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Late-stage diversification of indole skeletons through nitrogen atom insertion

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Abstract: Compared to peripheral late-stage transformations, mainly focusing on C–H functionalizations, reliable strategies to directly edit the core skeleton of pharmaceutical lead compounds still remain scarce, despite the recent flurry of activity in this area. Herein, we report the skeletal editing of indoles through nitrogen atom insertion, accessing the corresponding quinazoline or quinoxaline bioisosteres via trapping of an electrophilic nitrene species generated from ammonium carbamate and hypervalent iodine. This reactivity relies on the strategic use of a silyl group as a labile protecting group that can suppress the inherent nucleophilicity of the nitrogen in indoles while allowing for subsequent product release. The utility of this highly functional group-compatible methodology in the context of late-stage skeletal editing of several commercial drugs is demonstrated.

One-Sentence Summary: Development of a late-stage indole editing strategy enabled by nitrogen atom insertion to access the bioisosteric quinazolines and quinoxalines.
Main Text:

Major advances in the field of late-stage functionalization have recently unlocked extraordinary structural diversity from common synthetic scaffolds, obviating the resource and time-consuming *de novo* synthesis of a library of derivatives (1). The development of numerous, versatile late-stage C–H functionalization strategies to modify target molecules has been a core tenet of this paradigm shift (2, 3), allowing the introduction of key peripheral modifications. In contrast, complementary approaches that can directly modify the underlying core skeleton of a molecule are less common, despite their potential to expand the accessible chemical space (4–11). Formal single atom insertion reactions to modify aromatic moieties have proven to be especially challenging given the inherent inertness of aromatic carbon-based skeleton towards cleavage of a carbon-carbon bond (12). Despite this formidable challenge, a limited number of carbon (13–16) or oxygen (17, 18) insertion or deletion reactions to reshape molecular architectures has been developed. Given the prevalence of nitrogen atoms in biologically active molecules, the direct modification of valuable core structures through single nitrogen atom manipulation is of particular significance (19) and especially interesting in the context of evaluating structure-activity relationships in medicinal chemistry settings. Although broad-scope methods to delete a nitrogen atom in molecular scaffolds have been recently disclosed (20–23), methods to insert a single nitrogen atom have remained limited, despite their immense potential for the synthesis of ubiquitous N-heterocycles. Apart from the classical Beckmann rearrangement of carbonyl derivatives (24), these methods are currently either restricted to structural motifs that are not commonly found in nature (e.g. indene, 2-arylindoles) or do not exhibit broad functional group compatibility, preventing their application to late-stage functionalization (25–32).

Indoles are among the most widespread nitrogen-containing heterocycles in medicinal chemistry compounds and natural products (33) and thus represent an ideal substrate class for the
development of late-stage skeletal editing reactions (6). Such an approach is particularly attractive if less naturally abundant, yet pharmaceutically interesting scaffolds, could be rapidly accessed (Fig. 1A). Direct insertion of a nitrogen atom into the indole scaffold would enable straightforward access to \(N,N\)-heterocycles without changing the substitution pattern on the starting indole. This transformation of the indole core into such bioisosteric motifs (34, 35), which are not commonly found as building blocks in medicinal chemistry libraries (36) yet are widely recognized as privileged pharmacophores in modern drug discovery (33, 37), could have a transformative impact on the field of late-stage diversification, facilitating the discovery and optimization of drug candidates.

Here we introduce a method for the insertion of a nitrogen atom into indoles affording \(N,N\)-heterocycles. Depending on the substitution pattern of the parent indole structure, either quinazolines or quinoxalines can be selectively accessed. This practical reaction tolerates a broad range of functional groups so that a wide set of natural products and commercial drugs can be transformed into their corresponding bioisosteric analogues.
Fig. 1. **Core derivatization of indoles.** (A) Diversification of indoles to access pharmaceutically interesting quinazoline motifs. (B) Mechanistic design for the transformation of indole skeletons into the corresponding quinazoline scaffold.

