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Perspective

Recent Scaffold Hopping Applications in Central Nervous System Drug Discovery

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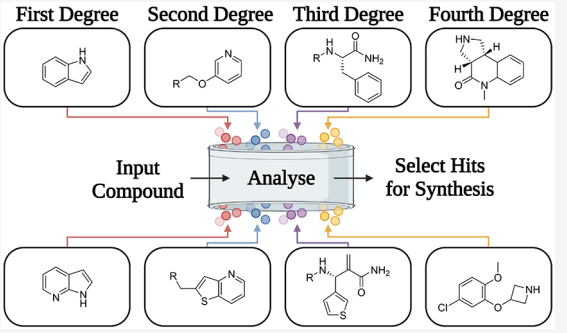
ABSTRACT: The concept of bioisosterism and the implementation of bioisosteric replacement is fundamental to medicinal chemistry. The exploration of bioisosteres is often used to probe key structural features of candidate pharmacophores and enhance pharmacokinetic properties. As the understanding of bioisosterism has evolved, capabilities to undertake more ambitious bioisosteric replacements have emerged. Scaffold hopping is a broadly used term in the literature referring to a variety of different bioisosteric replacement strategies, ranging from simple heterocyclic replacements to topological structural overhauls. In this work, we have highlighted recent applications of scaffold hopping in the central nervous system drug discovery space. While we have highlighted the benefits of using scaffold hopping approaches in central nervous system drug discovery, these are also widely applicable to other medicinal chemistry fields. We also recommend a shift toward the use of more refined and meaningful terminology within the realm of scaffold hopping.



1. INTRODUCTION

The quest from lead candidate identification to the clinic is long and arduous, often spanning decades and on average costing in excess of US $1 billion.[1] The work of a medicinal chemist is often focused on the process of lead optimization, which in itself is no small undertaking. Lead optimization generally involves countless structure−activity relationship (SAR) studies and physicochemical parameter optimizations that lead to refined pharmacophore models and optimized drug candidates. This process involves the design and synthesis of large compound libraries that focus on arrays of bioisosteric replacements to extract relevant pharmacophore details. As the knowledge and capabilities of medicinal chemistry have grown, the strategies for bioisosteric replacements have expanded and become increasingly ambitious.

Among other bioisosteric replacement strategies, scaffold hopping is an exciting technique that has been applied widely in drug discovery efforts to explore lead drug candidates. Since its inception by Schneider and co-workers in the late 20th century, scaffold hopping has cemented its place in the arsenal of medicinal chemists.[2] Scaffold hopping relies on the fundamental concept that biological targets do not show activity for empirical structures, but that activity is induced by the consequent intermolecular interactions that occur between a ligand and the target. As a result, structurally disparate molecular scaffolds can have similar biological activities due to the ability to replicate analogous intermolecular interactions. This is the fundamental concept behind bioisosterism and is a central tenet of medicinal chemistry.

This perspective will briefly discuss historical milestones of classical isosterism, bioisosterism, and scaffold hopping. We have also highlighted and discussed recent examples of scaffold hopping approaches within the central nervous system (CNS) drug discovery field. In doing so, we have utilized what we believe to be a more useful classification of these approaches and suggest a shift to more meaningful technical language in this space, which is applicable to all fields of medicinal chemistry, not just CNS drug discovery.

1.1. A Brief History Classical Isosterism and Bioisosterism. The classical concept of isosterism has existed since the early 1900s with Langmuir, Grimm, and Erlenmeyer providing a number of definitions of classical chemical isosteres that focused on atoms, or groups of atoms, that were similar in size or electronic properties (Figure 1). The term "bioisostere" was coined by Friedman in 1951 to describe atoms, groups of atoms, or molecules that are isosteric and that illicit a comparable biological response (Figure 1).[3] Definitions of bioisosterism have since evolved to encompass broader structural changes to account for our ever-expanding knowledge base. Thornber described possibly the broadest working

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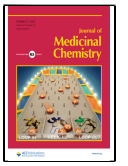

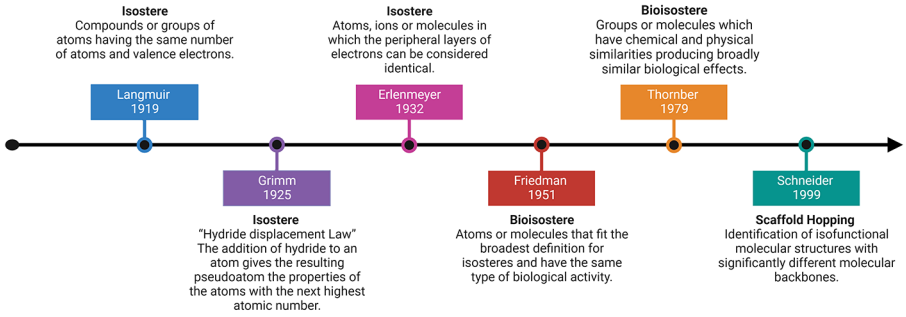

Figure 1. Historical definitions of terms related to isosterism, bioisosterism, and scaffold hopping.

definition of bioisosterism in 1979 that focuses on functional groups or molecules with physical and chemical similarities, which produce broadly similar biological effects (Figure 1).[4] As these definitions have continued to evolve there has also been an increasing appreciation for the complexity of biological systems and an understanding that bioisosteres that work for one target may not work for others. Bioisosteres are frequently incorporated in lead optimization studies to (1) identify key pharmacophoric features (e.g., hydrogen bond donors and hydrogen bond acceptors), (2) improve physicochemical properties (e.g., lipophilicity), (3) remove metabolic liabilities, (4) improve synthetic accessibility, and (5) identify novel chemotypes and patent busting opportunities.[5,6] Possibly one of the simplest and most recognizable examples of this is the replacement of an ester with the corresponding amide. This relatively simple bioisosteric approach can also be illustrated by a wide variety of other possible ester/amide replacements, highlighting the huge chemical space that can be investigated through bioisosteres.[7] Application of the principles of bioisosterism continues to drive lead identification and optimization in the drug discovery pipeline.[6] Bioisosteres of common functional groups and structural motifs have been discussed extensively elsewhere and will not be further discussed here.[6−9]

1.2. Scaffold Hopping. As a concept, scaffold hopping can be considered as an extension of traditional bioisosteric replacement strategies. Scaffold hopping broadly involves the replacement or redesign of core structure moieties while keeping pendant groups in comparable positions and 3D space. This can manifest itself in a number of different structural changes. Scaffold hopping focuses on replacement of larger structural motifs, ranging from heterocyclic substitution to major structural overhauls. Scaffold hopping approaches may also utilize *in silico* comparisons of 3D shape and electrostatic characteristics, as well as docking studies. However, as will be discussed in future sections, some more basic medicinal chemistry approaches can also constitute scaffold hopping. In the absence of strict modern definitions, there is often a blurred line between what changes are deemed bioisosteric replacements and what constitutes scaffold hopping.

Scaffold hopping is routinely used to optimize compounds similarly to the way traditional bioisosteric replacements are used (e.g., to explore key pharmacophore features, remove metabolic liabilities, improve physicochemical properties) but also often has the added benefit of circumventing structural features protected by IP (known as patent busting). A resurgence in the use of natural products as pharmaceutical leads has also seen scaffold hopping frequently used to derive more synthetically accessible and biologically stable natural product analogues.[10−13] The concepts of bioisosterism and scaffold hopping have evolved steadily over the last century and remain fundamental principles of modern drug discovery. This perspective aims to highlight the potential of scaffold hopping as a bioisosteric replacement strategy and discuss recent applications of scaffold hopping in the CNS drug discovery realm.

Historically, the term scaffold hopping has not been well-defined. It is often used ambiguously throughout the literature and the appropriateness of its use is typically left up to the authors' preference. Scaffold hopping has been routinely used to describe structural changes ranging from single atom replacements to complete structural overhauls. In the broadest sense, scaffold hopping involves developing compound derivatives with different core features that maintain pendant groups in comparable position and 3D space. A useful classification system was described by Sun and co-workers in 2012.[14] This work categorized the degree of scaffold hopping (ranging from 1° to 4°) based of the strategy of structural changes and specific replacements that are made (summarized in Table 1).[14] Although the lines between different types of scaffold hopping approaches can still become blurred, these categorizations are certainly a useful starting point in classifying scaffold hopping approaches. In each case, the changes that are proposed as scaffold hopping focus on changes to the core of various drug candidates. We have used the classifications proposed by Sun and co-workers as a framework for this perspective.[14] Applying the categorizations suggested by Sun and co-workers while keeping in mind the requirement for these techniques to be applied to core structures of candidate molecules provides a useful basis moving forward for future reports of scaffold hopping. This will hopefully bring to light a more rigorous description of scaffold hopping for authors to follow in the future. Various recent examples of 1°−4° scaffold hopping approaches in the CNS drug discovery field will be highlighted and discussed

Table 1. Summary of Degrees (1°−4°) of Scaffold Hopping, as Proposed by Sun and Co-workers[14]

degree of scaffold hopping	general description
first (1°)	heterocyclic core replacements maintaining pendant moieties in comparable space
second (2°)	pseudo-ring structures: modulating conformational restriction through ring opening and ring closing by the introduction of new heterocyclic cores
third (3°)	small-molecule-derived pseudopeptides and peptidomimetics
fourth (4°)	topology- or shape-based structural overhauls

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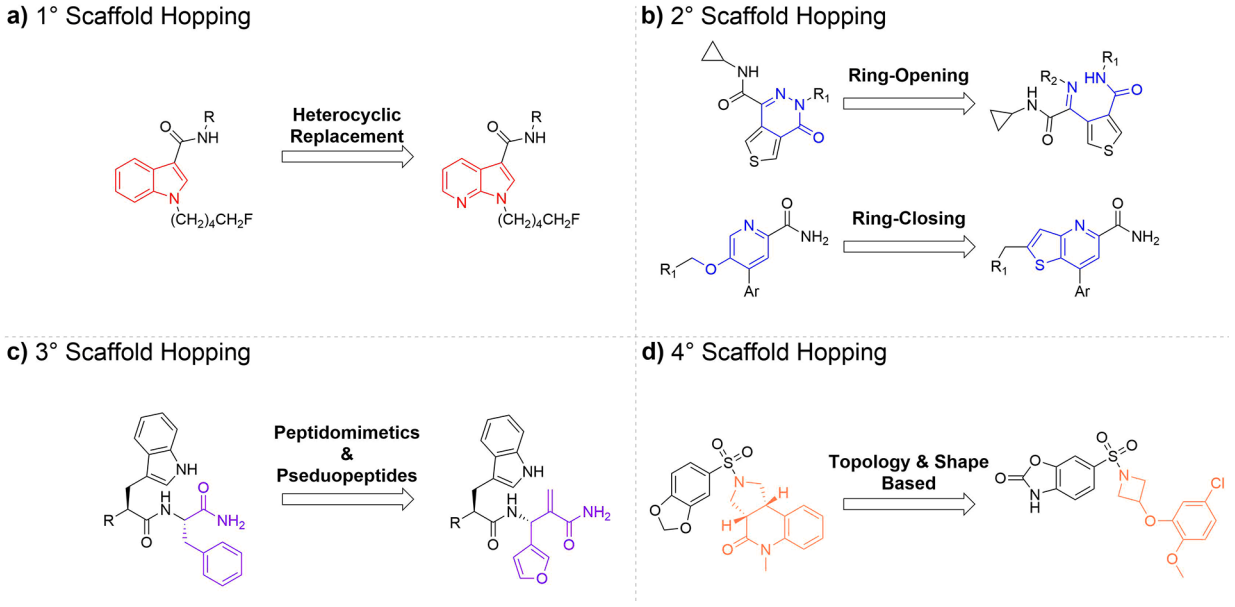

Figure 2. Illustrative examples of different types of scaffold hopping approaches as classified by Sun and co-workers.[14] (a) 1° Scaffold hopping: heterocyclic replacement.[15] (b) 2° Scaffold hopping: conformational restriction through pseudo-ring structures.[16] (c) 3° Scaffold hopping: small-molecule-derived pseudopeptides and peptidomimetics.[17,18] (d) 4° Scaffold hopping: topology- or shape-based structural overhauls.[19]

throughout this work. Importantly the reader should remember that, in the literature, the approaches described in this perspective are all described as scaffold hopping, thereby contributing to, and also highlighting, the ambiguity of the term.

1.2.1. 1° Scaffold Hopping: Heterocyclic Replacement. First degree (1°) scaffold hopping is the most common form reported throughout the literature. This level of scaffold hopping includes the substitution of single atoms within a heterocyclic core, as well as different (but highly similar) heterocyclic cores that maintain pendant moieties in similar space and positioning (Figure 2a). This approach represents the simplest form of scaffold hopping and is often employed in SAR studies. Experienced medicinal chemists can often perform this solely by inspection, though *in silico* modeling can also be used, to generate compounds with a high degree of similarity. Although 1° scaffold hopping often only encompasses small structural changes, it can be extremely useful in identifying key ligand binding interactions, modulating pharmacokinetic properties, and identifying diverse chemotypes.

1.2.2. 2° Scaffold Hopping: Pseudo-Ring Structures (Ring-Opening and -Closing). Second degree (2°) scaffold hopping begins to move toward more significant structural changes to cores of candidates through modulating conformational restriction, either through use of more rigid ring-closed systems or more flexible ring-opened systems as core structures (Figure 2b). These opposing modifications are closely linked by their respective abilities to promote potential drug−target interactions. A ring-closing approach can be used to minimize the entropic cost of adopting a particular molecular conformation, often leading to improved target engagement.[20] On the other hand, ring-opened analogues can give pendant groups more flexibility such that they are able to fit more favorably into dynamic binding pockets. Although conformational restriction can also be achieved by other chemical means, this often does not produce significantly different core structures−a key defining factor associated with 2° scaffold hopping. This generally manifests as a new heterocyclic core structure in derivative compounds.

1.2.3. 3° Scaffold Hopping: Peptidomimetics and Pseudopeptides. The realm of peptidomimetics and pseudopeptides encompasses a vast array of techniques and strategies to produce improved peptide-esque candidate molecules. Within this large field, third degree (3°) scaffold hopping is the modification of a protein or peptide chain by the introduction small molecule derived moieties as a replacement for amino acids (Figure 2c). This is focused on introducing structures that replace amino acids while maintaining the secondary structure of peptide chains (such as α-helices and β-sheets) and their ability to interact with secondary structures of biological targets. This is a major application of 3° scaffold hopping, although we believe that some non-proteinogenic amino acid substitutions should also be classified within this definition. Application of 3° scaffold hopping under this definition has been discussed in the relevant section (section 3.1.3). The application of 3° scaffold hopping offers opportunities in peptide therapeutics and discovery to overcome a number of notorious problems such as metabolic stability and bioavailability.[14] 3° Scaffold hopping represents a very specific niche in the peptidomimetic field; however it is important to be able to distinguish this approach from other strategies aiming to undertake similar mimetic outcomes.

