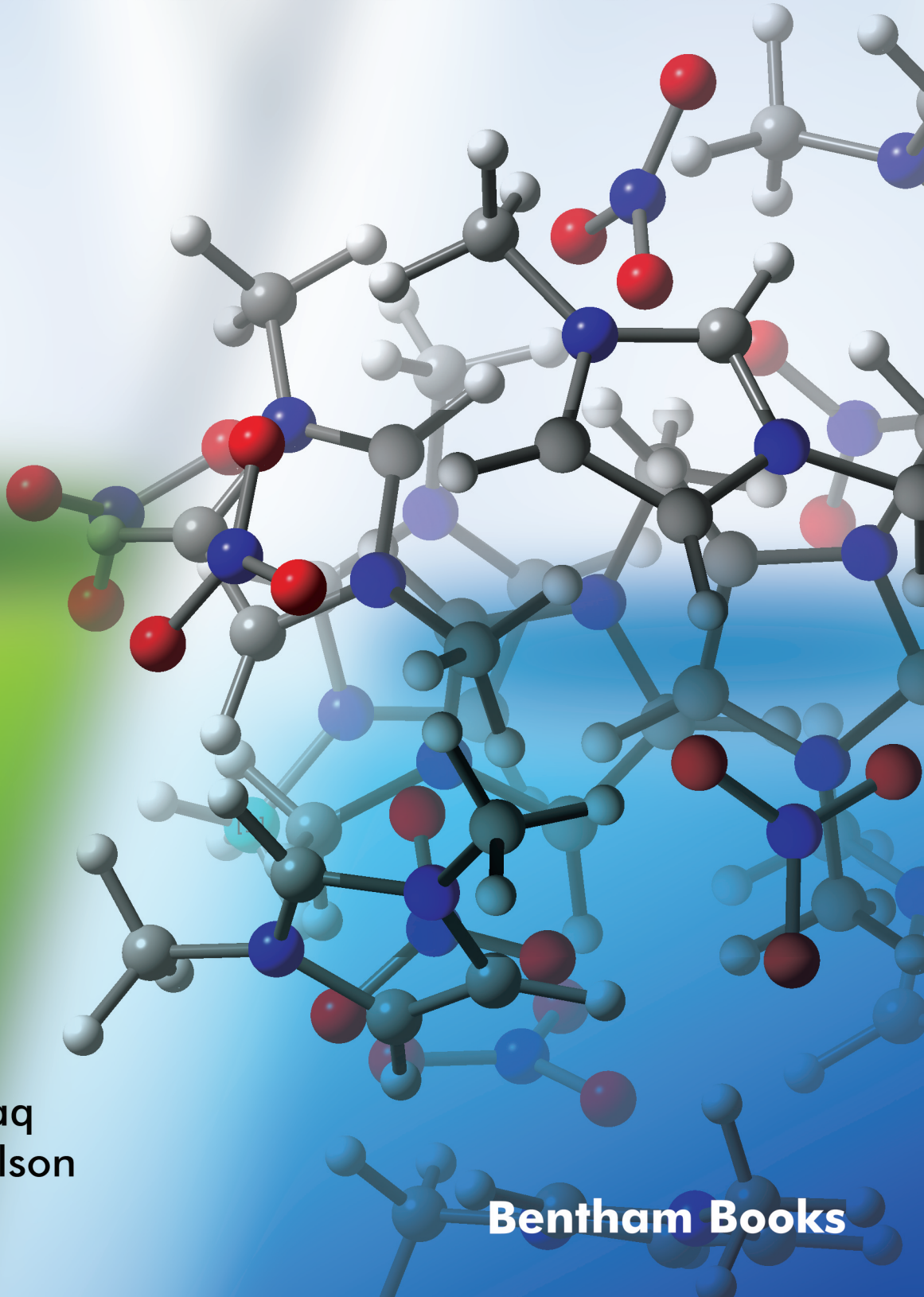
FRONTIERS IN COMPUTATIONAL CHEMISTRY



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Bentham Books

Frontiers in Computational Chemistry

(*Volume 5*)

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Frontiers in Computational Chemistry

Volume # 5.

Editors: Zaheer Ul-Haq and Angela K. Wilson

ISSN (Online): 2352-9458

ISSN (Print): 2352-944X

ISBN (Online): 978-981-14-5779-1

ISBN (Print): 978-981-14-5777-7

ISBN (Paperback): 978-981-14-5778-4

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PREFACE

Computational chemistry is an important partner to experiment in understanding a very broad range of chemical problems, providing insight not possible or not easily possible to obtain via experiment, and enabling a greater understanding of experiment when it is possible. The span of computational chemistry approaches in terms of both method and applicability is significant – with methods including electronic structure calculations (*e.g.*, density functional theory (DFT)) and free energy relationships (*e.g.*, QSAR, QSPR), with applications spanning from in-depth description of the spectroscopic properties of the smallest of atoms and molecules to the design of new molecules and materials in medicine.

The focus of ***Frontiers in Computational Chemistry*** is on the application of computational chemistry approaches to biological and organic processes.

In this fifth volume, the six chapters address a diversity of topics including:

Chapter 1 "**Recent Advances and Role of Computational Chemistry in Drug Designing and Development on Viral Diseases**" Amit Lochab, Rakhi Thareja, Reena Saxena, Sangeeta D. Gadre.

This chapter outlines a number of approaches that are commonly used in drug design, including structural-based and ligand-based computational strategies, and the role of quantum mechanics and molecular mechanics. A brief overview of how these methods have been utilized in the development of drugs against viral disease, addressing ebola, zika, hepatitis C, and coronavirus is provided.

Chapter 2 "**Molecular Modeling Applied to Design of Cysteine Protease Inhibitors – A Powerful Tool for the Identification of Hit Compounds Against Neglected Tropical Diseases**" Igor José dos Santos Nascimento, Thiago Mendonça de Aquino, Paulo Fernando da Silva Santos-Júnior, João Xavier de Araújo-Júnior, and Edeildo Ferreira da Silva-Júnior.

