Diversification of Indoles and Pyrroles by Molecular Editing: New Frontiers in Heterocycle-to-Heterocycle Transmutation

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Abstract: *Skeletal editing via single-atom insertion reactions involving nitrogen heterocycles have been reported by two innovative and complementary methods for the conversion of pyrroles and indoles to pyridines, quinolines and quinazolines. The use of electrophilic carbynyl cation equivalents and in situ generated nitrenes enables molecular editing to transform heterocycles forming the foundation of best-selling pharmaceuticals. Considering the importance of heterocycles in medicinal chemistry, biology and natural products, these methods offer innovative approach to complex molecular structures by heterocycle diversification and peripheral editing.*

1. Introduction

Heterocycles dominate the food, perfume, and pharmaceutical industry.[1] In the plethora of active medicinal compounds, the presence of heterocycles containing nitrogen is especially prominent (Figure 1).[2] In 2022, FDA approved 26 small molecule drugs among which an astounding 24 hinged upon nitrogen heterocycles.[3] In 2021, among the 10 most prescribed medications sold in the US, 6 featured nitrogen heterocycles in their structure.[4] For example, Lipitor (Atorvastatin) is a pyrrole containing drug that is widely applied as a blood cholesterol controller. Lipitor is among the world's best-selling drugs of all time and annually surpasses 100 million prescriptions in the US alone.[5] Other classes of biologically active or natural compounds, such as Vitamin B12 and porphyrins contain pyrrole and are critical for the development of nerve cells and oxygen transport. Many pyrrole-containing drugs exhibit anticancer, antipsychotic (Moban) and antiinflammatory properties.[6] Benzofused pyrrole analogues, indole motifs, are widely encountered in medicinal chemistry and biochemistry, such as Tryptophan, an essential amino acid, and *Imitrex* (Sumatriptan), a pivotal antimigraine drug. Annually, 6 million prescriptions of Sumatriptan are issued in the US for the treatment of severe headaches.[7] Six-membered nitrogen-heterocycles, such as pyridines are equally important. For example, Biktarvy (Bictegravir), a 3-component pyridine-containing antiviral, is the 10th best-selling drug worldwide, enabling controlled management of HIV/AIDS.[8]

Nitrogen-containing heterocycles are typically synthesized by condensation reactions, such as Paal-Knorr, Fisher or Hantzsch methods that have been adopted for industrial synthesis.[1,2] At the same time, molecular rearrangements epitomize one of the most intriguing methods for the synthesis of heterocycles (Figure 2).[9] Atom insertions have been pioneered in the 19th century rendering possible interconversion of carbo and heterocycles to useful products to the general public. Carbon insertion by Ciamician and Dennstedt (1881),[10] nitrogen insertion by Beckmann (1886)[11] and Schmidt (1924),[12] are the earliest reports that are familiar to the practitioners or organic synthesis worldwide.

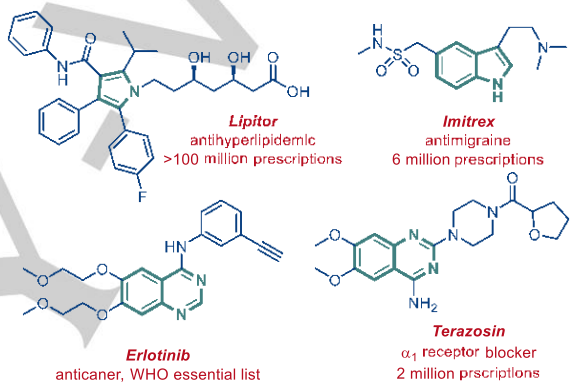

Figure 1. Best-selling medicines with pyrrole, indole and quinazoline scaffold.

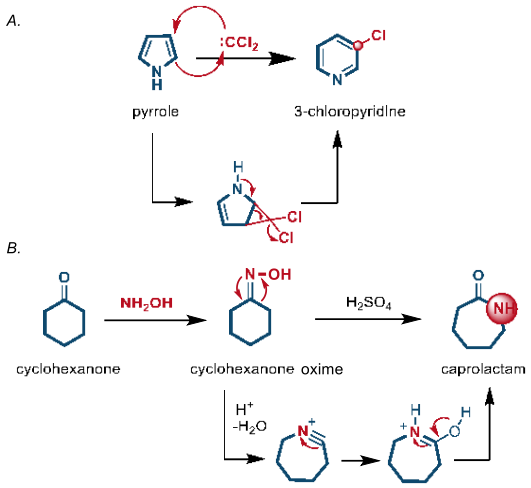

Figure 2. Atom insertions: (A) Ciamician-Dennstedt rearrangement involving carbon insertion; (B) Beckmann rearrangement involving nitrogen insertion.

