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Role of medicinal chemistry in the current scenario

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Abstract
Medicinal chemistry is defined as an interdependent mature science, a combination applied medicine and basic chemistry that involves discovering, developing, identifying andinterpreting the biologically active compounds. It plays major role in drug research and development by taking advantage of recent technique with advanced knowledge of different branches of related sciences. Since it can be seen as a melting pot of organic chemistry with molecular pharmacology further emphasizes the study of the relationship of drug molecules structural activity so it requires knowledge of chemical and pharmacology concepts. The source of medicinal chemistry lies in all branches of biology and chemistry, which started its journey in the war against various diseases in Ehrlich's hands, who dreamed of a "magic bullet" to combat various infectious diseases. ADMET assessment of therapeutic drug classes influence on therapeutic decision. Top-flight medicinal chemists can play greater roles in improving drug-creation efficiencies and clinical success rates, thereby increasing the overall cost-effectiveness of the enterprise and, in turn, more quickly satisfying unmet medical needs.

Keywords: medicinal chemistry, drug molecules, molecular hybridization, molecular docking, QSAR study, ADMET assessment

Introduction

Medicinal chemistry involves theoretical areas which regard drug design and development evaluations of absorption, distribution, metabolism, excretion and toxicity. Interpretation of the mechanism of action of SAR construction and molecular level of the drug molecules are important areas of drug design and discovery [1].

Drug Discovery, Design and Development

Medicinal chemistry play important role in drug discovery by relying on understanding and expertise in biology of disease, organic chemistry, pharmacokinetic characteristics and in-vivo and in-vitro Pharmacological screening with the goal of reducing side effects and optimizing effectiveness. The days go by when a chemist would expect to start and end a career by finely designing a complex synthesis of multi stage targets and by producing 10-20 compounds a year, feel that they have done a good job [2]. The days have passed when huge libraries of high throughtput screening (HTS) are made, which add only numbers to a collection. Compound consistency is now of utmost importance, whether it is based on innovation, physiochemical properties or purity.

The medicinal chemist today is part of a team that mainly handles all of the components of the drug process. They need outstanding communication and interpersonal skills, so that they can operate Effectively as part of a multi-functional project team comprising biologists and computer chemists [3-5].

Hybrid Molecule Concept and Approaches

In order to develop hybrid molecules that contain a variety of pharmacophoric groups, continuous research on the finding of economic and potential cancer agents emphasizes. Within this thesis we agreed to extend our work by synthesizing the synthetic analogs of 1,3,4-oxadiazole and azo derivatives. The reason for this study is to demonstrate the versatility of anti-inflammatory and antimalarial substituents. The study shows Molecular hybridisation (MH) is a reasonable development strategy for new ligands or prototypes which, by adequate fusion of those subunits, will lead to the design of a new hybrid architecture with pre-selected Model characteristic features based on recognition of two or more identified bioactive derivatives in the molecular structure of pharmacophoric subunits [6-7].

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 [8].

