Capsid (CA) Protein as a Novel Drug Target: Recent Progress in the Research of HIV-1 CA Inhibitors

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Abstract: The capsid (CA) protein is the major structural component of HIV-1 and plays a key role in the regulation of viral life cycle. Inhibition of CA will affect the viral assembly and budding processes, causing decreased viral infectivity. This review describes the structure and function of the HIV-1 CA and latest progress in the discovery of HIV-1 CA inhibitors.

Key Words: HIV-1, AIDS, capsid inhibitor, antiviral agents, CA-N, CA-C, mutation.

1. INTRODUCTION

Within the last decade, highly active antiretroviral therapy (HAART), typically comprise at least three drugs chosen from the well-established drug classes: nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs], nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), have dramatically decreased the morbidity and mortality from HIV infection. However, severe adverse events and other tolerability issues with these drugs can lead to low patient adherence resulting in sub-optimal drug usage, the development of resistance and virological failure. Therefore, the discovery and development of new anti-HIV agents with a novel mechanism, greater potency and lesser toxicity, and broad-spectrum anti-HIV activity remain continuously warranted. During its replicative cycle, HIV-1 gag encodes a precursor polyprotein (Pr55gag) that is necessary for virion particle formation and egress from the host cell. Gag expression alone is sufficient for virus-like particle (VLP) formation, suggesting that the HIV-1 (Human immunodeficiency virus type 1) gag gene contains sufficient information for directing VLP assembly and budding [1]. Pr55gag is proteolytically cleaved into the mature proteins by the viral protease (PR): MA (matrix), CA, NC (nucleocapsid) and p6, as well as the spacer peptides SP1 and SP2 (Fig. (**1**)), and the mature pol-encoded PR, reverse transcriptase (RT) and integrase (IN). Cleavage of Gag is a temporally ordered process with the formation of CA representing the terminal step [2]. The HIV-1 CA protein forms a coneshaped core structure that surrounds the viral genome in the HIV-1 particles. The core of the HIV-1 particle is composed of a ribonucleoprotein complex (RNP), which is surrounded by a CA shell consisting of CA protein aggregates. During maturation, CA proteins assemble into a conical core. CA proteins facilitate HIV infection of nondividing cells [3]. So, HIV-1 CA proteins play an important role in virus assembly and infectivity and can be a target for the development of inhibitors. This review describes the structure and function of the HIV-1 CA and latest progress in the discovery of HIV-1 CA inhibitors.

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Fig. (1). The retrovirus gag gene encodes the major viral structural protein Gag.

2. THE STRUCTURE OF HIV-1 CA PROTEIN

During the assembly stage of HIV-1 replication cycle, several thousand copies of the viral Gag polyprotein associate at the cell membrane and bud to form an immature and non-infectious virions (or virus particles). The HIV-1 CA protein is formed by two independently folded domains separated by a flexible linker [4]. Structural studies of the CA protein of several retroviruses have revealed that CA protein is composed of an N-terminal domain (CA-N) and a C-terminal domain (CA-C). The CA-N and CA-C are separated by an apparently flexible linker region (Fig. (**2**)), which allows the two domains to orient independently in solution.

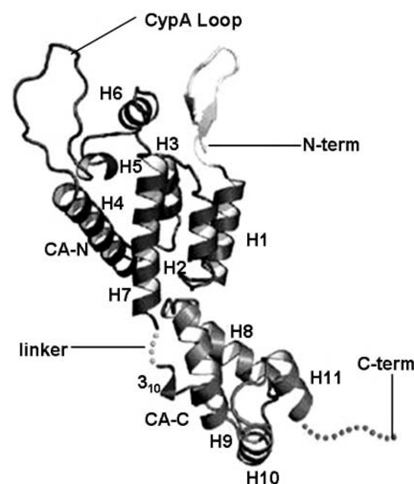

Fig. (2). Structural model for the HIV-1 CA protein based upon crystal structures of the protein's CA-N and CA-C [6].

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There are three different CA functional surfaces in immature particle assembly: one surface encompasses helices 4 to 6 in the CA-N, a second surrounds the crystallographically defined CA dimer interface in the CA-C, and a third surrounds the loop preceding helix 8 at the base of the CA-C. Mature CA protein formation requires a distinct surface encompassing helices (H) 1 to 3 in CA-N (Fig. (**2**)), in good agreement with a recent structural model for the viral CA protein. The CA protein core, formed by about 2000 copies of CA protein, rearranges to produce a mature, conical structure. The amino-terminal domain protein of HIV-1 CA protein refolds into a β-hairpin/helix tertiary structure that is stabilized by a buried salt bridge formed between the positively charged primary imino group of a proline residue and the negatively charged carboxyl group of a conserved aspartate [5].

