

Natural products against HIV latency

Kouharu Otsuki, Mi Zhang, Wei Li*

Abstract

Antiretroviral therapy has achieved great success in suppressing human immunodeficiency virus (HIV) replication and transforming HIV infection from a fatal disease to a manageable chronic disease. However, the latent HIV reservoir persists in the body of HIV-infected individuals and is prone to reactivation. Therefore, the development of new treatment methods aimed at a complete cure for HIV is needed. The leading strategy for HIV eradication is based on eliminating and preventing the reactivation of latent reservoirs through an approach known as “shock and kill.” This strategy involves the use of latency-reversing agents (LRAs) to activate the HIV provirus in latent viral reservoir cells. Many LRAs can be obtained from natural resources, including plants and marine organisms. In this review, we provide an overview of natural products used to eliminate HIV latency.

Keywords: Diterpenoid, Human immunodeficiency virus, Human immunodeficiency virus latency, Shock and kill, Thymelaeaceae

This review was conducted to summarize the outline of natural product-derived latency-reversing agents (LRAs) for human immunodeficiency virus (HIV), elimination. The search was conducted using SciFinder and PubMed scientific databases. The information on clinical trials and anti-HIV drugs were collected from ClinicalTrials.gov and the official search system of Food and Drug Administration (FDA) of the United States and Pharmaceuticals and Medical Devices Agency (PMDA) of Japan. Parts of the discussion were based on a manual search of articles in the reference lists.

1 Acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV)

Acquired immunodeficiency syndrome (AIDS) is a global health concern. In 2019, more than 38 million individuals, including 1.8 million children, were infected worldwide. Since the start of the epidemic 35 years ago, approximately 75 million people have been infected and more than 32 million have succumbed to AIDS-related illnesses^[1]. HIV, the causative agent of AIDS, replicates primarily within CD4⁺ T cells and leads to their depletion over time, eventually causing AIDS^[2].

HIV is an enveloped RNA virus belonging to the genus *Lentivirus* within the family *Retroviridae*. HIV consists of two copies of positive-strand RNA enclosed within the core of the viral particle and can be classified into two types: HIV-1 and HIV-2^[3]. The life cycle of HIV involves a series

of steps: binding, fusion, reverse transcription, integration, replication, translation assembly, and budding and maturation (Figure 1)^[4-5]. Several antiviral drugs targeting these key steps in the life cycle of HIV have been developed^[6].

2 Current status of antiretroviral drugs

Antiretroviral therapy (ART) is a standard therapy for HIV-1 infection tailored according to the symptoms of patients. It uses an optimal combination of multiple antiviral drugs to suppress the viral life cycle^[7]. HIV infection and AIDS, previously fatal conditions, are now manageable chronic conditions owing to the successful development of ART, which has led to effective viral suppression and reduction in the viral load to undetectable levels in patients^[8-9]. Anti-HIV drugs can be divided into the following five groups based on their mechanisms of action: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), and entry inhibitors (Figure 1)^[10]. In Japan, total of 31 anti-HIV drugs belonging to the these categories have been approved by the PMDA as of January 2021 (Table 1)^[10]. As per their effect, a drug with a stronger suppressive effect on HIV is called the “key drug”, whereas those supplementing the key drug and enhancing viral suppression are called “backbones.” In current ART regimens, it is common to use a combination of two “backbones” (NRTI) and a “key drug” (INSTI, PI, or NNRTI)^[8,11-12]. However, even lifelong ART cannot completely eradicate HIV from a patient because of persistent latent cell reservoirs^[13]. Therefore, lifelong therapy with expensive drug regimens with possible short-term or long-term toxic effects is unavoidable^[10].

3 HIV latency and plausible therapeutic strategies toward HIV cure

HIV can establish a state of latent infection in CD4⁺ T cells upon infection^[14]. CD4⁺ T cells are the major target cells for HIV and are the predominant cell type harboring latent HIV^[15]. When activated T cells are infected, the infection progresses and results in the transcription of viral mRNA, protein production, and generation of new viral

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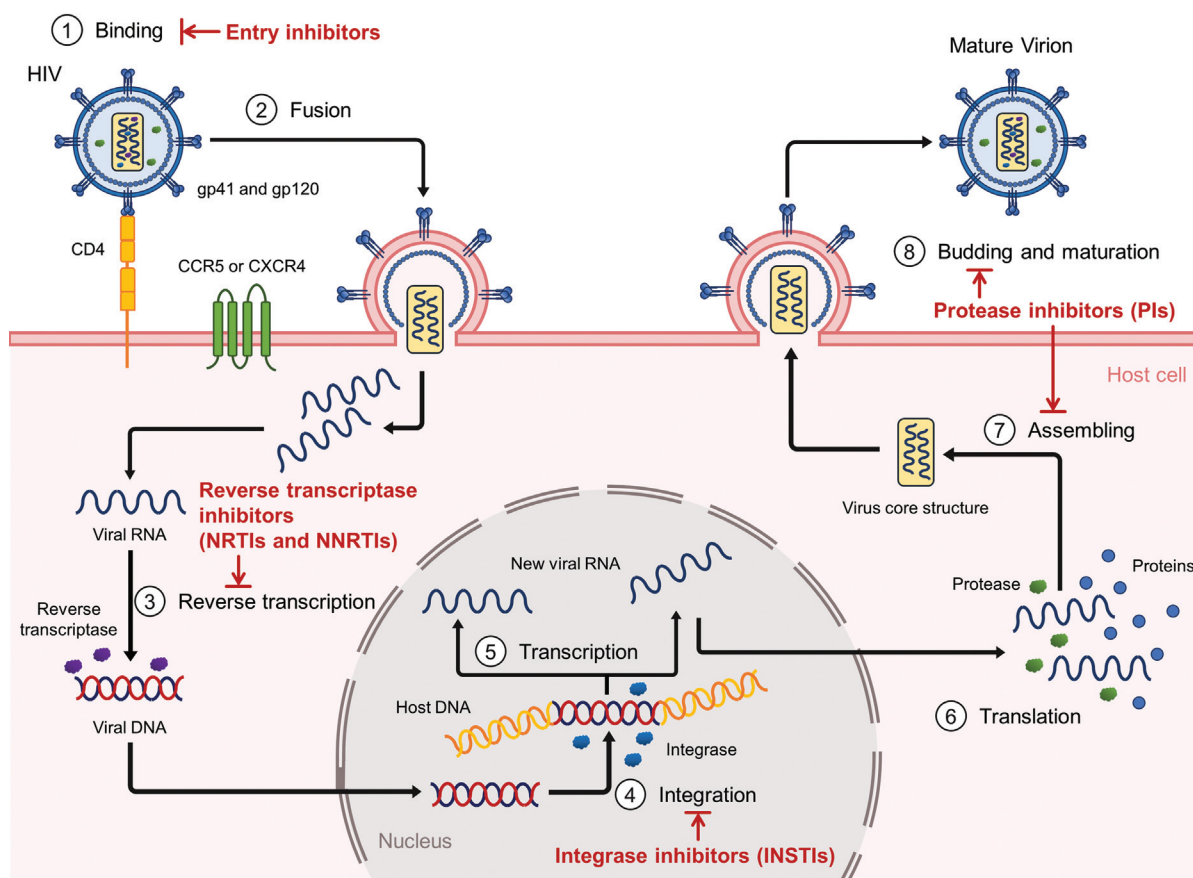