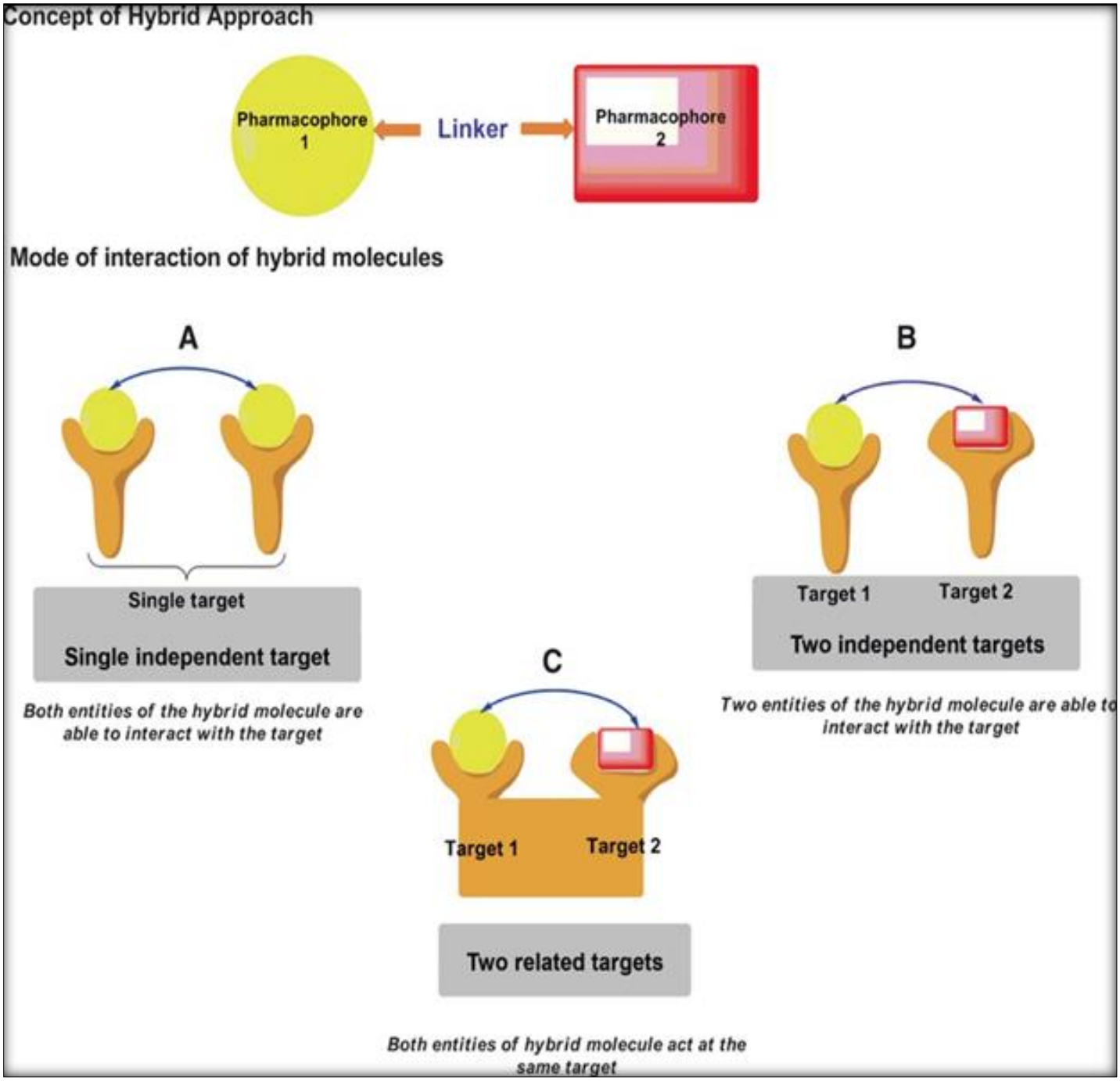

Fig 1: Concept of Hybrid Approach

Green Chemistry

Green chemistry is at the frontiers of this ever-evolving interdisciplinary science and publishes work aimed at reducing the environmental impact of the chemical industry by creating a technology base which is essentially non-toxic to living things and the environment. For those who practice chemistry in industry, education and research, the Green chemistry presents big challenge [9-16]. The emergence of green chemistry was seen as a reaction to the need for man-made products and the techniques used to manufacture them to mitigate the damage to the environment. From the reduction of waste to waste disposal, Green chemistry could cover anything correctly. Any industrial waste should be disposed of in the best way possible without harming the environment and living beings. Substances and the type of a material used in a chemical process should be selected to mitigate the risk for chemical incidents, including leaks, explosions and fires[17-18]. Chemistry can be driven at all levels by these principles: science, education and public perception. To protecting the environment from pollution, the first definition defines the basic idea of green chemistry. The remaining principles focus on nuclear economics, pollution, solvents and other energy-intensive media, the transformation of renewable resources and chemical degradation into quick, environmentally friendly non-toxic substances [19-23].