2.1. N-Terminal Region of CA

CA-N (residues 1–146 in the intact protein) is composed of five coiled-coil α-helices and two additional short α-helices following an extended proline-rich loop. The β-hairpin consists of a 1-13 amino-acid residues and is exposed on the surface of CA-N of the immature CA protein. The amino-acid residues of Ser16-Lys30, Ser33-Ser44, Thr48-Val59, His62-His84, Arg100-Ala105, Thr110-Thr119 and Val126-Ser146 form an α-spiral, while Pro85-Pro99 constitutes the binding site of the peptidyl-prolyl isomerase cyclophilin A (CypA) (Fig. (**2**)). The CA-N dimerizes in solution and crystallizes as a symmetrical dimer created by parallel packing of CA helix 9 against its symmetry-related mate [7].

2.2. C-Terminal Region of CA

Each CA-C monomer is composed of a short 3_{10}-helix followed by an extended strand and four α-helices connected by short loops. The CA-C domain also has a region of 20 amino acids at the beginning of the polypeptide chain called the major homology region (MHR), which is highly conserved in retroviruses. The CA-C dimerization is created by parallel packing of H9 against its symmetry-related mate (Fig. (**2**)).

3. THE FUNCTION OF HIV-1 CA

Substitution of three major phosphorylation sites of HIV-1 CA protein, i.e. Ser-109, Ser-149 and Ser-178, could significantly reduce uncoating activity of purified core particles [8]. CA protein regulates spatial arrangement of Gag within the virions. The CA-N domain and CA-C domain not only intervene in the generation of the mature core but also the immature CA structure. After liberation as a mature protein, CA protein forms the shell of the viral core [9]. Proper cleavage/maturation of CA protein is a requirement for core condensation and proper core formation [10].

3.1. The Function of the CA-N

The CA-N domain is composed of seven α-helices, of which two regions are important for immature virion formation: encompassing H1 and H2 and surrounding H4 and H7 [11-13]. The mutation of N-terminal residues does not interfere with particle production, but mutant virions often have defects in reverse transcription and core assembly as well as loss of infectivity. Trp23 and Phe40 are members of a conserved group of CA-N hydrophobic residues in HIV-1 CA protein. Ala substitutions at Trp23 and Phe40 result in a post-entry defect, making the produced virions noninfectious. Having been aberrant cores, the produced virions are unable to initiate reverse transcription in infected cells. The CA protein interacts with the RNA genome primarily through the basic CA-N. Because of CA-N being dependent on an arginine-rich motif, protein determinants for interaction with the RNA genome are localized in the CA-N terminus [14]. In this aspect, Asp51 located in the CA-N of HIV-1 CAp24 plays an important role by forming a salt bridge with the free imino terminus Pro1 following proteolytic cleavage and liberation of the CA protein from the Pr55Gag precursor. The D51A mutation has been found essential for virus replication and virus CA protein formation [15].

3.2. The Function of the CA-C

The CA-C is required for Gag oligomerization, CA dimerization and viral assembly, which is a critical assembly determinant [16]. Mutations of the dimer interface residues of HIV-1 CA-C measurably reduce viral particle production but do not completely block it, suggesting that CA-C dimerization may be important not only for the stability of the viral shell, but also for the assembly process [17]. The flexibility of CA-C undergoes conformational rearrangements in the presence of different binding partners, since CA-C has a specific affinity for negatively charged lipids. Mutation of a central residue at the homodimerization interface (Met185 to Ala) was shown to impair CA protein assembly and abolish viral infectivity. CA-C dimerization is the major driving force in Gag assembly and virus budding, because the isolated CA-C of HIV-1 (amino acid residues 147–231) dimerizes in solution with nearly the same affinity as the full-length protein. The CA-C fragment is intended to regulate HIV-1 RNA packaging [18]. It is critical for Gag-Gag interactions during virus assembly and CA-CA interactions during core formation [19]. CA-C can initiate the dissociation of Gag protein and precipitate the formation of viral particle [20,21]. The amino-terminal end of the CA-C is highly conserved across retroviral CA proteins, and initiates both assembly and post-assembly functions [22]. Mutations in the HIV-1 MHR (CA protein 153–172) and adjacent C-terminal region affect VLP assembly, membrane affinity, and the multimerization of the Gag structural protein. Partial deletion or a small number of substitution mutations in MHR has been found to significantly affect VLP production, while certain MHR mutations eliminate viral infectivity with no discernable effect on VLP production. K158A and Y164A mutations blocked virus assembly, while Q176A had no major effect on virus assembly or budding. Mutations K158A, F168A and E175A (adjacent to the MHR C terminus) impaired VLP assembly [23].

3.3. The Function of the CA Protein Interdomain Linker Region

Mutations in this region can reduce the efficiency of virus particle assembly, with PrGag proteins and particles accumulating in the cellular plasma membranes. The CA protein linker region is required for the proper alignment of CA protein domains [24].

