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Scaffold Hopping in Drug Discovery: Innovation in Pharma Industries and Academia

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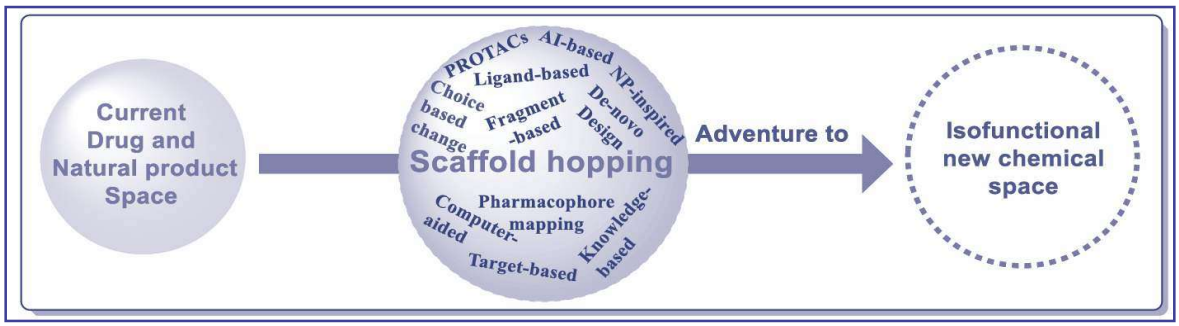
The medicinal chemistry strategy plays crucial roles in the drug discovery process starting from selection and synthesis of new compounds to the study of structural modulation for required preclinical profile of compounds. Modern medicinal chemists are currently implementing scaffold hopping strategy to expand the existing drug and chemical space, introducing new molecules with chemically different core structures, and yet binding to the same biological target. Scaffold hopping is important not only in the early stages of drug discovery where a novel active compound must be identified, but also in lead optimization where a variety of chemical properties, physicochemical properties, PK-PD, and toxicity problems of a bioactive molecule or natural product can be resolved via identification of a novel core structure. Scaffold replacements afford to discover the architecture of the therapeutic-valued molecules within patent space of interest. This review presents a brief account of scaffold hopping, creating new chemical space, applications to various stages of Pharmaceutical science research, and successful discovery of drugs.



Scaffold hopping as a concept and patentability

In the year 1999, Gisbert Schneider coined the term Scaffold hopping.[1] It is a process that identifies isofunctional structures with different molecular backbones. This can be achieved by modifying either the central core structure or side chains of the known active compound, which leads to a novel molecular structure that has 3D structure and biological properties similar to the parent compound.[2] The new molecules developed through this strategy successfully dodge the patent space of the original drug and become patentable. Patentability-claim of generated new chemical entities is always a challenging issue. The scaffold hopping strategy overcomes the issue of patentability and creates the new chemical space outside of existing patented chemical island.[3]

Keywords: Scaffold hopping; Drug discovery; chemical space; Patentability; PK-PD

Balancing novelty with drug-like properties in chemical space.

Scaffold hopping is a useful strategy in drug design to 'jump' in different areas of chemical space. The key feature of scaffold hopped analogues is that they have structurally distinct templates with similar biological activity. This approach is employed by medicinal chemists in order to get drug-like qualities, avoid unfavourable ADME-tox features, find readily synthesizable molecules that resemble complex natural products, and to secure intellectual property right. Thus, this is an attractive strategy to achieve

