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Recent advances in natural anti-HIV triterpenoids and analogues

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Abstract

The HIV/AIDS epidemic is one of the world's most serious health challenges. Although combination antiretroviral therapy provides effective viral suppression, current medicines used against HIV cannot completely eradicate the infectious disease and often have associated toxicities and severe side effects in addition to causing drug resistance. Therefore, the continued development of new antiviral agents with diverse structures and novel mechanisms of action remains a vital need for the management of HIV/AIDS. Natural products are an important source of drug discovery, and certain triterpenes and their analogues have demonstrated potential as pharmaceutical precursors for the treatment of HIV. Over the past decade, natural triterpenoids and analogues have been extensively studied to find new anti-HIV drugs. This review discusses the anti-HIV triterpenoids and analogues reported during the period of 2009 to 2019. The article includes not only a comprehensive review of the recent anti-HIV agent development from the perspective of medicinal chemistry, but also discusses structure–activity relationship analyses of the described triterpenoids.

Keywords

anti-HIV activity; triterpenes; natural products; medicinal plants; structural modification

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

1 | INTRODUCTION

As of 2017, about 36.9 million people worldwide were estimated to be living with HIV-1 infection.[1,2] Although combination antiretroviral therapy (cART) provides effective viral suppression, current medicines cannot cure HIV-1 infection and often have associated toxicities and severe side effects in addition to causing drug resistance. For example, although access to highly active antiretroviral therapy (HAART) has increased in recent years, rising to nearly 22 million people (59% of people living with HIV) in 2017, this therapy cannot achieve the ultimate goal of complete eradication of HIV and patients have to undergo long-term treatment, which can result in permanent damage to tissues or organs. Besides, the virus rapidly develops resistance to the drugs. Both problems underline the need to develop new therapeutic strategies against HIV/AIDS to complement the existing ones.[3,4] During the last decade, much effort has been made to find effective anti-HIV agents from natural products.[5,6] Many classes of natural product derivatives have been evaluated with varying success.[7,8] For example, triterpenoids and their analogues have been extensively studied for their diverse structures and anti-HIV activities.[9] Most recently, triterpenoids have been found to influence a broad range of virus-host fusion by wrapping the HR2 domain widespread in viral envelopes.[10] As early as 1994, betulinic acid (**1**) (Figure 1) was shown to inhibit the infectivity of HIV-1 *in vitro*.[11] Subsequently, numerous betulinic acid derivatives were synthesized with the goal to develop anti-HIV drugs.[12,13] Systematic structural modifications ultimately resulted in the identification of 3-*O*-(3′,3′-dimethylsuccinyl) betulinic acid (DSB), known as bevirimat (BVM, **2**) (Figure 1). BVM plays significant anti-HIV activity in H9 lymphocytic cell lines with an EC_{50} value of less than 0.35 nM and a selectivity index of 20,000.[14] BVM is defined as a novel strategy against HIV and termed a maturation inhibitor. BVM inhibits HIV-1 protease, which causes the last cleavage of the Gag polyprotein, leading to the accumulation of the p25 capsid-small peptide 1 (SP1) intermediate and thus resulting in noninfectious HIV-1 virions. BVM dimeglumine (MPC-4326, formerly PA-457), a potent HIV-1 maturation inhibitor, reached the most advanced stage of drug development.[15] Although BVM exhibited promising pharmacokinetic (PK) profiles in clinical trials and was shown to be safe and effective in reducing viral loads in HIV-1-infected patients, its effectiveness was compromised by the high baseline drug resistance of HIV-1 variants with polymorphism in the putative drug binding site.[16] Naturally occurring polymorphisms in the SP1 region of Gag (e.g., SP1-V7A) (Figure 2) led to a variable response in some BVM-treated patients.[17–19] The reduced susceptibility of SP1-polymorphic HIV-1 to BVM led to the discontinuation of its clinical development.[20,21] In addition, disadvantages of BVM include its poor solubility in aqueous and biologically pertinent organic media as well as high plasma protein binding. Eventually, the development of BVM was halted in 2010 after reaching Phase IIb clinical trials. Thereafter further investigations of BVM derivatives are being carried out to improve polymorphic virus coverage, reduce protein binding and obtain better pharmaceutical properties.

Two important reviews by Kuo *et al.*[22] and Singh and Bodiwala[23] were published just before the period covered in this article, the former more specifically concentrating on anti-HIV triterpenoids and analogues. Two additional extensive reviews of the literatures reported on

anti-HIV triterpenoids and derivatives were also published.[24,25] Acyl derivatives of triterpenic oximes exhibit important pharmacological, including anti-HIV, activity.[26] Related chemistry and pharmacology of synthetic triterpenoid dimers obtained from natural compounds were reviewed recently.[27] The structures and anti-HIV activities of protostane and fusidane triterpenoids covering the literature until 2013 were briefly reviewed (together with several other activities).[28] Verma discussed a raft-targeting method for prevention and therapy of AIDS using natural products, especially euphane-type triterpenes.[29] In another review, natural products including lignans, triterpenes, chlorogenic acid derivatives and farnesyl hydroquinones, *in vivo* metabolites and synthesized derivatives as potential anti-viral agents were described.[30] A review covering the literature from 1991 to 2012 presented microbial transformation of diterpenoids and some triterpenoids with anti-HIV activities.[31] In 2014, the antitumor and antiviral activities of pentacyclic triterpenes were discussed.[32] Herein, this review describes the recent advances on anti-HIV triterpenoids and synthetic analogues covering the period from 2009 till 2019, with more than 300 anti-HIV triterpenes discussed. The article includes not only a comprehensive review of the recent anti-HIV drug development from the perspective of medicinal chemistry but also discusses structure–activity relationship analyses of the described triterpenoids.

2 | PENTACYCLIC TRITERPENOID

2.1 | The lupane group

Plant-derived pentacyclic triterpenoids of lupane families provide a versatile structural platform for the discovery of new biologically active compounds. Even small structural alterations in these triterpenoid derivatives can cause remarkable differences in their activity, making a convincing case for a systematic study of structure–activity relationships in this compound class. The multi-activity profile of lupane-type terpenoids can be a benefit for overcoming HIV-1 resistance by simultaneously affecting multiple targets. Both betulinic acid (**1**) and betulin (**3**) (Figure 1) are important lupane triterpenoids that exhibit many favorable biological effects, including anti-HIV, anti-cancer, anti-malarial and anti-inflammatory properties, but cause minimal toxicity to unaffected cells.[33] Betulinic acid is commonly found in some species of the family Betulaceae, while **3** is a major constituent in the bark of white-barked birch trees with isolated yields up to 22% (dry weight) and can be easily converted synthetically to **1** in high yields.[34] Many studies have been devoted to the investigation of betulinic acid, betulin and their derived compounds. The last related review was published in 2014.[35] It has been pointed out that structural changes at different positions of betulinic acid/betulin can result in significant differences in the anti-HIV mechanism of action. For example, betulinic acid derivatives altered at the C-28 position are HIV-1 entry inhibitors such as compounds RPR103611 (**4**), IC9564 (**5**) and A43D (**6**) (Figure 1), among which A43D was effective against multiple HIV subtypes and displayed the strongest inhibition toward the clade C HIV-1 strains.[36] On the other hand, betulinic acid analogues modified at the C-3 rather than C-28 position, like BVM, are HIV-1 maturation inhibitors. Furthermore, simultaneous modifications at C-3 and C-28 led to the identification of A12–2 (**7**) (Figure 1), a bifunctional HIV inhibitor with an EC_{50} value of 0.0026 μM at least 20 times more potent than either **2** or **5**.[37] Over the past ten years, extensive work has been directed towards the optimization of the C-3 and C-28 side chains of betulinic acid and

betulin derivatives and analogues (Table 1). C-3 modifications comprise oxidation, acylation, conjugation and heterocycle substitution, while C-28 alterations include amination, esterification and conjugations. In addition, chemical modifications at other positions like C-30 were also reported. Sousa *et al.* provided insight into the functionalization of betulinic acid and its analogues in the latest review.[38]

Three betulin analogues (**8**~**10**) (Table 1) were found to inhibit HIV-1 infection by acting on multiple steps in the HIV-1 replication cycle in both MT-2 cells and primary human T cells. Betulone (**8**) targets reverse transcription, integration, viral transcription, Gag production and maturation. 3-Oxo-lup-20(29)-en-28-al (**9**) inhibits HIV-1 infection by targeting integration, viral transcription and Gag production. 28-Acetoxy-3β-hydroxy-lup-20(29)-en-30-al (**10**) targets reverse transcription, viral transcription and Gag production. Compounds **8**–**10** inhibited HIV-1 infection of human primary lymphocytes and infections with protease inhibitor- and BVM-resistant HIV-1 variants with similar IC_{50} values.[39] Betulinic aldehyde and nitrile derivatives were identified to show anti-HIV-1 activity using a single-cycle replication assay, which can differentiate whether a derivative targets the late or early steps in the viral life cycle. The betulinic nitrile derivative (**11**) and aldehyde derivatives (**12**–**15**) (Tables 1 and 2 and Figure 3) inhibit a late step in virus replication in HEK 293T cells.[40]

Different C-3 conformationally restricted 3-*O*-acyl derivatives were synthesized to explore the conformational space of the C-3 pharmacophore of betulinic acid. The 3'*S* isomer of compound **16** (Table 1) displayed slightly better activity than **2** in acutely infected MT-2 cell lines.[41] Click chemistry was used to synthesize hybrid molecules of triterpene sapogenins and HBD (helix zone-binding domain)-containing peptides. P26–BApc (**17**) (Table 1) exhibited anti-HIV-1 activity against both T20-sensitive and -resistant HIV-1 strains and improved pharmacokinetic properties.[42] The sugars attached to pharmaceutically important natural products could lead to improved key pharmacological properties and/or molecular mechanisms of action. A 37-member library of betulinic acid C3-neoglycosides was synthesized and each glycosylated derivative was tested for anti-HIV activity in CEM-SS cells infected with $HIV\text{-}1_{IIIB}$. Nineteen of 32 ester-linked compounds displayed at least a twofold improvement over betulinic acid. Among these compounds, L-Fuc derivative (α:β/1:2) **18** (Table 1) was the most active.[43] In 2016, Liu *et al.*[44] synthesized a series of C-3 phenyl- and heterocycle-substituted derivatives of C-3 deoxybetulinic acid and deoxybetulin. When compared with BVM, betulinic acid-derived analogue **19** containing a 4-subsituted benzoic acid moiety exhibited comparable anti-HIV activity against wild-type virus in MT-2 cells using variants of the NLRepRlucP373S virus in a multiple cycle assay. Furthermore, compared with **2**, the potency of **19** was less affected by the presence of human serum displaying a similar pharmacokinetic profile in rats. In addition, 4-benzoic acid deoxybetulin analogue **20** exhibited comparable antiviral potency toward wild-type and V370A viruses compared with **19**, while in the presence of human serum albumin (HAS), **20** was threefold more potent than **19** (Figure 4). Compounds **19** and **20** demonstrated potency towards the polymorphic V370A with EC_{50} values of 0.23 and 0.21 μM, respectively. [44]

Three C-28 glutamine ester derivatives of betulinic acid (**21**–**23**) (Tables 1 and 2) were more potent against BVM-resistant viruses in an HIV-1 multi-cycle replication assay (Table 3). In

addition, compounds **21**–**23** showed markedly improved microsomal stability compared with **6**.[45] Betulinic acid C-28 derivatives (**24**–**26**) (Table 1) displayed selective anti-HIV-2 activity at nanomolar concentrations. A shorter C-28 side chain was required for optimal anti-HIV-2 activity.[46] Different ionic derivatives of betulinic acid were prepared by straightforward coupling chemistry; they displayed significantly improved water solubility without disrupting the structurally related bioactivity. These compounds had lower IC_{50} values towards HIV-1 protease than **1**; particularly, **27** and **28** (Figure 5) showed IC_{50} values roughly two and three times lower, respectively, than that of **1**.[47]

Various 28,30-disubstituted and 3,28-disubstituted betulinic acid derivatives were also synthesized. Compound **29** (Table 1) showed improved solubility and anti-HIV potency. Using a cyclic secondary amine to form the C-28 amide bond significantly increased the metabolic stability of the derivatives in pooled human liver microsomes. Compounds **30** and **31** (Table 1) displayed potent anti-HIV activity.[48] A collection of C-28 alkyl amine derivatives of BVM was synthesized and tested for their ability to block CA-SP1 processing and virus replication by using wild-type and a V7A variant of NL4–3. Some derivatives (**32**–**39**) (Tables 1 and 4) showed markedly greater potency than BVM against an HIV-1 clade B clone (NL4–3) and robust antiviral activity against a variant of NL4–3 containing the V7A polymorphism in SP1. One of the most potent compounds (**37**) also strongly inhibited a multi-clade panel of primary HIV-1 isolates.[49] Among a series of synthetic betulinic acid derivatives with C-28 substitution, all active compounds showed only anti-maturation effects, as confirmed by TZM-bl assay, in blocking the HIV replication. Compound **40** (Table 1) exhibited the best anti-HIV activity and good in *vitro* metabolic stability in pooled human liver microsomes.[50]

The integration of privileged motifs into promising natural product skeletons is an effective strategy for discovering potent derivatives. Two “privileged fragments”, caffeic acid and piperazine were integrated into BVM. Compound **41** (Table 1) is a maturation inhibitor with improved metabolic stability and its activity was increased by threefold against NL4–3 and 51-fold against NL4–3/V370A (EC_{50}: 0.15 μM).[51] Compound **42** (Tables 1 and 5) exhibited much improved activity against several HIV-1 strains carrying BVM-R polymorphisms and was at least 20-fold more potent than BVM against the replication of NL4–3/V370A.[52] To improve the water solubility of BVM, different hydrophilic substituents were added at the C-28 position. Compound **43** (Table 1) showed higher hydrophilicity associated with a 2.5-fold increase in activity, a higher selectivity index and a better antiviral profile. Also, NMR indicated a direct interaction between **43** and the domain CA-SP1eNC.[53] In 2017, a series of betulin-derived *a*-keto amides was identified as inhibiting HIV-1 maturation. When tested in a panel of 62 HIV-1 isolates covering a diversity of CA-SP1 genotypes including A, AE, B, C, and G using a PBMC based assay, GSK8999 (**44**) (Figure 6) was potent against 57 of 62 isolates. Particularly, compound **44** showed potency towards the polymorphic V370A and T371A with IC_{50} values of 0.025 and 0.008 μM, respectively.[54] Furthermore, GSK2838232 (**45**), the only α-keto amide betulin derivative investigated in a Phase I clinical study, had low to moderate relative bioavailability (6%–40%) and was metabolized through hepatic Phase I oxidation, Phase II glucuronidation and biliary excretion, according to these preclinical studies. In clinical studies, GSK2838232 (100 and 200 mg) with 100 mg ritonavir

for 11 days exhibited good safety but was significantly influenced by CYP3A4 and P-gp inhibitors.[55]

