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A REVIEW OF COMPUTATIONAL CHEMISTRY IN THE DEVELOPMENT OF NOVEL ANTI-HIV DRUGS

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ABSTRACT

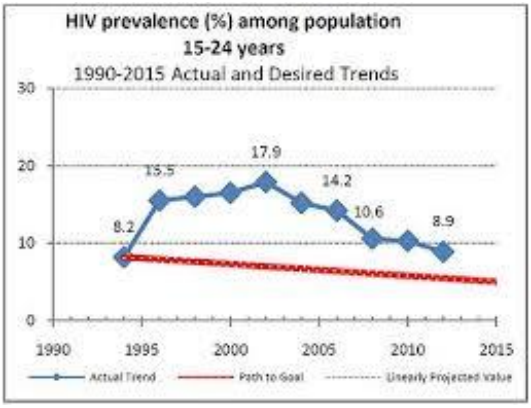
Aquired Immune Defeciency Syndrome or in short AIDS has evolved into a worldwide pandemic in the recent decades. Computer assisted drug discovery techniques have played a crucial role in the development of newer drugs for AIDS. Most of these techniques targets various stages present in HIV life cycle. Computational methods offer effective drug candidates for comparatively lower costs and lesser time frame. It can be expected that by the effective utilization of computational drug development techniques, the once dreaded disease AIDS will ultimately be eradicated.

Keywords: AIDS, Computatational techniques, HIV, Ligand, Pharmacophore.

INTRODUCTION

AQUIRED IMMUNE DEFECIENCY SYNDROME

Computational chemistry has played a key role in anti HIV drug development. In the absence of a successful preventive vaccine, the spread of human immunodeficiency virus (HIV) infection has caused a worldwide pandemic.Approximately 33million people are currently living with HIV-1, approximately 2.1 million people die every year of acquired immunodeficiency syndrome (AIDS) and associated complications, and there are 2.5 million new infections every year **[1].** The first anti-HIV drug, azidothymidine (AZT), was approved in 1987 , and more than 30 anti-HIV drugs are currently used for clinical treatment**[2].** Although highly active antiretroviral therapy is effective in controlling the progression of AIDS, the combined use of multiple drugs is greatly hindered by the emergence of drug-resistant HIV strains. More and more new anti-HIV drugs are therefore needed for clinical treatment.



Computational techniques are increasingly employed in drug discovery and optimization. Techniques applied to anti- HIV drug research are classified as **[3]**

(1) Ligand methods-based on known-active compounds that can infer biological activity such as classical quantitative structure-activity relationships(QSAR).
(2) Structure based methods –rely on the 3-D structure of protein receptors such as molecular docking and molecular dyanamics.
(3) Universal methods-structure or ligand based such as 3-D QSAR or 3-D pharmacophore elucidation .

Homology modeling is usually useful when an experimental 3-D structure of protein receptor is not available. Although multiple methods are applied to anti- HIV drug development, receptor structure-based molecular docking and ligand-based QSAR are the most frequently used methods. The HIV life cycle has multiple stages, including entry, reverse transcription, integration, protein translation, assembly, and release. Throughout the entire process, many viral proteins and host receptors can be targeted for drug development.

The recent progress of anti-HIV drug development via computational methods are applied to seven main targets**. [4]**

(1) Enzyme HIV reverse transcriptase
(2) Enzyme HIV protease
(3) Enzyme HIV integrase
(4) Human α-glucosidase
(5) Co-receptor CXCR4
(6) Co-receptor CCR5

HUMAN A GLUCOSIDASE

Inhibitors of ***α*** glucosidase prevent the transformation of gp160 into gp41 and gp120 and therefore inhibit membrane fusion of the virus with lymphocytes. These inhibitors could serve as novel anti-HIV drugs , converting ***α*** -glucosidase to a target of several computer-aided drug discovery campaigns**.[5].**

