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Classification of Scaffold Hopping Approaches

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Abstract

The general goal of drug discovery is to identify novel compounds that are active against a preselected biological target with acceptable pharmacological properties defined by marketed drugs. Scaffold hopping has been widely applied by medicinal chemists to discover equipotent compounds with novel backbones that have improved properties. In this review, scaffold hopping is classified into four major categories, namely heterocycle replacements, ring opening or closure, peptidomimetics, and topology-based hopping. The structural diversity of original and final scaffolds with respect to each category will be reviewed. The advantages and limitations of small, medium, and large-step scaffold hopping will also be discussed. Software that is frequently used to facilitate different kinds of scaffold hopping methods will be summarized.

Keywords

scaffold hopping; classification; drug design; similarity; ring opening; peptidomimetics

Introduction

In a modern drug discovery, biologically relevant compounds are usually generated from high throughput screening (HTS) or virtual screening (VS). For a new target, HTS might be the only way to identify bioactive compounds. However, for targets that are well known, retrieval of active compounds by screening tens of thousands to millions of structurally diverse compounds is neither economical nor efficient. Actually, due to the limited number of druggable targets [1,2], a large fraction of therapeutically interesting targets are not new and exploration of novel chemistries for these targets could be based on known ligands or ligand-protein complex structures. Historically, many marketed drugs were derived from other known drugs or natural products [3,4]. Thereafter, an important question arises in how to design economically viable drugs based on this knowledge while at the same time maintaining or improving efficacy and pharmacokinetic (PK) profiles of existing therapies by designing novel structural scaffolds (chemotypes).

Scaffold hopping, also known as lead hopping [5,6], is one strategy for discovering structurally novel compounds [7]. Scaffold hopping methods typically start with known active compounds and end with a novel chemotype by modifying the central core structure of the molecule [3]. Although the concept of scaffold hopping is relatively young [8,9], the strategy has been applied from the beginning of drug discovery. Not only applied to jumpstart a project with known ligands, scaffold hopping is also widely used in lead optimization approaches [10,11]. Since many compounds in corporate libraries are failed

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compounds with poor physicochemical and PK properties, the hit molecules from HTS can inherit these unfavorable properties. These properties depend on how mature the compounds are in the drug discovery pipeline. Sometimes, modification of side chains is sufficient to overcome the undesirable properties associated with the parent molecule, while at other times, the core structure or the scaffold of the parent molecule has to be modified.

In the last decade, published research works on scaffold hopping have increased exponentially [10,11], yet limited effort has been made to characterize the frequently used scaffold hopping methods. In this review, scaffold hopping is classified into four major categories – heterocycle replacements, ring opening or closure, peptidomimetics, and topology-based hopping. The structural diversity of original and final scaffolds with respect to each category will be reviewed. The advantages and limitations of small, medium, and large-step scaffold hopping will also be discussed. The small step hops, represented by swapping carbon and nitrogen atoms in an aromatic ring or replacing carbon with other hetero-atoms in a ring, result in a low degree of structural novelty. Topology based hops, on the other hand, always lead to a high degree of novelty. Significantly more examples of small to medium step scaffold hopping are found in publications. This illustrates the tradeoff between degree of structural novelty and success rate of achieving comparable biological activities [3]. There are many methodologies that enable the generation of scaffold hops. These include use of 2D fingerprints and 3D pharmacophores in the context of virtual screening. These “enabling” technologies are out of the scope of this review. The interested reader can find illuminating discussions on these topics in the following references [5,12–18].

History

The concept of scaffold hopping was introduced in 1999 by Schneider et al., as a technique to identify isofunctional molecular structures with significant different molecular backbones [9]. The simple definition emphasized two key components of scaffold hopping – different core structures and similar biological activities of the new compounds relative to the parent compounds. The two requirements seem to conflict with the similarity property principle, which states that compounds with similar chemical structures usually possess similar physicochemical properties and biological activities [19]. Actually, the principle does not exclude the possibility of structurally diverse compounds from binding to a same target. The similarity property principle is generally held since ligands that can fit in the same pocket should share certain structural similarity, i.e., similar shape and similar electropotential surface, although the ligands may belong to different chemotypes. Due to the fact that the repulsive penalty in the Lennard-Jones potential is extremely sensitive to the interatomic distances, the landscape of activity is far from linear – addition or removal of a small methyl group may result in large changes in biological activity [20], while the similarity metrics are insufficient in reflecting this nonlinearity. In addition, the flexibility of both proteins and small molecules further complicates the relationship between similarity and activity. Nevertheless, the similarity property principle is still the pillar of modern drug discovery, such as structure-activity relationships (SAR), and scaffold hopping is not an exception of this principle.

Historically, a large fraction of marketed drugs are derived from natural products, natural hormones, and other drugs through scaffold modification [4]. Revisiting these successful examples and other newly published examples supplies useful guidance for medicinal chemists to create novel chemical entities based on known bioactive molecules.

Morphine and tramadol

Opium, one of the earliest known drugs, has been used for over a thousand years for relief of pain. Morphine, the major component of opium, is a potent analgesic, but its medical use is limited by its addictive potential. Morphine acts on the μ–opioid receptor to increase tolerance to painful stimuli. Besides its addictive liability, morphine has other adverse side effects, including nausea, vomiting, and respiratory depression. Morphine is a rigid 'T' shaped molecule (Fig. 1a). By breaking six ring bonds and opening up three fused rings, the new drug Tramadol is more flexible, resulting in reduced potency and reduced side effects (Fig. 1b). The 2D structures of Morphine and Tramadol are very different, but 3D superposition of both molecules, as calculated by using the Flexible Alignment program in Molecular Operating Environment (MOE) [21], demonstrates that the key pharmacophore features are conserved. Figure 1c shows the shared spatial position of the positively charged tertiary amine, the aromatic ring, and the hydroxyl group attached to phenyl ring (the methoxyl group in Tramadol is demethylized by CYP2D6). Although Tramadol is only one-tenth of the potency of Morphine, it is almost completely absorbed after oral administration, and lasts for up to 6 hours. The transformation from morphine to tramadol by ring opening is one of the earliest examples of scaffold hopping [4].

Antihistamines

Histamine is an organic nitrogen compound derived from decarboxylation of the amino acid histidine [22]. It has multiple physiological functions, including triggering the inflammatory response and regulating immune response, sleep, and allergies [22]. The classical antihistamines possess two aromatic rings joined to one carbon or nitrogen atom and together with one positive charge center. This is represented by the structure of Pheniramine (Fig. 2a). Pheniramine, also known as Avil, is an antihistamine used to treat allergic conditions such as hay fever or urticaria [23]. It competes with histamine for histamine H1-receptor sites, to reduce the intensity of allergic reactions and tissue injury response involving histamine release. An analog of Pheniramine called Cyproheptadine, has significantly improved binding affinity against the H1- receptor. This was achieved by locking both aromatic rings of Pheniramine to the active conformation via ring closure, and by introducing the piperidine ring to further reduce the flexibility of the molecule (Fig. 2b). This rigidified molecule is also better absorbed. In addition, the structural changes achieve other medical benefits in the prophylaxis of migraine, because Cyproheptadine can antagonize the 5-HT2 serotonin receptor. Isosteric replacement of one phenyl ring in Cyproheptadine with thiophene produces Pizotifen (Fig 2c), which proves to be a better medicine for treatment of migraine [24]. Azatadine (Fig 2d) was developed by the Schering-Plough Corporation as a typical potent sedating antihistamine [25]. It is formed from Cyproheptadine by replacing one phenyl ring with pyrimidine that improves the solubility of the molecule. The 2D structures are different, but 3D superposition shows that the pharmacophore orientation is similar, e.g., the spatial position of the basic nitrogen and the two aromatic rings overlap (Fig. 2e and 2f).

These antihistamine examples show that small changes in molecular structures can result in different activity profiles, thus different medical uses. It also clearly demonstrates that reduction of molecular flexibility can increase the potency of molecules, presumably by reducing entropy loss upon binding to the targets.

Classification of Scaffold Hopping Approaches

According to the definition of scaffold hopping, derivatives obtained from the parent compounds have novel core structures. The question is how different the derivative molecules must be from their parents in order for the evolution to be classified as scaffold

hopping. In other words, how novel is novel? Boehm *et al* classified two scaffolds as different if they were synthesized using different synthetic routines, no matter how small the change might be [3]. This statement has been proven true in many cases where the chemical structures are closely related but different patents can be claimed, or different new drug applications can be approved by the Food and Drug Administration (FDA). For example, the major structural variation between the two phosophodiesterase enzyme type 5 (PDE5) inhibitors Sildenafil and Vardenafil is the swap of a carbon atom and a nitrogen atom in the 5–6 fused ring, (Fig. 3a and 3b) but the difference is enough for the two molecules to be covered by different patents [26]. The two cyclooxygenase II (COX-2) inhibitors Rofecoxib (Vioxx™) and Valdecoxib (Bextra™) differ by only the 5-member hetero rings connecting the two phenyl rings (Fig. 3c and 3d), yet they were sold by Merck and Pharmacia/Pfizer separately [27].

We rationalize the concept of scaffold hopping by focusing on the degree of change associated with the original parent molecule. Minor modifications like replacing or swapping carbon and heteroatoms in a backbone ring, are classified as a 1° hop. More extensive ring opening and closures is classified as a 2° hop. Replacement of peptide backbones with non-peptic moieties falls into the category of a 3° hop. Finally a complete new chemical backbone that only retains interactions is characterized as a 4° hop.