Recently, conjugations between betulinic acid/betulin and AZT have been reported. A one-pot synthesis of ester-linked conjugates of betulinic acid with AZT and its derivatives or with 3TC was accomplished. This direct synthesis provided a scalable procedure for preparing anti-HIV hybrid conjugates. Compounds **46**–**48** (Table 1) exhibited very good anti-HIV activity against HIV-1_{IIIB} infected MT-4 cells.[56] Alternatively, betulin/betulinic acid conjugation with AZT was achieved via a triazole linkage by click chemistry. Compounds **49** and **50** (Table 1) showed potent anti-HIV activity.[57] Various trisubstituted betulinic acid derivatives were prepared containing 3-*O*-acyl and 28-amide side chains and a propynyl group at the C-2 position of ring A of the lupane core. Then, a series of C-2 triazole-linked bioconjugates of lupane triterpenoids with AZT were synthesized based on a CuI-catalyzed 1,3-cycloaddition between alkynes and azides (Figure 7). The proposed strategy concerning AZT–betulinic acid hybrid molecules as potential anti-HIV agents makes it possible to vary the C-3 and C-28 pharmacophores in the triterpene moieties.[58] Fourteen conjugates of 3,28-di-O-acylbetulins with AZT were prepared and nine conjugates (**51**–**59**) (Tables 1 and 2) exhibited potent anti-HIV activity with EC_{50} values ranging from 0.040 to 0.098 μM in HIV-$1_{NL4–3}$ infected MT-4 cells.[59]

Several fluorinated derivatives of BVM were synthesized. Compound **60** (Table 1), which has a trifluoromethyl group added to C-30 of its isopropenyl group, exhibited similar potency as BVM against HIV-$1_{NL4–3}$.[60]

At the C-3 position, benzoic acid can be a suitable replacement for the dimethyl succinate side chain of BVM. SAR studies showed that the benzoic acid unit conferred topographical constraint on the pharmacophore and was associated with a lower shift in potency in the presence of human serum albumin. To possibly improve the polymorphic coverage of betulinic acid derivatives, a series of C-3 benzoic acid-substituted betulinic acid derivatives was synthesized through modifications at the C-28 position. The dimethylaminoethyl amides **61** and **62** (Figure 8) exhibited improved potency toward BVM-resistant viruses and increased C_{24} values in rat oral PK studies (Table 6).[61] In the continued efforts, C28 amine derivatives were designed and synthesized. Compared with the C-28 amide series, the C-28 amine derivatives exhibited further improvements in HIV-1 inhibitory activity toward polymorphisms in the Gag polyprotein as well as improved activity in the presence of human serum. Compared to the C-28 amide **61**, the C-28 amine compound **63** (Figure 8) containing a thiomorpholine dioxide showed two- to four-fold improved potency towards the screened viruses, such as wild type, V370A and ΔV370, exhibited low shifts in the EC_{50} values toward V370A and ΔV370 viruses in the presence of human serum or human serum albumin, and demonstrated improved potency towards the polymorphic T371A and V362I virus variants as well as low plasma exposure following oral administration to rats (Table 7).[62]

Structure–activity relationships (SARs) led to the design of specific C-17 amine moieties and ultimately enabled the discovery of BMS-955176, also known as GSK3532795 (**64**) (Figure 8), as a second-generation maturation inhibitor that combines broad coverage of

polymorphic viruses (EC_{50} <15 nM toward a panel of common polymorphisms representative of 96.5% HIV-1 subtype B virus) with a favorable pharmacokinetic profile in preclinical species.[63] Compound **64** exhibited potent activity (EC_{50}: 3.9 nM) toward a library (n = 87) of gag/pr recombinant viruses representing 96.5% of subtype B polymorphic Gag diversity near the CA/SP1 cleavage site and a median EC_{50} of 21 nM toward a library of subtype B clinical isolates assayed in peripheral blood mononuclear cells (PBMCs) (Table 7). Potent activity was maintained against a panel of reverse transcriptase, protease, and integrase inhibitor-resistant viruses, with EC_{50} values like those for the wild-type virus. A 5.4-fold reduction in EC_{50} occurred in the presence of 40% human serum plus 27 mg/mL of human serum albumin, which corresponded well to an *in vitro* measurement of 86% human serum binding. Time-of-addition and pseudotype reporter virus studies confirmed that the compound acts late in the virus replication cycle. Compound **64** inhibits HIV-1 protease cleavage at the CA/SP1 junction within Gag in virus-like particles (VLPs) and HIV-1-infected cells, and it binds reversibly and with high affinity to assembled Gag in purified HIV-1 VLPs. Finally, in *in vitro* combination studies, the compound showed no antagonistic interactions with representative antiretrovirals of other mechanistic classes.[64] A concise and scalable synthesis of **64** starting from betulin in seven steps and 47% overall yield has been described. The synthesis is framed by an oxidation strategy highlighted by a CuI mediated aerobic oxidation of betulin, a highly selective PIF mediated dehydrogenation of an oxime, and a subsequent Lossen rearrangement, which occurs through a unique reaction mechanism for the installation of the C17 amino functionality.[65] Compound **64** demonstrated better anti-HIV potency than BVM with no significant safety issues in its Phase IIa studies. However, Phase IIb studies with **64** were terminated due to gastrointestinal intolerance.[66]

In addition, 3D-QSAR and molecular docking studies were also applied to help define the structural requirements responsible for the anti-HIV activity of betulinic acid derivatives. In 3D-QSAR studies, both the CoMFA and CoMSIA methods were satisfactory based on the statistical validation results as well as the contour map analysis. Molecular docking was used to explore the binding mode between these derivatives and HIV gp120. The correlation of the results obtained from 3D-QSAR and docking studies can serve as useful guidelines for the further modification of betulinic acid to produce useful anti-HIV agents.[67]

Two A-seco lupane derivatives (**65** and **66**) (Figure 9) showed weak inhibitory activity against HIV-1 protease (IC_{50} 15.7 and 25.4 μM, respectively).[68] In another report, the synthesis and evaluation of anti-HIV activity of mono- and diamides of 2,3-secolupane acids were reported, and compound **67** (Figure 10) showed anti-HIV activity.[69] Lupane triterpene oximes (**68** and **69**) (Figure 11) were synthesized using oxonitrile recyclization and the ThorpeeZiegler cyclization. Both **68** and **69** effectively suppressed the reproduction of HIV-1 *in vitro* (EC_{50} 0.06 μM).[70] In a concurrent study, lupeol and betulin derivatives were prepared and evaluated for their ability to perturb X4- and R5-tropic HIV-1-envelope (Env)-mediated fusion membrane in a cell-to-cell fusion model. Compounds **70**–**75** (Table 1 and Figure 12) showed a wide arrange of inhibitory activity.[71] Recently, six novel lupane-type C-3 triterpenones with C-28 heterocyclic moieties were synthesized. Compound **76** (Figure 13) (EC_{50} < 10 nM) showed significant anti-HIV potency in MT2 cells infected with 92HT599 in a 40% serum binding assay.[72]

30-Oxo-calenduladiol (**77**) (Figure 14) is a specific CCR5 antagonist that inhibits CCR5-mediated HIV-1 infection. It binds to the CCR5 receptor without triggering cell signaling or receptor internalization, and inhibits RANTES (regulated on activation normal T cell expressed and secreted)-mediated CCR5 internalization, intracellular calcium mobilization, and cell chemotaxis.[73] Six new and 20 known lupane triterpenoids were isolated from the stem of *Cassine xylocarpa* and root bark of *Maytenus cuzcoina*. In addition, some derivatives were prepared by chemical modification of the isolates. Sixteen compounds, including **78**, from this series displayed inhibitory effects on HIV-1 replication with IC_{50} values in the micromolar range (Table 1).[74] 2-Acetoxyalphitolic acid (**79**) and 3-acetoxyalphitolic acid (**80**) (Figure 15) were isolated from the leaves and twigs of *Garcinia hanburyi*. They displayed anti-HIV-1 activities in anti-HIV-1 reverse transcriptase (IC_{50} values 116.9 and 16.3 μg/mL, respectively) and syncytium assays (EC_{50} 5.6 and 6.0 μg/mL, SI 2.8 and 3.3).[75]

2.2 | The oleanane and ursane groups

Acylated oleanolic (**81**) and maslinic (**86**) acid derivatives were synthesized through solution and solid-phase procedures. Some acylated derivatives (**82**–**85** and **87**) (Figure 16) proved to be potent inhibitors of the HIV-1-protease with IC_{50} values between 0.31 and 0.8 μM.[76] Oleanene derivatives **89** and **90** were prepared from germanicol (**88**). Compounds **88–90** (Figure 17) were assessed for their ability to perturb X4- and R5-tropic HIV-1-envelope (Env)-mediated fusion membrane in a cell-to-cell fusion model. However, the olean-18-ene derivatives were inactive.[77] Glycyrrhizic acid was conjugated with tert-butyl esters of amino acids or benzyl esters of dipeptides containing two residues of L-amino acids (Met, Phe, Pro, and Ile or dipeptides Gly-Leu and Gly-Phe). Conjugates **91** and **92** (Figure 18) containing dipeptide fragments -Gly-Leu-OH and -Gly-Phe-OH, respectively, expressed anti-HIV-1 activity in cultures of MT-4 cells and were 90–70 times less cytotoxic than AZT. The selectivity indexes of the compounds exceeded those of glycyrrhizic acid by 110 and 34 times, respectively.[78] In another report, a series of maslinic acid derivatives containing amino acid or peptide at C-28 were synthesized using solution and solid-phase synthetic procedures. Compounds **93** and **94** (Figure 19) showed anti-HIV-1 activity in MT-2 cells infected with viral clones carrying the luciferase gene as a reporter.[79]

Di- and trisubstituted amides of glycyrrhizic acid containing fragments of heterocyclic and aromatic amines (2-aminopyridine, 4-aminopyridine, 5-aminouracil, sulfadimezine, sulfapyridazine, and L-histidine methyl ester) were synthesized using the dicyclohexylcarbodiimide method. Compound **96** exhibited marked anti-HIV activity, efficiently inhibiting the accumulation of virus-specific protein p24 (ID_{50} = 52.8 μM) and total viral antigens, decreasing RT activity (ID_{50} = 52.8 μM), and effectively protecting cells from death (102–123%) and from viral infection. Compound **95** was less active than **96** (Figure 20).[80] The newly developed method for synthesizing glycyrrhizic acid 3-O-galactosides produced primarily 3-O-α-D- (**97**) or β-D-galactopyranoside (**98**) (Figure 21) depending on the reaction conditions. When tested for inhibition of accumulated HIV-1-specific protein p24, compound **97** exhibited an index of selectivity 2.9-fold greater than that of glycyrrhizic acid. Compound **98** was more cytotoxic toward MT-4 cells and exhibited only weak anti-HIV-1 activity.[81]

A-*seco*-triterpenoids with a methylketone group were synthesized via a Grignard reaction. 3-Methyl-1-cyano-19β,28-epoxy-2,3-seco-2-nor-18αH-olean-3-one (**99**) (Figure 22) inhibited *in vitro* reproduction of HIV-1 (EC_{50}: 7.2 μg/mL).[82] Morolic acid derivatives (**100**–**102**) (Figure 23) showed anti-HIV-1 activity with EC_{50} values of 15, 14 and 39 μM, respectively.[40] C-3 modified moronic acid analogues **103**–**111** (Figure 24) diverse substitutions at the 3*β* position were tested against HIV-1_{IIIB}; however, none of them showed significant anti-HIV activity.[41]

Nine new and three known olean-18-ene triterpenes were isolated from *Cassine xylocarpa* and *Maytenus jelskii*. Five compounds (**112**–**116**) from this series displayed potent antiviral activity with IC_{50} values in the micromolar range; **112** and **116** being the most active compounds (Figure 25). Compared with currently licensed antiretroviral drugs, these compounds have a different target; they act as inhibitors of enhancer-dependent transcription.[83]

Correspondingly, transactivator of transcription (Tat), an early virus-encoded protein required for the efficient transcription of the HIV genome, could be developed as a target for small molecular therapeutics. Celastrol (**117**) (Figure 26) isolated from *Tripterygium wilfordii* exhibited high inhibitory activity against Tat. By covalently modifying the cysteine thiols, celastrol inhibits Tat transactivation function as well as the transcription elongation of the HIV proviral genome through mechanisms other than Tat–TAR (transactivation-responsive region) interaction.[84] 22*β*-Acetoxyglycyrrhizin (**118**) and 3-O-*β*-D-glucuronopyranosylglycyrrhetinic acid (**119**) (Figure 27) showed anti-HIV activities with IC_{50} values of 29.5 and 41.7 μM, respectively.[85]

Recently, the anti-HIV and other pharmacological activities of ursolic acid were reviewed.[86] A new series of HIV-1 protease inhibitors with pentacyclic triterpenoids as P2 ligands and phenylsulfonamide as P2′ ligands were synthesized. These compounds exhibited micromolar inhibitory potency. Among them, compound **T1c** (**120**) (Figure 28) exhibited HIV-1 protease inhibition with an IC_{50} value of 0.12 μM, thus, showing 67 times the inhibitory activity of its raw material ursolic acid (8.0 μM).[87] A-seco ursolic acid derivatives (**121**–**124**) (Figure 29) showed inhibitory activity against HIV-1 protease (IC_{50} 5.7, 17.6, 3.9 and 88.1 μM, respectively).[68]

2.3 | Others

3*a*-Methoxyserrat-14-en-21*β*-ol (**125**) and 3*β*-methoxyserrat-14-en-21*β*-ol (**126**) and their curcumin, kojic acid, quercetin, and baicalein conjugates were evaluated for *in vitro* anti-HIV-1 RT activity in infected C8166-CCR5 cells (Figure 30). Compound **127**, the conjugate of two molecules of **126** and one molecule of kojic acid, exerted significant anti-HIV activity with an EC_{50} value of 0.12 μg/mL.[88] An efficient synthesis of epiceanothic acid (**128**) (Figure 31) starting from betulin (**3**) was accomplished in 12-steps with a total yield of 10%. Epiceanothic acid (EC_{50}: 15.6 μM) exhibited moderate HIV-1 inhibition in acutely HIV-$1NL_{4-3}$ infected MT-4 cells.[89]

3 | TETRACYCLIC TRITERPENOID

3.1 | The lanostane group

Five highly oxygenated lanostane-type triterpenoids, ganoderic acid GS-1 (**129**), ganoderic acid GS-2 (**130**), ganoderic acid GS-3 (**131**), 20(21)-dehydrolucidenic acid N (**132**) and 20-hydroxylucidenic acid A (**133**), as well as several known compounds were isolated from the fruiting body of *Ganoderma sinense* (Figure 32). Compounds **130**, **132**, and 20-hydroxylucidenic acid N (**134**) and ganoderiol F (**135**) inhibited HIV-1 protease with IC_{50} values of 30, 48, 25, 22 μM, respectively.[90] Three new tricyclic rearranged lanostane triterpenoids, kadcotriones A–C (**136**–**138**), together with a biogenetically related lanostane-type triterpenoid (**139**), were isolated from *Kadsura coccinea* (Figure 33). Compounds **137** and **139** exhibited anti-HIV-1 activities with EC_{50} values of 30.29 and 54.81 μM, respectively.[91] Later, 11 triterpene acids including kadcoccinic acids A–J (**140**–**149**) and **150** (Figure 34) were also isolated from the stems of *Kadsura coccinea* by the same group. Except for **149**, these compounds feature a rearranged lanostane skeleton with a 6/6/5/6 tetracyclic ring system. Compounds **140** and **141** are the first triterpenoids with a 2,3-seco-6/6/5/6-fused tetracyclic skeleton. Among them, compounds **143** and **146** demonstrated anti-HIV-1 activity with respective EC_{50} values of 62.0 and 58.7 μM.[92] In a computational study on *Ganoderma lucidum* triterpenoids, ganoderat acid-B (**151**) (Figure 35) showed the best affinity to HIV-1 protease (binding energy= −7.49 kcal/mol and Ki= 0.001 mM), better than that of nelfinavir.[93] Another lanostane triterpene, garcinuntine (**152**) (Figure 36), isolated from the roots of *Garcinia nuntasaenii* Ngerns. & Suddee was inactive.[94]