Fig 2: Principles of Green Chemistry

Microwave Assisted Organic Reactions

The microwave-assisted reactions are eco-friendly gives more yields, short reaction time, minimum exposure of hazardous chemicals and short reaction time so these features of microwave assisted synthesis are handy tool for academic research and industry. Green Chemistry is the application of chemicals used to eliminate or reduce the use and use of toxic materials, and one of the aspects of green chemistry is the use of microwave for organic reaction due to its utility. The chemistry of the microwave involves using radiation from a microwave to perform a chemical synthesis and the microwave work among the radio waves of 0.3 to 30 GHz. The frequency of 2.45 GHz is suggested for use in lab reactions as this frequency has a adequate depth of penetration in the lab reactions and a frequency spectrum of microwave surpluses with a number of radio frequencies above 30 GHz [24].

Heating Mechanism

In a microwave oven, material can be heated by means of high-frequency electromagnetic waves. The heat is produced by the interaction of the electric field component of the wave with the charge particle of the material.

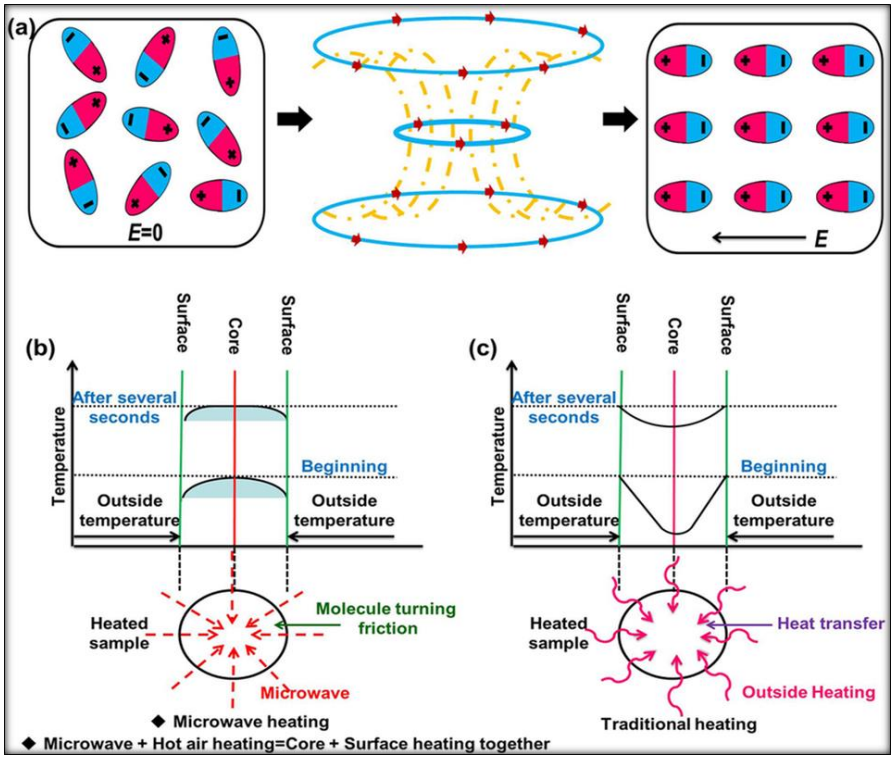

Fig 3: Microwave and Traditional Heating

Dipolar Polarization

It is a mechanism that generates heat in polar molecules. By revealing the correct frequency of the oscillating electromagnetic field, polar molecules attempt to follow the field and align themselves with the field in process [25].

Conduction Mechanism

It produces heat through the resistance of an electrical current. In a conductor, the electromagnetic oscillating field causes electrons or ions to oscillate, resulting in an electrical cureent and this current faces internal resistance that heats the engine.

Interfacial Mechanism

Interfacial polarization is a very difficult phenomenon to handle in a simple way and easily seen as a combination of conduction and dipolar polarization effects. This mechanism is important for a process in which a dielectric material is not homogeneous, but consists of one dielectric being included in another [26].

Effects of Solvents

Every solvent and reagent will absorb microwave energy differently.

They each have a different degree of polarity within the molecule, and therefore, will be affected either more or less by the changing microwave field.