Figure 1. HIV life cycle. Some steps of HIV life cycle targeted by antiretroviral therapy: fusion and entry inhibitors block steps 1 and 2, NRTIs and NNRTIs block step 3, integrase inhibitors block step 4, and protease inhibitors block steps 7 and 8. HIV: human immunodeficiency virus; NRTIs: nucleoside/nucleotide reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors.

particles^[16]. However, when the resting T cells are infected, the provirus may enter quiescent T cells, whereby it integrates in the host genome and exists in a latent state^[17]. Therefore, HIV latency can be defined as the persistence of integrated HIV genome in host DNA, which is transcriptionally silent but replication competent^[18]. Latently infected cells are indistinguishable from normal non-infected cells and exhibit negligible to nil expression of viral proteins^[14]. As a result, latently infected cells can escape immune response and clearance, which is a major challenge in HIV eradication^[19].

The resting memory CD4⁺ T cells are one of the most characteristic latent reservoirs for HIV-1^[20]. Additionally, T cell subsets other than memory T cells, hematopoietic progenitor cells, and macrophages may be involved in the preservation of the HIV reservoir^[14]. The latent HIV reservoir is established during the early stage of HIV infection. Although ART cannot prevent the establishment of latent, persistent HIV infections, it can reduce the pool size of infected cells. Multiple mechanisms maintain HIV latency within the HIV infected cells, including the absence of key nuclear host transcription factors (for example NF- κ B) in resting CD4⁺ T cells, trans-activator of transcription (Tat) and associated host factors that promote efficient transcriptional elongation, epigenetic modifications inhibiting HIV gene expression, and transcriptional interference^[21-22]. To eliminate these latently infected cells, gene-based therapy and the use of

immunosuppressants, vaccines, and the reactivation of latent reservoirs have been proposed^[23-26]. The leading strategy for HIV eradication is based on the reactivation and elimination of latent reservoirs through a “shock and kill” approach. This strategy involves the use of LRAs to activate the HIV provirus in latent viral reservoir cells^[27]. Additionally, the “block and lock” approach has recently been introduced and is aimed at long-term HIV remission or preventing viral rebound along with a functional cure. Since this approach generally targets HIV transcription, it is likely to affect not only replication-competent but also translational-competent reservoirs^[28].

4 LRAs used in the “shock and kill” approach

Various small molecules with potential as LRAs have been identified *in vitro*. These include histone deacetylase (HDAC) inhibitors, histone methyltransferase (HMT) inhibitors, protein kinase C (PKC) activators, bromodomain (BRD) inhibitors, and toll-like receptor (TLR) agonists^[29]. Cellular pathways that enforce HIV latency are targeted by LRAs. HDAC inhibitors and HMT inhibitors inhibit epigenetic silencing of the HIV promoter, and PKC activators and TLR agonists promote the nuclear translocation of transcription factors. Additionally, BRD inhibitors reverse HIV latency by affecting the formation of transcription initiation complex (Figure 2)^[15,30-31].

Table 1**Anti-HIV drugs approved in Japan (up to January 2021)**

Generic name	Proprietary name	Abbreviation	Approved in
Nucleoside/Nucleotide reverse transcriptase inhibitors (NRTIs)			
Zidovudine	Retrovir	ZDV (or ZDV)	November 1987
Lamivudine	Epivir	3TC	February 1997
Zidovudine/Lamivudine	Combivir	AZT/3TC (or CBV)	June 1999
Abacavir	Ziagen	ABC	September 1999
Tenofovir	Viread	TDF	April 2004
Abacavir/Lamivudine	Epzicom	ABC/3TC (or EPZ)	January 2005
Emtricitabine	Emtriva	FTC	April 2005
Emtricitabine/Tenofovir	Truvada	TDF/FTC (or TVD)	April 2005
Emtricitabine/Tenofovir alafenamide	Descovy	TAF/FTC (or DVY)	December 2016
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Nevirapine	Viramune	NVP	December 1998
Efavirenz	Stocrin	EFV	September 1999
Etravirine	Intelence	ETR	January 2009
Rilpivirine	Edurant	RPV	May 2012
Rilpivirine/Emtricitabine/Tenofovir alafenamide	Odefsey	RPV/TAF/FTC (or ODF)	August 2018
Doravirine	Pifeltro	DOR	January 2020
Protease inhibitor (PI)			
Ritonavir	Norvir	Rtv	September 1999
Lopinavir/Ritonavir	Kaletra	LPV/r	December 2000
Atazanavir	Reyataz	ATV	January 2004
Fosamprenavir	Lexiva	FPV	January 2005
Darunavir	Prezista	DRV	November 2013 May 2015
Darunavir/Cobicistat	Prezcobix	DRV/c (or PCX)	November 2016
Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide	Symtuza	DRV/c/TAF/FTC (or SMT)	June 2019
Integrase inhibitors (INSTIs)			
Raltegravir	Isentress	RAL	June 2008
Elvitegravir/Emtricitabine/Tenofovir/Cobicistat	Stribild	EVG/cobi/TDF/FTC (or STB)	May 2013
Elvitegravir/Emtricitabine/Tenofovir alafenamide/Cobicistat	Genvoya	EVG/cobi/TAF/FTC (or GEN)	June 2016
Dolutegravir	Tivicay	DTG	March 2014
Dolutegravir/Abacavir/Lamivudine	Triumeq	DTG/ABC/3TC (or TRI)	March 2015
Dolutegravir/Rilpivirine	Juluca	DTG/RPV (or JLC)	November 2018
Bictegravir/Emtricitabine/Tenofovir alafenamide (or BVY)	Biktarvy	BIC/TAF/FTC	March 2019
Dolutegravir/Lamivudine	Dovato	DTG/3TC	January 2020
Entry inhibitors			
Maraviroc	Celsentri	MVC	January 2009

4.1 HDAC inhibitors (HDACis)

HDACis have been studied as antineoplastic agents owing to their widespread epigenetic activities; they are also one of the most studied LRA classes (Figure 3). These compounds inhibit HDAC recruited to the HIV long terminal repeat (LTR) promoter, induce the expression of HIV in cell reservoirs, and reactivate HIV latency^[32].

