International Journal of Scientific Research in Chemistry (IJSRCH)
© 2021 IJSRCH | Volume 6 | Issue 1 | ISSN : 2456-8457

Recent Strategic Advances in Pharmaceutical Chemistry

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Article Info
Volume 6, Issue 1
Page Number: 30-43

Publication Issue :
January-February-2021

Article History
Accepted : 01 Feb 2021
Published : 05 Feb 2021

ABSTRACT

Pharmaceutical chemistry encompasses drug design, drug synthesis, and the evaluation of drug efficacy (how effective it is in treating a condition) and drug safety trained pharmacists and physicians how to prepare medicinal remedies from natural organic products or inorganic materials. Pharmaceutical chemists evaluate the bioactivity of drugs and drug metabolites. Toxicologists assess drug safety and potential adverse effects of drug therapy. When a drug has been approved for human studies, clinicians and physicians monitor patients' response to treatment with the new drug. Theoretical chemists construct molecular models of existing drugs to evaluate their properties. These computational studies help medicinal chemists and bioengineers design and synthesize compounds with enhanced biological activity. The field of pharmaceutical chemistry is diverse and involves many areas of expertise. Natural-product and analytical chemists isolate and identify active components from plant and other natural sources. This Perspective aims to present a recent strategic innovations in pharmaceutical chemistry and drug discovery.

Keywords : Pharmaceutical chemistry, Target-Guided Synthesis, Bioorthogonal Uncaging Strategies, Structural Water Molecules.

I. INTRODUCTION

The extremely rapid accumulation of biological data in the postgenomic era as well as the development of computational chemical biology have stimulated an unprecedented revolution in medicinal chemistry, and the paradigm for discovery of pharmacologically interesting molecules has changed over the past few decades from a largely molecules has changed over the past few decades from a largely serendipitous, trial-and-error approach to a much more sophisticated and multifaceted approach, which has greatly improved the efficiency of drug discovery resulting in a significant acceleration of the overall process[1]. The strategy of bioorthogonal chemistry expertise in biology of disease, organic. Photoactivatable-inspired chemistry with high

temporal and spatial precision was first proposed by integrating related innovations in related fields[2]. Drug repurposing (also called repositioning, redirecting, reprofiling) is a polypharmacology-driven strategy for generating additional value from an existing drug by targeting diseases other than that for which it was originally intended. This has significant advantages over new drug discovery since chemical synthesis steps, manufacturing processes, reliable safety, and pharmacokinetic properties in early clinical developmentat phases (Phase I and Phase IIa trials) are already available.

In recent years, with the continuous development of bioinformatics and cheminformatics, drug repurposing has gradually developed into a data-driven innovative drug development strategy. Recent work has demonstrated that bioinformatics-based methodologies have the potential to provide the kind of systematic insights into the complicated relationships among diseases, targets, and drugs that are needed for successful repositioning[3-4]. With the guidance of bioinformatics and cheminformatics, recent progress has also been made in exploration of the chemical space of existing drugs for novel bioactivities with translational potential For example, zileuton (27, trade name ZYFLO) is an orally bioavailable inhibitor of 5-lipoxygenase and thus inhibits formation of leukotrienes (LTB4, LTC4, LTD4, and LTE4); it is used for the treatment of asthma. Based on previous studies indicating that the leukotriene pathway is involved in human tauopathy (bioinformatics), it was recently shown that aged tau transgenic mice treated with zileuton exhibit reversal of learning impairments, memory deficits, and neuropathology.

Suberanilohydroxamic acid (SAHA, vorinostat, 28), an approved histone deacetylase (HDAC) inhibitor, was used for treating cutaneous T cell lymphoma. Previous studies suggested that 28 showed potential anti-inflammatory activity (cheminformatics), though the underlying mechanisms remained. unclear. Based on this, Lu et al. reported drug repurposing of HDAC inhibitors as agents to alleviate neutrophilic inflammation in idiopathic pulmonary fibrosis and acute lung injury via binding with leukotriene A4 hydrolase, thereby inhibiting leukotriene B4 biosynthesis.

It is a modern design and development paradigm for drugs focused on the synthesis of a pharmacophoric composition of various bioactive substances in order to create a new synthetic compound with greater affinity and efficacy compared to the drugs used in parents. Furthermore, this approach will lead to compounds with changed selectivity profiles, specific and/or dual action modes and undesirable side effects reduced[5-7].