1° hop: Heterocycle replacement

The heterocycles functioning as cores of drug molecules usually provide multiple vectors projecting to different directions. Replacing the C, N, O, and S atoms in a heterocycle, while maintaining the outreaching vectors can result in novel scaffolds. Improved binding affinity is likely to be achieved if the heterocycle is directly involved in interactions with the target protein.

CB1 Inhibitors—Rimonabant (Acomplia™) is an anorectic anti-obesity drug produced and marketed in Europe by Sanofi-Aventis. Its inverse agonist effect on the cannabinoid 1 receptor (CB1) causes a reduction in appetite. Rimonabant was the first selective CB1 receptor antagonist to be approved for use in humans. However, the anti-obesity drug failed to win approval from the FDA to enter the US market, due to safety concerns. Boström's group at AstraZeneca initiated a scaffold hopping approach, attempting to discover novel CB1 antagonists with improved physicochemical and Distribution, Metabolism, and Pharmacokinetic (DMPK) properties [28]. They tried to replace the methylpyrazole core in Rimonabant with a range of five- and six-member rings, including thiazoles, pyrroles, and pyrazines (Fig. 4) [29,30]. The newly designed compounds were ranked by ease of synthesis and shape similarity against Rimonabant, as computed with ROCS (Rapid Overlay of Chemical Structures) [31]. All three new scaffolds resulted in novel classes of CB1 receptor antagonists, but their safety profiles have not been fully examined [28].

CB2 Inhibitors—Sharing 44% sequence similarity with the CB1receptor, the CB2 receptor is expressed primarily in cells of the immune system [32]. Modulation of the immune system might be realized via antagonists and inverse agonists of the CB2 receptor. Merck scientists [33] discovered a potent and selective triaryl bis-sulfone CB2 inhibitor a few years ago (Fig. 5a). In a recent backup program, they attempted to remove some unfavorable activities, such as calcium channel blockage and cytochrome P450 2C9 inhibition, associated with the triaryl compound. In order to achieve this goal, they searched for less hydrophobic analogs. By replacing the central phenyl ring in the triaryl compound (Fig. 5a) with spirocyclopropyl piperidine (Fig 5b), the biaryl derivative demonstrated the same potency against CB2 and selectivity against CB1. This is indicated by their nicely superimposed structures as shown in Figure 5c. Furthermore, the rat calcium channel

affinity was reduced from 0.5 μM to 8 μM, and the 2C9 activity reduced from 3.5 μM to 30 μM. The replacement of the third aromatic ring with the saturated ring system also makes the molecule more druglike [34,35], with calculated logP value dropping from 2.81 to 1.48 [36].

COX-1 and COX-2 inhibitors—Non-steroidal anti-inflammatory drugs (NSAIDs) function by inhibiting the enzyme cyclooxygenase (COX), which catalyzes the biosynthesis of prostaglandins (PGs) from arachidonic acid (AA). There are two enzymes in humans that catalyze the first step in the biosynthesis of PGs, namely COX-1 and COX-2. Although catalyzing the same reaction, COX-1 and COX-2 are different in sequence (~60% identity), tissue distribution, and physiological function. The COX-1 isozyme plays a role in gastroprotection and vascular homeostasis, while the COX-2 isozyme is mainly involved in inflammatory processes [37,38]. Selective inhibition of the COX-2 isozyme could circumvent the adverse ulcerogenic effects associated with classical NSAIDs, such as aspirin and ibuprofen [39]. Although COX-1 and COX-2 only share 60% sequence homology, the protein backbones, especially the ligand binding sites, are very similar to each other (Fig. 6a) [40,41]. On the other hand, the subtle structural differences at the ligand binding sites are sufficient to generate COX-2 selective inhibitors [42].

The first COX-2 selective inhibitor, DuP 697 (Fig. 6b), was discovered in 1990 [43]. The structure of DuP 697 was the template for the design of the diarylheterocyclic family of selective COX-2 inhibitors. These include later marketed drugs Celecoxib and Rofecoxib (Fig. 6c and 6d). Dup 697, however, failed to reach the market due to safety issues [39]. Rofecoxib, also known as Vioxx, was withdrawn from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use, while its close analogue, Celecoxib, is still in use for the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation, and menstrual symptoms.

The three diarylheterocyclic COX-2 selective inhibitors differ from each other mainly in the backbone heterocyclic rings (Fig. 6b-6d). Their activity levels against COX-2 are comparable [39] but their pharmacology is totally different. It is not yet fully understood whether the relative selectivity levels or the kinetic behavior of inhibition causes the differences [40,44], but the effects of heterocyclic replacement on the pharmacokinetic (PK) and pharmacodynamic (PD) behavior of a compound are clearly demonstrated in this example. This example shows that the impact of 1° scaffold hopping on the mechanism of action (MOA) of a drug molecule is not always predictable. However, 1° scaffold hopping is a good strategy to improve the success rate in drug discovery.

Software—For 1° hopping, the software MORPH is a useful tool for generating novel aromatic rings systematically without changing the coordinates of the ring atoms [45]. MORPH can generate new molecules by altering individual rings and fused ring systems, while at the same time maintaining user-defined constraints. To overcome the potential issues regarding synthetic feasibility and chemical stability associated with creating novel aromatic systems systematically [46], natural products and marketed drugs can serve as templates for generating a pool of druglike scaffolds [47]. Another molecular design software package, Recore [48], is also based on this kind of scaffold library generation. A comprehensive list of software used in scaffold hopping was presented by Brown *et al* [10,16].

2° hop: Ring opening and ring closure: Pseudo ring structures

Most druglike molecules contain at least one ring system, so ring opening and ring closure are two immediate strategies to create novel scaffolds. Since molecular flexibility

contributes greatly not only to the entropic component of the binding free energy, but also to membrane penetration and absorption [49], ring opening and closure are useful strategies for improving the drug-like properties of molecules. Ring opening and closure manipulate the flexibility of a molecule by controlling the total number of free rotatable bonds. This can be accomplished in a variety of ways.

Ring closure—Intramolecular hydrogen bonds (HB) usually offer direct hints on where to close a ring, as shown in following examples. Intrigued by the potential intramolecular HB between the *o*-alkoxy group and biaryl NH (Fig. 7a), a Glaxo SmithKline (GSK) group synthesized a series of indole compounds (Fig. 7b) as Prostaglandin EP1 receptor antagonists [50]. The ring closure design successfully locked the molecule into a bioactive conformation. One of the resulting indole compounds (Fig. 7b), where R was *iso*-butyl, showed low nM and sub-nM activities in binding and functional EP1 antagonist assays [50].

Other frequently used ring closure ideas include converting an alkyl chain to cyclohexane, piperizine or piperidine [51], converting an *o*-hydroxylbenzoyl group to quinazoline [52], and converting an arylamine or arylamide to a fused ring system [53].

Ring Opening—Although ring closure has a positive impact on the binding free energy, it does so by producing potentially negative impacts on solubility and other ADME properties [34]. In order to overcome the adverse effects of too many rings in a molecule, medicinal chemists may practice ring opening, in order to enhance the druglikeness of molecules.

Pyridopyrimidinone is a typical moiety of protein kinase inhibitors. PD166285 (Fig. 8a), a 6-aryl substituted pyridopyrimidinone, is a broad-spectrum tyrosine kinase inhibitor [54]. In an attempt to design novel tyrosine kinase inhibitors using PD166285 as a template, Furet *et al.* opened up the pyrimidone ring and moved the nitrogen atom in position 1 of the pyrimidine ring to position 5 to form a pseudo 6-member ring with the adjacent urea through intramolecular hydrogen bonding (Fig. 8b) [55]. Since the urea in pyrimidinyl urea did not adopt the low energy extended conformation, *ab initio* calculations and data mining were carried out to confirm that the pseudo cyclic conformation was favorable. The pseudo ring design concept was further supported by the assay results – the pyrimidinyl urea compound (Fig. 8b) exhibited submicromolar inhibition against several tyrosine kinases, such as c-Src, EGFR, and c-Abl [55]. Although the physicochemical properties of the pseudo ring compound and its parent bicyclic compound were not mentioned in the paper, the calculated logP value of the urea derivative is 1 log unit lower than its parent compound [36].

In another approach involving novel antiangiogenic agents, a Novartis team opened the phthalazine ring in a known dual KDR and Flt-1 inhibitor PTK787/ZK222584 (Fig. 9a) [56]. The anthranilic amide moiety is ready to form a six-member pseudo ring through intramolecular hydrogen bonding (Fig. 9b). Ring opening resulted in minimal changes on activity and selectivity [56]. A close analogue of this compound, Motesanib/AMG 706, (Fig. 9c) was successfully transitioned to clinical trials [57]. This example demonstrates that ring opening was not only a useful strategy to generate new chemical classes from templates, but also a promising method to improve druglike properties.

Ring opening and closure—Ring opening and ring closure can be applied simultaneously on the same molecule, which may cause ring shift or ring migration [58]. MK2 (MAP (mitogen-activated protein) kinase-activated protein kinase 2) plays a crucial role in signaling and synthesis of TNFα (tumor necrosis factor α). Potent and selective MK2 inhibitors can potentially be developed into anti-cancer drugs. To discover novel MK2 inhibitors, Velcicky's group opened up the pyrimidinone ring of the parent pyrrolo-pyrimidone structure (Fig. 10a) while maintaining the attached amide group, and then

swapped the 5- and 6-member rings [59]. The resulting compound (Fig. 10b) was 4-fold less potent than its parent compound. Re-connecting the amide group to the phenyl ring to reduce the flexibility of the amide boosted the affinity a factor of 25. The final dihydroisoquinolinone compound (Fig. 10c) showed 84 nM potency against MK2 [59]. Although there is significant structural variation between the original and final compounds, both scaffolds overlaid very well (Fig. 10d). Introduction of the two sp^3 carbon atoms in ring closure increased the saturation level of the molecule, thus enhancing the possibility of the compound becoming a drug [60].

