International Journal of Research in Engineering, Science and Management
Volume-2, Issue-2, February-2019
www.ijresm.com | ISSN (Online): 2581-5792

Role of Computer Aided Drug Design in Drug Development and Discovery: An Overview

Sameera Begum[1], S. M. Shahidulla[2]
[1]*Student, Department of Pharmaceutics, Deccan School of Pharmacy, Hyderabad, India*
[2]*HoD, Department of Pharmaceutics, Deccan School of Pharmacy, Hyderabad, India*

***Abstract*: The process of drug development and discovery is very challenging, expensive and time consuming. It has been accelerated due to development of computational tools and methods. Over the last few years, computer aided drug design also known as in silico screening had become a powerful technique. This review provides an insight about developmental chain, approaches and applications of CADD, various data sources, computational method for the discovery of new molecular entities. The crucial steps of in silico drug designing like docking, multi-target searching and design, pharmacophore development, conformation generation, quantitative structure activity relationship(QSAR).**

***Keywords*: Drug discovery, Computer aided drug design, Docking, multi-target searching, QSAR.**

1. Introduction

The drug discovery process is a very complex and includes an inter disciplinary effort for designing effective and commercially feasible drug. In pharmaceutical medicinal as well as in other scientific research; a computer plays a very important role even in development of new compound in quest for better therapeutic agent [1]-[3].

For this purpose, Computer Aided Drug Design [CADD] Centre works with collaboration between structure biologists, biophysicists and computational scientists for discovery of new chemical entities. CADD and bioinformatics tools provide benefits of drug receptor interactions, speed up drug discovery and development [4], [6].

CADDD will be employed in this overview of the area to cover the entire process. Both computational and experimental techniques have important roles in drug discovery and development and represent complementary approaches. CADD entails:

1. Use of computing power to streamline drug discovery and development process.
2. Leverage of chemical and biological information about ligands and/or targets to identify and optimize new drugs.
3. Design of in silico filters to eliminate compounds with undesirable properties (poor activity and/or poor Absorption, Distribution, Metabolism, Excretion and Toxicity, ADMET) and select the most promising candidates.

Fast expansion in this area has been made possible by advances in software and hardware computational power and sophistication, identification of molecular targets, and an increasing database of publicly available target protein structures. CADDD is being utilized to identify hits (active drug candidates), select leads (most likely candidates for further evaluation), and optimize leads i.e. transform biologically active compounds into suitable drugs by improving their physicochemical, pharmaceutical, ADMET/PK (pharmacokinetic) properties. Virtual screening is used to discover new drug candidates from 3-dimensional chemical structure databases. It is intended to reduce the size of chemical space and thereby allow focus on more promising candidates for lead discovery and optimization. The goal is to enrich set of molecules with desirable properties (active, drug-like, lead-like) and eliminate compounds with undesirable properties (inactive, reactive, toxic, poor ADMET/PK. The rapid growth of virtual screening is evidenced by increase in the number of citations matching keywords “virtual screening.

A. Brief history of CADD

- In 1900: the concept of receptor and lock-and-key was given by P.Ehrich (1909) and E. Fisher (1894).
- 1970s: the concept of Quantitative structure-activity relationships (QS- AR) was established, it had Limitations: 2- Dimensional, retrospective analysis.
- 1980s: Beginning of an era of CADD Molecular Biology, X-ray crystallography, multi-dimensional NMR Molecular modeling along with computer graphics.
- 1990s: modern techniques like Human genome Bioinformatics along with combinatorial chemistry and High-throughput screening were introduced in the world of innovative medical science.

B. Benefits of CADD:

- Cost savings many biopharmaceutical companies use CADD in order to reduce cost burden [7].
- Traditional experimentation requiring animal and human models are now replaced by CADD, which saves both time and cost [8].
- It is hoped that in case of certain diseases like

influenza, computational drug designing will play an important role in reducing the chances of drugs resistance and thus would lead to production of lead compounds which would target the causative factor [8].

- CADD has also led to construction of high quality data sets and libraries that can be optimized for high molecules diversity or similarity [9].

C. Limitations in CADD

- Lack of accurate experimental data that restricts further advancements of CADD [10].
- Some procedures concerning computer Aided drug designing are time consuming, especially while looking for a proper lead component [11].