A plethora of in silico approaches have been developed to facilitate the repositioning of drug-like molecules, including virtual screening, reverse pharmacophore profiling, or binding pocket comparisons. For example, NorA is the most important efflux pump of Staphylococcus aureus as it confers multidrug resistance. Astolfi et al. constructed a ligand-based 3Dpharmacophore model of efflux pump inhibitors (EPIs) based on the S. aureus (ModB and ModC) NorA EPIs library. The best model was screened against approved drugs, leading to the discovery of novel and potent NorA EPIs, including three nonantibiotic approved drugs dasatinib, used to treat certain cases of chronic myelogenous leukemia and acute lymphoblastic leukemia), gefitinib (30, used for certain breast, lung, and other cancers), and nicardipine, used to treat high blood pressure and angina) that were able to restore the antibacterial activity of ciprofloxacin against resistant S. aureus strains overexpressing NorA. Using a computational screen of an FDA-approved drug library, the proton pump inhibitor lansoprazole was repositioned as an anticancer drug by binding to the thioesterase domain of human fatty acid synthase. Multiple ligand simultaneous docking (MLSD) is a computational tool used to investigate interactions between a biotarget and substrate in the presence of an inhibitor. In 2011,

Li et al. described a novel approach to drug discovery by combining fragment-based drug design with drug repositioning using MLSD. This led to the identification of celecoxib and its analogues as new inhibitors of signal transducer and activator of transcription 3 (STAT3).36a In 2014, they further reported the identification of raloxifene and bazedoxifene as novel inhibitors of IL-6/GP130 protein–protein interaction through MLSDderived drug-repositioning methodology. Novel in silico drug design approaches, especially those related to machine-learning algorithms, are being utilized for in silico drug repositioning, an exemplified by drug profile matching, topological graph theory, and other computational methodologies. Because of the limited variety of drugs on the market, it is necessary to expand the selection of drugs or drug-like molecules (investigational compounds)[8-10]. As we know, development of repurposed drugs is also limited by challenges in the regulatory path. Widening the scope of compound library beyond approved drugs can help overcome this shortcoming.

For example, three pyrimidinone derivatives 33a–c, previously known as nonapproved HIV-1 non-nucleoside reverse transcriptase inhibitors, were reported to inhibit cell proliferation and facilitate cell differentiation via inhibiting (a nontelomeric) endogenous reverse transcriptase.

"Privileged Structure" Repositioning

The hit rates by repositioning of commercially available approved or experimental drug libraries are usually quite low, and the hits often have low structural diversity. As a supplement, compound collections based on privileged structures offer the potential of libraries encompassing favorable physicochemical profiles and containing privileged scaffolds known to target various cellular targets, thereby increasing the success rate of discovering selective molecules that inhibit specific targets.

1,6-Naphthyridine-7-carboxamide (in pink) has been regarded as a promising motif with drug-like properties. Among structurally diverse HIV-1 integrase inhibitors, the 8-hydroxy-[1,6]naphthyridine L-870,810 was a promising anti-HIV drug candidate, but in spite of its pharmacological activity, the development of 55 was halted during phase I clinical studies (reasons unknown). Nevertheless, because of its desirable druglike properties, novel derivatives of 55 (substitutions at the 5-and 8-positions) were designed to overcome the limitations of naphthyridine-7-carboxamides as antiviral compounds and to reposition them as novel cytotoxic anticancer agents. Finally, further structural decoration of the 5,8-disubstituted-[1,6]-naphthyridines (on 7-carboxamide) afforded novel molecules 56a–c with remarkable cytotoxicity toward a set of cancer cell lines and high potency against selected oncogenic kinases[11-12].

Target-Guided Synthesis (TGS) Approaches

Target-guided synthesis (TGS) has proven a robust strategy in recent years for its original concept: using the biological target itself to assemble its selective ligands directly from a pool of fragments bearing complementary reactive functional groups. The approaches, bridging the gap between chemical synthesis and bioactivity assays, are divided into two major approaches: the kinetic TGS (KTGS) approach, namely, the kinetically controlled reactions involving irreversible bond formation, and the thermodynamically controlled reactions involving reversible reactions (also known as dynamic combinatorial chemistry, DCC). Both strategies have been extensively and successfully implemented for hit finding for receptors and enzymes,89 such as neuraminidase, carbonic anhydrase, kinase/phosphatase, cyclooxygenase-2, etc. Particularly, structure-guided fragment linking of precursors that display weak affinity to the target (the KTGS approach) is considered a robust way to rapidly find potent inhibitors, basedon cooperative binding[13-15].

