

# The State of the Science: A 5 - Year Review on the Computer - Aided Design for Global Anti - AIDS Drug Development

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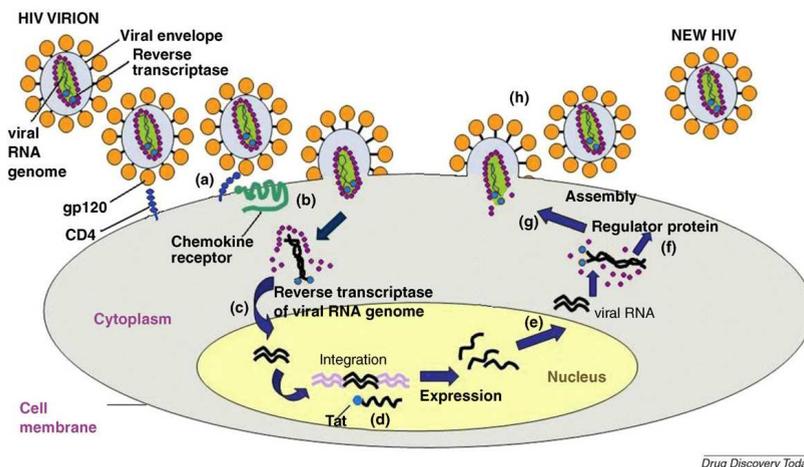
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## 1. Introduction

Since acquired immune deficiency syndrome (AIDS) was recognized by the U.S. centers for disease control and prevention in 1981 (Gallo, 2006), a large number of patients have died due to human immunodeficiency virus (HIV) related causes. In 2009, there were an estimated 33.3 million (31.4 million-35.3 million) persons living with HIV, 2.6 million (2.3 million-2.8 million) persons newly infected by HIV, and 1.8 million (1.6 million-2.1 million) dying due to AIDS. Research on vaccines is one of several strategies to reduce the worldwide harm from AIDS, however, these are early results, and have either not been developed to the point of human testing, or not been fully peer reviewed and replicated by other teams (Girard et al., 2006). Thus, the AIDS patient's treatment continues to focus on seeking the chemical anti-HIV agents. The current anti-HIV drugs approved by Food and Drug Administration (FDA) belong to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs), fusion inhibitors (FIs) and entry inhibitors. The highly active antiretroviral therapy (HAART), which combines over three drugs, has dramatically improved the quality of patients' life (Barbaro et al., 2005; Gulick et al., 2003; Hammer et al., 1996). Three drugs are used together in order to reduce the likelihood of resistance. However, the therapeutic effect is confined by the side effects and toxicity due to long-term use, and the emergence of drug-resistant (Louie & Markowitz, 2002). The multiple steps of HIV replication cycle present novel therapeutic targets other than reverse transcriptase (RT) and protease (PT) for drug development (Greene, 2004; Tan et al., 2010) (Fig. 1). Continued efforts have been made on discovering new inhibitors that target not only RT, PT, IN and the transmembrane glycoprotein gp41, but also other viral targets, achievements on which have been reviewed comprehensively in literatures (Citterio &

Rusconi, 2007; Hazuda et al., 2009; Mastrolorenzo et al., 2007; Qian et al., 2009; Ravichandran et al., 2008; Stanic & Grana, 2009; Tan et al., 2010).



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Fig. 1. The reproductive cycle of HIV. (a) Attachment. HIV attaches to CD4 and a chemokine receptor on the surface of a T cell. (b) Fusion. The virus fuses with the cell membrane and releases the virion core into the host cell. (c) Reverse transcription. The HIV enzyme called reverse transcriptase converts the single-stranded viral RNA to double-stranded viral DNA. (d) Integration. The viral DNA is integrated into cellular DNA by the HIV enzyme integrase. (e) Transcription. The virus uses the host enzyme RNA polymerase to create copies of the HIV genomic material and messenger RNA (mRNA). The mRNA is then used to produce long chains of viral proteins. (f) Regulator proteins. These are essential for the HIV viral cycle because they dramatically increase HIV gene expression. (g) Assembly. The HIV enzyme PT hydrolyzes the long chains of viral proteins into functional small proteins. New virions are then assembled with the small viral proteins and RNA. (h) Budding. The newly assembled virions use the cellular envelope as cover and bud off from the host cell.

Computer-aided drug design (CADD) is a rapidly evolving field to provide novel approaches for satisfying the needs of drug discovery (Durrant & McCammon, 2010; Sangma et al., 2010). By employing CADD or a combination of experiments and computational methods, a lot of novel inhibitors have been discovered that can inhibit HIV replication by interacting with the specific target(s). The use of CADD approaches can promote more efficient leads discovery and optimization as well as provide insights into target-ligand interactions. As the broad set of CADD approaches continues to develop, with innovative methods continually appearing, the impacts of CADD on drug discovery will undoubtedly continue to expand. In this chapter, we will take a look at the novel anti-HIV inhibitors discovered by CADD approaches in the past five years.

## 2. New developments of anti-HIV inhibitors

### 2.1 HIV fusion/entry inhibitors

The fusion of the viral membrane with host cell, cluster of differentiation 4 (CD4) cell, undergoes the following steps: (1) The N-terminal of the cell surface receptor CD4 binds to

the active cavity of envelope glycoprotein gp120, an essential envelope glycoprotein of HIV mediating the recognition between HIV and CD4; (2) The binding process induces an interacting area exposing to the host cell chemokine, such as C-X-C chemokine receptor type 4 (CXCR4) or C-C chemokine receptor type 5 (CCR5), which are the co-receptors for viral-cell interaction; (3) gp41, another envelope glycoprotein of HIV binding with gp120, is triggered by foregoing events to undergo a great conformational change, thereby allowing the viral-cell membrane fusion and viral genomic materials entry.

Accordingly, the fusion/entry inhibitors are designed to block three main targets, the CD4-gp120, gp120-CCR5/CXCR4 and CD4-gp41 interactions.