3.2 | The dammarane group

Several dammarane triterpene derivatives were synthesized and evaluated for HIV-1 protease inhibitory activity. The mono- and di-succinyl derivatives **153**–**157** (Figure 37) were significant inhibitors of HIV-1 protease with EC_{50} values of 2.7, 6.5, 3.9, 2.7 and 5.4 μM.[95] Three other triterpenoids, (20*R*)-20,25-epoxy-dammaran-2-en-6*a*,12*β*-diol (**158**), (20*R*)-20,25-epoxy-3-methyl-28-nordammaran-2-en-6*a*,12*β*-diol (**159**) and isodehydroprotopanaxatriol (**160**), isolated from an acidic hydrolysate of *Panax ginseng* (Figure 38), showed inhibitory activity against HIV-1 protease with EC_{50} values of 10.5, 10.3, and 12.3 μM, respectively.[96] In the screening of a panel of purified compounds isolated from *Aglaia* sp. (Meliaceae) for inhibition of early steps in the lentiviral replication cycle, the 3,4-secodammarane triterpenoid **161** (Figure 39), exhibited potent inhibition of HIV-1 infection (IC_{50} = 0.48 μg/mL), while cytotoxic effects and inhibition of cell proliferation were observed only at concentrations exceeding 10.69 μg/mL.[97]

3.3 | Cycloartane group

Four cycloartane triterpenoids, angustific acid A (**162**), angustific acid B (**163**), angustifodilactone A (**164**) and angustifodilactone B (**165**) (Figure 40), were isolated from the branches of *Kadsura angustifolia*. Compound **162**, characterized by the presence of a C-16/C-17, C-20/C-21 conjugated diene and a C-1/C-7 ester bridge formed in rings A and B, exemplified a novel structural skeleton for 3,4-secocycloartane triterpenoids. Compound **162** exhibited the most potent anti-HIV activity with an EC_{50} value of 6.1 μg/mL in infected

C8166 cells and a therapeutic index of more than 32.8.[98] Two cycloartane triterpenoids, cycloccidentalic acids A and B (**166** and **167**), and five related saponins, cycloccidentalisides I–V (**168**–**172**) (Figure 41), were isolated from *Cassia occidentalis*. Compounds **167** and **170** showed modest anti-HIV-1 activities with EC_{50} values of 2.23 μM and 4.36 μM, respectively.[99]

Eight cycloartane triterpenoids carinatins A–H (**173**–**180**), secaubryolide (**181**) and dikamaliartane D (**182**) (Figure 42) were isolated from the leaves and twigs of *Gardenia carinata* and evaluated for anti-HIV-1 activities using HIV-1 reverse transcriptase and syncytium inhibition assays using the $^{\Delta Tat/Rev}$MC99 virus and 1A2 cell line system. Compounds **173**, **174**, **177**–**179**, and **182** exhibited significant inhibitory activities by significantly reducing the number of syncytium formations in the syncytium inhibition assay. Compound **182** showed the most potent anti-HIV-1 activity (EC_{50} < 8.3 μM). In the reverse transcriptase assay, only compounds **175** and **182** were active against HIV-1 reverse transcriptase, with IC_{50} values of 85.7 and 68.7 μM, respectively.[100]

Two metabolites (**184** and **185**) were obtained by microbial transformation of the triterpene nigranoic acid (**183**) in a culture of Trichoderma sp. JY-1, a fungus obtained from the branches of *Kadsura angustifolia*. Compound **184** was characterized with an unusual 17(20),17(*E*)-ene structure, while compound **185** featured an unprecedented 18(13→17β)-abeo-secocycloartane skeleton. Additionally, compounds **183**–**185** (Figure 43) showed weak anti-HIV activity with EC_{50} values of 10.5, 8.8 and 7.6 μg/mL and therapeutic index values of 8.48, 9.12 and 10.1, respectively.[101] In another report, the microbiological transformation of the triterpene nigranoic acid (**183**) to 3,4-secocycloarta-4(28),17(20),24(*Z*)-triene-7β-hydroxy-16β,26-lactone-3-oic acid (**186**) and 3,4-secocycloarta-4(28), 17(20)(*Z*),24(*Z*)-triene-7β-hydroxy-16β-methoxy-3,26-dioic acid (**187**) (Figure 44) by the freshwater fungus *Dictyosporium heptasporum* YMF1.01213 was demonstrated. Compound **186**, characterized by the presence of a formed C-16/C-26 ester bridge, exemplifies a novel nine-membered lactone ring structural skeleton for 3,4-secocycloartane triterpenoid. In addition, compounds **186** and **187** exhibited weak *in vitro* anti-HIV activity with respective EC_{50} values of 15.3 and 18.1 μg/mL.[102] In a recent report, a novel cycloartane triterpenoid alkaloid, kleinhospitine E (**188**), and six cycloartane triterpenoids (**189**–**194**) (Figure 45) were isolated from *Kleinhovia hospita*. Compound **188** is the first cycloartane alkaloid possessing an unusual γ-lactam with an oxopropylidene side chain. Compounds **189**, **190**, and **194** were assigned as cycloartane triterpenoids with a 9α,10α-cyclopropyl ring, which is found rarely among naturally occurring compounds, while **192** and **193** were established as isomers of **190** containing a 21,23-diacetal side chain. Compound **194** exhibited anti-HIV activity with an EC_{50} value of 0.8 μM.[103]

In our Natural Products Research Laboratories, 12 known cycloartane triterpenoids (**195**–**206**) (Figure 46) with four different skeletons were isolated from the roots of *Souliea vaginata* and screened for their anti-HIV activity. Among these compounds, beesioside I (**195**) showed the highest potency against HIV-1_{NL4-3} with an EC_{50} value of 2.32 μM. Further modification at the C-3 position of the aglycone (**207**) of **195** led to a series of derivatives (**208**–**221**) (Figure 47). Among them, compound **214** was the most potent with an

EC_{50} value of 0.025 μM and TI value greater than 800, comparable to those of BVM. Other analogues exhibited strong to weak inhibition of HIV-1 replication in MT-4 cells.[104]

3.4 | Limonoid group

Three limonoids, trichiconin A (**222**) with a unique carbon skeleton featuring a rearranged A,B-ring system and trichiconins B (**223**) and C (**224**) (Figure 48) with an unprecedented A,B,D-seco skeleton, were isolated from the twigs of *Trichilia connaroides*. Compounds **223** and **224** showed modest anti-HIV activity with EC_{50} values of 5.9 and 3.6 μM, respectively, while **222** was inactive.[105] Sixteen limonoids, ciparasins A–P (**225**–**240**) (Figure 49), were isolated from *Cipadessa cinerascens*. Ciparasins E–G (**229**–**231**) contain a rare gamma-hydroxylbutenolide moiety at C-17. Ciparasins B (**230**) and P (**240**) showed significant anti-HIV activity with EC_{50} values of 5.5 and 6.1 μM, respectively.[106] Five limonoids, sundarbanxylogranins A–E (**241**–**245**) (Figure 50), were isolated from the seeds of *Xylocarpus granatum*. Sundarbanxylogranin A (**241**) is a rare limonoid containing a bicyclo[5.2.1]dec-3-en-8-one scaffold as the ring A/B-fused core; whereas sundarbanxylogranin B (**242**) is a typical mexicanolide with an 8*a*,30*a*-epoxy ring. Sundarbanxylogranins C–E (**243**–**245**) belong to a small group of limonoids containing a C1-O-C29 oxygen bridge; both former compounds have a 29-OMe group but with different orientations. Compound **242** exhibited moderate anti-HIV activity with an IC_{50} value of 23.14 μM.[107]

Krishnolides A–D (**246**–**249**) (Figure 51), four khayanolide-type limonoids with a 2-carbonyl group, were isolated from the seeds of *Xylocarpus moluccensis*. Compounds **246**–**249** are unique khayanolides containing two large ester substituents of five or four carbon atoms at the C-3 and C-30 positions, respectively. Compound **246** with an 8,14-epoxy group exhibited moderate anti-HIV activity with an IC_{50} value of 17.45 μM.[108]

3.5 | Nortriterpenoids of the Schisandraceae

Three nortriterpenoids, schigrandilactones A–C (**250**–**252**) (Figure 52), were isolated from *Schisandra grandiflora*. Compounds **250** and **251** contain a spirocyclic moiety, and compound **252** has a new oxygenated pattern. Compounds **250**–**252** displayed EC_{50} values of 80.2, 20.8, and 5.1 μg/mL in infected C8166 cells.[109] A nortriterpenoid, 20-hydroxymicrandilactone D (**253**) (Figure 53) was isolated from *S. lancifolia*. Compound **257** showed anti-HIV-1 activities with EC_{50} value of 99.0 μg/mL.[110] Six nortriterpenoids, schirubridilactones A–F (**254**–**259**) (Figure 54) were isolated from *S. rubriflora*. Compounds **254**–**259** showed anti-HIV-1 activity with EC_{50} values of 30.1, 15.2, 14.3, 80.8, 66.8, and 50.1 μg/mL and a selectivity index of 5.1, 9.0, 8.7, 2.2, 3.1, and 3.5, respectively.[111]

A novel triterpenoid, schinarisanlactone A (**260**) (Figure 55), with an unprecedented skeleton of a 5/7/7/5/7/5/6/5-fused octacyclic ring system was isolated from *Schisandra arisanensis*. Compound **260** showed significant inhibition (11.8% survival rate) against the HIV virus at 10 μM.[112] Three unique nortriterpenoids, schilancitrilactones A–C (**261**–**263**) (Figure 56), were isolated from *S. lancifolia*. Compound **261** has a 5/5/7/5/5/5-fused hexacyclic ring system with a C29 backbone, while **262** and **263** feature a 5/7/5/5/5-fused pentacyclic ring system with a C27 skeleton. Compound **263** showed anti-HIV-1 activity

with an EC_{50} value of 27.54 μg/mL, while **261** and **262** were not active (EC_{50} >100 μg/mL).[113] Two new highly oxygenated nortriterpenoids, schilancidilactones V and W (**264** and **265**) (Figure 57), were isolated from *S. wilsoniana*. They showed moderate anti-HIV-1 activity with EC_{50} values of 3.05 and 2.87 μg/mL, respectively.[114] Schisphendilactones A and B (**266** and **267**) (Figure 58) isolated from *S. sphenanthera* exhibited anti-HIV-1 activity with EC_{50} values of 8.79 and 1.09 μg/mL, respectively.[115] Schisarisanlactones A (**268**) and B (**269**) (Figure 59), were isolated from *S. arisanensis*. Compounds **268** and **269** have an unprecedented 5/5/7/5/5-fused pentacyclic ring system. Compound **268** showed significant inhibition (15.5% survival rate), while compound **269** exhibited moderate activity (39.8% survival rate) against the HIV virus at 10 μM.[116]

3.6 | Others

Four types of piscidinol A derivatives were synthesized and evaluated for their ability to inhibit HIV-1 protease (PR). Among these tirucallane-type triterpene derivatives, an A-seco derivative (**270**) moderately inhibited HIV PR (IC_{50} 38.2 μM). However, the 2,2-dimethylsuccinic acid (DMS) acylated tirucallane derivatives (**271**–**273**, ranging from 50 to 100 μM) (Figure 60) were more inhibitory against the enzyme.[117] Chemical investigation of the vines and leaves of *Momordica charantia* resulted in the isolation of 14 cucurbitane triterpenoids, kuguacins F–S (**274**–**287**) (Figure 61). Compounds **285** and **287** showed anti-HIV-1 activity with EC_{50} values of 7.2 and 3.7 μg/mL, respectively.[118]

Kadheterilactone A (**288**) and kadheterilactone B (**289**) (Figure 62) were isolated from *Kadsura heteroclite.* Compounds **288** and **289** were inactive against HIV-1 PR and RT.[119] A pair of triterpenoid epimers, kadcoccitones A (**290**) and B (**291**) (Figure 63), together with a biogenetically related compound, kadcoccitone C (**292**), were isolated from *K. coccinea*. These epimers featured an unprecedented carbon skeleton with a 6/6/5/5-fused tetracyclic ring system unit and a C9 side chain. Compounds **290** and **292** showed anti-HIV-1 activity with EC_{50} values of 47.9 and 32.7 μg/mL, respectively.[120]

Viral protein R (Vpr) is an accessory protein that plays important roles in the viral pathogenesis of HIV-1. In an anti-Vpr assay, the $CHCl_3$-soluble extract of *Picrasma javanica* bark exhibited potent anti-Vpr activity. Furthermore, related research on quassinoids previously isolated from the extract demonstrated that compounds **293**–**307** (Figure 64) exhibit anti-Vpr activity. Among these compounds, javanicin I (**307**) exhibited the most potent anti-Vpr activity in comparison with that of the positive control damnacanthal. The structure-activity relationship analysis suggested that, in 2,12,14-triene-1,11,16-trione-2,12-dimethoxy-18-norpicrasane quassinoids, a methyl group at C-13 is the critical factor for a potent inhibitory effect in TREx-HeLa-Vpr cells.[121]

4 | PERSPECTIVES AND CONCLUSIONS

HIV infection remains a major threat worldwide, especially in developing countries. Although antiretroviral multi-drug treatment can provide durable repression of HIV, these drugs have limited clinical benefit due to the emergence of drug resistance and severe side effects, which have hampered their usefulness to most people suffering from AIDS. Therefore, finding new drugs with novel targets is of clinical significance to treat infected

persons and furthermore to ultimately achieve the goal of complete eradication of HIV. Natural products are an important potential source for HIV-AIDS drug discovery. Over the past ten years, extensive research on natural products has revealed that triterpenoids and their derivatives are an important reservoir of anti-HIV drug leads. It appears that pentacyclic triterpenes are the most promising lead compounds for further development of novel antiviral drugs. The rational design of substituents linked to the C-3 and C-28 positions of betulinic acid and analogues is critical in attaining new derivatives with improved anti-HIV activity. Although the development of BVM as the first-in-class HIV-1 maturation inhibitor was halted due to the high baseline drug resistance of HIV-1 variants with polymorphism, further studies identified the second-generation maturation BMS-955176 (**64**), which showed significantly improved anti-HIV activity toward BVM-resistant variants. Unfortunately, the development of BMS-955176 was also discontinued by the pharmaceutical company GSK for gastrointestinal intolerance and treatment-emergent drug resistance by patients. However, due to the proven biological properties demonstrated by betulinic acid derivatives, many studies involving them are still reported in the literature. These studies conclude that artful modification both at C-3 and C-28 can effectively overcome HIV-1 resistance and improve antiviral activity in the presence of human serum. However, the effect of functionalization at other positions such as C-30 should not be neglected. Besides antiviral activity, solubility and microsomal stability should be considered. The corresponding SAR from the prior studies is a powerful prototype that affords optimal lead compounds to be emphasized for future endeavors. Even though betulinic acid is an interesting scaffold for developing antiviral agents and has attracted more attention, other classes of triterpenoids also offer unprecedented opportunities for the discovery of novel antiviral therapy. These results make it clear that natural triterpenoids and their synthetic derivatives will continue to be promising candidates for the development of novel anti-HIV drugs.