4. HIV-1 CA PROTEIN RESTRICTION FACTORS AND INHIBITORS

During the stage of the HIV-1 replication cycle, the CA protein plays an important role in the assembly of the polyprotein shell of the central core particle (or CA protein) of the mature virus. Concomitant with virions release from the host cell, the precursor protein is cleaved by the viral PR into mature proteins, including the viral CA protein, which is required for infection of susceptible target cells. Recent studies in retrovirology have found that human cells possess a number of intrinsic antiviral responses, named as restriction factors, whch, can restrict viral replication by regulating the function of the CA protein, Up to now, the restriction factors of CA protein has been reported as the following: TRIM-5α, TRIMCyp-mediated, MAPK-ERK2, and C-PKA. In addition, recently some HIV-1 CA protein inhibitors have been also reported by randomly drug screening, which include PA-457 and CAP-1, CAI, NYAD-1, small molecular entities, as well as some oligopeptides, mimical to the fragment of CA p24, e.g. PAATLEEMMTA.

4.1. CA Protein Restriction Factors

The retroviral restriction factor TRIM5α is the largest TRIM5 isoform (~ 493 amino acid residues) and contains the B30.2(SPRY) domain that has a tripartite motif which includes a RING domain, B-box 2 domain, and coiled-coil (cc)domain [25]. Interacting in a specific manner with the HIV-1 CA protein, TRIM-5α accelerates disassembly of the retroviral CA protein and may prematurely expose the viral RNA or viral enzymes of degradative processes or disrupt CA protein associations with the retroviral core. CA protein associations are critical for reverse transcription. The linker region between the coiled-coil and B30.2 domains of TRIM5α is necessary for efficient TRIM-5α trimerization, which makes a major contribution to its avidity for the retroviral CA protein, and to the ability to restrict virus infection. The TRIM-5α blocks infection by particular retroviruses at an early stage [26]. Deletion of the TRIM-5α coiled-coil disrupts the interaction with HIV-1 CA–NC complex [27].

TRIMCyp is a protein that consists of the structure domains of TRIM-5 fused with a carboxy-terminal CypA moiety [28]. The TRIMCyp-mediated blocking of HIV-1 infection occurs before the earliest step of reverse transcription and has been shown to bind the monomeric HIV-1 CA protein. The restriction involves both CA protein binding and effectors functions [29].

The CA protein is phosphorylated by protein kinase MAPK-ERK2, the three major phosphorylation sites of CA(p24) being Ser-109, Ser-149, and Ser-178. During the reverse transcription process, CA(p24) serine phosphorylation is essential for the viral uncoating process, so phosphorylation of CA(p24) on these residues is directly implicated at the early steps of infection.

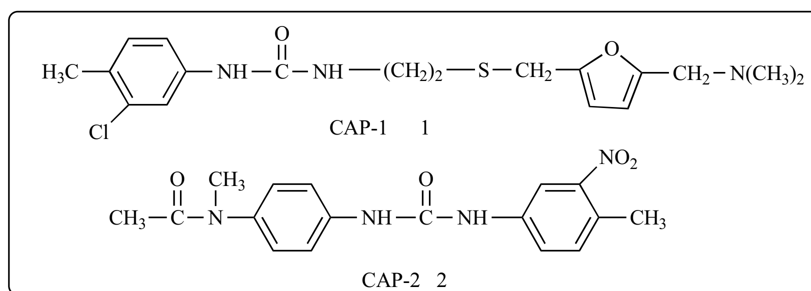
The C-PKA kinase catalyzed phosphorylation of the viral CA protein so as to regulate HIV-1 infectivity. Phosphorylations of CAp24gag protein at the serine residues are required for viral infectivity. The reverse transcription process does not function in CAp24gag mutants with mutated serine phosphate acceptor sites. Phosphorylation of HIV-1 CA protein probably generates some repulsive forces among protein-protein interactions that participate in viral core destabilization and viral particle uncoating [30].

4.2. Inhibitors Targeted at HIV-1 CA

4.2.1. CAP

CAP-typed compounds are the firstly found small molecular Inhibitors of HIV-1 CA. Recently, Kelly *et al.* reported that two CAP derivatives of CAP-1 [N-(3-chloro-4-methylphenyl)-N'-{2-[({5-[(dimethylamino)-methyl]-2-furyl}-methyl)-sulfanyl]-ethyl}urea,1], and CAP-2, [1-(4-(N-methyl-acetamido)-phenyl)-3-(4-methyl-3-nitrophenyl)urea, 2] were potential HIV-1 CA Inhibitors that were proved to inhibit CA protein assembly by binding to an apical site on the CA-N of the HIV-1 CA [31].

CAP-1, binding in a deep pocket in CA-N, formed at the junction of H1, H2, H4, and H7. In the presence of CAP-1, CA protein undergoes a remarkable conformational change, in which Phe32 is displaced from its buried position in the protein core to open a deep hydrophobic cavity that serves as the ligand binding site. The binding model is illustrated (Fig. (**3**)), and showed that the CAP-1 inserts into the pocket that vacated by Phe32 through binding with the CAP-1 aromatic ring moiety. The binding affinities of CAP-1 with the cavity are closely related to the formation of hydrogen bonds from the urea NH groups with the backbone oxygen of Val59, and the interaction of dimethylamonium group with the side-chains of Glu28 and Glu29. So, virus particles exhibit heterogeneous sizes and abnormal core morphologies when treated with CAP-1, consistent with inhibition of CA–CA interactions during virus assembly and maturation [32]. Toxicity and antiviral activity of CAP compounds were tested using and the results showed that CAP-1 was non-toxic under the conditions employed, and its application led to dose-dependent reductions in supernatant infectivity, while CAP-2 was too cytotoxic for *in vivo* evaluations [31].