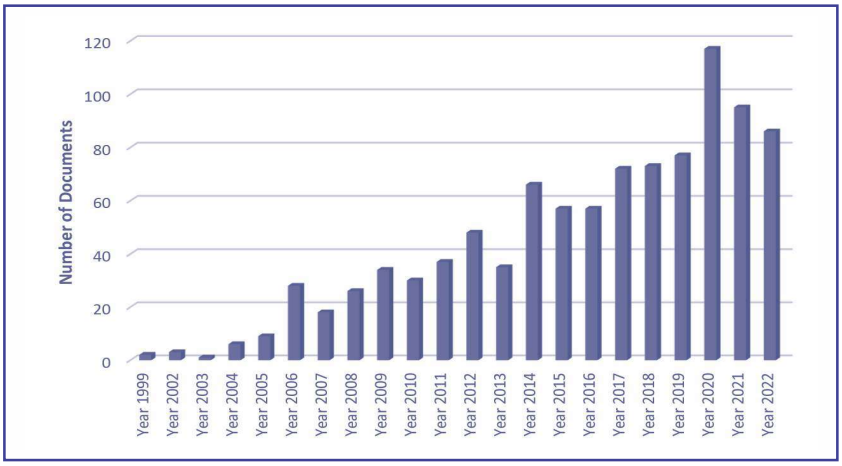


Figure 1."Documents"(article, review, conference paper, bookchapter, patent, letter, Editorial) published; data collected from Reaxys.

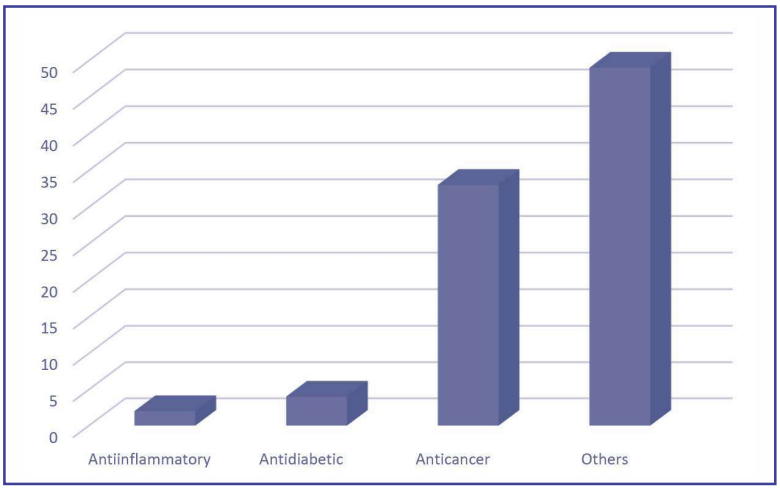


Figure 2. Scaffold hopping strategy in various therapeutic research from 2019-2022 (Number of Publications and patents); data collected from Reaxys.

novelty within confined drug-relevant chemical space.[4]

Scaffold hopping - a highly practiced research area

The number of documents generated from research on scaffold hopping, as presented in the Figure 1, clearly indicates that year-wise documents publication is highly increasing and scaffold hopping is a highly practiced research area in the pharma sector and academia.

Scaffold hopping - therapeutic research area

Scaffold hopping as an important strategy is frequently considered in various therapeutic research. Among various diseases, the anticancer drug discovery uses more frequently the scaffold hopping strategy (Figure 2).

Scaffold hopping in Pharmaceutical industry

Various drugs have been successfully discovered by using the scaffold hopping strategy.

Kinase Inhibitor

Heteroatom replacement, a strategy of scaffold hopping, was investigated by Wyeth Pharmaceutical company. The research focused on the AstraZeneca drug gefitinib that was introduced to market in 2003, which led to the successful development of bosutinib drug, approved by USFDA in 2012. 'Nitrogen' atom in the quinazoline ring is replaced with 'Carbon' to form quinoline ring system (Figure 3). To retain the pharmacophoric importance of quinazoline ring 'N' atom, a cyano group is introduced at relevant position of quinoline ring.[3]

PDE 5 Inhibitor

In 1994, Pfizer filed a patent covering the use of sildenafil drug that was approved by the USFDA in the year 1998 and Bayer Pharmaceuticals introduced in 2003 the vardenafil drug (Figure 4). Both drugs are phosphodiesterase 5 (PDE5) enzyme inhibitors. The major structural variation between these drugs is the swap of a carbon atom with a nitrogen atom in the 5-6 fused ring.[5]

Cyclooxygenase (COX 2) inhibitor

The cyclooxygenase 2 (COX-2) inhibitor drugs rofecoxib (VioxxTM) and valdecoxib (BextraTM) were discovered by use of scaffold hopping strategy on the structure of celecoxib drug, a COX-2 inhibitor. They differ by only the five-member hetero ring connecting two phenyl rings (Figure 5). Rofecoxib was introduced to market by Merck in 1999 and the valdecoxib drug was developed by Pharmacia/Pfizer and approved by USFDA in 2001.[6]

