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SCAFFOLD HOPPING: A BLESSING TO MEDICINAL CHEMIST

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Article History
Received: February 2025 | Accepted February 2025 | Published March 2025

ABSTRACT

Scaffold hopping also known as lead hopping is an important strategy used in lead optimization during drug discovery. It includes conversion of an explicit part of a potentially active compound to an alternative structure to discover isofunctional structure. The main goal of scaffold hopping is of creating a structurally different template of chemical structure while safeguarding desired biological activity. It helps in reducing various toxicity issues, obtaining an intellectual property, and addresses issues related to less potency or stability of the drug. Scaffold hopping tools such as isosteric ring replacement include ring opening and closing, functional group isosterism, functional group reversion, chain shortening, chain elongation, and scaffolding. It has truly been a blessing to medicinal chemist since it provides a means to modify the structure and improve physicochemical properties. It also opens the scope for intellectual property if the designed structure is novel.

Keywords: *Scaffold hopping, isosteric ring replacement, functional group isosterism, optimization, core structure, lead optimization.*

INTRODUCTION:

Scaffold hopping known as lead hopping is widely used during drug discovery [1]. Schneider et al. in 1999 coined the term scaffold hopping for referring to a compound that have same activity but different key structures. Scaffolding techniques usually involves a novel chemotype obtained by linking different functionalities to the central structure of the molecule. [2]. In such a case the bioactivity is maintained or enhanced [3].

Scaffold is obtained from the compound by removing substituent group and retaining ring system and linker fragment between rings. Several different scaffold hopping techniques are used, including closing / opening the ring, and topology-based scaffold-hopping. The most used method is heterocycle replacement which involves a rearrangement or change in the quantity of heteroatoms within the core [1]. Because many compounds create negative physicochemical and pharmacokinetic properties, molecules can inherit many undesirable characteristics. In some cases, modifying a side chain is sufficient to overcome the undesirable properties of structures associated with the parent molecule, and in some cases, the basic structure or scaffolding of the parent molecule must be altered. There are many methods that allow the production of scaffold hops. This includes the use of 2D fingerprints and 3D pharmacophores [5].

Compounds with similar structures have identical physicochemical as well as biological activities [6].

CLASSIFICATION OF SCAFFOLD HOPPING APPROACHES:

Scaffold hopping approaches can be classified based on how different the structures are generated by scaffold hops.

Boehm et al. categorised two scaffolds differently when synthesized from two different synthetic routes irrespective of small changes. This has been verified to be correct since the organic properties are interconnected and the applications for new drugs may be accepted by the USFDA. For example, there is a significant structural difference among the two phosphodiesterase 5 (PDE5) inhibitors namely sildenafil and vardenafil (Figure 1a and 1b) but the modification is sufficient for two molecules to be covered through two different patents. Similarly, two cyclooxygenase 2 (COX-2) inhibitors of rofecoxib and valdecoxib (Figure 1c and 1d) are distinguished by hetero rings connected via two phenyl rings [2].

