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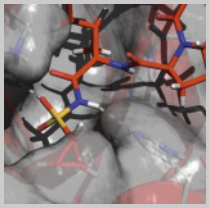

Medicinal Chemistry and Chemical Biology Highlights

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Skeletal Editing of Heterocycles – A New Tool for Lead Exploration?

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Abstract: Many new methods for single atom skeletal editing of heterocycles have been developed in the past few years with obvious applications to discovery chemistry. In this perspective, we assess the recent advances in this field and the potential application to lead exploration campaigns.

Keywords: Heterocyclic chemistry · Lead exploration · Medicinal chemistry · Skeletal editing · Synthesis

Introduction

A popular topic in the synthetic chemistry literature over the past two years is that of 'single atom skeletal editing'. The term, as defined by two of the leading researchers in this area, Mark Levin and Richmond Sarpong,[1] refers to the alteration of a ring system in a molecule of interest to insert, remove or replace a single atom. Implicit in this definition is the assumption that both molecules are of interest for their structure activity relationship and that minimal synthetic steps are required to achieve the transformation. To the chemical designer such 'scaffold hopping'[2] is a familiar process when carried out with a pen and paper, in front of the fumehood or nowadays using structure-based design software. While simple to design, such analogues are often far from simple to synthesise and so methods offering to facilitate direct scaffold hops are of high interest (Fig. 1). The synthetic chemistry literature however is a graveyard of methods that promised to revolutionise the experience of the chemical designer never to be cited again.[3] Will single atom skeletal editing find a routine place in the medicinal chemist's toolbox and speed up the scaffold hopping process?

From our perspective as chemists working on lead exploration programs, we tried to identify what makes an attractive method. A typical program begins with a 'hit' and the chemistry team must quickly determine its 'optimisability' and establish initial structure activity relationships (SAR). Once the profile of a compound across several parameters has been established, the emphasis (in our company at least) switches to a more intense phase of SAR study where the chemical scope of the lead is investigated in more breadth. In this context, scaffold hops to identify new chemical classes are a key part of this approach. As the program progresses and the SAR becomes better understood, the focus narrows to a smaller number of scaffolds for fine tuning and balancing a range of desirable properties. It is in the first and middle phases that skeletal editing methods would appear to have their most general applicability starting with facile generation of structural diversity and moving into targeted scaffold hops.

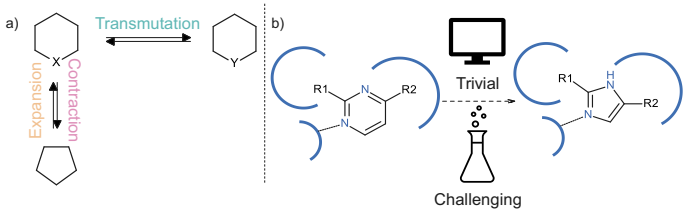

Fig. 1. a) Concepts in single atom skeletal editing. b) Scaffold changes are easy to design but can be much more challenging to execute in the laboratory.

In our view the ideal skeletal editing method should fulfil the following criteria:

1. The method should not introduce additional large substituents or functional groups.
2. Existing substituents on the modified ring should be tolerated and not majorly perturbed.
3. It should convert one common ring system into another.
4. There should be minimal requirement for preinstalled reactive functional groups.
5. The synthetic sequence should be as short as possible.

Points 1 and 2 reflect the fact that objective of a scaffold hop is generally to switch to another core while maintaining the key structural features required for target binding. Introducing major structural changes can be useful for hit expansion but is generally not desirable once some basic SAR has been established. Points 3, 4 and 5 relate to the substrate scope and practical execution of the method. Fig. 2 illustrates some recently published methods for skeletal editing and comments on their attractiveness in light of the above criteria.[4]

Atom Transmutation Strategies

A familiar tactic in lead optimisation is the 'nitrogen scan' where each unsubstituted carbon of an aryl ring is systematically replaced with nitrogen. In 2023, the Levin group published a powerful method for this transformation that converts an azide bearing aromatic carbon into a nitrogen (Fig. 2a).[5] The method is conceptually simple and transforms the most common ring system in both drug and agrochemical candidates into the second most common.[6] It has a reasonably broad substrate scope albeit with some limitations and moderate yields, which is not necessarily a problem for discovery chemistry. The main drawback is the requirement for a preinstalled azide moiety, but it is shown that this can be installed using a CH-borylation reaction, thus merging the power of late-stage functionalisation with skeletal editing. Using this method, the overall CH → N transformation takes four steps, none of them trivial, which may limit its competitiveness with *de novo* synthesis of the desired analogue. The Levin group has also developed a related method that converts quinolines into quinazolines (Fig. 2b).[7] This method also has good functional group tolerance on the ring but relies on an initial oxidation of