Another special ring closure yields macrocyclic molecules. Macrocycles here refer to those molecules with rings containing nine or more atoms. This kind of ring closure is used to constrain the conformation [61–64]. Since the whole molecule is changed from a linear structure to a cyclic structure, macrocyclic ring closure is a special kind of scaffold hopping.

In summary, ring closure can potentially lock a flexible molecule into its bioactive conformation, thereby reducing the entropy penalty upon interacting with the target protein. On the other hand, too many rings, especially aromatic rings, in one molecule tend to reduce the druglikeness of the molecule [60]. Introduction of saturated ring systems can both suppress the molecular flexibility and maintain druglikness, but the synthetic feasibility will inevitably suffer from newly introduced chiral centers or spiro-like structures [65].

Software—There is no particular software available to generate ring opening or ring closure design ideas. Since variation of the ring system in a molecule is usually associated with conformational changes, the Cambridge Structural Database (CSD) [66,67] is a valuable source for low-energy molecular conformations that can be used to validate design concepts [68].

3° hop: Pseudopeptides and Peptidomimetics

Biologically active endogenous peptides, such as peptide hormones, growth factors, and neuropeptides play a vital biological function in our bodies. Imbalance of these peptides can cause different human diseases, including diabetes, cancer, osteoporosis, and endometriosis [69]. The development of peptides into clinically useful drugs is largely hampered by their poor metabolic stability and low bioavailability [69]. Design of small molecules to mimic the structural features of peptides using active peptide conformations as templates has shown promising results for some challenging targets [70,71]. The application has been extended to targets involved in protein-protein interactions (PPI), where small molecules are designed to mimic the interacting moieties of proteins. The major goal of peptide-based drug discovery is to reduce the peptide character in order to enhance the resistance to proteolysis, while maintaining the key chemical features for molecular recognition. Scaffold hopping is a typical method used to carry out the peptide to small molecule transition.

Secondary structures such α–helices [72–74], β-sheets [75], and β/γ–turns [76] are frequently observed at the interfaces of peptide-protein and protein-protein interacting partners. Synthetic structures have been designed to mimic these secondary structures [77–80]. In these designs it is important that the synthetic scaffolds position the side chains consistently with the helical and turn structures. Maintaining the backbone hydrogen bonding interactions is the major task for β-sheet mimetics. These strategies have been reviewed elsewhere [71], so the focus of this review will be placed on the scaffold hopping designs where derivative molecules are structurally similar to their parents.

Triggering apoptosis—Apoptosis, or programmed cell death, plays a major role in maintaining homeostasis and removal of damaged or malignant cells [81]. Imbalances in apoptosis pathways are linked to several therapeutically important disease areas, including

oncology, cardiovascular diseases, and neurodegenerative diseases [82–85]. Smac (the second mitochondrial activator of apoptosis) interacts with XIAP (X-linked inhibitor of apoptosis) by inserting its N-terminal sequence, AVPI (ALA-VAL-PRO-ILE) (Fig. 11a) into the XIAP-caspase-9 interaction pocket, thus releasing capase-9 and causing cell death. Modified peptides and peptide mimetics have been designed to compete with AVPI/Smac in order to cause apoptosis. Wist *et al*. replaced one peptide bond with an oxazole ring (Fig. 11b), aiming at enhancing druglikeness by reducing the peptide character [78]. The resulting Smac mimics, AoxSPF, AoxSPW, AoxSPY, and AoxSPI, could bind to the Baculovirus Inhibitor of apoptosis protein Repeat 3 (BIR3) domain of XIAP with much lower binding affinity. AVPI interacts with BIR3-XIAP mainly through backbone hydrogen bonding, forming an anti-parallel β–sheet structure. The oxazole replacement changed the hydrogen bonding features of both carbonyl and amine in the peptide bond (Fig. 13), resulting in the loss of key backbone interactions. Indeed, the crystal structure of AoxSPW bound to BIR3-XIAP indicated that the compound formed two fewer HBs with the protein [78].

Cohen's group [86] utilized the software CAVEAT [87] to generate design ideas for small molecules using the crystal structure of a modified tetrapeptide, AVP-2,2-diphenylamine (Fig. 11c), as a template [88]. The original CAVEAT hits were identified as either synthetically infeasible or chemically unstable, but the bicyclic motif inspired the authors to manually search the literature for similar scaffolds. The resulting azabicycloocatane compound (Fig. 11d) demonstrated a better docking score than the tetrapeptide (Fig. 11a), and high binding affinities against XIAP, ML-IAP, and c-IAP with K_i values of 140, 38, and 33 nM, respectively [86]. Replacing the side chain of VAL with t-butyl, and PRO with azabicycloocatane, improved the PK properties and bioavailability of the compound [86]. Similar bicyclic scaffolds were observed in design of the inhibitors of prolyl oligopeptidase (POP), a target for the treatment of neurodegenerative and psychiatric diseases [89].

Angiotensin II—The octapeptide hormone angiotensin II (Ang II) is involved in a range of physiological activities, such as vasoconstriction, aldosterone release, cell differentiation, and tissue repair, through interaction with angiotensin 1 and 2 (AT_1 and AT_2) receptors [90,91]. Ang II, given by the sequence DRVYIHPF (Fig. 12a), is believed to adopt a turn structure centered at Tyr at position 4 while activating the AT_1 receptor [92–94]. Several β–turn and γ –turn mimetics have been designed as Ang II receptor ligands [95–97]. By replacing the central residues Tyr at position 4 and Ile at position 5 with a benzodiazepine (Fig. 12b), a well- known β –turn mimetic scaffold [98], the new pseudopeptide exhibited high binding affinities against both AT_1 and AT_2 receptors with K_i values of 14.9 nM and 1.8 nM respectively [97]. The benzodiazepine-based β–turn design can position key residues of Ang II into locations similar to that of γ–turn mimetics [97,99]. The metabolic stability of the pseudopeptides is always a concern due to the remaining peptide bonds in the molecules, but it was not discussed in the paper.

Software—Recore [48] and CAVEAT [87] are useful for designing suitable scaffolds to replace parts of peptides. Pharmacophore modeling packages by Chemical Computing Group [100], Accelrys [101] and Schrödinger [102] are also widely applied in peptidomimetic design [70,103,104].

4° hop: topology/shape-based scaffold hopping

Successful stories of topology/shape-based scaffold hopping are rare in the literature. One possible reason is that many attempts have been made, but most failed and thus not published. Another possibility is when the new chemotype is significantly different from its template, scientists might consider the process as virtual screening, rather than scaffold hopping. This type of scaffold hopping can be generated using virtual screening, as

demonstrated in the following examples, but we wish to retain the distinction in that virtual screening is a technology that enables scaffold hopping. Ultimately, scaffold hopping focuses on discovering novel core structures, usually ignoring potential conflicts between side chains and targets, while virtual screening aims at whole molecules as hits.

Lipoxygenase inhibitors

Schneider and coworkers identified a novel 5-lipoxygenase (5-LO) via similarity searching of a natural product collection and natural product-derived combinatorial libraries. The scaffold hopping approach, enabled by similarity search, was performed with topological pharmacophore models derived from 43 known 5-LO inhibitors [105]. The scaffold of the best hit was not represented in any of the known inhibitors, and the overall structure was significantly different from the query molecules.

ZIPA-FtsZ inhibitors

To pursue novel antibiotics effective against resistant mutants, a Wyeth team chose to interrupt cell wall biosynthesis by targeting bacterial ZipA-FtsZ protein-protein interactions [106–108]. The template they chose was a weak HTS hit (Fig. 13a), possessing potential toxicity and intellectual property issues. The use of a shape-based ROCS search with compound 13a as template led to the discovery of novel scaffolds with low 2D similarity against their template. This implies that these ROCS-identified scaffolds could not be found by 2D search methods. The ROCS hits were less potent, but they did not show toxicity and intellectual property issues associated with pyridyl-pyrimidine core of molecule 13a [108]. One of the ROCS hits (Fig. 13b) was co-crystallized with ZipA. The binding geometry of compound 14b showed similarities to the geometry of template 13a used in the ROCS search.

BCL-xl (B-cell lymphoma-extra large) inhibitors—Sun and his colleagues [109] at Roche discovered a new series of BCL-xl inhibitors using the published structure of ABT-737 (Fig. 14a) as a template [110]. They attributed the tight binding between ABT-737 and BCL-xl to the π– π stacking network formed between the ligand and the protein (Fig. 14b), and attempted to identify a molecular scaffold to mimic the π – π stacking topology. A CSD [67] query was created to capture the key topological requirements, including the angle between the two aromatic planes and the distance between the centroids of both aromatic planes (Fig. 14c). Searching nearly a half-million crystal structures in CSD led to a novel scaffold mimicking the π– π stacking feature in ABT-737 (Fig. 15a). Taking advantage of transferable SAR, ABT-737 side chains were added to the novel scaffold to achieve comparable binding benefits as its parent template. Finally, with less than a few dozen compounds synthesized, the Roche scientists discovered a series of BCL-xl inhibitors, among which the most active inhibitor (Fig. 15b) was reported equi-potent to ABT-737, but more than 200-daltons smaller and much less hydrophobic.

Software—The CSD is not just a crystal structure database of small molecules, it also has a powerful search engine and tools for query construction and structure mapping. The CSD package is a suitable topology hopping tool, by enabling users to define different topological requirements, including dihedral angle, point-to-plane distance, and plane-to-plane angle [66]. ROCS is another powerful topology-based scaffold hopping tool [108]. The grid-based method SHOP has also been used to identify novel scaffolds with significant different chemotypes from the queries they were derived from [111,112].