Recently, the tetrazine bioorthogonal reaction has been used by Astex Pharmaceutical to stitch together functional proteolysis targeting chimeras (PROTACs) for degrading anticancer drug targets BRD4 and ERK1/2 within living cells. Notably, in situ assembly of two small compounds within a cell demonstrated higher efficacy than simply adding the preassembled compound. However, DCC represents a promising approach for a highly efficient generation of libraries.89 As yet, however, this approach is limited by the techniques used for the analysis of protein–binder complexes and the few appropriate reactions. Several techniques have been used to the analysis of protein-directed DCL. These include X-ray crystallography, NMR spectroscopy, HPLC, and mass spectrometry[16-20]. X-ray crystallography and NMR spectroscopy are high-resolution techniques, but are time consuming. Notably, competitive MS binding assays have proved to be an effective method for the affinity determination of single molecule toward a protein of interest, which has been readily extended to the screening of compound collections as well. In the search of new γ-aminobutyric acid transporter 1 (GAT1) inhibitors, an exploratory research was undertaken in which pseudostatic hydrazone libraries were generated by DCC and screened against GAT1 using MS binding assays. Hydrazone 88 bearing a 2′,4′-dichlorobiphenyl moiety was identified as a robust binder with low nanomolar affinity (pKi =. Further optimization afforded 89 (pKi = 6.9) as a stable carba analogue of hydrazone. Besides, the efficient dynamic-combinatorial MS technique has the advantages of providing detailed information on mass shifts. In recent years, the disulfide or boronic acid/boronate ester dynamic systems coupled with protein MS analysis has been employed in the rapid discovery of JmjC histone demethylases and nucleic acid demethylases[21-28].

Bioorthogonally Activated Chemotherapy (Bioorthogonal

Uncaging Strategies)

To avoid toxic side effects on healthy cells and tissues, much research has been directed at the design of cancer-specific strategies (selective delivery of chemotherapeutic drugs to cancer cells), for example, by using prodrugs via controlled activation, which are inactive precursors of cytotoxic agents, but can be biochemically converted into their active forms in a spatially controlled manner[29-32]. Recent advances in bioorthogonal catalysis are increasing the ability of medicinal chemists to manipulate the fate of molecules in complex biological systems. Consequently, bioorthogonal uncaging (bioorthogonally activated chemotherapy, also termed "click to release") have been recently reported as an experimental prodrug therapeutic strategy to control drug release by the application of solid metals (mainly palladium) as implantable activating devices to catalyze various chemical reactions in biocompatible environments and to modulate the cytotoxicity of anticancer agents in specific biological settings.104,105 While soluble palladium species such as Pd2+ complexes exert inherent cytotoxicity, Pd(0) catalysts are biocompatible and seem to be the safer agents. Recently, Unciti-Broceta reported palladium-labile biorthogonal prodrugs of several anticancer drugs, including cytotoxic gemcitabine (2),105d 5-fluorouracil (90, 5FU),105e,f floxuridine (91),105g and vorinostat (28)105h by introducing a Pd(0)-cleavable group (N-propargyloxycarbonyl (N-Poc) promoiety) at positions that are mechanistically relevant for the bioactivity of the original anticancer agents. There remains great interest in novel bioorthogonal uncaging strategies, as exemplified by the newly disclosed inverse electron-demand Diels–Alder reaction and gold-triggered uncaging chemistry[33]. Another prominent example is the application of the highly strained alkene transcyclooctene and ene ether to mask functional groups, including amines and alcohols which is then liberated upon reaction with a tetrazine. In 2018, the

group of Wang reported a concentration-sensitive bioorthogonal prodrug activation approach by taking advantage of reaction kinetics-controlled tetrazine–cyclooctyne click reaction, and spontaneous cyclization-based release. This study robustly demonstrated the concept of enrichmenttriggered prodrug activation specifically in mitochondria and the critical feasibility of treating the related clinical diseases such as cancer and acute liver injury[34].

Photodynamic Therapy

Photodynamic therapy (PDT) is well studied and established in clinical application since the approval of the first drug, porfimer sodium, based on the characteristics of strong metabolism of tumor cells, after injection of photosensitizers (drugs), the concentration of tumor tissue is notably higher than that of neighboring normal tissues. At appropriate time, light irradiation with specific wavelength could activate photosensitizers, produce reactive oxygen species (such as singlet oxygen), and specifically kill cancer cells and destroy neovascularization.120 PDT has proven a promising treatment option for various kinds of cancers and nonmalignant diseases including infections. Even though several photosensitizers have been clinically approved already, the development of additional photosensitizer with high phototoxicity, low dark-toxicity, and favorable aqueous solubility is very challenging for PDT. Several methods have been employed to obtain more efficient and less toxic photosensitizers. For example, conjugation with tumor-specific ligands (including small molecules, peptides, and proteins) significantly improves the selectivity of the active photosensitizer toward specific cells. In 2017, the conjugates 107 and 108 were synthesized by coupling zinc phthalocyanine to gonadotropin-releasing hormone (GnRH) analogues.