A solvent that is more polar, for example, will have a stronger dipole to cause more rotational movement in an effort to align with the changing field. A compound that is less polar, however, will not be as disturbed by the changes of the field and, therefore, will not absorb as much microwave energy. Unfortunately, the polarity of the solvent is not the only factor in determining the true absorbance of microwave energy, but it does provide a good frame of reference. Most organic solvents can be broken into three different categories: low, medium, or high absorber. The low absorbers are generally hydrocarbons while the high absorbers are more polar compounds, such as most alcohols [27-30].

Table 1: Difference between Conventional vs Microwave Heating

Sr. No	Conventional Heating	Microwave heating
1	The heating mechanism involves only heat conduction.	Heating mechanism involves polarization and conductivity.
2	The vessel must be in physical contact with the source of the surface that also, for example, is a source of higher temperature.	There is no need for physical contact with a higher level of temperature.
3	It requires a lower heating rate.	Heating rate for microwave is multiple fold high.
4	The reaction mixture generally starts from the reaction vessel's surface.	Reaction mixture heating initiates directly inside mixture.
5	There is heating by thermal or electrical source.	Heating happens by electromagnetic wave.
6	Compound in the mixture is heated equally in conventional heating.	Different components can be specifically heated in microwave.

Computer Aided Drug Design (CADD)

Computer technology has been instrumental in stimulating and calculating things that have been too complex for human imagination. The crushing capacity becomes a research and exploration tool simply because of its incredible speed and storage capacity. But if designers were to behave like scientists and leave everything to simulations and computerized emergence at least two negative impacts would have. In the design process the designer would be reduced to a less innovative workhorse. But more seriously, unprocessed formalism, with no cultural content or meaning, would result. To develop the potential in computer aided drug design we need to:

- Visulalise abstracts structures.
- Connect cognitive analytical processes to visual computing.
- Take advantage of the computers generative power by exploiting the "engine of the unanticipated [31]".

Molecular Docking Studies

Molecular docking can be used to model the atomic interaction of protein and small molecules so that the behavior of small molecules is knowledgeable on the site of target proteins binding and to forecast essential biochemical processes. The purpose of scoring function is to delineate in reasonable computational time the correct possesses from incorrect possesses or binders from the inactive compounds. As the scoring method, the binding affinity between protein and ligand is determined by different assumptions as calculation [32].

The docking process involves two basic steps:

1. Prediction of the conformation of the ligand within these sites of orientation position.
2. Assessment of the binding affinity [33].

Quantitative Structure-Activity Relationship (QSAR)

QSAR includes the design of predictive pharmacological behavi or models as a function of the molecular and structural details of any compound library. In drug discovery and extensive research, QSAR has been used to integrate molecular information not only with pharmacological activities but also with other physiochemical properties such as QSPR. QSAR oftenly accepted for diagnostic and predictive process used to know relation between biological activities and chemical structures. This prediction techniques that not feasible or too time consuming. QSAR is the final outcome of a theoretical approach that often starts with a suitable descriptor of molecular structure and ends with some conclusion, predictions of molecular activity in the studied physiochemical, environmental and biological process. The final output of QSAR consists of various mathematical equations related to biological activity in the chemical structure. QSPR/QSAR received a advantage with the development of more complex descriptors and software [34].