Summary

The pharmaceutical industry is facing dramatic challenges, primarily caused by reduced output of new medicines, drug price pressures, and global economic downturn [113]. On the other hand, the unmet medical needs for rare and neglected diseases are not adequately addressed [114]. The situation strongly calls for more efficient ways to accelerate the pace of drug discovery. With the explosion of drug discovery related data in recent years [115–121], the mission becomes possible by making the best use of the available information. More recently, the National Institutes of Health Chemical Genomics Center (NCGC) prepared a complete collection of all approved drugs – the NCGC pharmaceutical collection (NPC) [122], and the NPC is being screened against multiple drug targets in a quantitative high throughput screening (qHTS) format [123]. The high quality titration-based assay results will supply sufficient templates for scaffold hopping approaches. Scaffold hopping, already widely accepted by medicinal chemists as a new design idea generator, is a proven tool useful for overcoming undesirable properties, such as poor exposure, toxicity, or unfavorable intellectual property (IP) position [16]. This paper summarizes strategies commonly used in scaffolding hopping, and it classifies these methods into four basic categories (Table 1). Successful stories are highlighted for each category, while the limitations are also analyzed. Currently, scaffold hopping efforts are largely unsupervised and focus on novelty of derivative compounds. Future software developments in scaffold hopping also need to incorporate guiding elements for achieving acceptable pharmacological properties, such as improved absorption, better PK profiles, and reduced toxicity. This would allow for a generalized scaffold-hopping approach that maximizes the chemical diversity while maintaining or even improving the biological activity and pharmacological profiles of the original drug.

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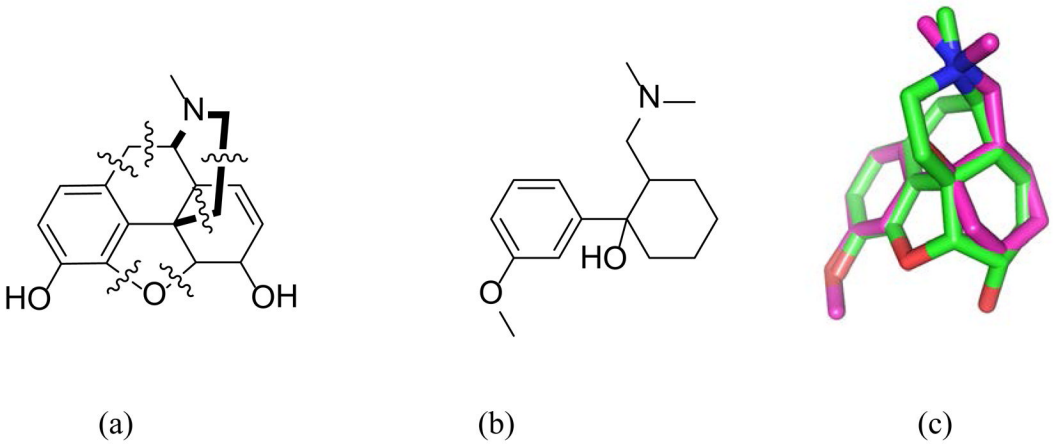


(a) (b) (c)

Figure 1.
Structures of pain killing drugs (a) Morphine, (b) Tramadol, and (c) 3D superposition of (a) in green and (b) in magenta.

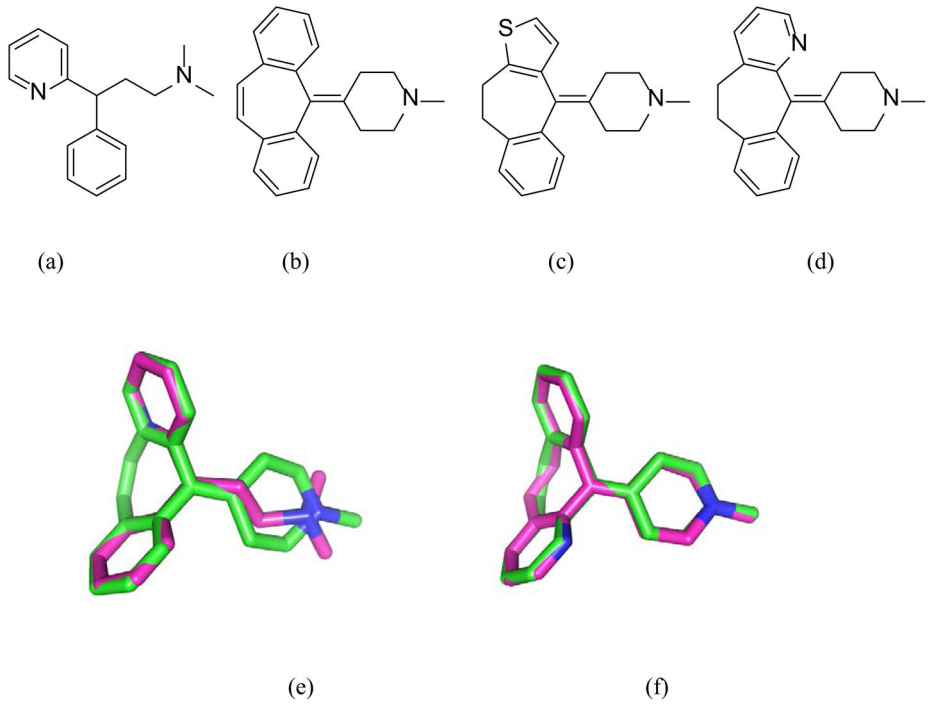


Figure 2.
Structures of antihistamine drugs (a) Pheniramine, (b) Cyproheptadine, (c) Pizotifen, (d) Azatadine, (e) superposition of drugs (a) in magenta and (b) in green, and (f) superposition of drug (b) in green and (d) in magenta.

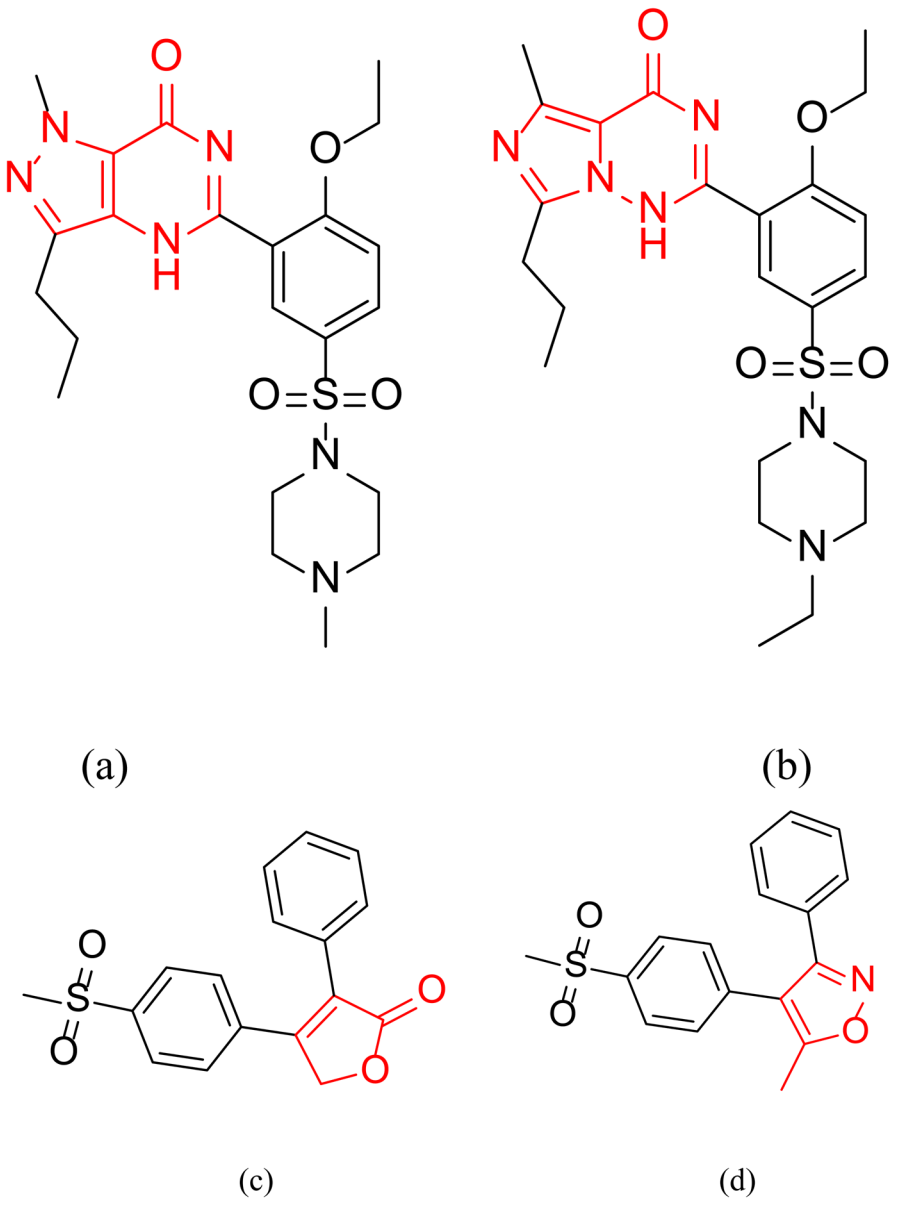


Figure 3.
Structures of phosophodiesterase enzyme type 5 (PDE5) inhibitors (a) Sildenafil, (b) Vardenafil, and cyclooxygenase (COX-2) inhibitors (c) Rofecoxib and (d) Valdecoxib.