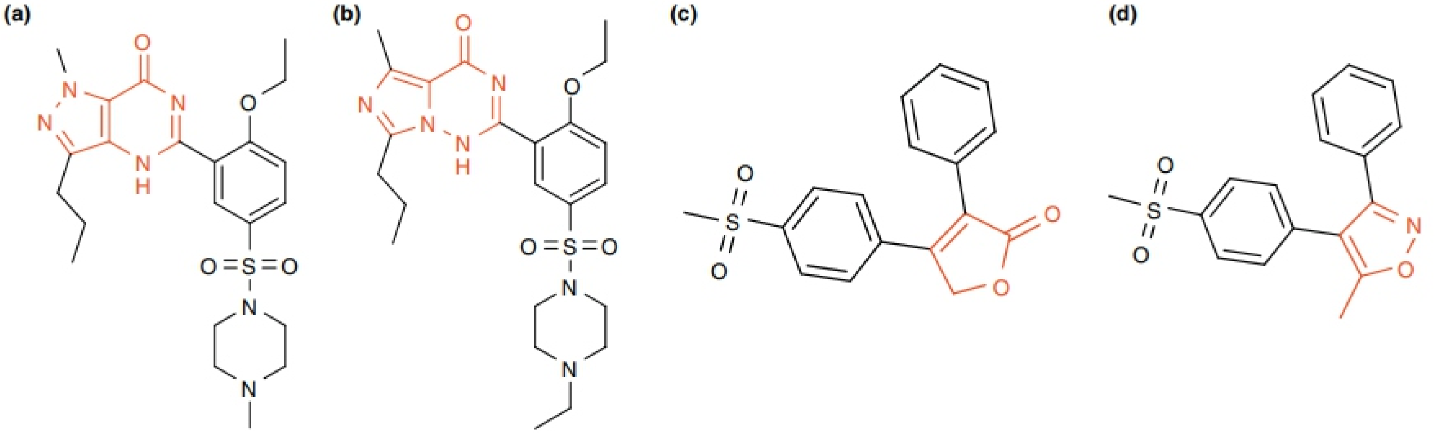

Figure 1: Phosphodiesterase type 5 enzymes inhibitors (a) sildenafil, (b) vardenafil and cyclooxygenase (COX-2) inhibitors, (c) rofecoxib and (d) valdecoxib.

This type of scaffold hopping is classified as 1° hop. The opening and closing of the ring are called as a 2° hop. Replacing the peptide framework to a nonpeptide moiety is 3° hop. Eventually, a novel chemical backbone is 4º hop [2].

1°HOP: HETEROCYCLE REPLACEMENT:

In general, heterocyclic ring act like a backbone of drug molecule. Replacement of carbon, nitrogen, oxygen, and sulphur atoms in the heterocyclic ring can lead to novel scaffolds. Enhanced binding interactions can be possibly achieved when the heterocyclic ring is involved in the interaction with targeted protein.

Rimonabant is an anorexic anti-obesity medicament which inhibits cannabinoid 1 (CB1) receptor. It acts as an appetite suppressant. This drug was not approved by U.S. FDA due to the associated safety concerns. Team at AstraZeneca started working for scaffold hopping technique, by improving physicochemical property, drug metabolism and pharmacokinetic properties. The strategy of scaffold hopping used resulted in novel classes of CB1 inhibitors [7]. Replacement of the methyl pyrazole backbone of rimonabant with a variety of five and six membered rings was carried out as depicted in Figure 2 [8].