1.2.4. 4° Scaffold Hopping: Topology Based Replacement. Fourth degree (4°) scaffold hopping encompasses large structural overhauls of the core features of lead candidates. This represents the most ambitious level of bioisosteric replacement where structural motifs are replaced with structurally dissimilar groups with comparable calculated 3D shape, electrostatic properties, and intermolecular binding capabilities (Figure 2d). As has been mentioned for previous levels of scaffold hopping this approach should focus on the core moiety of candidates and retain pendant groups in comparable orientations. The successful implementation of 4° scaffold hopping in drug discovery is comparatively more limited, likely due to the drastic structural changes that this

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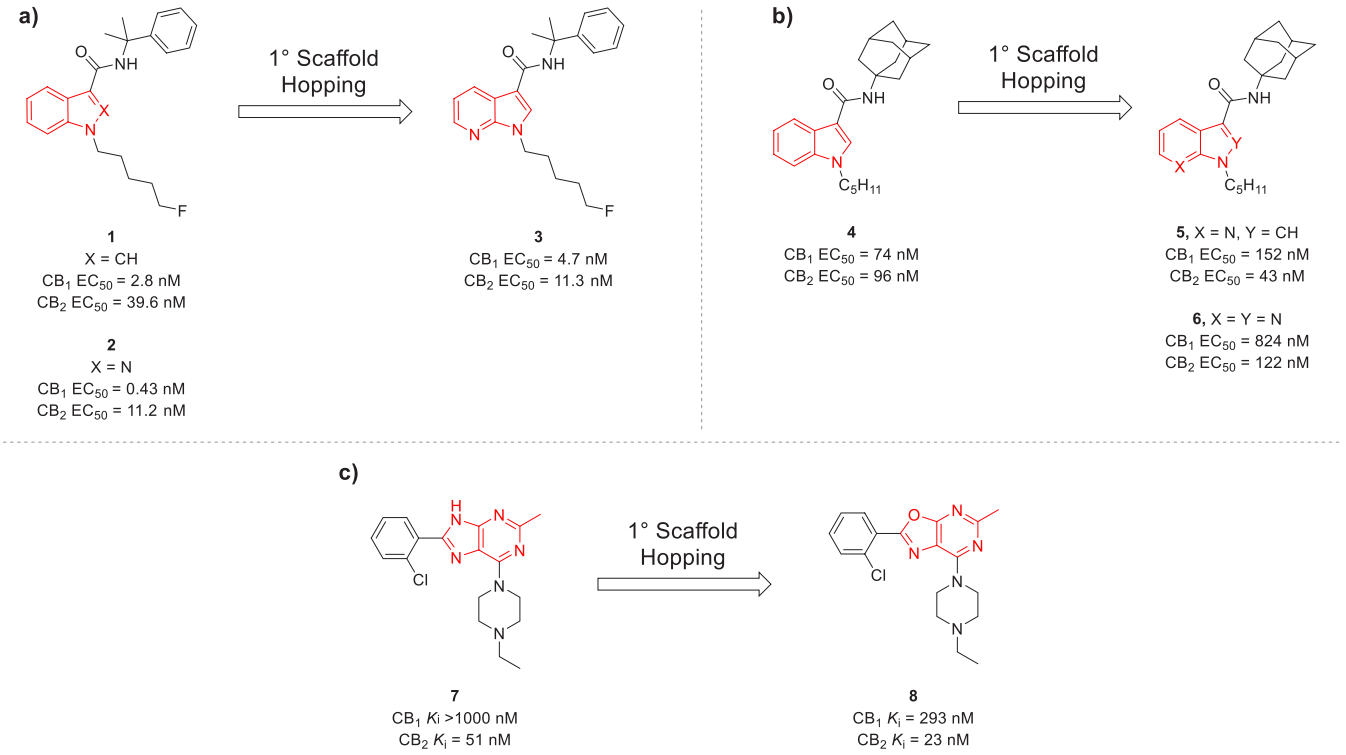

Figure 3. 1° Scaffold hopping used in the design of synthetic cannabinoid receptor ligands. (a) Exploration of CB ligands **1** and **2** by Banister and co-workers.[15] (b) Incorporation of 7-azaindole and pyrazolo[3,4-*b*]pyridine cores (**5** and **6**, respectively) into **4** explored by Moir and co-workers to improve CB_2 selectivity.[42] (c) Purine replacement of **7** with oxazolo[5,4-*d*]pyrimidine **8** undertaken by Tuo and co-workers to discover CB_2 neutral antagonist.[43] EC_{50} = half maximal effective concentration; K_i = inhibition constant.

approach undertakes. This approach is generally aided by *in silico* modeling of compound shape and electrostatics. Although successful applications of 4° scaffold hopping are scarce, they show vast potential for exploring and developing highly diverse compound libraries for various biological targets. It also represents a highly valuable method for circumventing composition of patents.

2. METHODS OF SCAFFOLD HOPPING

2.1. The Eye of a Medicinal Chemist. Medicinal chemists often perform scaffold hopping to generate compound libraries without computational aid. These modifications generally contain functionalities commonly seen within medicinal chemistry such as ring closure or opening and heterocyclic replacements.[21] These modifications allow exploration of the chemical space of druggable pockets to deduce the pharmacophore (critical atoms or functionalities necessary for potent biological activity) and auxophore (atoms that may hinder binding of the pharmacophore).[22] However, without computational aid, molecular similarity with respect to shape and electron distribution cannot be quantified.[23] This can lead to the unnecessary synthesis of compounds that appear similar on paper but have dissimilar three-dimensional structures and biological activities.

2.2. *In Silico* Design. More complex and ambitious scaffold hopping methods are often undertaken through *in silico* screening and design. Algorithms developed from existing medicinal chemistry data sets permit higher degree scaffold hopping and deduce a measure of similarity, or dissimilarity, between compounds.[24] Different software packages can be employed to perform this based on the type of scaffold hopping required.[14,25−30] For example, MORPH is commonly utilized in 1° scaffold hopping to generate novel aromatic ring systems from its library of drug-like scaffolds.[14,25] CAVEAT and Cresset Spark are commonly used in higher degrees of scaffold hopping to identify structurally distinct fragments with comparable shape and electrostatic features.[14,26,27] Additionally, weighted holistic atom localization and entity shape (WHALES) is a similarity based method commonly used when scaffold hopping from natural products to synthetic mimetics.[29,30] Developments in molecular modeling and docking abilities have greatly advanced the ability of a medicinal chemist to undertake informed and logical structural overhauls of lead drug candidates.

Artificial intelligence (AI) has proved to be another valuable tool for discovery of novel therapeutics, with machine learning analyzing heterogeneous data sets aiding in target identification and hit-to-lead optimization.[31] AI is capable of being trained to develop quantitative structure−activity relationship (QSAR) models and predict appropriate leads, physiochemical properties, ADME, drug sensitivity and response, drug−drug interactions, blood−brain barrier (BBB) permeability, and more.[31] However, despite this vast potential, the lack of high-quality data sets available to train accurate algorithms for CNS drug discovery limits its capabilities at present.[31]

This represents a limited discussion around how scaffold hopping can be undertaken and is not the focus of this perspective; however it should be noted the wide array of approaches that can be undertaken as well as the continuing growth in this field. The expansion and capabilities within this field will certainly aid in these approaches (particularly more ambitious approaches such as 4° scaffold hopping) being used successfully. We acknowledge that several recent publications have discussed various approaches toward scaffold hopping

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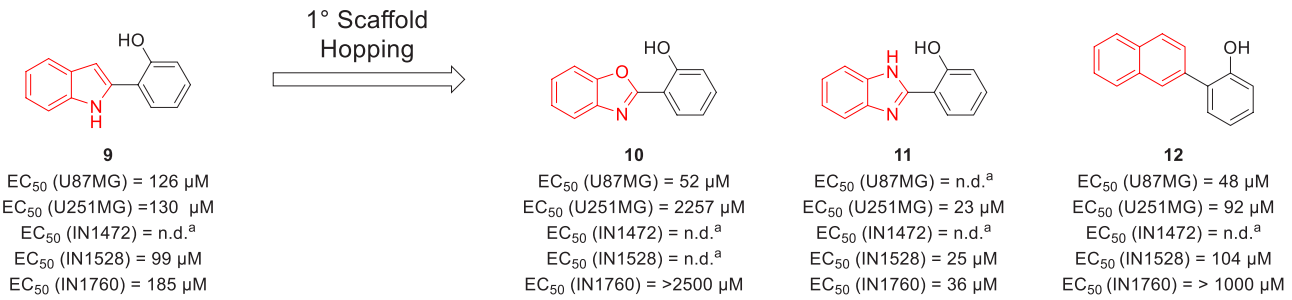

9
EC_{50} (U87MG) = 126 μM
EC_{50} (U251MG) =130 μM
EC_{50} (IN1472) = n.d.[a]
EC_{50} (IN1528) = 99 μM
EC_{50} (IN1760) = 185 μM

10
EC_{50} (U87MG) = 52 μM
EC_{50} (U251MG) = 2257 μM
EC_{50} (IN1472) = n.d.[a]
EC_{50} (IN1528) = n.d.[a]
EC_{50} (IN1760) = >2500 μM

11
EC_{50} (U87MG) = n.d.[a]
EC_{50} (U251MG) = 23 μM
EC_{50} (IN1472) = n.d.[a]
EC_{50} (IN1528) = 25 μM
EC_{50} (IN1760) = 36 μM

12
EC_{50} (U87MG) = 48 μM
EC_{50} (U251MG) = 92 μM
EC_{50} (IN1472) = n.d.[a]
EC_{50} (IN1528) = 104 μM
EC_{50} (IN1760) = > 1000 μM

Figure 4. 1° Scaffold hopping approach used in work by Sherer and co-workers to explore glioblastoma targeting compounds. EC_{50} values represent antiproliferative activity. U87MG and U251MG are commercially available glioblastoma cell lines. IN1472, IN1528, and IN1760 are patient derived glioblastoma cell lines.[45] EC_{50} = half maximal effective concentration. [a]EC_{50} not determined.

and point readers in the direction of these publications.[21,24,29,30,32−34] The remaining discussions in this work will be about applications of scaffold hopping in CNS drug discovery.

3. CENTRAL NERVOUS SYSTEM DRUG DISCOVERY

CNS associated disease states account for a considerable proportion of the global burden of disease, with relatively limited effective treatments available. CNS drug discovery is often hindered by a number of challenges including but not limited to (1) identification and validation of translational drug targets, (2) establishment of disease-relevant preclinical models, and (3) the need for drug candidates to exhibit BBB permeability.[35] These challenges are exemplified by the large number of drugs targeting CNS diseases that have failed in clinical trials in recent years.[36] In the CNS drug discovery landscape, scaffold hopping provides unique opportunities to modulate drug-like molecular properties to improve BBB permeability and reduce the likelihood of undesirable CNS removal by efflux transporters. Various scaffold hopping approaches have been employed in the development of psychoactive substances, neuroinflammation modulators and neurodegeneration treatments, among many others.

3.1. Recent Scaffold Hopping Highlights in CNS Drug Discovery. Although the focus of this perspective is applications of scaffold hopping in CNS drug discovery, it should be noted that applications of the various degrees of scaffold hopping are reported across most major drug discovery realms such as anticancer, antiviral, and antimicrobial research, among others.[10,11,37−40]

3.1.1. First Degree (1°) Scaffold Hopping in CNS Drug Discovery. As discussed, 1° scaffold hopping is common and is generally considered in SAR library designs as heterocyclic replacements are often used to probe ligand−target interactions and to eliminate metabolic liabilities.[5] This approach changes core structures through heterocyclic replacements. Importantly these replacements maintain pendant moieties in the same or comparable positions and space. More than 85% of biologically active compounds contain a heterocycle or heterocyclic core in their structure, highlighting the significance of the role they play in the drug discovery process.[41]

Cannabinoid receptors 1 and 2 (CB_1 and CB_2, respectively) have been identified as therapeutic targets for the treatment of a range of disease states including neuropathic pain and neurodegenerative diseases (e.g., Alzheimer's disease and Huntington's disease). The use of 1° scaffold hopping to derivatize new psychoactive substances has also been noted as a way for clandestine chemists to circumvent detection from law enforcement while still maintaining high potency at CB receptor ligands (Figure 3).

Banister and co-workers used a 1° scaffold hopping approach in the identification of new synthetic cannabinoid **3** (Figure 3a).[15] This ligand was discovered through heterocyclic replacement of known, highly potent, synthetic cannabinoids **1** and **2** (Figure 3a).[15,44] Although a slight drop in potency was observed, the 1° scaffold hopping derivative **3** was still shown to be a potent synthetic cannabinoid receptor ligand (Figure 3a).[15] This approach has clearly been useful in identifying this novel psychoactive cannabinoid chemotype. Moir and co-workers took several similar approaches in the development of CB_2-selective synthetic cannabinoids (Figure 3b).[42] Among other SAR investigations, this work employed a 1° scaffold hopping approach in the exploration of **4** (Figure 3b) to probe CB_1 and CB_2 receptor selectivity.[42] CB_2-selective ligands are desirable as it is hypothesized that they can provide therapeutic benefit without inducing the frequently reported psychoactive effects of cannabinoid ligands that are associated with CB_1 activity. Heterocyclic replacements of the indole core of **4** with a 7-azaindole and a pyrazolo[3,4-*b*]pyridine (**5** and **6**, respectively) were explored.[42] Interestingly, both heterocyclic replacements saw a desired shift toward CB_2 selectivity (Figure 3b). The 7-azaindole derivative **5** saw a decreased potency for CB_1 and an increased potency for CB_2 compared to **4** (Figure 3b). The pyrazolo[3,4-*b*]pyridine derivative **6** saw an overall loss of potency (Figure 3b), but still saw a shift toward CB_2 selectivity.[42] Results from both of these studies suggest N-containing heterocycles at the 7-position promote desirable CB_2 selectivity (Figure 3a,b). Derivatives such as these exemplify 1° scaffold hopping by manipulating single atoms to produce structurally distinct heterocyclic cores while maintaining pendant group positioning. As previously mentioned, 1° scaffold hopping is the most conservative approach but still is useful in identifying new chemotypes. In this case, this scaffold hopping has also been important in identifying key pharmacophore features that can elicit CB receptor potency and desirable CB_2 selectivity (where applicable).