### 2.1.1 The entry inhibitors targeting CD4-gp120

HIV-1 gp120 consists of five conserved (C1-C5) and five variable (V1-V5) protein domains (Horuk, 2009), among which the conserved domains form the core domain of gp120, while the variable domains contribute to the surface of gp120. On the other hand, gp120 is also divided into three functional regions, an inner domain involved in interactions with gp41 and the formation of trimer that is the bioactive conformation of gp120, an outer domain exposed to the molecule surface and is highly glycosylated, and a bridging sheet resulted by the great conformational change following the binding of CD4 and gp120 (Teixeira et al., 2011).

Multi-target HIV-1 entry inhibitors hexa-arginine-neomycin-conjugate (NeoR6) and nona-D-arginine-neomycin-conjugate (Neo-r9) are mimics of V3 loop of gp120 which is involved in the interaction between HIV-1 and CXCR4, exhibiting high antiviral potent and low cytotoxicity. While, Berchanski et al. assumed that both NeoR6 and Neo-r9 may inhibit HIV-1 entry by interfering with the CD4-gp120 binding (Berchanski & Lapidot, 2007). A homology model of unliganded HIV-1 III<sub>B</sub> gp120 was constructed for subsequent docking with NeoR6/Neo-r9. Full geometric-electrostatic docking and flexible docking were performed respectively. It was found that these two multi-target inhibitors were apt to bind to gp120 at the CD4 binding site and mutations in the CD4 binding region greatly attenuate the energetic favor of NeoR6/Neo-r9-gp120 complexes. Simultaneously, another mechanism of anti-HIV-1 activity of NeoR6/Neo-r9 was described as the interference of gp120-CXCR4 interaction. This means that NeoR6/Neo-r9 inhibits HIV-1 in a multi-approach.

The CD4-binding site on gp120, which is a hydrophobic pocket occupied by CD4 Phe43, could be suggested as an ideal target for molecules that interfere with gp120-CD4 interaction. Caporuscio et al. performed a computational analysis containing molecular dynamics (MD) simulation, pharmacophore modeling, virtual screening and molecular docking to identify small molecules targeting the CD4 binding cavity and thereby blocking gp120-CD4 interactions (Caporuscio et al., 2009). Finally, two compounds, **2** and **4** (Fig. 2), with micromolar activity ( $EC_{50} = 22$  and  $9 \mu\text{M}$ , respectively), low toxicity and, more importantly, novel scaffolds were identified from a database containing more than 200,000 available compounds.

BMS-378806 was discovered recently as a small molecule inhibitor targeting the binding of host-cell CD4 with viral gp120 protein and showed potent anti-HIV activity at a nanomolar range (Ho et al., 2006). Docking calculations and the Comparative Molecular Field Analysis (CoMFA) model on BMS-378806 and its analogs revealed that the azaindole ring and methyl groups seem to play an essential role on binding with the CD4 cavity of gp120 through hydrogen bond or hydrophobic interactions. This is consistent with the previous theoretical

studies and facilitated the novel drug design based on scaffolds of BMS-378806 and its analogs (Kong et al., 2006; Teixeira et al., 2009).

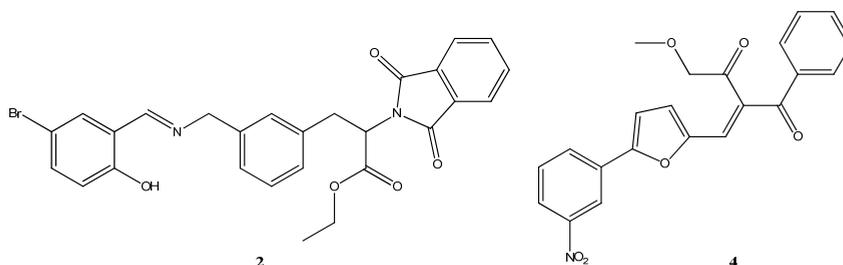


Fig. 2. The structure of entry inhibitors

Compound NBD-556 discovered by high-throughput screening few years ago was shown to mimic CD4-induced conformational changes in gp120 and accordingly compete CD4 binding with gp120 (Haim et al., 2009). Starting with the structures of NBD, Lalonde et al. defined the chemotype of NBD with three functional regions and performed two orthogonal screening methods, GOLD docking and ROCS shape-based similarity searching based on these three different regions (Lalonde et al., 2011).

### 2.1.2 The fusion inhibitors targeting gp41

HIV-1 gp41 is a complex polypeptide, consisting of seven domains, a transmembrane region (TM) which anchors gp41 on the virus surface, a membrane proximal region (MPER) locating near the viral membrane as its name implies, C-terminal helical heptad repeat (CHR) and N-terminal helical heptad repeat (NHR) linked by a flexible loop region, a fusion peptide proximal region (FPPR), and a fusion peptide region (FP) which is responsible for binding to host cell membrane. Among which, the CHR and NHR regions are the core structure of gp41 where most peptide inhibitors are derived from (Naider & Anglister, 2009). In fact, gp41 shows bioactivity in a trimeric form as gp120, and contains a critical inhibitory target site—a hydrophobic cavity in the NHR trimer structure for the binding of CHR trimer followed by gp41 6-Helix formation (Strockbine & Rizzo, 2007). However, the total 3D structure of gp41 is still unknown. Thus, this limits the development of HIV-1 FIs targeting gp41.