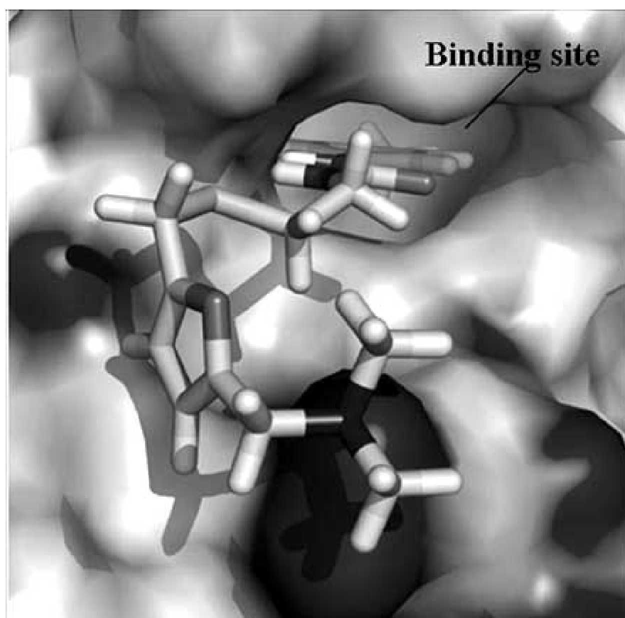


Fig. (3). The CAP-1 binding site of HIV-1 CA protein [32].

4.2.2. Betulinic acids

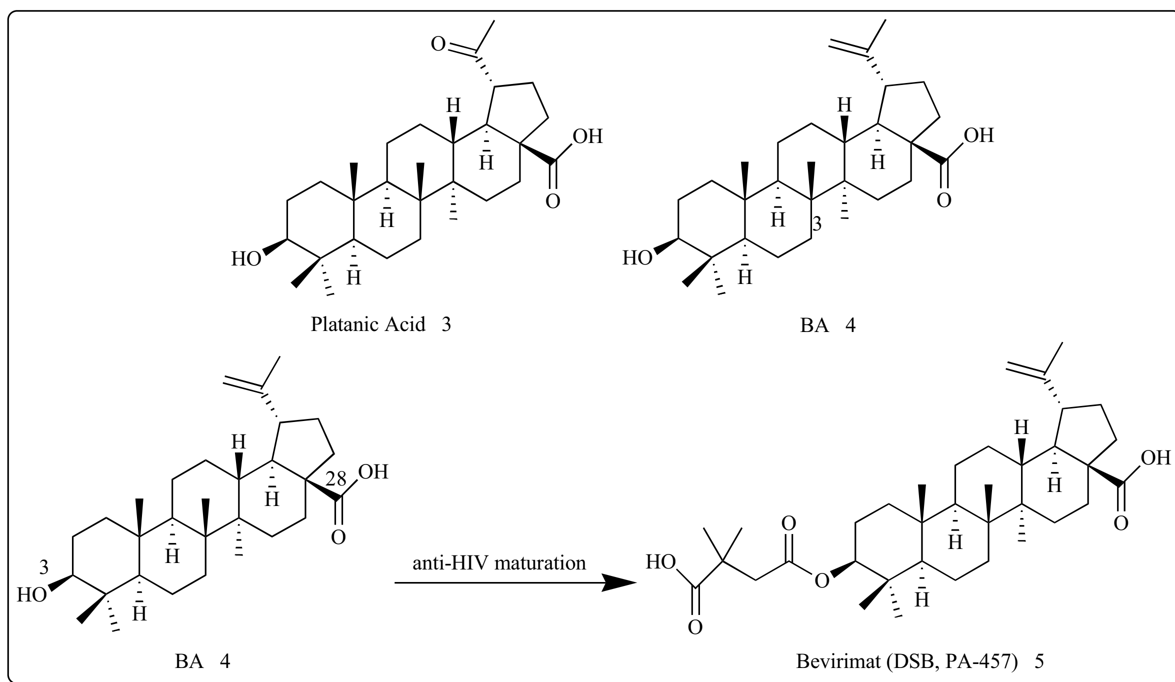
Platanic acid(3) and Betulinic acid (BA, 3β-hydroxy-lup-20(29)-en-28-oic acid, 4) are pentacyclic triterpenes extracted from Syzigium claviflorum, which showed modest anti-HIV-1 activity with IC_{50} values of 1.4 and 6.5 μM, respectively. Because BA can be availability from various natural sources, including white birch trees, it was selected as a lead in an anti-HIV drug discovery program.