Tuo and co-workers have also reported an application of 1° scaffold hopping on reported CB_2 receptor agonist **7** leading to the discovery of novel CB_2 receptor competitive neutral antagonist **8** (Figure 3c).[43] They replaced the purine core of CB_2 agonist **7** with the similar oxazolo[5,4-*d*]pyrimidine core seen in **8** as a means of investigating the pharmacological significance of the purine core.[43] Compared to lead compound **7**, the oxazolo[5,4-*d*]pyrimidine derivative **8** saw an increase in CB_2 affinity concomitant with a large drop in CB_2 selectivity (Figure 3c).[43] The authors found that this change in core

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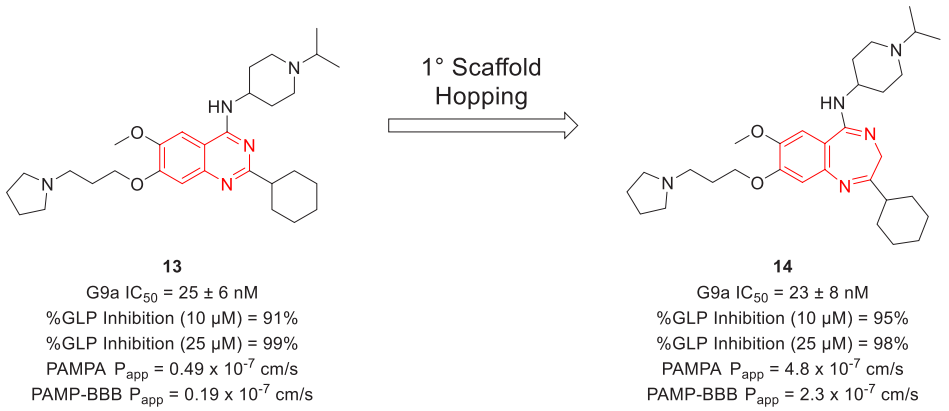

Figure 5. 1° Scaffold hopping approach used by Milite and co-workers in the discovery of novel G9a/GLP inhibitors derived from quinazoline lead **13** through the introduction of 1,4-benzodiazepine core in **14**.[47] P_{app} = apparent permeability based on results from PAMPA analysis. IC_{50} = half maximal inhibitory concentration.

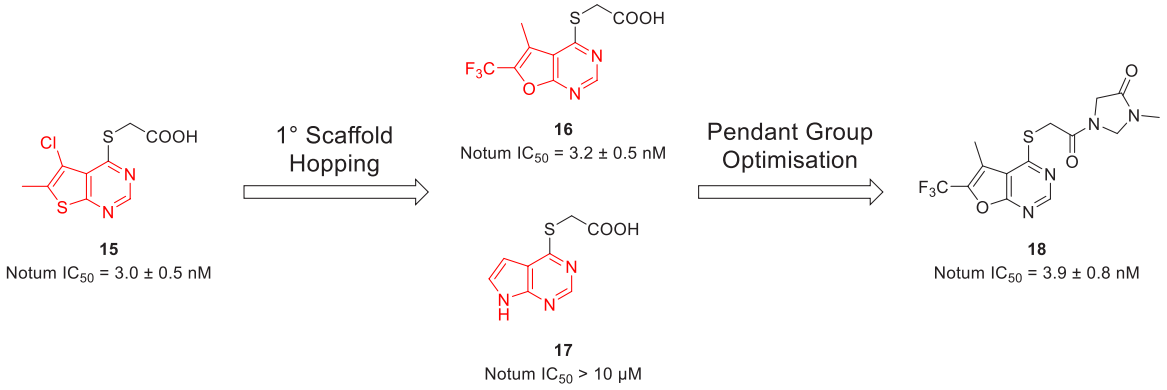

Figure 6. 1° Scaffold hopping used in the discovery and development of new chemotypes targeting notum inhibition reported by Atkinson and co-workers.[51] IC_{50} = half maximal inhibitory concentration.

structure changed the ligand's mode of action at the CB_2 receptor from an agonist (**7**) to a competitive neutral antagonist (**8**).[43] In this case, K_i values are used as a tool for comparison given the different functional readouts of these compounds *in vitro*. Although the therapeutic use of CB_2 neutral antagonists has not been thoroughly explored, this is an unexpected outcome that resulted from a relatively simple scaffold hopping investigation. Further work in this area would certainly investigate any potential therapeutic benefit of a CB_2 neutral antagonist.

Work recently published by Sherer and co-workers highlights an extensive application of 1° scaffold hopping to identify new candidates targeting glioblastoma through the generation of reactive oxygen species (ROS).[45] This work explored diverse heterocyclic replacements of the 2-substituted indole core of lead **9** (Figure 4). The scaffold hops explored in this work were guided by computational modeling with ShaEP software.[46] Replacements of the indole core of **9** with a benzoxazole (**10**), benzimidazole (**11**), and napthalene (**12**) highlight 1° scaffold hopping applied in this work (Figure 4). In each case, these compounds were screened for antitumor activity in numerous established and patient-derived glioblastoma cell lines (U87MG, U251MG, IN1472, IN1528, and IN1760, Figure 4). Compared to the 2-phenylindole lead **9**, the benzoxazole **10** showed a reduction in overall activity across all cell lines (Figure 4), whereas the benzimidazole and naphthalene derivatives (**11** and **12**, respectively) both showed overall improvements.[45] Lead compound **9** reduces proliferation by the formation of ROS leading to autophagic cell death.[45] Interestingly in this case, it seems that the presence of the 2-hydroxyphenyl moiety in the position is more important for the generation of ROS, rather than specific ligand−target interactions. This application of 1° scaffold hopping introduced a wide variety of heterocycles while maintaining the 2-hydroxyphenyl moiety in comparable position.[45] This highlights the broad potential of 1° scaffold hopping and has been successful in identifying a range of new chemotypes with antiproliferative activity against glioblastomas.

Milite and co-workers used 1° scaffold hopping in their search for novel lysine methyltransferases 1C (G9a) and 1D (GLP) inhibitors.[47] These enzymes methylate a range of protein targets, and their dysregulation has been implicated in several neurodegenerative conditions, as well as numerous oncological contexts.[48−50] A variety of quinazoline based compounds (exemplified by **13**, Figure 5) have been reported as potent inhibitors of G9a and GLP. The authors have noted a distinct limitation in the chemotypes of compounds used as chemical tools to explore G9a and GLP, with the space somewhat crowded by quinazoline derivatives such as **13**.[47] They therefore replaced the quinazoline core of **13** with the similar ring-expanded 1,4-benzodiazepine core as seen in **14** (Figure 5). This heterocyclic replacement appears to have been driven by chemical intuition but was also explored through *in silico* docking studies, which suggested that the 1,4-benzodiazepine derivative **14** was capable of mimicking the binding interactions of **13**. The 1° scaffold hopping derivative

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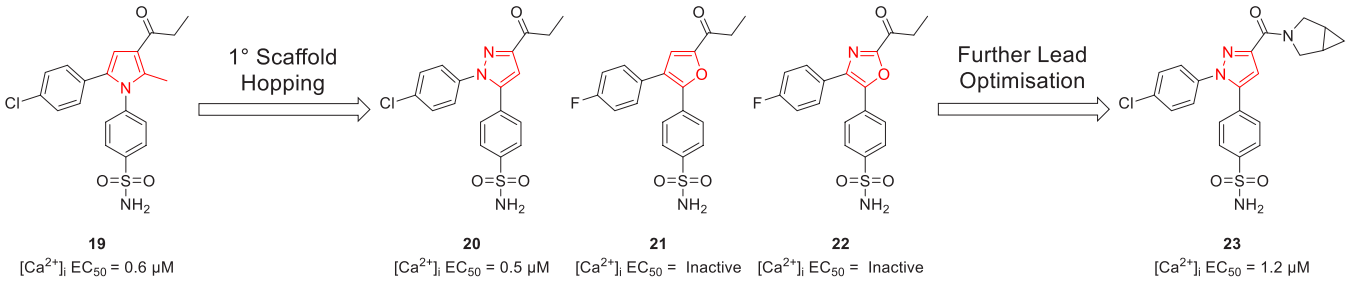

Figure 7. 1° Scaffold hopping approach used in development of α7 nAChR PAMs reported by Ledneckzi and co-workers through replacement of the pyrrole core of **19** with various 5-membered heteroaromatic cores (**20**, **21**, and **22**) and further optimization of the ethyl ketone moiety to yield **23**.[54] EC_{50} = half maximal effective concentration.

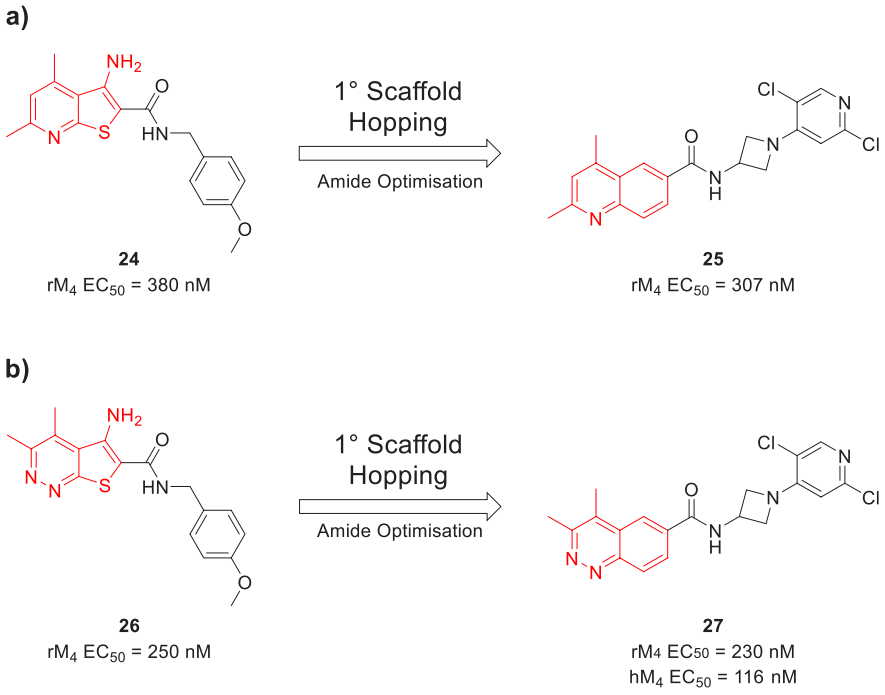

Figure 8. 1° Scaffold hopping reported for the identification of M_4 PAMs. (a) Based on thieno[2,3-*b*]pyridine scaffold seen in **24**.[57] (b) Based on thieno[2,3-*c*]pyridazine scaffold seen in **26**.[59] rM_4 = rat M_4 receptor; hM_4 = human M_4 receptor; EC_{50} = half maximal effective concentration.

14 had comparable G9a inhibition activity to **13** and improved GLP inhibition (Figure 5).[47] Compound **14** also displayed improved cell and BBB permeability (measured through a parallel artificial membrane permeability assay, PAMPA) compared to quinazoline **13** (Figure 5). This application of 1° scaffold hopping by the introduction of the 1,4-benzodiazepine ring of **14** illustrates how this approach can be used to optimize pharmacokinetic properties as well as expanding chemotypes known for G9a and GLP inhibition.

Atkinson and co-workers used heterocyclic replacement to identify a new core scaffold that was identified as a potent notum inhibitor (Figure 6).[51] Notum has been identified as a promising target for the treatment of neurodegeneration through targeting of the Wnt signaling pathway.[51−53] In this case, the thieno[3,2-*d*]pyrimidine core of **15** was substituted with the similar furo[2,3-*d*]pyrimidine core seen in **16**. This heterocyclic replacement led to the discovery of a new chemotype for notum inhibitors that maintained comparable inhibitory activity (Figure 6).[51] Alternative heterocyclic replacements such as the introduction of a 7*H*-pyrrolo[2,3-*d*]pyrimidine core seen in **17** saw a complete loss of activity (Figure 6).[51] Results such as this highlight the role that 1° scaffold hopping can have in identifying key pharmacophoric features. In this case, the presence of a H-bond acceptor in the 5-membered heterocyclic component appears crucial. Slightly varied heterocyclic substituents were also explored simultaneously to optimize binding capabilities and reduce lipophilicity (as seen in **16**), though it should be noted that these substituents are retained in similar positions compared to the parent compound **15**. Further optimization of the carboxylic acid moiety of **16** led to the discovery of **18** (Figure 6), a novel, potent notum inhibitor chemotype with improved plasma exposure and CNS penetration relative to **15**.[51] In this application, 1° scaffold hopping has elucidated important pharmacophore information as well as generating new chemotypes identified as notum inhibitors.

A 1° scaffold hopping approach reported by Ledneczki and co-workers was used in the development of positive allosteric modulators (PAMs) of α7 nicotinic acetylcholine receptors (α7 nAChRs).[54] α7 nAChRs are implicated in cognitive processes and have been validated with *in vivo* models as potential drug targets for conditions such as Alzheimer's disease and schizophrenia.[55] Among various other SAR explorations of pendant groups, Ledneczki and co-workers

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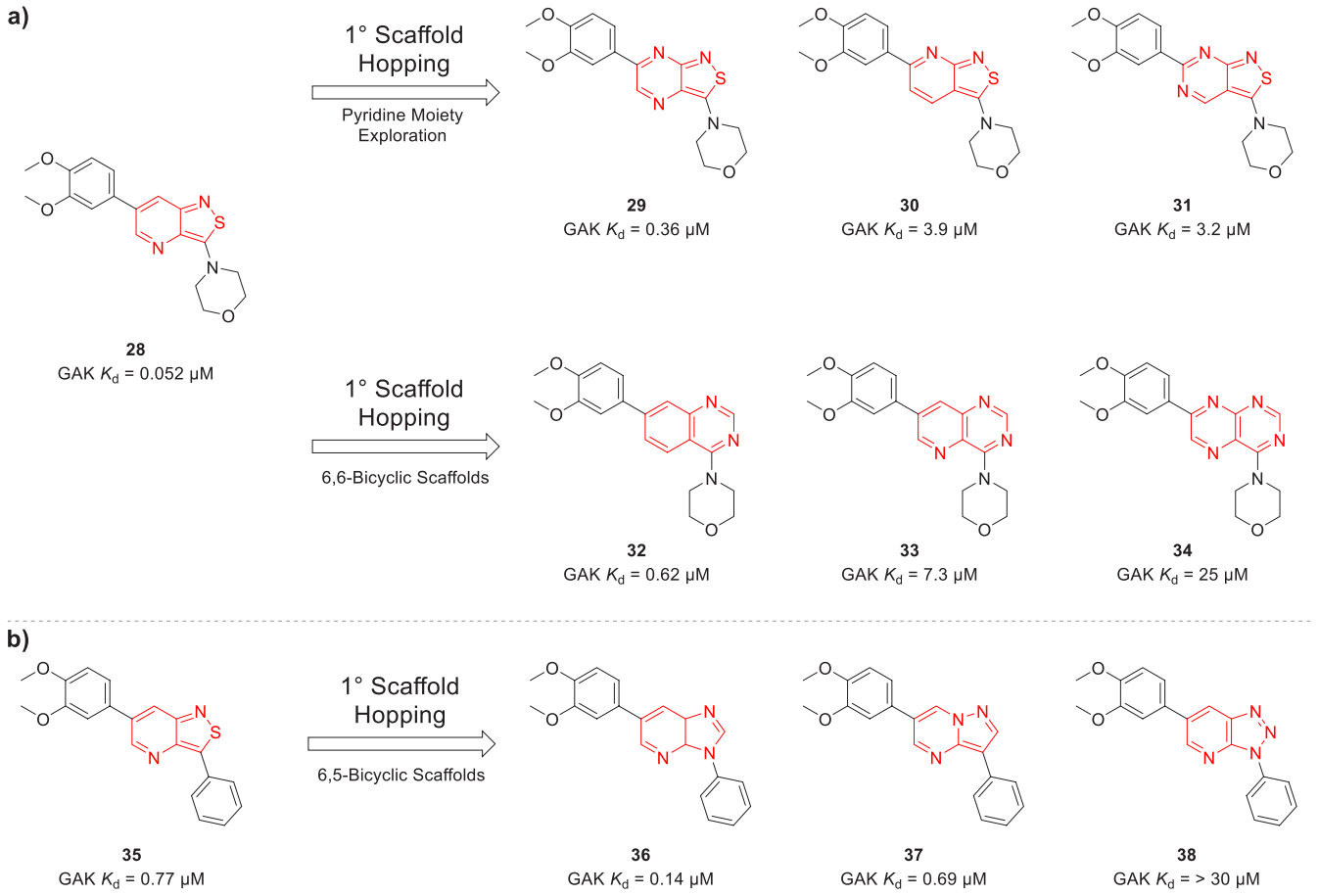