The impact and importance of computational chemistry in drug development is significant. However, the drug discovery process is truly a fine art, with numerous methods and strategies available. In this chapter, the authors consider a number of different molecular modeling techniques, and demonstrate their use in the development of cysteine protease inhibitors. Cysteine proteases are known to play important roles from growth and development of plants to bone development in humans and animals. In this study, the design of cysteine protease inhibitors against a number of tropical diseases is considered.

Chapter 3 "**Application of Systems Biology Methods in Understanding the Molecular Mechanism of Signalling Pathways in the Eukaryotic System**", Aditya Rao S.J. and M. Paramesha.

Signalling pathways are critical cascades of reactions that can impact metabolic functions from cell division to cell death. Understanding the underlying mechanisms of signalling pathways is critical, as this can provide insight about how abnormalities can impact the activation or deactivation of signalling events. The authors provide an overview of computational routes that can be used to understand signalling path mechanisms, including systems biology and data mining. Wnt signalling pathways are the focus of this chapter due to their role in growth to cancer.

Chapter 4 "**Implementation of the Molecular Electrostatic Potential over GPUs: Large Systems as Main Target**" J. César Cruz, Ponciano García-Gutierrez, Rafael A. Zubillaga, Rubicelia Vargas and Jorge Garza.

Electrostatic interactions are vital to non-covalent interactions which are prevalent in biological systems. A very useful means to gain insight about these electrostatic interactions is via the molecular electrostatic potential (MEP). MEP is generated using quantum mechanical methods, which represents a significant computational challenge for all but the smallest of molecules. This chapter provides two routes to extend the utility of MEP to larger molecules, utilizing graphical processing units (GPUs) to generate the MEP. The theoretical details are provided, as are a number of useful examples of the application of the methods.

Chapter 5 "**Molecular Electron Density Theory: A New Theoretical Outlook on Organic Chemistry**" Luis R. Domingo, Nivedita Acharjee.

This chapter highlights molecular electron density theory (MEDT), which was introduced by the co-author, Luis Domingo, in 2015. MEDT is based upon the philosophy that changes in electron density rather than molecular orbital interactions drive molecular reactions. The authors discuss a broad range of quantum mechanical principles and approaches that are a part of MEDT and facilitate the understanding of molecular interactions and reactions. The authors provide a long list of reactions, and conclusions that can be drawn from MEDT about these reactions.

Chapter 6 "**Frontier Molecular Orbital Approach to the Cycloaddition Reactions**", Anjandeep Kaur.

Cycloaddition reactions, more specifically, 1,3-dipolar cycloaddition reactions, play a critical role from drug discovery to materials design. Controlling the regioselectivity, enantioselectivity, and diastereoselectivity of these reactions is a major challenge. In this chapter, the reactivity and selectivity of a wide variety of 1,3-dipolar cycloaddition reactions is overviewed. A Frontier Molecular Orbital (FMO) approach is considered.

We hope that the readers will find these reviews to be valuable, and that they may inspire trigger further research in the field. We are grateful for the timely efforts made by the editorial personnel, especially Ms. Mariam Mehdi (Assistant Manager Publications), Mr. Obaid Sadiq (Manager Bentham Books), and Mr. Mahmood Alam (Director Publications) at Bentham Science Publishers.

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CHAPTER 1

Recent Advances and Role of Computational Chemistry in Drug Designing and Development on Viral Diseases

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Abstract: The growing number of contagious viral diseases among different geographic regions has become a threat to human health and the economy on a global scale. Various viral epidemics in the past have caused huge casualties due to lack of effective vaccine, the recent outbreak of COVID-19 is a good example of it. Drug designing and development is a lengthy, tedious and expensive process that is always associated with a high level of uncertainty as the success rate of their approval as a drug is very low. Computer-aided drug designing by utilizing *in silico* methods has shown prominent ways to develop novel drugs in a cost-efficient manner and has evolved as a rescue in the past few years. Interestingly, the highest FDA approval reached a maximum (59 drugs) in 2018 for which a lot of credit goes to the successful development of computational chemistry tools for drug designing in the last two decades. These methods provide better chances of getting hit compounds in a far more accurate and faster way. Drug designing is a cyclic optimization process that involves various steps like creating a molecule, selecting the target for this molecule, analysing the binding pattern and estimating the pharmacokinetics of the molecule. The final development of a drug candidate is cumulative of positive results obtained in each aforementioned step. Various computational techniques/approaches such as molecular dynamic studies, homology modelling, ligand docking, pharmacophore modelling and QSAR can be utilized in each phase of the drug discovery cycle. In this chapter, we aim to highlight the recent advances that have taken place in developing tools and methodologies that lead to *in silico* preparation of novel drugs against various viral infections like Ebola, Zika, Hepatitis C and Coronavirus.

Keywords: Computational chemistry, Homology modeling, *In Silico*, Ligand-based drug designing, Ligand docking, Multi target drug designing, Pharmacophore modeling, Protein target, Quantum mechanics, Structure-based drug designing, Viral infection, Virtual screening.

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INTRODUCTION

There is a huge global effort indulged in wiping out the infectious viral diseases. Viral infections include various contagious diseases like Ebola, Hepatitis, HIV-AIDS, Rabies, Zika and Corona viruses. These ailments cause a huge impact on both the economy and health. Methods in controlling these diseases like vaccination, public awareness through advertisement and campaigns cause a reduction in the budget which is not that effective also. The current available drugs for the disease have their own limitations of being toxic, less potent and high cost. There are several viral microbes that gain resistance toward these drugs and there is always a continuous need for developing new effective drugs. Studies show that the traditional path for discovering drugs and bringing it to market costs around 2 billion USD. In addition, they require a long time, and the process is highly laborious to establish their safety and effectiveness. At the starting of the 20^{th} century, the drug industry was used to screen out various natural and synthetic compounds experimentally in search of therapeutic characteristics for a particular target. Then the compound was optimized for better pharmacological properties having less toxicity which after clinical trials used to take on an average of ~15 years to come in the market [1]. The concerns over various incurable diseases and an inadequate number of potent drugs have forced us to develop innovative drugs with high specificity and potency for the respective target. The ways in which these microbes are mutating their genes to make a come back in our world have proved to be hazardous in an irreparable fashion as is evident from the outbreak of the pandemic of Covid-19 in December, 2019. This has further added the interests of the researchers in fast and efficient drug discovery tools.