Vorinostat (suberoylanilide hydroxamic acid or SAHA) is the most studied LRA with HDAC inhibitory activity. It is a hydroxamic acid derivative and a structural analog of the antibiotic trichostatin A isolated from *Streptomyces hygroscopicus*^[33]. Vorinostat exerts potent antitumor activity with low toxicity. It is the first HDACi approved by the FDA in 2006 for the treatment of cutaneous T-cell lymphoma (CTCL)^[34-35]. Additionally, synthetic small molecules, such as valproic acid and panobinostat, and the natural product, romidepsin, have been approved by the FDA for treating malignant tumors or neuropsychiatric disorders. These compounds have undergone several clinical trials as an LRA. Identification of its therapeutic target by drug repositioning is expected^[36].

Romidepsin is a bicyclic depsipeptide produced by *Chromobacterium violaceum* No. 968 (*Chromobacterium* genus). It received regulatory approval from the FDA for the treatment of CTCL in 2009 and for the treatment of peripheral T-cell lymphoma in 2011^[37-38]. Romidepsin exerts antitumor effects and has been investigated for probable drug repositioning for HIV eradication^[39]. The HIV induction potency of romidepsin has been observed in cell lines as well as peripheral blood mononuclear cells (PBMCs) at extremely low concentrations. Moreover, this compound is more efficacious in multiple cell models compared to vorinostat^[40]. Accordingly, a series of romidepsin derivatives have been isolated and characterized, including thailandepsins, spiruchostatins, chromopeptide A, and romipeptides (Figure 4)^[41-44]. Recently, a clinical trial demonstrated that significant viral reactivation can be safely induced using romidepsin in HIV-suppressed individuals undergoing long-term ART. Six aviremic HIV-infected adults received romidepsin intravenously (5 mg/m²), once weekly for 3 weeks along with continuing ART. Romidepsin safely induced HIV

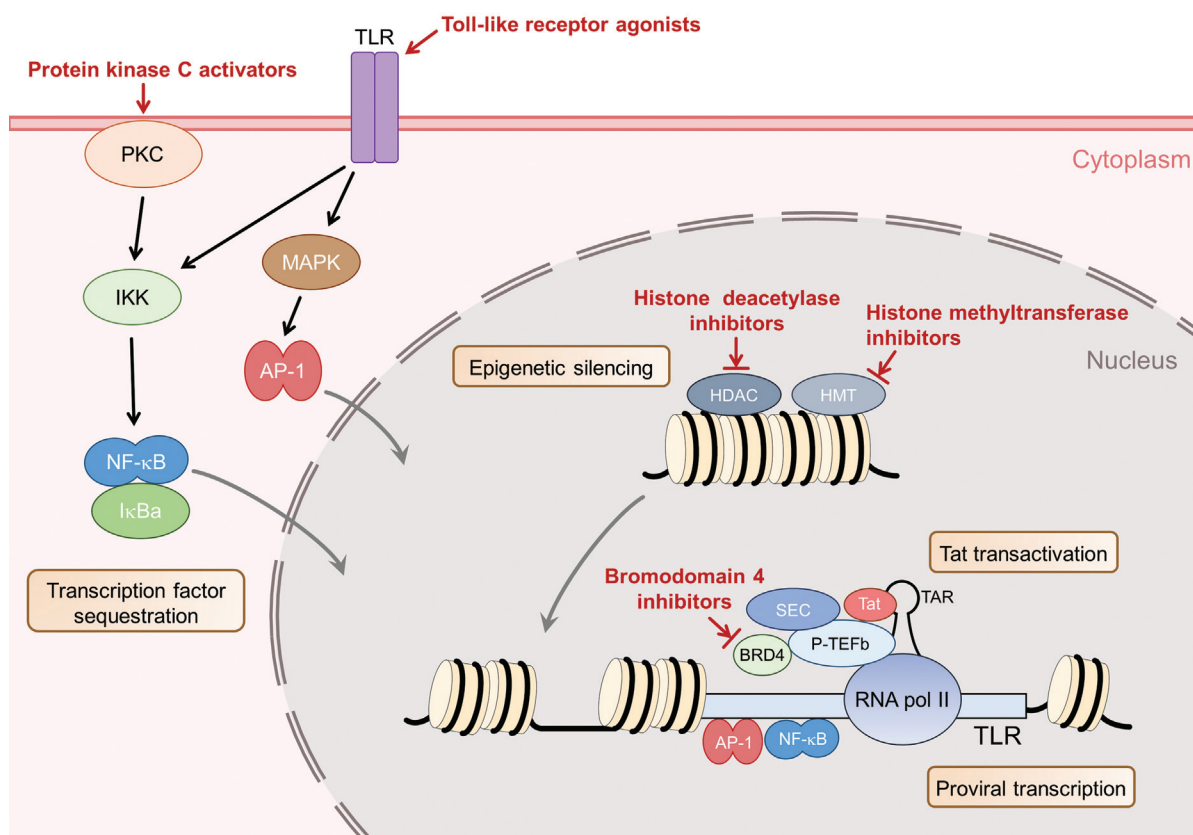


Figure 2. LRAs activate the HIV provirus in latent viral reservoir cells via diverse mechanisms. LRAs: latency-reversing agents; HIV: human immunodeficiency virus.

transcription, resulting in the appearance of HIV RNA in the plasma of five out of six patients^[45-46]. These results suggest that further optimization of this strategy is warranted for durable induction of the viral reservoir.

4.2 HMT inhibitors (HMTis)

HMTis can reverse epigenetic silencing along with HDACis. Some of the specific HMTis, including chaetocin

(a fungal mycotoxin from *Chaetomium minutum*), BIX-01294 (a diazepin-quinazolin-amine derivative), and 3-deazaneplanocin A (a cyclopentenyl analog of 3-deazaadenosine), can reverse HIV latency in cell lines as well as cells derived from patients (Figure 5)^[47]. *In vitro*, HMTis synergistically induce the expression of latent HIV in combination with HDACis^[48]; accordingly, they are being proposed as therapeutic adjuvants for the eradication of latent HIV-1 reservoirs (Table 1).

