Analysis for LEI_401

Overview of All Predicted Disconnection Sites



All Positions

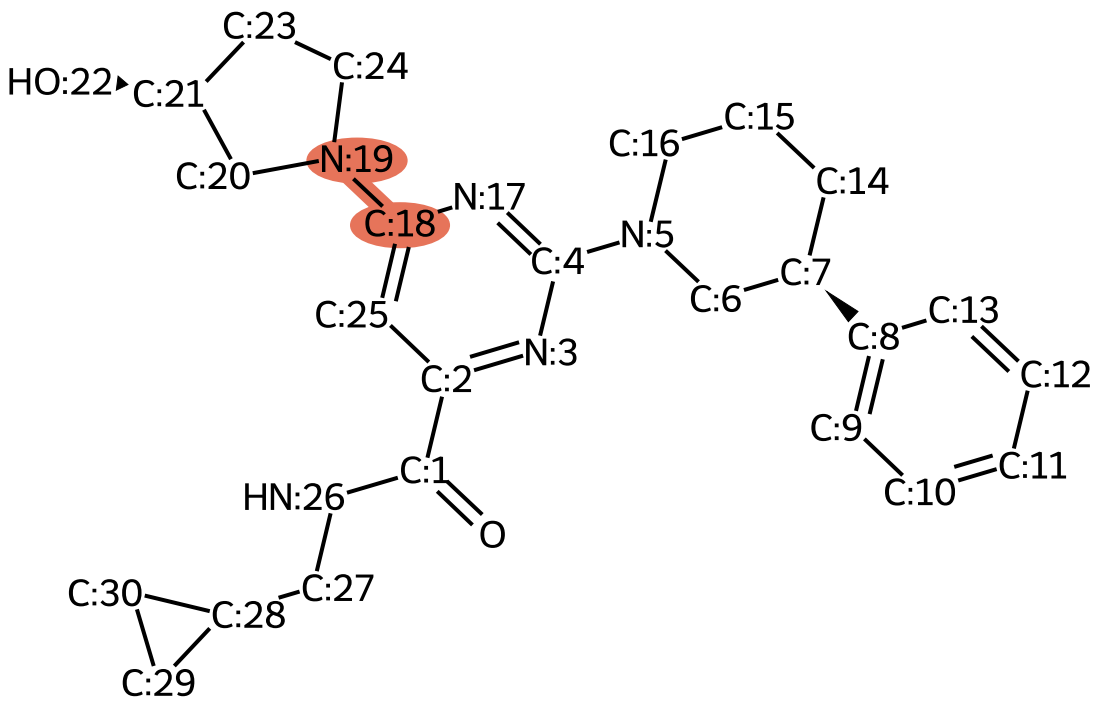
Priority 1: `C:4 N:5`



Position for Priority 1

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Importance Score:** `4`
- **In Ontology:** True
- **Rationale:** Identified from Inter-Fragment Analysis (C), this is a very high importance disconnection that convergently couples the phenylpiperidine fragment to the central imidazole core. This modern cross-coupling reaction is robust and strategically sound for scaffold construction (goal c). The synthesis would require a di-halogenated imidazole, and chemoselectivity between the two coupling sites would need to be controlled, possibly via differential reactivity of the halides (e.g., Br vs. I).