D. Approaches used in rational drug design

1) Known 3-D structure of protein

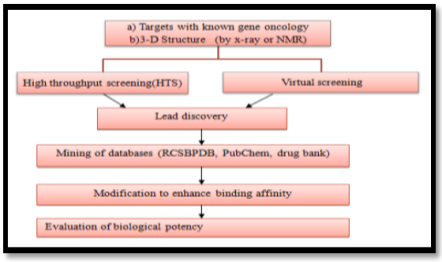

Fig. 1. Approach of drug design with known target

2) Structure of 3-D protein is not known (For new molecule)

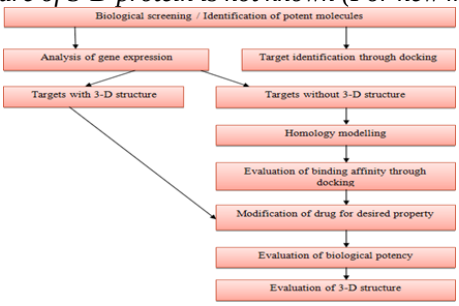

Fig. 2. Approach of drug design with unknown target

After the above two approaches those have been shown in (Fig. 1) and (Fig. 2), following properties are required to be checked for the examination of drug like properties in compound:

- Examination of QSAR, potency, docking and scoring, multi - regression analysis.
- Reactivity evaluation like nucleophile, electrophilic and radial attack.
- Preclinical evaluation [12]-[14].

E. Significance of CADD in drug discovery and development

- Filtration of large compound libraries into smaller compounds sets of predicted activity those could be further tested experimentally.
- Gives information about optimization of lead compounds, whether to increase bio affinity and pharmacokinetic properties like absorption, distribution, metabolism, excretion (ADME) as well as toxicity knowledge.
- Designing of novel compounds containing one functional group in a chemical compound or new chemo types by joining different fragments [15].

2. Working of computer aided drug design

A. Stages of computer aided drug design

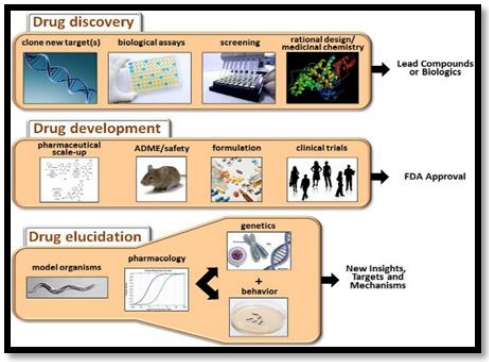

Fig. 3. Working of CADD

Computer aided drug designing process consists of 3 stages:
Stage 1: Involves identification of therapeutic target and building a heterogenous small molecule library to be tested against it. There is development of virtual screening protocol initialized by docking of small molecules.
Stage 2: The selected hits are checked for specificity by docking at binding sites of other known drug targets.
Stage 3: The selected hits are subjected to computational ADMET profiling studies and those who pass these studies are called leads.

Target Identification–It is the first key stage in the drug discovery pipeline. Identification of correct targets from thousands of candidate macromolecules is a tedious process, which can be achieved by literature referring, Genomic analysis, and pathway analysis [13].

Target Validation–After target identification, a rigorous evaluation is needed to demonstrate that modulation of target will have desired therapeutic effect. Target validation process determines whether modulation of target will have desired therapeutic effect.

Lead optimization–Leads can be identified with the help of techniques like Structure based design. At this point, the structure of the target protein in complex with the lead molecule can be extremely useful in suggesting ways to improve the affinity of the lead for the target. Leads which are used in this case may be far from perfect, thus they should be optimized in order to increase their affinity for the target sites. Optimization may be obtained by altering their structural features [14].

IN SILICO ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) –Prediction Techniques like molecular

modelling, data modelling are used to study the interaction of proteins involved in ADMET process [15].

Multi-target Drug Searching and Designing Through CADD:

The CADD technique is very useful in; searching drugs against multiple targets could be performed in which various hits are generated against multiple targets. In which the true-hits rates should be high than comparison to false- hits rates against of targets because it is needed in searching of multi-target searching for enrichment [16]-[18].

Drug - receptor interaction analysis through CADD:

Experimental work, analysis and computer simulation used for information of drug- receptor interaction and finding a new active compound.