Drug discovery using computational chemistry is established very well from the past few years due to development in combinatorial chemistry with computational screening and optimizing tools, with enhanced, fast and efficacious results. The computational methods help in predicting the conformational interactions of active drugs with the target sites. High throughput screening (HTS) and Computer Aided Drug Discovery (CADD) techniques have helped in suggesting favourable drugs out of huge libraries in a short time by understanding the interaction between the target molecule and the proposed drug. The drug discovery process includes several computational approaches before the clinical trials, right from the beginning in which identification of target and their association with a particular disease is considered for studies. The second step is to investigate the interaction of proposed drug molecules with validated target which is followed by the optimization of lead molecules for the improvement in their potency and biological toxicity [2, 3].

This chapter aims to give an overview of different computational approaches and tools for the development in drug designing based on explanation from quantum mechanics. This covers various optimization procedures for enhancing potency of lead compounds. Finally, recent applications of CADD in designing drugs for viral diseases such as Ebola, Zika, Hepatitis C and Coronavirus are discussed.

The first modelling approach in computational drug development method is to identify the probable target related to particular disease. Generally, these targets can be proteins, enzymes or complex bio molecules having specific bioactivity. CADD can be divided into Structure based drug design (SBDD) and Ligand based drug design (LBDD) based on the availability of the structures of the above bio molecule targets as shown in Fig. (**1**). Both approaches are complimentary to each other as SBDD employs known structure of the target moiety for the screening of active new compounds. The structural information of target is used to find new lead compounds by suggesting a design of potent molecule or through screening from virtual libraries and databases. Whereas LBDD is a suitable approach, when the crystal structure of drug target is not available. However, one must clearly understand that SBDD is based on the drug-target structure where in the binding efficiency by a specific ligand/drug is given major importance which may be studied using several docking tools. On the other hand, LBDD makes use of ligands of the target *i.e.* potential drugs shortlisted to bind to the biological target of the drug [4].

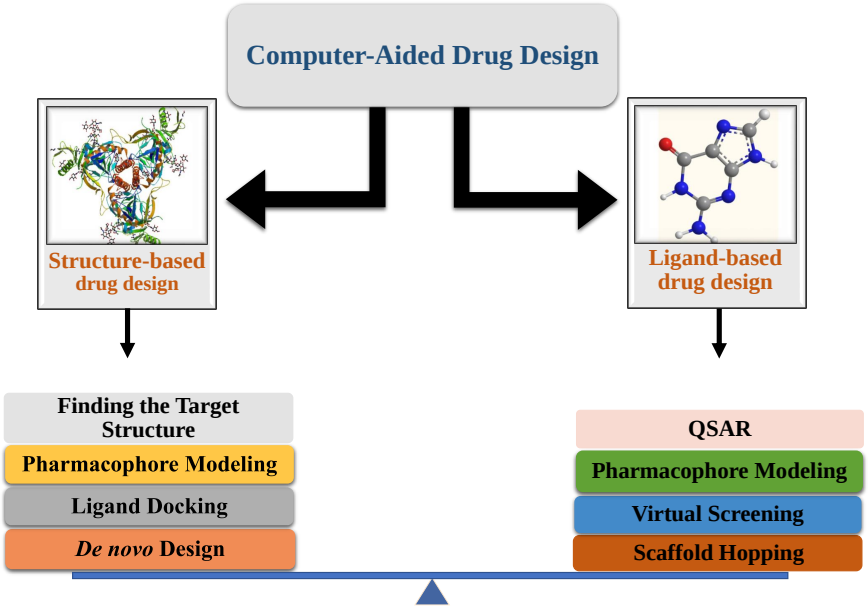

Fig. (1). Computer-Aided Drug Design.

CHAPTER 2

Molecular Modeling Applied to Design of Cysteine Protease Inhibitors – A Powerful Tool for the Identification of Hit Compounds Against Neglected Tropical Diseases

Igor José dos Santos Nascimento[1], Thiago Mendonça de Aquino[1], Paulo Fernando da Silva Santos-Júnior[1], João Xavier de Araújo-Júnior[2] and **Edeildo Ferreira da Silva-Júnior[1,2,*]**

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Abstract: Cysteine proteases play numerous and extremely important roles in the life cycle of parasitic organisms with medicinal importance. From general catabolic functions and protein processing, cysteine proteases may be key to parasite immunoevasion, excystment/encystment, and cell and tissue invasion. Parasite cysteine proteases are unusually immunogenic and have been exploited as serodiagnostic markers and vaccine targets. The research focused on the development of new drugs actives toward this macromolecular target is an important task, where the rational design is considered as a critical step on it. The discovery of new drugs is a complex and multidisciplinary process, which includes an in-depth knowledge of organic chemistry, pharmacology, biochemistry, computer sciences, and others. This process involves high costs and several scientific fields, leading to the necessity to develop new processes that involve optimization of molecular modeling applied to the identification of bioactive molecules. These techniques could increase the probability of obtaining a rational-designed compound, with high activity and safety, which could be considered as a potential drug in the future. Thus, the use of computational techniques has become increasingly common in medical chemistry laboratories due to their low costs and high correlation with experimental results from assays. A broadly used technique in the rational design of active compounds is molecular docking of small ligand at the active site from the biological targets. In this chapter, we will demonstrate in detail different molecular modeling techniques applied to the development of new inhibitors against cruzain (*Trypanosoma cruzi*); falcipain (*Plasmodium falciparum*); SmHDAC8 (*Schistosoma mansoni*); nsP2 (Chikungunya virus) enzymes; and others, such as cathepsin family; caspase family, $3C^{pro}$ (Enterovirus 71) and $3CL^{pro}$ (Coronavirus).

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Finally, studies have revealed that the application of molecular modeling is a powerful tool for predicting new active and productive molecules against infectious diseases.

Keywords: Cysteine Proteases, Drug Discovery, Molecular Modeling, Neglected Tropical Diseases, Virtual Screening.

INTRODUCTION

According to the World Health Organization (WHO), Neglected Tropical Diseases (NTDs) refer to a set of 20 bacterial, parasitic, or viral diseases involving vectors or hosts with complex life cycles. In 2018, NTDs affected about 1.5 billion individuals that are living in social exclusion and poverty in 149 different countries, representing 11% of all global diseases [1 - 3].