N-substituted pyrrole derivatives, such as NB-2 and NB-64, were recently identified by Jiang et al. as the novel HIV-1 entry inhibitors which inhibit HIV-1 fusion and entry in low concentration by occupying the gp41 cavity and interfering with the gp41 six-helix bundle (6-HB) formation (Jiang et al., 2004). Molecular docking and mutational analysis revealed that N-substituted pyrrole binds to gp41 cavity through hydrophobic and ionic interactions and conserved residue Lys574 in the cavity is one of the key factors for 6-HB formation and HIV infection. When docking NB-2 into the gp41 hydrophobic pocket, docking results indicated that the carboxyl group of the molecule prefers to bind with Lys574 forming a salt-bridge (He et al., 2007). Also in the molecular docking analysis, a 3D-Quantitative structure-activity relationship (QSAR) CoMFA model was generated based on 23 pyrrole derivatives (He et al., 2007). The obtained model showed a satisfied correlative predictive capacity with statistical results of  $R^2 = 0.984$  and  $r^2 = 0.463$ . The descriptors selected for modeling were

related to the shape and electron reactivity for C atoms. This indicates that substitution of electron-rich groups on the phenyl ring of pyrrole derivatives may result in improving biological activity. Based on above conclusions, a series of structure-modified N-phenyl-2,5-dimethylpyrrole derivatives with *m*-COOH on the benzene ring were designed and synthesised with a more effective inhibitory activity than N-phenylpyrrole analogs (Liu et al., 2008). These results suggested that nonpolar interactions are the main interactions of binding, while polar interactions adjust the orientation of the molecules binding into the target site. This guided authors to design and synthesize a series of 2-aryl-5-(4-oxo-3-phenethyl-2-thioxothiazolidinylidene-methyl)furans 3a-o with better inhibitory activity than NB-2 and NB-64 (Jiang et al., 2011). Compounds **12l** and **12m** (Fig. 3) showed high potency against infection by laboratory-adapted and primary HIV-1 IIIB strains with EC<sub>50</sub> at a low nanomolar level (18 and 14 nM, respectively) and inhibited HIV-1-mediated cell-cell fusion and the gp41 six-helix bundle formation.

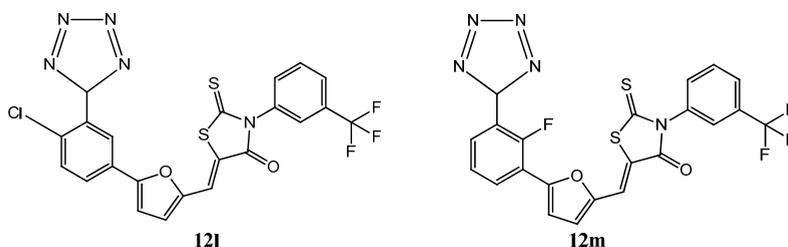


Fig. 3. The molecular structures of designed inhibitors by Jiang et al.

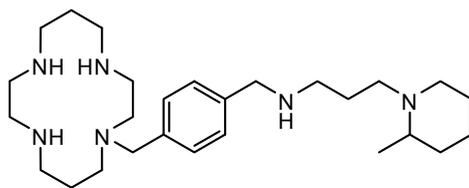
The additional analyses with molecular mechanics Poisson Boltzmann surface area (MM-PBSA)/ molecular mechanics Generalized Born surface area (MM-GBSA) were carried out to predict the binding mode of NB-2/NB-64 and gp41 (Cong et al., 2010). Based on above studies, Tan et al. obtained six new derivatives of NB2 using *de novo* design and screened out a series of molecules with novel structures using the Leapfrog and Autodock programs. They obtained a potent fusion inhibitor (IC<sub>50</sub> = 41.1 µg/mL) by the structure-based modification. Unfortunately, the inhibitive activity of these compounds isn't greater than that of NB2 (Tan et al., 2011).

### 2.1.3 The entry inhibitors targeting co-receptor CCR5/CXCR4

A 3D-pharmacophore model was developed based on a great number of pyrrolidine-based and butane-based CCR5 antagonists as HIV-1 entry inhibitors targeting CCR5 (Kong et al., 2008). The most reliable hypotheses consisted of two positive ionizable points and three hydrophobic groups, with R<sup>2</sup> of 0.924. The 74 external compounds were predicted with this model, yielding a correlation coefficient of 0.703. This potent model may be applied to the design and screening of the novel compounds.

Zhuo et al. took a series of 1,3,4-trisubstituted pyrrolidine-based CCR5 receptor inhibitors into account for CoMFA and CoMSIA (Comparative Molecular Similarity Indices) analysis (Zhuo et al., 2008). Compared with CoMSIA model (r<sup>2</sup> = 0.958, q<sup>2</sup> = 0.677), the CoMFA model was more predictive and reliable with better statistical data of r<sup>2</sup> = 0.952 and q<sup>2</sup> = 0.637. Further contour mapping showed that introduction of the electron-rich fluorine atoms into the molecule may promote the antiviral potent in some extent.

To compare the differences between ligand-based and receptor-based approaches, Perez-Nueno et al. performed virtual screenings applied on identifying highly active CXCR4 and CCR5 antagonists, using ligand shape-matching and ligand-receptor docking approaches (Perez-Nueno et al., 2008). For ligand-approach virtual screening, the shape-based and the property-based approaches were carried out in a library consisting of 248 and 354 known CXCR4 and CCR5 inhibitors, respectively, and some 4700 similar presumed inactive molecules. For the receptor-based approaches, the models of CXCR4 and CCR5 were built derived from bovine rhodopsin. Then, two highly active molecules, AMD3100 and TAK779, were docked against CXCR4 and CCR5, respectively, followed by a docking-based virtual screening by using the docked AMD3100 and TAK779 conformations as templates. Compared with property-matching and docking-based tools, the ligand-based shape-matching approach provided better performance. Moreover, the enrichments for CXCR4 was better than those for CCR5. Based on above results, Perez-Nueno et al. continued to perform a prospective virtual screening combining docking-based, pharmacophore modeling, QSAR analysis and shape-matching techniques, and five highly active compounds were finally identified using above computational tools, with the best activity values of 22 nM (molecule 10, Fig. 4) (Perez-Nueno et al., 2009).