The Beckmann rearrangement now finds successful application in the synthesis of Nylon polymer with the current market value of $14.6 billion.[13] Industrially, Nylon continues to be manufactured by the Beckmann rearrangement route. Another noteworthy application is the first 15-membered macrolide antibiotic Azithromycin.[14] This crucial broad-spectrum antibiotic is formed via ring expansion of Erythromycin incorporating a

nitrogen atom in the aglycone ring, and now accounts for more than 80% total prescriptions of macrolide antibiotics with 10 million prescriptions annually.[4] Yet another example is sparteine, a lupin alkaloid with antiarrhythmic properties and chiral ligand for asymmetric synthesis. One of the most efficient routes to (–)-sparteine consists of the combination of Schmidt and photochemical Beckmann rearrangements for the enantiomer of this useful natural product.[15]

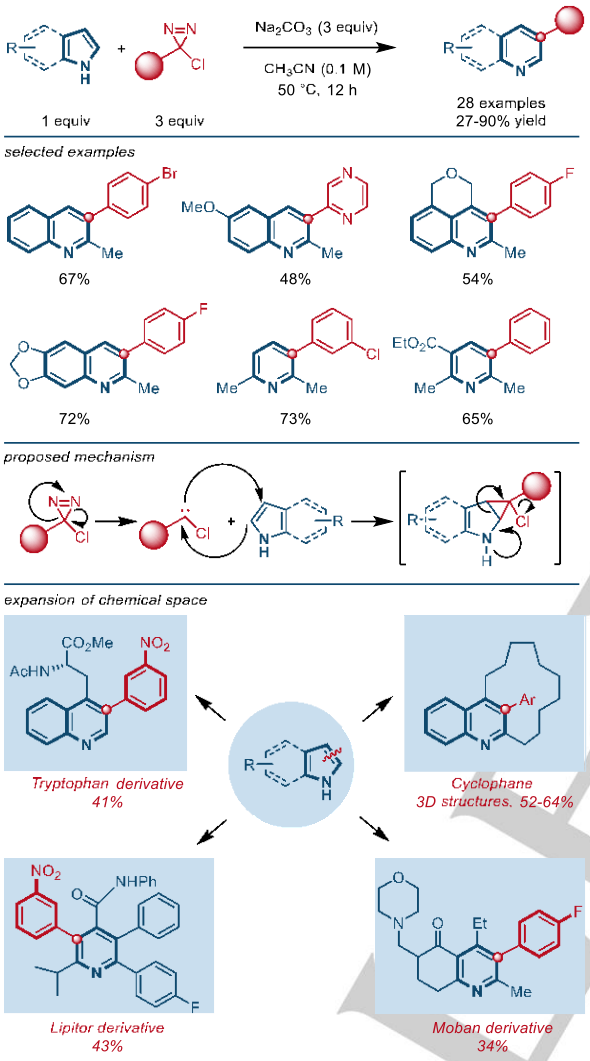

Figure 3. Carbon insertion in interconversion of pyrroles and indoles to pyridines and quinolines by Levin and co-workers.

Historically, the importance of heterocycles has served as a springboard to stimulate new research insights and explore innovative avenues in organic synthesis.[16] Recently, two reports by the groups of Levin[17] and Morandi[18] have demonstrated original ring expansion protocols that enable to directly engage pyrroles and indoles for the synthesis of polysubstituted pyridines, quinolines and quinazolines. Most crucially, the precise inter-conversion of these five-membered nitrogen heterocycles may provide the basis for rapidly exploring structure-activity relationships in medicinal chemistry and result in safer, more effective, and more bioavailable drugs with the immense potential to benefit mankind.[16a,b]

In particular, the value of skeleton editing approaches for potential applications in the pharmaceutical industry should be noted. The main potential benefit of this novel synthetic platform is in reinforcing the prospect of using single-atom insertion for late-stage diversification of pharmaceuticals where nitrogen-containing heterocycles are the staple of medicinal chemistry research.[1-3]