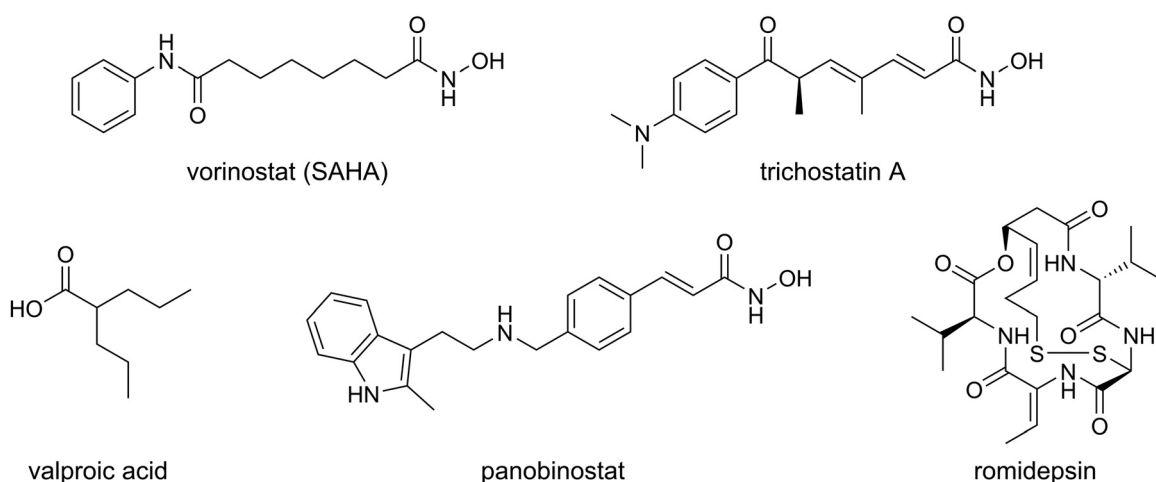


Figure 3. Structures of major histone deacetylase (HDAC) inhibitors.

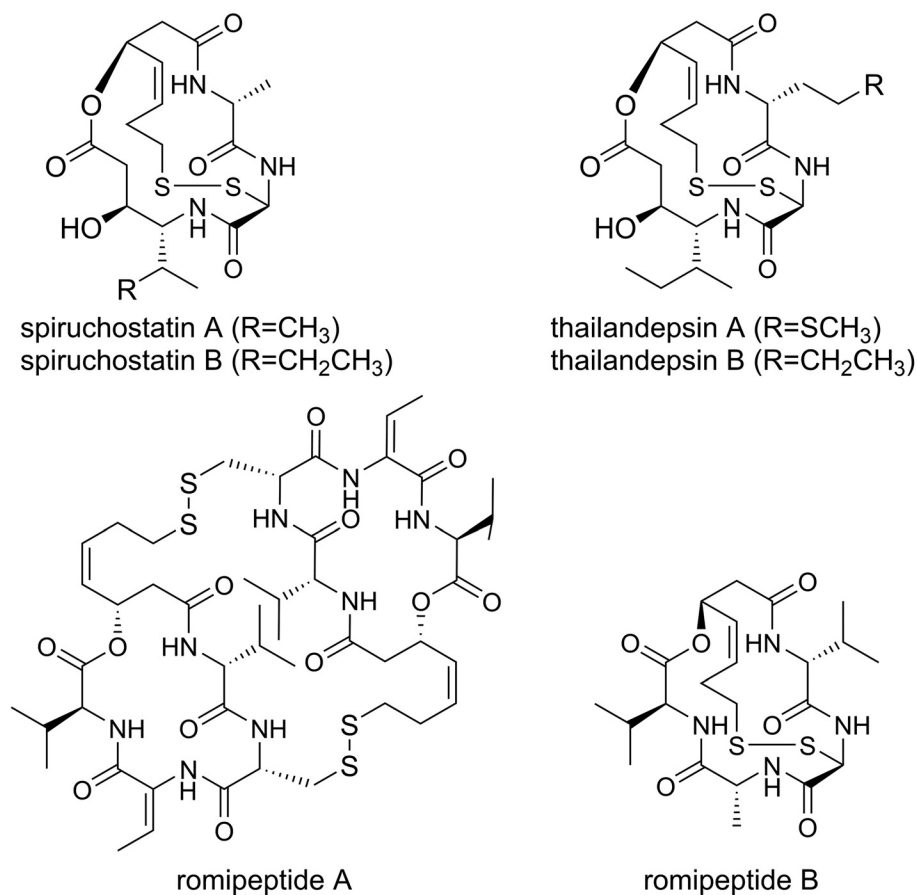


Figure 4. Structures of romidepsin derivatives.

4.3 Protein kinase C (PKC) activators

PKC activators constitute another major class of LRA and have attracted increasing attention. These compounds include diterpenoids, such as prostratin, ingenol-3-angelate (PEP005), and gnidimacrin, which are isolated from plants belonging to the family *Euphorbiaceae* and *Thymelaeaceae*; and bryostatins, which are isolated from marine organisms (Figure 6)^[49–53]. PKC is involved in the regulation of various cellular functions such as proliferation, cell death, gene transcription, and translation. PKC activators induce the activation of transcription factors such as NF-κB and Tat, which further bind to HIV LTR

and activate HIV mRNA transcription^[54–56]. Additionally, PKC activators can downregulate the expression of the cell surface receptors in PBMCs, including that of CD4, CXCR4, and CCR5^[47,57]. Therefore, PKC activators can inhibit *de novo* HIV infection and reactivate latent HIV in infected cells.

4.3.1 Bryostatin-1

Bryostatin-1 is a highly oxygenated macrolide with 11 asymmetric centers. It was initially isolated from a bacterial symbiont, *Candidatus Endobugula sertula*, of the marine bryozoan, *Bugula neritina*^[58]. The structure of

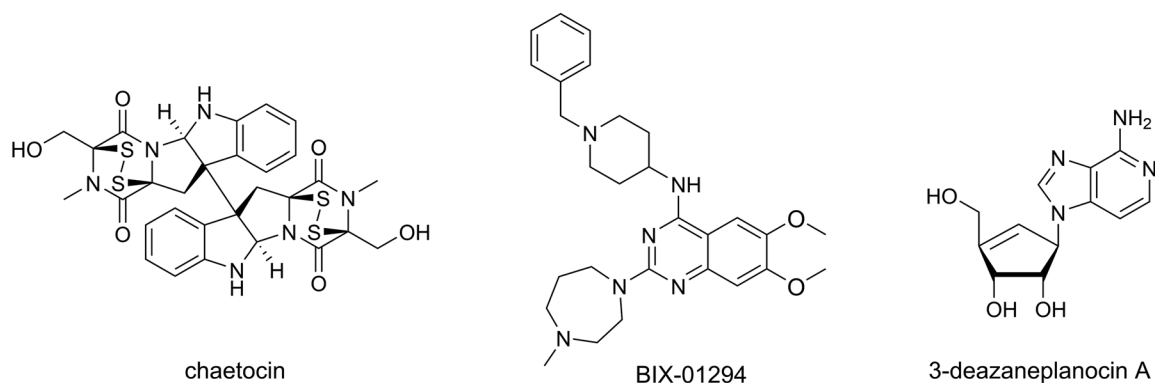


Figure 5. Structures of major histone methyltransferase (HMT) inhibitors.