A recent study shows that hydroxypyridinone and 5-aminolaevulinic acid conjugates could substantially enhance the formation of phototherapeutic metabolite and phototoxicity. In 2018, a novel series of porphyrin-based water soluble derivatives were reported as potential sensitizers for effective PDT against breast cancer. In 2018, two advanced boron dipyrromethene (BODIPY)-based photosensitizers with a glibenclamide-derived moiety were reported to behave as singlet oxygen provider with high photostability. This direction will continue to be a hot topic in the field of anticancer drugs. In the future, it would be of high interest to explore if the photodynamic effectiveness may be improved and, at the same time, if the systemic toxicity may be reduced by photosensitizers that circulate in their inactive form in the normal tissues and are activated only by specific conditions in cancer cells (e.g., lower pH value, reducing environment). Furthermore, research in this direction should pay attention to questions like: a high concentration of glutathione present in the tumor tissues can consume reactive oxygen species; PDT is often followed by recurrence because of incomplete ablation of tumors[35].

Multiparameter optimization

A high-quality drug should exhibit a good balance of efficacy against its therapeutic targets, physicochemical properties, ADME properties (absorption, distribution, metabolism, and elimination) and safety. In other words, drug discovery is a multiparameter optimization (MPO) process in which the aim is to find novel pharmaceutical molecules that meet the multiple drug-like criteria. Examples are “rule of 5”, “beyond rule of 5”, and “lead-like drugs”157–160 and ligand efficiency metrics (such as lipophilic efficiency).161 Half of all therapeutic targets cannot be modulated with small-molecules that comply with the rule of 5. Macrocycles have been found to be in “beyond rule of 5” space and were especially useful in drugging targets that have large, flat, or groove-shaped binding sites. Avoidance of toxicity and optimization of drug-like propertie is a critical issue at the late stage of drug discovery[36]. Thus, in drug optimization, structure–property (or toxicity) relationship studies should be focused on a range of targets, not merely

activity. Drug discovery for the CNS disorders still faces huge challenges, for example, the optimization of lead compounds into drug candidates is difficult due to the strict physicochemical properties required to penetrate the blood–brain barrier. In 2010, a druglikeness CNS MPO algorithm was designed by Pfizer, which has parametrized medicinal chemistry design space for CNS drug candidates.165a Since then, significant progress has been made in application of this simple-to-use design algorithm.165b,c The significance of understanding the kinetics of the interaction between a ligand and its target has been acknowledged for a long time. Ligand–target residence time (structure–kinetic relationship, SKR) has also been valued as a key drug discovery parameter, and it is still receiving sustained attention. Numerous recent research articles from the medicinal chemistry community provide compelling arguments for more widespread assessment of binding kinetics and discussion of SKR. The binding of ligand with target is influenced by multiple factors, including hydrogen bonds and hydrophobic interactions, residual mobility, desolvation, dynamics, and the local water molecule. Experimental tools to (un)binding kinetics are nowadays available, but reliable computational methods for predicting kinetics and residence time are still lacking. Most attempts have involved molecular dynamics (MD) simulations, which are CPU-intensive and not yet particularly accurate. In 2016, Mollica et al. reported a new scaled-MD-based protocol, verified by directly comparing computational predictions, experimental kinetics measurements, and X-ray crystallography, which seems to have potential for predicting kinetics and drug residence times in drug discovery. In considering structure–property–activity relationships, multiple aspects of ligand–protein binding need to be considered, including surface water networks coating protein-bound ligands and water-mediated ligand functional group cooperativity.

Off-rate screening by surface Plasmon resonance (SPR) is an efficient approach to kinetically sample the hit-to-lead chemical space using unpurified reaction products. Recent study demonstrated that the lifetime of the drug–target complex is governed by interactions in the transition state for ligand binding rather than the ground state of the enzyme–ligand complex, and the on-rates can play a key role in drug–target residence time. In 2018, an efficient computational method, for the ranking of drug candidates by their residence time and giving insights into ligand–target dissociation mechanisms, was reported[37].

Antibody-Recruiting Molecules

Synthetic immunology, i.e., the development of synthetic systems to modulate immunological functions, is a newly established field. One focus of research has been to find synthetic small-molecular agents, named antibody-recruiting molecules (ARMs), that can enhance antibody binding to disease-relevant viruses or cells, thus promoting their immune-mediated clearance. Early in 2009, Spiegel et al. reported several ARMs that target prostate cancer. They designed new bifunctional ARMs to bind to HIV-1 gp120 and antidinitrophenyl (DNP) antibodies, simultaneously. Anti-DNP antibodies are abundant in the human bloodstream. By connecting these two fragments together, ARMs (exemplified by 128, derived from the existing molecule 127 (BMS-378806)) could mediate the formation of a ternary complex, leading to blocking virus entry and antibody-mediated immune clearance of gp120-bearing cells. In 2014, computationally driven modification of ARMs targeting HIV-1 gp120 gave an optimized molecule (derived from 129), which was almost 1000-fold more potent than 128 in gp120-binding and cell-based antiviral assay. It was also effective against multiple HIV pseudotypes in laboratory and clinic. In 2016, Genady et al. reported the discovery of radiolabeled ARMs (exemplified by 131) that target prostate-specific membrane antigen and anti-DNP antibodies for combined immunotherapy and radiotherapy[38].