2. Diversification of Indoles and Pyrroles by Molecular Editing

In the report by Levin,[17] the authors enlist α-chlorodiazirines as precursors to chlorocarbenes, which enable ring expansion of pyrroles and indoles to pyridines and quinolines (Figure 3), whereas the traditional rearrangement via dichlorocarbenes (Ciamician-Dennstedt) is limited to the formation of halo-substituted motifs. Curiously, this new method avoids the competing Riemer-Tiemann formylation that occurs in the traditional Ciamician-Dennstedt rearrangement, thus increasing the yields and selectivity of the desired products. The α-chlorodiazirine precursors are easily prepared by Graham oxidation of amidines, generating carbynyl cation equivalents. This is followed by a [2+1] cycloaddition and ring expansion. By exploiting this reaction pathway, the authors were able to synthesize an impressive range of substituted pyridine and quinoline heterocycles directly from pyrroles and indoles. Substrates with different substituents in the aryl group of α-chlorodiazirines, such as electron-withdrawing or donating groups, underwent the ring expansion in generally high yields of 59-83%. Impressively, coupling with other heterocycles is also possible by this method, such as the pyrazine product (48%).

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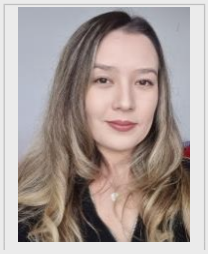
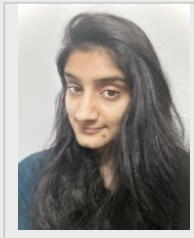
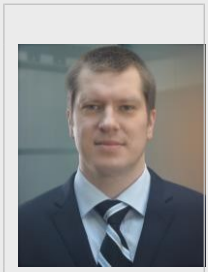


Lakshita Anand received her B.Sc. in Pharmacy from UIPS, Panjab University, India, in 2017, followed by M.Sc. in Process Chemistry at NIPER, India, under the guidance of Prof. Joydev K. Laha in 2019. Currently, she is a Ph.D. student at Rutgers University pursuing sustainable materials chemistry in the laboratory of Prof. Frieder Jaekle.



Michal Szostak received his Ph.D. from the University of Kansas in 2009. After post-doctoral stints at Princeton University and University of Manchester, in 2014, he joined the faculty at Rutgers University, where is currently Professor of Chemistry. His research group is focused on the development of new synthetic methodology based on transition-metal-catalysis, amide bonds, NHC ligands, and application to the synthesis of biologically active molecules. He is the author of over 240 publications.



Undoubtedly, the power of this approach lies in the direct interconversion of bioactive heterocycles.[16] Although it is important to note that the presence of a substituent on C2 position of the original heterocycle resulted in higher yields, a Tryptophan derivative with no C2 substituent was synthesized in 41% yield. Furthermore, a cyclophane motif was also synthesized readily owing to the non-aromatic ring contorted from the plane of the indole starting material. Intriguingly, the reaction regioselectivity in the case of pyrrole conversion into pyridines was determined to be controlled by hydrogen bond donor effects in the case of substrates like Lipitor derivative, and steric hinderance for motifs without hydrogen bond donors, such as Moban derivative.

In the report by Morandi,[18] the authors exploit the reactivity of electrophilic nitrenium species to accomplish the single-atom ring expansion of indoles to quinazolines (Figure 4). Although many reagents are available for nitrene insertions as capable C–N bond forming agents for the addition to unsaturated bonds, aziridinations, aminations or amidations, in the current study the authors successfully devised an in situ generated nitrenium from ammonium carbamate and hypervalent iodine. This nitrene is attacked by the silyl-protected indole, enabling direct ring expansion of indoles to quinazolines. Indoles with a broad range of C2–C8 peripheral substitution are amenable to this process. Various sensitive functional groups that serve as pharmacophores in medicinal chemistry are readily compatible, including unprotected alcohols, amines, esters, amides and halogens. Furthermore, C2/C3 fused indoles are suitable for this process, enabling access to quinoxalines by alternative bond insertion. Clearly, this intermolecular access to quinazolines empowers the exploration of bioactive structures by heterocycle-to-heterocycle interconversion. For example, the authors demonstrated the facile access to previously unexplored unnatural amino acids. Furthermore, this ring expansion was extended to the direct interconversion of melatonin and Pindolol, a natural hormone and important beta-blocker for hypertension treatment, permitting the synthesis of their quinazoline counterparts. The reaction was also applied to polycyclic indole scaffolds to synthesize key intermediates, such as APD334 for the treatment of autoimmune disorders, thus further highlighting a potential impact of this novel process on drug research.