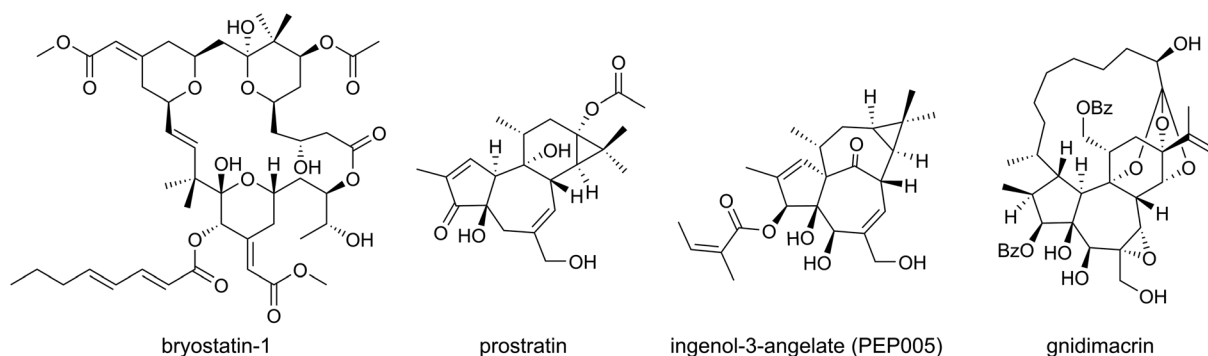


Figure 6. Structures of major protein kinase C (PKC) activators.

bryostatin-1 was determined in 1982 using X-ray crystallography. The synthesis of bryostatin-1 involves 29 steps and was achieved in 2017^[59]. To date, more than 20 structurally related bryostatins have been isolated from marine invertebrates and characterized^[60–62]. Bryostatin-1, the most thoroughly investigated analog, is the most anticipated LRA which might be approved for HIV treatment. Bryostatin-1 exhibits various biological activities, including the regulation of PKC, the key player in the pathophysiology of complex diseases such as cancer, Alzheimer's disease, and AIDS^[59]. Unlike other natural PKC activators, such as phorbol ester, 12-O-tetradecanoylphorbol 13-acetate (TPA), and ingenol ester, which exert serious proinflammatory and tumor-promoting effects, bryostatin-1 and its analogs have almost no adverse effects and thus, show promise for clinical use^[50–51].

Bryostatin-1 can activate PKCs by binding to the N-terminal C1 domains of PKCs, resulting in autophosphorylation, protein translocation, and ubiquitination of PKC^[63]. The binding between bryostatin-1 and PKC was investigated using all-atom molecular dynamic simulations of PKC-ligand-membrane complexes^[64]. The results indicated that the ester at C-1, the hydroxy at C-26, and the carbonyl of the ethyl acrylate at C-21 are the main functional groups involved in PKC binding (Figure 7). Additionally, the intramolecular hydrogen bonds between the hydroxy groups at C-3 and C-19 are important for the activity.

Bryostatin-1 has been tested in more than 30 phase I and II clinical trials for cancer and in a phase I clinical trial for HIV/AIDS eradication, albeit at a dose that proved insufficient to detect PKC activation or transcription modulating effects^[53,65]. In a double-blind phase I clinical trial, the 12 aviremic patients infected with HIV-1 and undergoing ART therapy were enrolled to compare the effect of bryostatin-1 at two different single doses of 10 mg/m² and 20 mg/m² along with a placebo. This drug was found to be safe at both doses; however, it did not show any effect on PKC activation or transcription of latent HIV owing to its low plasma concentrations^[66]. Bryostatin analogs have recently been used as preclinical candidates for HIV eradication^[67].

4.3.2 Prostratin

Although bryostatin-1 is the most studied PKC activator in clinical use, various natural products such as tigliane, ingenane, and daphnane as well as their analogs, have also been considered as LRAs as they are potent PKC activators. Prostratin, the most notable LRA and a

tigliane-type diterpenoid, was first isolated from *Pimelea prostrata* (Thymelaeaceae) and characterized in 1976^[68]. Prostratin has also been isolated from *Daphnopsis racemosa* (Thymelaeaceae), *Homalanthus nutans* (Euphorbiaceae), *Stillingia sylvatica* (Euphorbiaceae), *Euphorbia fischeriana* (Euphorbiaceae), *E. triangularis* (Euphorbiaceae), *E. cornigera* (Euphorbiaceae), and *E. grandicornis* (Euphorbiaceae)^[51,69–71]. Among these, *H. nutans*, the Samoan medicinal plant, triggered attention towards prostratin^[72]. Structurally, prostratin comprises a 5/7/6/3-tetracyclic ring system and seven contiguous stereocenters. In 2008, prostratin was chemically synthesized using a five-step semi-synthetic protocol using phorbol^[73]. Using this approach, a series of prostratin analogs with modification at C-13 were synthesized. Structure-activity relationship (SAR) studies have revealed that some analogs exhibit up to a 100-fold increase in activity compared with prostratin. Ten years later, the total synthesis of (±)-prostratin from cyclopentadiene involving 23 steps was accomplished^[74].

Prostratin can inhibit HIV infection via downregulating the expression of entry receptors (CD4, CCR5, and CXCR4) by activating the PKC pathway and can effectively reduce HIV latency^[75]. Unlike other phorbol esters, prostratin exhibits lower inflammatory activity and no tumor-promoting effect^[76]. The binding of tiglianes to PKC has rarely been reported. According to the crystal structure of PKCδC1≡ complexed with phorbol 13-acetate (PDB code: 1PTR), tigliane forms five hydrogen bonds in the activator pocket: two bonds with Gly-253, two bonds with Thr-242, and one bond with Leu-251. These findings revealed that the C-3 ketone group and the C-4 and C-20 hydroxyl groups are mainly responsible for PKCδC1≡ (Figure 8)^[77]. A related phorbol ester, 12-deoxyphorbol 13-phenylacetate (DPP), was initially isolated from *Euphorbia poissonii* in 1979 (Figure 9)^[78]. Although its activities resemble those of prostratin, DPP is 20–40-fold more potent in certain cell lines and PBMCs obtained from HIV-1 positive donors^[79–80]. Studies on the PKCδ show that unlike phorbol 13-acetate, prostratin and DPP are not selective to the C1B domain and display different binding and pharmacological features compared to phorbol esters^[73,81]. However, to date, the effects of prostratin on the latent HIV reservoir in humans remains unknown.