Classification of Scaffold hopping

In the scaffold hopping strategy, various types of structural modulation of drugs/ bioactive agents while retaining the key pharmacophoric features are practiced by the pharma sector and academia.[7]

Heterocycle replacement (1° hop)

1° hop refers to minor alterations, such as switching or substituting heteroatoms and carbon in a backbone ring. (Figure 6). Replacing the heteroatoms in a heterocycle that functions as the core of the

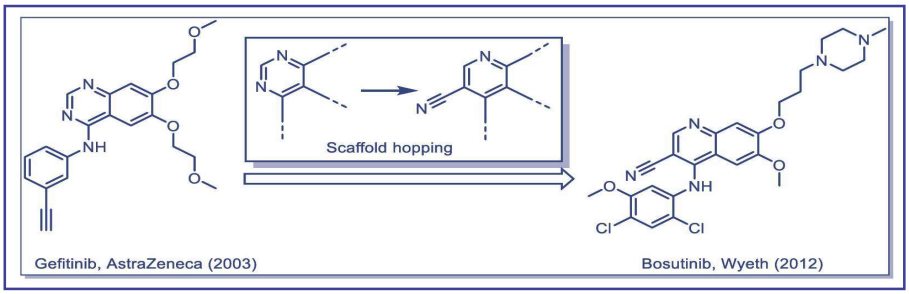


Figure 3. Scaffold hopping strategy in kinase inhibitor.

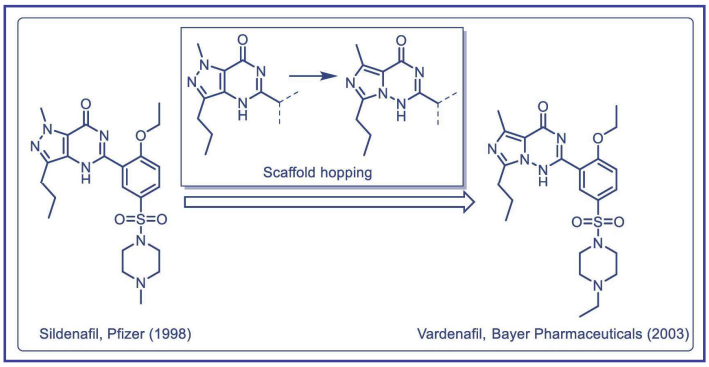


Figure 4. Scaffold hopping strategy in PDE 5 inhibitor.

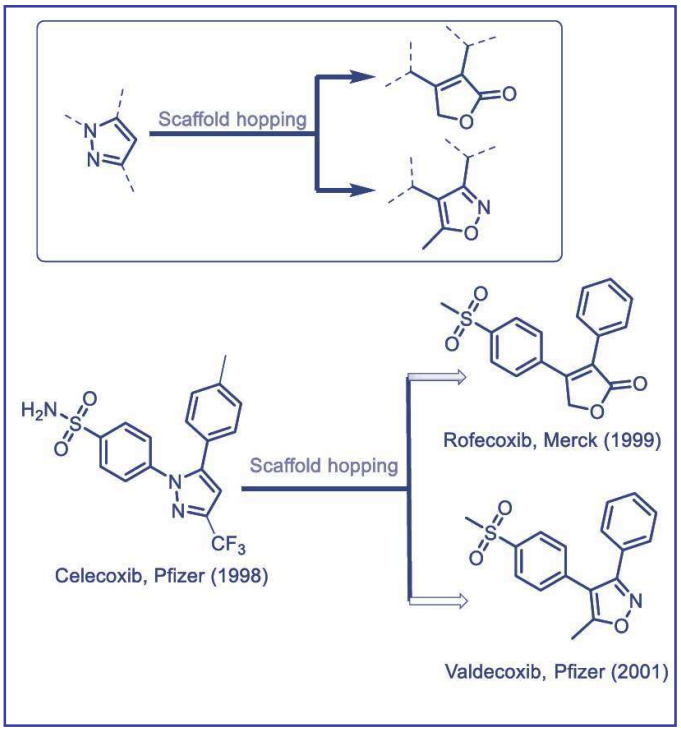


Figure 5. Example of scaffold hopping strategy in cyclooxygenase (COX 2) inhibitors.