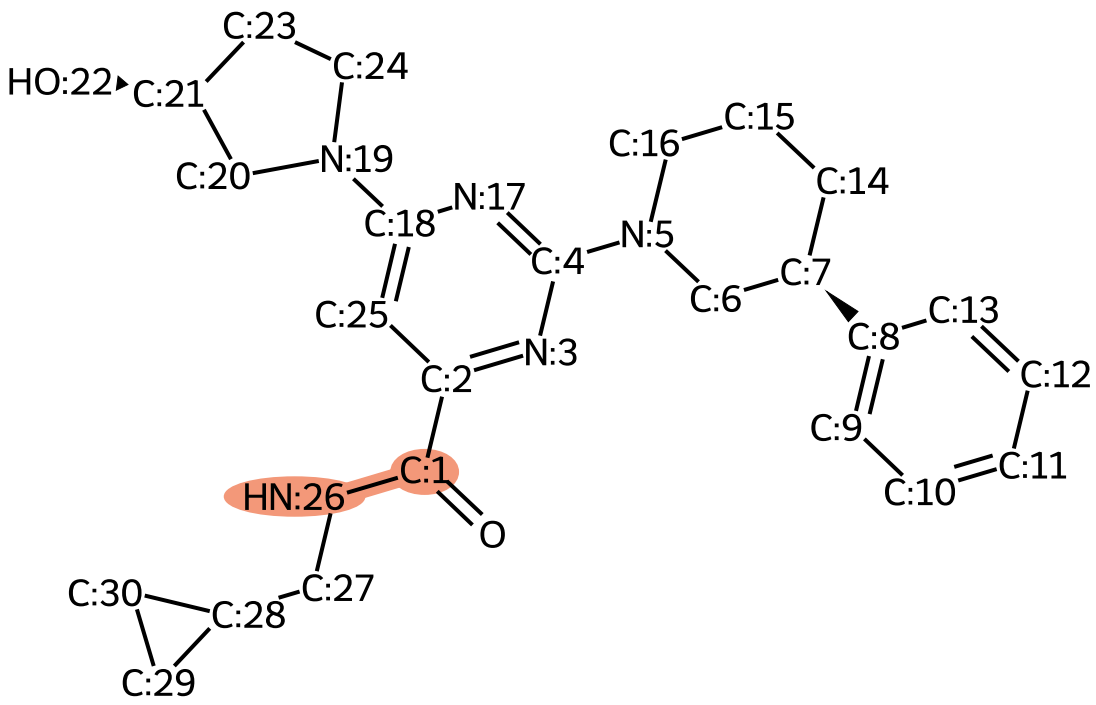
Priority 2: `C:18 N:19`



Position for Priority 2

- **Forward Reaction:** Buchwald-Hartwig/Ullmann-Goldberg/N-arylation secondary amine
- **Importance Score:** `4`
- **In Ontology:** True
- **Rationale:** Identified from Inter-Fragment Analysis (C), this is a key convergent disconnection of the hydroxypiperidine fragment. A C-N cross-coupling is a powerful method for building the core scaffold (goal c). The free hydroxyl group on the piperidine fragment might require protection to prevent interference with the palladium catalyst, a potential chemoselectivity issue.