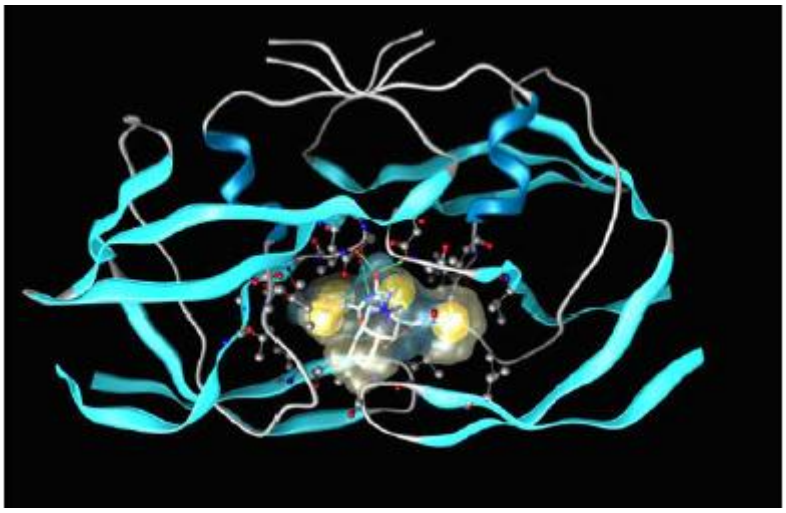
HIV-1 REVERSE TRANSCRIPTASE(RT)

Reverse transcriptase (RT) is a key enzyme playing a pivotal and multifunctional role in replication of HIV-1, and, hence, developed as an interesting drug target for anti-AIDS agents . The target has been subject to intensive study since the early 1990s, and a multitude of computational methods has been applied to this target. The PDB includes more than 240 crystal structures of HIV-1 RT and mutants complexed with more than 80 small organic ligands. Due tothis vast amount of crystal structures available, the majority of the approaches focus on structure-based design, which allows for studying of existing compound classes and derivationof analogues that could behave in a similar way. NNRTIs (non-nucleoside reverse transcriptase inhibitors) represent the main class of HIV-RT inhibitors, and four NNRTIs have already been approved by the FDA: etravirine , developed by Tibotec, delavirdine , marketed by Pfizer, efavirenz , developed by Bristol Myers-Squibb, and nevirapine , marketed by Boehringer Ingelheim. Despite their chemical differences, NNRTIs all bind to HIVRT allosterically in the same non-substrate hydrophobic pocket (the non-nucleoside

inhibitor-binding pocket, NNIBP) with a common binding mode , which is called “butterfly-like” binding mode . Computational methods have played a crucial role in the development of NNRTIs. Methods applied for structure-based modeling include docking in many variants, molecular field analyses like CoMFA, CoMSIA or GRID/GOLPE to quantitatively explain affinity differences within a single compound class. These approaches led to the discovery of novel compound classes, such as 3',4'-di-O-(S) camphanoyl-(+)-cis-khellactone (DCK) analogs , pyrrolyl aryl sulfones (PASs) , 2,6- difluorobenzyl-ℵ-methylthymines , o-substituted-Nsubstituted- N-acylthiocarbamates, 2 alkylamino-6-[1-(2,6-difluorophenyl)alkyl]-3,4-dihydro-5-alkylpyrimidin- 4(3H)-ones ,thiocarbamates, and 1- arylsulfonyl-1,3-dihydro-2H-benzimidazol-2-ones**. [6]**

HIV PROTEASE (PR)

From the beginning of the development of HIV PR inhibitors, a combination of classical medicinal chemistry with molecular modeling played a vital role . First generation inhibitors were designed to mimic the transition state in the cleavage site of HIV PR . As soon as the three D structure of HIV PR became available, structural information enriched the development process, allowing for a better understanding of activity. Still, a large number of ligand-based methods were applied too. 3D-QSAR, like CoMFA, CoMSIA, and pharmacophore modeling have been reviewed. Catalytic activity arises from two conserved aspartic acids at the center of the tunnel floor . To wrap around a substrate protein chain or an inhibitor, two flexible beta-hairpin structures termed “flaps“ open up and close over the ligand as illustrated. Since the introduction of HIV PR inhibitors in the highly active anti-retroviral therapy HAART, contributed substantially to the infection.