**Molecule 10**

Fig. 4. The structure of entry inhibitor targeting co-receptor CCR5/CXCR4

## 2.2 HIV reverse transcriptase inhibitors

### 2.2.1 The structure of HIV-1 reverse transcriptase

HIV-1 RT transforms a single-stranded viral genomic RNA into a double-stranded DNA that is lately integrated into the genome of the host cell (Himmel et al., 2009). HIV-1 RT is a dimer made up of two subdomains (Fig. 5). One subdomain, a 66-kD subunit (p66), consists of 560 amino acid residues, and the other subdomain, a 51kD subunit (p51), consists of 440 residues and is close to p66. The sequences of the first 440 residues for both p66 and p51 are same. The larger subunit of the RT heterodimer, p66, includes two domains: the N-terminal polymerase domain and the C-terminal Ribonuclease H (RNH) domain. They are responsible for the two catalytic activities of RT (Sarafianos et al., 2009). The N-terminal polymerase domain is made up of four subdomains: fingers (residues 1-85 and 118-155), palm (residues 86-117 and 156-236), thumb (237-318), and connection (319-426) (Jacobomolina et al., 1993). The structures of the individual subdomains in p51 and p66 are same, but the arrangement of subdomains in order is different. The nucleic-acid binding cleft is constructed chiefly by five subdomains (fingers, palm, thumb, connection, and RNH) coming from p66 subunit. The connection and thumb subdomains in p51 subunit construct the floor of the binding cleft. In the presence of nucleic acids, the p66 subunit assumes an "open" conformation, in which the thumb rotates away from the fingers forming a large

clef that affords a space for double-stranded nucleic acid substrates. On the other hand, in the absence of nucleic acid, the p66 subunit presumes a “closed” conformation, in which the thumb rotates toward the fingers to cram this clef. The binding clef is formed so that the nucleic acid contacts with both the polymerase and the RNH subdomains; these are placed about 17 or 18 base pairs apart on the nucleic acid substrate.

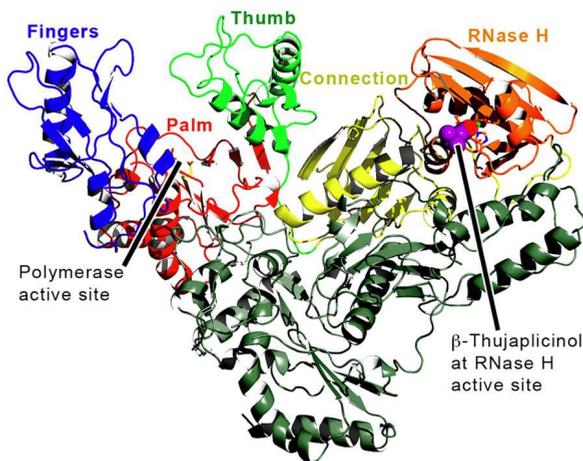


Fig. 5. Overview of RT Structure (Himmel et al., 2009). An RT ribbon diagram of the RT/ $\beta$ -thujaplicinol structure is shown. The subdomains of the p66 subunit (including the RNase H domain) are colored as follows: fingers, blue; palm, red; thumb, green; connection, yellow; RNH, orange; and the p51 subunit, gray.  $\beta$ -thujaplicinol is shown spacefilled in magenta and red.

### 2.2.2 The quantitative structure activity relationship-based drug design

Pawar et al. studied the correlation of the chemical structure of Isatin analogues and their anti-HIV activity using Multiple Linear Regression Analysis (MLRA) and k Nearest Neighbor Molecular Field Analysis (kNN MFA), respectively (Pawar et al., 2010). New chemical entities were designed according to the results obtained from QSAR studies. The most promising compounds were chosen from molecular modeling studies. Finally, they found that compound **N21** (Fig. 6) showed significant RT inhibitory activity and was comparable with standard Navirapine.

Using isosteric replacement in the central B-ring of diarylpyrimidine compounds, Qin et al. designed a series of diarylaniline and 1,5-diarylbenzene-1,2- diamine derivatives (Qin et al., 2010). The most promising compound **37** (Fig. 6) showed significant anti-HIV activity ( $EC_{50}$  values are 0.003  $\mu$ M against HIV-1 wild-type strains and 0.005  $\mu$ M against several drug-resistant strains, respectively). Their results demonstrated an important structure-activity relationship (SAR) for diarylanilines that an  $NH_2$  group on the central benzene ring ortho to the anilinemoiety is crucial for interaction with K101 of the NNRTI binding site in HIV-1 RT, likely by forming H-bonds with K101.

Hu et al. studied a series of HIV-1 RT inhibitors (2-amino-6-arylsulfonylbenzonitriles and their thio and sulfinyl congeners) using QSAR. Topological and geometrical descriptors, as well as quantum mechanical energy-related and charge distribution-related descriptors

generated from CODESSA, were applied to depict the molecules (Hu et al., 2009). Using Principal component analysis (PCA) distinguishes training set. Six approaches: multiple linear regression (MLR), multivariate adaptive regression splines (MARS), radial basis function neural networks (RBFNN), general regression neural networks (GRNN), projection pursuit regression (PPR) and support vector machine (SVM) were utilized to generate QSAR models between anti-HIV-1 activity and HIV-1 RT binding affinity. The results showed that the capacities of prediction of PPR and SVM models were dominant.

The most common resistant mutation by clinical observation is the substitution of lysine to asparagines at codon 103 of RT (K103N) (Bacheler et al., 2001). In order to obtain the necessary structural information for receptor-based inhibitors design, molecular docking combined with 3D-QSAR was applied to a series of structurally diversified HIV-RT inhibitors (Juan, 2008). Using two methods established 3D-QSAR models. The first method was the flexibility-based molecular alignment (FMA), similar to receptor-based alignment, which sampled the biological space of K103N mutant HIV-RT. FMA was finished by docking the inhibitors to four mutant HIV-RT structures with PDB codes: 1SV5, 2IC3, 1FKP and 1FKO. The best superposition of the inhibitors advised novel inhibition of nevirapine-resistance. The second method was the dataset division which utilized the principal component analysis (PCA) to classify the dataset into training and test sets. Predictive statistical models were obtained using the FMA method for the molecular alignment of compounds based on known structures of HIV-RT complexes. Similarly, employing the most descriptive compounds (MDC) method displayed fitness for the division of dataset compounds. The result showed the relevance of hydrophobic and flexible properties of the inhibitors to favor binding interactions at the active site of mutant HIV-RT.