After acquiring knowledge of bio molecular structure bio molecular docking is performed; which involves confirmation and orientation 'pose' of small molecule (ligand) in the cavity (active site) of target protein.

Docking is used to identify and optimize drug candidates by examining and modeling molecular interactions between ligands and target macromolecules.

Structure (target)-based design requires structural information for the receptor which can be obtained from X-ray crystallography, NMR or homology modeling.

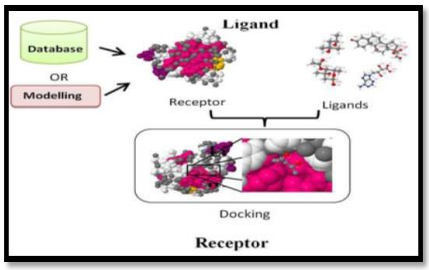

Fig. 4. Docking with receptor and ligand

Molecular docking can be separated into two sections as shown in the figure below,

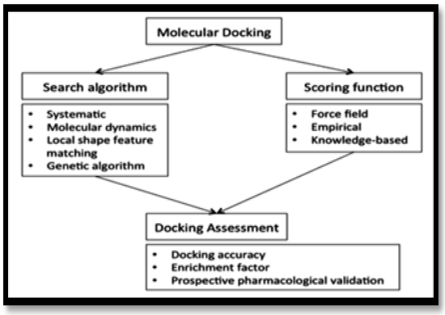

Fig. 5. Molecular docking

B. Types of docking

The following are primarily applied methods for docking:

(1) Rigid Docking (Lock and Key)

In rigid docking the internal geometry of both the receptor and ligand are targeted as rigid. Both the receptor and ligand is maintained fixed and docking is executed.

(2) Flexible Docking (Induced fit)

In induced fit docking both the ligand and the receptor are conformationally flexible. An enumeration on the rotations of one of the molecules (usually smaller one) is performed and energy is calculated; later the most optimum pose is selected.

Docking can be between

- Protein-Ligand

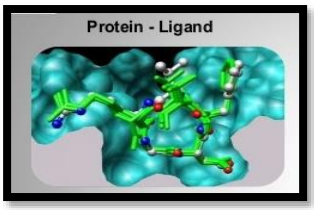

Fig. 6. Protein-Ligand Docking

- Protein-Protein

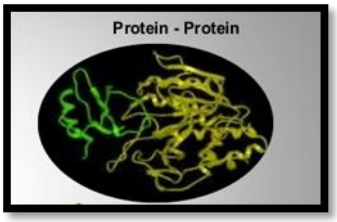

Fig. 7. Protein-Protein Docking

- Protein-Nucleotide

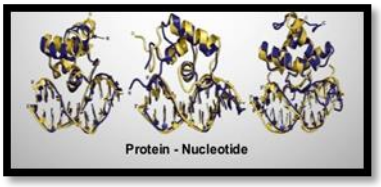

Fig. 8. Protein-Nucleotide Docking

These are the following types could be:

- *Protein docking:* Most of the computer studies needed protein which is involve in docking because majority of structures are known.
- *Protein - protein docking:* In this, two proteins bodies are assumed as two rigid solid bodies also with the help of geometric surface models and data structures binding mode is selected.
- *Protein - ligand docking:* It gives accurately analysis about molecular interaction. Here complementary contact surfaces are smaller than protein-protein docking. Small ligand adapt surface of receptor and fit into complementary site (ligand should be flexible molecule).
- *Other important phenomenon than structure flexibility:* Presence of single water molecules between ligand molecule and protein molecule leads

to complex formation and plays an important role [19]-[21].

Pharmacophore Development Through CADD:

Pharmacophore is defined as the three-dimensional arrangement of chemical functional groups which is responsible of biological activity. Now a days pharmacophore model (has been shown in Fig. 9) development has become an important part of drug discovery, design, optimization and development [22], [23]. Through the CADD, screening of Pharmacophore is performed which contains different scaffold containing compound but contains similar 3-D functional group arrangement [24], [25]. Pharmacophore methods find different types of compounds having common arrangement. Before using generated pharmacophore it should be validated with external data. If any suitable pharmacophore formed, virtual screening fastens [26], [27].

IUPAC defines pharmacophore as: "the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response. The pharmacophore can be considered as the largest common denominator shared by a set of active molecules."