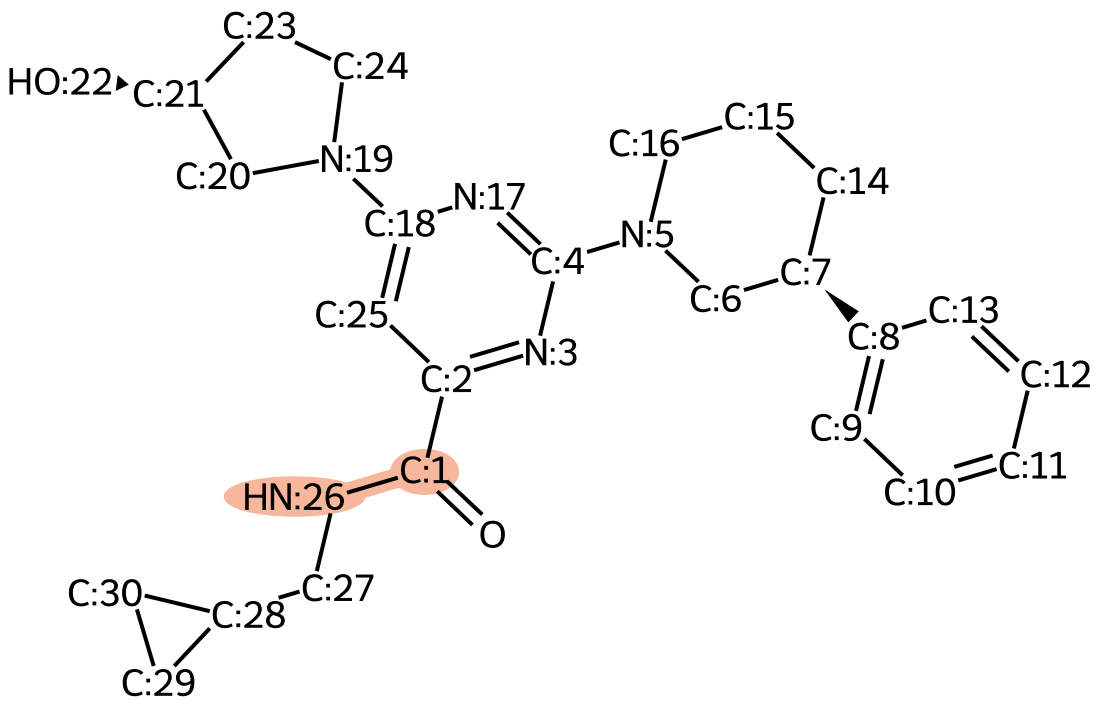
Priority 3: `C:1 N:26`



Position for Priority 3

- **Forward Reaction:** Carboxylic acid to amide conversion
- **Importance Score:** `3`
- **In Ontology:** True
- **Rationale:** Identified via Strategic Bond Analysis (D), this amide bond disconnection is a classic, high-importance step. The forward reaction is a robust and high-yielding amide coupling, simplifying the molecule to a carboxylic acid precursor and commercially available cyclopropylmethylamine (goals a, b). The secondary amines on the piperidine rings are significantly less nucleophilic, so chemoselectivity should be high.