Human serum albumin-derived drug delivery.

Human serum albumin (HSA) is the most abundant protein in sera (30–50 g/L human serum), where it primarily functions as a natural transporter for a myriad of molecules. Being an intrinsic protein of the human blood, it exhibits no immunogenicity. It also has a long circulatory half-life (about 19 days) due to its binding affinity for the recycling neonatal Fc receptor. Thus, HSA is an ideal drug carrier for targeted delivery and for improving the pharmacokinetic profile (half-life extension) of drugs. Several albumin-related small-molecular drug delivery technologies have been developed, including in vivo noncovalent or covalent endogenous HSA targeting, coupling of small molecule drugs to exogenous albumin. and encapsulation of drugs into albumin coated nanoparticles. Most small-molecular drugs are short-lived species in the circulatory system and can be rapidly eliminated via glomerular filtration. Noncovalent binding of small-molecular drugs to HAS could protect them against enzymatic degradation and renal clearance, affording slower clearance and a prolonged half-life in vivo.

For example, FMS(3)-gentamicin was developed as a long-acting prodrug derivative by linking three (2-sulfo)-9-fluorenylmethoxycarbonyl (FMS) moieties to three amino moieties of gentamicin (132) to provide increased affinity for albumin. Compound 134 is a fatty acid-like platinum(IV) prodrug designed to improve drug delivery via enhanced interaction with HSA.192 The clinically relevant glucagon-like peptide 1 (GLP-1) was functionalized with diflunisal (135, albumin binder) and indomethacin (136, albumin binder) to afford a divalent GLP-1 analogue 137 with a longer circulatory half-life and absorption time compared to its monovalent equivalent . Kratz et al. established an in vivo covalent conjugation strategy that exploits endogenous HSA as a drug carrier. In this approach, the prodrug binds selectively and rapidly to the cysteine-34 residue on the surface of HSA after intravenous administration, thereby generating an in situ transport form of the drug in the blood[39].

Covalent Inhibitors or Probes

An attractive increase in the potency and pharmacokinetics of a drug-like compound is to evoke the formation of a covalent bond. Compared with noncovalent inhibitors, the advantages of covalent compounds lie in the following aspects: higher potency, long residence time, and decreased drug resistance. In the past several years, many covalent drugs such as telaprevir, abiraterone, carfilzomib, and afatinib have been used in clinical, ushering in a new era for covalent modifiers.

Covalent inhibitors should remain a key focus of contemporary drug discovery, especially in the initial structure-based design optimization, as exemplified by human tissue transglutaminase inhibitor. Complementarily, allosteric modulators are sought after as a means to avoid undesirable side effects of covalent or active site inhibitors. In 2016, the first covalent and potent cannabinoid 1 receptor (CB1R) allosteric modulator was reported, which can be used as an effective chemical probe for characterizing CB1R allosteric ligand-binding motifs.214 In 2018, the first covalent positive allosteric modulator 163 for the metabotropic glutamate receptor 2 (mGlu2, a class C GPCR) was reported, which advanced the understanding of the mGlu2 PAM interaction. The main hurdle for covalent inhibitors is the lack of selectivity. Apart from selecting a warhead or modulating of electrophilic warhead reactivity, substantial efforts are required to optimize noncovalent reversible interactions to facilitate target-selective recognition and the overall potency. For example, through crystallography, kinetic, and molecular simulation studies, interaction of cyanamide-based covalent JAK3 inhibitor 164 with residue Cys909 was optimized affording potent and selective JAK3 inhibitors as exemplified by 165, with substantially enhanced activity and selectivity. Y181C-mutated HIV-1 strain is one of the key clinically observed mutants. In 2017, Jorgensen's group took

Y181Cmutated HIV-1 reverse transcriptase as the target for drug design. Based on the protein crystallography, it was found that the carbon − chlorine bond catechol in diethers compound is oriented toward Tyr181, and its replacement with an electrophilic warhead could make covalent binding of Cys181 variants. Consequently, electrophilic group-bearing compounds were designed and synthesized. This is the first successful application of the irreversible covalent inhibition strategy to HIV-1 reverse transcriptase. Based on activity results, it is found that small chemical alterations of warheads often cause significant differences in activity. Therefore, diversity-oriented selection of warheads make possible the systematic exploration of the chemical space. Besides the most popular acrylamide, additional electrophilic traps have undergone considerable development as "privileged warheads" in chemical biology (exemplified by sulfonyl fluoride and isothiocyanate). The exploration of warheads with chemical reactivity toward target enzymes for incorporation into parent compounds is expected to afford novel covalent drugs. Design of boron-containing molecules has recently attracted much attention. Boron differs from carbon in that it has a vacant p-orbital that is receptive to a reversible covalent bond formation with a Lewis base under physiological conditions. Recently, boronic acid was proven a structurally and mechanistically differentiated electrophile from other cysteine reacting moieties, arising from the ability of boronic acids to generate a reversible covalent bond with oxygen nucleophiles (Lewis base) of the target protein[40].