To transform indole scaffolds into the corresponding quinazoline motifs, we needed to identify a suitable reagent to act as an electrophilic nitrogen atom donor. We chose to investigate *in-situ* generated electrophilic iodonitrenes, accessed by combining commercially available hypervalent iodine with nitrogen sources (Fig. 1B). In the context of skeletal editing, these reagents have already been harnessed in nitrogen deletion rather than insertion reactions (22), besides exhibiting other unique reactivity patterns (38–40). In our design, a stepwise (2+1) cycloaddition would initially provide an aziridine intermediate. Subsequent elimination of iodobenzene, followed by aromatization of the reaction intermediate, would facilitate the desired ring expansion reactions towards the quinazoline product (15).
A key challenge in the overall design is the inherent nucleophilicity of the unprotected indole nitrogen which could directly react with the electrophilic iodonitrene species. This would lead to the generation of a labile isodiazene intermediate, which would ultimately promote the degradation of the underlying carbon skeleton by the formation of unstable carbon-centered radicals after the release of gaseous nitrogen (Fig. 2A) (22). Our design overcomes this intrinsic challenge through the strategic use of a protecting group, which is capable of both suppressing the inherent nucleophilicity of the nitrogen and acting as a sufficiently labile electrofuge to release the product. We investigated silyl-based groups due to their aptitude for stabilizing positively charged intermediates and their potency as electrofuges (41). Additionally, the silyl group’s susceptibility to hydrolysis can be appropriately adjusted by changing the substituents on the silicon atom (42). Indoles bearing silyl-based as well as other commonly used protecting groups, such as tert-butyloxycarbonyl (Boc), acetyl (Ac) and methyl, were evaluated under the initial reaction conditions. As might be expected based on the proposed mechanism, only silyl groups were effective in providing the desired quinazoline product 8a (Fig. 2B), with tert-butyldimethyl (TBS) protected indoles undergoing the desired transformation most efficiently.
Fig. 2. Reaction development. (A) Inherent challenge associated with the nucleophilicity of the nitrogen in indole substrates. (B) Control by labile protecting group to enable product formation. (C) Optimization of the nitrogen atom insertion reaction. Reactions were performed on 0.1-mmol scale. *Yield and conversion were determined by GC analysis of the crude reaction mixture using n-dodecane as an internal standard. †Yield of the isolated product 8a of a 1.0-mmol scale reaction. PIFA = [bis(trifluoroacetoxy)iodo]benzene, PIDA = (diacetoxyiodo)benzene.

Besides the choice of labile protecting group, the reaction conditions were further optimized by investigating the effect of the other reaction parameters (Fig. 2C). Commercially available [bis(trifluoroacetoxy)iodo]benzene (PIFA) in methanol in combination with ammonium carbamate as the nitrogen source proved to be the preferred reagent mixture to suppress undesired oxidative decomposition of the indole core and obtain the product in high yield. With the optimized reaction conditions in hand, the scope of the iodonitrene-enabled skeletal ring expansion was explored using this operationally simple protocol (Fig. 3). The compatibility of the nitrogen atom insertion method with diverse substitution patterns as well as common functional groups on the TBS-protected indole precursors was evaluated. Quinazoline products featuring electron-withdrawing
substituents, such as halogens (8b–8f), esters (8g, 8h), nitriles (8i, 8j), and sulfones (8k), as well as electron-donating groups, such as ethers (8m–8o) and silyl ethers (8p), were obtained in moderate to good yields from the corresponding TBS-protected indole precursors. In most cases, except for nitrile-bearing indole precursors, full conversion of the starting materials was observed. Likewise, carboxylic acids (8l), alkenes (8q) and alkynes (8r) were compatible under the optimized reaction conditions. An unprotected piperidine-substituted indole could be transformed into the corresponding product (8s), although in lower yield likely due to the propensity of the secondary amine to form isodiazabenzenes leading to degradations. Indole substrates bearing acetals, as well as primary, secondary or tertiary alcohol groups, performed comparably well under the reaction conditions leading to the desired quinazoline products 8t–8w. This strategy also accessed the 1,3,8-triazanaphthalene core (8x) from the TBS-protected aza-indole in moderate yield (for more details see Supplementary Material). Additionally, indoles bearing adjacent pyridine and benzofuran motifs, common heterocyclic handles, were efficiently transformed into the corresponding quinazoline moieties (8y, 8z). Despite their structural simplicity, synthetic protocols to access most of these quinazolines are unreported, as existing methods do not allow easy access to the 2-H quinazoline products (43). TBS-protected indoles featuring substituents on the 2-, 3- or 7-position (8ab, 8ac, 8ad), as well as 2,3-disubstituted indoles (8ae), were successfully converted to the corresponding quinazoline motifs in good yields showing the reaction’s compatibility with proximal substituents (Fig. 3B). The identity of product 8ab was further confirmed by X-ray analysis. This is an important result, as most biologically active indole derivatives are substituted at the 2 and/or 3 position of the indole scaffold (33).