Figure 9. Various 1° scaffold hopping approaches taken by Wouters and co-workers in the exploration of cyclin G associated kinase (GAK) inhibitors. (a) (top) 1° Scaffold hopping approaches used to explore the pyridine portion of **28** with various 6,5-bicyclic scaffold and (bottom) exploration of **28** through introduction of various 6,6-bicyclic scaffolds. (b) 1° Scaffold hopping used to explore **35** through 6,5-bicyclic scaffolds.[61] K_d = Dissociation constant.

performed heterocyclic replacements (Figure 7) of the pyrrole core of **19** with various other 5-membered aromatic heterocycles such as a pyrazole (**20**), furan (**21**), and oxazole (**22**).[54] In this work, compounds were assessed through a functional $[Ca^{2+}]$ influx ($[Ca^{2+}]_i$) assay to detect subtle changes in $[Ca^{2+}]_i$, where desirable activity is reflected by low $[Ca^{2+}]_i$ EC_{50} values. It should also be noted that removal of the methyl substituent of **19** was tolerated and hence is not conserved in 1° scaffold hopping derivatives (**20**−**22**).[54] This hypothesis led to the exploration of the several 5-membered heterocyclic replacements, which produced an array of results. Compared to the pyrrole core lead, **19** had slightly improved activity whereas the highly similar furan (**21**) and oxazole (**22**) analogues saw a complete loss of activity (Figure 7).[54] These "activity cliffs" based on relatively small changes are reflective of known α7 nAChR PAM SAR studies.[54] Further optimization of the ethyl ketone moiety of **20** led to the introduction of the amide seen in **23**, which has slightly reduced activity but has shown efficacy *in vivo* (Figure 7).[54] Similar to previous discussions, the application of 1° scaffold hopping in this context has been used to explore an array of chemotypes of nAChR PAMs and elucidated important pharmacophoric features. Optimization of 1° scaffold hopping derivative **20** has identified **23**, which has shown efficacy *in vivo*.

Two complementary studies utilized 1° scaffold hopping approaches in the discovery of new chemotypes as muscarinic acetylcholine receptor subtype 4 (M_4) PAMs. M_4 receptors have been identified as potential drug targets for the treatment of various CNS disease states such as Parkinson's disease and schizophrenia.[56] Both strategies were based on similar 1° scaffold hopping strategies (Figure 8a,b) of highly similar lead compounds, **24** and **26**, that were identified *via* high-throughput screening. The β-amino carboxamide moiety (seen in both **24** and **26**, Figure 8) has been reported for a range of M_4 PAMs but is associated with poor solubility and varying degrees of P-gp efflux, as well as accounting for a structural alert (namely the aromatic amine group).[57,58] In each 1° scaffold hopping approach, the methyl substitution pattern of the pyridine and pyridazine cores of **24** and **26**, respectively, were maintained and the β-amino carboxamide moieties of **24** and **26** (Figure 8) were replaced with phenyl rings.

The first reported approach using 1° scaffold hopping reported by Long and co-workers explored the replacement of 3-amino-4,6-dimethylthieno[2,3-*b*]pyridine core of structures such as **24** with a 2,4-dimethylquinoline core, exemplified by **25** (Figure 8).[57] Subsequent amide optimization identified a variety of compounds such as **25** with rM_4 PAM activity that was comparable to the lead **24** (Figure 8a).[57] Although the amide substituents of these derivatives vary in structure, the

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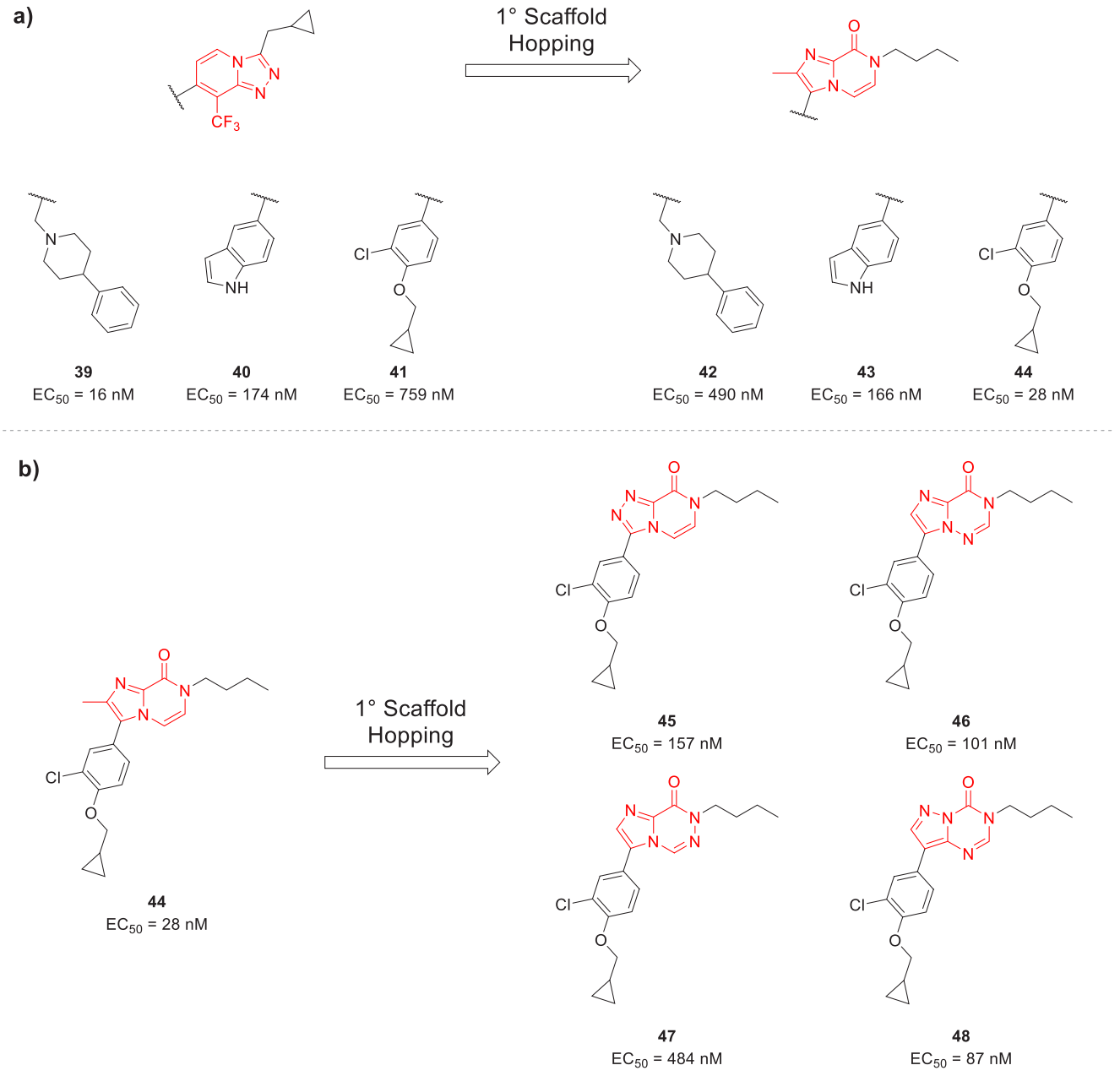

Figure 10. 1° Scaffold hopping reported by de Lucas and co-workers in the exploration of $mGlu_2$ PAMs. (a) 1° Scaffold hopping of **39**−**41** through introduction of imidazo[1,2-*a*]pyrazin-8-one core. (b) 1° Scaffold hopping of imidazo[1,2-*a*]pyrazin-8-one **44**.[63] EC_{50} refers to $mGlu_2$ PAM EC_{50} values for various compounds.[63] EC_{50} refers to $mGlu_2$ PAM EC_{50} values for various compounds. EC_{50} = half maximal effective concentration.

pendant groups (amide and methyl substituents) are maintained in a similar position and space, a key factor in 1° scaffold hopping. Unfortunately, the physicochemical properties of these compounds (such as **25**, Figure 8a) were poor (high predicted hepatic clearance and high plasma protein binding), making them unsuitable lead candidates.[57] Even so, this application of 1° scaffold hopping has highlighted another advantage in the removal of the suspected structural alert (aromatic amine) through a heterocyclic replacement. Beyond this, this application has again illustrated the usefulness of 1° scaffold hopping in the generation of new chemotypes for targeting biological systems, in this case in diversification of M_4 PAMs.

The second example of this 1° scaffold hopping approach, reported by Temple and co-workers, replaced a 3,4-dimethylthieno[2,3-*c*]pyridazine with a 3,4-dimethylcinnoline core (exemplified by **26** and **27**, respectively, Figure 8b).[59] Again, similar amide optimization afforded derivatives with comparable or improved M_4 PAM activity (exemplified by **27**) to lead **26** (Figure 8b). 3,4-Dimethylcinnoline derivative **27** was also reported to show PAM activity in human M_4 receptors with improved potency compared to that at rM_4 receptor (Figure 8b).[59] These 3,4-dimethylcinnoline derivatives were also hampered by high predicted hepatic clearance and plasma protein binding, although they showed a slight improvement compared to the previously reported 2,4-dimethylquinoline derivatives (e.g., **25**).[59] The authors also noted that they undertook a wider range of 1° scaffold hopping approaches investigating these leads, which did not provide any new meaningful results.[57] Although again the progression of

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these compounds was hampered by poor physicochemical properties, the application of 1° scaffold hopping has generated a new chemotype that no longer has the undesirable aromatic amine moiety. Further medicinal chemistry efforts around these compound series (Figure 8a,b) would be required to further progress these candidates.

Another extensive 1° scaffold hopping study was reported by Wouters and co-workers for the exploration of cyclin G associated kinase (GAK) inhibitors as potential therapeutics for Parkinson's disease, as well as a myriad of other drug discovery areas.[60−62] This work focused on three clear 1° scaffold hopping explorations based on the leads **28** and **35** (Figure 9).[61] The first of these strategies looked to explore the importance of the position of the nitrogen in the pyridine ring of the isothiazolo[4,3-*b*]pyridine scaffold of **28**. A selection of these replacements is shown in Figure 9a. The isothiazolo[3,4-*b*]pyrazine (**29**), isothiazolo[3,4-*b*]pyridine (**30**), and isothiazolo[3,4-*d*]pyrimidine (**31**) replacements all showed a significant reduction in affinity compared to the lead **28** (Figure 9a).[61] This application of 1° scaffold hopping highlighted key structural features required for activity, particularly the nitrogen at the 4-position of **28** (Figure 9a). A second 1° scaffold hopping exploration of **28** focused on the introduction of several 6,6-bicyclic heterocycle scaffolds as replacements of the 6,5-bicyclic core of **28**; a selection of these is shown in Figure 9a.[61] This included the replacements of the isothiazolo[4,3-*b*]pyridine scaffold of **28** with quinazoline (**32**), pyrido[3,2-*d*]pyrimidine (**33**), and pteridine (**34**) cores.[61] Similarly to the exploration discussed previously, these 6,6-bicyclic replacements also saw significant losses in activity (Figure 9a).[61] The best candidate in this case (**32**) saw a 10-fold reduction in activity compared to **28**. The third 1° scaffold hopping that was performed explored the isothiazole portion of **35**. In this case a phenyl substituent (rather than a morpholine substituent) was used due to synthetic accessibility. A series of 6,5-bicyclic scaffolds that maintained the important pyridine substitution identified through their previous investigations were introduced (Figure 9a). This exploration proposed new core scaffolds such as an imidazo-[4,5-*b*]pyridine (**36**), pyrazolo[1,5-*a*]pyrimidine (**37**), and [1,2,3]triazolo[4,5-*b*]pyridine (**38**), among other similar scaffolds (Figure 9b).[61] The introduction of the imidazo[4,5-*b*]pyridine (**36**) saw a 4-fold improvement in activity, while the pyrazolo[1,5-*a*]pyrimidine (**37**) yielded comparable activity to **35**, and the [1,2,3]triazolo[4,5-*b*]pyridine (**38**) saw activity abolished (Figure 9b).[61] This 1° scaffold hopping approach again highlighted some key structural features that are required in the pharmacophore of potent candidates. The results of this study suggest a key relationship with electronics of the ring system. These 1° scaffold hopping applications suggest that the introduction of particularly electron rich ring systems is detrimental to activity (Figure 9a,b). Additional analyses of various SARs of **28** and **35** throughout these 1° scaffold hopping approaches are discussed by Wouters and co-workers and will likely be further investigated to identify groups that may rescue any losses in activity. This work has illustrated the accessibility of 1° scaffold hopping through the introduction of a large array of heterocyclic replacements. Although many derivatives saw losses in activity compared to **28**, this has generated a library of new chemotypes that have potential to be optimized through further medicinal chemistry efforts.