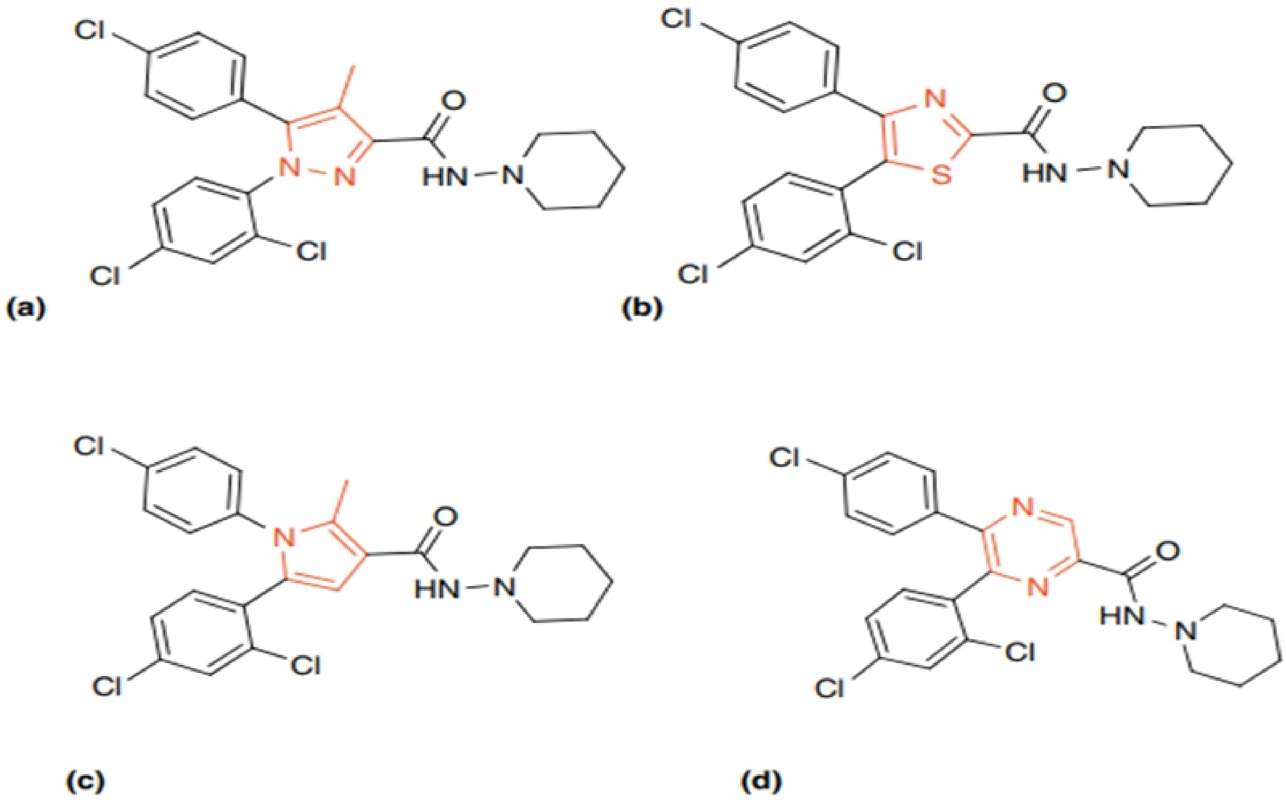

Figure 2: Structure of the CB1 antagonists (a) rimonabant, (b) thiazole derivative, (c) pyrrole derivative, and (d) pyrazine derivative.

Cannabinoid 2 receptor inhibitor is having 44% of sequence resemblance like CB1 receptor. Merck scientists optimized potent as well as triaryl bis-sulfone CB2 inhibitor, to modify some unfavoured conditions like blocking of calcium channels and cytochrome P450 [1].

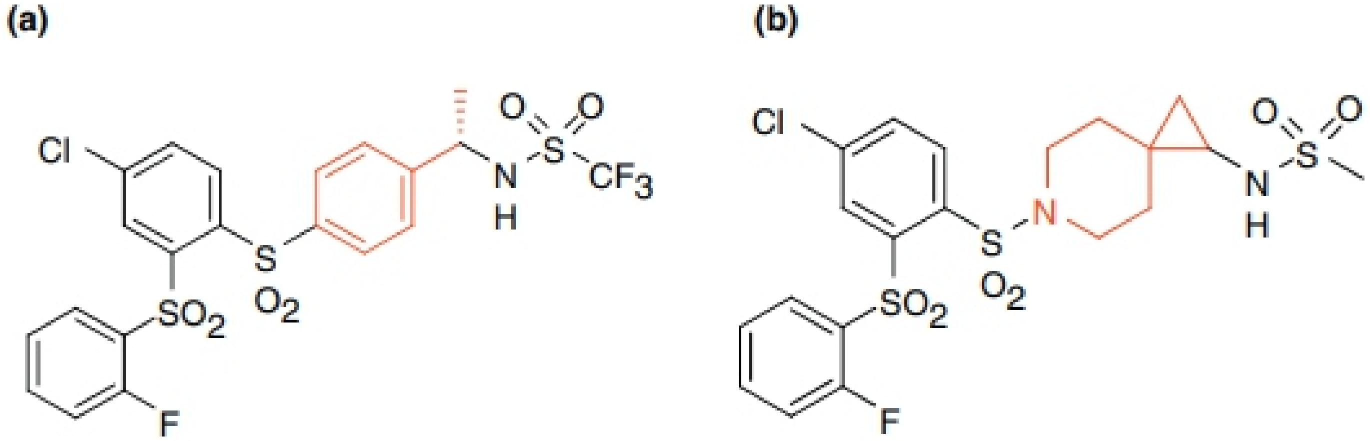

Figure 3: Triaryl bis-sulfone CB2 receptor inhibitor (a) its biaryl analogy (b). The superposition.

2 ˚HOP- RING CLOSING AND RING OPENING-

Opening and closing of ring is an approach for enhancing physicochemical features of a molecule. Ring opening and closure alters the flexibility of molecule [1].

Ring closure- Intramolecular hydrogen bonds

(HBs) generally intimate where to close a ring. The below example shows a possible hydrogen bonding among the alkoxy compound and biaryl group [4]. Most common concept comprises conversion of an alkyl chain to cyclic hexane ring, converting o-hydroxylbenzoyl to quinazoline, and altering an arylamine to linked ring structure[5]. There will be no entropy loss because of limited binding, as the intramolecular HBs have reduced molecular flexibility of the parent compound.