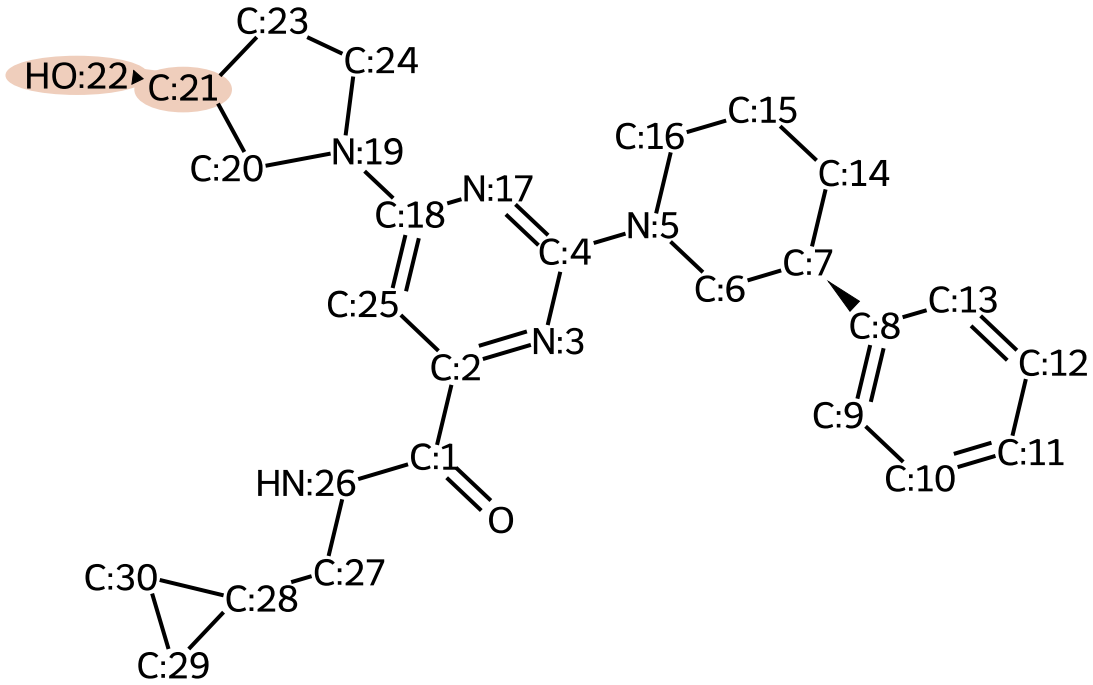
Priority 4: `C:1 N:26`



Position for Priority 4

- **Forward Reaction:** Acylation of Nitrogen Nucleophiles by Acyl/Thioacyl/Carbamoyl Halides and Analogs_N
- **Importance Score:** `3`
- **In Ontology:** True
- **Rationale:** Identified via Strategic Bond Analysis (D), this is an alternative high-importance disconnection for the amide bond via a more reactive acyl chloride. This reaction is often very fast and high-yielding (goal b), though it requires an extra step to prepare the acyl chloride from the acid. Chemoselectivity is generally excellent.

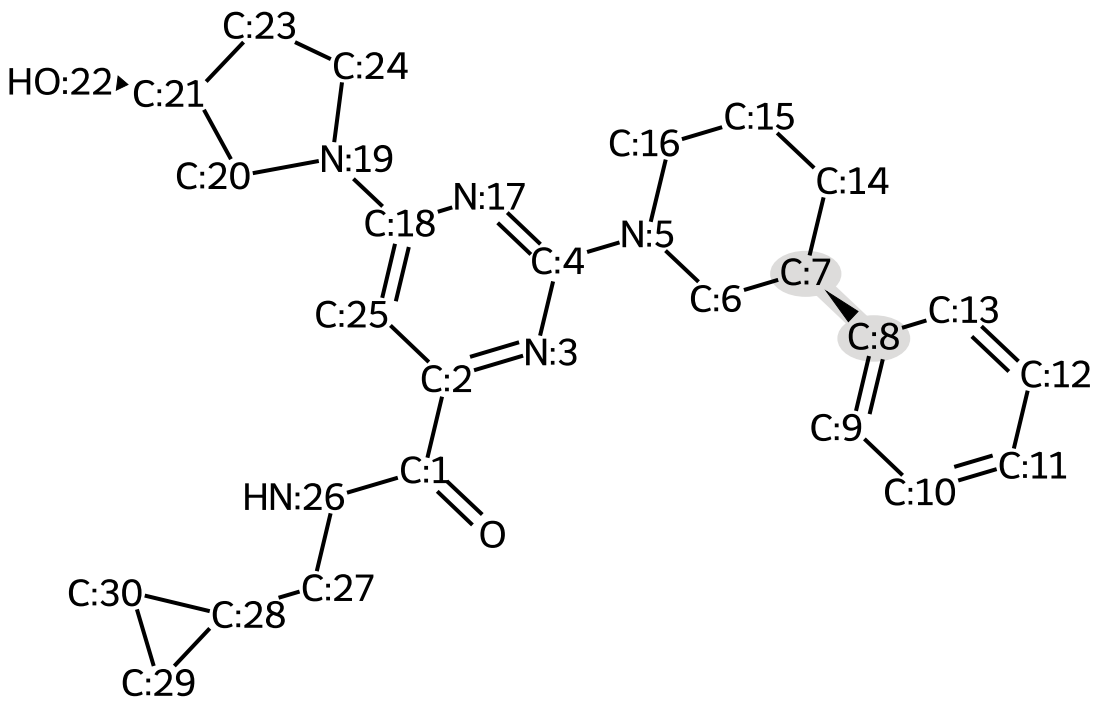
Priority 5: `C:21 0:22`



Position for Priority 5

- **Forward Reaction:** Reduction of ketone to secondary alcohol
- **Importance Score:** `3`
- **In Ontology:** True
- **Rationale:** Identified from Stereochemical Analysis (F) and FGI Analysis (H), this disconnection allows for the creation of the C21 stereocenter. The forward asymmetric reduction of a ketone precursor is a powerful strategy for stereochemical control (goal e) and is a robust reaction (goal b). This approach offers excellent control over the final product's stereochemistry.