4.3.3 Ingenol-3-angelate

Ingenol-3-angelate (ingenol mebutate, PEP005) is an ingenane-type diterpenoid that was first isolated in

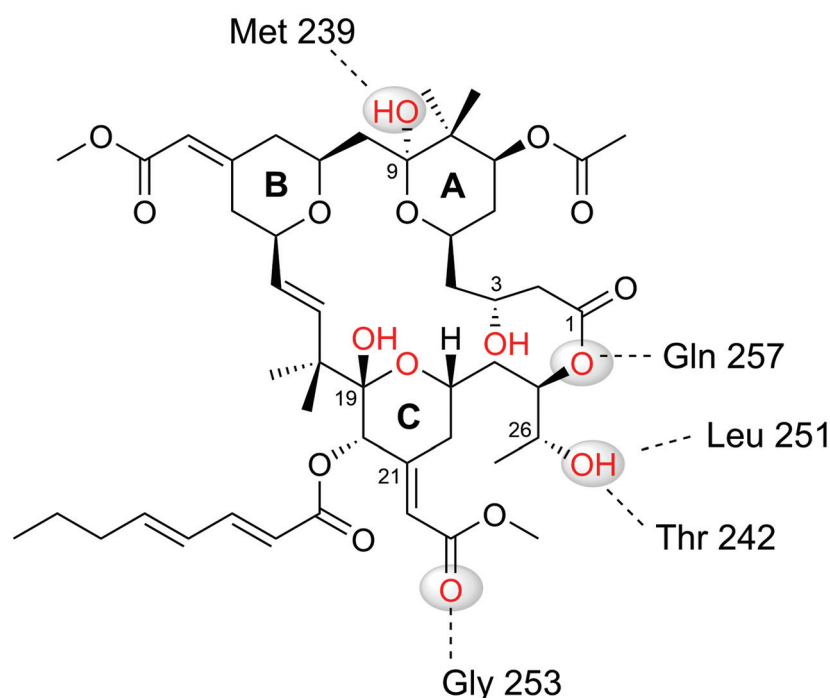


Figure 7. Hypothetical bryostatin-1 binding to PKC.

1980 from the latex of *Euphorbia paralias* (Euphorbiaceae)^[82]. It is mainly isolated from plants of the genus *Euphorbia*, such as *E. antiquorum*, *E. bermentiana*, *E. canariensis*, and *E. peplus*^[83–86]. Ingenol-3-angelate effectively reactivates latent HIV via activating the pS643/S676-PKC δ /I κ B α /NF- κ B pathway in an *in vitro* model of HIV-1 latency. However, it does not induce the expression of NF- κ B protein. Notably, the effect of ingenol-3-angelate in reactivating latent HIV expression was more potent both *in vitro* and *ex vivo*

when used in combination with JQ-1 [bromodomain-containing protein 4 (BRD4) inhibitors] than when used alone^[87].

The SAR between ingenol esters and anti-HIV activity has been analyzed using various derivatives synthesized using semi-synthetic strategies^[88]. The presence of an acyl group at C-3 or C-5 and a hydroxyl group at C-20 in ingenol is important for its anti-HIV activity. An ingenol analog with a 2-naphthyl group at C-3 [3-(2-naphthoyl) ingenol] showed 2 to 3-fold HIV-1 replication inhibitory

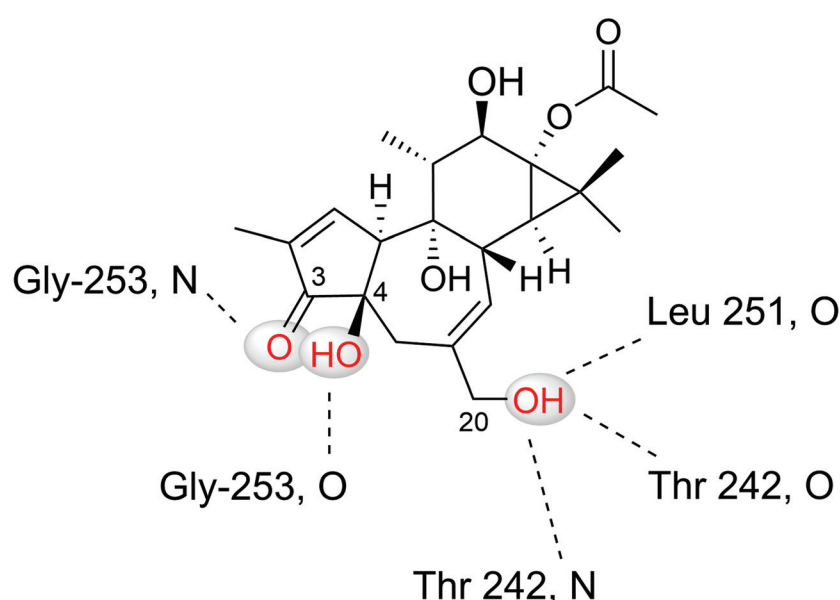


Figure 8. Hydrogen bond networks at the phorbol 13-acetate binding site according to the crystal structure of PKC δ C1B complexed with phorbol 13-acetate (PDB code: 1PTR).

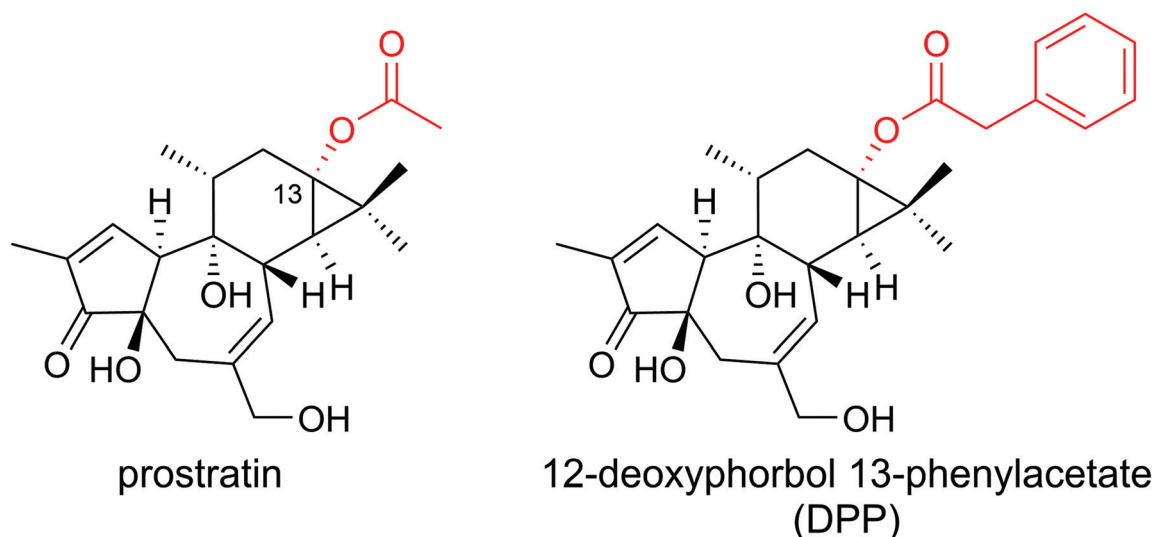


Figure 9. Structure of 12-deoxyphorbol 13-phenylacetate (DPP).

activity and latent HIV-1 reactivation activity than ingenol-3-angelate (Figure 10). The ingenol was synthesized for the first time in 2002; however, the process was complex and required more than 40 steps^[89]. In 2014, the synthetic scheme of (+)-ingenol was improved using an inexpensive material, (+)-3-carene, and comprised only 14 steps^[90]. PICATO gel, which was approved by the FDA in 2012 for the topical treatment of actinic keratosis, contains ingenol-3-angelate as an active component^[91-92]. Since ingenol-3-angelate has been used clinically, it is expected to be a potential therapeutic candidate drug for eradicating HIV infection via drug repositioning.