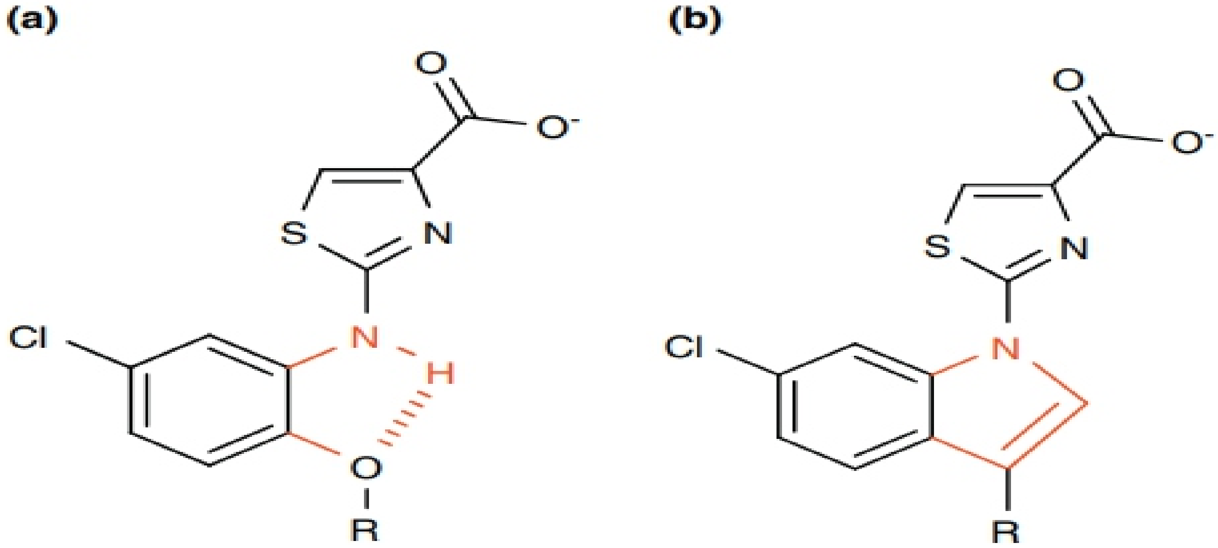

Figure 4: PG EP1 receptor antagonists: (a) biaryl amine series and (b) indole series.

Ring opening- Ring opening enhances the physicochemical as well as kinetic properties of a molecule. Pyridopyrimidinone [Fig (4a)] is an antineoplastic agent that specifically targets protein kinase; used for treating cancer, PD166285 target is used as a template for designing a novel tyrosine kinase inhibitor, the opening of pyrimidone ring migrates the N atom from the 1st to 5th position of the pyrimidine ring forming a six-membered ring [6]. The observed log P value of the urea derivative is 1 log unit less than that of the molecule which is derived [7].Many rings like aromatic rings, tends to reduce the physicochemical properties of drug. Adding a cycloalkane ring can reduce the molecular flexibility and maintain ADME properties.[8].

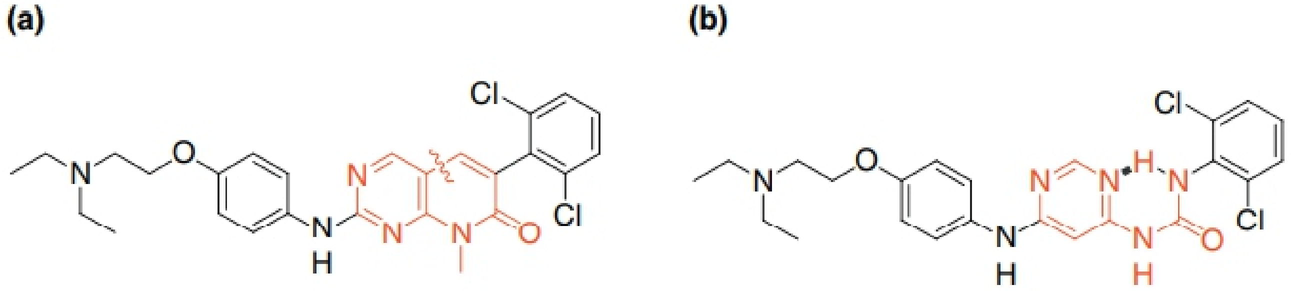

Figure 5: Tyrosine kinase inhibitors: (a) pyridopyrimidinone PD 166285 and (b) corresponding urea derivative.