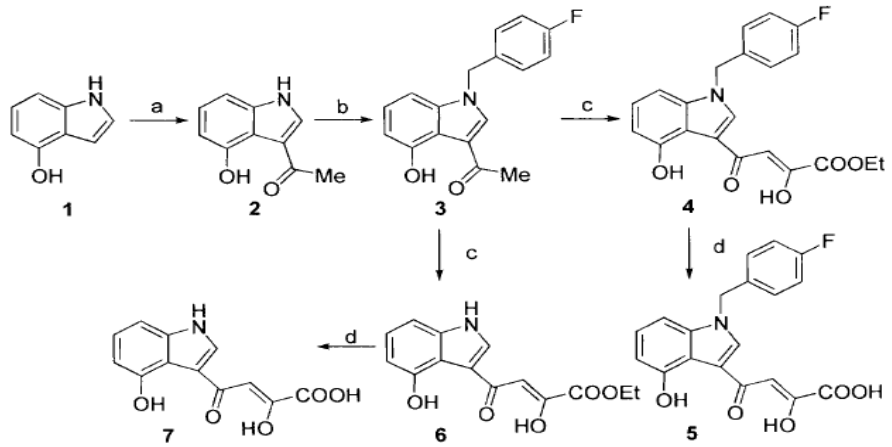


Danuravir is the most potent HIV PR inhibitor that is known. A series of danuravir derivatives was evaluated with 3D-QSAR and docking methods , demonstrating that the ligand-based and receptor-based results were in agreement with the experimental results**. [7]**

HIV INTEGRASE (IN)

Before 2007, the development of HIV IN inhibitors proceeded slowly, mainly due to the lack of 3D information about IN completely complexed with DNA. Deng *et al.* derived a 3D pharmacophore model from previously known inhibitors using Accelrys’ software Catalyst and detected novel chalcones with submicromolar activity **[8].** The cellular protein lens epithelium-derived growth factor, or transcriptional coactivator p75 (LEDGF/p75), plays a crucial role in HIV integration. The protein–protein interactions (PPIs) between HIV-1 integrase (IN) and its cellular cofactor LEDGF/p75 may therefore serve as targets for the development of new anti-HIV drugs. Although HIV-1 IN plays a key role in integration, the process takes place in a more complex environment *in*

vivo. Before integration, viral cDNA becomes associated with a number of viral and cellular proteins to form a large nucleoprotein assembly called a preintegration complex. LEDGF/p75 is a cellular protein that has recently been identified and validated as a novel cellular cofactor of HIV integration and replication. LEDGF/p75 binds HIV-1 IN via a small (~80 residues) IN-binding domain (IBD, amino acids 347–429) within its C terminal region. IBD is both necessary and sufficient for interaction with HIV-1 IN. The crystal structure of the dimeric catalytic core domain of HIV-1 IN complexed with the LEDGF/p75 IBD has recently been reported (PDB code 2B4J). The most critical interacting residues of the IBD are Ile 365, Asp366 and Phe406; there have been recent reports that mutation of these LEDGF/p75 residues destroyed interaction with HI 1IN.Therefore, it is mainly focused interest on the LEDGF hotspot residues Ile365 and Asp 366, supposing that a small molecule able to mimic this IBD dipeptide might inhibit IN– LEDGF/p75 recognition. Group **[9,10]**



Scheme 1. *Reagents and conditions*: a) $POCl_3$, $CH_3CON(CH_3)_2$, 12 h, RT; b) 4-fluorobenzyl bromide, K_2CO_3, DMF, 10 min, 100 °C, 100 W; c) diethyl oxalate, dry CH_3ONa, THF, two separate steps under the same conditions: 2 min, 50 °C, 250 W; d) 2N NaOH, MeOH, 90 min, RT.