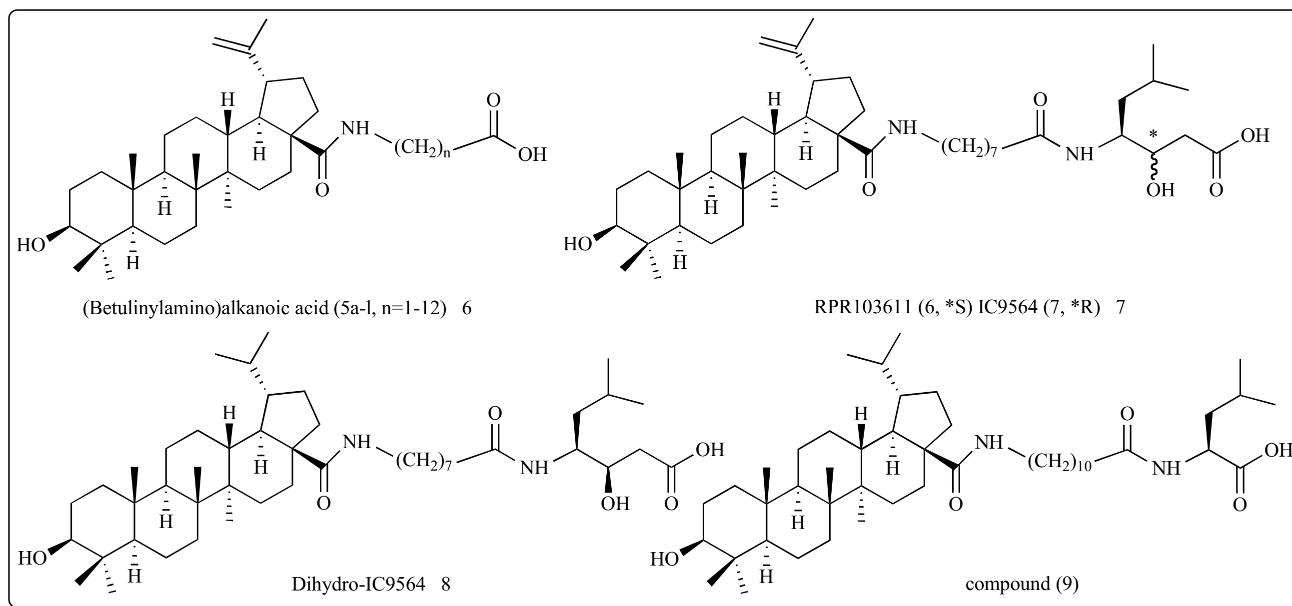
There are three classes of chemically modified BA derivatives. Class I possesses side-chain modification at the C-3 position of BA, such as DSB (also designated as PA-457). Class II possesses side-chain modification at the C-28 position such as IC9564. Class III possesses side-chain modification at the C-3 and C-28 position simultaneously, such as compounds in Table **1**. Usually, C-3 modified BA is demonstrated to inhibit HIV-1 maturation process acting as maturation inhibitors, and C-28 modified BA blocks HIV-1 entry process serving as entry inhibitors. Thus, C-3 and C-28 modified BA acts as dual inhibitors targeted at both of maturation and entry processes.

4.2.2.1. Side-Chain Modification at the C-3 Position of BA

As HIV-1 maturation inhibitors, the most potent C-3 modified BA derivatives is PA-457 [3-O-(3',3'-dimethylsuccinyl BA), 5], which blocks virus maturation by decreasing the ability of PR to access the CA/p2 processing site.

PA-457 inhibits replication of both prototypic and clinical HIV-1 isolates and retains activity against viruses resistant to the three classes of approved drugs targeting at the viral enzymes RT and PR [33]. It disrupts a late step in Gag processing involving conversion of the CA protein precursor (p25) to mature CA (p24), resulting in the formation of defective, noninfectious virus particles. CA-SP1 is the primary viral determinant for this novel inhibitor of HIV-1 replication. Using *in vitro* resistance selection experiments, the determinants of PA-457 activity have been mapped to the region flanking the CA-SP1 cleavage site [34]. PA-457 is unlikely to cause drug–drug interactions when given in combination with currently approved HIV-1 therapies. In the presence of PA-457-treated cultures, virions are noninfectious and exhibit an aberrant particle morphology characterized by a spherical, acentric core and a crescent-shaped, electron-dense shell lying just inside the viral membrane [35]. PA-457 is currently in Phase IIb clinical trials and shows good oral bioavailability, safety and pharmacokinetic profiles [35-38].