From 2012 to 2018, only 3.1% of all 256 approved new drugs were addressed to the NTDs' treatment [2, 4]. Among these, six approved drugs were obtained from drug repurposing based on *in silico* studies), new formulations or biological studies, evidencing a profound lack of interest in research addressed to the discovery of new drugs and treatments for such diseases [5 - 7]. Thus, the major reason for this lack of interest by pharmaceutical companies is related to the high financial costs for drug designing and development. Recently, it has been estimated that US$ 3.4 million are necessary for the preclinical phase, increasing up to 8.6 and 21.4 million dollars in the II and III clinical phases, respectively. Finally, the low financial return generated by this type of pharmacotherapeutic agents is also a complex factor [8 - 11].

Considering this, the current trend of the drug discovery process remains on the combination of Computer-Assisted Drug Design (CADD) tools (*in silico* methods) and combinatorial chemistry and/or high-throughput screening (HTS) studies to improve the ability to discover promising agents or scaffolds [12, 13]. This trend reduces costs by decreasing the number of molecules to be tested, minimizes the possibility of failure due to physicochemical properties, and allows to comprehend the pharmacological mechanism at a molecular level [14 - 16].

The CADD strategy is subdivided into two large groups: Ligand-Based Drug Design (LBDD), in which all information about ligand structures and their biological activities are considered (*e.g.* Quantitative Structure-Activity Relationship (QSAR) and similarity modeling). In contrast, Structure-Based Drug Design (SBDD) considers information about the 3D-structure of biological targets and also ligands' structures (*e.g.* molecular docking and dynamics simulations) [13 - 15]. Moreover, the homology modeling (HM) is based on the production of an atomic model (as an SBDD method), built from the amino acid sequence of a

biomacromolecular target, as well as homologous proteins [17, 18]. In this context, CADD has become an essential and powerful tool for drug designing of new agents against NTDs. From this, several drugs have already been discovered by this approach, such as Saquinavir (antiviral), Zanamivir (antiviral), Norfloxacin (antimicrobial), Dorzolamide (antiglaucoma), and Oxymorphone (narcotic analgesic) (in clinical trials) [13].

CA-clan papain-like cysteine proteases (CP) represent a group of targets present in several parasites associated with NTDs that have been exhaustively explored in various virtual screening studies. These enzymes are proteases that irreversibly hydrolyze nucleophilic attack-mediated peptide bonds that generate a tetrahedral intermediate. Furthermore, cysteine proteases are present in different life forms of various NTD-mediating parasites, participating in diverse biological processes [19 - 21]. Thus, they constitute potential targets for drug design and development of antiparasitic compounds, such as the promising vinyl sulfone K777 (Fig. **1**), in the preclinical stage against Chagas disease, for example [19, 22, 23].

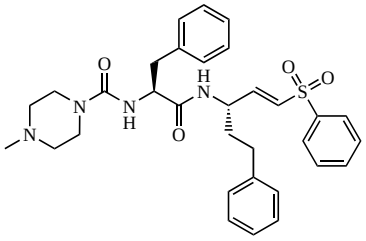

Fig. (1). Most promising vinyl sulfone (K777) found in the literature.

This chapter summarizes a compilation of studies involving the application of molecular modeling approaches for developing new cysteine protease inhibitors. It will focus on the development of inhibitors against cruzain (*Trypanosoma cruzi*), falcipain (*Plasmodium falciparum*), SmHDAC8 (*Schistosoma mansoni*), nsP2 (Chikungunya virus), cathepsin-S, -K, -B, and -L (human), $3C^{pro}$ (Enterovirus 71), $3CL^{pro}$ (Coronavirus), and caspase-1 and 3 (human) by using virtual screening techniques.

VIRTUAL SCREENING IN DRUG DEVELOPMENT

The discovery of new drugs is a complex and time-consuming process that requires a high degree of knowledge in different areas of science and has faced many changes and challenges in recent decades [24]. Recently, the development of drug has included virtual screening methods in which molecules do not

CHAPTER 3

Application of Systems Biology Methods in Understanding the Molecular Mechanism of Signalling Pathways in the Eukaryotic System

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Abstract: A signalling pathway is a cascade of reactions carried out together by a group of molecules in a system to bring out the metabolic functions starting with cell division to cell death. When signalling pathways interact with one another, they form networks, which allow cellular responses to be coordinated, often by combinatorial signalling events. Any abnormal change affecting the activation or deactivation of such signalling events leads to the abnormal physiological cellular functions. The understanding of the molecular mechanism of signalling pathways is beneficial to understand the pathological scenery and treatment. Recent advancements in computational methods have given a new insight to understand the molecular mechanism involved in signalling pathways. The use of systemic and computational tools is crucial in systems biology as the complexity of the biological system is more, a vast amount of data is being generated and the scattered pieces of information has to be integrated into a meaningful order. The present chapter deals with the utilization of systems biology tools, and data mining techniques to understand the molecular mechanism of 'Wnt signalling pathway; an intercellular pathway which regulates critical aspects of cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during embryonic development', with the integrated software platforms, which could help to address the future research problems in biology and medicine.

Keywords: Axin, Cancer, β-catenin, GSK-3β, Network analysis, Pathway prediction, Systems biology, Tankyrase, Therapeutics, Wnt signalling pathway, Wnt ligands, Wnt protein.

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INTRODUCTION

Intercellular Signalling Pathways

Cells communicate through cellular pathways, which play a significant role in their development. These pathways can be considered as 'control knobs' as they not only induce or block cellular differentiation during growth [1] but also control cellular behaviour [2, 3]. This can be exploited for biomedical applications in regenerative medicine [4, 5] as well as in providing valid drug targets [6, 7]. The intercellular signalling pathways have attracted many researchers due to their prevalent and diverse roles. The conservation of these intercellular signalling pathways across different species has made them the best-studied systems in biology in recent times. For many intercellular pathways, their association with ligands, receptors, intracellular effectors, transcription factors, and modulators have been identified, and their interactions have also been characterized. However, with the existing knowledge on the behaviour of intercellular pathways, some of the most basic operational questions still remained unanswered. These answers help in understanding specific molecular interactions, including how cell receives, processes and treats extracellular signals within the cell.