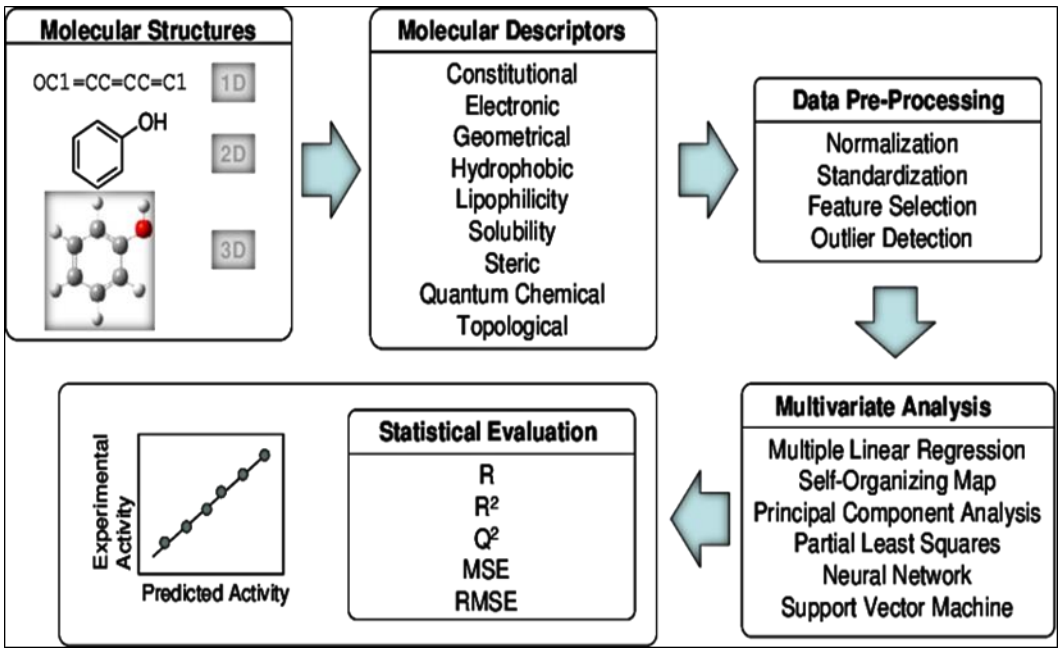

Fig 4: General Steps involved in QSAR Modeling

Proteins, peptides and peptidomimetics

At present, PPI modulators may be grouped into three classes: antibodies, peptides/peptidomimetics and small molecules. Antibodies have been used to identify protein surfaces that are important for interaction. Monoclonal antibodies (mAbs) are the most successful class of PPI inhibitors at present. Because of their high specificity for their target protein and their stability in human serum, they currently dominate the PPI modulators that have high therapeutic value. Most of the antibodies have common general methods of production and purification since their properties are similar[35]. 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 [37].

Molecular pharmacodynamics significance, potential and challenges

Not only do the currently exploited macromolecular targets for drugs and biologics include only a modest fraction of the estimated theoretical number (*vide supra*), but many of the potential ways by which these targets might serve therapeutic purposes, in terms of molecular mechanism of action (MMOA), have been underexploited to date; to wit, enzymes have most often been targeted with competitive inhibitors, and receptors most often with competitive antagonists or, less commonly, with full agonists[38]. This situation has been changing with increasing rapidity, but Swinney and Anthony build a compelling case that, "the importance of [testing the three hypotheses implicit to target-based approaches] may be an underappreciated challenge that, if neglected, could contribute to increased attrition rates for such approaches. In other words, it is clearly difficult to rationally identify the specific molecular interactions from all of the potential dynamic molecular interactions that will contribute to an optimal MMOA, [and] the key biochemical nuances [for achieving] an optimal pharmacological response could be missed [by adhering solely to] target-based approaches". Gleeson and colleagues also recently explained why overemphasizing drug-to-target binding affinity during lead optimization can actually increase the odds of producing candidate drugs having substandard biopharmaceutical character (unacceptable ADME profile). Imming *et al.* compellingly argue the importance of considering the dynamics of drug–target interactions, which we term molecular pharmacodynamics, towards attaining optimal, or even acceptable, clinical profiles [39].