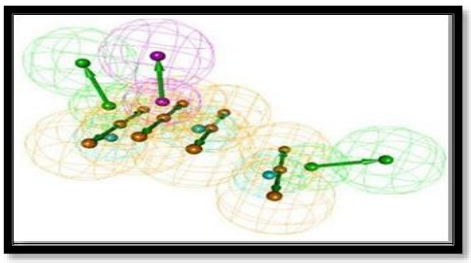

Fig. 9. Example of pharmacophore model

A pharmacophore gives good knowledge about molecular interactions of various compounds to their target structure and these features are complimentary to each other in 3-D space. Pharmacophore could be more better though combination with shape and volumes for proper fitting into the site of the receptor because wrong shape prevents fitting of compound into the receptor [28].

Quantitative Structure Activity Relationship (QSAR) Studies Through CADD:

For many cases in which structural based approaches are not applicable because of absence of target macromolecule structure information, in those cases QSAR approach is used [29], [30].

QSAR gives information about relationship between chemical structure and biological activity in the form of a mathematical expression. The main advantages of QSAR method is to identification of properties of novel chemical compounds in which there is no need of synthesis and testing of them [31].

Clinically Approved Drug Discovered Through CADD Approaches:

Some examples of clinically approved drugs with year of approval and therapeutic actions developed through CADD approaches.

Applications:

Bioinformatics in Computer-Aided Drug Design: CADD methods are heavily dependent on bioinformatics tools, application and on the support side of the hub, information technology, information management, software applications, databases and computational resources all provide the infrastructure for bioinformatics. On the scientific side of the hub, bioinformatics methods are used extensively in molecular biology, genomics, proteomics, other emerging areas (i.e. Metabolomics, transcriptomics) and in CADD research. There are several key areas where bioinformatics supports CADD research.

- Graph Machines for the Prediction of activities of molecules: In the past few years, QSAR has become a major field of research in the chemical industry. In a typical QSAR/QSPR scenario, a database of measured properties or activities of molecules is available, and it is desired to infer, from those data, the

Table 1
List of some clinically approved drug discovered though CADD approaches [32]-[34]

Drug	year of approval	Therape-UTIC action
Captopril	1981	Antihypert-ensive
Saquinavir	1995	Human immunodef-icieny Virus (HIV) inhibitor
Indinavir	1996	Human immunodeficiency Virus (HIV) inhibitor
Aliskiren	2007	Human rennin inhibitor
Boceprevir	Phase III clinical trials	Hepatitis C virus (HCV) inhibitor
Nolatrexed	Phase III clinical trials	In Liver cancer

Table 2
Different tools and databases [10]

Tool	Brief description with uses
BLAST	Basic local alignment search tool; used for sequencing of DNA and protein
Discovery studio	Software; used for modelling and simulation
Pub Med	Free search engine; used for searching matter related to medical and life sciences
PDB	Protein data bank; used to collect information related to macromolecule
Chem Draw	Part of the Chem office programs; used to draw chemical molecule
Auto Dock	Software; used for molecular docking

property/activity of molecules that have not yet been synthesized.

- In Silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) Prediction: Studies indicate that poor pharmacokinetics and toxicity are the most important causes of costly late stage failures in drug development and it has become widely appreciated that these areas should be considered as early as possible in the drug discovery process. Combinatorial chemistry and high throughput screening have significantly increased the number of compounds for which early data on absorption, distribution, metabolism, excretion (ADME) and toxicity (T) are needed. With use of in silico tools it is possible to model the most relevant pharmacokinetic, metabolic and toxicity endpoints, thereby accelerating the drug discovery process.

3. Conclusion and future prospects

- Computer Aided Drug Design, its application and development has made great progress in order to make a significant impact in both industry and academics. CADD approach provides valuable information for target identification and validation, lead selection, small-molecular screening and optimization, but still, it needs to be kept in mind that experimental tests have a role to play in this field. Due to large scale usage of CADD in industrial field, propelled by increasingly powerful technology.
- In the future, it is expected that Computer Aided Drug Designing will comprise of integration of computer aided chemistry and biology, along with chemoinformatics, bioinformatics, thus leading to creation of a new field Pharmacoinformatics.
- Development and application of computational techniques for prediction of free energies of binding and salvation.
- Development and application of new methods for carbohydrate computational chemistry.
- Bimolecular simulation studies of proteins, sugars and DNA.
- QM/MM studies of the condensed phase.