Another successful application of 1° scaffold hopping in the development of metabotropic glutamate 2 receptor ($mGlu_2$) PAMs has been published by de Lucas and co-workers.[63] Activation of $mGlu_2$ is able to normalize excessive glutamatergic neurotransmission and leads to decreased excitability, which may be useful in the treatment of disorders such as schizophrenia and epilepsy.[64,65] PAMs of $mGlu_2$ have been identified as potential therapeutic candidates for these disease states.[66,67] This work utilized *in silico* screening (ROCS and EON software from Openeye Scientific) of the [1,2,4]-triazolo[4,3-*a*]pyridine core of $mGlu_2$ PAMs **39**−**41** to identify the imidazo[1,2-*a*]pyrazin-8-one core replacement (as seen in **42**−**44**) based on shape and electrostatic similarities (Figure 10a).[68,69] In this case, the two cores had visible similarities in shape and electrostatic character; however the imidazo[1,2-*a*]pyrazin-8-one core displayed reduced lipophilicity and improved *in vitro* clearance.[63] This work applied 1° scaffold hopping exploration on a number of different structures such as **39**−**41**. This primarily encompassed the exploration of imidazo[1,2-*a*]pyrazin-8-one derivatives (such as **42**−**44**) with an array of pendant moieties maintained in comparable substitution positions. Generally, heterocyclic replacement of the [1,2,4]triazolo[4,3-*a*]pyridine (**39**−**41**) core with the respective imidazo[1,2-*a*]pyrazin-8-one (**42**−**44**) maintained some $mGlu_2$ PAM activity, although the extent varied considerably (Figure 10a).[63] Some replacements saw a large loss in potency (such as **39** vs **42**), comparable potency (such as **40** vs **43**), and increase in potency (such as **41** vs **44**, Figure 10). Although there is some variability, all derivatives still maintained sub-micromolar $mGlu_2$ PAM potency (Figure 10a).[63] This work also undertook a further 1° scaffold hopping exploration of identified imidazo[1,2-*a*]pyrazin-8-one core lead **44**, which involved the introduction of a range of different heterocyclic cores (Figure 10b). This included the introduction of [1,2,4]triazolo[4,3-*a*]pyrazin-8-one (**45**), imidazo[2,1-*f*][1,2,4]triazin-4-one (**46**), imidazo[1,2-*d*][1,2,4]triazin-8-one (**47**) and pyrazolo[1,5-*a*][1,3,5]triazin-4-one (**48**) cores (Figure 10b).[63] None of these cores were able to improve on the highly potent activity of **44** (Figure 10b); however in each case moderate $mGlu_2$ PAM activity was maintained.[63] Although less potent, these derivatives did show favorable metabolic stability compared to the parent compound **41**, though this would need to be optimized further.[63] This work highlights another extensive 1° scaffold hopping approach that has generated new chemotypes, highlighted key pharmacophore features, and improved pharmacokinetic properties.

There are likely further recent examples of heterocyclic replacements throughout the CNS drug discovery landscape, reflecting its common role in lead exploration and optimization. This discussion has focused primarily on published research that has focused on the use of scaffold hopping. In the wider context of the exploration of chemical space, 1° scaffold hopping represents a relatively conservative approach. It is important to reiterate that 1° scaffold hopping involves the replacement of a heterocyclic core with another heterocycle that maintains pendant moieties in similar positions and space. This has been shown throughout the examples discussed in this section. It is not surprising, and has been illustrated here, that compounds that are highly similar often (although not always) retain at least some level of biological activity when compared to starting compounds. Despite this approach being somewhat simplistic, it is often an important process in lead discovery and optimization in the drug discovery process.

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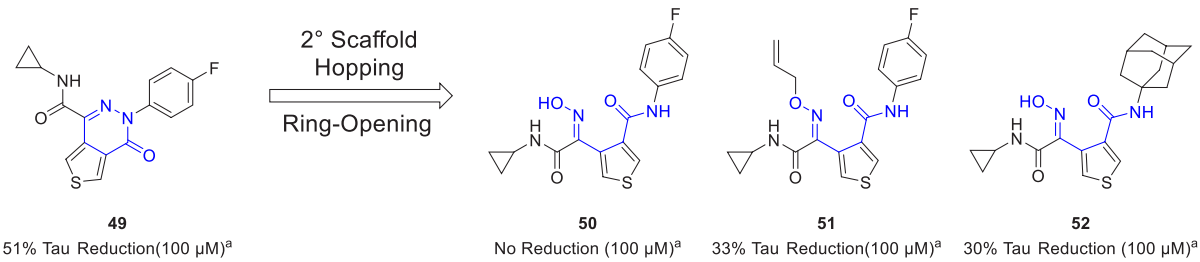

Figure 11. Ring opened analogues of aminothienopyridazines reported by Moir and co-workers as novel inhibitors of tau aggregation for the treatment of Alzheimer's disease. Tau reduction refers to reduced observed fluorescence in thioflavin T fluorescence assay compared to control.[16]

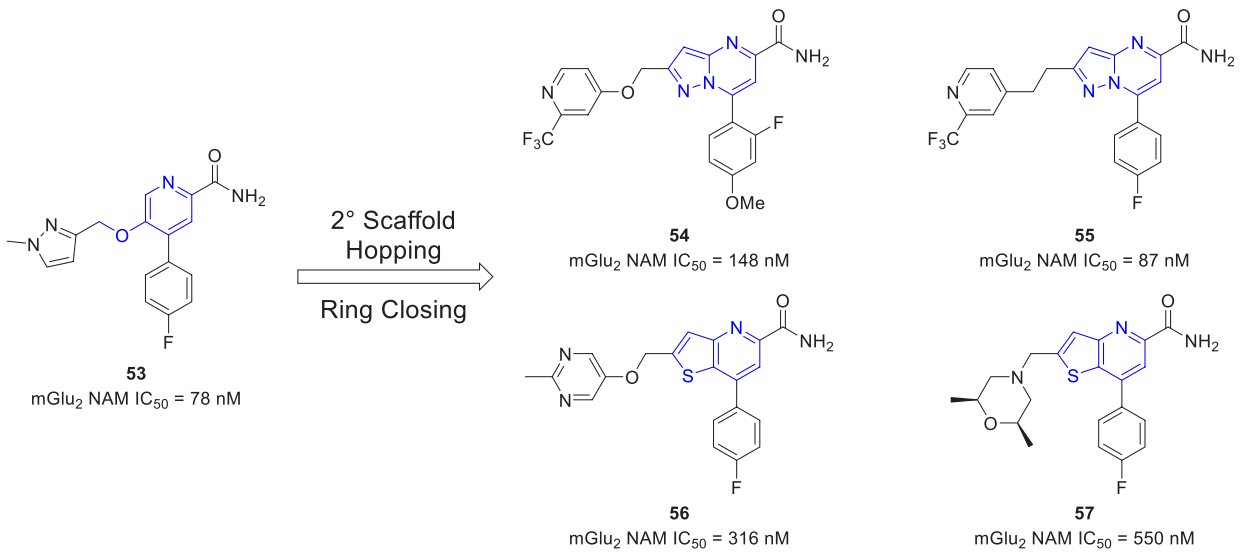

Figure 12. 2° Scaffold hopping ring-closing approach taken by Childress and co-workers in the exploration of $mGlu_2$ NAMs from lead compound **53**.[74] IC_{50} = half maximal inhibitory concentration.

3.1.2. Second Degree (2°) Scaffold Hopping in CNS Drug Discovery. Second degree scaffold hopping encompasses structural modifications that change conformational restriction specifically through ring-closures and ring-openings to introduce new core structures. This approach generally either increases conformational flexibility (ring-opening) or rigidity (ring-closing), although in many applications of this approach the effect of these changes may not be predictable without structural information about the biological target. This is distinct from more traditional conformational restrictions as this results in the introduction of a new heterocyclic core compared to the parent compound. Examples of both ring-opening and ring-closing applications of 2° scaffold hopping in the CNS drug discovery landscape are highlighted and discussed in the following sections.

3.1.2.1. Ring Opening. Inhibiting tau protein aggregation has been identified as a potential disease-modifying strategy for the treatment of neurodegenerative states such as Alzheimer's disease.[70] Ballatore and co-workers identified and explored a series of aminothienopyridazines (exemplified by **49**, Figure 11) as small molecule tau aggregation inhibitors.[71] Using **49** as a lead, Moir and co-workers reported a series of tau aggregation inhibitors based on a 2° scaffold hopping ring-opening approach by breaking the nitrogen−nitrogen bond of the pyridazine ring to yield thiophene core derivatives **50**−**52** (Figure 11).[16,71] These three ring-opened analogues showed varying degrees of biological activity compared to the lead **49** (Figure 11). The lead **49** and 2° scaffold hopping analogues **51** and **52** showed tau aggregation inhibition in a thioflavin T fluorescence assay.[72] Analogues **50** and **52** showed greater reduction of higher order tau aggregates based on a filter trap assay whereas **49** and **51** showed comparable activity (data not shown).[16] Interestingly, the proposed mechanism of tau aggregation inhibition by **49** is through the oxidation of cysteine residues.[73] The oxidizing properties of the ring-opened analogues were also investigated. These results confirmed the oxidizing activity of **49** but suggested that inhibitory activity of **50** and **52** (and possibly **51**) may occur through other mechanisms.[16] This work has highlighted a successful application of a 2° scaffold hopping approach where analogous ring-opened analogues maintained some level of biological activity, although further investigations are required to confirm mechanisms of action. This has generated new chemotypes targeting tau aggregation, potentially through a different mechanism from the parent compound, a particularly interesting result.

3.1.2.2. Ring Closing. The introduction of new heterocyclic cores to produce more rigid scaffolds is a more common application of 2° scaffold hopping. This approach was taken by Childress and co-workers, who reported a series of $mGlu_2$ negative allosteric modulators (NAMs).[74] The therapeutic potential of $mGlu_2$ NAMs is relatively unexplored; however, given the role that $mGlu_2$ plays in various CNS disease states (as discussed in section 3.1.1) their development is an interesting prospect for new therapeutics and as *in vitro* and *in vivo* molecular tools. This work built off lead compound **53**

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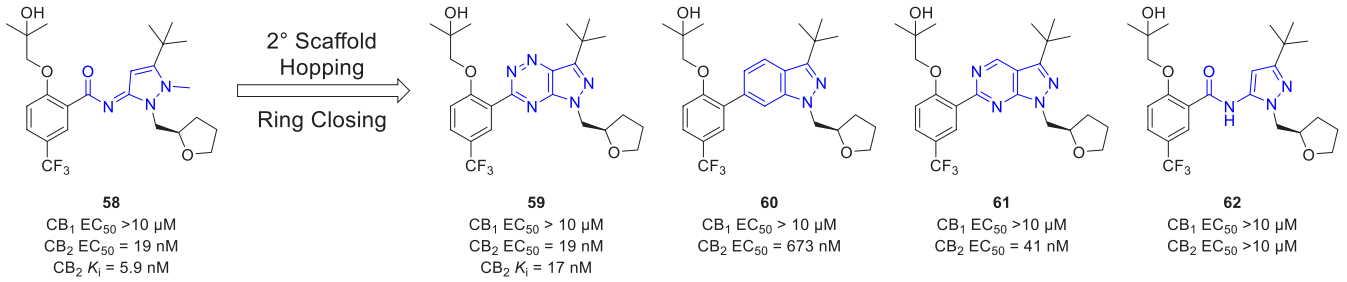

Figure 13. 2° Scaffold hopping ring-closing analogues investigated by Moir and co-workers in the investigation of selective CB_2 receptor agonists from potent and selective CB_2 agonist **58**.[77] EC_{50} = half maximal effective concentration; K_i = inhibition constant.

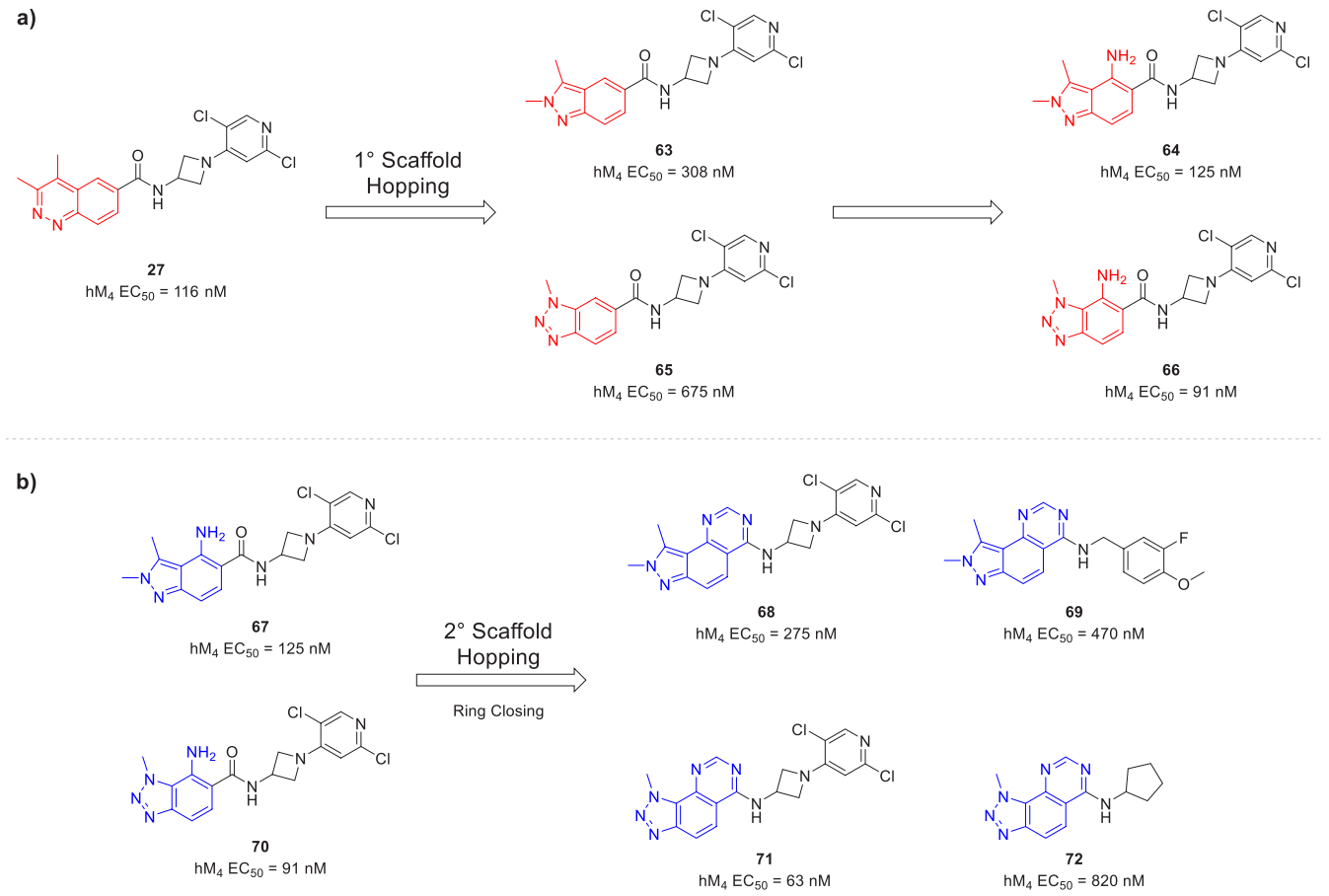

Figure 14. (a) 1° Scaffold hopping approach and (b) 2° scaffold hopping approach taken by Temple and co-workers in the discovery of new M_4 PAM chemotypes.[78] hM_4 = human M_4 receptor; EC_{50} = half maximal effective concentration.