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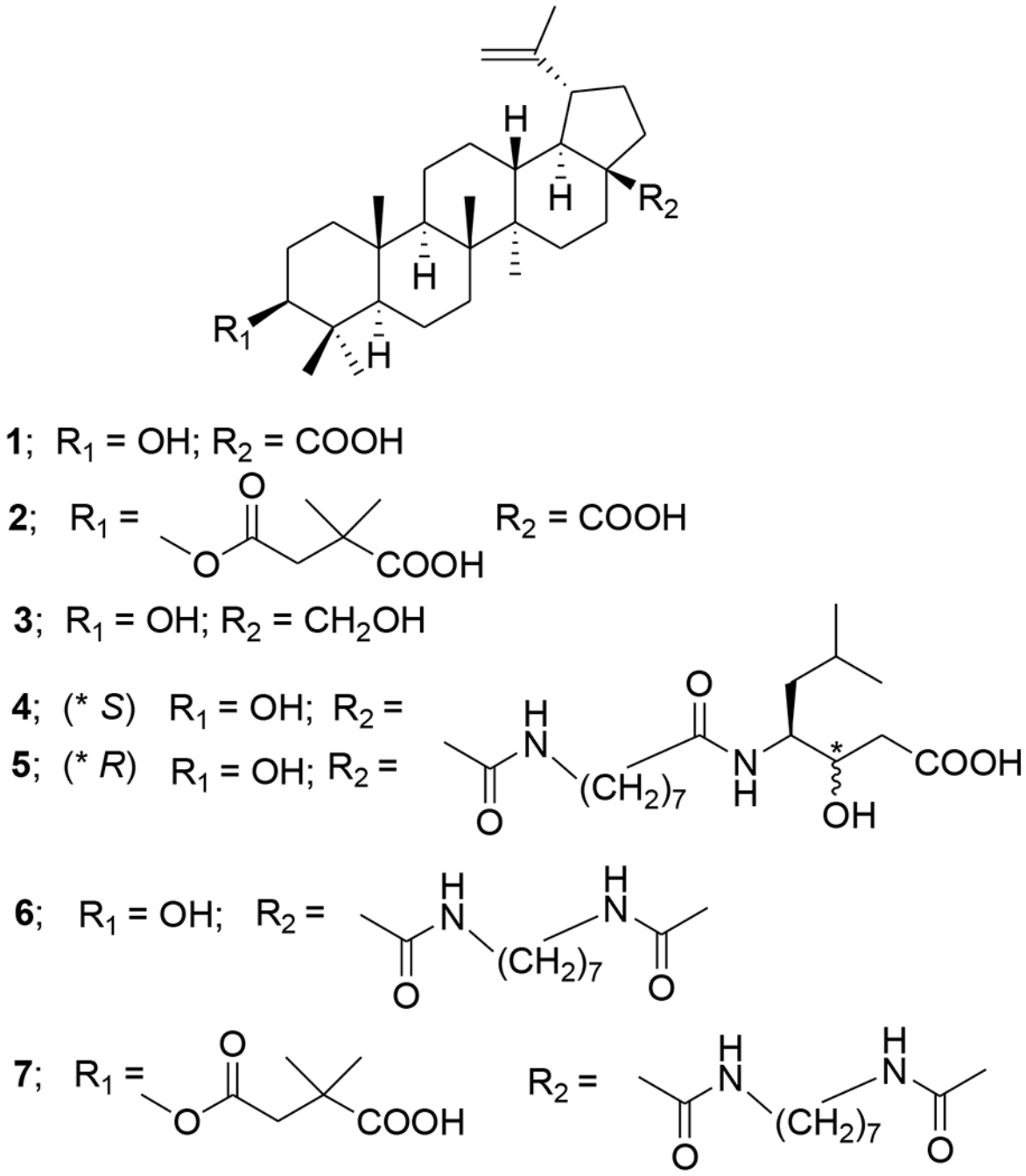


FIGURE 1.
Chemical structures of compounds **1**–**7**

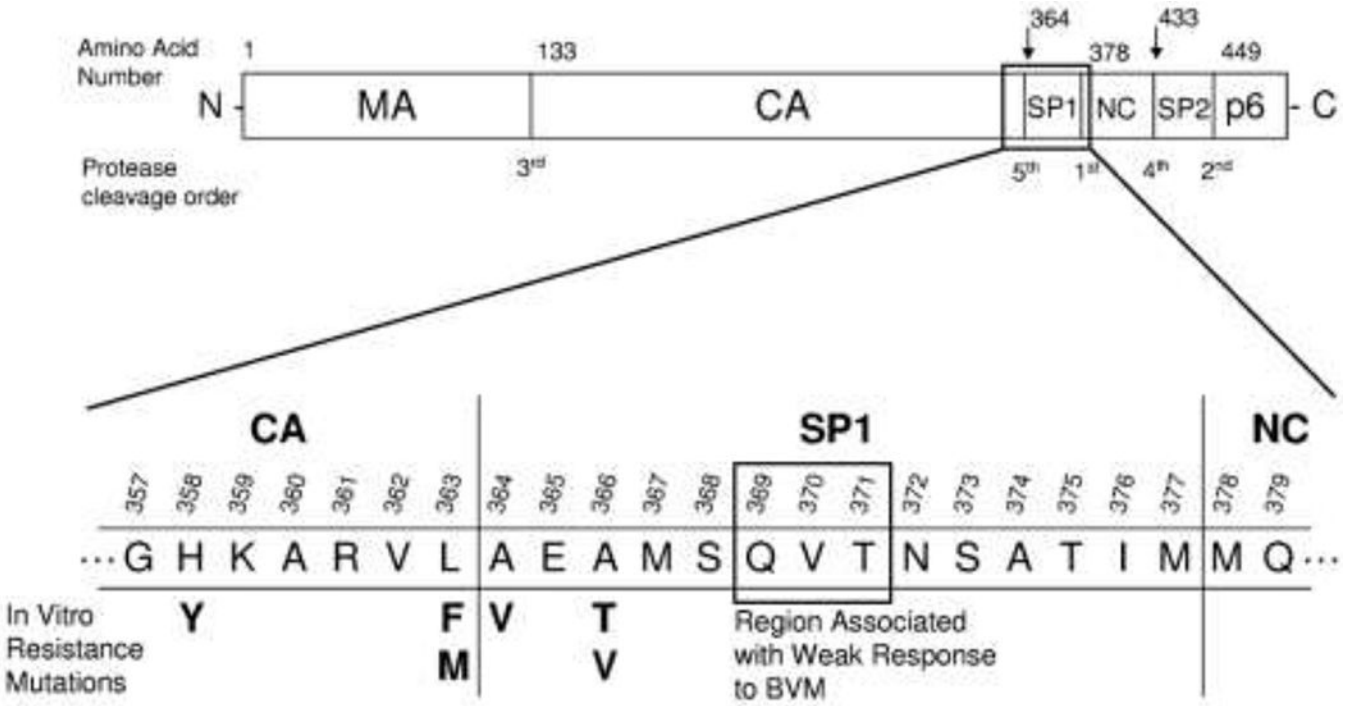


FIGURE 2.

Schematic of HIV-1 Gag polyprotein showing amino acid residues associated with bevirimat susceptibility. MA, matrix; CA, capsid; SP1, small peptide 1; NC, nucleocapsid; SP2, small peptide 2. Reproduced with permission from [19].