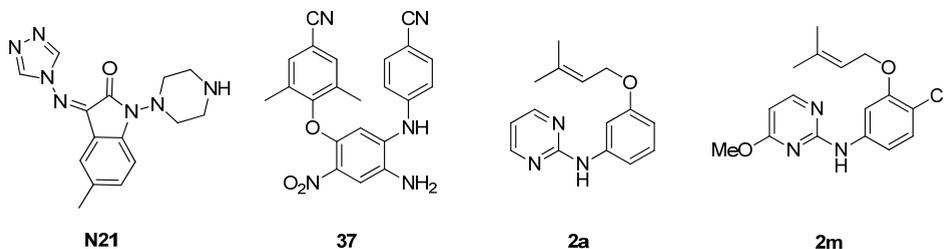


Fig. 6. Structure of reverse transcriptase inhibitors

### 2.2.3 The fragment-based drug design

Geitmann, M. et al. identified a novel scaffold inhibiting wild type and drug resistant variants of HIV-1 RT in a library consisting of 1040 fragments using screening strategy (Geitmann et al., 2011). The fragments were remarkably different from already known NNRTIs, as demonstrated by a Tversky similarity analysis. A screening project involving surface plasmon resonance (SPR) biosensor-based interaction analysis and enzyme inhibition was used. Ten hits were chosen, and then hits' affinities and resistance profiles were evaluated using wild type and three drug resistant enzyme variants (K103N, Y181C, and L100I). One fragment with EC<sub>50</sub> at a low  $\mu$ M level against all four tested enzyme variants was chosen.

Employing the BOMB program yielded NNRTI leads (Jorgensen et al., 2006). BOMB generated compounds into an active site by adding user-selected substituents to a core. The

core can stuff four substituents and/or linked together. The BOMB libraries include more than 100 cores and 600 substituents, which are general fragments in drugs. A screening search was executed for each compound, each conformer was the best location by all kinds of optimally positioned, and the lowest-energy one was chosen. The output from BOMB contained its predicted activities value, receptor-ligand binding energetic and structural informations, and predicted properties including solubility and cell permeabilities using QikProp program (Jorgensen & Duffy, 2002).

Based on the above design considerations, virtual libraries were formed using two motifs, U-Het-NH-Ph and Het-NH-Ph-U, where U is an unsaturated, hydrophobic group and Het is an aromatic heterocycle. The first motif had been more commonly employed, so initial attention was directed at the latter one. Using NH<sub>3</sub> as the core built the ligands, positioned to hydrogen bond with the K101 carbonyl group. Het includes 61 five- and six-membered heterocycles, and 47 alternatives for U. Using above approach obtained 100 lead compounds. In order to narrow the possibilities for the compounds, Monte Carlo simulations using free-energy perturbation simulations were carried out. The present computational strategy had been effective in identifying a 30  $\mu$ M lead compound **2a** (Fig. 6) that could be rapidly progressed to a 10 nM **2m** (Fig. 6) NNRTI (Jorgensen et al., 2006).

## 2.3 HIV integrase inhibitors

### 2.3.1 The structure of HIV-1 integrase

HIV-1 integrase (IN) is a 288-residue enzyme with molecular weight of 32-KD, which is encoded by the pol gene. IN consists of three functional domains as follows: the N-terminal domain (NTD, residues 1-49) with a non-conventional HHCC zinc-finger motif, promoting protein multimerization; the catalytic core domain (CCD, residues 50-212) containing a canonical DDE motif and involved in DNA substrate recognition; the C-terminal domain (CTD, residues 213-288) binding DNA non-specifically and helping to stabilize the IN-DNA complexes (Fig. 7). At present, the structures of IN three respective domains and conjunctural structures of CCD with CTD/NTD have been solved through X-ray and NMR

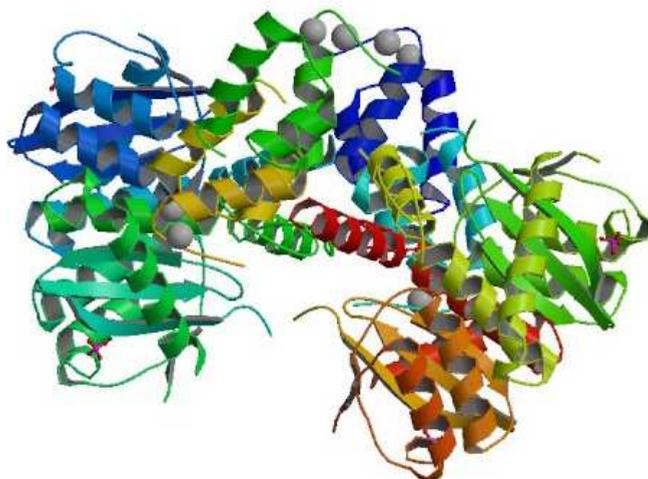


Fig. 7. The structure of HIV integrase (Wang et al., 2001)

spectroscopy (Li et al., 2011). Unfortunately, the full-length structure of IN is still unknown, which thus limit the development of HIV-1 IN inhibitor design. But, the complete structure of the Primate foamy virus (PFV) IN complexed with the substrate DNA and IN inhibitors raltegravir or elvitegravir has recently been obtained (Hare et al., 2010).

IN mediates the integration of viral DNA into host genome in two steps. Firstly, two nucleotides are removed from each 3'-end of each strand of viral DNA to produce new hydroxyl ends (CA-3'OH), which is termed as 3'-processing. Secondly, the recessed 3'-ends of viral DNA are covalently joined to the host genome, which named DNA strand transfer. The DNA strand transfer occurs in nucleus. During the integration procedure, divalent metal ions, such as Mg<sup>2+</sup> or Mn<sup>2+</sup>, are necessary.

### 2.3.2 The Quantitative structure activity relationship-based drug design

QSAR analysis is the most common method for investigates into the relationship of structure and bioactivity, and, more importantly, may provide beneficial suggestion for subsequent novel anti-HIV drug design.