Current trends in medicinal chemistry and future perspectives

With abundant data from genomics and proteomics, there is no doubt that there will be many more drug targets in the coming decades. It has been estimated that if all marketed drugs were considered with known molecular targets, these targets would number only 482. Based on genomics/proteomics and ligand-binding studies, it is now estimated that nearly 5000 targets could be hit by traditional drug substances, 2400 by antibodies and another 800 by protein pharmaceuticals. These targets include enzymes, receptors, ion-channels, transport proteins and DNA or RNA. These numbers seem to suggest a bright future for medicinal chemists; however, for target-based drug-design approaches, bottlenecks are the availability of 3D structures of biomolecular targets and, at an earlier and more basic level, bioassays based on identified targets that provide feedback suitable for iterative design efforts[40]. Considering the present situation in the pharmaceutical industry, the global economy, and the funding situation for public-sector research, the future viability of drug discovery and medicinal chemistry is debatable. Here, we review the recent literature that encompasses the debate concerning different models for drug-design and development research. The advantages and disadvantages of each model are discussed. In the past two decades, the advent of combinatorial chemistry, and high-throughput synthetic and natural product screening, has overloaded the start of the pipeline with hit compounds. Screening millions of compounds at super speed, however, does not mean that we find compounds that will make it to preclinical and clinical development[41]. This is one place where medicinal chemistry should continue to play a major role in the future. Medicinal chemists must create lead compounds from validated hits, via hit-to-lead chemistry/biology, and subsequently incorporate the full array of 'drug-like' properties via lead optimization, before extensive and costly late-stage preclinical development occurs. Once medicinal chemists create or identify lead compounds, further work on preclinical pharmacology and toxicology will be carried out, with critical evaluation of the data. The overarching goal is to achieve 'fail

early, fail cheap', because the more often that candidate drugs enter clinical trials and fail, the less profit is delivered by the enterprise in aggregate, and the less interest there is in continued investment. The past decade has produced lead compounds in large numbers; however, the later-stage clinical pipelines are lean, and major pharmaceutical companies have been losing their patent protection for blockbuster drugs at a frightening rate[42]. In the past two decades, the cost of developing a drug has sky-rocketed, with an estimated cost of at least a billion dollars for bringing a drug to the market. The vast majority of the drug-development funding is provided by the private sector, and at present, the majority of drug creation is still implemented in industry, with a mandate for commercial success (i.e., profits). Some are predicting that in the next few years pharmaceutical companies will widely adopt a different model, much more of a risk-minimized approach. It is even possible that, in the Western world at least, soon the majority of science (i.e., medicinal chemistry) will be conducted in public-sector settings and, moreover, with companies outsourcing most of the preclinical development and even Phase I clinical trials. Companies will choose only the most promising compounds and will focus their strengths on conducting clinical trials and gaining approval for marketing. This type of public-sector– industrial partnership could potentially create a win–win situation for both sides. Such a scheme was proposed by Chas Bountra, head of the Structural Genomics Consortium at the University of Oxford (UK). In his proposal, intellectual property (IP) restrictions would be lifted, and academics would publish preliminary data on prospective drug candidates, which would mostly comprise medicinal chemistry and pharmacological findings. Preclinically validated compounds would then be selected by industry, financial negotiations would take place, and the development process to bring the drug to the market would be continued in the private sector. This would save initial costs of research for industry, and also support academic research, wherein medicinal chemistry would play an increased role. The model of collaboration through academic–industrial partnerships has already gained momentum in the UK. For example, the Wellcome Trust has initiated a seeding drug discovery initiative program, which has committed awards to 19 academic institutions and 11 companies for research projects. A recent report lists at least six pharmaceutical companies partnering with academics in four countries, including nine US academic institutions. However, do such models deny the medicinal chemist his/her creativity and force him to give away or cheaply sell out IP? This remains to be seen in the success of this partnership between academics and industry over time. With the slowed pace of clinical drug development in the next decade, more focus will be placed on a stronger role for science in drug creation. In the current situation, pharmaceutical companies simply cannot take big failures. If the number of compounds sent for full-blown preclinical development is limited based on improved mechanistic studies and early preclinical filtering done in academic/public-sector settings, companies will be better positioned to handle the remaining unavoidable development risks. If this scenario were to become increasingly prevalent during the coming decades, one might argue that, historically, nearly all major drug discoveries were made in industry, and thus, that the proposed model of academic–industrial partnerships would greatly set back the already slower pace of availability of new drugs in the market. In addition, some would say that academic researchers, who are not driven by commercial success, might devote excessive time to endless questions related to the science behind molecular mechanisms. However, recent reports document that, in contrast with widespread assertions that almost all new drugs are created in the private sector, the public sector in fact contributed directly or indirectly to the discovery of 153 products in the past 40 years (9.3% of the approved drugs by FDA). Of these 153 marketed products, 93 small molecules, 36 biological agents, 15 vaccines, eight *in vivo* diagnostic materials, and one over-the-counter drug originated either wholly or partly from public-sector research institutions. These figures should tend to allay fears concerning negative impacts on the pace and cost-effectiveness of discovery and innovation but, perhaps, instead raise questions concerning the industrialization of academic institutions and diversion from the supposed primacy of education missions. These proposed changes in industry to concentrate more on drug development and leave the initial-stage 'science' to the academic domain are in concert with recent trends in NIH focus, where there have been shifts toward translational research. Although translational research may, in principle, refer even to basic research that ultimately leads to clinical outcomes, the starting point with respect to medicinals tends to be a molecular entity that modulates a biochemical pathway and leads to an understanding of a disease, and possible therapeutic application. Some intend that translational research will focus more on therapeutic pipeline research, so that it will fill the gap left by industry in the R&D sector in the next few years. According to the Director of the NIH, Francis Collins, the NIH wants to create a non-traditional way of fostering drug development. The investment of the NIH in translational academic research would, in part, be intended to 'de-risk' projects that might otherwise be economically unattractive to the private sector. Such efforts will elucidate molecular mechanisms of human diseases, and will also bring out the risks associated with the interactions of drug targets, and off-target effects. Some of these pipeline research efforts must, necessarily, be supported by medicinal chemists, from the initial creation of molecular entities to their modification as needed during risk assessments, which will be based on molecular-level understanding of deleterious interactions of the chemical entity with human physiology. Although public-sector research may slow the drug-creation and development processes in their earlier stages, increasingly detailed studies related to the pharmacological, pharmaceutical, and toxicological effects of a molecular entity should provide feedback in the final stages of drug development to the clinicians who make the decisions to proceed with or kill a project, and thereby increase efficiency by reducing the failure rate. This scenario would, at least, limit the number of candidates proceeding to full-blown preclinical development, and thence, to even more expensive clinical trials. The partnership of academia with industry will also benefit from increased sharing of information. The aforementioned Wellcome group is pushing for open-access chemistry, where genomic and proteomic data, as well as the results of cheminformatics analyses, are made widely available to academicians. In the last two decades, big pharmaceutical companies and research institutes have generated a tremendous amount of data that were heretofore available only internally, or provided only to partner organizations in heavily guarded fashion; now, large bodies of these data have been made available to the public domain, and