There are several ground-breaking features of the reports by Levin and Morandi. First and foremost, previously inaccessible, medicinally-important derivatives were successfully synthesized by these new protocols, enabling new avenues for synthetic studies and biological applications.[16a,b] This is possible because both reactions feature high tolerance for diverse substitutions and functional groups.

Furthermore, the reactive carbenic and nitrenic intermediates show precise control of the reaction selectivity. The α-chlorodiazirine reagent can be regarded as stable carbynyl cation equivalent. While nitrenes offer greater thermodynamic stability over carbenes,[19] the in situ generation of electrophilic nitrenium from ammonium carbamate and hypervalent iodine is exceedingly mild and selective. These reagents invoke exploration of mild and efficient resources for electrophilic transformations.[9] The regioselectivity of pyrrole expansion can be controlled by both steric and hydrogen bond donor effects, thus opening new prospects in regioselective ring expansions.

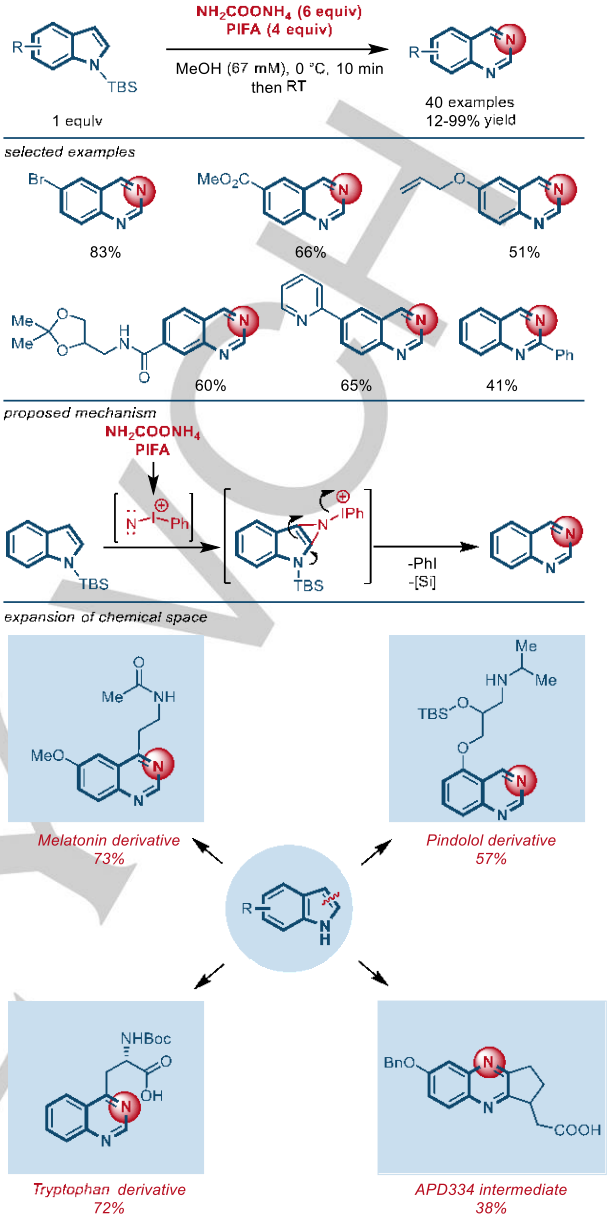


Figure 4. Nitrogen insertion in interconversion of indoles to quinolines and quinazolines by Morandi and co-workers.

Likewise, the regioselectivity of the indole expansion is controlled by the ring fusion to afford quinazolines or quinoxalines. Further, the α-chlorodiazirine reagent avoids the competing Reimer-Tiemann formylation, since it only contains one chlorine atom, significantly improving on the original Ciamician-Dennstedt pathway. This can be compared with the nitrene insertion, affording α-amino-aziridinium as the reactive intermediate. Finally, complex 3D molecules such as cyclophane derivatives, bridged heterocycles and unnatural amino acids can be synthesized in high yields, providing a pathway to assemble novel and attractive molecular architectures.