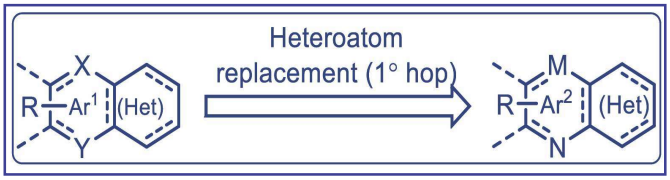


Figure 6. Heterocycle replacement (1° hop).

drug molecule while retaining linked functional motifs and pharmacophores results in novel scaffold. Pizotifen, a more effective medication for the treatment of migraines, is created when one of the phenyl rings in the antihistaminic drug cyproheptadine is switched out for thiophene. The solubility of the molecule is increased when one of the phenyl rings in cyproheptadine is replaced with a pyrimidine ring to create azatadine.[8]

Ring opening and closure (2° hop)

Most drug-like molecules possess at least one ring system. The ring opening and ring closure are two scaffold hopping 2° hop strategies to create novel scaffolds (Figure 7). 2° hop is a useful strategy for improving the drug-like properties, because molecular flexibility or rigidity aspect contributes greatly to the entropic component of the binding free energy, membrane penetration, absorption, and to manipulate the flexibility of a molecule by controlling total number of free rotatable bonds. Morphine, an opioid receptor agonist is a rigid 'T' shaped molecule, breaking six ring bonds and opening three fused rings, the new drug tramadol is more flexible, resulting in reduced potency and reduced side effects.[9]

Pseudopeptides and peptidomimetics (3° hop)

Replacement of a peptide backbone with a non-peptic moiety is included into the category of scaffold hopping 3° hop. Due to their poor metabolic stability and limited bioavailability, peptides' clinical usage is significantly hampered. Using active peptide conformations as templates, small molecules that mirror the structural characteristics of peptides have shown encouraging outcomes (Figure 8). The major goal of peptide-based drug discovery is to reduce the peptide character for enhancing the molecular resistance to proteolysis, while retaining the key chemical features for molecular recognition. Replacing the central residues of angiopoietin II (Ang II) containing Tyr at position 4 and Ile at position 5 with a benzodiazepine-based mimetic, a well-known b-turn scaffold exhibited high binding affinities against both angiotensin II receptor type 1 (AT1) and angiotensin II receptor type 2 AT2 receptors with K_i values of 14.9 nM and 1.8 nM.[10]

Topology or shape-based scaffold hopping (4° hop)

A complete new chemical backbone that only retains molecular interactions of the ligand with the target is characterized as a 4° hop scaffold hopping (Figure

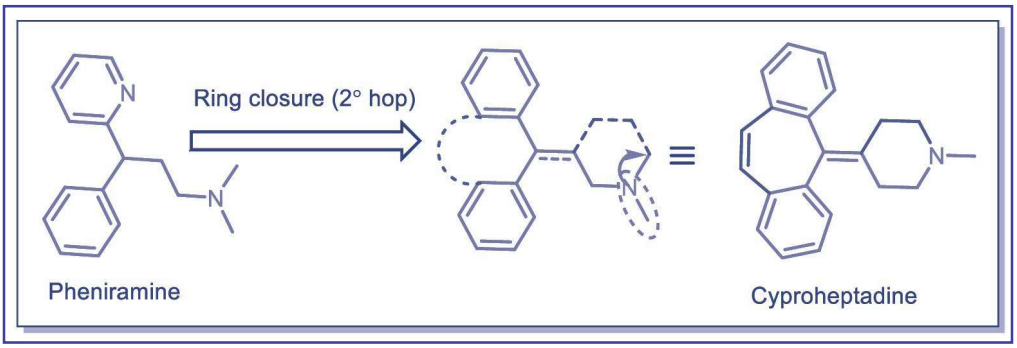


Figure 7. Ring closure (2° hop).