3°HOP: PSEUDOPEPTIDES AND PEPTIDOMIMETICS-

We can design a small compound by taking into consideration the structural properties of peptides by use of conformations of a peptide which is vital. This complies with targets having protein-protein interactions [9]. Scaffold hopping is a characteristic process that converts peptides into small compounds. 2º structures for example alpha helix, beta-sheet and beta-gamma turn are commonly seen in peptide-protein interface [8].

4° HOP- TOPOLOGY/SHAPE-BASED SCAFFOLD HOPPING-

This type of scaffold hopping can be brought forth by virtual screening. Scaffold hopping concentrates mainly on optimizing new core structures, by ignoring probable clashing between adjacent side chains [1].

A 5,6-membered fused heteroaromatic scaffolds which represent some essential structural similarities for optimum anticancer activity depending on the lead containing an indole ring was optimized. Suitable replacement of -OCH_3 and trimethoxybenzoyl groups (required groups for anticancer activity)[10]. Amongst the molecules that are synthesized from the core scaffold, NH group at 1st position of the heteroaromatic core forms non potent anticancer activity and N atom at 7th position have a good stability. The 7-azaindole 9 and pyrazolo- [1,5-b]pyridazine 10 core comprised molecule have an effective anticancer activity than the indole core. Most remarkably, 7-azaindole core with 6-methyl substitution show a potent in vitro anticancer activity with good metabolic stability and solubility. Therefore, scaffold hopping strategy helps to design a compound which is an oral administrated drug that reaches systemic circulation , with reformed pharmacokinetic and pharmacodynamic properties and wider intellectual property right[10].

SCAFFOLD HOPPING VIA CHAIN SHORTENING AND CHAIN LENGTHENING:

Another effective strategy for obtaining a potential compound can be done by chain lengthening and shortening process. In pyrithiobac, a chain shortening process is observed where in the removal of diamino carbamate takes place by forming a sulfur bridge (Fig:6). In the next example chain lengthening is observed by adding O and CH_2in mandipropamide resulting in similar potent activity [2].