WHAT IS WNT?

The term Wnt stands for 'wingless- related integration site' which is derived from two words, namely 'wingless' and 'int'. The sequencing studies in Drosophila revealed the homogenicity of its wingless gene with oncogene int-1. Hence int/wingless family was considered as Wnt family. Wnts are involved in many crucial cellular processes like regulating the cell growth, motility, differentiation during embryonic development, controlling cell proliferation and cell fate apart from activating diverse signalling cascades. The degradation rate of β-catenin, a secondary messenger that acts as a transcriptional co-regulator in cell proliferation, is controlled by Wnt signalling. β-catenin will be degraded by multiple protein complexes when the Wnt pathway is inactive. This protein complex can be inactivated by the activity of receptor-targeted inhibitors, which results in accumulation of β-catenin [8]. This suggests that the β-catenin level can be externally controlled by the involvement of ligands, thus controlling Wnt signalling. The concentration of β-catenin is found to be different from cell to cell due to the variations in biochemical pathways and their fold-change resulted by the stimulation from external ligand but found to be uniform across cells [9]. This adaptive response of cells to external stimuli to produce β-catenin is controlled by Wnt genes [9]. Thus, it is possible to control the response of Wnt signals in turn controlling the cell fate decision by controlling the level of stimulation [10].

Types of Wnt Signalling Pathway

Based on the involvement of β-catenin, the Wnt pathway can be classified as follows:

1. Canonical Signalling Pathway
   - β-catenin dependent
   - β-catenin independent
2. Non-Canonical Signalling Pathway

CANONICAL PATHWAY

β-Catenin Dependent Canonical Pathway

The canonical pathway is also known as Wnt/β-catenin dependent signalling pathway [11] and also considered as a first identified pathway, which involved in the vital process such as cell proliferation, ribosome biogenesis, and inhibition of apoptosis [12]. Maintenance of intracellular β–catenin is associated with the canonical Wnt pathways. The activation of the canonical pathway starts with the binding of Wnt ligand to its receptor (Fig. **1**). The 'β-catenin destruction complex' is composed of scaffold protein Axin, glycogen synthase kinase-3β (GSK-3β), Casein Kinase-1α (CK-1α), and the tumour suppressor adenomatous polyposis coli (APC) [13, 14]. This destruction complex exhibits the sequential phosphorylation by the CK-1α and GSK-3β enzymes present in the destruction complex and is targeted by ubiquitination and proteasome degradation [12, 15 - 17]. Thus, it controls the concentration of β-catenin accumulation in the cytoplasm and, in result, it will impede the signalling activity of Wnt/ β-catenin in the nucleus. Meanwhile, in the absence of β-catenin, transcriptional repressor Groucho binds to TCF (T-cell factor)/LEF (lymphoid enhancer factor), which inhibits the transcription of genes. Stabilization of β-catenin is initiated by Wnt protein, when it binds to the transmembrane receptor Fz (Frizzled) and the co-receptor LRP5/6 (low-density lipoprotein receptor-related protein-5/6) [18, 19]. The Wnt protein, Fz and LRP5/6, forms receptor complex, which facilitates the Dishevelled (Dvl) protein to the membrane, which leads to the formation of Signalosome [12]. The Signalosome provides the platform to the "β-catenin destruction complex," resulting in disassembly of "β-catenin destruction complex" initiated by CK-1α, which phosphorylates LRP5/6. As a result of this, cytoplasm abundant of β-catenin translocates to the nucleus, which ultimately displaces the transcriptional repressor Groucho and binds to TCF (T-cell factor)/ LEF (lymphoid enhancer factor) and triggers the expression of target genes [12, 17, 20 - 22].

CHAPTER 4

Implementation of the Molecular Electrostatic Potential over GPUs: Large Systems as Main Target

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Abstract: The molecular electrostatic potential (MEP) is a useful tool to design and develop drugs. However, the evaluation of this property using quantum chemistry methods presents a challenge for molecules of medium or large size since this is computationally expensive. In this chapter, we showed two implementations of this property over graphics processing units (GPU). In the first instance, we discussed some details that must be considered when GPUs are involved in high-performance computing. After this step, the algorithms considered to evaluate MEP over GPUs are exposed to observe the main differences between a method with minimal approximations and another one where usual approximations are implemented in many quantum chemistry codes. The benefits provided by these graphics cards are evidenced when our implementations are applied over molecules of considerable size like those found in protein-ligand complexes, where usually the electrostatic potential is modeled by a set of point charges.

Keywords: Cuda-C, GPUs, Molecular Electrostatic Potential, Multipolar Expansion, Proteins.

INTRODUCTION

Electrostatic interactions are crucial to form non-covalent interactions in biological systems where many biomacromolecules contain electrical charges in a great variety of fragments built with small charged molecules and monoatomic ions. As an example, we can mention globular proteins, which are polyelectrolytes with ionized amino acid residues like Asp and Glu with a negative charge, and Lys and Arg with a positive charge; these four types of

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residues represent about a quarter of all residues in an average protein [1]. In general, the biological activity of a protein shows up by interacting selectively with another biomolecule, large or small, and the electrostatic contribution to the binding energy is crucial in many cases [2, 3]. To visualize better the tendency of favorable electrostatic interactions between two molecules, instead of using the representation of positive and negative surface charges it is more accurate to display the molecular electrostatic potential (MEP), since even in proteins with a small net charge, patterns of positive and negative electrostatic potential are over the molecular surface [1]. The complementarity of the MEP between different fragments dictates the formation of a complex, and sometimes such a complementary is more important than a different sign of their net charges [4]. Besides, the charged state of some polypeptides is modulated by post-translational modifications like phosphorylation, in response to extracellular signals, changing the MEP locally and creating new binding epitopes for specific targets. Many of the mutations that lead to cancer involve ionizable residues [4]. Nucleic acids are among the strongest natural polyelectrolytes, which contain a phosphate group (PO^-_4) for each base in their sequence so they can interact favorably with molecules displaying surfaces of positive MEP (see Fig. **3** of Honig and Nicholls [4]). Phospholipid membranes also have strong electrostatic interactions with proteins and other biomolecules. Therefore, the computation of the MEP is desirable for these cases.