References

[1] Joseph TL, Namasivayam V, Poongavanam V and Kannan S: In silico approaches for drug discovery and development. Bentham Science Publishers 2017; 3:3-74.
[2] Gilda HL, Hugo OV and Ibon A: Strategies for indirect computer aided drug design. Pharmaceutical research 2013; 10(4): 475-486.
[3] Luu, KT, Kraynov E, Kuang B, Vicini P and Zhong WZ: Modelling, simulation, and translation framework for the preclinical development of monoclonal antibodies. AAPS J. 2013; 15:551-558.
[4] Dutta S and Sachan K: Computer - aided drug design a new approach in drug design and discovery. International Journal of Pharmaceutical Sciences Review and Research 2010; 4(3):146-151.
[5] Zhong WZ and Zhou SF: Molecular science for drug development and biomedicine. Int. J. Mol. Sci. 2014; 15: 20072-20078.
[6] Xiao X, Min JL, Lin WZ and Liu Z: Drug - target: predicting the interactions between drug compounds and target proteins in cellular networking via the benchmark dataset optimization approach. J. Biomol. Struct. Dyn. 2015; 33:2221-2233.
[7] Bharath EN, Manjula SN, Vijaychand A. In Silico Drug Design tool for overcoming the innovation deficit in the drug discovery process. International journal of Pharmacy and Pharmaceutical sciences2011;3(2):1-5.
[8] Mallipeddi PL, Kumar G, White SW, Webb TR. Recent Advances in Computer-Aided Drug Design as Applied to Anti-Influenza Drug Discovery. Current Topics in Medicinal Chemistry2014;14:1875-89.
[9] Ou- Yang SS, Lu JY, Kong XQ, Liang ZJ, Luo C, Jiang H. Computational drug discovery. ActaPharmacologicaSinica2012;33:1131–40.
[10] Bharath EN, Manjula SN, Vijaychand A. In Silico Drug Design tool for overcoming the innovation deficit in the drug discovery process. International journal of Pharmacy and Pharmaceutical sciences2011;3(2):1-5.
[11] Jorgensen WL. The Many Roles of Computation in Drug Discovery. Science 2004; 303:1813-17.
[12] Mandal S, Moudgil M and Mandal SK: Rational drug design. European Journal of Pharmacology 2009; 625: 90- 100.
[13] OuYang SS, Lu JY, Kong XQ, Liang ZJ, Luo C and Jiang H: Computational drug discovery. ActaPharmacologicaSinica 2012; 33:1131-1140.
[14] Barakat KH, Houghton M, Tyrrel DL and Tuszynski JA: Rational drug design rational drug design: one target, many paths to it. In pharmaceutical sciences: Breakthroughs in Research and Practice 2017:1144-1174.
[15] Sliwoski G, Kothiwale S, Meiler J and Lowe EW: Computational methods in drug discovery. Pharma- cological reviews 2014; 66:334-395.
[16] Ma XH, Shi Z, Tan C, Jiang Y, Go ML, Low BC and Chen YZ: In silico Approaches to multi-target drug discovery. Pharmaceutical Research 2010; 27(5):739-749.
[17] Ambure P and Roy K: CADD modelling of multi-target drugs against alzheimer's disease. Current Drug Targets 2017; 18(5):522-533.
[18] Abdolmaleki A, B Ghasemi J and Ghasemi F: Computer aided drug design for multi-target drug design: SAR/QSAR, molecular docking and pharmacophore methods. Current Drug Targets 2017; 18(5):556-575.
[19] Manju K, Gunjan P and Anju G: Review on introduction to molecular docking software technique in medicinal chemistry. International Journal of Drug Research and Technology 2017; 2(2):8.
[20] Thomas L and Matthias R: Computational methods for bio molecular docking. Current Opinion in Structural Biology 1996; 6:402-406.
[21] Mura C and McAnany CE: An introduction to biomolecular simulations and docking. Molecular Simulation. 2014; 40(10-11):732-764.
[22] Guner OF: History and evolution of the pharmacophore concept in computer-aided drug design. Current Topics in Medicinal Chemistry 2012; 2:1321-1332.
[23] Krishna S, Shukla S, Lakra AD, Meeran SM and Siddiqi MI: Identification of potent inhibitors of DNA methyl- transferase 1 (DNMT1) through a pharmacophore-based virtual screening approach. Journal of Molecular Graphics and Modelling 2017:25.
[24] Macalino SJY, Gosu Y, Hong S and Choi S: Role of computer-aided drug design in modern drug discovery. Archives of Pharm. Res.2015; 38(9):1686-1701.
[25] Moffat JG, Vincent F, Lee JA, Eder J and Prunotto M: Opportunities and challenges in phenotypic drug discovery: an industry perspective. Nature Reviews Drug Discovery. 2017; 16(8):202.
[26] Laeeq S, Sirbaiya AK, Siddiqui HH and Zaidi SMH: An overview of the computer aided drug designing. World Journal of Pharmacy and Pharmaceutical Sciences 2014; 3(5):963-994.
[27] Yu W and MacKerell AD: Computer-aided drug design methods. antibiotics: Methods and Protocols 2017:85-106.
[28] Kapetanovic IM: Computer-aided drug discovery and development (CADDD): In silico – chemico - biological approach. Chemico - Biological Interactions 2008; 171: 165-176.
[29] Yang SSO, Jun-yan LU, Kong XQ, Liang ZJ, Cheng LUO and Jiang H: Computational drug discoery. ActaPharma- cologicaSinica 2012; 33:1131-1140.