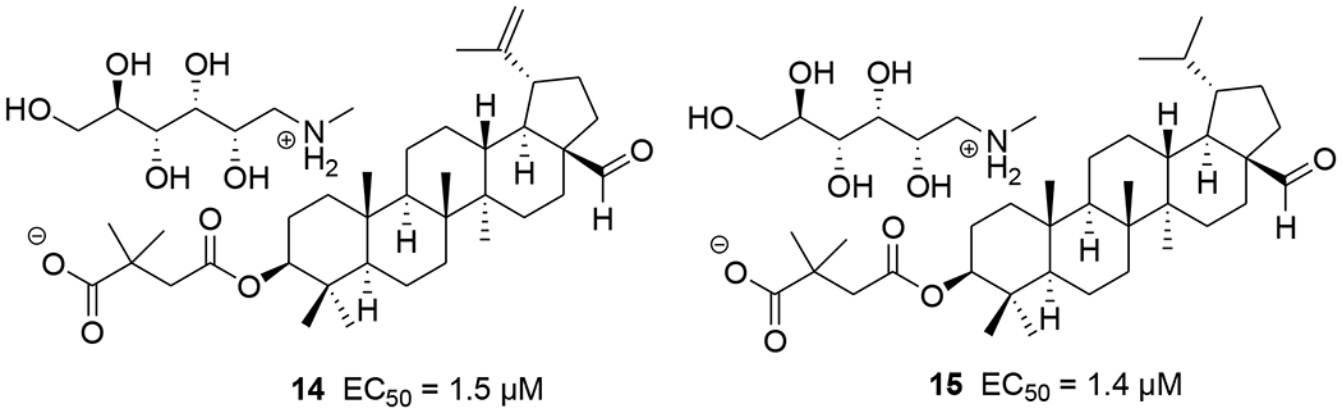


FIGURE 3.
Chemical structures of compounds **14** and **15**

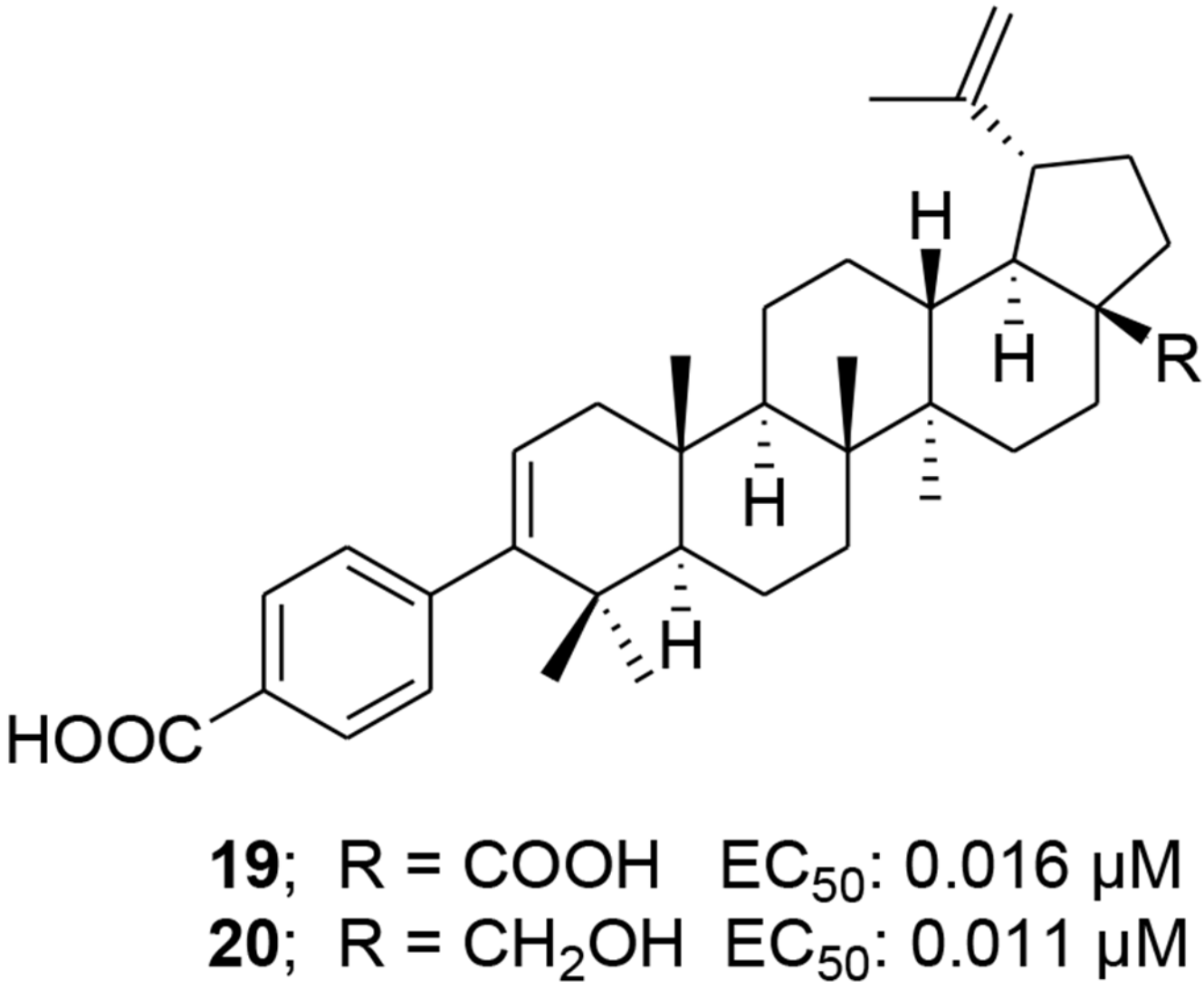


FIGURE 4.
Chemical structures of compounds **19** and **20**

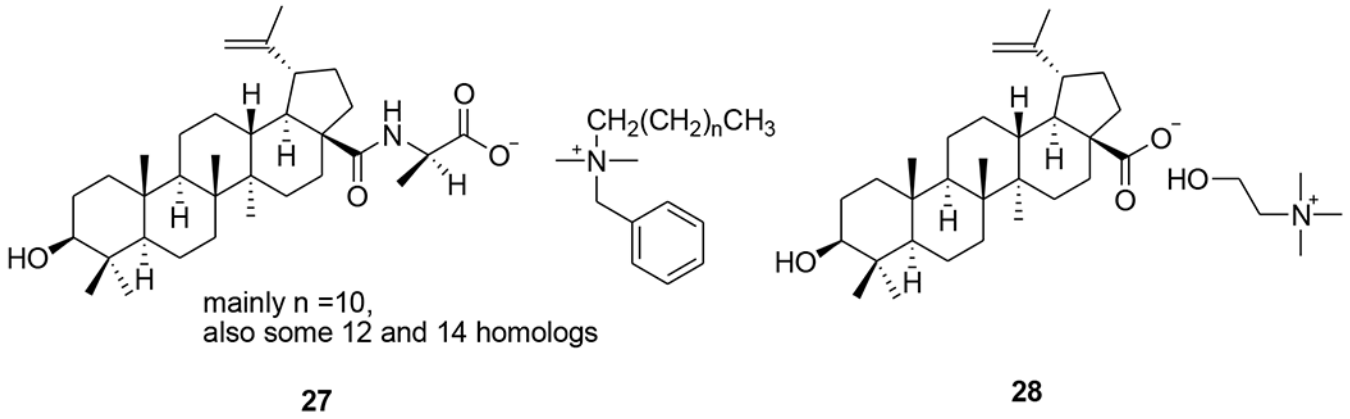


FIGURE 5.
Chemical structures of compounds **27** and **28**

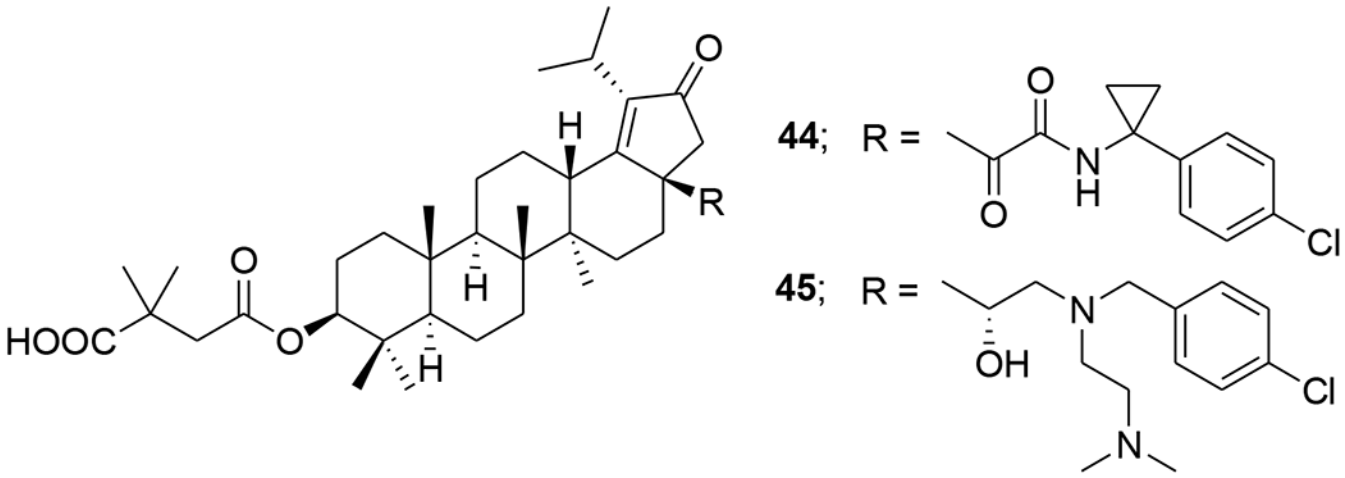


FIGURE 6.
Chemical structure of compounds **44** and **45**

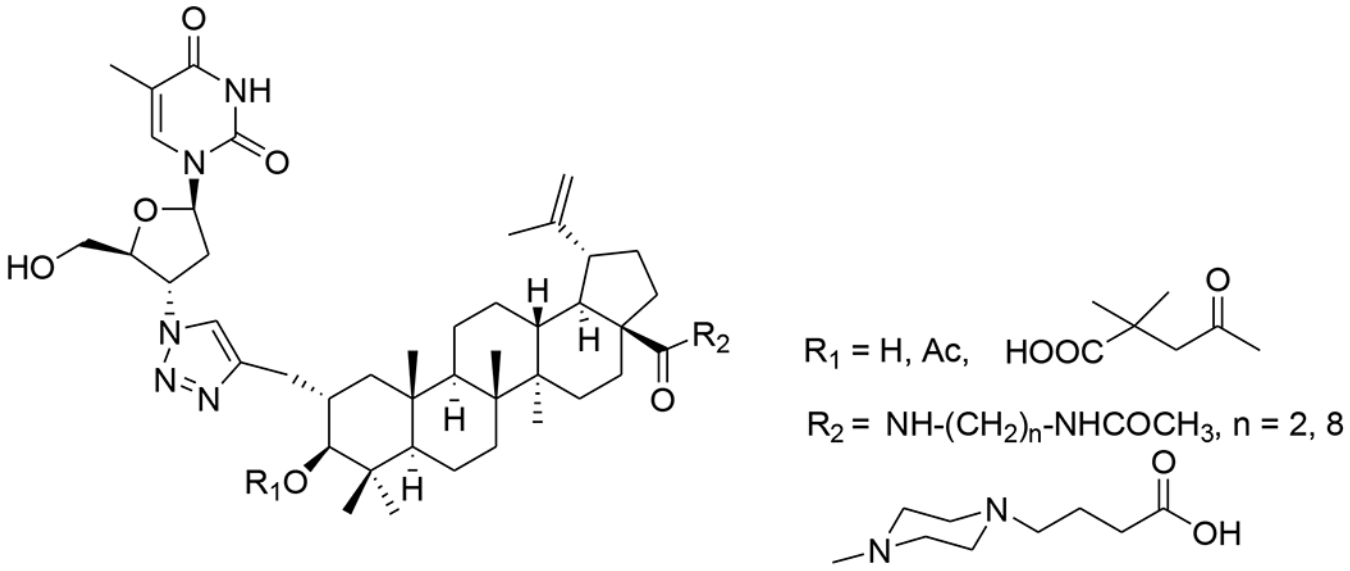


FIGURE 7.
Chemical structure of AZT–betulinic acid conjugates

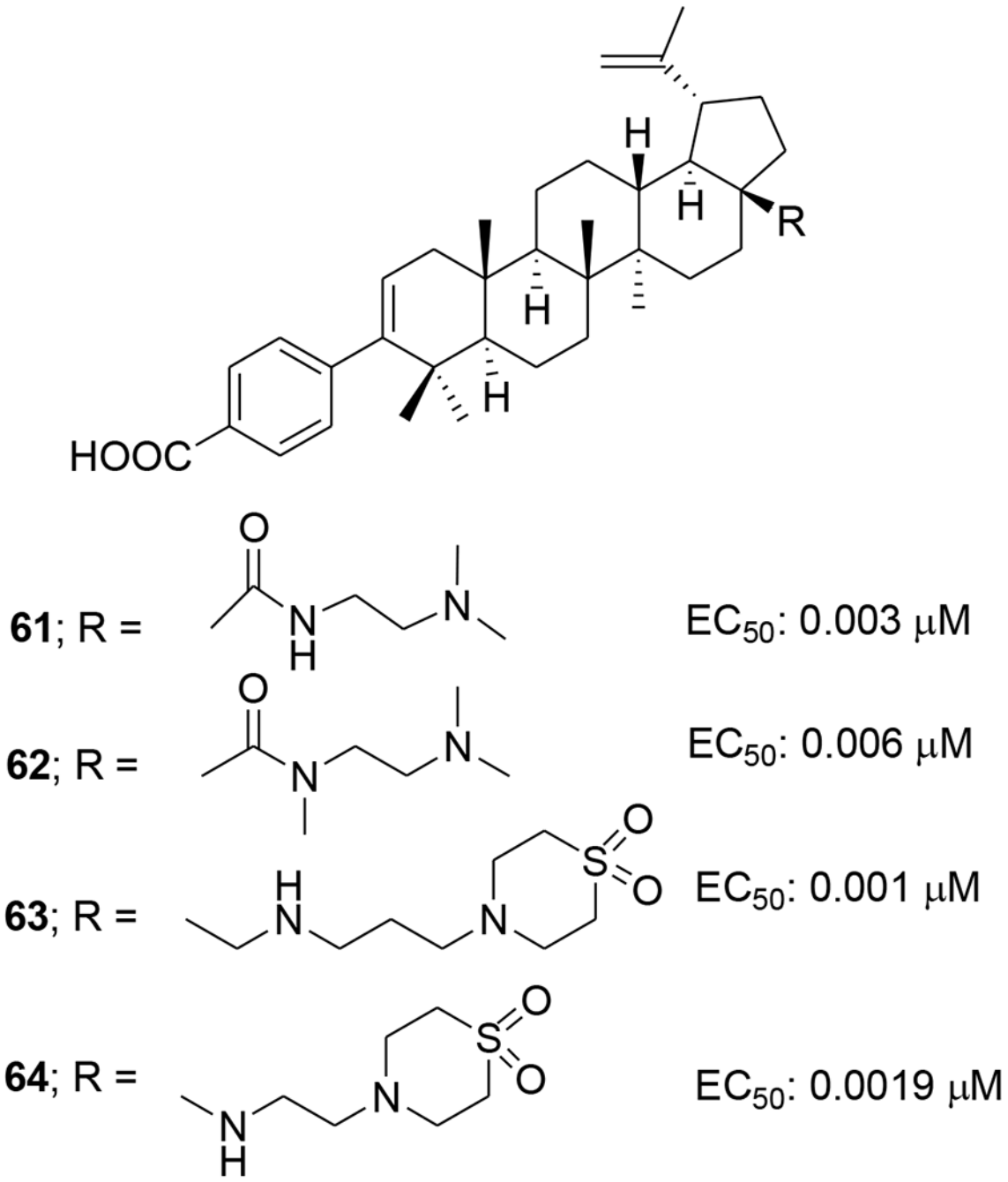


FIGURE 8.
Chemical structures of compounds **61**–**64**

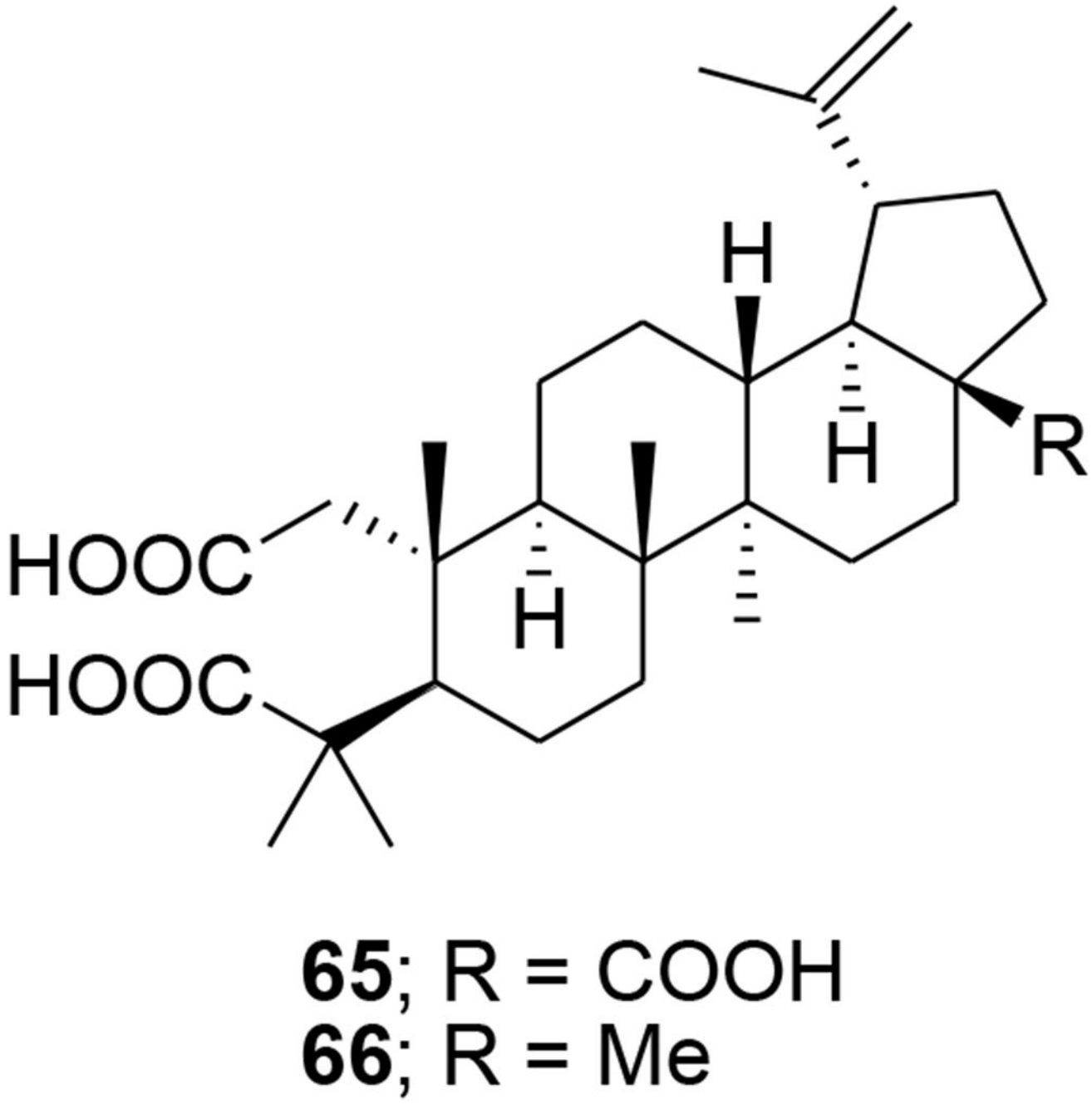


FIGURE 9.