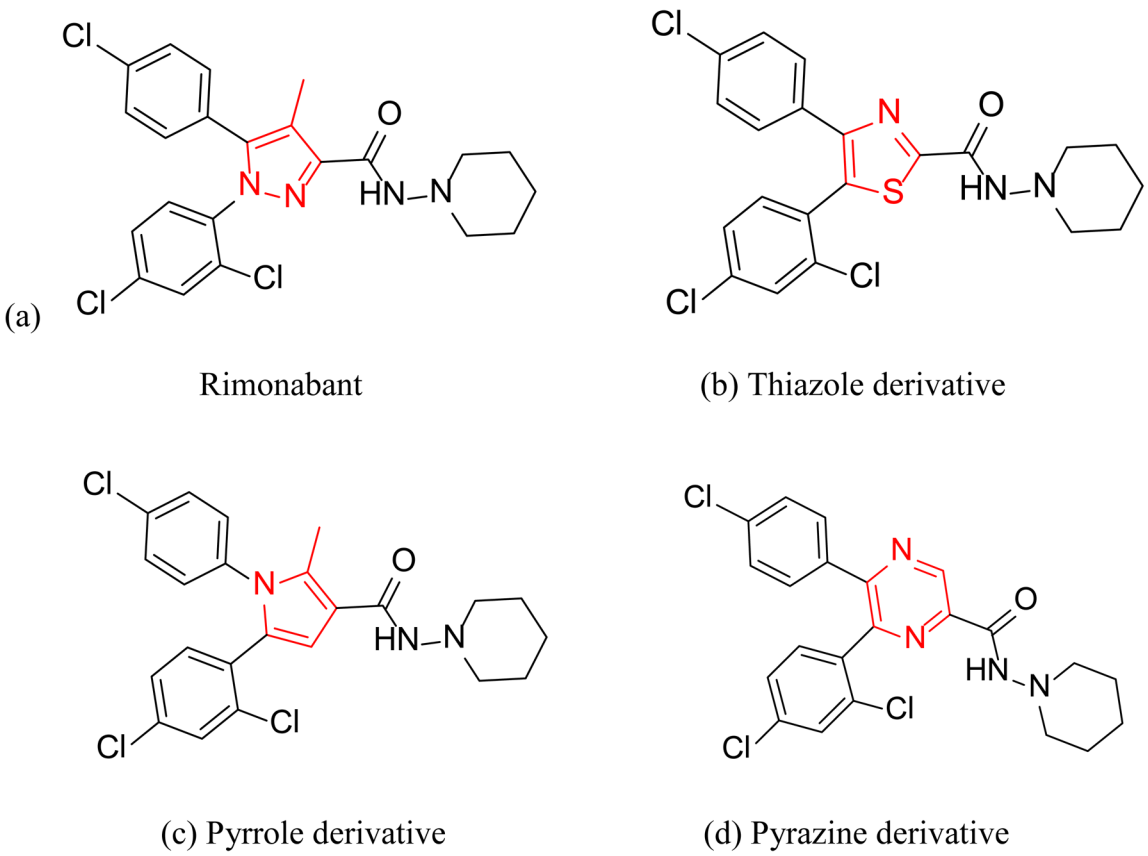


Figure 4.
Structure of the Cannabinoid 1 (CB1) antagonist Rimonabant and its derivatives.

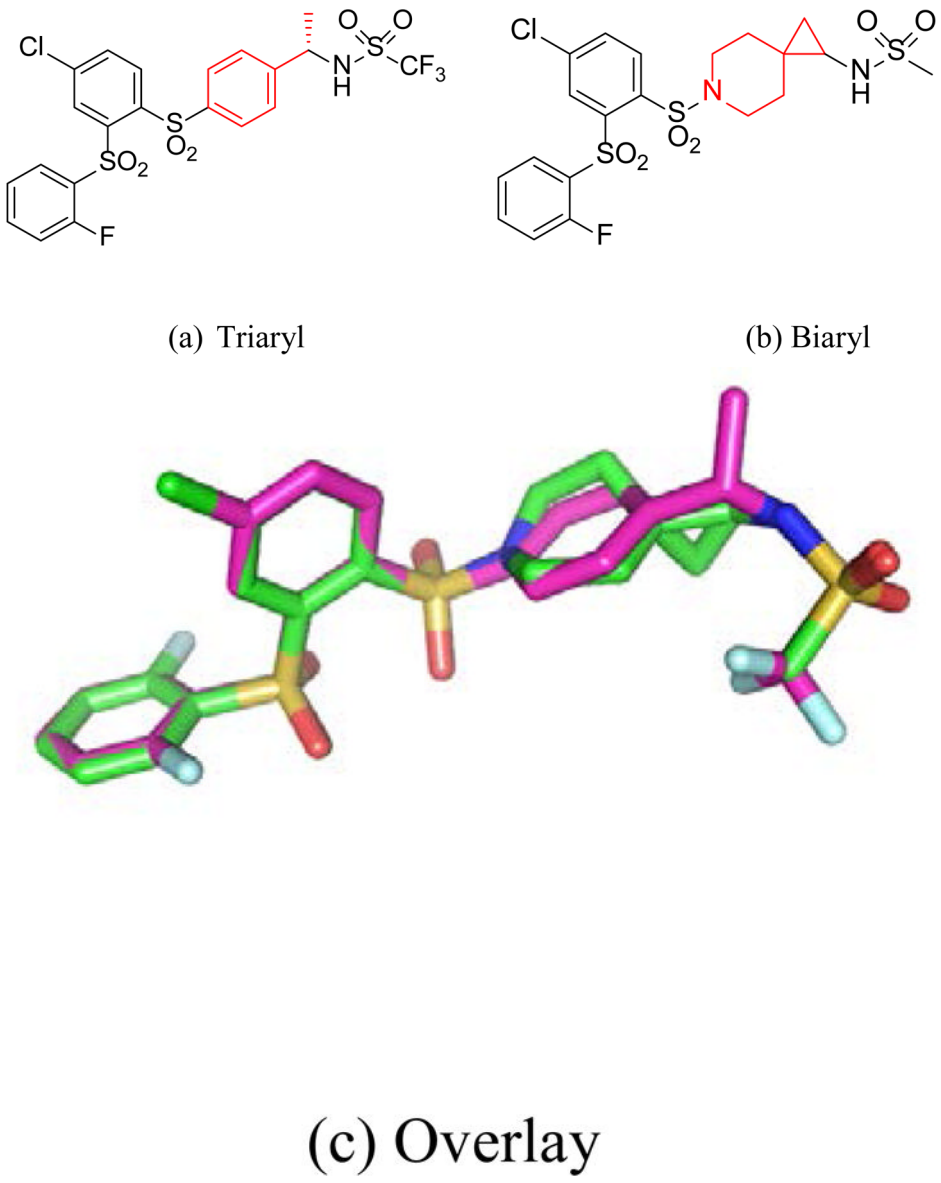


Figure 5.
Structures of a triaryl bis-sulfone Cannabinoid 2 (CB2) receptor inhibitor (a) and its biaryl analog (b). The superposition of both structures (c) (molecule (a) in magenta and (b) in green) was calculated by using the Flexible Alignment program in MOE [21].

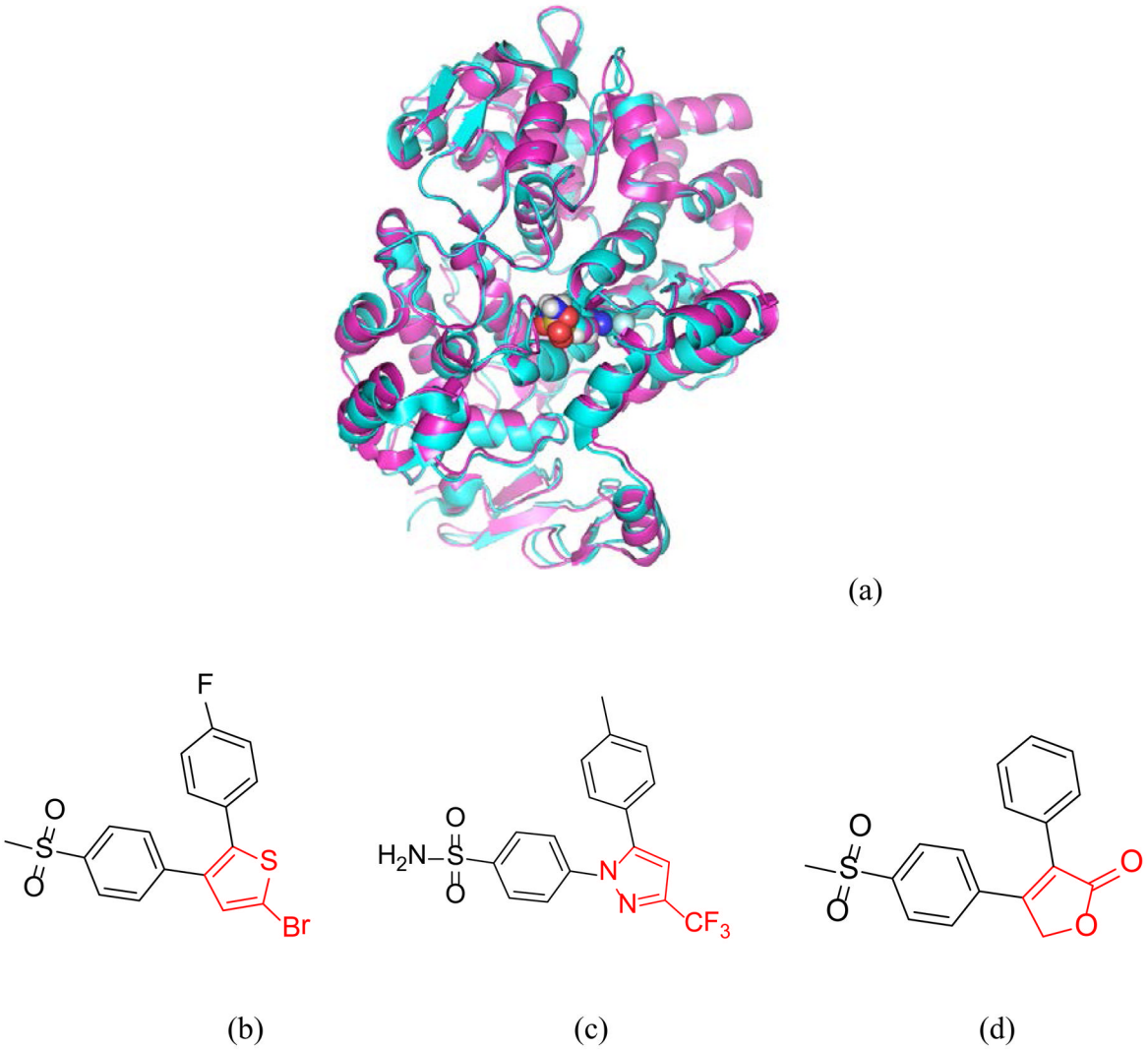


Figure 6.