Nunthaboot et al generated a single 3D-QSAR models for 89 HIV-1 IN inhibitors of a whole variety of 11 structurally different classes using CoMFA and CoMSIA (Nunthaboot et al., 2006). The best CoMFA model yielded the  $q^2 = 0.698$  and the  $r^2 = 0.947$ . Contour mapping of CoMFA emphasized steric interactions and electrostatic interactions as the important files contributing to the activities of inhibitors. The best CoMSIA model gave  $q^2 = 0.724$  and  $r^2 = 0.864$ . CoMSIA contour revealed the significance of hydrogen bond between Glu152, Lys156 and Lys159 residues and the side chains of inhibitors. Saiz-Urra *et al* obtained another QSAR model with a  $r^2$  of 0.669 based on 172 compounds that belong to 11 different classes using GETAWAY descriptors, Atom-Weights, Geometry and Topology (Saiz-Urra et al., 2007).

It's not difficult to see that descriptors applied in QSAR analysis are essential to the predict ability of QSAR model. While, not only descriptors, but also analysis technique, statistic method and other parameters show great influence on reliability and accuracy of predict model. Leonard *et al.* performed 3D-QSAR analysis by molecular shape analysis (MSA) technique based on 36 styrylquinoline derivatives (Leonard & Roy, 2008). Unlike common QSAR, the so-called Jurs descriptors, which are total polar surface area (TPSA), relative polar surface area (RPSA), relative hydrophobic surface area (RASA) and relative positive charge (RPCG), were applied, along with five statistical methods including stepwise regression, genetic function approximation (GFA), multiple linear regression with factor analysis (FA-MLR), partial least squares regression with factor analysis (FA-PLS) and genetic partial least squares (G/PLS). According to results, the best validation statistics were obtained with stepwise regression and GFA derived model with  $r^2_{\text{pred}}$  and  $r^2_{\text{test}}$  being 0.611 and 0.664, respectively. More importantly, compared with previous analysis with the same object through CoMFA and docking studies (Ma et al., 2004), the introduction of Jurs descriptors into MSA significantly improved the predictability of QSAR model. Similar research carried out on carboxylic acid derivatives recently (Cheng et al., 2010b) indicated that the combination of the replacement method (RM) method which were used to select descriptors with the support vector machine (SVM) by which mathematical models were obtained, along with 3D-MoRSE (3D-Molecular Representation of Structure based on Electron diffraction) descriptors were the best regression approaches to build QSAR models with the satisfied  $r^2$  of 0.852.

De melo et al. applied multivariate QSAR method to 4,5-dihydroxypyrimidine carboxamides HIV-1 IN inhibitors with four descriptors containing the energy of the highest occupied molecular orbital, the component vector to the overall polarizability in the Y plane, the total energy, and the sum of the bond electrotopological values of carbon-carbon aromatic bonds in which the carbons are not substituted and got a reasonable model with  $q^2 = 0.58$ ,  $r^2 = 0.87$  (de Melo & Ferreira, 2009). Interestingly, all of the four descriptors chosen to predict the inhibitory activity of investigated compounds were relate to the electronic distribution, which indicates a requisite relation between the HIV-1 IN inhibition and the electronic distribution of the investigated inhibitors.

Theoretically, QSAR study belongs to ligand-based drug design approach, but the information of receptor is also useful sometimes to QSAR modeling. Dhaked et al. developed a receptor-based 3D-QSAR method—comparative residue interaction analysis (CoRIA) on 81 molecules belonging to 13 structurally different classes of IN inhibitors (Dhaked et al., 2009). This receptor-based model revealed that Asp64, Thr66, Val77, Asp116, Glu152 and Lys159 are key residues influencing the binding of ligands with IN. According to suggestions of the CoRIA models, a **known molecule** (Fig. 8) of data set was modified to a **new molecule** (Fig. 8) with higher anti-HIV activity by intensifying the van der Waals interaction with residues Asp64 and Asp116 and the Columbic interaction of residue Thr66, and while reducing the Columbic interaction with Val77. The activity value ( $pIC_{50}$ ) was improved from 4.92 to the best 5.22

Ravichandran et al. obtained a QSAR model with  $R^2_{CV_{ext}}$  of 0.630 and  $R^2_{Pred}$  of 0.688 using 1,3,4-oxadiazole substituted naphthyridine derivatives (Ravichandran et al., 2010). The descriptors valence connectivity index order, lowest unoccupied molecular orbital and dielectric energy exhibited significant affect on the inhibition of HIV-1 IN activity by 1,3,4-oxadiazole substituted naphthyridine derivatives. Coefficient of these descriptors indicated that highly branched, unsaturated and long chain groups as well as high electro negativity are favorable for HIV-1 IN inhibitory activity; in contrary, the increased dielectric constant of the compounds is unfavorable. The selected descriptors could serve as a novel guideline for the design of novel and potent antagonists targeting HIV-1 IN.

Chalcones are discovered as a novel class of HIV IN inhibitors with satisfied antiviral activity. But, unfortunately, many chalcones are non-specific inhibitors and possess cytotoxicity. Based on two chalcones previously reported (Deng et al., 2006), Deng et al subsequently developed five six-feature pharmacophores and two four-feature pharmacophores aiming to discover non-chalcone-based compounds with low cytotoxicity . The best pharmacophore model was applied as a query to search a small molecule database, 44 compounds were chosen and showed high inhibitory potency at  $IC_{50}$  values  $<100 \mu M$ . Among these molecules, compound **62** (Fig.8) stood out finally as the most active molecule with  $IC_{50}$  value of  $1.9 \mu M$  and  $0.6 \mu M$  for 3-processing and strand transfer process, respectively (Deng et al., 2006).