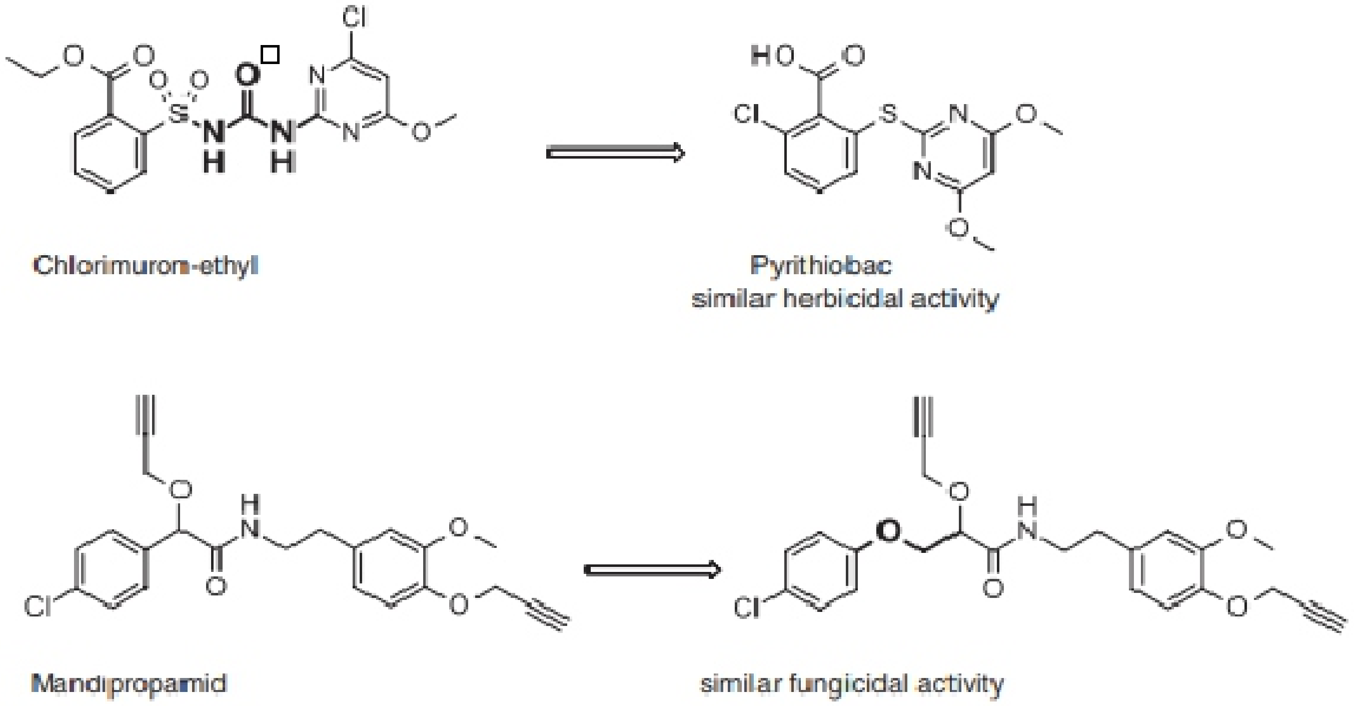

Figure 6: Scaffold hopping by altering chain shortening and chain lengthening process.

SCAFFOLD HOPPING BY TOPOLOGICAL PHARMACOPHORE SEARCH:

Pharmacophore features are very important as it gives us information about the chemical property of a drug having a specific biological activity which acts as a boon for determining the change we can make in the structure so it can be more acceptable with a potent activity, by considering two methods core replacement and virtual screening.

Virtual screening mainly focuses on finding novel chemical structures, core replacement is the one which is focusing only on the part of the molecule to be replaced, techniques have been invented based on two- or three-dimensional representations of molecular structures and various definitions of biophore / pharmacophores [9].

SCAFFOLD HOPPING BY CORE REPLACEMENT:

The program CAVEAT helps to understand the basics before carrying out the procedure. CAVEAT helps in identifying the framework of molecule make a template which can for understanding the position of a functional group in different confirmation. It searches 3D database for a compound It can classify structural backbone [5].

SCAFFOLD HOPPING BY VIRTUAL SCREENING:

Scaffolding is able to be completed via virtual screening. With help of its entire molecule not just its scaffold can be useful to undergo changes. A novel scaffolding idea could be confirmed irrespective of its chemical background. It aims at whole molecule rather than its core[5].

PHARMACOPHORE-BASED TWO-DIMENSIONAL DESCRIPTORS-

CATS (Chemically Advanced Template Search) is the first tool to be used for hopping studies [5].CATS retrieved a larger number of relevant structures than a conventional fingerprint-based search thus CATS seems to be a useful tool for database mining [1]

In a potential test, CATS was applied for predicting a novel cardiac Ca^{2+} channel blocking agents. Mibefradil, a well-known T-channel antagonist (IC50 1.7 mm) (Figure7) 1can be operated as the main structure for CATS, twelve compounds were chosen, among them nine compounds have potent activity (75%)[1].

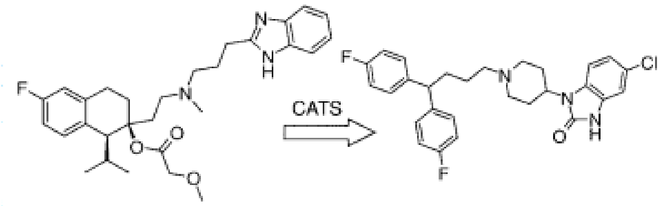

Figure7: Mibefradil structure derived from CATS

STUDY OF INSILICO SCAFFOLD HOPPING:

FIRST CASE STUDY- The quinoline-4-acyloxy scaffold is mainly taken into consideration for study. The Derivatives 1 and 2 both are strong-acting nor epinephrine analogs. The derivative 2 acts as a lead of quinolin-4-yloxy class and has less toxicity even at greater concentrations [11].

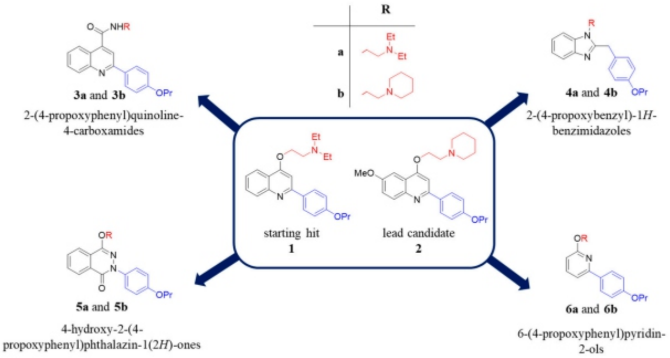

Figure 8: Structures of the derivatives 1 and 2, novel synthesized molecules obtained from the *in silico* scaffold hopping.