(a) Overlay of X-ray crystal structures of Cyclooxygenase 1 (COX-1) in magenta (PDB id: 3KK6) and COX-2 in cyan (PDB id: 3LN1) in complex with Celecoxib, and structures of diarylheterocyclic COX-2 selective inhibitors (b) DuP 697, (c) Celecoxib, and (d) Rofecoxib.

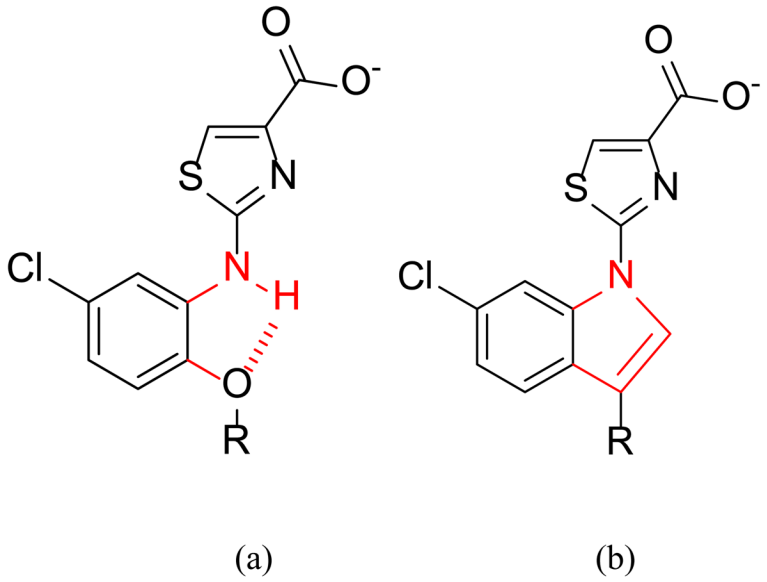


Figure 7.

Prostaglandin EP_1 receptor anatagonists. (a) biaryl amine series and (b) indole series. It is worth noting that reduction in entropy loss due to binding might be limited, since the intramolecular HBs of the parent compounds have already reduced molecular flexibility.

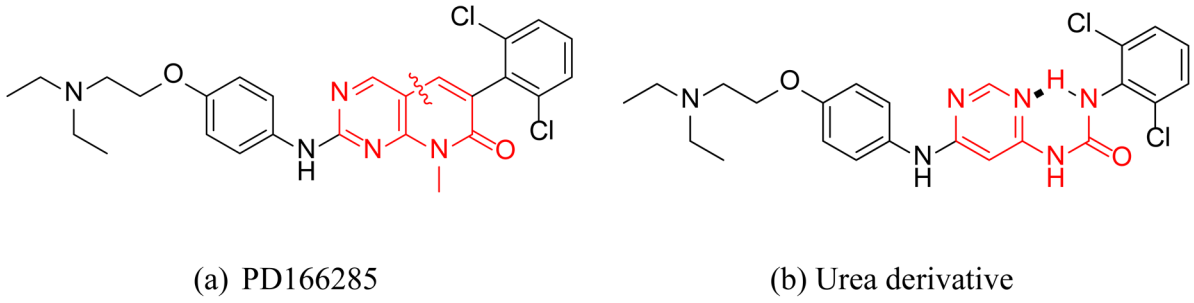


Figure 8.
Structures of tyrosine kinase inhibitors. (a) Pyridopyrimidinone PD 166285 and (b) its urea derivative.

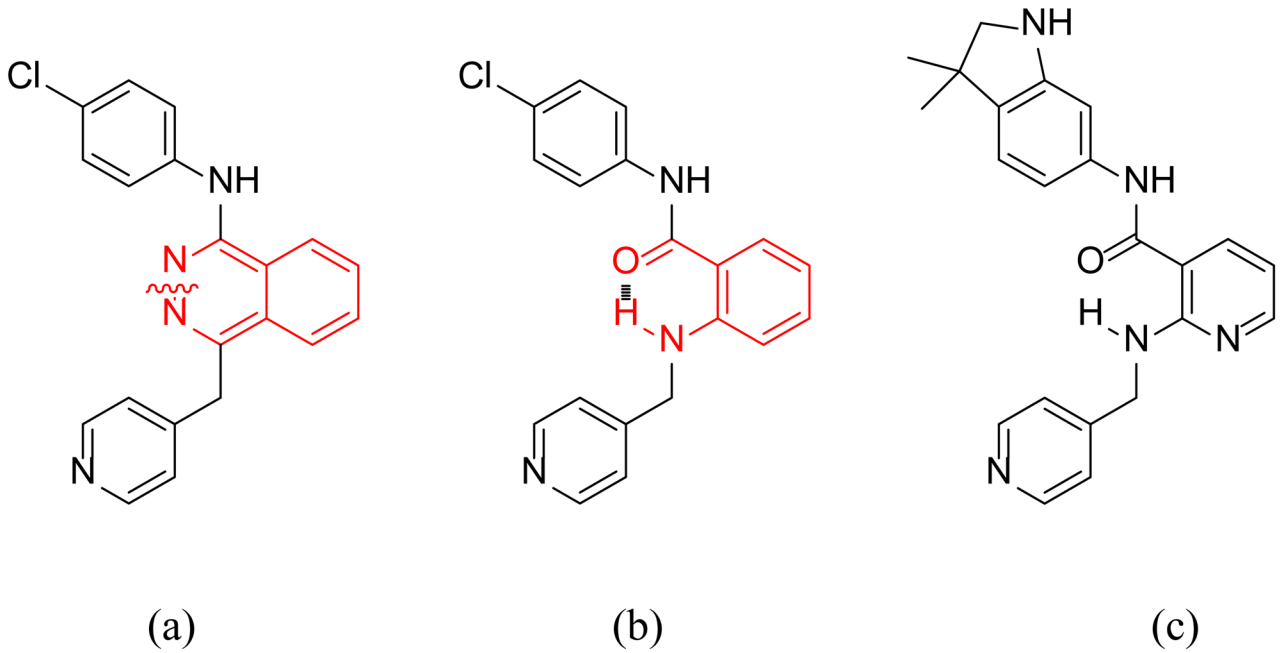


Figure 9.
Structures of antiangiogenic agents. (a) Phthalazine PTK787/ZK222584, (b) its anthranilic amide analogue, and (c) Motesanib/AMG 706.