Chemical structures of compounds **65** and **66**

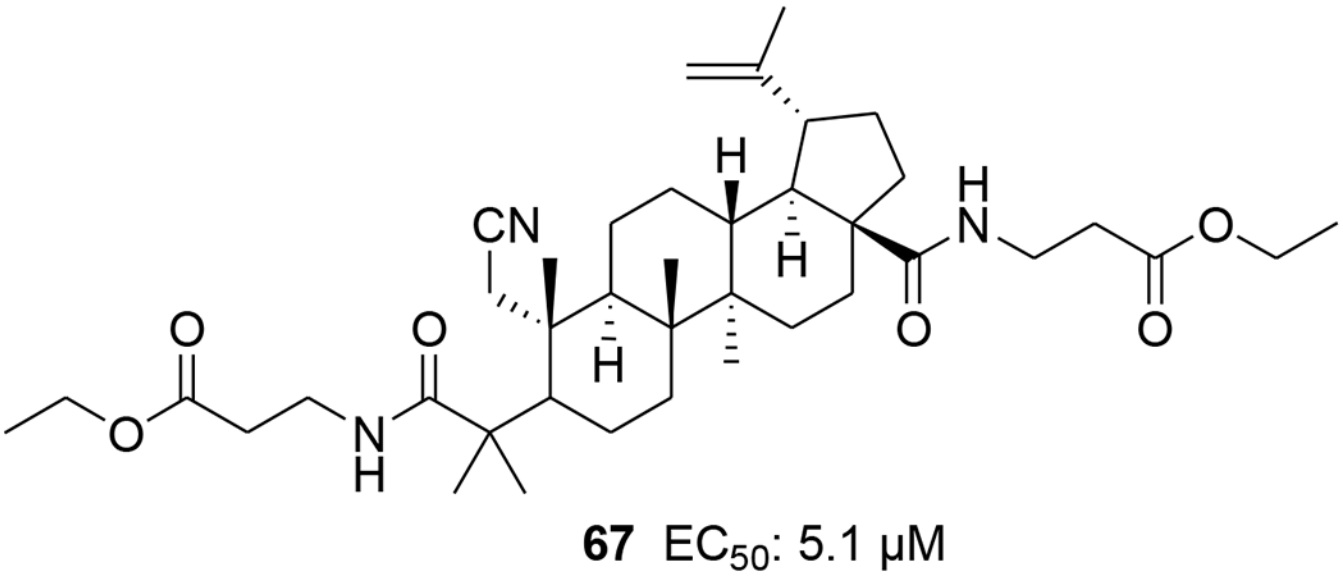


FIGURE 10.
Chemical structure of compound **67**

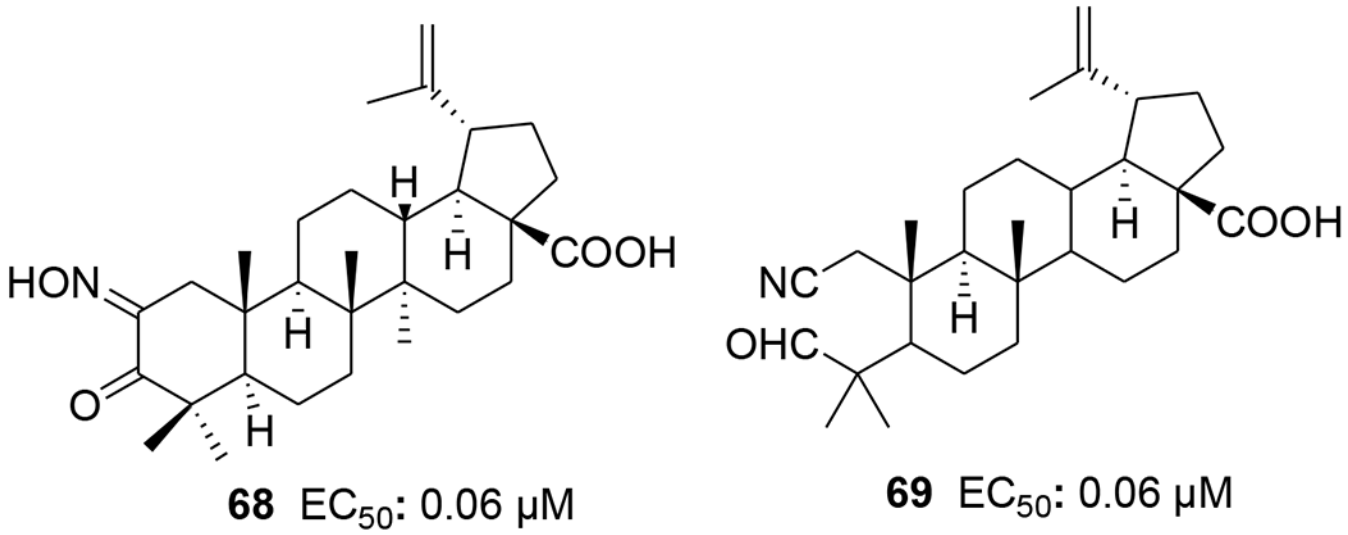
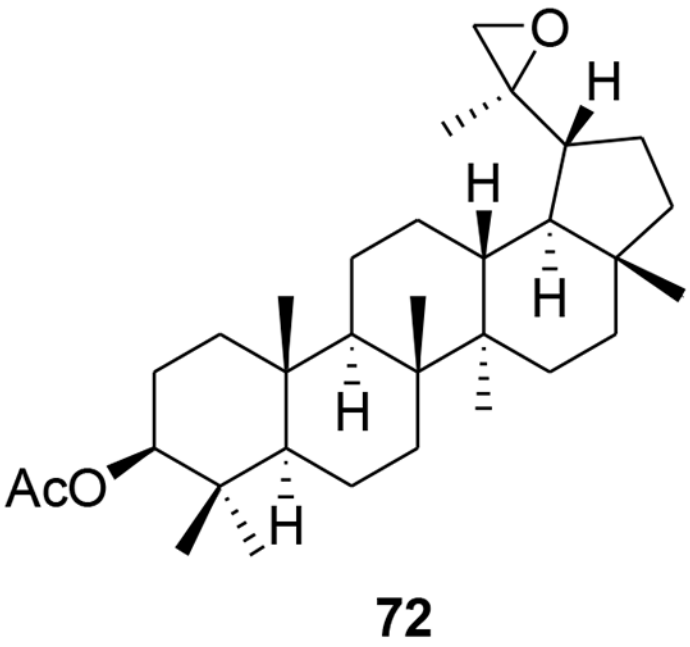
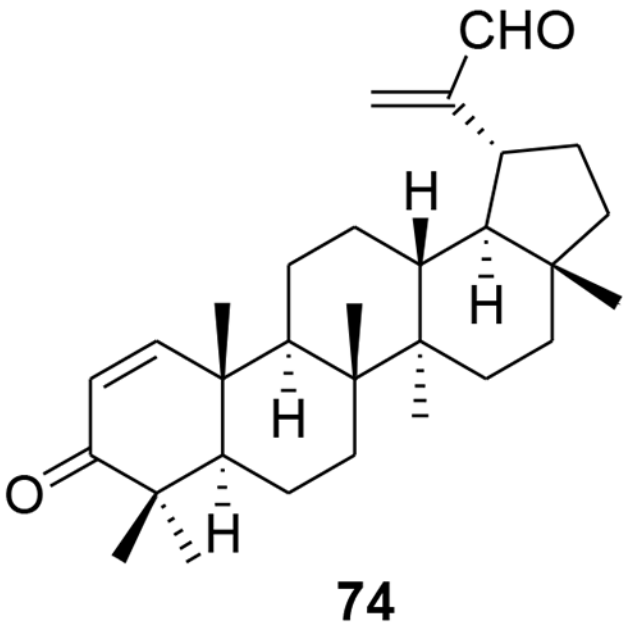


FIGURE 11.
Chemical structures of compounds **68** and **69**

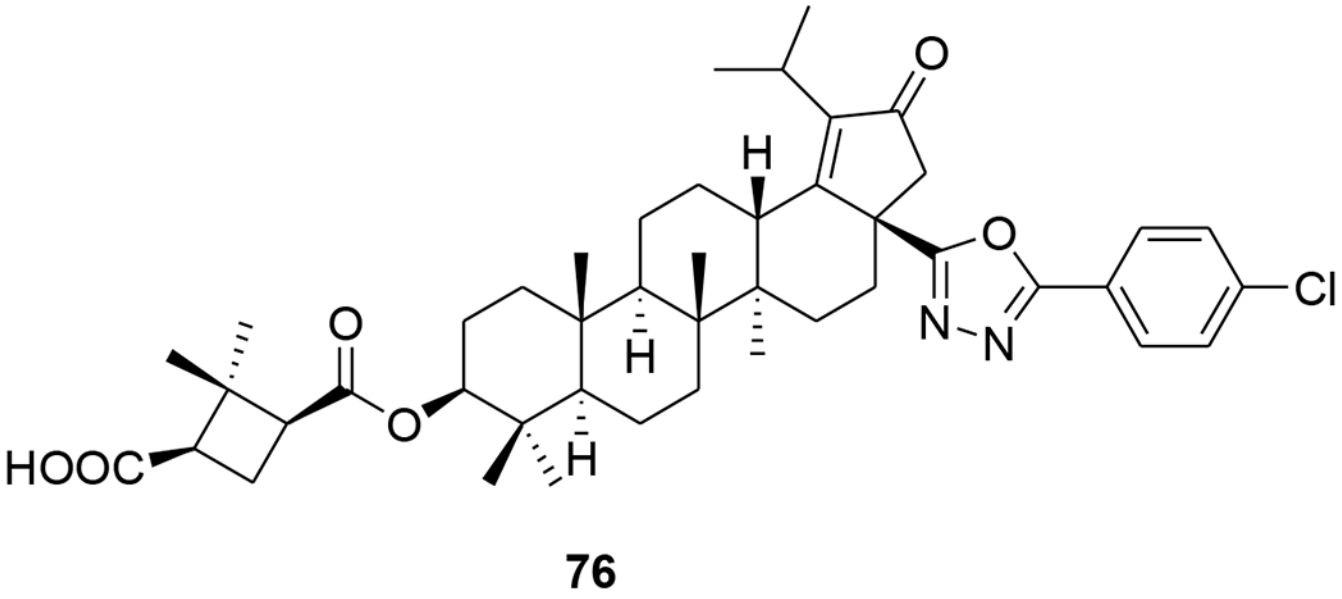


72



74

FIGURE 12.
Chemical structures of compounds **72** and **74**



76

FIGURE 13.
Chemical structure of compound **76**

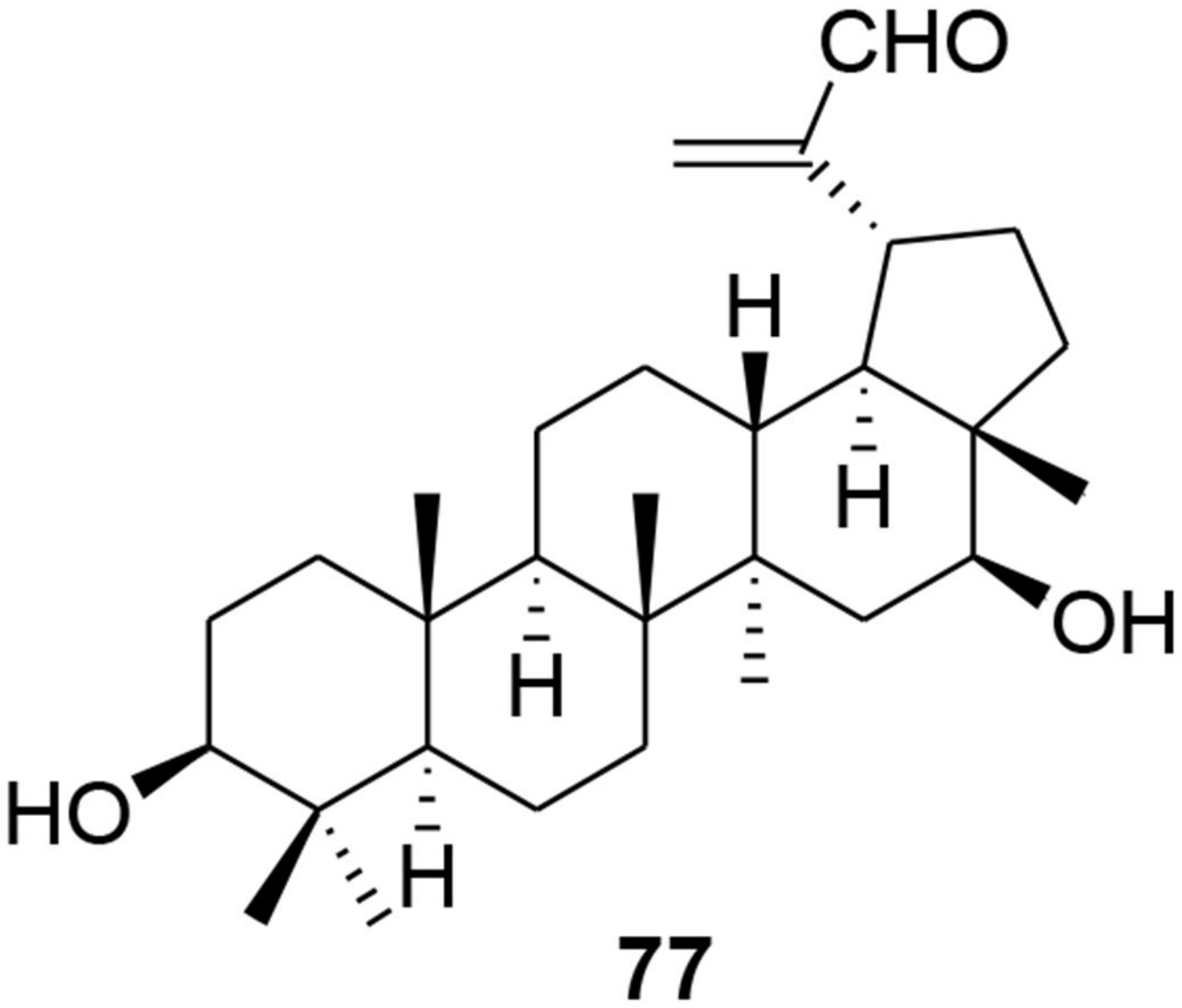


FIGURE 14.
Chemical structure of compound **77**

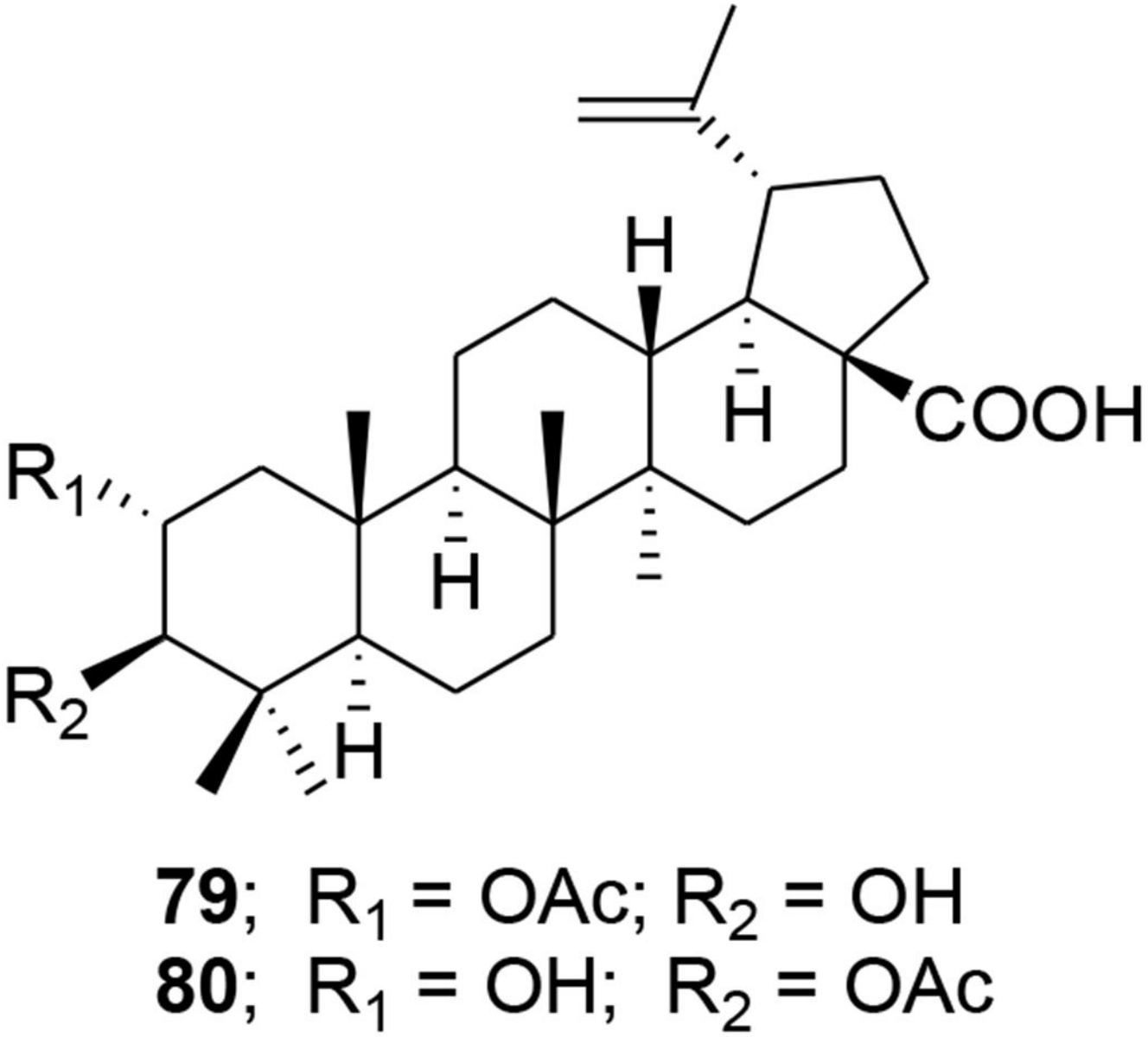
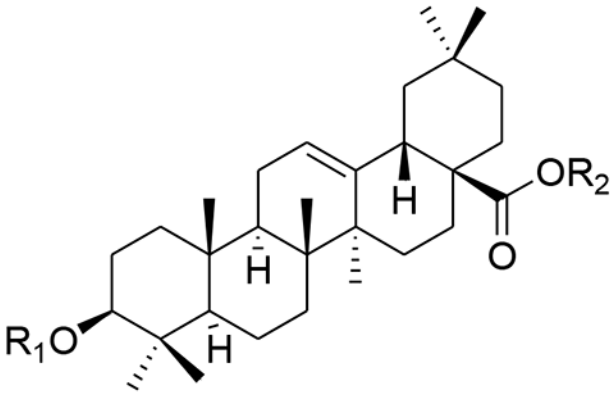
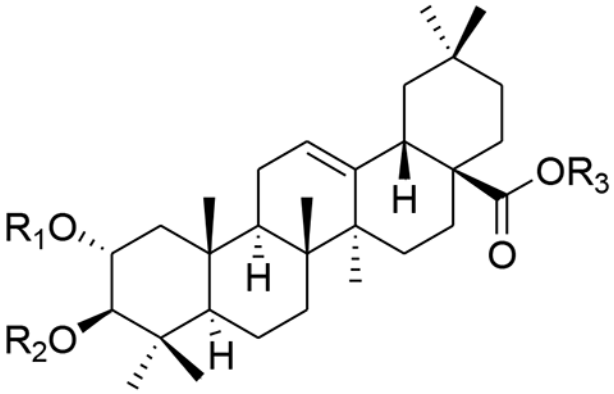