4.3.4 Gnidimacrin

Gnidimacrin is a daphnane-type diterpenoid. It was initially isolated from *Gnidia subcordata* (Thymelaeaceae) as a potent antitumor agent^[93]. Structurally, gnidimacrin is a 1-alkyldaphnane with a macrocyclic ring spanning the diterpenoid skeleton and is classified as a rare diterpenoid known as the macrocyclic daphnane. Gnidimacrin is

present in a limited number of species and has been isolated from *Pimelea prostrata* (Thymelaeaceae), *P. ligustrina* (Thymelaeaceae), *Stellera shamaejasme* (Thymelaeaceae), and *Daphne odora* (Thymelaeaceae)^[49,94,95]. More recently, a novel gnidimacrin derivative that is highly oxygenated on the left side of its macrocyclic ring, was isolated from *Daphne odora* (Figure 11)^[95].

The anti-HIV activity of gnidimacrin was first evaluated in 2011^[96]. This compound was found to exhibit low cytotoxicity and was extremely potent with an EC₉₀ of less than 1 nM (EC₉₀ = 0.4 nM). Further investigation revealed that gnidimacrin induced HIV-1 replication and decreased the frequency of HIV-1 latently infected cells by selectively activating protein kinase C β I and β II in an *ex vivo* model using PBMCs^[97]. Gnidimacrin exerts these effects at low picomolar concentrations; hence, it is more potent than other LRAs such as SAHA or prostratin^[97-98]. As the potency of PKC activators as LRA is strongly enhanced in combination with other LRAs, the combinations of gnidimacrin with LRAs of other major classes, such as

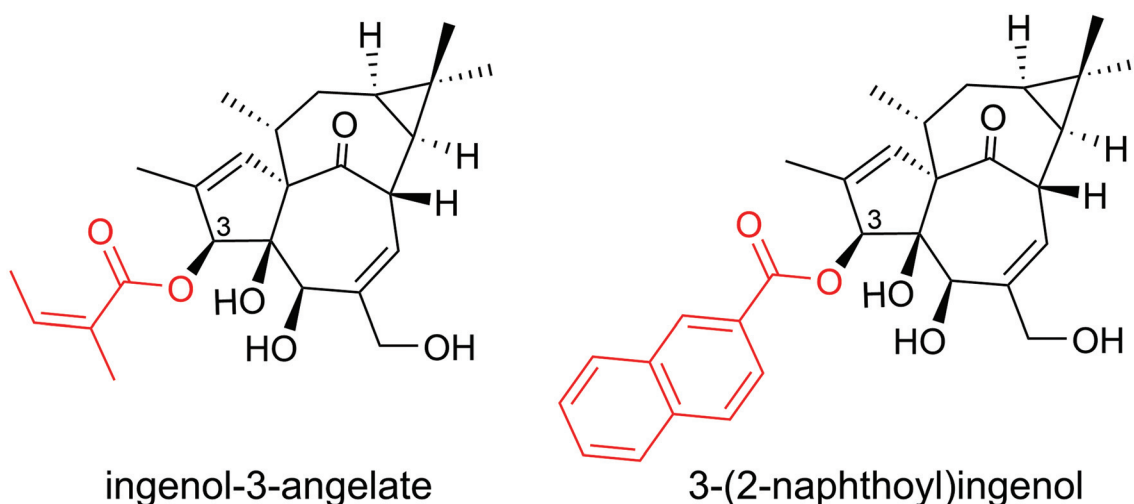


Figure 10. Structures of 3-(2-naphthoyl)ingenol.

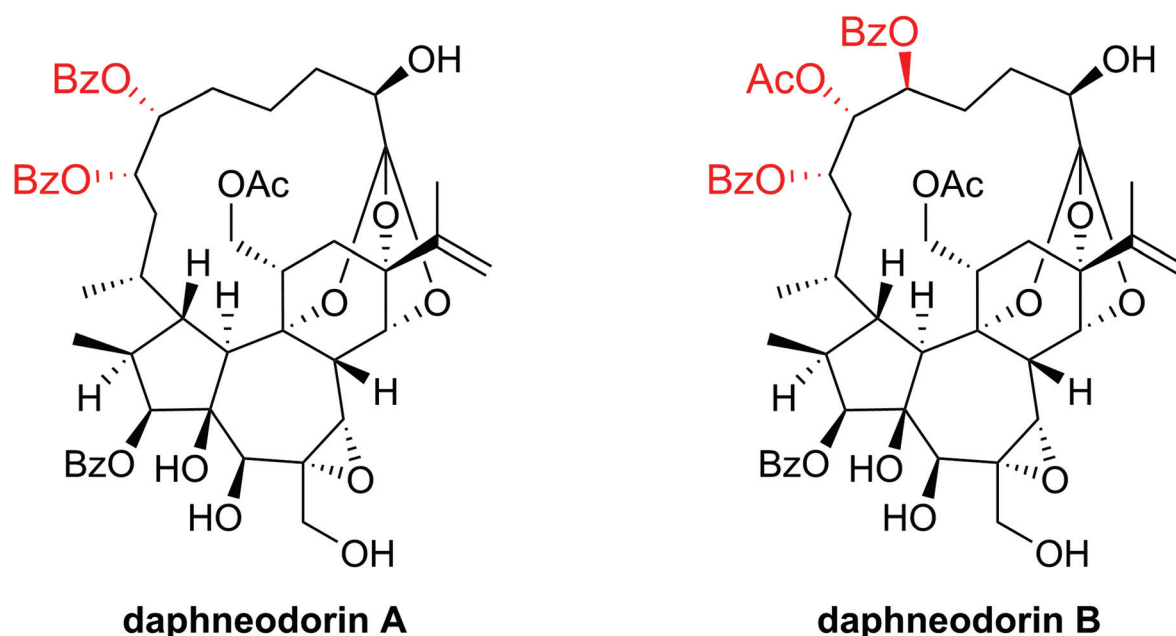


Figure 11. Structures of novel gnidimacrin derivatives isolated from *Daphne odora*.