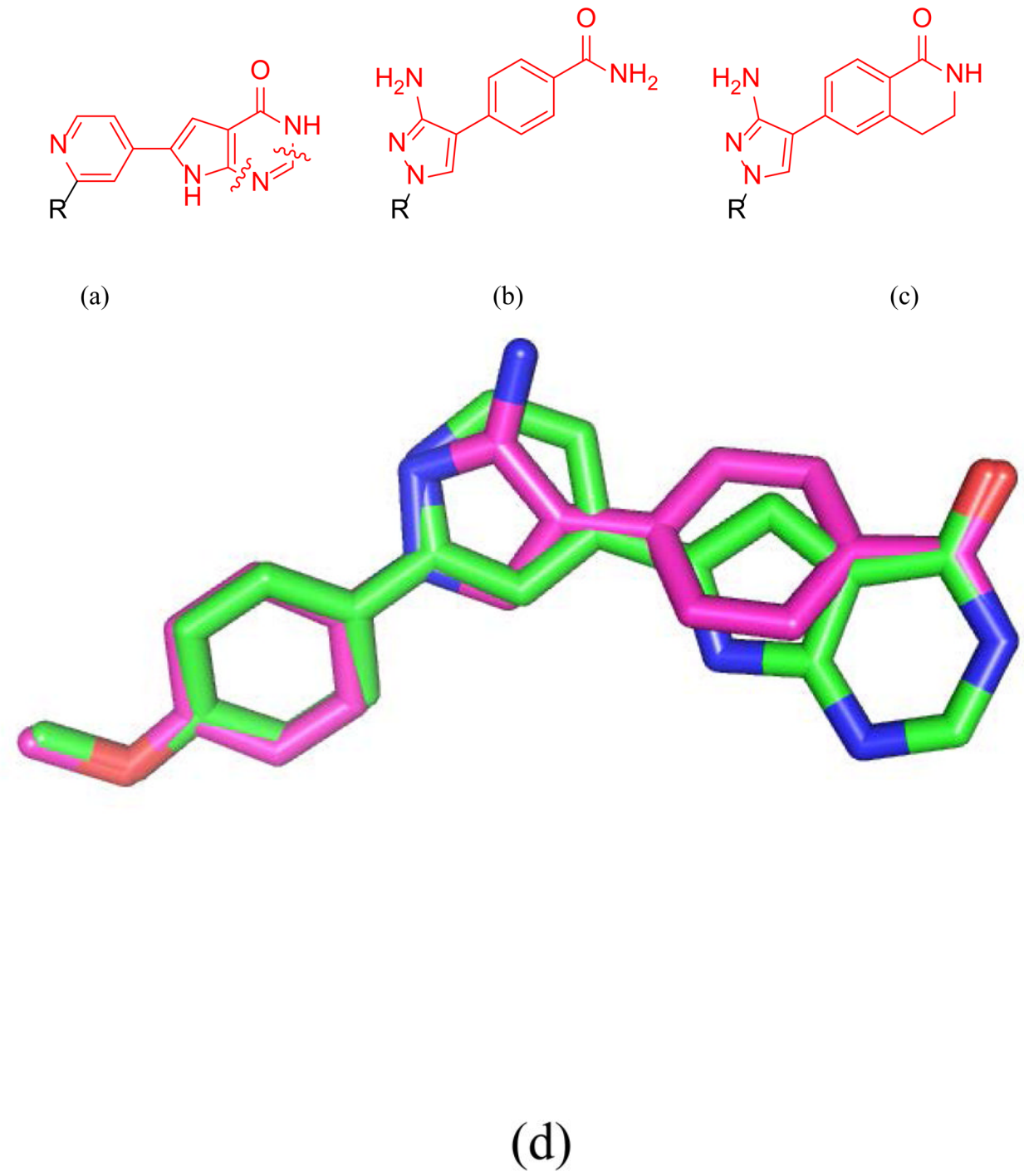


Figure 10.
Structures of MAP (mitogen-activated protein) kinase-activated protein kinase 2 (MK2) inhibitors. (a) Pyrrolo-pyrimidone template, (b) amide analogue, (c) dihydroisoquinolinone derivative, and (d) the overlay of (a) in green and (b) in magenta.

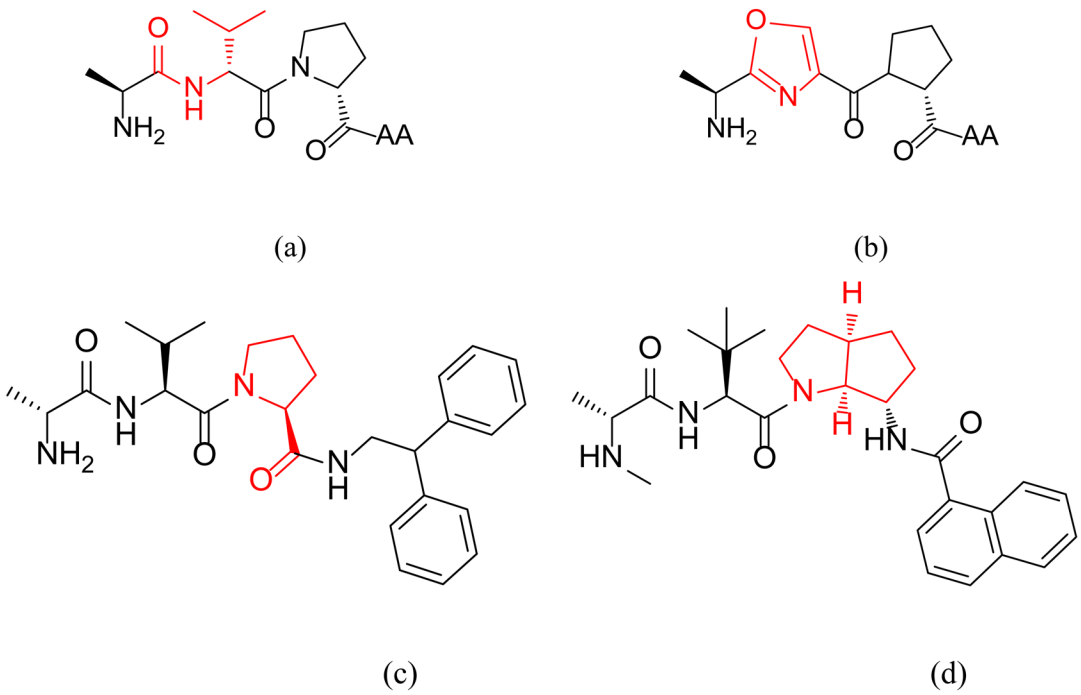


Figure 11.
Structures of (a) Smac N-terminal tetrapeptide AVPI, (b) an oxazole derivative, (c) modified Smac tetrapeptide, and (d) an azabicyclooctane analogue.

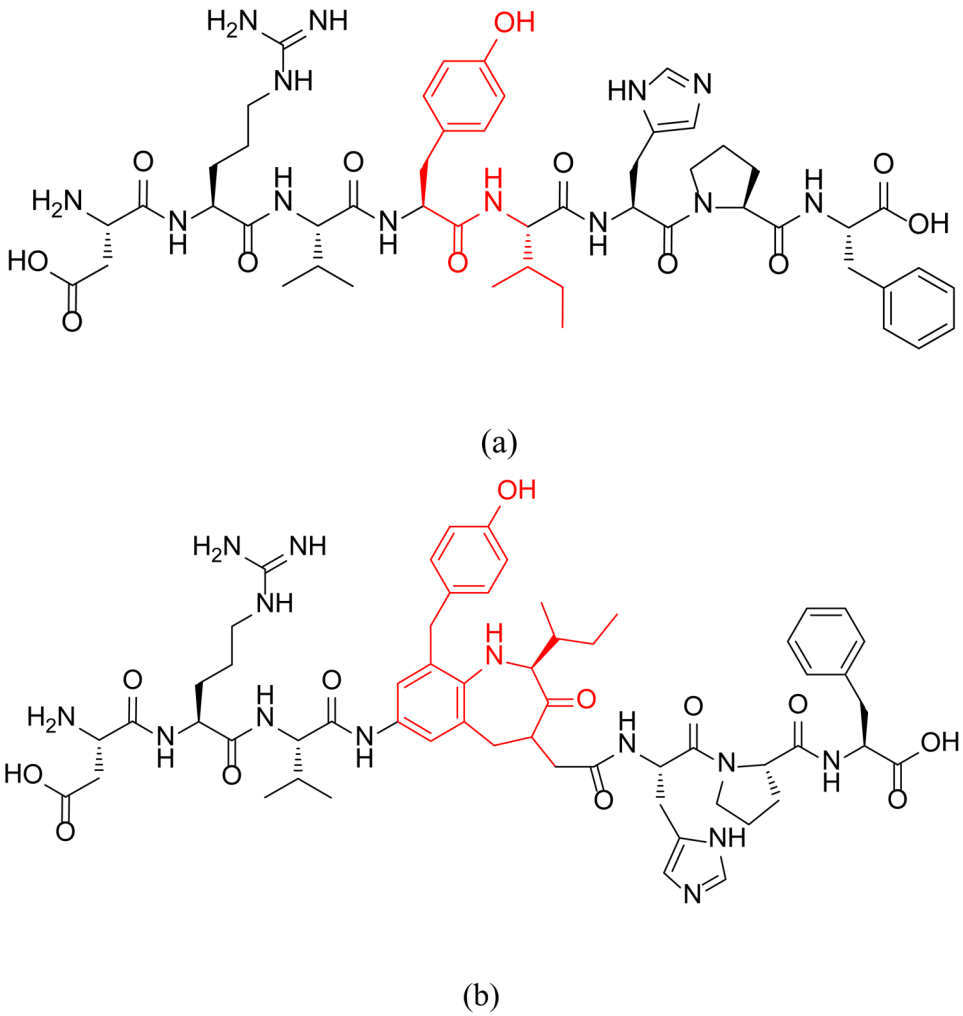


Figure 12.
The structures of (a) Ang II (DRVYIHPF) and (b) benzodiazepine-based β–turn mimetic.