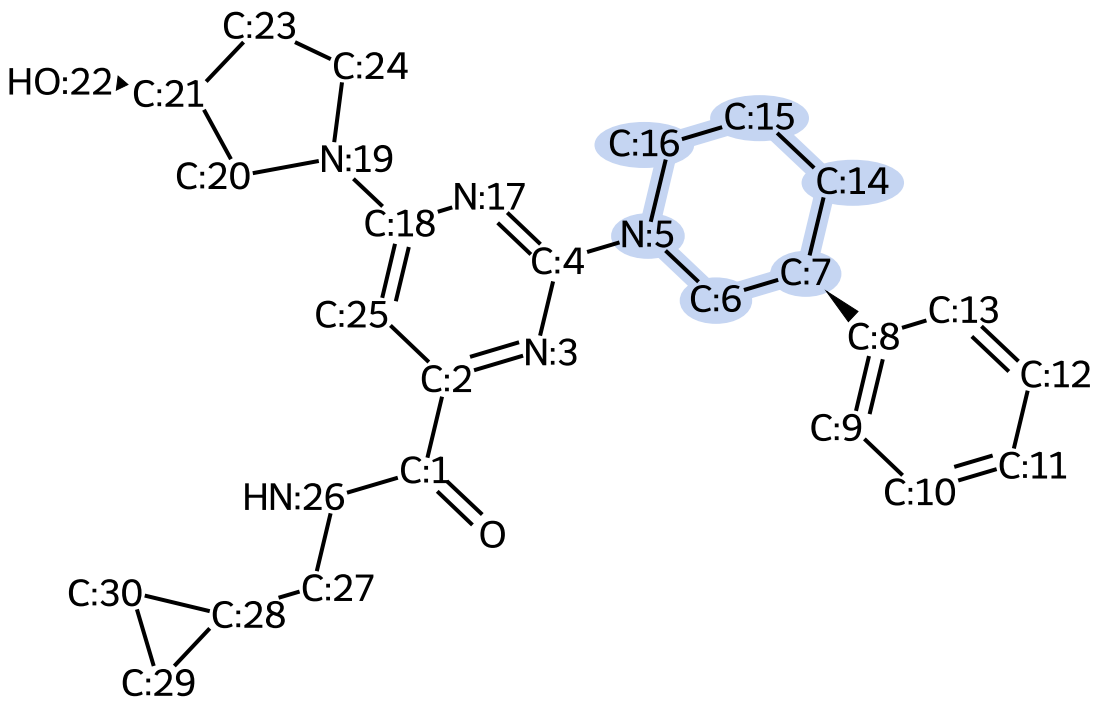
Priority 6: `C:7 C:8`



Position for Priority 6

- **Forward Reaction:** Suzuki coupling with boronic acids
- **Importance Score:** `2`
- **In Ontology:** True
- **Rationale:** Identified via Strategic Bond Analysis (D), this C-C bond disconnection breaks down a key fragment. However, since chiral 3-phenylpiperidine is accessible, this is less strategic than connecting the whole fragment to the core. A Suzuki coupling would be a reliable method (goal b) but adds steps compared to using the intact piperidine.