Exploring Water-Binding Pockets (Structural Water Molecules) in Structure-based Design.

Water molecules are important components in protein channels and are often found around ligands in protein crystal structures. Water-mediated interactions, especially hydrogen bonds, play key roles in drug binding. Careful examination of these water molecules and their energetics can contribute to successful drug design, as exemplified by neuronal nitric oxide synthase inhibitors, nonpeptidic urea HIV protease inhibitors, and benzoxaborole non-nucleoside polymerase inhibitors of HCV. Recently, several structural and computational studies to explore water-binding pockets have been reported. One way to systematically improve existing weak binders could focus on identifying and later chemically optimizing those moieties with a particular proximity or orientation to water molecules in the protein−binder complex. For example, the X ray structure of the antiviral drug Arbidol with influenza hemagglutinin revealed a highly ordered water molecule adjacent to Arbidol, and this was exploited in the structure-based design of Arbidol analogues. Addition of a meta-hydroxyl group to the thiophenol group of Arbidol to replace the water molecule in the binding pocket afforded 196, which showed significantly increased affinity for both H1 (98-fold) and H3 (1150-fold) hemagglutinin subtypes. A recent study indicated that the introduction of a hydroxyl group to form a water-mediated hydrogen bond may not necessarily improve the binding affinity between ligand and target because hydrophobic effects also play an important role in ligand binding affinity in some cases. The M2 proton channel of influenza A is a well-validated target for the antiviral drugs, such as amantadine and rimantadine. Recent disclosed X-ray crystal structures of the M2 proton channel with bound inhibitors reveal that the inhibitors engage in and disrupt transmembrane networks of hydrogen-bonded water and that small molecules can enable potent inhibition by targeting key water molecules[41]. Generally, it is thought that a protein binder can achieve affinity by extending into a region occupied by unfavorable water molecules or lose affinity by displacing water molecules from a region where it was relatively stable. However, the real situation is much more complicated. The prevailing thermodynamic theories of the past few years claim that water was observed

largely in terms of an entropic gain after it was displaced by a ligand, which are now known to be too idealistic. In most cases, as water molecules can be difficult to locate by X-ray diffraction methods, especially when they are not tightly bound to biomacromolecules, NMR spectroscopy can be used as a valuable technique to assess those water molecules. By increasing the (perdeuterated) protein concentration, Water-LOGSY titration experiments help to get useful information about the location of protein-bound water in the surroundings of the ligand and ligand binding modes even in the case of weak binders, which are extremely beneficial to specific optimization of the ligand to enhance binding affinities[42].

Stabilization of Protein Inactive Conformations or Protein−Protein Interactions

A large number of medicinal chemists have engaged in the design and development of protein kinases inhibitors. However, in comparison, targeting protein kinases with small compounds that bind outside the highly conserved ATP pocket to stabilize inactive protein conformations has been regarded as a fresh approach in kinase-targeted drug design that is worthy to be promoted because these compounds often have improved pharmacological profiles compared to inhibitors exclusively targeting the ATP pocket. However, traditional screening approaches for kinase inhibitors are often based on enzyme activity, and it has been recognized that they may miss ligands that stabilize inactive protein conformations. An example of a way to overcome this issue is provided by a study to find selective Met tyrosine kinase inhibitors in which a high-throughput virtual screening of a ChemNavigator compound database was employed for directed discovery of inhibitors targeting the Met tyrosine kinase domain (i.e., compounds that stabilize the kinase domain in its inactive conformation).

In 2010, Kluter et al. reported a kinase binding assay using a pyrazolourea type III inhibitor and enzyme fragment complementation technique that is suitable to screen stabilizers of enzymatically inactive kinases. In the same year, Whelligan et al. reported the first systematic exploration of compounds binding to an unusual, inactive conformation of the mitotic kinase Nek2. Recently, a novel series of competitive shikimate kinase inhibitors that stabilize an inactive open conformation of the enzyme by targeting the dynamic apolar pocket surrounding the natural substrate was disclosed. Novel pleckstrin homology domain-dependent covalentallosteric inhibitors of the kinase Akt were identified via structure-based design, which bind covalently to a distinct cysteine residue of the kinase and stabilize the inactive protein conformation. To sum up, stabilization of an inappropriate and inactive conformation for enzymatic catalysis seems an innovative and promising approach for dissecting conformation dependent signaling of protein kinases and finding drug candidates. Certainly, there is a significant challenge to adapt screening methodologies and downstream techniques to identify and optimize stabilizers of inactive conformations[43].