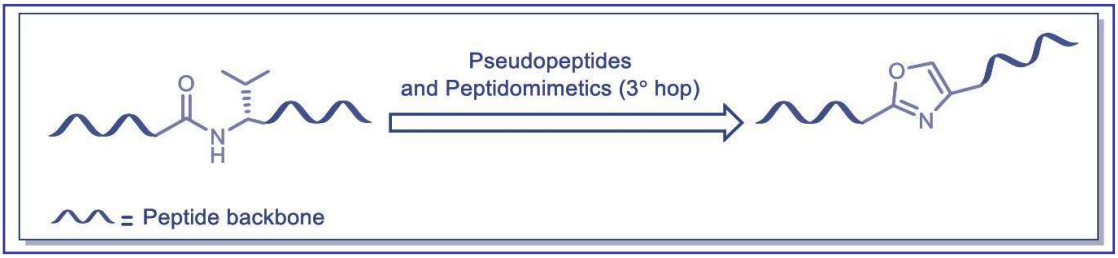


Figure 8. Pseudopeptides and peptidomimetics (3° hop).

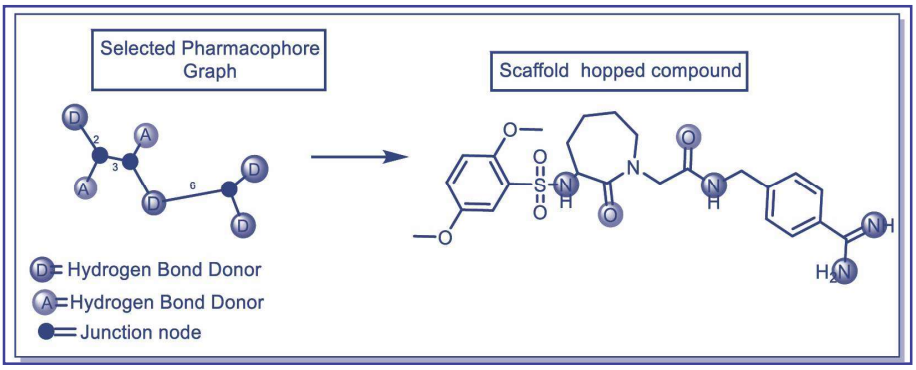


Figure 9. Topology or shape-based scaffold hopping (4° hop).

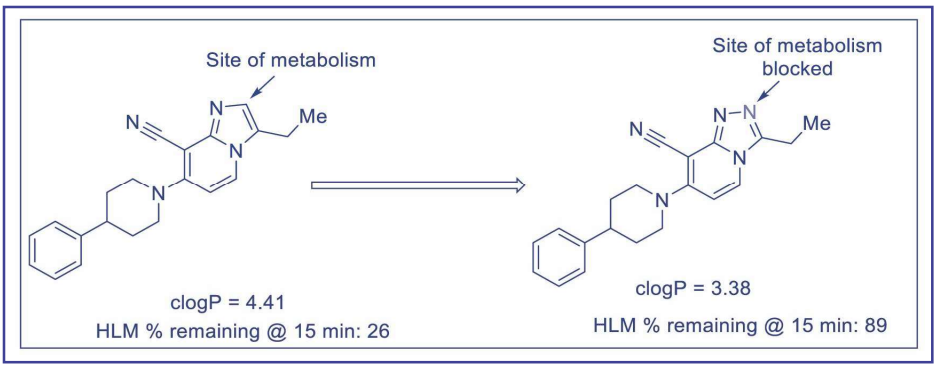


Figure 10. Improvement in metabolic stability using scaffold hopping strategy.

9). There are many examples of topology or shape-based scaffold hopping in this category. Instead of scaffold hopping, the procedure may be referred to as structure-based virtual screening when the new chemotype differs greatly from its original template.[11,12]

Scaffold hopping in changing PK-PD profile

Metabolic stability

Cid et al. reported[13] an interesting application of scaffold hopping by switching from imidazopyridine to 1,2,4-triazolopyridine scaffold (Figure 10). It afforded significant improvement in metabolic stability with decrease in clog P property of the molecule. The metabolism site in the imidazopyridine ring is blocked by incorporation of an additional nitrogen atom in the ring as 1,2,4-triazolopyridine motif. In addition, lipophilicity of the molecule is reduced. The scaffold hopped 1,2,4-triazolopyridine-based analog showed improved metabolic stability in human liver microsomes.