some institutions are investing heavily to capitalize. In the USA, for example, University of California at San Francisco has established a large center for research into drug design and development. Pfizer is reportedly drawing up a grand plan to invest in drug development-ready research in academia through a series of collaborations with leading medical centers. One of the first of these projects, which was announced in November of 2010, is also with University of California at San Francisco; the aim is to expand this model to collaboration with medical centers worldwide. A few other translational research centers are focusing on basic research related to medicinal chemistry. While major pharmaceutical companies like Pfizer and the Wellcome Trust have publicized plans for partnership with academic institutions, what is the role of small pharmaceutical companies in future drug discovery and medicinal chemistry? Biotechnology companies, and small and medium entities (SMEs), have been involved in partnership with academic institutions or state-funded research institutions for more than a decade. In fact, many small pharmaceutical companies and startup biotechnology companies are spin-offs of academic research innovations, and this will likely continue over the next 10 years. There are examples of mixed ventures that resulted in drug-discovery centers in the USA, UK and Canada. Certainly, not all SMEs are closely connected to academic or other public-sector institutions. The roles that such organizations play are very actively evolving, and will undoubtedly complement efforts of other players, fill key gaps and simply compete for partnership. With many state-assisted universities facing the challenge of severe budget crises, one of the possible ways to retain the vitality of research and training is to partner with the private sector, despite the associated compromises. Professors and their students would have to orient themselves for some form of translational output, apart from basic research. A collateral benefit of such academic-industry partnerships is that they will help keep a domestic pharmaceutical R&D job market. Companies are aggressively cutting costs, in unprecedented ways, at present. If academics are not willing to participate in collaborations, companies may, ultimately, outsource most of the early discovery-stage work, likely to SMEs, but also to other countries, which would further diminish job opportunities for domestic graduates. With proper academic–private partnerships, it should be possible to keep a component of basic research and academic independence yet participate in the challenging applied research aimed at unmet medical needs while simultaneously compensating for the changing funding environment. However, there are significant concerns about the way the public–private model works. Project milestones will be set, and will be periodically evaluated for successful attainment by a steering committee. Even when the milestones are achieved by a project investigator, if the results suggest that the risks are too great to take the project to industry for the later stages of drug development, funding will be terminated. In such situations, academics are left in the middle of nowhere. The IP distribution issue was already mentioned earlier. Another drawback to this model stems from the greatly increased rate of acquisitions, mergers, and reorganizations of pharmaceutical companies over the past two decades. Following such events, if new leadership is not interested in a project in that an academic institution is participating, funding would likely be terminated in the middle of a project. Another major drawback for academics is the constraints that are placed on the publication of data. What can be published invariably depends on approval by the industrial partner. If important data are only partially publishable, a manuscript may not be accepted, particularly by journals with high impact factors. Without publication, students working on projects may be challenged to convince their review committees of acceptance of their not-peer-reviewed/unpublished work. At the same time, supervisors or project leaders will face the challenge of submitting research-funding applications to federal agencies with fewer publications in a particular field in which they are seeking funds. In the USA, this will represent an even greater obstacle than in the past, as new NIH guidelines require recent publications in the field in that the principle investigator is looking for funding in, rather than depending more on total numbers of past publications by the principle investigator. Above all, a major question to be addressed in this model is, do academicians lose too much of their academic freedom by engaging in such research? Thus, for a medicinal chemist, there are real compromises. The discipline of medicinal chemistry is largely an applied science, and, apart from issues of academic freedom, medicinal chemists always experience the intrinsic risks. Compensatory incentives are associated with the great potential for end results that are beneficial to society. If society maintains an interest in the creation of new medicinals towards addressing unmet medical needs, then the centrality of medicinal chemistry as well as its scientific power and potential in these endeavors must be fully appreciated, and recognized with altered economic policies and adjustment of funding structures in ways that reflect the unique attributes of the enterprise. The model of the NIH creating translational research centers, which emphasizes that it will help take the scientific discoveries to practical applications by turning the research output into actual drugs or treatments, has also caused debate. If the NIH gets heavily involved in creating drugs, and especially during their development, is NIH partially converting itself into a public-sector pharmaceutical company? There will be polarization among academics between those that have support or are funded by industry, and those that never partner with industry. According to Roy Vagelos, former Chairman of Merck, the NIH should stick to basic research. There is also concern that if the focus of the NIH funding shifts excessively to the drug-development process rather than remaining on basic science, this will pull resources away from producing new knowledge and discoveries [43].