CXCR4

CXCR4 is an appealing target for antiviral drug development. AMD3100 was the first promisingCXCR4 antagonist, but it proved to be unsuitable for the treatment of AIDS in later studies . Before 2011, the CXCR4 antagonist development depended on traditional chemical synthesis and drug design to mimic the available part of SDF-1α/CXCR4 structures. The first low molecular weight antagonist,AMD3100, is a representative example . T22 is a representative polypeptide antagonist of CXCR4, which was synthesized with chemical modification from the horseshoe crab hemocytic polypeptides T134 is a small-sized analog of T22 with reduced positive charges, highly potent activity, and significantly less cytotoxicity . Two other CXCR4 antagonists, ALX40-4C and vMIP II, are active against the AMD3100 resistant strains . .A three-dimensional model of human CXCR4 was constructed via homology modeling according to the high-resolution bovine rhodopsin structure **[11]**

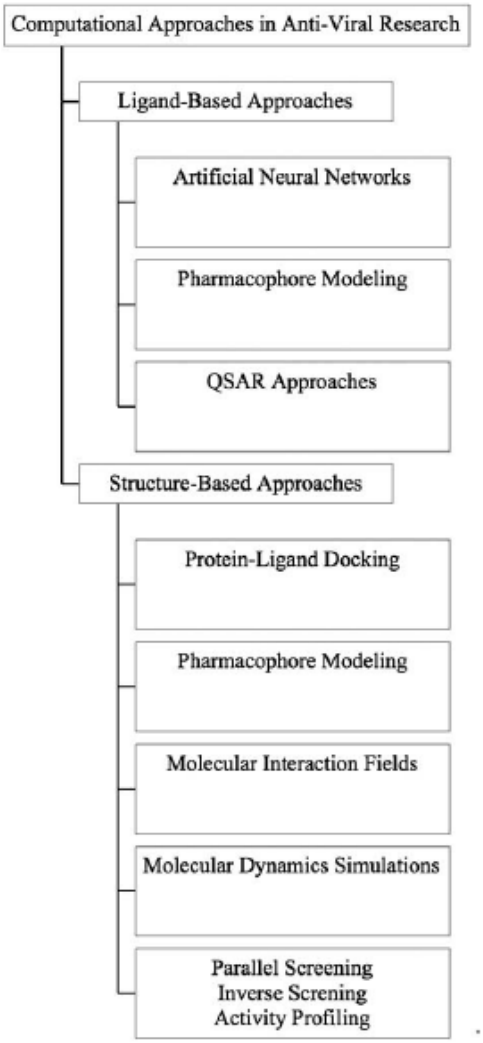
CCR5

Vicriviroc is a small-molecule CCR5 antagonist that has entered phase III clinical trial.Homology modeling was the main computational method for CCR5 antagonist development before 2013. Several studies were performed on the human CCR5 structure construction via homology modeling by using the X-ray structure of the bovine rhodopsin receptor . Additionally, a homology model of

human CCR5 was developed based on the reported CXCR4 structure as a template. The 2.7 Å-resolution crystal structure of human CCR5 bound to the marketed HIV drug maraviroc was reported recently. The reported structure revealed a ligand-binding site that was distinct from the proposed major recognition sites for chemokines and gp120, providing insights into the mechanism of the allosteric inhibition of chemokine signaling and HIV entry. The high-resolution crystal structure of CCR5 enables structure-based drug discovery for the treatment of HIV-1 infection **[12]**

COMPUTER AIDED DRUG DESIGNING

Computer-Aided Drug Design (CADD),also known as computer assisted molecular design(CAMD),is a specialized discipline that uses computational methods to simulate drug receptor interactions.CADD methods are heavily dependent on bioinformatics tools, applications and databases **[13].**Computational approaches in the development of novel drugs especially anti viral drug research can be classified as below.



LIGAND-BASED APPROACHES

Molecular similarity represents the central concept of all ligand-based modeling and screening techniques, Molecular characteristics can be represented by physiochemical descriptors in 1D (e.g., molecular weight, atom counts, number of H-bond donors, logP, pKa), 2D (e.g., topological descriptors), and 3D (physicochemical properties including location constraints, shape descriptors) space **[14].** The rapid calculation and high efficiency of these methods implicate their wide acceptance and application in pharmaceutical industry. More advanced chemical similarity methods include, e.g., pharmacophore models, feature trees,shape-based models, and QSAR models.