[30] Yuan S, Chan HC and Hu Z: Using PyMOL as a platform for computational drug design. Wiley interdisciplinary reviews: Computational Molecular Science 2017; 7(2):20.
[31] Jackson RC: Update on computer-aided drug design. Current Opinion in Biotechnology 2012; 6:646-651.
[32] Borhani DW and Shaw DE: The future of molecular dynamics simulations in drug discovery. Journal of Computer-Aided Molecular Design. 2012; 26(1):15-26.
[33] Abdulfatai U, Uzairu A and Uba S: Quantitative structure- activity relationship and molecular docking studies of a series of quinazolinonyl analogues as inhibitors of gamma amino butyric acid aminotransferase. Journal of Advanced Research 2017; 8: 33-43.
[34] Vijayakrishnan R: Structure - based drug design and modern medicine. Journal of Postgraduate Medicine 2012; 55(4):301-304.
[35] VanDrie JH: Computer-aided drug design: the next 20 years. Journal of Computer - Aided Molecular Design 2007; 21:591-601.
[36] Hartman GD, Egbertson MS and Halczenko W: Non- peptide fibrinogen receptor antagonists. Discovery and design of exosite inhibitors. J Med Chem 2012; 35(24): 4640-4642.
[37] He LW, Dai WC and Li NG: Development of orally active thrombin inhibitors for the treatment of thrombotic disorder diseases. Molecules 2015; 20(6):11046-11062.
[38] Kim CU, Lew W and Williams MA: Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: Design, synthesis and structural analysis of carbocyclicsialic acid analogues with potent anti-influenza activity. J Am ChemSoc 1997; 119(4):681-690.
[39] Mallipeddi PL, Kumar G, White SW and Webb TR: Recent Advances in computer-aided drug design as applied to anti-influenza drug discovery. Current Topics in Medicinal Chemistry 2014; 14:1875-1889.
[40] Vavricka CJ, Liu Y, Kiyota H, Sriwilaijaroen N, Qi J, Tanaka K, Wu Y, Li Q, Li Y, Yan J and Suzuki Y: Influenza neuraminidase operates via a nucleophilic mechanism and can be targeted by covalent inhibitors. Nature Communications 2013; 4:1491.
[41] An J, Lee DC and Law AH: A novel small-molecule inhibitor of the avian influenza H5N1 virus determined through computational screening against the neuraminidase. J Med Chem 2009; 52(9):2667-2672.
[42] Li C, Wang Z, Cao Y, Wang L, Ji J, Chen Z, Deng T, Jiang T, Cheng G and Qin FX: Screening for novel small- molecule inhibitors targeting the assembly of influenza virus polymerase complex by a bimolecular luminescence complementation-based reporter system. Journal of Virology 2017; 91(5):02282-16.
[43] Schames JR, Henchman RH, Siegel JS, Sotriffer CA, Ni H and McCammon JA: Discovery of a novel binding trench in HIV integrase. J Med Chem 2004; 47(8):1879-1881.