Yeung et al.[14] described, when a phenyl motif is changed to a pyridyl or pyrimidyl ring by scaffold hopping strategy, it imparts metabolic stability (Figure 11). The metabolic stability is typically increased by adding nitrogen atoms to aromatic systems to enhance half-life.

Pharmacodynamic, physiochemical and pharmacokinetic properties

Liu et al. investigated[15] the scaffold hopping strategy for improvement in physiochemical and pharmacokinetic profile, while retaining the *in vitro* activity. The scaffold hopping of imidazo[1,2-a]pyrazines with pyrazolo[1,5-a] pyrimidines increases polarity at relevant site of molecule and improves physicochemical and pharmacokinetic profiles, while retaining the molecule's pharmacodynamic potency (Figure 12).

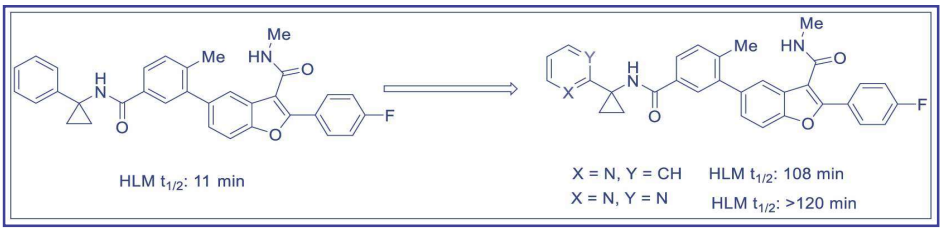


Figure 11. Metabolic stability using scaffold hopping.

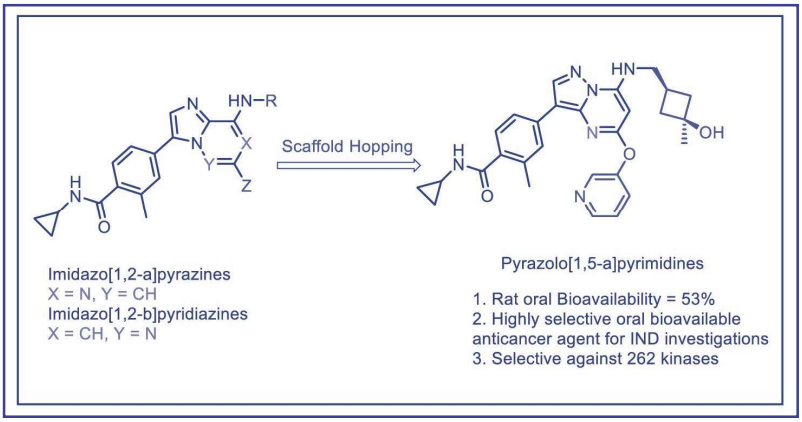


Figure 12. Scaffold hopping strategy for improvement in *in vitro* activity, physicochemical and pharmacokinetic profile, while retaining *in vitro* activity.

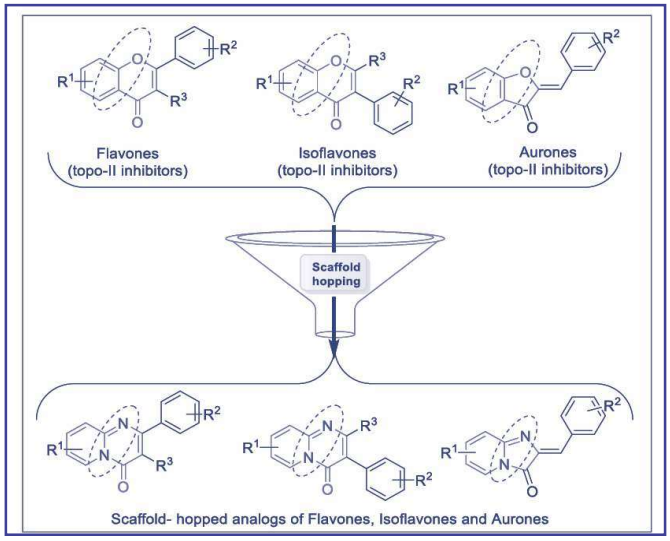


Figure 13. New scaffold hopped analogs of flavones, isoflavones, and aurones; improvement in activities and reduction in toxicity.