(Figure 12), which showed high $mGlu_2$ NAM potency and selectivity (Figure 12) as well as good CNS penetration.[74] Its use as an *in vivo* tool was, however, hampered by high plasma clearance.[74,75] The same researchers looked to further explore the central pharmacophore of **53** through a ring-closing approach around the aryl ether linker (Figure 12). To do this, they introduced cyclized pyrazolo[1,5-*a*]pyrimidine (such as **54** and **55**) and thieno[3,2-*b*]pyridine (such as **56** and **57**) cores. This highlights the key feature of 2° scaffold hopping whereby conformational restriction (in this case around the ether bond) is introduced through a new heterocyclic core. They also simultaneously explored the effect of introducing various aromatic and aliphatic pendant groups although these always remained in comparable substitution positions (Figure 12).[74] The introduction of the pyrazolo[1,5-*a*]pyrimidine and thieno[3,2-*b*]pyridine cores generally saw a loss in $mGlu_2$ NAM potency (Figure 12), although this could be rescued through pendant group optimization.[74] Generally, the pyrazolo[1,5-*a*]pyrimidine derivatives (such as **54** and **55**) were more potent compared to thieno[3,2-*b*]pyridine derivatives (such as **56** and **57**).[74] Although there was a general loss of potency from this approach, several of these compounds showed improved *in vitro* pharmacokinetic properties (clearance and half-life) compared to parent compound **53**. Although the effect of conformation restriction around this moiety cannot be elucidated purely from biological results, further computational work with a recently reported $mGlu_2$ X-ray crystal structure may be able to elucidate how this impacts binding.[76] Although further optimization of these chemotypes is required, this work has highlighted a 2° scaffold hopping

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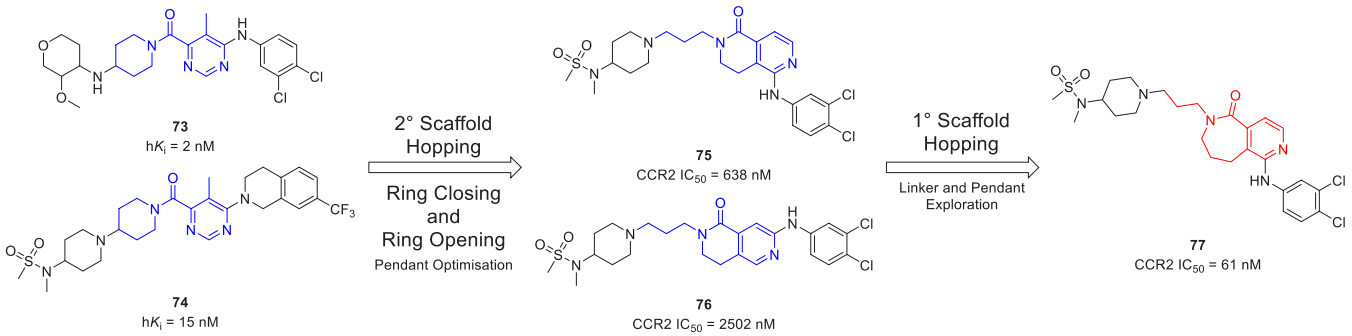

Figure 15. "Cut and sew" approach used by Qin and co-workers in the development of CCR2 antagonists from lead molecules **73** and **74**.[80] K_i = inhibition constant; IC_{50} = half maximal inhibitory concentration.

ring-closing approach and identified a range of new chemotypes as $mGlu_2$ NAMs with improved pharmacokinetic properties.

Work done by Moir and co-workers in the synthetic cannabinoid medicinal chemistry space has also exemplified an application of 2° scaffold hopping (Figure 13) through a ring closing approach.[77] This work explored pharmacophoric features that would elicit potent and specific CB_2 agonist activity. In this work, the authors designed a ring-closed analogue of the -ylidene acetamide moiety of **58** (Figure 13) to the novel pyrazolo-[2,3-*e*]-[1,2,4]-triazine (**59**, Figure 13) scaffold in an effort to improve pharmacokinetic properties, eliminate toxicity, and expand the knowledge base around the SAR of this series of compounds.[77] The triazine ring-closed analogue **59** showed comparable CB_2 potency and selectivity to the lead **58** (Figure 13).[77] Although **58** and **59** show similar potencies, there is a 3-fold drop in CB_2 receptor affinity between **58** and **59** (Figure 13).[77] The authors suggest that the ring-closed triazine analogue **59** maintains a favorable planar structure and promotes several $\pi-\pi$ interactions within the binding site of the CB_2 receptor.[77] This hypothesis is supported by the complete loss of activity in the analogous amide analogue **62** (Figure 13), which loses the planar structure around this moiety.[77] Other ring-closed derivatives such as the indazole **60** and pyrazolo-[2,3-*d*]-pyrimidine **61** also showed desirable functional activity albeit with lower potencies (Figure 13).[77] These derivatives highlight the importance for planarity around this moiety in these compounds. Comparison of **60** with **59**/**61** also highlights the importance of the H-bond acceptor in the pharmacophore (Figure 13). Although this work explored a range of other SARs, the 2° scaffold hopping ring-closing approaches yielded several new chemotypes that showed desirable CB_2 potency and selectivity. This lays a platform for the development of new CB_2 selective ligands through further optimization of the pendant moieties. This application of 2° scaffold hopping has also illustrated how the introduction of conformation restriction through ring closing can be used to maintain or promote desirable biologically active conformations.

Another publication from Temple and co-workers has built on the 1° scaffold hopping approaches discussed previously (Figure 8), by taking a ring-closing approach in the identification of new chemotypes as M_4 PAMs (Figure 14).[78] As previously mentioned, M_4 PAMs have been explored to treat a range of CNS related conditions. This work utilized an initial 1° scaffold hopping of the previously discussed 3,4-dimethylcinnoline (see Figure 8) core compounds (exemplified by **27**, Figure 14a).[78] This initial exploration looked at maintaining the nitrogen−nitrogen bond and methyl substituents of **27** through heterocyclic replacement with 2,3-dimethylindazole and 1-methylbenzo[*d*][1,2,3]triazole cores (**63** and **65**, respectively). However, this led to reduced activity (Figure 14a) and a steep SAR that could not be adequately explored.[78] The activity of **63** and **65** could be rescued by the installation of the β-amino carboxamide moiety (such as structures **64** and **66**, Figure 14a), seen in the original lead candidates (such as **24** and **26**, Figure 8).[78] However, as previously mentioned, the aromatic amine, seen in **67** and **70** (Figure 14b), elicits a structural alert for further drug development, and comparable compounds were also hampered by solubility issues.[57,58,79] Temple and co-workers then used a 2° scaffold hopping ring-closing by forming a 6-membered ring through the β-amino carboxamide moiety of **67** and **70**. This was done through introduction of the 8,9-dimethylpyrazolo-[3,4-*h*]quinazoline (exemplified by **68** and **69**, Figure 14b) and 1-methyl[1,2,3]triazolo[4,5-*h*]quinazoline (exemplified by **71** and **72**, Figure 14b) cores.[78] These tricyclic cores maintain the electrostatic character of the β-amino carboxamide while mitigating the toxicity concerns. Direct comparisons between the 2,5-dichloropyridine pendant group containing compounds (**67** vs **68** and **70** vs **71**) show that these fused tricyclic cores led to generally comparable activity (Figure 14b).[78] A number of other pendant moieties, such as the 3-fluoro-4-methoxybenzyl amine (**69**) and cyclopentylamine (**72**), also maintained some level of M_4 PAM activity albeit with lower potencies.[78] This ring closing approach, like previous examples, introduced new heterocyclic cores through the closure of a pseudoring structure. In this case, this generated a range of new chemotypes as M_4 PAMs while improving the perceived toxicity profile. Despite these investigations, these compounds were still limited by pharmacokinetic characteristics such as predicted hepatic clearance and plasma protein binding and would require further optimization to overcome these.[78] This study incorporated aspects of both 1° and 2° scaffold hopping making it a particularly interesting example. Across the various scaffold hopping approaches an array of chemotypes for M_4 PAMs has been identified. It has been included in this section as the use of the ring closure and subsequent conformational restriction as a means of mitigating toxicity concerns is particularly interesting.

3.1.2.3. "Cut and Sew": Simultaneous Ring-Opening and Ring-Closing Approaches. Intriguingly, there are several published 2° scaffold hopping approaches that have utilized both ring-opening and ring-closing approaches. Qin and co-workers aptly named this method a *cut and sew* approach.[80] Within the definitions used in this work, this falls within 2°

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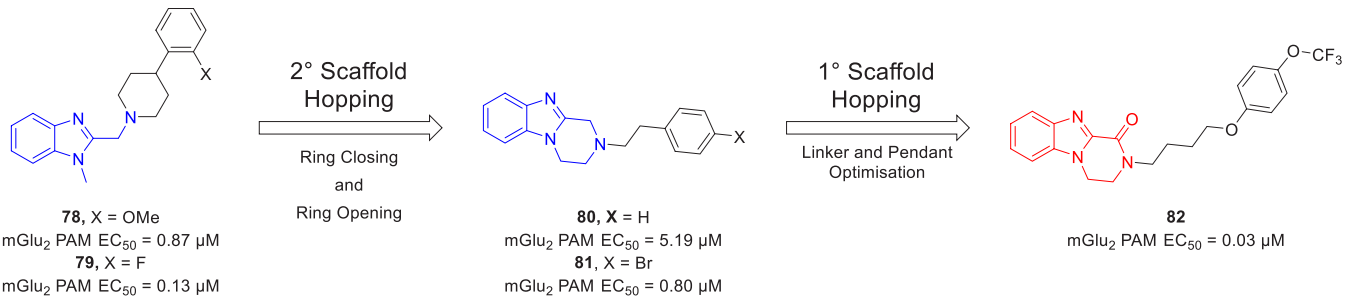

Figure 16. 2° Scaffold hopping "cut and sew" approach utilized by Szabó and co-workers in the exploration and development of $mGlu_2$ PAMs from reported hits **78** and **79**.[84] EC_{50} = half maximal effective concentration.

scaffold hopping, encompassing both ring-closing and ring-opening changes to lead molecules through the introduction of new heterocyclic cores.

CC chemokine receptor-2 (CCR2) has been identified as a potential therapeutic target for a range of inflammatory diseases such as multiple sclerosis and neuropathic pain.[81,82] Qin and co-workers used a *cut and sew* approach in the discovery and exploration of new chemotypes as CCR2 antagonists (Figure 15).[80] This work built on a series of high affinity CCR2 antagonists licensed by Boehringer-Ingelheim that feature pyrimidine carboxamide core moieties (exemplified by structures such as **73** and **74**).[83] This work looked to improve drug-like properties and *in vivo* efficacy compared to previously reported CCR2 antagonists.[80] A simultaneous ring-opening of the piperidine ring linker and ring-closure from the amide (*cut and sew*) to the aromatic moiety was undertaken to form a 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one core (exemplified by **75**, Figure 15).[80] Both the 5- and 7-substituted 3,4-dihydro-2,6-naphthyridin-1(2*H*)-one cores (**75** and **76**, respectively) were investigated, with the 5-substitution shown to better maintain CCR2 antagonist activity (Figure 15). It is logical that further optimization of the pendant moieties in these chemotypes (**75** and **76**) may lead to much more potent candidates. The identification of structures such as **76** encompasses the 2° scaffold hopping undertaken in this work through the unique *cut and sew* approach. Further optimization of **76** saw a 1° scaffold hopping approach applied that introduced a 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepin-5-one core (as seen in **77**, Figure 15).[80] This use of 1° scaffold hopping rescued CCR2 antagonist potency and identified yet another chemotype for the development of CCR2 antagonists.[80] This work has utilized a range of scaffold hopping approaches and has illustrated the potential for these techniques to generate different chemotypes. The *cut and sew* approach is particularly interesting whereby in these molecules conformational restriction is decreased in some moieties while being increased around others.

Szabó and co-workers also utilized a *cut and sew* approach to develop a series of $mGlu_2$ PAMs.[84] This target is implicated in a large array of CNS disease states, as mentioned previously throughout this perspective. Taking inspiration from known $mGlu_2$ PAMs (**78** and **79**, Figure 16) originally developed by Pfizer and GlaxoSmithKline, Szabó and co-workers undertook an SAR approach that looked at a ring opening of the piperidine ring linker and simultaneous ring closure toward the 2-alkyl benzimidazole moiety (such as **80**, Figure 16).[84−86] This led to the implementation of the tricyclic dihydropyrazino-benzimidazole moiety seen in **80** and **81** that maintained some $mGlu_2$ PAM activity, albeit notably lower than parent compounds.[84] Like the previous example, this approach simultaneously increased and decreased conformation restriction around certain groups through the introduction of a new heterocyclic core feature, highlighting the implementation of *cut and sew* 2° scaffold hopping. The authors also undertook a further 1° scaffold hopping approach of this new core as well as optimization the linker and phenyl group to yield derivatives (exemplified by **82**, Figure 16) to afford improved activity and improved metabolic stability.[84] The design and optimization of these derivatives was supported by several *in silico* pharmacophore models based on developed leads (such as **80** and **81**) showing similar pharmacophoric features.[84] The binding mode of optimized compound **82** was explored in an $mGlu_2$ homology model and corresponded well to the modeled binding of other known $mGlu_2$ PAMs, further highlighting the success of this 2° scaffold hopping approach.[84] Compound **82** also showed good brain penetration and subsequent *in vivo* efficacy in a mouse schizophrenia model, albeit at relatively high doses (30 mg/kg).[84] Again, this example includes both 1° and 2° scaffold hopping approaches and has been included in this section as the *cut and sew* approach has been, in our opinion, the more important step in diversifying these compounds in this work by generating completely new tricyclic core moieties as $mGlu_2$ PAMs.

Various applications of 2° scaffold hopping targeting CNS relevant disease targets have been discussed in this section. Anecdotally, our search of the literature appears to suggest that ring-closing approaches are comparatively more frequently used as a means of controlling pharmacophore features versus ring-opening strategies. It generally appears that ring-opening and ring-closing approaches have relied on chemical intuition and, in some cases, have been included as part of broader SAR studies. In each case, these approaches have undertaken ring-opening or ring-closing (or both) and changed some level of conformational restriction, and in each case, this introduced a new heterocyclic moiety as the core. This is a key aspect in the classification of 2° scaffold hopping approaches. Importantly these approaches are distinctly different from the previously described 1° scaffold hopping but in the literature are often described under the same umbrella term, showing the need for adapting toward more refined language around these approaches.