Conclusion

Rapid advances in our collective understanding of biomolecular structure and, in concert, of biochemical systems, coupled with developments in computational methods, have massively impacted the field of medicinal chemistry over the past two decades, with even greater changes appearing on the horizon. In this perspective, we endeavor to profile some of the most prominent determinants of change and speculate as to further evolution that may consequently occur during the next decade. The five main angles to be addressed are: protein–protein interactions; peptides and peptidomimetics; molecular diversity and pharmacological space; molecular pharmacodynamics (significance, potential and challenges); and early-stage clinical efficacy and safety. We then consider, in light of these, the future of medicinal chemistry and the educational preparation that will be required for future medicinal chemists. Given current economic constraints, industry may increasingly shrink or

outsource the early stages of drug creation and development. The next decade will see increased medicinal chemistry collaboration between industry and public-sector institutions; productivity will depend on recognizing and addressing various caveats. Given current trends, medicinal chemistry trainees should continue to emerge as chemists first and foremost, furthermore having computational and cheminformatics acumen considerably greater than in years past. To be maximally effective, however, they will also need to gain strong working understandings in key areas of biochemistry and structural biology, as well as pharmacology, pharmaceutics, toxicology, and the clinical sciences; early introduction and persistent exposure as part of well-structured graduate programs could effectively enable this aim to be met.

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