Evaluation of the MEP is not an easy task if this is obtained from its definition [5, 6]

$$\Phi(\mathbf{r}_2) = \sum_A \frac{Z_A}{|\mathbf{r}_2 - \mathbf{R}_A|} - \int d\mathbf{r}_1 \frac{\rho(\mathbf{r}_1)}{|\mathbf{r}_1 - \mathbf{r}_2|}, \quad \textbf{(1)}$$

where precisely the charges in the system are involved in computing this property. In this case, Z_A represents the nuclear charge of each atom in the system, and the electron density is represented by $\rho(\mathbf{r})$. From definition (1), one can deduce that there are sites in a molecule where nuclei command and, therefore $\phi(\mathbf{r})$ is positive, and regions where the electron density rules and consequently $\phi(\mathbf{r})$ is negative; this characteristic has been widely used in quantum chemistry applications [7 - 11]. For molecular systems, we need the electron density from quantum chemistry methods, or from experimental information, to use equation (1). In this chapter, we will deal only with theoretical approaches related to the electronic structure of atoms and molecules. Thus, the evaluation of the MEP could be computationally expensive and some times prohibitive for systems of considerable size. This contribution aims to discuss two algorithms to obtain the MEP over graphics processing units (GPU). In our group we have developed

some strategies to implement grid-based methods over GPUs to determine quantum chemistry scalar and vector fields like the electron density and derivatives of it. As we can see from equation (1) this property is directly involved with the MEP, and for that reason, we think that an analysis of its implementation over GPUs is appropriate currently, since this hardware has high availability.

GRAPHICS PROCESSING UNITS IN QUANTUM CHEMISTRY

Graphics processing units have gained a relevant role in the high-performance computing, particularly in quantum chemistry [12 - 19] or in computational modeling based on molecular dynamics [20 - 23]. The number of threads and the memory involved in a GPU of the last generation are desirable to developers of parallel computing applications. In our group, we have reported the evaluation of scalar and vector fields defined in quantum chemistry, over grids with the use of GPUs. In specific, we have developed the graphics processing units for atoms and molecules (GPUAM) [24, 25] code with the primary purpose of the development of an application where personal computers with an installed GPU can be used for demanding computational tasks. This code uses WFN or WFX files as input data, which are ASCII files, and they can be used in any computational system. These files are obtained from programs like GAMESS [12], Gaussian [13], or NWChem [14]. Besides, the Molden2AIM [26] code allows us to use other formats to convert the corresponding files in WFN or WFX formats, which contain nuclei coordinates, exponents of the basis set, and the coefficients $\{c_v^i\}$ that give the best representation of Hartree-Fock or Kohn-Sham orbitals in terms of a basis set, even correlated methods can be used if the coefficients of natural orbitals are in these formats. In this chapter, we do use Terachem [15, 16, 18], which has been designed from scratch to be executed on GPUs and the files delivered by this code are transformed to WFX format by using Molden2AIM. With wfn or wfx files, the GPUAM evaluates a scalar or vector field, assigning one thread of the GPU to one point of the grid. At the end of this process, GPUAM writes the final results in permanent memory through files with cube format, which is a standard extension introduced by Gaussian, Inc. This procedure is sketched in Fig. (**1**).

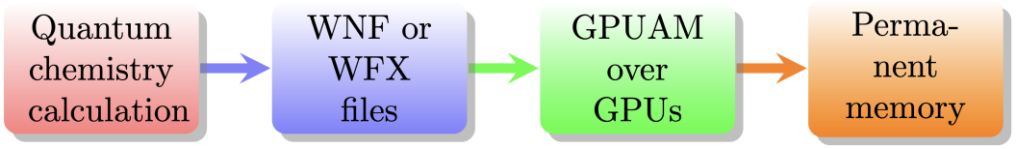

Fig. (1). Procedure to obtain a scalar or vector field defined in quantum chemistry using GPUAM.

In GPUAM, the grid is distributed over a GPU, or over the GPUs defined by a

CHAPTER 5

Molecular Electron Density Theory: A New Theoretical Outlook on Organic Chemistry

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Abstract: Organic Chemistry has evolved continuously as the backbone for the sustainability of different disciplines such as medicinal chemistry, chemical biology, biochemistry, biotechnology, material science, polymers, and nanotechnology. The beauty of organic reactions lies in their unique structural framework, reactivity, and selectivity, interesting stuff for molecular modelling research. However, theoretical interpretations of organic reactions have not been able to keep pace with the ever-increasing efficiency of computational chemistry software along the last two decades. This is probably due to the popular use of the Frontier Molecular Orbital (FMO) theory to study the course of organic reactions during the last 40 years, in spite of its failure and criticism in several cases. In 2016, Domingo proposed a new theory, called "**Molecular Electron Density Theory (MEDT)**" to study molecular reactivity of organic reactions, which is backed up by the use of quantum chemical tools. This theory proposes the decisive role of electron density changes in the reactivity of organic molecules, being opposed to FMO concepts. MEDT has been successfully applied to rationalize the experimental outcome of several Diels-Alder reactions, sigmatropic rearrangements, electrocyclic reactions, and [3+2] cycloaddition reactions. MEDT covers the detailed analysis of Conceptual DFT (CDFT) indices, exploration of the Potential Energy Surface (PES), calculation of the global electron density transfer (GEDT), topological analysis of the Electron Localization Function (ELF) and Quantum Theory of Atoms in Molecules (QTAIM), and Non-Covalent Interactions (NCI) with the aid of molecular modelling software. MEDT correlates the changes in electron density along a reaction path with the activation energies and establishes the polar character associated with the reorganization of the molecular mechanism to reach a meaningful insight into the reactivity of organic molecules. MEDT can be applied to study the mechanism, reactivities and selectivities of organic reactions, particularly those showing chemo-, regio-, and stereoselectivities in the synthesis of biologically active products. This chapter aims to provide a detailed description of the basic theoretical concepts covered by MEDT to design a precise computational model of an organic reaction. Some applications of MEDT have also been illustrated in the concluding section for ready reference.