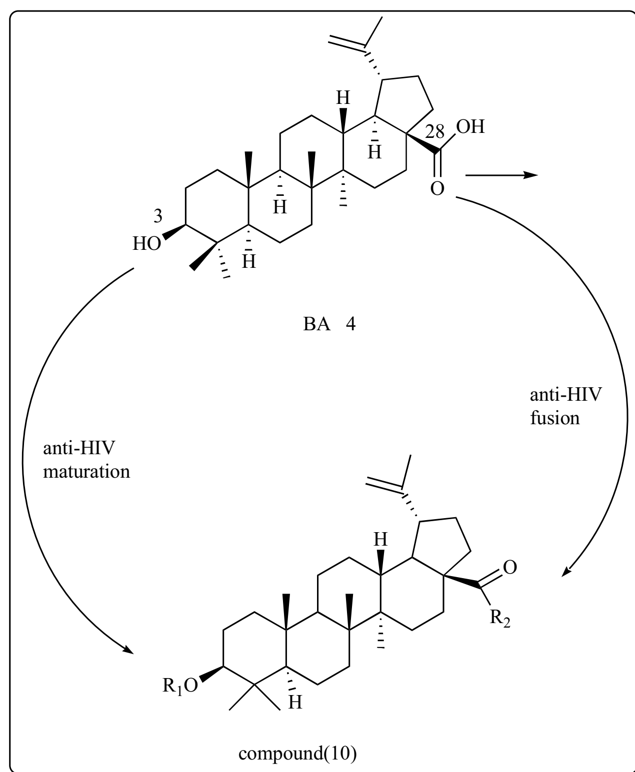


4.2.2.2. Side-Chain Modification at the C-28 Position of BA

C-28 modified BA analogs are potent HIV-1 entry inhibitors. Increment of the chain length between the C-28 amide bond moiety and the terminal carboxylic acid group can significantly influence the anti-HIV-1 potency of the derivatives. Amide side chains between amino-octanoic acid and amino-dodecanoic acid (6g–k, n=7–11, 6) showed increased antiviral potency and amino-undecanoic acid (6j, n=10) is proved to be optimal [39]. Some compounds with two amide moieties at different positions of the C-28 side chain were prepared by condensation of these C-28 ω-aminoalkanoic acid derivatives with a second aminoalkanoic acid, in which, small peptide amide derivatives of the parent octanoic acid analog 6g showed more potent than other derivatives. This led to the discovery of RPR103611(7, *R) that can modulate the antiviral potency and inhibit the infectivity of several HIV-1 strains in a 10nM concentration range [40-42]. IC9564 (7, *S) has equally potent anti-HIV-1 activity to it's stereoisomer of RPR103611 [45]. Dihydro-IC9564 (8), having a saturated isopropyl rather than isopropenyl group, and Compound(9), having a L-leucine derivative of (betulinylamino)-

Table. 1. The Effect of BA Derivatives (Compounds (10)) Against HIV-NL4-3 in MT-4 cells [44]

Compounds (10)	R_1	R_2	EC_{50} (uM)	IC_{50} (uM)
10a (IC9564)	H	—NH(CH$_2$)$_7$—C(=O)—NH— COOH OH	0.053	>10
10b (DSB)	HO O O	OH	0.075	7.5
10c	HO O O	L-Leucine	0.015	
10d	HO O O	—NH—(CH$_2$)$_{10}$—COOH	0.012	6
10e	HO O O	—NH—(CH$_2$)$_7$—C(=O)—NH COOH	0.096	>10
10f	HO O O	—NH—(CH$_2$)$_7$—NH—COCH$_3$	0.0026	8
10g	H	—NH—(CH$_2$)$_7$—NH—COCH$_3$	0.047	>10



undecyclic acid, were studied and found to have equally potent anti-HIV-1 activity with RPR103611 and IC9564.