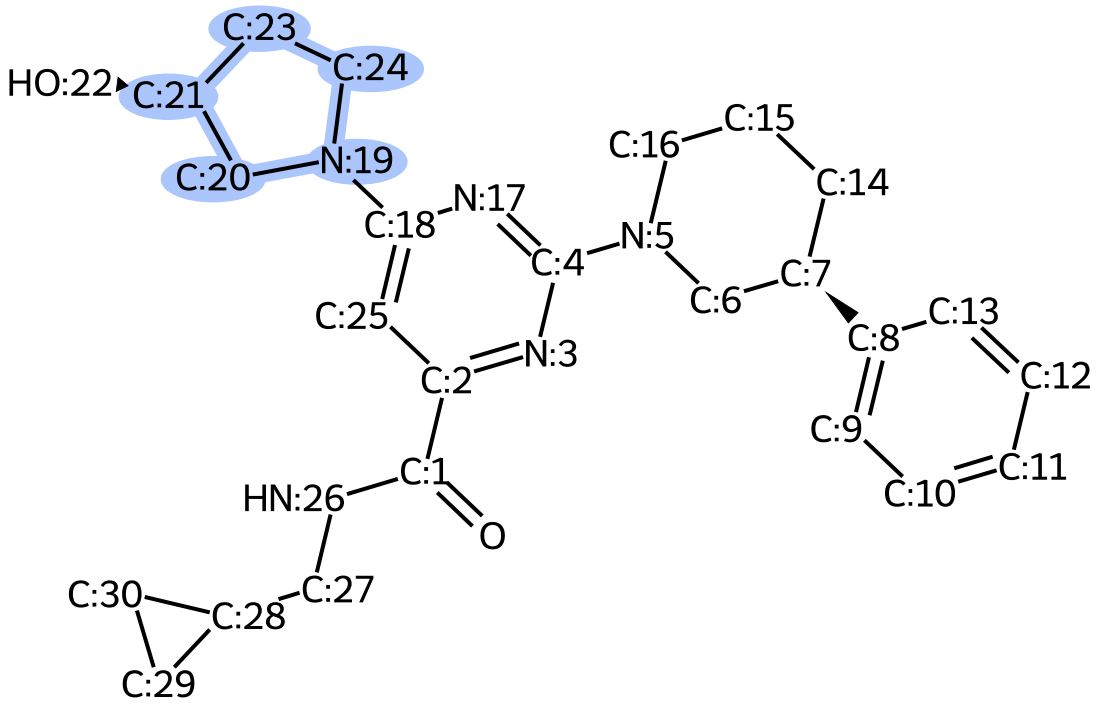
Priority 7: `N:5 C:6 C:7 C:14 C:15 C:16`



Position for Priority 7

- **Forward Reaction:** Arene hydrogenation
- **Importance Score:** 2
- **In Ontology:** True
- **Rationale:** Identified via FGI Analysis (H.i), this disconnection simplifies the 3-phenylpiperidine starting material to 3-phenylpyridine. The forward hydrogenation of a pyridine derivative is a common way to access piperidines (goal a). Asymmetric hydrogenation conditions could potentially be employed to set the C7 stereocenter (goal e).