3.1.3. Third Degree (3°) Scaffold Hopping in CNS Drug Discovery. Currently, the prevalence of peptides as CNS therapeutics is limited due to drawbacks including rapid proteolytic degradation, poor target selectivity, rapid excretion due to a lack of specific transport systems, and limited BBB permeability.[87,88] Although there are significant limitations that follow the use of peptides as CNS therapeutics, natural

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peptides are privileged scaffolds that are highly potent and selective with potential in the field of personalized medicine.[88,88]

The term peptidomimetic is used throughout literature to describe compounds with small changes (such as peptide bond replacements) to small molecules that elicit a similar biological response to an endogenous peptide. Peptidomimetics are structural analogues of peptides that maintain structural elements and functionality of the native peptide but contain altered units or chemically distinct features.[89] In the context of 3° scaffold hopping, synthetic modifications derived from small molecules are introduced to a protein or peptide such as unnatural amino acid substitutions and secondary structure mimics (primarily turn mimetics).[89] In this discussion, this idea was used to distinguish 3° scaffold hopping from the myriad of other peptidomimetic strategies. In each case, the role of 3° scaffold hopping has focused on maintaining biological activity while reducing peptide character and proteolytic susceptibility.[14,90] The presence of this type of approach in the CNS field is currently limited but will certainly improve viability of peptide based therapeutics as CNS targeting drug candidates.[90,91]

3.1.3.1. Unnatural Amino Acid Substitution. A major focus in 3° scaffold hopping is the modification and substitution of amino acid side chains.[90] Side chain topography is an essential component for molecular recognition; hence its modification can reduce proteolytic susceptibility to improve a peptide's half-life. Scaffold hopping of side chains can also help to improve pharmacokinetic properties leading to enhanced bioavailability. Identification of an appropriate amino acid substitute can be achieved by scanning single residues of a parent scaffold, genotype−phenotype linkage display from phage or yeast technology,[92] or computational and rational design.[90,93] Common examples involve side chain isosteres. For example, L-arginine (**83**) contains a highly basic guanidine (pK_a = 12.5) functional group that exists in a protonated, ionized state at physiological pH. This results in predominantly ionic interactions with negatively charged functional groups. Substitution of this functional group is commonly performed to modulate its strong ionic interactions or to introduce new interactions such as $\pi-\pi$ stacking or van der Waals interactions (Figure 17). Substitution with an amino-imidazoline (**84**) or amino-pyridine derivative (**85**) can be performed to reduce basicity, increase lipophilicity, or introduce aromaticity (Figure 17).[87]

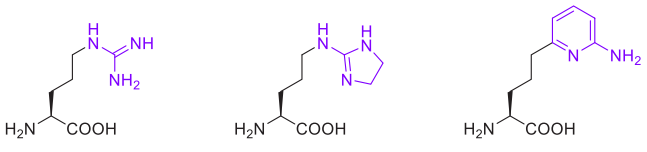

Figure 17. Common bioisosteres of (L)-arginine (**83**) such as amino-imidazoline (**84**) and amino-pyridine (**85**).[87]

Significant efforts have been directed toward the design of opiates that mimic μ-opioid receptor endogenous peptides, endomorphin-1 (EM-1) and endomorphin-2 (EM-2), to treat chronic pain. These endogenous peptides are poor clinical candidates as they have short half-lives and cannot cross the BBB. (Thienyl)-α-methylene-β-amino acid (Map) has been previously identified as a nonproteinogenic and structurally constrained amino acid.[18,94,95] Liu and colleagues utilized Map as an unnatural amino acid modification with a thiophene side chain in efforts to improve the binding affinity, bioavailability, and half-life of endomorphins. In doing so, they identified that substitution of the terminal phenylalanine residue in EM-1 (**86**) with (2-thienyl)Map (**87**, Figure 18) gave a 5-fold increase in binding affinity toward the μ-opioid receptor with significantly improved selectivity over the δ-opioid receptor (K_i ratio δ/μ: **86** = 2338 and **87** = 21327).[18,95] Furthermore, they tested antinociception following peripheral administration to evaluate the ability of (2-thienyl)Map to cross the BBB and elicit a response relative to **86**, which cannot cross the BBB. This deduced that at a dose of 16 mg/kg **87** had an efficacy of 86% with a maximal possible effect of 25% at 60 min postadministration. This represented a significant improvement relative to **86** and an exciting discovery that displayed enhanced peptide serum half-life and delivery across the BBB.[18]

3.1.3.2. Turn Mimetics. The development of turn mimetics is a well-established and successful strategy in the peptidomimetic drug discovery landscape.[96] In the context of 3° scaffold hopping, turn mimetics have been developed through the introduction of small molecule derived moieties. This gives peptide structures that are similar to the parent peptides and are only changed in specific positions. Other turn mimetic strategies such as peptide backbone methylation and linear α,δ-disubstituted δ-amino acids are well established and have been discussed elsewhere.[87] α-Helix turn mimetics have also been investigated with promising results outside of the CNS drug discovery field.[97]

Patients with neurodegenerative disorders, including Alzheimer's disease, present with characteristic toxic protein aggregates containing amyloid fibrils (Aβ) composed of β-sheets. Deike and co-workers used turn mimetics to investigate important features of Aβ_{40}, a key pathogenic species associated with the amyloid hypothesis for Alzheimer's disease.[98] This work investigated the importance of the turn motif in Aβ_{40} for fibrillization through the introduction of several different turn mimetics. In this work, turn mimetics were introduced to replace various amino acid residues in the turn motif of Aβ_{40} (highlighted in purple, **88**, Figure 19). Replacements of this motif were made with unnatural turn mimetics such as bicyclic BTD (**89**) and aromatic TAA (**90**).[98] Two separate introductions of **89** as a replacement of either $G_{25}-S_{26}$ or $N_{27}-K_{28}$ caused no fibrillization of the protein, highlighting the importance of this feature for fibrillization. In contrast, the introduction of **90** as a replacement for amino acid residues $G_{25}-S_{26}$ caused a greater fluorescence measurement of fibrils, suggesting an increase in fibrillization.[98] Deike and co-workers also investigated the effect of these Aβ_{40} turn mimetic conjugates as additives with wild-type Aβ_{40}. This study demonstrated that the conjugate that incorporated **89** as a turn mimetic at $G_{25}-S_{26}$ residues increased the lag time of fibrillization (time taken for fibrils to form).[98] Other turn mimetics with various amino acid substitutions in this work showed similar results, although the effects were less pronounced.[98] In this example, 3° scaffold hopping has been utilized as a tool to better understand the turn motif of Aβ_{40} and its role in Aβ fibrillization. Although these derivatives cannot be used themselves as therapeutics, models such as these can be crucial as molecular tools to explore other disease models.

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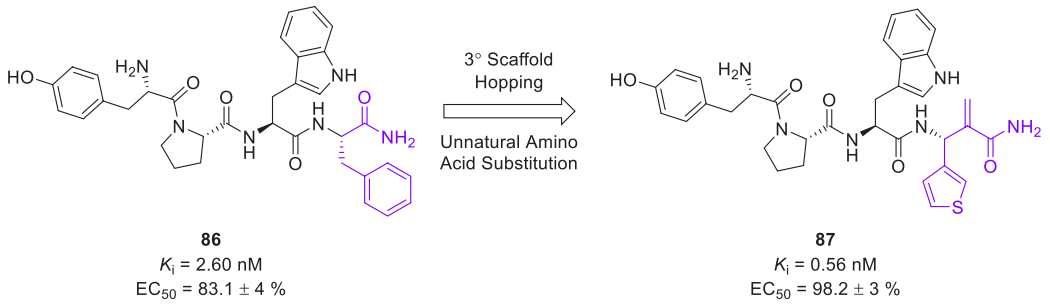

Figure 18. Substitution of a phenylalanine residue seen in μ-opioid receptor agonist **86** with a (thienyl)-α-methylene-β amino acid **87**.[23] EC_{50} = half maximal effective concentration; K_i = inhibition constant.

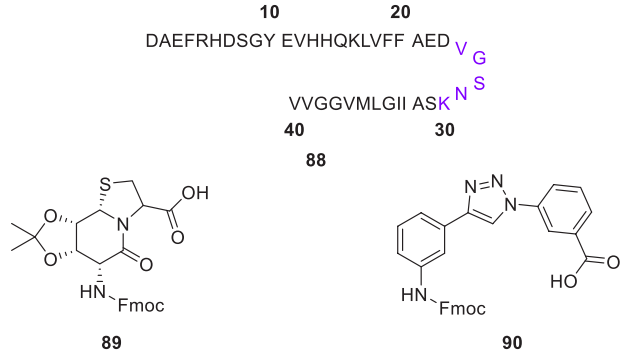

Figure 19. Amino acid residues in the turn motif of Aβ_{40} (**88**) and turn replacements BTD (**89**) and TAA (**90**).[98]

In conjunction with β-sheet mimetics, β-turn mimetics have been extensively studied to design small molecule mimetics that disrupt the β-turn-mediated recognition motif to modulate protein binding. β-Turns contain four amino acid residues: three acting as recognition sites and one as a structural site. Whitby and co-workers aimed to develop a β-turn mimetic template that geometrically accommodates all natural amino acid triplet combinations seen within a β-turn.[99] They performed scaffold hopping against a vast library of β-turn mimetics within the Protein Data Bank identifying a *trans*-pyrrolidine-3,4-dicarboxamide scaffold that closely resembles the rigid triangular geometry of a β-turn (calculated from a set of 10245 β-turns within the PDB) stabilized by intramolecular H-bonding.[99] This was confirmed as a β-turn mimetic following screening campaigns against the μ-opioid receptor whose endogenous ligand, endomorphin (**86**, Figure 20), structurally resembles a β-turn.[99] This yielded **91** with submicromolar affinity for the μ-opioid receptor. Although **91** was not selective for the μ-opioid receptor over the κ-opioid receptor, the *trans*-pyrrolidine-3,4-dicarboxamide scaffold was found to sufficiently act as a synthetically accessible β-turn mimetic template (Figure 20).[99] This proof-of-concept study established that the peptide backbone could successfully be replaced by a mimetic and afford modulation of a β-turn activated receptor.[99] This represents another particularly interesting application of 3° scaffold hopping, which has identified novel chemotype targeting opioid receptors.

Although there are significant obstacles to overcome in the development of peptides and proteins to treat CNS disorders, the prevalence of 3° scaffold hopping approaches to reduce the peptide character and improve the pharmacokinetic profile of proteins and peptides is increasing. Examples within a CNS drug-discovery context are limited, likely due to the discussed challenges in CNS peptide-based drug discovery; however 3° scaffold hopping approaches provide a possible avenue that will help to address some of these obstacles. As this perspective moves to more drastic scaffold hopping applications, it is important to recall that in the literature all these different scaffold hopping approaches are described by the same terminology. The jump to 3° scaffold hopping particularly highlights the usefulness of the categorization proposed by Sun and co-workers and used throughout this work.[14]

3.1.4. Fourth Degree (4°) Scaffold Hopping in CNS Drug Discovery. 4° Scaffold hopping is the most ambitious structural replacement approach and typically leads to dramatic structural modifications. 4° Scaffold hopping is primarily categorized by structurally disparate core structures that retain comparable shape and electrostatic interactions. As a result, the chemotypes generated using this method can differ significantly in their chemical structures compared to parent compounds.[14] Although topology-based scaffold hopping identifies structurally distinct compounds, the success rate of this approach is comparatively low relative to other scaffold hopping

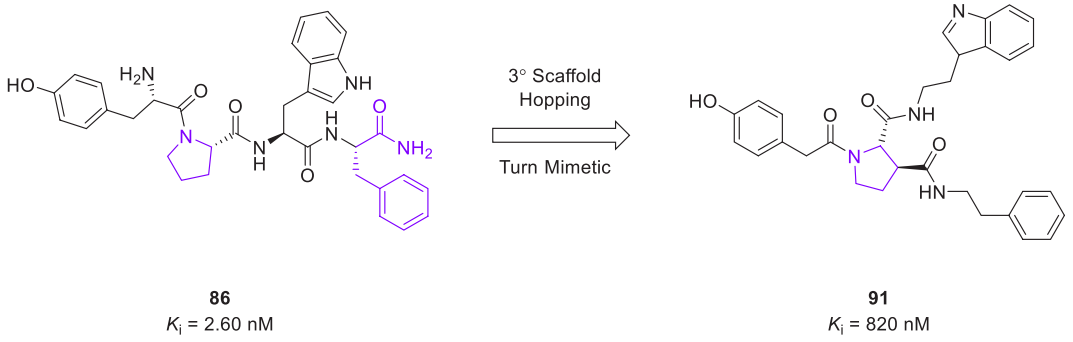

Figure 20. Turn mimetic of μ-opioid receptor ligand endomorphin (**86**) to yield **92**.[99] K_i = Inhibition Constant.

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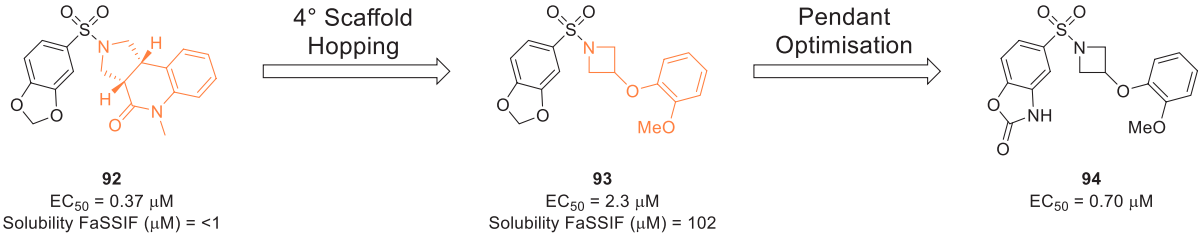


92
EC_{50} = 0.37 μM
Solubility FaSSIF (μM) = <1

93
EC_{50} = 2.3 μM
Solubility FaSSIF (μM) = 102

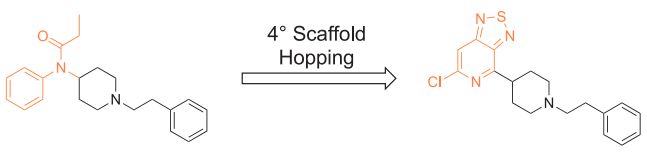
94
EC_{50} = 0.70 μM

Figure 21. Pendant group optimization of tricyclic **92** to azetidine aryl ether **93**. Additional scaffold hopping and optimization of **93** gave compound **94** with improved passive permeability and reduced efflux.[19] EC_{50} = half maximal effective concentration; FaSSIF = fasted state simulated intestinal fluid solubility.

approaches, impacting its representation in the literature.[14] Due to the complex nature of 4° scaffold hopping, it is often aided by *in silico* modeling to understand and illustrate similarities between derivatives and parent molecules that are not immediately obvious by simple inspection.