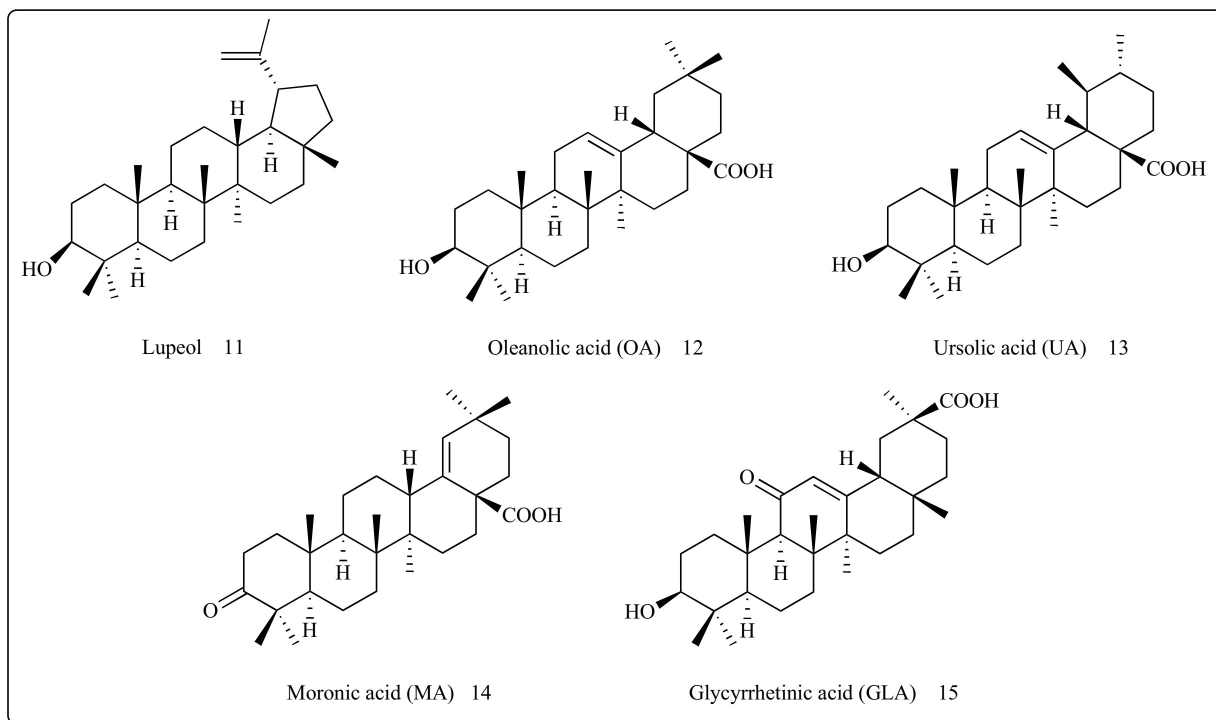
4.2.2.3. Side-Chain Modification at the C-3 and C-28 Position of BA

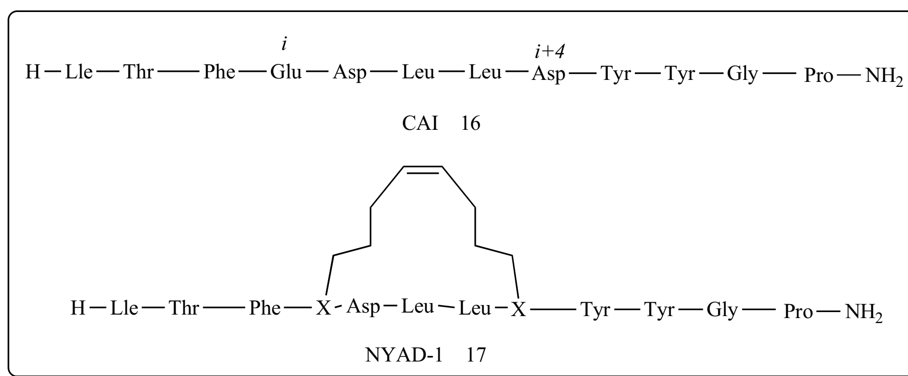
The C-3 side chain of the BA derivatives is the pharmacophore for anti-maturation activity, while the C-28 side chain is the pharmacophore for anti-entry activity. Structurally, the C-3 and C-28 pharmacophores of these two classes of compounds are located at the opposite sites of the BA pentacyclic ring system [43]. Compounds (10) are the series of BA derivative that incorporates both pharmacophores into one BA molecule.

DSB and IC9564 are the most potent mono-functional BA derivatives respectively to class I and II. Compound 10e with bi-functional groups has an identical side chain to that of IC9564 at C-28 and to that of DSB at C-3, which is more potent anti-HIV activity than either mono-functional compound. Two bi-functional BA derivatives compound 10c and 10d exhibit improved anti-HIV-1 activity with EC_{50} values of 0.015 and 0.012uM respectively, when compared with the corresponding mono-functional BA derivatives. However, both bi-functional 10f and it's C-28 mono-functional analogs 10g without a terminal carboxylic acid, are quite potent against HIV-1 induced fusion (Table **1**). Therefore, the terminal carboxylic acid at C-28 is not a requirement for anti-HIV entry activity. Instead, a carbonyl moiety near the terminal of C-28 side chain, such as the one in –CONH-$(CH_2)_7$NH–$COCH_3$, may be critical for preserving potent anti-entry activity. Compound 10f and 10g are more potent than the DSB or IC9564, exhibiting active in both anti-HIV-1 entry and anti-HIV-1 maturation assays.

4.2.2.4. Modification at other Position of BA

By replacing the betulin core with other triterpenes, the obtained new BA derivatives were found to have potentially lower cytotoxicity with improved pharmacological profiles, and more SAR information was obtained. Lupeol (11) has the same skeleton as BA but lacks the C-28 carboxylic acid. OA (12) and UA (13) have a six-membered E ring rather than the five-membered E ring found in BA. MA (14) and





UA differ at the double bond position. GLA (15) has a carboxylic acid at C-30 rather than at C-28 [44]. All compounds (11-15) were evaluated for their anti-HIV-1 activities and the results indicated that none of these analogs had better potency than the prototypes of RPR103611 and IC9564, except for that the toxicity of MA derivative is generally lower than that of BA derivatives. This finding implies that changing the betulin core may alter the cytotoxicity profile without impairing anti-HIV potency. So, the BA triterpenoid skeleton and the C-28 side chain moiety are the pharmacophores for antiviral potency.