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Keywords: Bond Critical Points, Bonding Evolution Theory, Conceptual DFT, Electron Density, Topology, Electron Localization Function, Global Electron Density Transfer, Intrinsic Reaction Coordinate, Laplacian, Molecular Electron Density Theory, Non-Covalent Interactions, Potential Energy Surface, Quantum Theory of Atoms in Molecules, Transition States Structures.

INTRODUCTION

Having evolved as a highly creative discipline of science, Organic Chemistry is widely applied in medicine [1, 2], nanotechnology [3], polymers [4], industrial synthesis [5], biochemistry [6], biotechnology [7], and cosmetics [8]. "structural beauty and wide applicability of organic molecules come from their" chemical framework, which defines their unique reactivity. Thus, the interpretation of organic reactivity is a tough challenge, crossing the scientific boundaries of physical, chemical, and mathematical theories. The ever-increasing speed and capabilities of computational resources have significantly reduced the time required to calculate mathematical functions, which has provided the mathematical solution for physical and chemical theories applied to study the energetics and reactivity of molecular systems.

All chemical changes are accompanied by the absorption or release of heat, and this intimate connection of matter and energy has been in the focus of studies to understand the course of a chemical reaction. The first link between the experimental energy barrier of a chemical reaction and the theoretical concept of “transition state” was put forward in the “Transition State Theory (TST)” [9]. The chemical changes are associated with changes in the bonding framework of a molecular system, which causes energy transformations along a reaction path. Thus, the interplay of theory and experiment is well understood when exploring the sequence of bonding changes along a chemical reaction. Understanding “chemical bonding” in its deepest aspect and the electronic structure of a molecule is, therefore, crucial to analyze the energetics of a chemical reaction.

The Lewis concept of chemical bonding [10] laid the foundation for the advent of two new theories, popularly used in Organic Chemistry, namely the Valence Bond Theory [11 - 13] (VBT) and Molecular Orbital Theory [14] (MOT). VBT and MOT are two approximate methods for the solution of Schrödinger’s equation [15]. Within VBT, organic reactivity is explained by hybridisation, resonance, inductive effect, and other relevant concepts. MOT evolved as a unique concept proposing the movement of electrons along molecular orbitals (MOs) in a molecule. MOT considers the Born Oppenheimer’s approximation [16], which considers a molecule as an entity and each electron moves under the influence of the potential field of all the nuclei, rather than being centered on one nucleus.

MOs are constructed by the linear combination of atomic orbitals [17] (LCAO) from each atom of the molecule. Huckel's Molecular Orbital Theory [18 - 20] is a popular approach used in Organic Chemistry, where MOs are built only from valence atomic orbitals. This concept was presented as a novel treatment of chemical reactivity and named Frontier Molecular Orbital (FMO) Theory by Fukui *et al*. in 1952 [21]. Many years later, the FMO theory gained serious interest, when it was applied by Woodward and Hofmann [22] in 1965 to interpret the electrocyclic ring opening of cyclobutenes. The FMO theory thus started gaining ground as a reliable theoretical approach for the interpretation of organic reactions, particularly cycloaddition reactions [23, 24]. The FMO concept was advocated in the 1960-70s by Woodward and Hoffmann [25], Fukui [26], and Pearson [27], which led to the use of FMOs for the interpretation of cycloadditions by Houk [28] in 1972-73. Failures of the FMO theory were also recognized [23], but such cases were labelled as uncommon, subject to special circumstances in the 1970s. The general failure of the FMO theory to interpret electrophilic aromatic substitutions, S_N2 reactions, and so-called "pericyclic reactions" was critically reviewed and questioned by M.J.S. Dewar [29] in 1989. The author pointed out two reasons for the popularity and general acceptance of the FMO theory in Organic Chemistry: (I) the FMO theory is claimed as the only alternative for the interpretation of "pericyclic reactions", which cannot be explained by any other concept [23]; (II) by using the FMO theory, calculations can be performed swiftly, and the reactivity of organic reactions can be interpreted without using any concept of Organic Chemistry, which naturally, led to the popularity of the FMO concept. Thus, although the failures of the FMO theory were recognized in many cases, it is applied as an easy approach reactivity to understand organic reactions, particularly "pericyclic reactions".

The growth of computational chemistry [30] in the 20^{th} and 21^{st} century has made it possible to explore the potential energy surface (PES) [31] defined under the TST [9]. Consequently, reactants, products, transition state structures (TSs) and intermediates can be characterized on the PES. Now, a proper quantum chemical approach is required to obtain the electronic energies of these stationary states. As a consequence, a new quantum mechanical modelling method based on the Hohenberg and Kohn theorem [32], called the Density Functional Theory (DFT) [33] was proposed using Kohn-Sham equations [34]. DFT expresses the ground state energy of a non-degenerated N electron system as a function of electron density (ρ). DFT has proved to be a major breakthrough in computational chemistry due to its accurate predictions of energy and reactivity, unlike *ab initio* calculations [35].

Electronic energies of the stationary points located on the PES of a reaction can be obtained precisely by DFT calculations, but a proper theoretical approach is

CHAPTER 6

Frontier Molecular Orbital Approach to the Cycloaddition Reactions

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Abstract: The frontier molecular orbital (FMO) theory has provided a powerful model for the qualitative understanding of reactivity and regioselectivity of the Cycloaddition reactions, based on the electronic properties of isolated reactants. The 1,3-dipolar cycloaddition reactions are explicable by the frontier molecular orbital approach, which is based on the assumption that bonds are formed by a flow of electrons from the highest occupied molecular orbital (HOMO) of one reactant to the lowest unoccupied molecular orbital (LUMO) of another. But the tricky part here was to decide which molecule supplied the HOMO and which supplied the LUMO. Furthermore, the computational chemistry techniques like $HOMO_{dipole}$-$LUMO_{dipolarophile}$/$HOMO_{dipolarophile}$-$LUMO_{dipole}$ energy gaps, electronic chemical potentials (μ), electrophilicity indices (ω) and the charge capacities (ΔN_{max}) are useful in indicating whether the reactions are under normal or inverse electron demand conditions. Also, the relative kinetics of cycloaddition reactions can be rationalized by utilizing $HOMO_{dipole}$-$LUMO_{dipolarophile}$ energy gaps and ΔN_{max}, from which it was found that increasing electron-withdrawing power of the dipolarophile substituents, the energy gap decreases and, thus, reactions with the same dipole became faster in Normal electron demand cycloadditions, while the reverse occurs in case of inverse electron demand conditions.