Peptidomimetics

Most of the antibodies have common general methods of production and purification since their properties are similar. The cost of developing antibodies may be less compared with new small-molecule drugs, because once the production and purification processes are established with one type of antibody, very similar methods can be used to produce and purify other types. Furthermore, it may be possible to reduce the cost of antibody production using different expression systems. Protein production and purification systems in mammalian or Escherichia coli or insect cells are well-established techniques. The use of plant cells may enable further cost reductions. Among biotechnology products, antibodies constitute a large number of therapeutic agents. At present, 24 mAb therapeutics have been

approved by the US FDA for marketing, and nearly 80 antibodies are in clinical development. In terms of antibody therapeutics, what is the role of the medicinal chemist? There are at least two major areas in the future where a medicinal chemist can contribute to the creation of mAb therapeutics. mAbs are being used in conjunction with small molecules as a combination therapy. Another developing trend is conjugation of small molecules to antibodies. At present, very few such examples exist; however, this trend seems likely to grow in the next 10 years. Recent data from clinical trials (Phase II) of brentuximab vedotin, a mAb targeting CD30 linked to an anti-microtubule agent, monomethyl auristatin E, showed the positive effects of the antibody–drug conjugate in anaplastic large-cell lymphoma and Hodgkin's lymphoma. Trastazumab–DM1, an mAb to human epidermal growth factor receptor-2 (HER2) conjugated to a maytansine derivative, is currently in clinical trials for HER2-positive breast cancer[36]. In the preparation of conjugates of mAb, a medicinal chemist needs to understand the protein chemistry and conjugation chemistry so that the conjugation process does not denature the protein or block the binding region of the antibody or the small molecule of interest. Although protein therapeutics have gained momentum in the past 20 years, there are problems associated with them. Despite the success of mAb therapeutics, the major disadvantages of mAbs are routes of administration as well as immunogenicity. Even humanized versions of mAbs can produce immunogenic responses. In terms of pharmaceutical interests, the major disadvantages are the routes of administration. Antibodies cannot be administered orally because of their large molecular weight, and therefore, they are administered via a parenteral route. Another major drawback of antibody therapeutics is the inability of these molecules to cross cell membranes, which largely restricts their application to extracellular target interventions. One way to circumvent this problem is to design small peptides or peptidomimetics to mimic the binding region of larger proteins to the macromolecular target of interest. For example, PPIs are concentrated in a few key residues placed in a particular 3D arrangement; these regions can be continuous or discontinuous in terms of protein sequence. If only a few amino acids mediate the contact between two proteins, then a compound mimicking properties of one of the interfaces of a protein should act as a competitive inhibitor and prevent the interaction between the binding partners. At present, more than 40 peptide therapeutics are on the market, and several are in clinical trial. Peptides, however, also suffer from disadvantages as drug candidates. Compared to antibodies, peptides are more susceptible to serum and tissue protease degradation and, partly on that basis, are often rapidly cleared from the circulation in a matter of minutes. Various strategies have been attempted to circumvent this general problem, most of which might be described as the design of modified peptides, either peptidal or non-peptidal peptidomimetics. x-ray crystallography- and NMR-derived 3Dstructures of complexes of proteins, with or without small-molecule ligands bound, have revealed structural motifs that are particularly important in PPIs. In the majority of cases, interacting domains exhibit secondary structure, such as α-helix, β-sheet/β-strand, or β-turn. Extensive research into peptide chemistry, the design of peptide therapeutics and peptidomimetics in recent decades has provided enough information to give a strong boost to further efforts over the next decade. Peptidomimetics designed based on key protein recognition motifs can be made stable against most of the enzymes that degrade proteins and peptides. Physicochemical and biopharmaceutical properties can be altered to achieve desired characteristics with peptidomimetics versus peptides and peptidomimetics can be more readily designed to traverse biological membranes. Peptidomimetics can be readily tagged with fluorescent or lanthanide (e.g., europium) chelating tags for ligand–receptor interaction studies or for imaging purposes. Such tagging tends to have