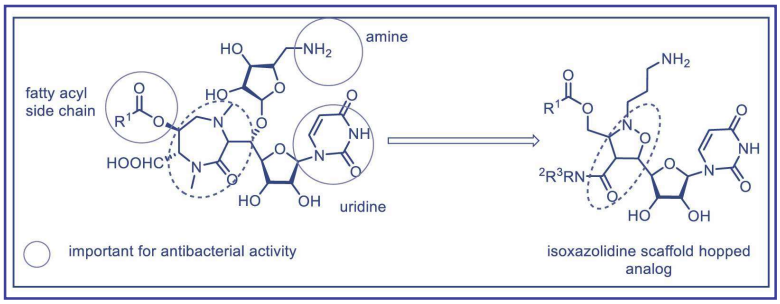


Figure 14. Scaffold hopping strategy in caprazamycin antibiotic.

Scaffold hopping of Natural products

Our group reported[16] for the first-time the scaffold hopping strategy on bioactive natural product flavonoids. Compared to parent flavones, isoflavones and aurones with equivalent functional motifs, the scaffold hopped analogs of these flavonoids displayed very high hTopoII-inhibitory activities, cytotoxic activities, and less toxicity to normal cells. The study showed the importance of a natural product-based scaffold hopping technique in the drug discovery (Figure 13).

Our group[17] also considered an iterative scaffold hopping strategy on scaffold hopping analogs of aurones by incorporation of the structural skeletons frequently present in known anticancer agents. They were synthesized via a new method of organocatalyzed umpolung chemistry. These iterative scaffold hopped analogs were found to possess important anticancer activities and appropriate physiochemical properties.

Yamaguchi et al. reported[18] scaffold hopping of glycyluridine antibiotic caprazamycins, those are excellent antimycobacterial agents effective against both drug-susceptible and multi-drug-resistant Mycobacterium tuberculosis strains (Figure 14). They replaced the structurally complex diazepanone moiety of caprazamycin with the isoxazolidine scaffold (Figure 14). The isoxazolidine-containing uridine derivatives exhibited good activity against *H. influenzae* ATCC 10211 (MIC 0.25–0.5 µg mL-1) and significant activity against vancomycin-resistant *E. faecalis* SR7914 (MIC 4–8 µg mL-1).

Conclusions

Scaffold hopping approach is an emerging strategy in the drug discovery process and it enables medicinal chemists to explore varied array of biologically-important new patentable molecules. The strategy has found promising applications in the research area from pharmacoinformatics to pre-clinical investigations. It provides improvement in pharmacodynamic potency, physicochemical properties, and pharmacokinetic profile, as well as reduction in toxicity of molecules. Scaffold hopping is highly practiced in pharmaceutical industries sector and academia. Many drugs and clinical trial

agents were successfully discovered by the scaffold hopping strategy. This medicinal chemistry strategy in combination with other design processes has potential in applications to various stages of pharmaceutical science research from computer-aided design to preclinical profile improvement.