ARTIFICIAL NEURAL NETWORKS (ANNS)

Artificial neural networks (ANNs) represent a potent technology for analyzing the descriptor space of large sets of compounds, allowing for elucidating rule sets for bioactivity. They are based on mathematical models and algorithms and are derived from knowledge acquisition and information procession methods of the human brain. During the learning phase, ANNs usually adapt its structure to the external or internal information and are particularly useful to find patterns in chemical data. Kohonen maps (also known as SOMs, self-organizing maps) are among the most popular concepts of ANNs, allowing for analyzing and visualizing high-dimensional data in low dimensional space **[15].**

PHARMACOPHORE MODELING

According to the official IUPAC definition by Wermuth, a pharmacophore describes the 3D arrangement of steric and electronic features necessary to trigger or block a biological response. Pharmacophores can be represented by three-dimensional chemical features, which include hydrogen bond donors and acceptors, aromatic rings, hydrophobic groups as well as positive and negative ionizable moieties **[16].** The shape of ligands can be represented by shape features, which essentially describe the van der Waals radii of the ligand atoms. By analysing active vs. inactive compounds, conclusions can be even drawn about the special properties of the binding pocket. A common way to computationally deduce pharmacophore models is to arrange the key interactions of active ligands in 3D space, with respect to conformational flexibility. the active molecules used for pharmacophore model development need to share the same binding mode. In case of diverse scaffolds of distinct binding modes, several pharmacophores can be developed and applied in a parallel way during virtual screening (see below). Pharmacophore modeling has been established as a major pillar of virtual screening and there are several popular software packages available for pharmacophore modeling, including CATALYST – now integrated to Discovery Studio, DISCO, GALAHAD , GASP , UNITY , MOE , PHASE , and LigandScout.

QSARAPPROACHES

QSAR (quantitative structure-activity relationship) techniques allow for statistically exploring the relationship between calculated properties derived from chemical structures and experimentally determined pharmacological properties. In contrast to virtual screening methods, which are mostly employed for hit identification, QSAR approaches are particularly useful in lead structure development andoptimization. Thereby, a training set of small organic molecules covering a broad range of activity on a certain target is used as a basis for the development of statistical models. One of the most important aspects of QSAR modeling is model validation. QSAR approaches attempt to predict and rationalize structure- activity relationships based on the spatial arrangements of chemical properties and atoms. A plethora of QSAR approaches and tools is available today. The most prominent 3D QSAR approaches are CoMFA (Comparative Molecular Field Analysis) and CoMSIA (Comparative Molecular Shape Indices Analysis). Both approaches derive statistical models that are visualized in color-coded contours around the molecule, indicating locations where electrostatic properties and spatial arrangements are favorable or unfavourable for biological activity. GRID/GOLPE is another 3D QSAR technique that has been applied in anti-viral drug research**[17].**

STRUCTURE-BASEDAPPROACHES

Structure-based methods are depending on the availability of structural data of the targets investigated. With rapidly growing knowledge on the 3D structure of biomolecules, protein-ligand docking, structure-based pharmacophore modeling, and related techniques have become increasingly popular in recent years. The Protein Data Bank (PDB) represents the largest public repository of experimentally determined protein structures (mostly determined by X-ray crystallography), currently comprising more than 50.000 structures of biomolecules and protein-ligand complexes. In case there is no structural information on a particular target (or mutant, etc.) available, homology modeling may be employed in order to derive the putative 3D structure of a target computationally. This technique attempts to construct a model of the target protein at atomic resolution based on a related homologous protein used as a template . In general,the success of homology modeling is predetermined by the degree of relation between the template and the model: the lower the similarity the lower the accuracy of the model.In order to build reliable models, the template should share at least 40% sequence identity. SWISS-MODEL is one of the most prominent web services available and is often used as a standard for comparisons.