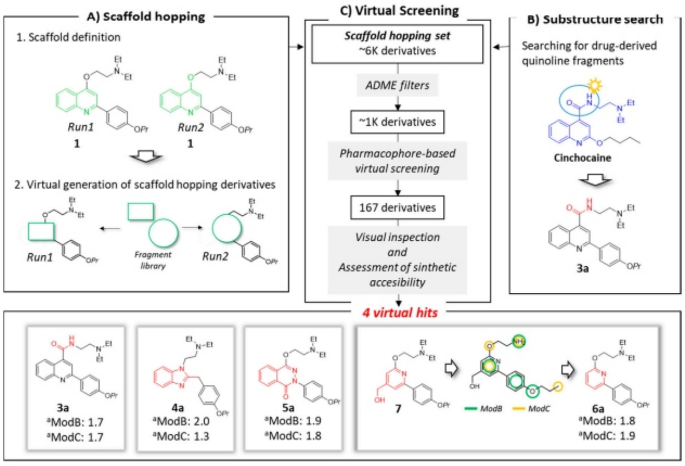

Figure 9: In silico scaffold hopping approach A): two runs performed on 1st derivative. green color indicates replacing is been carried B): previously obtained drug is been searched blue color is used for highlighting fragment C): virtual screening method, ModB and ModC are represented in green and yellow color shows its chemical properties.

Derivative 1 is selected as quinoline representative directing scaffold hopping approach Replacement of only the quinoline framework with 1456 smaller compounds, no changes were made at the 2nd and 4th position of quinoline ring (run-1).

Derivative 2 quinoline ring along with the oxygen on 4th position is considered for scaffold hopping (run-2). Then the hopping of both the derivatives is carried out independently by ligand based virtual screening [12].

Two libraries were merged to find 6393 scaffold hopping sets (panel C) in correlation with this a substructure search from 1456 compounds is carried out with quinolone ring as reference showing the previously available drug of cinchocaine mixed with the previous database and sets are formed.

In second, 1089 derivatives were successively virtually analyzed by using the two pharmacophore models as references. From a single pharmacophore, only compounds presenting a fitness score of 1.7 were preserved and select a compound fitting both models.

In third procedure, the obtained molecule (167 molecules) analyzed by observing a novel compound with a new scaffold with required pharmacophoric properties.

Considering in silico results, four hits obtained (3a–6a), each one having a contrasting core, were considered liable for the further experiment, hit 6a was customized initially from the 7th derivative, presence of methyl hydroxy group greatly reduces the chemical synthetic property of drug. Hence the hydroxy-methyl removal takes place, only the pyridine ring is considered to optimize compound 6a (Fig9) [12].

SECOND CASE STUDY- In this study PIM-kinase is antitumor drug target. Saluste and co-workers by keeping in consideration the primary activity and high target selectivity as well as ADMET properties found a scaffold by replacing imidazopyridazine scaffold with triazolopyridine [13].

Seed 1st has a 0.024 nM value of half-maximal inhibitory concentration (IC50). Seed 2nd with IC50=155 nM. Seed 3rd having IC50=130 nM, focused mainly on improving its pharmaceutical properties, using 500 molecules from three seed compounds for carrying out its molecular docking. As shown in table 2 potent novel hops are generated from every sample compound [13].

There are approximately 51,66,40 successful structurally hoped molecules from all three seeds. Seed 1 which shows high activity has total 11 compounds with good pharmacological activity and 102 of them have a good docking score, so here we can conclude that scaffold hopping is a dynamic tool in optimizing molecules [13].

CONCLUSION:

Numerous amounts of tools are present till date, but scaffold hopping is a very potent tool for the optimization of a novel potent compound. In this article most of the possible strategies of scaffold hopping are studied along with their successful implementation. Scaffold hopping mainly changes the backbone or framework of a molecule with similar biological activity**.** It has proved to be successful in optimizing the molecules in terms of their properties, activity, potency as well as opened doors for intellectual property.

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