HDACis, were evaluated. Among the seven HDACis, including vorinostat, romidepsin, chidamide, thiophenyl benzamide (TPB), pyridine-modified TPB derivative (TPyB), N-(2-Aminophenyl)-4-[1-(2-thiophen-3-ylethyl)-1H-[1,2,3]triazol-4-yl]benzamide (T247), and RGFP966, TPB with the highest selectivity index (SI) calculated from latent HIV-1 activation in U1 cells and cytotoxicity in Human Histiocytic leukemia U937 cell line (U937), was evaluated in combination with gnidimacrin. The results

revealed that the combination of TPB and gnidimacrin showed more potent HIV-1 activation with a higher SI than gnidimacrin alone. This effect was also demonstrated in *ex vivo* experiments using the PBMCs of patients with latent infections^[99].

Gnidimacrin derivatives have been semi-synthesized for SAR studies. Findings have revealed that the C-5 and C-20 hydroxyl groups of gnidimacrin are important moieties for the anti-HIV activity of the derivatives. Some

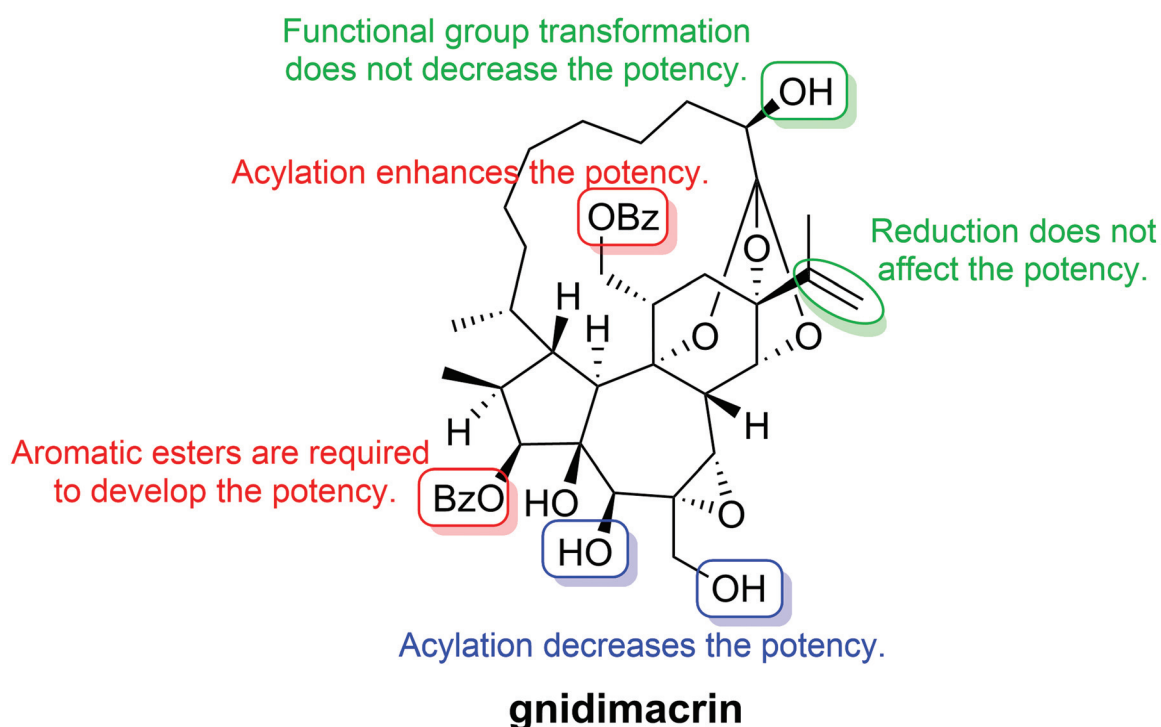
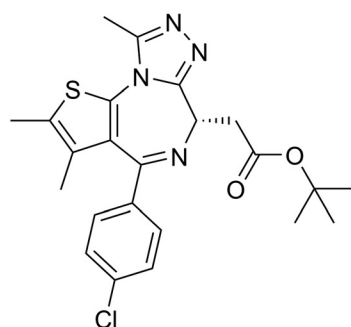


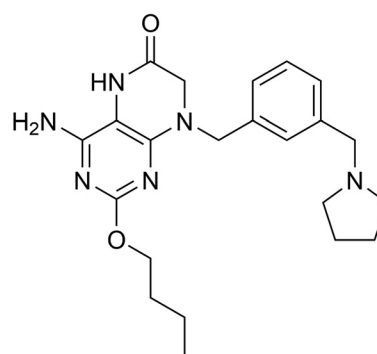
Figure 12. Structure-activity relationship correlation of gnidimacrin derivatives.

Bromodomain (BRD) inhibitors



JQ-1

Toll-like receptor (TLR) agonists



vesatolimod (GS-9620)

Figure 13. Structures of other classes of LRAs.

modifications at C-2', C-18, and $\Delta 15,16$ were found to be acceptable, including that replacing the C-3 benzoic acid ester with other aromatic acyl groups (Figure 12)^[100]. Further elucidation of SAR should be useful for developing gnidimacrin or structurally related compounds as candidate drugs for clinical trials.

4.4 Other classes of LRAs

Other classes of LRAs, including BRD inhibitors (for example, JQ-1) and TLR agonists (for example, vesatolimod/GS-9620) have also been reported (Figure 13). JQ-1 is a thienotriazolodiazepine and a selective inhibitor of BRD4. JQ-1 can induce the expression of latent HIV through a mechanism different from the T cell activation pathway^[101]. Vesatolimod (GS-9620) acts as a potent and selective agonist of toll-like receptor 7 (TLR7) and mediates both HIV and immune cell activation *in vitro* and HIV activation in PBMCs isolated from HIV-infected individuals with suppressed infection^[102]. More recently, a study based on simian-human immunodeficiency virus (SHIV)-infected rhesus monkeys reported that the combined use of neutralizing antibody (PGT121) and vesatolimod/GS-9620 delayed viral rebound following the discontinuation of ART in acutely infected animals^[103]. Furthermore, in a phase Ib study, vesatolimod showed high safety and tolerability in adults infected with HIV, suggesting its potential for treating HIV infection in combination with other agents^[104].

5 Conclusions and perspectives

HIV infection is now considered a chronic disease owing to the development of ART. However, it is not completely curable even after 30 years since its discovery^[105]. Current ART regimen effectively suppresses HIV-1 replication and proliferative viral infection but does not affect latently infected cells bearing transcriptionally-silenced provirus. The development of a therapeutic modalities to eliminate or contain these latent reservoirs is necessary. If the latent HIV reservoir can be eliminated from the body of infected individuals by treatment with novel LRAs in addition to ART, it may be possible to eradicate HIV infection. Apart from HIV eradications,

the effects of LRA in other aspects have not yet been elucidated. Therefore, more detailed studies evaluating their safety and efficacy in animal models and humans are indispensable. The discovery of novel natural products and their derivatives will continue to play an important role in driving these studies.

Conflict of interest statement

Wei Li is the editorial board member of this journal and other authors declare no conflicts of interest.

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Author contributions

All authors participated in the study design, conducting the research, and writing of the manuscript. All authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

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