Sharma et al. generated a pharmacophore model based on a series of 3-keto salicylic acid chalcones and related amides as novel HIV-1 IN inhibitors (Sharma et al., 2011). A set of pharmacophoric sites were obtained, including H-bond acceptor (A), H-bond donor (D), hydrophobic group (H), negatively charged group (N) and aromatic ring (R). To identify a common pharmacophore hypothesis, the top twenty pharmacophore hypotheses were selected to undergo further analysis by partial least square (PLS) regression-based 3D-QSAR. The best hypothesis exhibited the highest predicted ability of  $q^2 = 0.57$  and  $r^2 = 0.74$ ,

consisting of six features, two H-bond acceptors, two hydrophobic groups, a negative group and one aromatic ring. Subsequently, CoMFA and CoMSIA 3D-QSAR model were built based on pharmacophore mapping. The combinational application of pharmacophore model with QSAR analysis afforded the best model with  $q^2$  and  $r^2$  values of 0.54 and 0.94, respectively, which would guide the rational design of more potent novel 3-keto salicylic acid IN inhibitors.

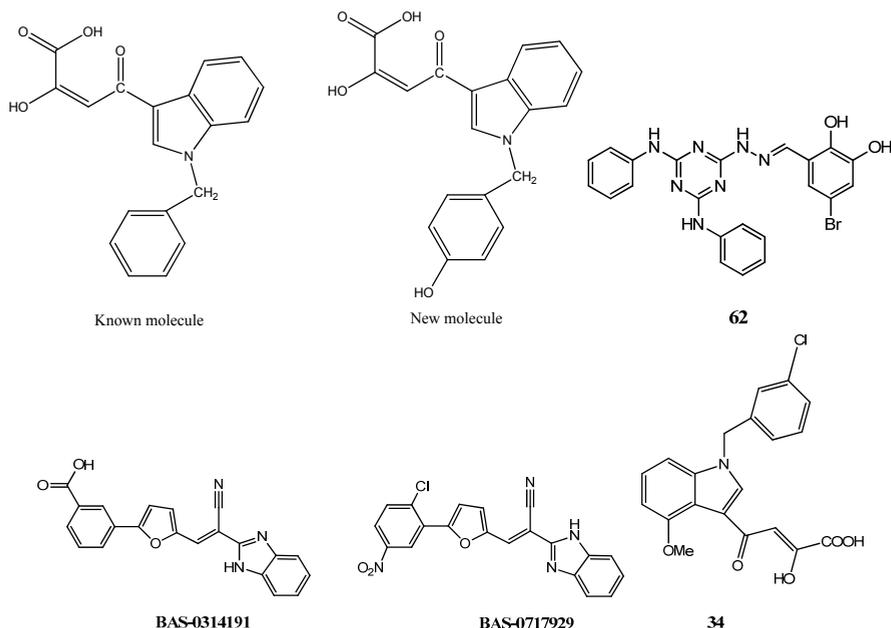


Fig. 8. The structure of integrase inhibitors

### 2.3.3 Combined the receptor-based and ligand-based drug design approach

As QSAR analysis, the pharmacophore model is built based on the structural information of ligands. While, only ligand-based or receptor-based research is not enough perfectly sometimes (Dayam et al., 2008) because the inhibition of inhibitors against IN is implemented through an integral processing with anticipation of both the IN enzyme and inhibitor molecules. Accordingly, it's becoming increasingly popular to combine the receptor-based drug design (RBDD) and ligand-based drug design (LBDD) approach so that both the small molecules and receptor can be taken into account and the result would be more rational and valid.

Tintori et al employed an innovative virtual screening approach consisting of the electron interaction potential technique, druglike property calculation, pharmacophoric model generation, and docking studies, with which both the long- and short- range interactions between molecules could be calculated (Tintori et al., 2007). As result, 12 compounds were eventually screened out from a database containing over 200,000 molecules to in vitro assay and one of them **BAS-0314191** (Fig. 8) displayed a comparative satisfied activity with  $IC_{50}$  value. Subsequent substructure codification identified a better molecule **BAS-0717929** (Fig.

8) with a higher  $IC_{50}$  value from 69 to 10  $\mu\text{M}$ . Using the same approach as Tintori, other hit compounds as IN binding inhibitors with corresponding  $IC_{50}$  values with **BAS-0717929** (Fig. 8) were discovered from a 200,000 molecule-contained database (Mugnaini et al., 2007).

Tintori et al. applied a novel multistep computational protocol for the development of structure-based pharmacophores which combined pharmacophore generation with conformational analysis, docking studies and MD simulation (Tintori et al., 2008). A conformational search was initially performed from the flexible loop region of IN to cluster the conformations with low enough energy. Then, three pharmacophore models were generated containing hydrogen bond acceptors, hydrogen bond donors and hydrophobic features based on the best conformation found in the most populated cluster and followed by a database screening using these three hypotheses alternately. As result, one hit compound was identified finally and showed satisfied  $EC_{50}$  value of 30  $\mu\text{M}$  and  $IC_{50}$  values of 25  $\mu\text{M}$  and 3  $\mu\text{M}$  toward 3-processing and strand transfer, respectively.

Zhang et al. have recently developed a 3-D pharmacophore model from two diketoacids (DKAs) inhibitors, MK-0518 and S-1360 (Zhang et al., 2009). For the strong anti-HIV potency and reliable drug-like properties, they mapped inhibitor conformations into the pharmacophore model and superimposed it in their docking model with IN core domain. Thus, the corresponding positions between the pharmacophore model and IN residues were identified, according which the pharmacophore was improved further. Finally, a better pharmacophore model including one hydrophobic feature, three hydrogen pair features and one hydrogen-bond donor feature was generated and displayed a higher retrieval capability and universality than previous studies (De Luca et al., 2008).