FIGURE 15.
Chemical structures of compounds **79** and **80**



81; $R_1 = R_2 = H$
82; R_1 = phthaloyl; $R_2 = H$
83; R_1 = gluraryl; $R_2 = H$
84; R_1 = 3,3-dimethylglutaryl; $R_2 = H$
85; R_1 = phthaloyl; R_2 = Bn



86; $R_1 = R_2 = R_3 = H$
87; R_1 = phthaloyl; $R_2 = H$; R_3 = Bn

FIGURE 16.
Chemical structures of compounds **81**–**87**

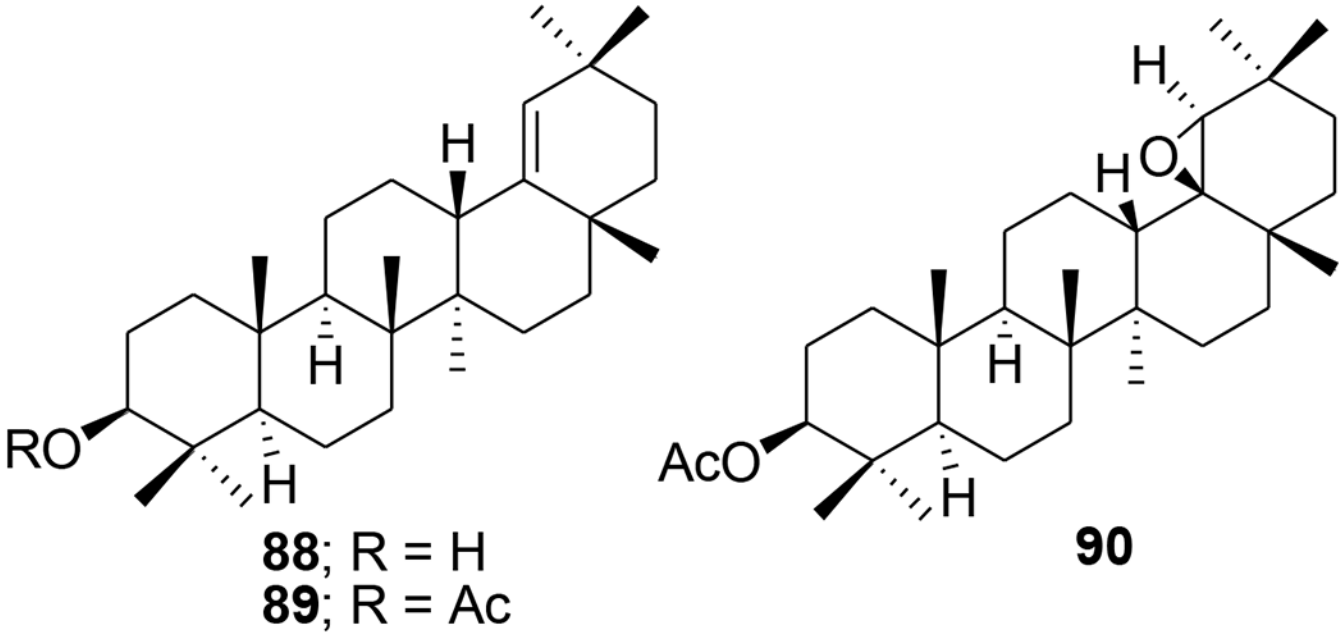


FIGURE 17.
Chemical structures of compounds **88**–**90**

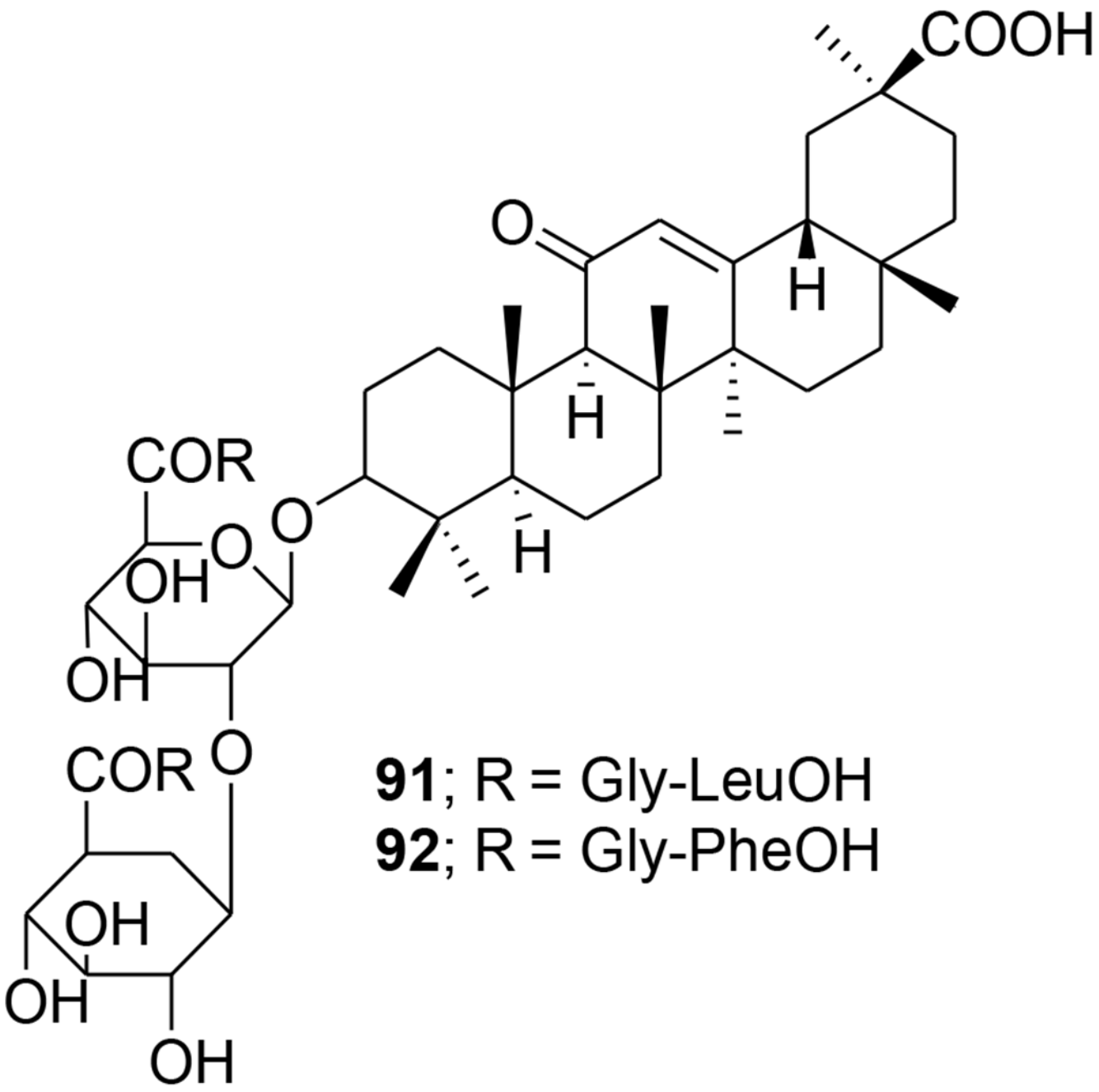


FIGURE 18.
Chemical structures of compounds **91** and **92**

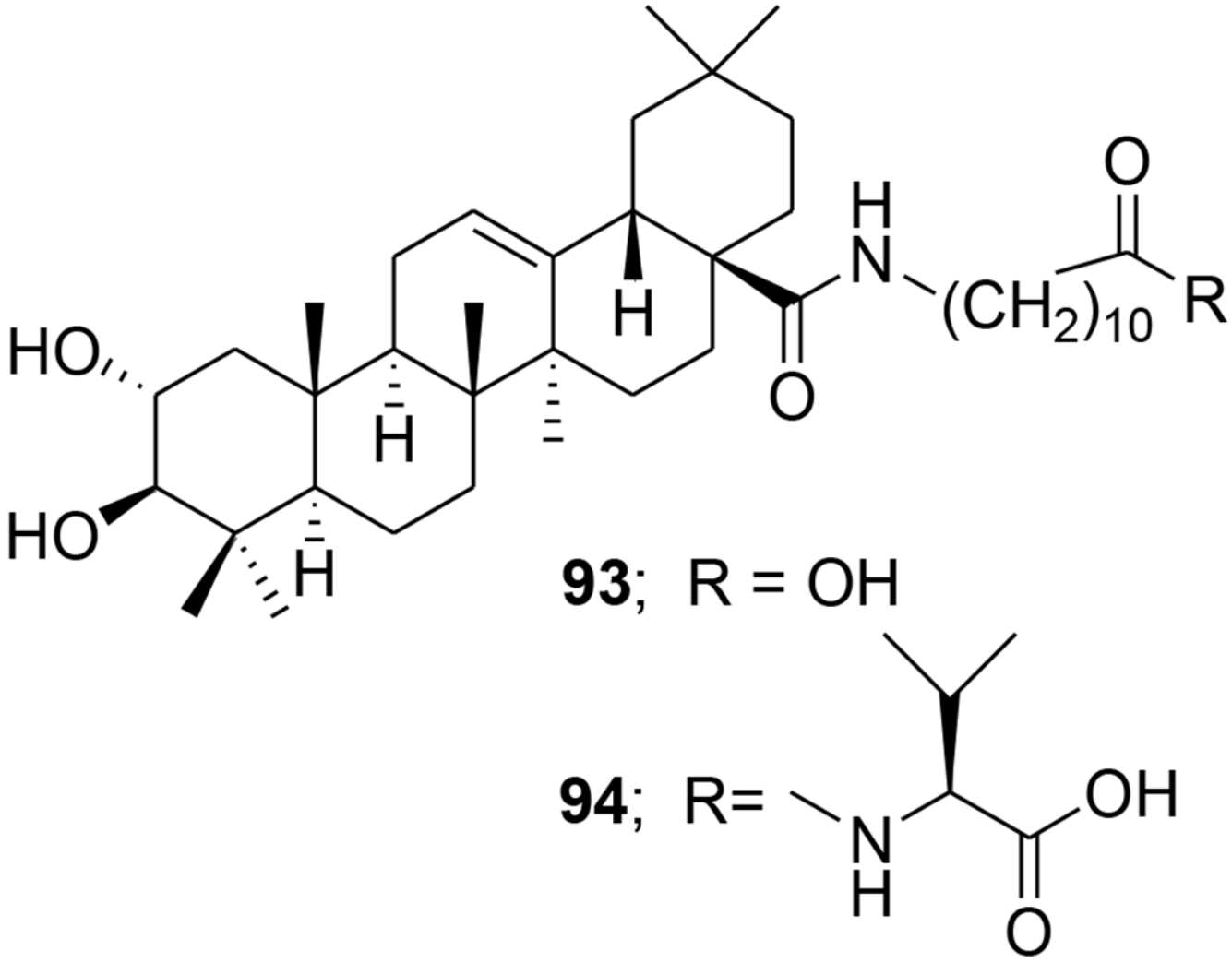


FIGURE 19.
Chemical structures of compounds **93** and **94**

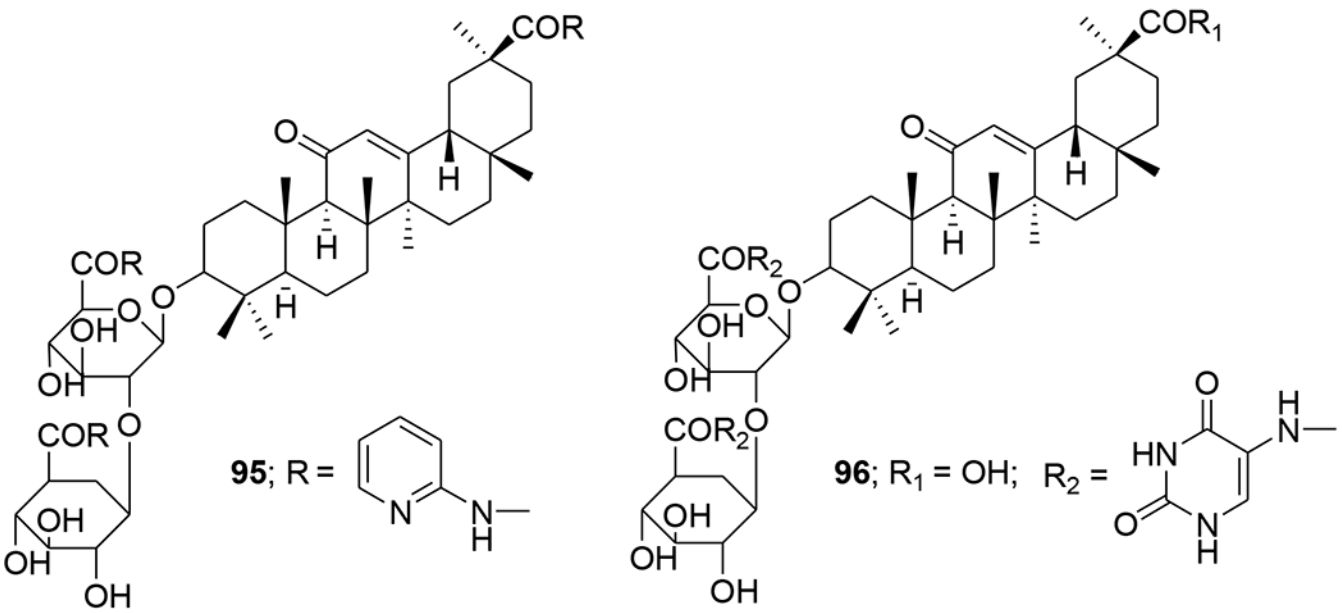