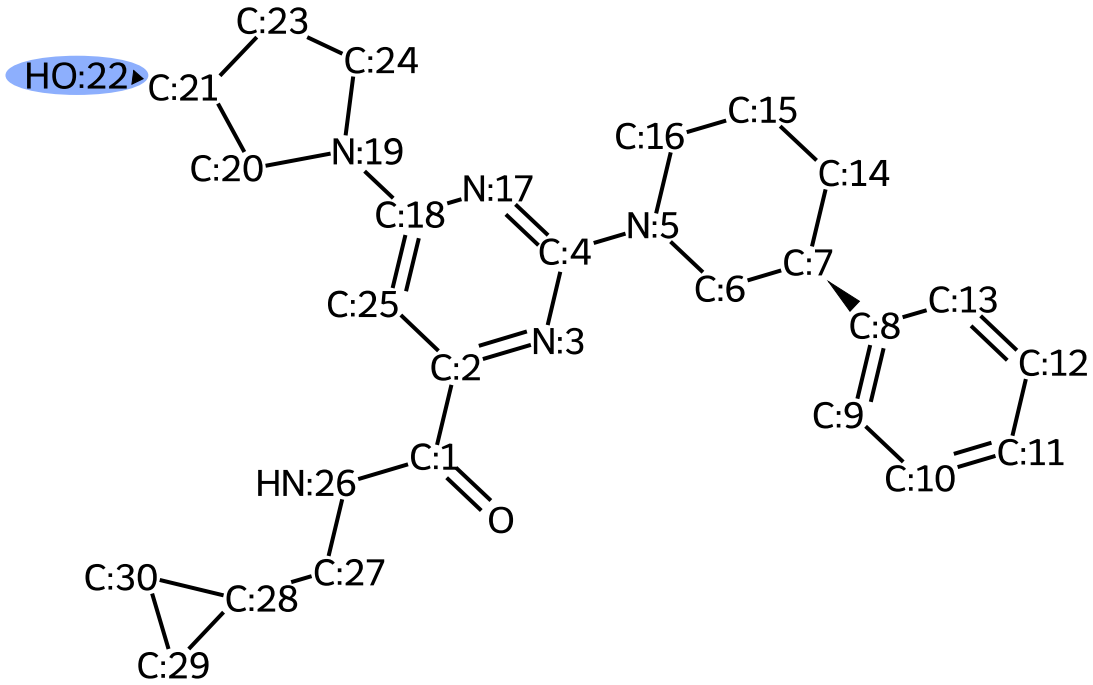
Priority 8: `N:19 C:20 C:21 C:23 C:24`



Position for Priority 8

- **Forward Reaction:** Arene hydrogenation
- **Importance Score:** 2
- **In Ontology:** True
- **Rationale:** Identified via FGI Analysis (H.i), this disconnection simplifies the 3-hydroxypiperidine fragment to 3-hydroxypyridine. While this simplifies the starting material (goal a), controlling the subsequent reduction of the ketone (formed from the hydroxyl) and setting the stereocenter would be a separate, critical step.

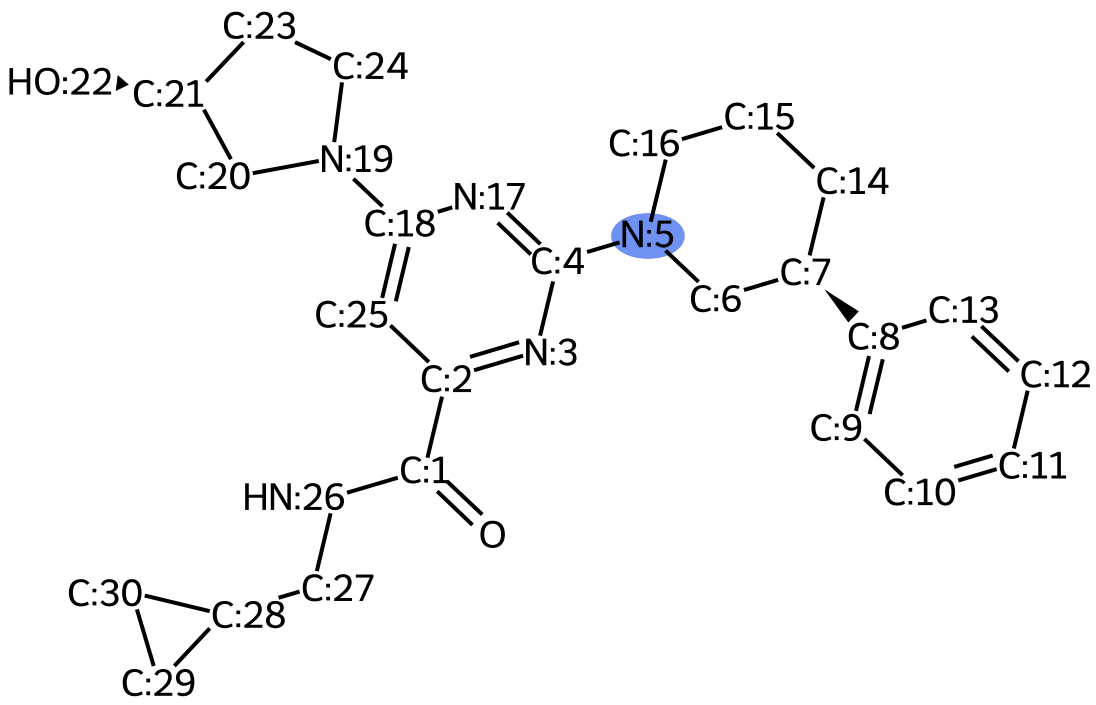
Priority 9: 0:22



Position for Priority 9

- **Forward Reaction:** Alcohol deprotection from silyl ethers
- **Importance Score:** 1
- **In Ontology:** True
- **Rationale:** Identified from Protecting Group Analysis (I), this represents a tactical deprotection step. The alcohol would likely need to be protected as a silyl ether during steps involving strong bases or organometallic reagents to avoid side reactions. This step addresses chemoselectivity but is of lower strategic importance.