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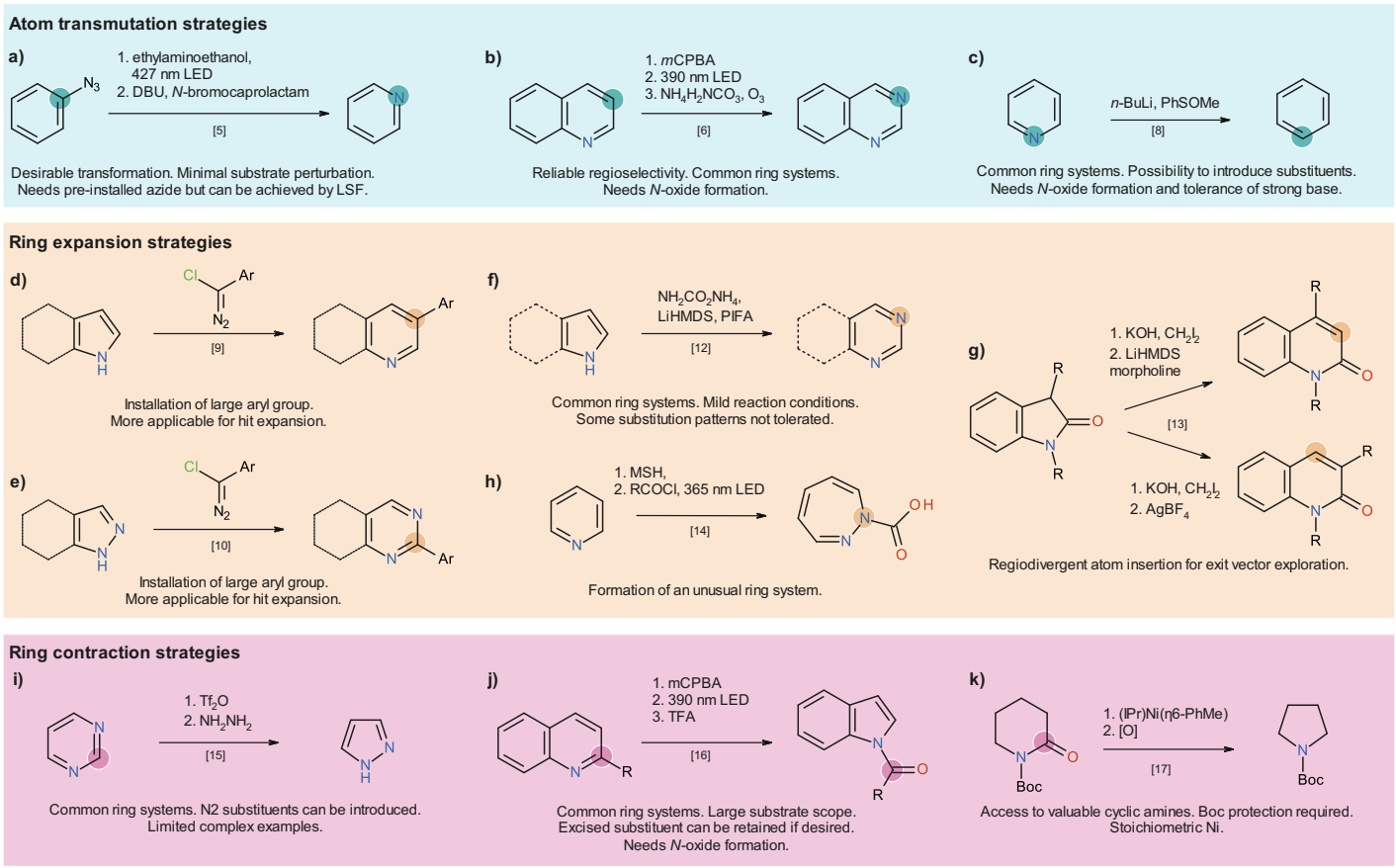

Fig. 2. Selected recently developed methods for single atom skeletal editing.

the quinoline to the *N*-oxide which may limit the substrate scope slightly.

In the opposite direction, the Sorensen group recently disclosed a method for converting pyridines to phenyl rings (Fig. 2c).[8] This method also relies on an initial oxidation to the *N*-oxide and uses strongly basic conditions but nicely complements the Levin method in the atom transmutation toolbox.

Ring Expansion Strategies

The concept of skeletal editing as a tactic for streamlining discovery synthesis is relatively modern but much of the fundamental reactivity used in the development of new method is not. The Levin group repurposed the century old Ciamician-Dennstedt rearrangement for the conversion of indoles/pyrroles into pyridines (Fig. 2d)[9] and developed a similar reaction for the conversion of pyrazoles into pyrimidines (Fig. 2e).[10] Again, the reactions are conceptually simple, a carbon atom is inserted into the C2-C3 bond of the pyrrole or the N-N bond of the pyrazole. However, in both cases the inserted carbon bears an aromatic group. For initial hit expansion or diversity-oriented syntheses this could be useful but as a true scaffold-hopping method, this large group is unlikely to be tolerated. In this regard, it could be interesting to revisit the original Ciamician-Dennstedt rearrangement which inserts a chloro substituted carbon,[11] a much smaller and also synthetically versatile motif. A complementary method for the ring expansion of pyrroles has been developed by the Morandi group (Fig. 2f).[12] A simple combination of LiHMDS, an ammonium source and hypervalent iodine-based oxidant inserts a nitrogen atom into the C2-C3 bond to form a pyrimidine. This method looks like a good scaffold hopping tactic and its application to generate analogues of tryptophan and melatonin has been nicely illustrated. Another example from the Morandi group is the ring expansion of oxindoles into 2-quinolones (Fig. 2g).[13] These ring systems are not as common in drugs/agrochemicals as pyridines, indoles, *etc.* but a nice feature of the method is that a simple switch of reaction conditions can lead to regiodivergent outcomes for the carbon insertion - this is an especially useful aspect when designing a scaffold-hopping strategy. A final ring expansion to note is the conversion of a pyridine into a 1,2-diazepine reported by the group of Ghiazza (Fig. 2h).[14] This is not a commonly seen ring system, but it could be considered and behave as an isostere of pyridine and open up IP free areas of chemical space. Direct access from pyridines could facilitate its use in lead exploration campaigns.