Evaluation of a diverse set of indole cores revealed pathways to either quinazoline or quinoxaline scaffolds, depending on the reactant’s substituents (Fig. 3C). 2,3-Disubstituted TBS-protected indoles bearing five or six-membered fused rings (9a, 9b) exclusively afforded the corresponding
quinoxaline products (10a, 10b) in good to excellent yields. This result further extends the utility of the protocol since five- and six-membered polycyclic indole scaffolds are prevalent in nature. Thus, straightforward access to less naturally abundant quinoxaline motifs could be streamlined synthetically. To gain deeper insight into the parameters influencing the selectivity, a seven-membered ring fused indole substrate (9c) was also tested, which rearranged to the quinazoline-like scaffold. However, due to the inherent ring strain, the reactive intermediate was attacked by the nucleophilic solvent, leading to the corresponding methoxy analogue (10c), as confirmed by single-crystal X-ray analysis, preventing rearrangement towards the aromatic quinazoline product. The regioselectivity for the fused five-membered 2,3-disubstituted indole scaffold (9a) was further rationalized by DFT calculations, suggesting that a rearrangement to the quinoxaline product is most likely explained by thermodynamic considerations, as the transformation into the corresponding quinazoline would result in the formation of a highly strained, energetically unfavored product (computational details can be found fig. S14) (44).
Fig. 3. Substrate scope for the single nitrogen atom insertion. Yields are given for isolated products. Reaction conditions: TBS-indole (1 mmol, 67 mM), ammonium carbamate (6 equiv) and
PIFA (4 equiv) in MeOH at 0 °C for 10 minutes, then at room temperature (rt) for up to 4 hours. 

(A) Investigation of the functional group compatibility of the reaction. (B) Effect of proximal substitutions on the reaction outcome. (C) Investigating the dependence of the reaction outcome on sterically constrained substrates. DFT calculations for the regioselective preference of substrate 9a. Gibbs free energies are indicated in kcal/mol at 0 °C. *Yield determined by 1H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane or mesitylene as an internal standard. 

*The reaction was performed on 0.2-mmol scale and the product was co-isolated with a side product in an approx. 1:1 ratio (for more details see Supplementary Material). 

To illustrate the reaction’s potential for expanding accessible chemical space, we applied it to naturally occurring amino acids and commercially available drug molecules (45). Protected tryptophan (11a) was transformed into the corresponding quinazoline product (12a) in good yields. Moreover, the reaction could be performed on 8-mmol scale, demonstrating the scalability of this process. The synthesis of this previously unexplored unnatural amino acid (12a) allows for the investigation of its effect on protein and peptide properties (46). The skeletal cores of both melatonin (11b), a widely encountered neurohormone (47), and pindolol (11c), a β-adrenoceptor antagonist used for high blood pressure treatments (48), were remodeled to afford the corresponding quinazolines 12b and 12c, demonstrating the functional compatibility with secondary amines and amides. Similarly, the molecular scaffold of N-feruloyl serotonin (11d), bearing an α,β-unsaturated amide, was transformed into the quinazoline derivative (12d) in excellent yield. Pimprinine-derived substrate (11e) as well as analogues of Brevianamide F (11f), which both exhibited diverse biological activities, such as fungicidal activities (49, 50), were transformed into the corresponding quinazoline products 12e and 12f. Alongside natural products
featuring variable functional handles attached to the core indole scaffold, widely encountered polycyclic indole derivatives have also been shown to possess diverse biological activities and interesting pharmaceutically relevant properties \( (51) \). Tricyclic tryptoline-3-carboxylic acid \( (11g) \) was successfully transformed into Lycoperodine-1-derived quinoxaline \( 12g \). Similarly, 1,2,3,4-tetrahydro-7-methoxycyclopent[b]indole-3-acetic acid \( (11h) \), a key intermediate in the synthesis of APD334, a drug candidate for the treatment of autoimmune diseases \( (52) \), was transformed into the corresponding quinoxaline core structure \( 12h \).
Fig. 4. Late-stage skeletal editing to access quinazoline and quinoxaline scaffolds.

Enantiomeric enrichment was not determined. Reactions were performed on 1.0-mmol scale unless otherwise stated. Standard reaction conditions: TBS-indole (1 equiv, 67 mM), H$_2$NCO$_2$NH$_4$ (6 equiv) and PIFA (4 equiv) in MeOH at 0 °C for 10 min, then at room temperature for up to 4 hours.
The reaction was performed on 8.0-mmol scale. \textsuperscript{a}Diastereoisomeric ratio 7:3. TBAF = tetra-\textit{n}-butylammonium fluoride, TFA = trifluoroacetic acid.

As indoles are widely encountered, pharmaceutically relevant substrates, we believe that this highly efficient protocol will enable the adoption of more skeletal editing steps in late-stage diversification strategies.

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**Author contributions:** JCR conceived the project. JCR, OG and AF performed the experiments. PF performed the DFT studies. BM supervised the research. JCR, OG and BM wrote the MS. All authors revised and approved the MS.

**Competing interests:** The authors declare no competing interests.
**Data and materials availability:** X-ray data for compounds (8n’, 8ab, 8ac, 10c, 12a, 12b, 12d’) are freely available at the Cambridge Crystallographic Data Centre under deposition numbers 2173003, 2173004, 2171863, 2171881, 2171882, 2172251, 2174296.

**Supplementary Materials**

- Materials and Methods
- Supplementary Text
- Figs. S1 to S23
- Tables S1 to S15
- xyz file with Cartesian coordinates