Chakka and co-workers employed pharmacophore-based virtual screening to optimize CNS and ADME properties of glycine receptor (GlyR) PAM **92** (Figure 21).[19] Glycine receptors have been implicated in various CNS disease states such as neuropathic pain and psychiatric disorders.[19,100] This work explored the composition of tricyclic lead **92**. The authors developed a virtual library, preselecting commercially available secondary amines based on similarity to the lead, evaluated using the Tanimoto coefficient, and selected desirable physiochemical properties (MW < 450 Da, cLogP < 4, PSA < 100 Å^2).[19,101] This led to substitution of the tricyclic core seen in **92** for a methoxyphenoxy azetidine core (**93**) to give improved solubility with a 6-fold reduction in potency (Figure 21).[19] Further SAR studies were performed on **93** in an effort to rescue potency, improve metabolic stability, and improve CNS permeability. This gave rise to compound **94** with improved passive permeability and solubility and low efflux.[19] These azetidine core compounds also reflect lead candidates that are far more synthetically accessible compared to the original lead **92**, highlighting one key advantage of this 4° scaffold hopping approach. *In silico* modeling suggested that **94** was able to adopt similar conformations and form analogous ligand−protein interactions to **92** in the allosteric binding pocket of the GlyR, further justifying this approach.[19] This work exemplified a 4° scaffold hopping approach and has led to the identification of a novel GlyR PAM chemotype, as well as improvement in a number of physicochemical properties.[19]

Floresta and co-workers utilized Cresset Spark software to generate a virtual library of structurally distinct fentanyl-like μ-opioid receptor ligands.[27,102] Fentanyl (**95**, Figure 22) has historically been used as a powerful opioid analgesic. However,



95
K_i = 1.35 nM

96
$^{Pr}K_i$ = 1.26 nM

Figure 22. 4° Scaffold hopping approach used in the exploration of μ-opioid receptor ligand fentanyl (**95**) and selected thiadiazolopyridinone analogue **96**.[102,105] K_i = inhibition constant; $^{Pr}K_i$ = predicted inhibition constant.

in recent times it has been associated with illicit use and strings of overdose fatalities.[103,104] As such, this study has implemented the use of quantitative structural−activity relationship (QSAR) studies to reduce the potency of fentanyl-like compounds to minimize the abuse risk for patients requiring pain management.[102] This study identified upward of 3000 structurally distinct compounds from a training set of 94 compounds.[102] Compound **96** substituted the phenyl amide for a thiadiazolopyridinone moiety, reducing the predicted affinity and thus potency compared to **96**.[102] By reducing the affinity and potency of these fentanyl-like compounds, the potential harm upon consumption and abuse can potentially be minimized.[102] It is important to note that these results are from *in silico* screening and may not reflect true activity, and scrutiny around this is certainly justified. However, the use of this approach to identify novel derivatives still remains a point of interest. Such studies are widely accessible and require relatively low computational power. This presents exciting opportunities for researchers to produce large structurally diverse libraries.

In a separate study, Floresta and co-workers completed 3D-QSAR models enabled by scaffold hopping to improve the affinity of cannabinoid receptor ligands.[106] The therapeutic significance of cannabinoid receptors has been discussed previously. Floresta and colleagues employed the Spark and Forge packages from Cresset to perform scaffold hopping and to train a 3D-QSAR model with 312 and 187 structurally diverse CB_1 and CB_2 receptor ligands, respectively (Figure 23).[27,106] Similarly to their previous study, this work identified a wide array of novel analogues starting from a known cannabinoid ligand (**97**, Figure 23). This approach was able to identify a range of structurally distinct moieties with similar shape and electrostatic properties that would likely be overlooked in more traditional SAR approaches. Examples of these substitutions include the introduction of a 4-chlorobenzisoxazole group seen in **98** and the cyanopentyl carboxamide moiety of **99** as replacements of the tetramethyl cyclopropyl ketone of **97** (Figure 23).[106] Again, this illustration of 4° scaffold hopping is exciting and highlights the diverse derivatives that can be obtained using this approach. Once again, however, biological data must be obtained to determine the actual activity of these *in silico* data-generated structures and validate this approach. Certainly, further applications of studies such as this where QSAR models and novel lead generation can be backed up by *in vitro* data would be invaluable for any drug discovery field.

As previously mentioned, 4° scaffold hopping is the most elaborate scaffold hopping approach and leads to the introduction of large structural changes. The examples presented herein have highlighted the advantages of this

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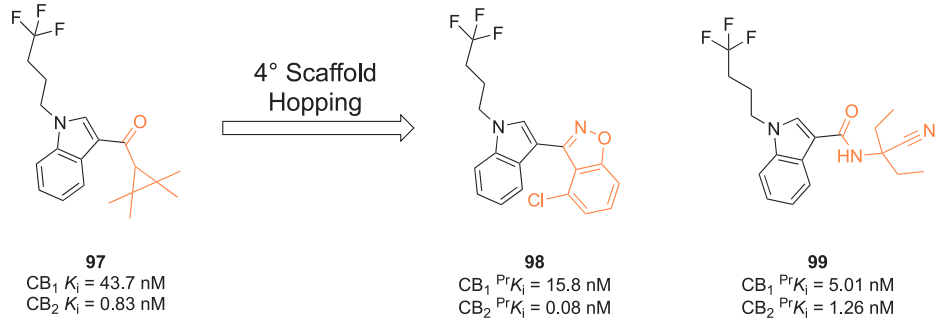

97
CB_1 K_i = 43.7 nM
CB_2 K_i = 0.83 nM

98
CB_1 $^{Pr}K_i$ = 15.8 nM
CB_2 $^{Pr}K_i$ = 0.08 nM

99
CB_1 $^{Pr}K_i$ = 5.01 nM
CB_2 $^{Pr}K_i$ = 1.26 nM

Figure 23. CB_1 and CB_2 receptor ligands **98** and **99** developed via scaffold hopping on Cresset and QSAR models performed on Forge from lead **97**.[106] K_i = inhibition constant; $^{Pr}K_i$ = predicted inhibition constant.

approach (such as mitigating pharmacokinetic liabilities and improving synthetic accessibility). However, the sparse examples of this type of approach are reflective of the difficulty of successfully implementing shape- and topology-based scaffold hopping. As will be further discussed in the following section and has been mentioned throughout this work, this scaffold hopping approach (4°) is also readily put in the same category as simple heterocyclic replacements despite being far more ambitious and distinct. This is a clear issue throughout the literature.

4. PERSPECTIVE

Scaffold hopping has been utilized by medicinal chemists in most fields of drug discovery. Within this perspective, we have shown how scaffold hopping has been used in the development of compounds designed as therapeutics for Alzheimer's disease, Parkinson's disease, neuropathic pain, schizophrenia, and other CNS conditions where drug attrition rates remain troublingly high. The technique of scaffold hopping itself has proven itself to be an indispensable tool in the exploration of lead candidates. The work shown and discussed throughout this perspective particularly highlights the usefulness of scaffold hopping to generate new chemotypes. This is certainly shown throughout the discussion of 1° and 2° scaffold hopping, with a multitude of novel core chemotypes generated quickly for a variety of biological targets. The transformative potential of scaffold hopping is exemplified by the successful application of 4° scaffold hopping by Chakka and co-workers (Figure 21), which represents a new era for structural exploration in medicinal chemistry.[19] This application truly highlights the potential and shows what the field is heading toward. While examples as successful as this remain scarce, we appear to be inching toward the holy grail of scaffold hopping in drug design, namely being able to accelerate the drug optimization process and reduce the pressure on synthetic chemists to make hundreds or even thousands of compounds to turn a hit into a lead or a lead into a clinical drug candidate. Along with the identification of new chemotypes, we have demonstrated that scaffold hopping can be used to improve pharmacokinetic properties, synthetic accessibility, and biological activity and to mitigate toxicity concerns. Although we have outlined how scaffold hopping offers exciting opportunities for pharmacophore exploration and optimization, it is still currently limited by computing power as well as the validity of screening techniques. As our ability to develop validated in silico biological screening models develops, this will enhance the scaffold hopping space exponentially, particularly in higher degrees of scaffold hopping (primarily 4° scaffold hopping). Despite these pitfalls, scaffold hopping's widespread applicability truly cements its place in the medicinal chemistry arsenal.

Throughout the literature, the term scaffold hopping is often used ambiguously. This may be reflective of its interpretation to incorporate a broad scope of structural changes. At its heart, scaffold hopping refers to modifying core structures of lead candidates while maintaining pendant moieties in comparable position and space. We believe that the categorizations suggested by Sun and co-workers offers a more limiting, and by extension a more descriptive and useful, categorization of scaffold hopping approaches.[14] Utilizing this framework and applying it when altering core structures of lead candidates should ensure that the term scaffold hopping becomes less ambiguous and more useful in the literature. It is our hope that the nomenclature relating to scaffold hopping proposed by Sun and co-workers and utilized here will continue to evolve in the coming years, but in our view it already represents a step in the right direction toward clearer and more meaningful terminology. The applications of scaffold hopping we have explored in this work have illustrated the usefulness of this type of terminology in distinguishing various scaffold hopping approaches. We hope this will lead by example in implementing this terminology.

Although the term scaffold hopping was coined only recently, the theory and implementation of its fundamental principles (isosteres and bioisosteres) have been cemented in chemistry theory for over a century. As our understanding of biological targets and our capacity to model biological and chemical environments continues to develop, our ability to apply various scaffold hopping approaches will continue to expand accordingly. Developments in this aspect of scaffold hopping have been discussed elsewhere; however there are promising signs in expanding our ability to explore chemical space through significant structural overhaul in a logical and guided process. Current techniques in this area have led to a host of success stories that have been highlighted here. However, with continued advances in this field, it is expected that successful applications of more ambitious scaffold hopping approaches (particularly 4°) will become more common in the literature. This represents an exciting time in the medicinal chemistry field. The authors of this review believe that continued, judicious use of scaffold hopping will be invaluable for improving the success rate of therapeutics across all fields of drug discovery in the clinic over the coming years.

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Notes

The authors declare no competing financial interest.

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Timothy B. Callis received a Bachelor of Science (Chemistry) with first class honors from the University of Sydney in 2018. Timothy was awarded an Australian Government Research Training Program Award scholarship and undertook a Ph.D. under the supervision of Prof. Michael Kassiou at the University of Sydney, focusing on the exploration of small molecules for the treatment of a range of neurodegenerative diseases. He completed his Ph.D. in 2022 and has taken up an industry position where he is currently working on the synthesis and development of novel small molecule therapeutics for the treatment of social dysfunction in mental health disorders.

Taylor R. Garrett received a Bachelor of Science (Chemistry and Pharmacology) with first class honors from the University of Sydney in 2021. This undergraduate degree included a year working as an analytical and synthetic chemist at the National Measurement Institute in the chemical reference materials division. In 2021, Taylor was awarded an Australian Government Research Training Program Award scholarship and began her Ph.D. under the supervision of Prof. Michael Kassiou studying novel chemotypes for exploring neuroinflammatory conditions.

Andrew P. Montgomery received a Bachelor of Medicinal Chemistry Advanced with first class honors from the University of Wollongong in 2014. In 2015, he received an Australian Government Research Training Program Award scholarship to undertake a Ph.D. under the supervision of Dr. Danielle Skropeta and Dr. Haibo Yu at the University of Wollongong. Andrew received his Ph.D. in 2019 and later that year took up his current position as a Drug Discovery Initiative Postdoctoral Fellow, working under the supervision of Prof. Michael Kassiou at the University of Sydney. His research is focussed on small molecule synthesis and computational studies for a variety of CNS drug discovery projects.

Jonathan J. Danon received his M.Sci. in Chemistry with Industrial Experience from the University of Bristol in 2011, spending one year of his degree working for AstraZeneca developing scale-up procedures for pharmaceutical intermediates and APIs. Funded by an EaStCHEM Studentship, he undertook a Ph.D. in Chemistry and subsequent postdoctoral position with Prof. David Leigh at the University of Edinburgh/University of Manchester from 2011 to 2016. After moving to Australia in 2017 to kickstart his academic medicinal chemistry career, he won a University of Sydney Postdoctoral Fellowship (2018−2021) to establish his independent research program. In 2022, he began a NHMRC research fellowship at the University of Sydney, focusing on developing novel PET tracers for studying disorders of the CNS.

Michael Kassiou received his Ph.D. in Organic Chemistry in 1992 from UNSW. He subsequently took up positions at ANSTO, the CEA-Service Hospitalier Frédéric Joliot Life Sciences group in France and the Johns Hopkins Medical Institutes in Baltimore USA. In 1996, he was awarded a Fogerty Fellowship based at the NIH National Institute of Drug Abuse (NIDA) USA. He then moved back to Sydney to Royal Prince Alfred Hospital as a Principal Hospital Scientist. In 2006, he took up a position at the University of Sydney in which he is currently Professor of Medicinal Chemistry. He is the Editor for the *Journal of Labelled Compounds and Radiopharmaceuticals*, Chief Editor for *Frontiers in Medicinal and Pharmaceutical Chemistry*, and Associate Editor for *ACS Chemical Neuroscience*.

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ABBREVIATIONS USED

ADME, absorption, distribution, metabolism, and elimination; Aβ, amyloid-β; AI, artificial intelligence; BBB, blood−brain barrier; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CCR2, CC chemokine receptor-2; CNS, central nervous system; EC_{50}, half maximal effective concentration; EM, endomorphin; FaSSIF, fasted state simulated intestinal fluid solubility; G9a, lysine methyltransferases 1C; GAK, cyclin G associated kinase; GLP, lysine methyltransferases 1D; GlyR, glycine receptor; IC_{50}, half maximal inhibitory concentration; IP, intellectual property; K_d, dissociation constant; K_i, inhibition constant; Map, (thienyl)-α-methylene-β-amino acid; M_4, muscarinic acetylcholine receptor subtype 4; hM_4, human muscarinic acetylcholine receptor subtype 4; rM_4, rat muscarinic acetylcholine receptor subtype 4; $mGlu_2$, metabotropic glutamate 2 receptor; NAM, negative allosteric modulator; nAChR, nicotinic acetylcholine receptors; PAM, positive allosteric modulator; PAMPA, parallel artificial membrane permeability assay; PDB, Protein Data Bank; PSA, polar surface area; QSAR, quantitative structure−activity relationship; SAR, structure−activity relationship; σ1R, sigma 1 receptor; σ2R, sigma 2 receptor; $T_{1/2}$, serum half-life; WHALES, weighted holistic atom localization and entity shape

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