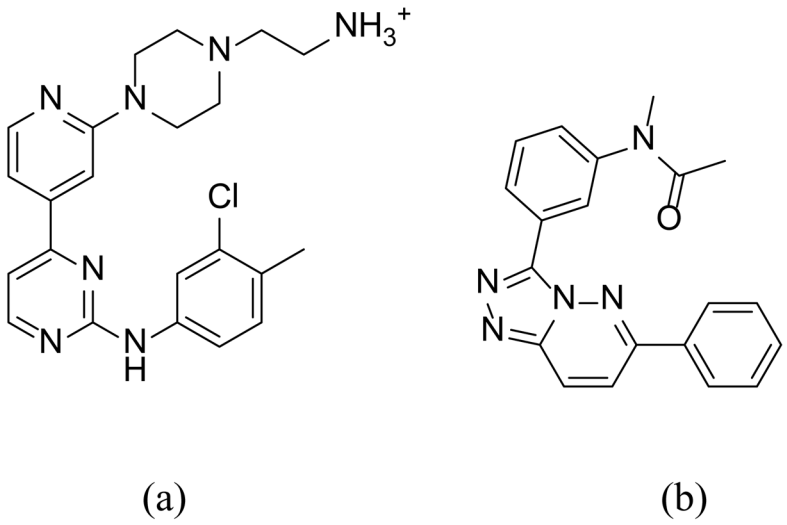
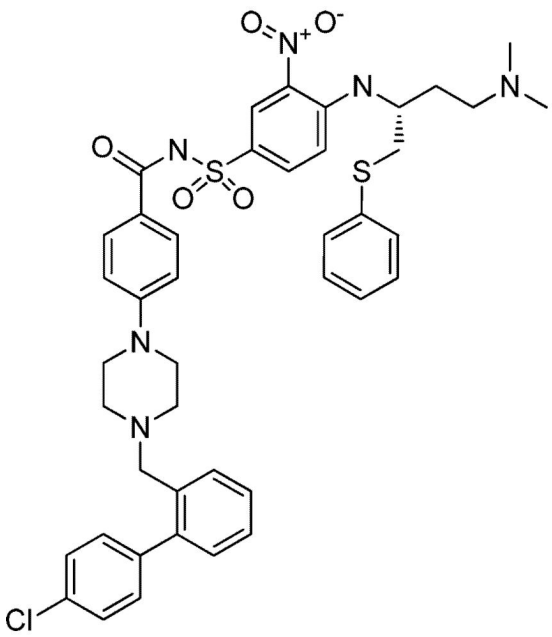
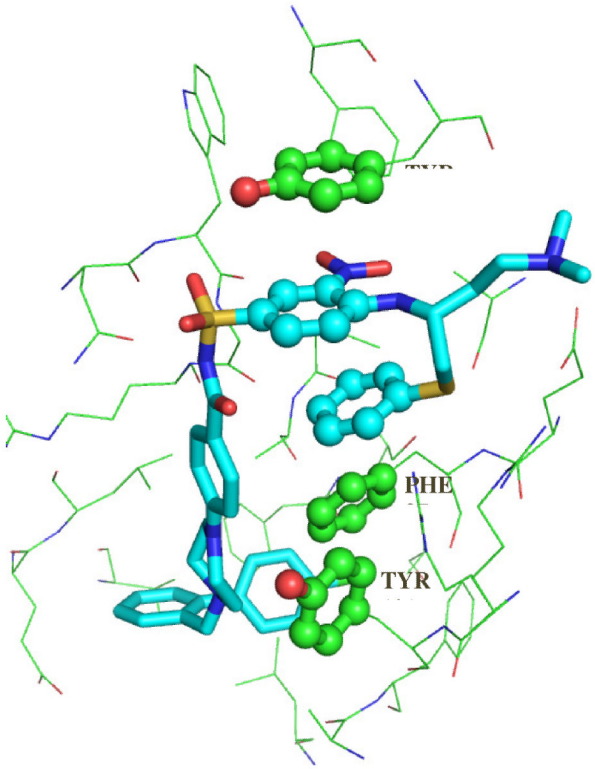


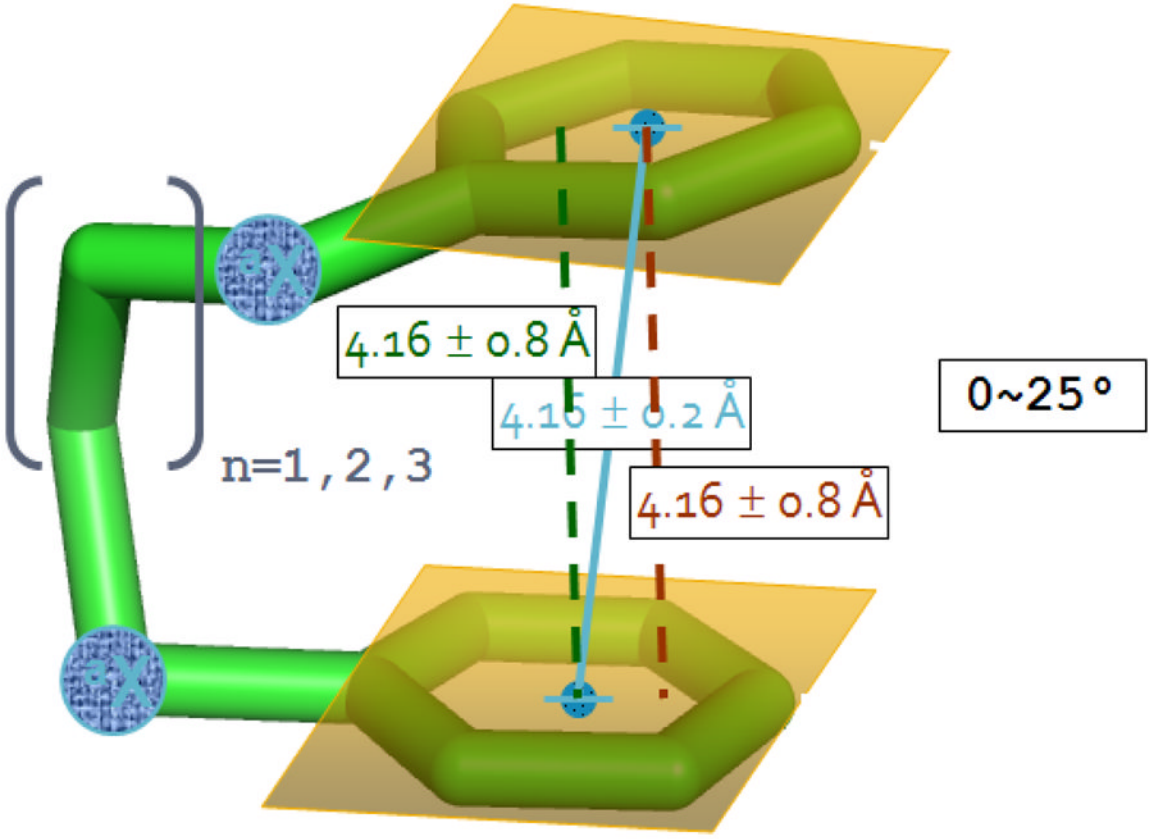
Figure 13.
Structures of ZipA-FtsZ inhibitors. (a) Pyridyl-pyrimidine template from HTS and (b) ROCS-identified hit.



(a)



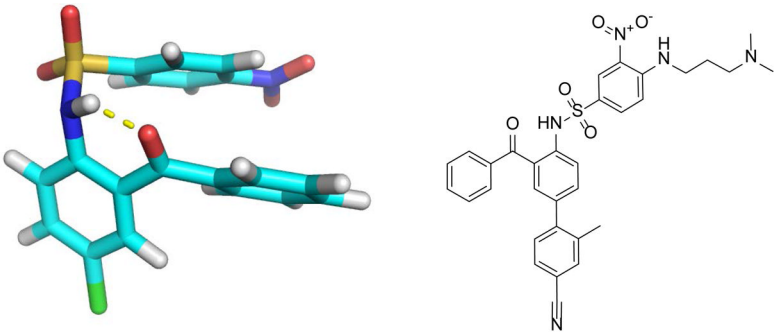
(b)



(c)

Figure 14.

(a) Structure of BCL-xl inhibitor ABT-737, (b) the ligand binding site of BCL-xl illustrating the π– π stacking network formed between the ligand ABT-737(cyan) and the protein BCL-xl(green), and (c) the Cambridge Structural Database (CSD) query for reproduction of the π– π stacking.

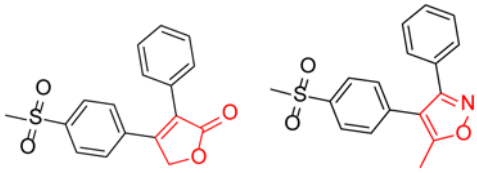
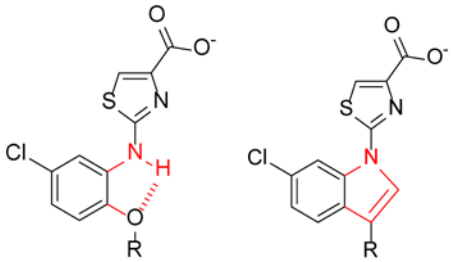
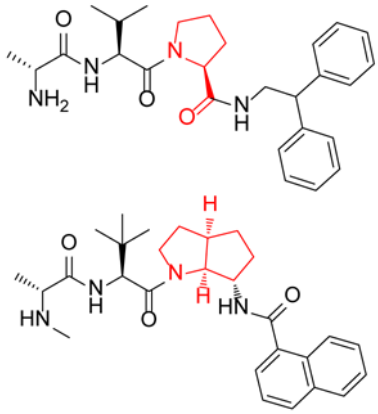
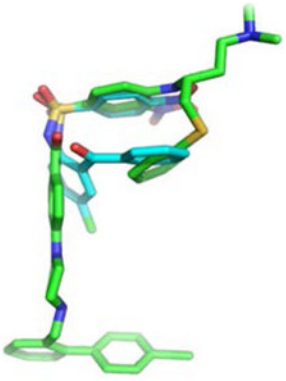


(a) (b)

Figure 15.
(a) The hit scaffold resulting from virtual screening of crystal structures in CSD and (b) the structure of the new BCL-xl inhibitor.

Table 1

The four types of scaffold hopping methods, their pros and cons, and frequently used software for each method.

Category	Definition	Pros and cons	Software
1°	 Heterocycle replacement	Pros: 1. High success rate 2. Immediate design Cons: 1. IP position 2. Limited changes in properties	MORPH [45] and Recore [48]
2°	 Ring opening/closure Cl	Pros: 1. Improve binding 2. Improve stability Cons: 1. Reduce solubility 2. Flatten molecule 3. Synthetic feasibility	CSD [67]
3°	 Pseudopeptide/peptidomimetic	Pros: Ready templates from bioactive peptides or PPIs Cons: Metabolic stability is a concern, especially for pseudopeptides.	Recore [48], CAVEAT [87], and pharmacophore modeling tools from CCG [100], Accelrys [101] and Schrodinger [102]
4°	 Topology-based hopping	Pros: Significantly different scaffold, implying novel properties Cons: Lower success rate.	CSD [67], ROCS[108], and SHOP [112,124]