4.2.3. Oligopeptides

Sequential overlapping Gag protein-derived oligopeptides having 22 to 24 amino acids long of HIV-1, were synthesized and tested *in vitro* for antiviral activity. One of the synthetic peptides PAATLEEMMTA with amino acids sequence from 339 to 349, which locats in the CA p24, was found to inhibit the virus replication in HIV-l-infected cell cultures [45]. There are three tripeptides found to be the most potent inhibitors against HIV-1 production, i.e. glycyl-prolylglycine-amide (GPG-NH2), alanyl-leucyl-glycine-amide (ALG-NH2), and arginyl-glutaminyl-glycine-amide (RQG-NH_2) from the carboxyl-terminal sequence of the HIV-1 CA p24. Substances that interfere with the proper assembly of p24 could be potential antiretroviral agents, so, peptide derived from the p24 amino acid sequence can block virus replication by interfering with CA formation and modifying HIV-1 morphogenesis [46].

Based on Gag-derived peptide fragments, 12-mer peptide (Compound (16)) was prepared and found to inhibit HIV-1 assembly *in vitro* by targeting at the HIV Gag intermediates [47], meanly at CA-C of HIV-1 CA protein, which founctioned as CA assembly inhibitor (CAI). CAI was the first peptide reported to disrupt the assembly of both immature and mature-like particles *in vitro*. CAI has been shown to form an amphipathic helix that makes important hydrophobic (H1) and N-terminal capping (H2) interactions within the binding pocket of CA-C [48]. However, CAI could not inhibit HIV-1 replication in cell culture due to its lack of cell permeability and hence is not suitable as an antiviral agent [49].

In order to stabilize the α-helical structure of CAI and convert it to a cell-penetrating peptide (CPP), a CAI modified peptide NYAD-1(17) was designed, synthesized and evaluated for it's anti-HIV-1 activity in MT-2 cell culture assay. The experimental results showed that NYAD-1 exhibited potent inhibition against HIV-1 replication with an IC_{50} value of 4.29μM. Circular dichroism (CD) spectum analysis elucidated that the hydrocarbon stapling enhanced α-helicity of NYAD-1.

NYAD-1 has a similar binding fashion to the CAI at the binding sites in the CA-C pocket. The binding site analyzed by NMR chemical shift perturbation test has been confirmed that NYAD-1 is bond at the residues 169–191 of the CA-C of HIV-1 CA protein, encompassing the hydrophobic cavity and the critical dimerization domain with an improved binding affinity over CAI. The bulky olefinic linker in the NYAD-1 molecule has been found not to perturbed the interactions at the binding site, which is on the solvent-exposed surface of the bound peptide. The tertiary structure shows that the hydrocarbon-stapled area in NYAD-1 is located in a non-interfering site distant from the hydrophobic pocket (Fig. (**4**)).

Fig. (4). Three-dimensional model of NYAD-1 bound to CA-C.

Experiment with laser scanning confocal microscopy indicated that NYAD-1 penetrated cells and colocalized with the Gag polyprotein during its trafficking to the plasma membrane where virus assembly takes place. Meanwhile, NYAD-1 was demonstrated to disrupt the assembly of both immature- and mature-like virus particles in cell-free and cell-based *in vitro* systems. More interestingly, NYAD-1 inhibited a large panel of HIV-1 isolates in cell culture at low micromolar potency, showing potential to be optimized as a new class of drugs for the treatment of AIDS and providing helpful information in designing peptidomimetics and small molecule drugs targeted at HIV-1 CA protein [50].

PERSPECTIVE

Resistance to currently approved antiretroviral drugs is increasingly common: an estimated 5–10% of infected peo-

ple are resistant to all available RT and PIs, and this number is growing rapidly. The HIV-1 CA protein is not only involved in the infectivity of the virus, but also the regulation of viral life cycle such as uncoating and subsequent reverse transcription. So, the CA protein is a different viral target and CA protein inhibitors might provide a new option in the treatment of AIDS.

ABBREVIATIONS

HIV-1	=	Human immunodeficiency virus type 1
AIDS	=	Acquired Immune Deficiency Syndrome
CA	=	Capsid
HAART	=	Highly active antiretroviral therapy
N(t)RTIs	=	Nucleos(t)ide reverse transcriptase inhibitors
NNRTIs	=	Nonnucleoside reverse transcriptase inhibitors
PIs	=	Protease inhibitors
VLP	=	Virus-like particle
MA	=	Matrix
NC	=	Nucleocapsid
PR	=	Protease
RT	=	Reverse transcriptase
IN	=	Integrase
H	=	Helices
RNP	=	Ribonucleoprotein complex
CA-N	=	N-terminal domain
CA-C	=	C-terminal domain
CypA	=	Cyclophilin A
MHR	=	Major homology region
BA	=	Betulinic acid

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