Ring Contraction Strategies

Complementary to ring expansion methods are ring contraction strategies. In 2022, the Sarpong group published the ring contraction of a pyrimidine into a pyrazole with deletion of the C2 carbon atom (Fig. 2i).[15] The method is mild and can provide access to N2 substituted pyrazoles that are sometimes tricky to obtain in a regioselective manner. Pyrazoles are a particularly important class of heterocycle in agrochemistry. The conversion of quinolines into indoles *via* the quinoline *N*-oxide has been accomplished by the Levin group (Fig. 2j).[16] A range of substitution patterns are tolerated and the C2 carbon is excised as an amide substituent on the indole nitrogen. This can be cleaved or alternatively left in place if the excised carbon bears an important substituent. Moving away from unsaturated heterocycles, another noteworthy method is the skeletal metalation process recently published by the Morandi group.[17] This can convert a lactam into a cyclic amine with excision of the carbonyl carbon (Fig. 2k). The substrate scope presented is relatively limited but the cyclo-metalated intermediate has the potential to be a very versatile intermediate that can be utilised in different ways.

As the above examples illustrate, the toolbox of skeletal editing methods available to the discovery chemist has expanded rapidly in the last few years but there is still a need for both new

and improved methods. The diversity of heterocyclic scaffolds and their different reactivity means that there are unlikely to be general methods that will work across multiple diverse scaffolds necessitating a broad toolbox. There are still many heterocycles of interest that cannot be interconverted using skeletal editing tactics, an obvious class being nucleobase analogues. Access to uncommon heterocycles is an opportunity for impactful methods as illustrated by Ghiazza's pyridine → 1,2-diazepine conversion.

Modern discovery chemistry is dominated by enormous libraries of building blocks that can be connected in almost infinite ways by a small number of reliable coupling reactions. The skeletal editing reactions discussed here operate in the same chemical space and thus must offer significant advantages and high reliability if they are to be adopted as routine methods. We argue that full exploitation of skeletal editing as a synthetic tactic in lead exploration requires a holistic view and a strategic change when designing a set of analogues for synthesis. For example, a scaffold hopping campaign could initially target the quinoline with the intention of converting it into the corresponding indole, quinazoline, indazole, and cinnoline[18] (Fig. 3a). In many cases this would represent fewer purchased building blocks and fewer synthetic steps (meaning less time) than a traditional approach. There is a parallel and synergy here with a synthetic strategy involving late-stage functionalisation for peripheral modifications and using these two approaches in parallel could be especially powerful for rapid exploration of SAR.[19] Both LSF and skeletal editing allow bioactive analogues to become synthetic starting materials thus increasing synthetic efficiency and the value of each compound synthesised. By viewing screening compounds in this way, skeletal editing in combination with automated parallel synthesis provides a strategy for scaffold hopping of entire classes of compound (Fig. 3b). This would provide a much richer dataset to evaluate the effect of a scaffold change than by making a single analogue.

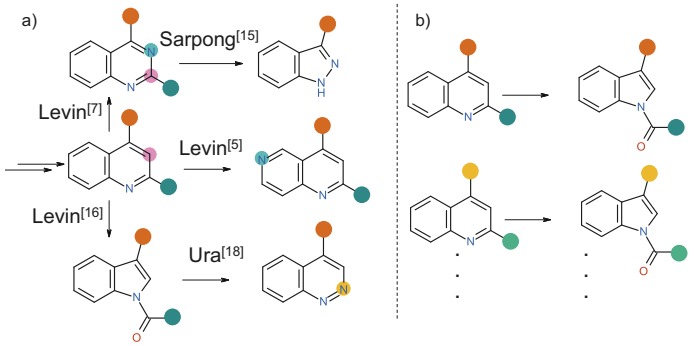

Fig. 3. a) Conceptual synthetic strategy for the production of a compound series by converting directly between bioactive analogues of interest b) Conceptual strategy for scaffold hopping of an entire series of analogues by parallel synthesis.

In conclusion, methods for single atom skeletal editing have made great progress in the last few years. However, the current paradigm of building block driven discovery chemistry presents a high barrier for widespread adoption without a strategic change in synthetic chemistry campaigns. Lead optimisation chemists should be on the lookout for opportunities to significantly streamline their analogue campaigns using skeletal editing and to stress-test the methods in a 'real-life' setting.

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