Single-Atom Skeletal Editing

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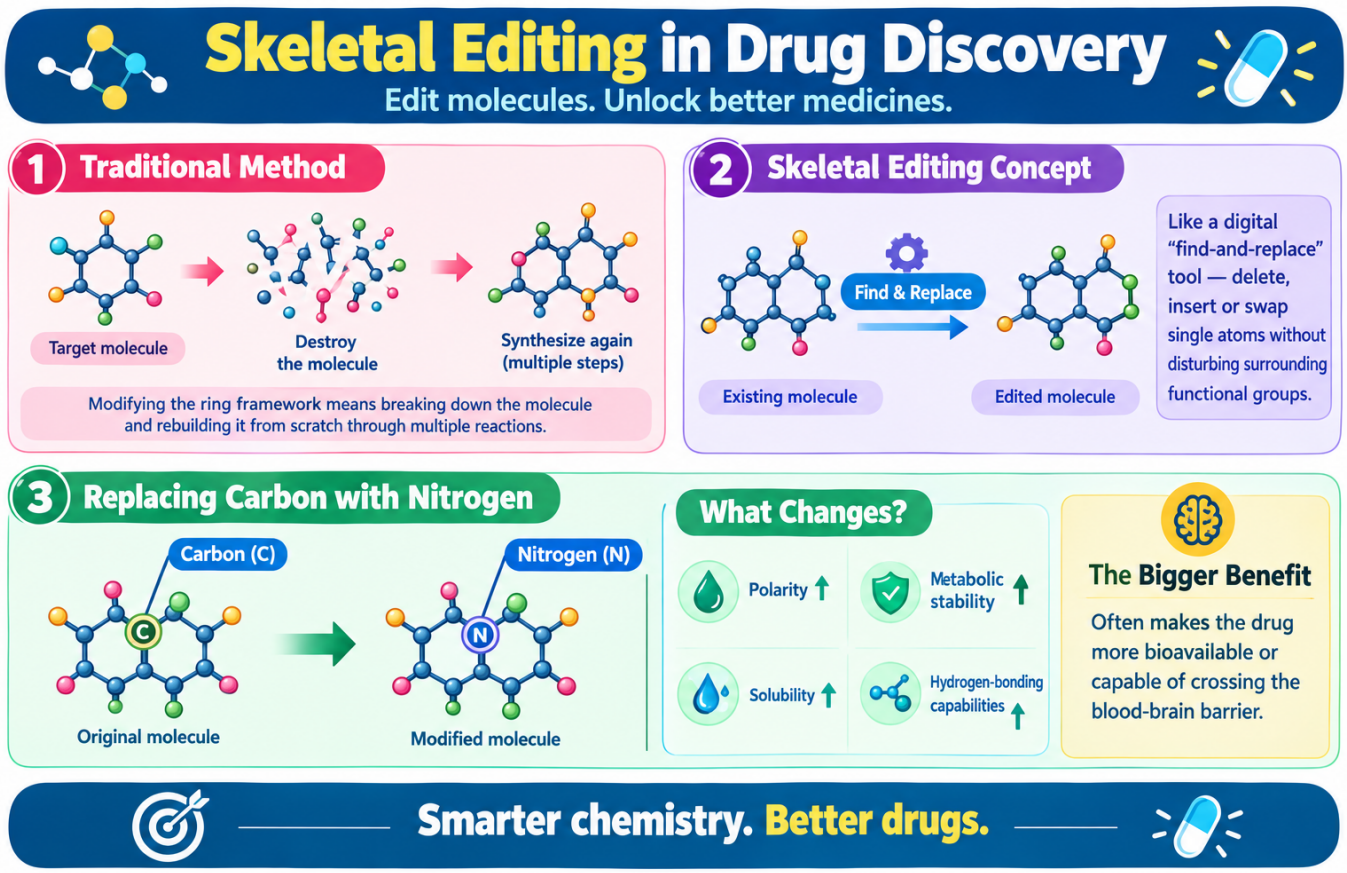
Why in News?

Chemists at ETH Zürich developed a milder, direct method for single-atom skeletal editing, allowing the direct swapping of a carbon atom for a nitrogen atom in core organic scaffolds.

Single-Atom "Skeletal Editing"

- **Traditional method -** In drug discovery, modifying the underlying ring framework of a complex molecule traditionally requires destroying the molecule and synthesizing it again from scratch over multiple step-by-step chemical reactions.
- **Skeletal Editing Concept -** Functions like a digital "find-and-replace" tool for molecules, enabling synthetic chemists to delete, insert, or swap single atoms inside a pre-existing, fully assembled molecular skeleton without disturbing surrounding functional groups.
- **Replacing Carbon with Nitrogen -** Swapping a carbon atom (C) for a nitrogen atom (N) alters a drug molecule's polarity, metabolic stability, solubility, and hydrogen-bonding capabilities.
- It often makes the drug more bioavailable or capable of crossing the blood-brain barrier.



Reaction Mechanism

- **Reagents Used -** Operates under mild conditions using a simple, commercially available combination of
  - **Hypervalent Iodine Reagent -** Phenyliodine(III) diacetate (PIDA) as the oxidant.
  - **Nitrogen Source -** Ammonium carbamate (H4N+H2NCOO) as a mild, safe nitrogen donor.
- **Cascade Pathway**
  - **Oxidative Cleavage -** The reagent selectively opens the double bond in the core indole ring.
  - **Oxidative Amidation & Hofmann-Type Rearrangement-** Inserts the nitrogen atom while removing a single carbon atom.
  - **Recyclization-** Spontaneously re-closes the ring structure into a benzimidazole scaffold.
- **High Functional Group Tolerance -** Unlike earlier atomic-swap methods requiring harsh reagents (such as ozone or hazardous azides), this mild protocol tolerates sensitive functional groups across highly complex, late-stage drug molecules.

Applications in Pharmaceutical Chemistry

- **Streamlining Drug Discovery -** Enables chemists to perform rapid testing by how adding nitrogen atoms into drug candidates impacts biological efficacy without building new molecules from scratch.
- **Accessing Bio-isosteres-** Facilitates direct interconversion between indoles and benzimidazoles.
- **Late-Stage Diversification -** Successfully demonstrated on complex, drug-like molecules, cutting down research timelines and hazardous chemical waste in pharmaceutical development.

Reference

[The Hindu | ‘Milder’ way to swap carbon for nitrogen atoms]