3. Summary and Outlook

There are several areas for future development of the exciting reports by Levin and Morandi to ensure broad

applicability in organic synthesis. Disadvantages relate to the use of unstable intermediates, which may present safety risks.[20] Due to the high reactivity and instability of carbenes and nitrenes, these reagents are often not the first choice for many chemists. Recent developments highlight the use of flow chemistry to attain efficient reaction control, while generating reactive intermediates.[21,22] With efficient flow chemistry in place, the possibility of scaling up to industrial applications might become feasible. Further, risks of toxicity of the related reagents have been noted,[23] thus it is critical that toxicity studies are conducted prior to large scale applications. Moreover, ideally, these methods would be demonstrated in a much larger set of biologically-active pyrroles and indoles to demonstrate compatibility with prospective field testing.[16] Teams of medicinal and process chemists continuously make possible the synthesis of novel functional scaffolds that benefit humans. If late-stage diversification strategies for efficient atom exchange reactions within heterocycles are established, a surge in the number of successful clinical trials could follow. Considering ubiquity of heterocycles in various facets of chemistry, this in turn could trigger advances in agriculture, biochemistry, neuroscience, engineering, materials and environmental science.

In particular, hypervalent iodine reagents, especially when used in large excess may cause hesitation in the adoption of these methods for industrial processes. One potential solution would be the successful implementation of flow chemistry.[21] This is supported by the already successful examples of multigram scale synthesis involving carbenes and improved mass transfer on decagram scale.[21a] Further, modifications of flow chemistry for nitrene insertion have already been reported by industrial groups to avoid contact with potentially explosive intermediates.[22b] Another option to consider is the use of photochemical[22a] and electrochemical[22b] approaches for this class of rearrangements.

An intriguing aspect of these transformations is that while the methods establish an important proof-of-concept highlighting the unique ability of skeletal editing to trigger heterocycle-to-heterocycle interconversion, this research platform could be further expanded by implementing a reversible process.[24] This chemistry can also be expanded beyond conventional nitrogen heterocycles that have already been well-explored in medicinal chemistry to research previously uncharted space as showcased, for example, by boron insertions,[25a] organometallic complexes,[25b] and N-to-C transmutations by employing alternating nitrogen deletions.[25c] Furthermore, other types of five-membered heterocycles, such as furans and thiophenes, are other possibility to undergo ring expansion, generating substituted derivatives.[26]

In summary, the reports by Levin and Morandi emphasize the abundance of opportunity of swapping heteroatoms by molecular transmutations. The dynamism of heterocycle-to-heterocycle interconversion strikes as a powerful approach to molecular editing. Clearly, there is immense potential in late-stage diversification of pharmaceuticals. The key future aspect is the practical implementation for the synthesis of useful pharmacophores. These innovative approaches open up vistas to explore chemistries of atom-to-atom interconversion in nitrogen-containing heterocyclic ring systems, which is of certain interest to chemists.

Acknowledgements

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Keywords: heterocycles • single-atom insertions • molecular editing • pyrroles • indoles

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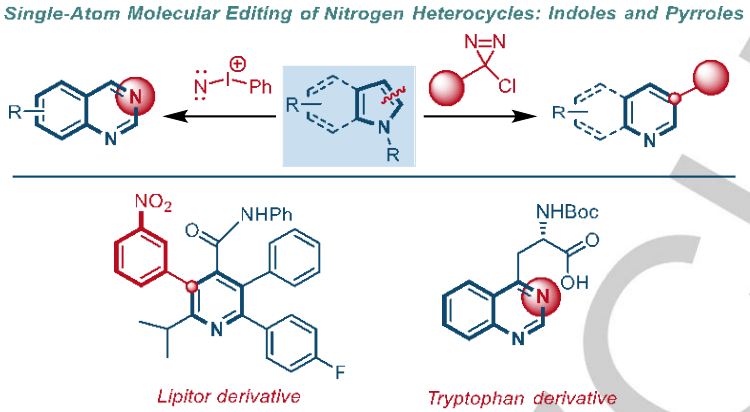

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