References

1. Schneider, G.; Neidhart, W.; Giller, T.; Schmid, G. (1999) "Scaffold-hopping" by topological pharmacophore search: a contribution to virtual screening. Angew. Chem. Int. Ed., 38, 2894-2896.
2. Böhm, H.-J.; Flohr, A.; Stahl, M. (2004) Scaffold hopping. Drug Discovery Today: Technol., 1, 217-224.
3. Southall, N. T.; Ajay. (2006) Kinase patent space visualization using chemical replacements. J. Med. Chem., 49, 2103-2109.
4. Medina-Franco, J. L.; Martinez-Mayorga, K.; Meurice, N. (2014) Balancing novelty with confined chemical space in modern drug discovery. Expert Opin. Drug Discovery., 9, 151-165.
5. Doggrell, S. A. (2005) Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. Expert Opin. Pharmacother., 6, 75-84.
6. FitzGerald, G. A. (2003) COX-2 and beyond: approaches to prostaglandin inhibition in human disease. Nat. Rev. Drug Discovery., 2, 879-890.
7. Sun, H.; Tawa, G.; Wallqvist, A. (2012) Classification of scaffold-hopping approaches. Drug Discovery Today., 17, 310-324.
8. Langdon, S. R.; Ertl, P.; Brown, N. (2010) Bioisosteric replacement and scaffold hopping in lead generation and optimization. Mol. Inf., 29, 366-385.
9. Tasler, S.; Müller, O.; Wieber, T.; Herz, T.; Krauss, R.; Totzke, F.; Kubbutat, M. H.; Schächtele, C. (2009) N-substituted 2'-(aminoaryl) benzothiazoles as kinase inhibitors: Hit identification and scaffold hopping. Bioorg. Med. Chem. Lett., 19, 1349-1356.
10. Fry, D.; Sun, H. (2006) Utilizing peptide structures as keys for unlocking challenging targets. Mini-Rev. Med. Chem., 6, 979-987.
11. Franke, L.; Schwarz, O.; Müller-Kuhrt, L.; Hoernig, C.; Fischer, L.; George, S.; Tanrikulu, Y.; Schneider, P.; Werz, O.; Steinhilber, D. (2007) Identification of natural-product-derived inhibitors of 5-lipoxygenase activity by ligand-based virtual screening. J. Med. Chem., 50, 2640-2646.
12. Nakano, H.; Miyao, T.; Swarit, J.; Funatsu, K. (2021) Sparse Topological Pharmacophore Graphs for Interpretable Scaffold Hopping. J. Chem. Inf. Model., 61, 3348-3360.
13. Cid, J. M.; Tresadern, G.; Vega, J. A.; de Lucas, A. I.; Matesanz, E. n.; Iturrino, L.; Linares, M. L.; Garcia, A. n.; Andre´s, J. I.; Macdonald, G. J. (2012) Discovery of 3-cyclopropylmethyl-7-(4-phenylpiperidin-1-yl)-8-trifluoromethyl [1, 2, 4] triazolo [4, 3-a] pyridine (JNJ-42153605): a positive allosteric modulator of the metabotropic glutamate 2 receptor. J. Med. Chem., 55, 8770-8789.
14. Yeung, K.-S.; Beno, B. R.; Parcella, K.; Bender, J. A.; Grant-Young, K. A.; Nickel, A.; Gunaga, P.; Anjanappa, P.; Bora, R. O.; Selvakumar, K. (2017) Discovery of a hepatitis C virus NS5B replicase palm site allosteric inhibitor (BMS-929075) advanced to phase 1 clinical studies. J. Med. Chem., 60, 4369-4385.
15. Liu, Y.; Laufer, R.; Patel, N. K.; Ng, G.; Sampson, P. B.; Li, S.-W.; Lang, Y.; Feher, M.; Brokx, R.; Beletskaya, I. (2016) Discovery of pyrazolo [1, 5-a] pyrimidine TTK inhibitors: CFI-402257 is a potent, selective, bioavailable anticancer agent. ACS Med. Chem. Lett., 7, 671-675.
16. Priyadarshani, G.; Amrutkar, S.; Nayak, A.; Banerjee, U. C.; Kundu, C. N.; Guchhait, S. K. (2016) Scaffold-hopping of bioactive flavonoids: Discovery of aryl-pyridopyrimidinones as potent anticancer agents that inhibit catalytic role of topoisomerase IIa. Eur. J. Med. Chem., 122, 43-54.
17. Kumar, G.; Das, C.; Acharya, A.; Bhal, S.; Joshi, M.; Kundu, C. N.; Choudhury, A. R.; Guchhait, S. K. (2022) Organocatalyzed umpolung addition for synthesis of heterocyclic-fused arylidene-imidazolones as anticancer agents. Bioorg. Med. Chem., 67, 116835.
18. Yamaguchi, M.; Matsuda, A.; Ichikawa, S. (2015) Synthesis of isoxazolidine-containing uridine derivatives as caprazamycin analogues. Org. Biomol. Chem., 13, 1187-1197.