greater limitations with small organic molecule ligands, where it may be more difficult to identify ways to attach tags so that they do not block essential pharmacophoric moieties. A wide variety of backbone and side chain modification strategies exist, along with the ready commercial availability of β-amino acids that can be easily incorporated. Examples of advanced development in this area include design of a stapled peptide reported recently, in which α-helix-mimicking secondary structure was introduced using an organic linker, a strategy termed 'hydrocarbon stapling'. The stapled peptide targeting myeloid leukemia cell differentiation protein 1 (MCL-1) was protease-resistant and exhibited enhanced cellular uptake. It was highly selective for the MCL-1 receptor, and binding studies suggested that it did not show any binding to the related and similar B-cell lymphoma 2 (BCL-2) family of receptors. Other examples include reports from Sun et al., and Yin et al., which illustrate how design, synthesis and suitable binding assays (fluorescence, NMR) as well as docking studies can be used in the design of cell-permeating peptidomimetics. Clinically relevant examples of peptidomimetics that modulate PPIs include p53:MDM2, smMLCK: calmodulin, Smac:BIR and Bak BH3:Bcl-2/bcl-Xl. There have been a number of projects aimed at modulating p53:MDM2 interactions. In one of the most recent reports, Lee et al. exploited pyrrolopyrimidine-based α-helix mimetics instead of stapled peptides to create a cell-permeable dual modulator, which modulates MDMX/MDM2 interactions. These types of examples refute the misconception that peptide-based drug design is not a fruitful means of drug creation. As more and more suitable peptidomimetics are designed, along with synthetic strategies designed to enable arrays of compounds to be produced for investigating SAR and subsequent modifications as needed for multidimensional optimization (e.g., deliverability, pharmacokinetics, clinical efficacy and safety), an increasing number of peptidomimetic-based drugs should appear in clinical trials and, eventually, the market[44].

CONCLUSION

The classical methods of drug design, preparation, and evaluation lead to substantial time delays, resulting in inefficient usage of data in the complex drug design process. This Perspective has focused on exploring strategic approaches to solving issues in lead identification and optimization projects that affect candidate development and quality and that are frequently encountered in drug development campaigns. Structure-based drug design intends to generate the protein and ligand molecules that have high affinity and specificity. Since the binding cavity of an identified drug is usually large and their possible protein interactions are still required to be explored, detailed understandingd of drug−protein interactions or selectivity-determining features are needed to increase the effectiveness of structure-based drug design. Precise knowledge of (non)covalent interactions between proteins and binders provides good foundations for rational design of covalent inhibitors, bisubstrate inhibitors, stabilizers of protein inactive conformations, and exploitation of the water-binding pocket (structural water molecules) for structural modification. Notably, covalent inhibitors attract tremendous attention. One advantage of covalent drugs is a reduced risk for the development of resistance, which is a major challenge in the treatment of cancer and infectious diseases. The key factor affecting the target specificity of covalent inhibitor is the warhead moieties' reactivity. Despite the huge information contributed by academia and industry in the past decades, a rational approach using the structure-based drug design with the aid of computational methods remains challenging. There are large flexible variations in the process of protein−ligand binding: there can be, beyond the protein and ligand, cofactors and solvent molecules that should be observed. Additionally, entropic contributions can be important because the protein and ligand often possess significant flexibility. In an recent study, the

role of protein conformational entropy and the response of water molecules located around the binding sites and ligand.

In most cases, drugs are identified from the biological screening of compound collection, followed by hit to lead optimization toward functional end points. A large number of failures in the late stages of drug development underlines the point that drug discovery is a multiparameter optimization process, and multiple properties should be enhanced to reach the stage where a molecule could be considered for in vivo studies. However, if a lead compound is not considered to be efficient, it will never transform to a drug candidate, irrespective of other properties, which makes the structure−activity and structure−property relationships as a central task during early to midstages of lead optimization. Structural diversity within chemical libraries increases the probability of identifying a lead molecule. In phenotype-based drug discovery, molecular diversity is even more significant due to absence of target information. Consequently, the features of screening collections are often balanced between diversity, physicochemical desirability, intrinsic complexity, and synthetic feasibility. Even then, multiparameter optimization of the lead compound for efficacy and drug-like properties is challenging not only because of synthetic considerations but also because of the limited ability to predict how compounds will interact with complex biological systems. Given the complexity of lead optimization, this process is mainly driven by knowledge, intuition, and experience. In this stage, diversity-oriented synthesis-facilitated medicinal chemistry with combinations of many cheminformatics tools, as exemplified by hierarchical multiple-filter database screening (in silico ADMET prediction), is an attractive strategy[45-46].

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Cite this article as :

Akshay R.Yadav, "Recent Strategic Advances in Pharmaceutical Chemistry", International Journal of Scientific Research in Chemistry (IJSRCH), ISSN : 2456-8457, Volume 6 Issue 1, pp. 30-43, January-February 2021.

URL : https://ijsrch.com/IJSRCH21614