PROTEIN-LIGAND DOCKING

Molecular docking algorithms attempt to predict the correct binding mode of a bioactive compound to a protein. The computational process is divided into two stages: First, the algorithm assesses the correct placement of the ligand in the binding site. In the second step, based on this protein-ligand pose, the affinity of the ligand to the protein is predicted **[18]** There is a widespread set of algorithmic approaches available for pose prediction, each of them performs well on some targets and worse on others; an algorithm with ubiquitous good performance could not be developed yet. This is reflected by the large amount of docking programs available, which are based on different algorithmic approaches, including incremental construction approaches (e.g., FlexX),shape-based algorithms (e.g., DOCK), genetic algo rithms (e.g., GOLD and AutoDock), systematic search (e.g., Glide), Monte Carlo simulations (e.g. LigandFit), and surface-based molecular similarity methods (e.g., Surflex). Therefore it is recommended to select an appropriate docking algorithm based on the target under investigation.

MOLECULARDYNAMICSSIMULATIONS

Molecular dynamics (MD) simulations allow for investigating motions of biomolecules as well as small organic compounds and complexes thereof for a short period of time. In particular, the induced fit effect upon ligand binding can be observed at an atomic level of detail. Calculations are highly computationally demanding. Analyzing the MD trajectories is a good way to gain knowledge on target structures, their flexibility, and their interaction with ligands and other proteins. E.g., by statistical analyses on the occurrence of certain protein-ligand interactions over the trajectory, the importance and contribution of such interactions to ligand affinity can be estimated. Snapshots of the trajectory may serve as a basis for screening approaches considering quasiflexible receptors. Docking, e.g., can be employed on a set of different target conformations derived from MD simulations in order to simulate protein flexibility to increase virtual screening success rates **[19].**

CONCLUSION

Computational aided drug designing play an important role in drug development. Molecular modelling techniques and virtual screening approaches have been shown to be powerful tools that allow for accelerating and guiding the drug development process in all stages. The high mutation

rate of HIV leads to the emergence of drug-resistant strains. Computational methods play an important role in modern anti-HIV drug development. To characterize the step of virus mutation, virtual screening and QSAR significantly reduce the time needed for drug discovery. Considering the enormous number of currently available compounds from sources, such as plants, marine organisms, and bacteria, computational methods are clearly promising and low cost. The advances of anti-HIV drug development via computational methods applied to seven key targets namely enzymes such as alpha glucosidase, reverse transcripters, integrase, protease,and coreceptors CXCR4,CXCR5 and anti HIV agents from natural sources. The application of computational approaches has the potential to rationally access the natural products' slumbering bioactivities in the most effective way. The cellular protein lens epithelium-derived growth factor, or transcriptional coactivator p75 (LEDGF/p75), plays a crucial role in HIV integration. The protein–protein interactions (PPIs) between HIV-1 integrase (IN) and its cellular cofactor LEDGF/p75 may therefore serve as targets for the development of new anti-HIV drugs. A structure-based pharmacophore model for potential small-molecule inhibitors of HIV-1 IN–LEDGF/p75 interaction was developed using the LigandScout software. The 3D model obtained was used for virtual screening of in-house chemical database, CHIME, leading to the identification of compound CHIBA-3002. The rational design, synthesis and biological evaluation of four derivatives were then carried out. Docking simulations were subsequently performed in order to investigate the possible binding mode of the new lead compound to HIV-1 IN. This study is a valid starting point for the identification of anti-HIV agents with a different mechanism of action from currently available antiviral drugs. The successful stories of CADD application in drug discovery in recent years have demonstrated the potential value of CADD in drug development. CADD approaches can provide valuable information for target identification and validation, lead selection, small molecular screening and optimization. In particular, those sub disciplines of CADD have demonstrated promising application for de- sign of drug. The latest technological advances (QSAR/ QSPR, structure-based design, combinatorial library de-sign, chemoinformatics & bioinformatics); the growing number of chemical and biological databases; and an explosion in currently available software tools are providing a much improved basis for the design of ligands and inhibitors with desired specificity.

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