Ferro et al. combined SBDD with LBDD approach to investigate the binding mechanism of HIV IN inhibitors and then obtained a set of structurally attractive lead compounds (Ferro et al., 2009). Employing combination of ligand-based pharmacophore and receptor-based docking approach, a series of 4-[1-(4-fluorobenzyl)-1H-indol-3-yl]-2-hydroxy-4-oxobut-2-enoic acids which have the 1H-benzylindole skeleton (Barreca et al., 2005; Ferro et al., 2007) were discovered as potent anti HIV-1 IN agents selectively inhibiting strand transfer step of IN. Moreover, docking result revealed that there is a large hydrophobic cavity defined by nonpolar residues L68, I73, V75, L158 and I162 in IN core domain, which is probably occupied by the 4-fluorophenyl ring of the inhibitor. Based on above results, Ferro et al. subsequently designed a series of new chloro-fluoro-benzylindoles analogues (Ferro et al., 2010) from the leading compound named CHI-1043 characterized by the presence of a methoxy group at C-4 of the indole system and bearing a fluorine atom on the para position of the benzyl moiety which was identified previously (De Luca et al., 2008). The best molecule, derivative **34** (Fig. 8), displayed a good antiviral activity ( $IC_{50} = 30 \text{ nM}$ , inhibit the in vitro strand-transfer step) and selectivity index, and, more important, higher efficiency and lower cytotoxicity than CHI-1043 (Ferro et al., 2010).

## 2.4 HIV protease inhibitors

### 2.4.1 The structure of HIV protease

HIV PT can process the viral into mature and infectious virus particle. Many studies reveal that it cause mature infectious virus particles through cleavage of the viral Gag and GagPol precursor proteins. HIV-1 PT is a homodimer with 99 residues per subunit (Fig. 9), and each subunit is composed of nine  $\beta$ -strands and one  $\alpha$ -helix (Noel et al., 2009).  $\beta$ -Strands 2 to 8 are involved in the formation of a jelly-roll $\beta$ -barrel topology within each subunit. The dimeric

interface contains an antiparallel  $\beta$ -sheet formed by the interdigitation of the N- and C-terminal  $\beta$ -strands in each subunit and by an interlocking and balanced pair of threonines, Thr26, in the active site (Noel et al., 2009). The active site-needling proteolysis is embed in the flap tips and crossing the subunit interface. At the subunit interface and the base of the active-site flap tips, Trp6 and Trp42 providing intrinsic fluorescence (FL) probes of the folding reaction. The result of NMR studies revealed that the mutations of HIV-1 PT variants at or near the interface always break the balance of monomer-dimer.



Fig. 9. Structure of HIV PR complexed with TL-3 (PDB: 3TLH) (Brik & Wong, 2003).

#### 2.4.2 Development of HIV protease inhibitors by CADD

Nelfinavir is a potent, non-peptidic inhibitor of HIV-1 PT, which turns out to be successful in the treatment of AIDS. But the potency of Nelfinavir ever-reduced along with HIV develops drug-resistance. Perez et al reported three new variants of Nelfinavir in their studies (Perez et al., 2007). They used minimization and MD simulations methods to optimize and modify original Nelfinavir. Three new inhibitors were designed employing binding free energies calculation and structure modification. The new inhibitors showed greater affinity for HIV-1 PT than Nelfinavir.

Nanoparticles as a new technology have been extensively used in many research fields. Yuan Cheng et al reported the design of carbon nanotubes as HIV-1 PIs (Cheng et al., 2010a). Using docking and MD simulation methods, they designed carbon nanotubes and explored the binding mode between carbon nanotubes and HIV-1 PT. They designed an atomistic model to investigate free energy and interaction between receptor and ligand. In addition, in order to investigate the behaviors of the PT in MD experiment, they used a coarse-grained model based on the atomistic model. The result of dynamics showed that the carbon nanotubes can preferable bind the active site of the HIV PR. It can stop the active flaps in turn to blocking the function of the PT. At the same time, they found that the simulation track is strongly influenced by the size of the carbon nanotube.

Jha et al. established effective prediction model of QSAR on some N-aryl-oxazolidinone-5-carboxamides for higher anti-HIV PT activities (Jha & Halder, 2010). Stepwise regression developed significant models showing importance of atom based descriptors like refractotopological state atom indices, Wang-Ford charges and different whole molecular descriptors. The high prediction ability of these QSAR models was confirmed by challenging these against an external dataset.

HIV-1 PT can specifically recognize their peptide substrates in extended conformations. General approaches for designing HIV-1 PIs often consist of peptidomimetics that feature this conformation. Arora et al evaluated the potential of triazole linked  $\beta$ -strand mimetics as inhibitors of HIV-1 PT activity employing the combination of computational and experimental approaches (Arora et al., 2009). Their studies suggested that nonpeptidic  $\beta$ -strand mimetics, termed triazolamers, offer attractive starting points for the rational design of PIs.

### 3. Perspectives

This chapter gives a brief review of recent achievements in discovering anti-HIV inhibitors by using CADD method. Readers are suggested to peruse the original articles for more detailed information. In addition to NRTIs, NtRTIs, NNRTIs, PIs, INIs, FIs and entry inhibitors provide great potential for the treatment patients of HIV infections. Studies on the viral proteins Tat, Rev, Vif and Nef may further afford new drug targets. Latest technological advances (Fischer & Hubbard, 2009) (e.g., protein crystallography, X-ray crystallography, computer resource, cheminformatics & bioinformatics), the growing number of chemical and biological databases, and an explosion in programs and software are providing an ever betterment tools for the design of anti-HIV inhibitors.

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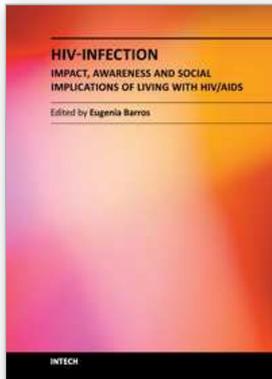
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## **HIV-infection - Impact, Awareness and Social Implications of living with HIV/AIDS**

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The past few decades have seen the escalation of HIV-infections and the 'frantic' search for new drugs to treat the millions of people that live with HIV-AIDS. However because HIV-AIDS cannot be cured, but only controlled with drugs, and the Antiretroviral (ARV) treatment itself results in some undesirable conditions, it is important to generate wider awareness of the plight of people living with this condition. This book attempts to provide information of the initiatives that have been used, successfully or unsuccessfully, to both prevent and combat this 'pandemic' taking into consideration the social, economic, cultural and educational aspects that involve individuals, communities and the countries affected.

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