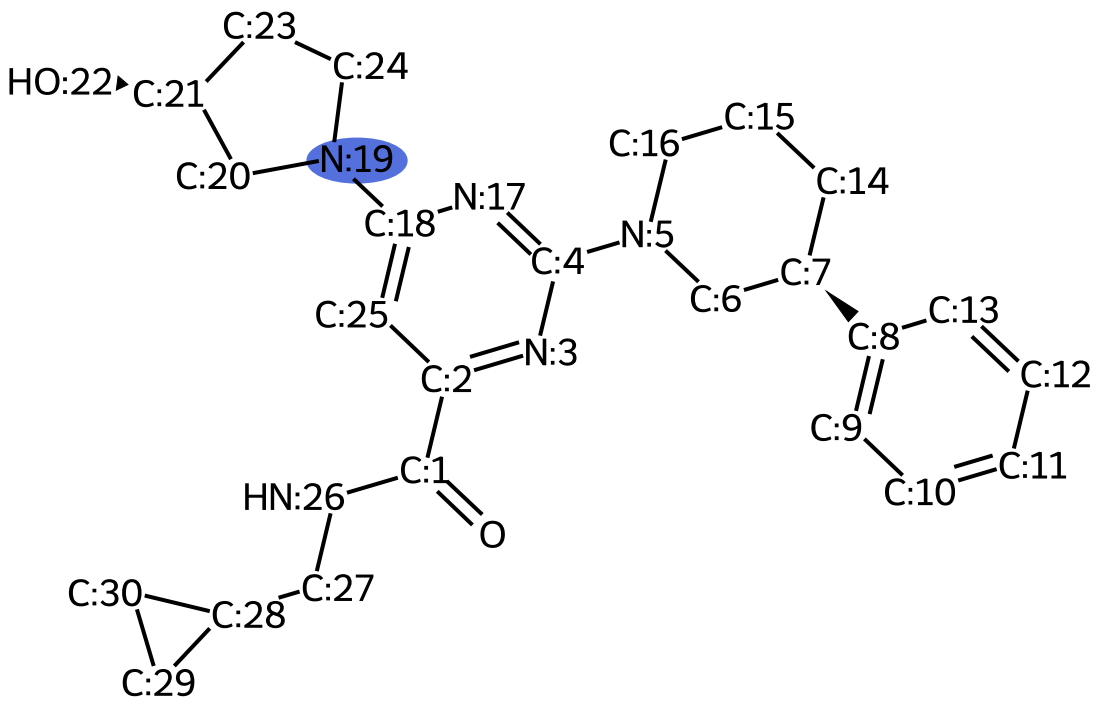
Priority 10: N:5



Position for Priority 10

- **Forward Reaction:** Boc amine deprotection
- **Importance Score:** 1
- **In Ontology:** True
- **Rationale:** Identified from Protecting Group Analysis (I), this is a tactical deprotection. The secondary amine of the piperidine may require Boc protection to prevent it from interfering in other reactions, such as the second C-N coupling. This step manages chemoselectivity and is of lower strategic importance.

Priority 11: N:19



Position for Priority 11

- **Forward Reaction:** Boc amine deprotection
- **Importance Score:** 1
- **In Ontology:** True
- **Rationale:** Identified from Protecting Group Analysis (I), this is another tactical deprotection step. Protecting this secondary amine could be crucial for achieving selectivity during a stepwise C-N coupling sequence on the imidazole core. It is a key step for controlling chemoselectivity.