Keywords: Cycloaddition, Chemical Potential, Charge Capacity, Diastereoselectivity, Dipolarophile, Electrophilicity, Enantioselectivity, Inverse Electron Demand Reactions, Normal Electron Demand Reactions, Regioselectivity, Stereochemistry.

INTRODUCTION

The language of chemistry is replete with orbitals, whether they be hybrid orbitals (in valence-bond models) or linear combination of atomic orbitals (in molecular orbital models). The power of the orbital concept cannot be avoided: almost everything in chemistry can be described, at a qualitative level by the appropriate use of an orbital model. The 'Orbital' concept, which was established by many

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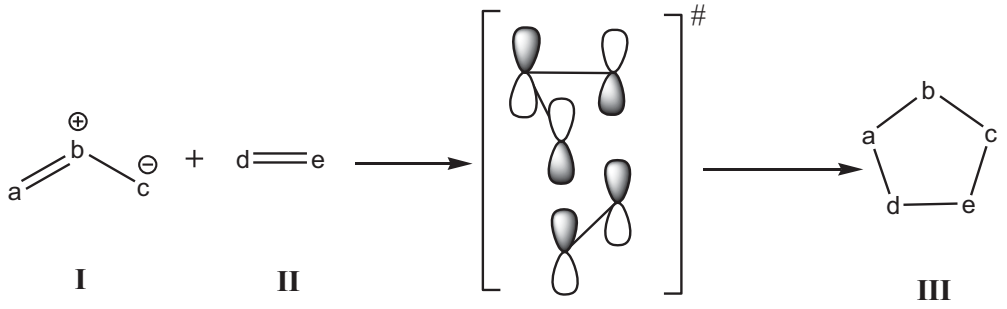
scientists, was initially used to construct the wave function of molecules through which molecular properties were usually interpreted [1]. In 1950's, Fukui developed Frontier molecular orbital theory on the basis of which he proposed that the pair of π-electrons occupying the highest orbital, which is referred to as frontier electrons, plays a decisive role in chemical activation of molecules. Instead of thinking about the total electron density, he focused on two particular orbitals, which act as an essential part in a wide range of chemical reactions and referred these orbitals as Highest occupied molecular orbitals (HOMO) and Lowest unoccupied molecular orbitals (LUMO) [2 - 4]. Based upon this FMO approach, he provided a simple and clear picture of theoretical interpretation of many reactions and 'The Overlap and Orientation' principle of Mulliken for the formation of molecular complexes [5, 6]. The utility of Fukui's study was further broadened by the role of symmetry orbitals pointed by Diels and Alder in the cycloaddition reactions. Based upon the symmetry of molecular orbitals, Woodward and Hoffmann proposed a principle called 'The conservation of orbital symmetry' to explain stereochemistry in pericyclic reactions [7 - 9]. The century-old class [10 - 13] of 1,3-dipolar cycloaddition (1,3-DC) is a well-studied field of organic chemistry. These reactions have a wide application in the synthesis of many pharmaceutically important compounds and intermediates [14, 15].

In the beginning, the concept of 1,3-dipolar cycloadditions was given by Smith in 1938 [16], but the generalization given by Huisgen, in 1960, made it widely applicable [17]. The research in the field of 1,3-dipolar cycloaddition reactions is utilized in almost every area of chemistry, from material chemistry [18] to drug discovery [19], indicating its diversity. 1,3-Dipolar cycloaddition is considered as an important reaction in synthetic organic chemistry where the two organic molecules *i.e.* a 1,3-dipole **I** and a dipolarophile **II,** join to give a five-membered heterocycle **III** (Scheme **1**). A number of simple and complex heterocycles of immense importance for the industrial and academic world can be prepared from simple and easily accessible molecules by 1,3-dipolar cycloaddition reaction. These reactions are commonly used as a key step in several organic syntheses [20].

As the control of stereochemistry is the major challenge in cycloaddition reactions, therefore, in recent years, such reactions have entered a new stage of development. Nowadays, controlling the regioselectivity, enantioselectivity, and diastereoselectivity of the 1,3-dipolar cycloaddition reactions is the main challenge. Their stereochemistry can be brought under control by either controlling the reaction by a metal complex acting as a catalyst or by selecting the appropriate substrate [21 - 23].



Scheme 1. Basic schematic representation of 1,3-dipolar cycloaddition reactions.

1,3-DIPOLE/YLIDE

Curtius was considered as a pioneer in the history of 1,3-dipoles with the discovery of diazoacetic ester, in 1883 [24]. The 1,3-dipole or an ylide has a positive and a negative charge spread over three atoms and possesses 4π-electrons [25]. Generally, the elements of groups 14, 15, and 16 are included in 1,3-dipoles among which nitrogen, carbon, and oxygen are the predominant ones and due to this limitation on the central atom of the dipole, a limited number of structures can be made by combination and permutations of these three atoms.

The elements of the higher row like sulfur and phosphorus, can also be included in 1,3-dipoles, but only a few cycloaddition reactions involving such types of dipoles have been published. The ylides or 1,3-dipoles can be represented by two octet-structures and two sextet structures. In the case of octet structure, the positive charge is present on the central atom while the two terminal atoms have a negative charge distributed over them. In sextet-structure, two among the four π-electrons are localized at the central atom. This structure explains the ambivalence of the 1,3-dipole but contributes little to resonance hybrid's electron distribution. The ambivalent nature of 1,3-dipole plays a major role in comprehending the regiochemistry, reactivity, and mechanism of 1,3-dipolar cycloadditions.

Classification of 1,3-Dipoles

1,3-Dipoles were categorized by Huisgen into two categories *i.e.* allyl anion type and propargyl/allenyl anion type 1,3-dipoles. They are also referred to as sp^2 and *sp* hybridized 1,3-dipoles, respectively.

Allyl Anion Type 1,3-Dipoles

The allyl anion type 1,3-dipoles are bent in nature and have four π-electrons in parallel to three *p*-orbitals, which are perpendicular to the plane of the dipole

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