FIGURE 20.
Chemical structures of compounds **95** and **96**

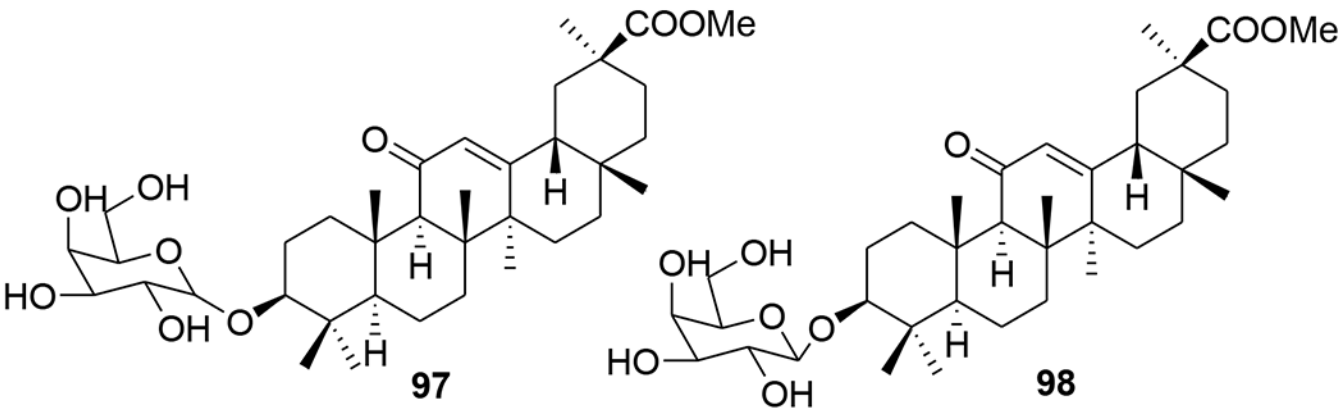


FIGURE 21.
Chemical structures of compounds **97** and **98**

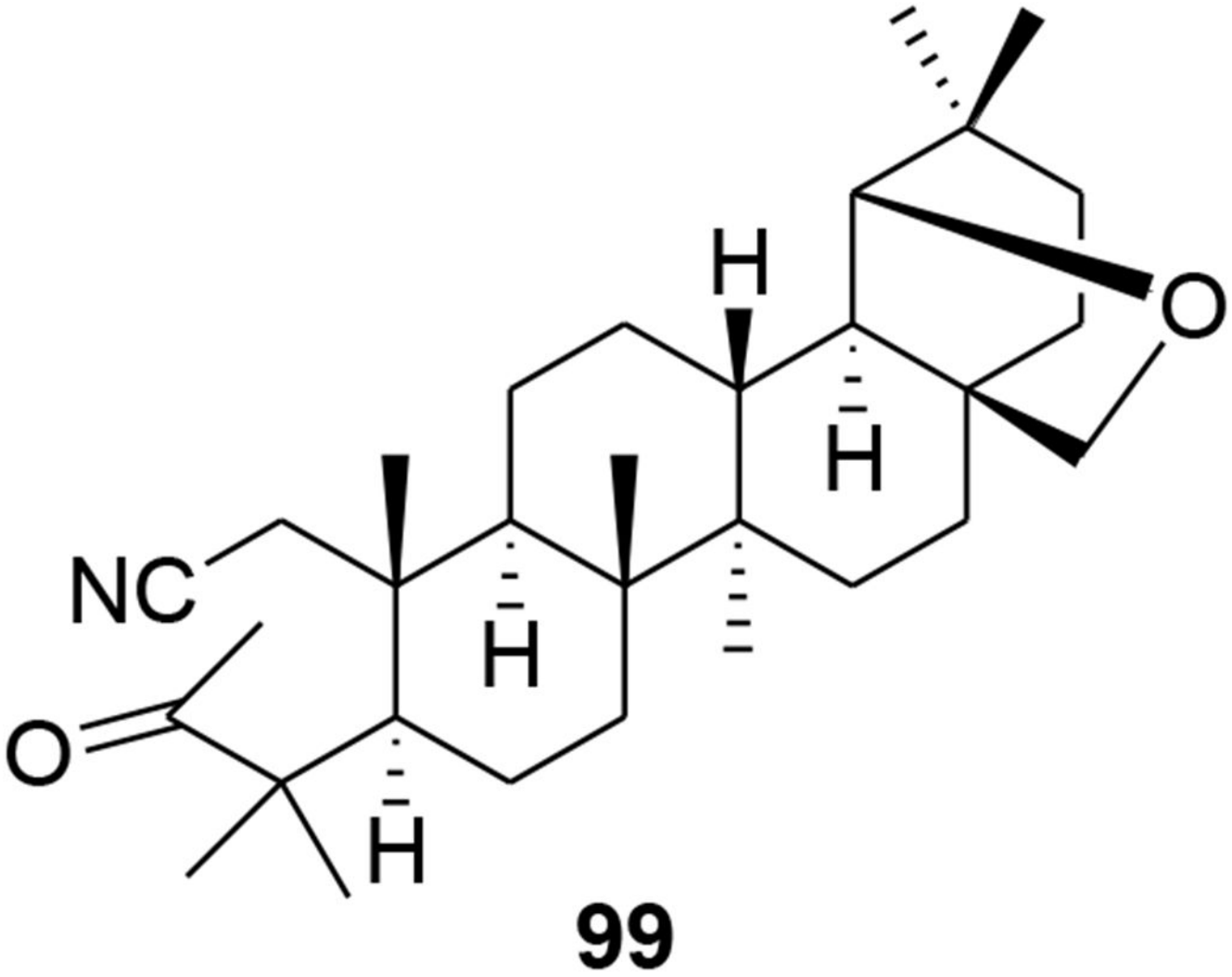


FIGURE 22.
Chemical structure of compound **99**

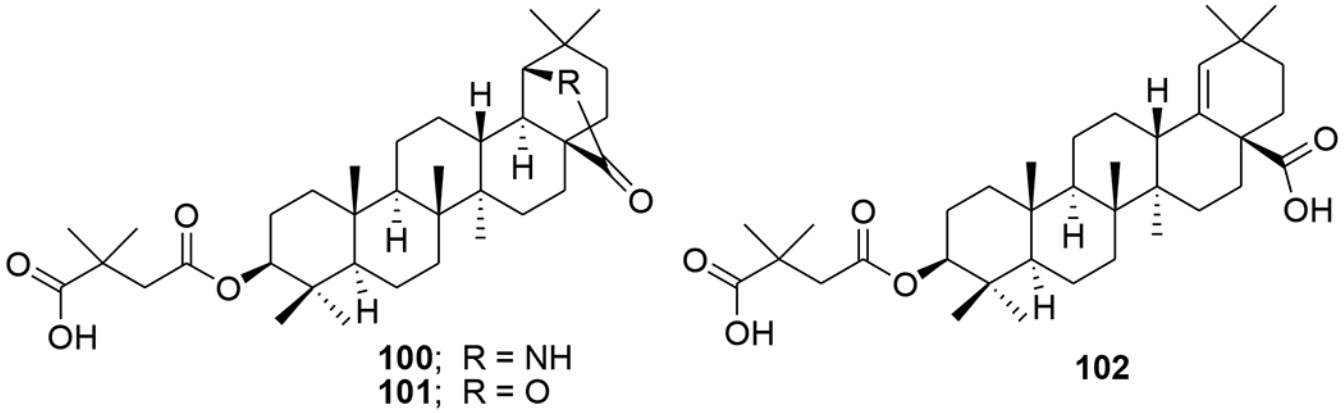


FIGURE 23.
Chemical structures of compounds **100**–**102**

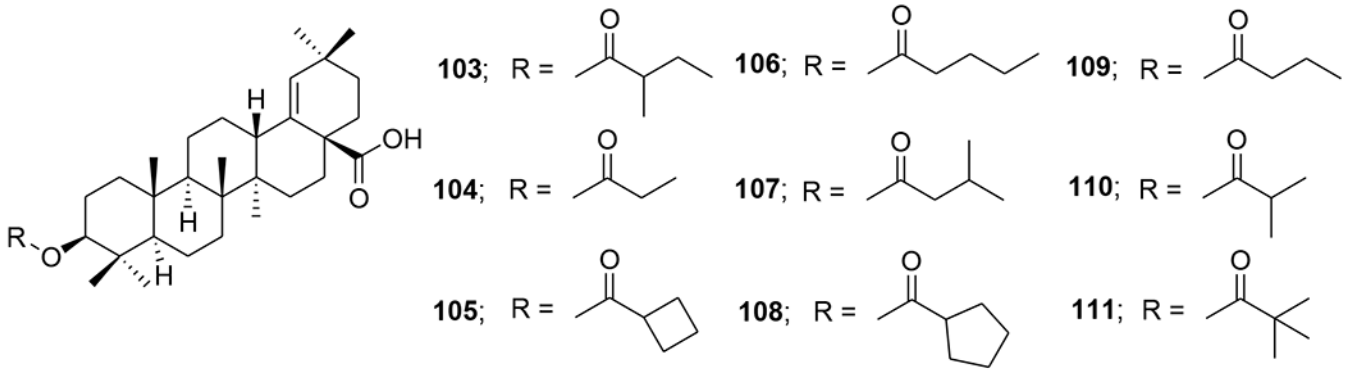


FIGURE 24.
Chemical structures of compounds **103**–**111**

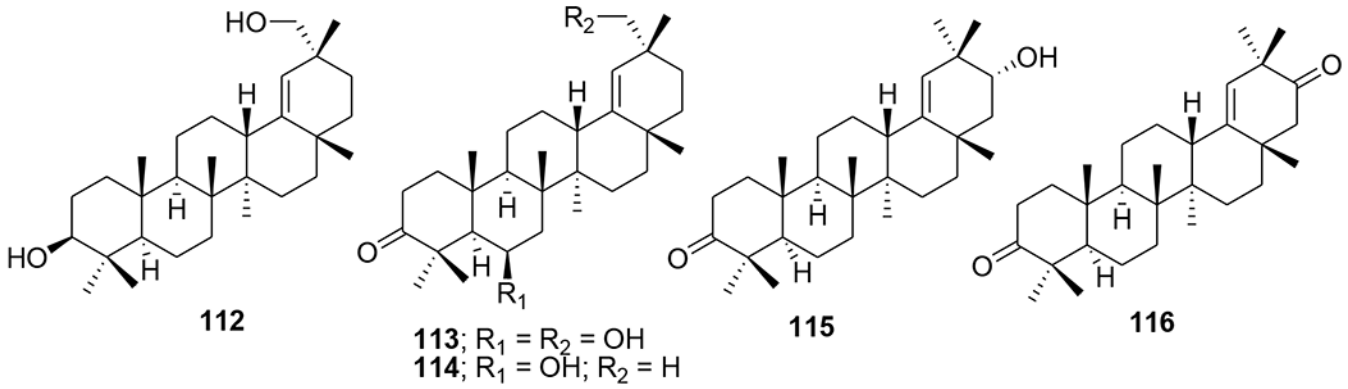


FIGURE 25.
Chemical structures of compounds **112**–**116**

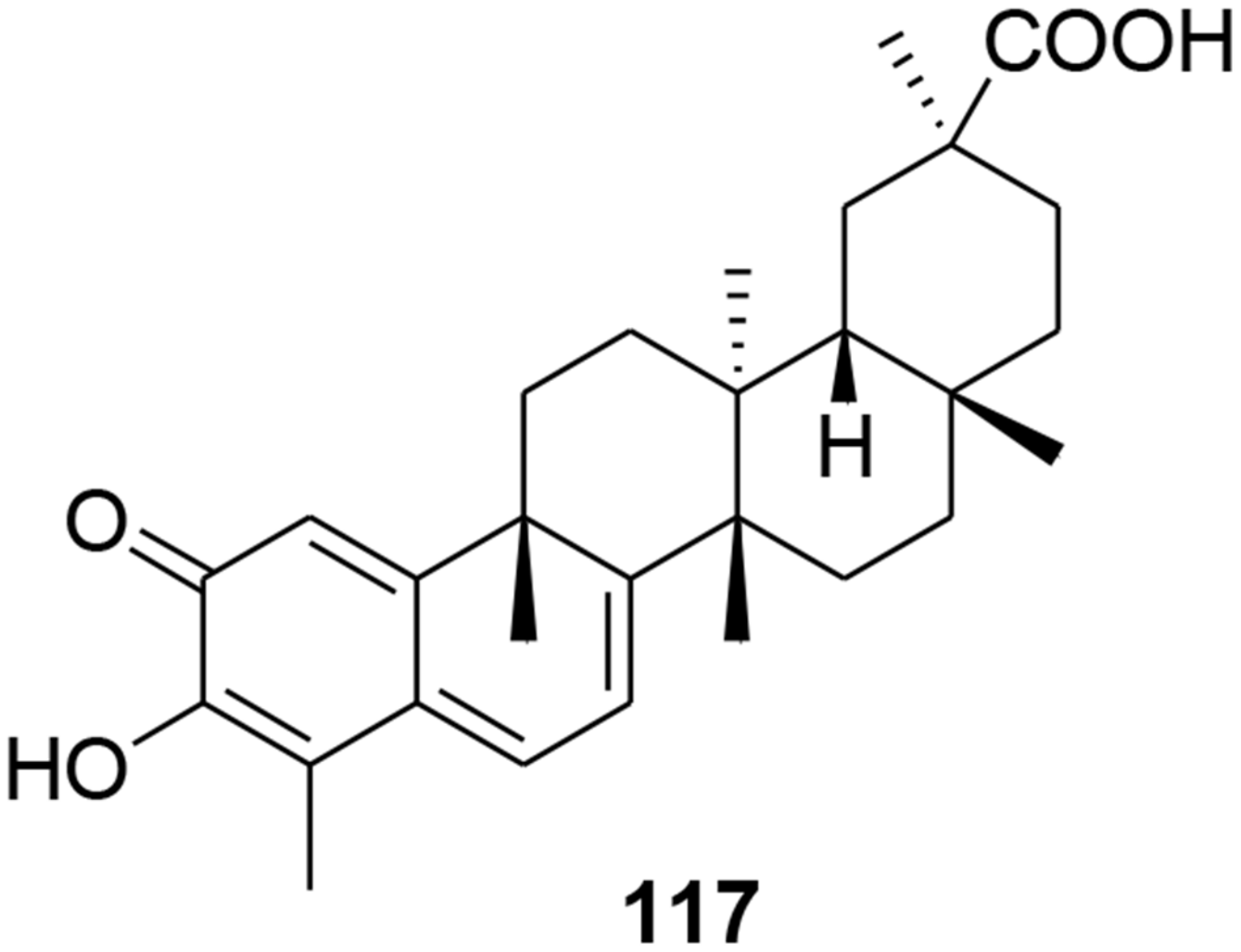


FIGURE 26.
Chemical structure of compound **117**

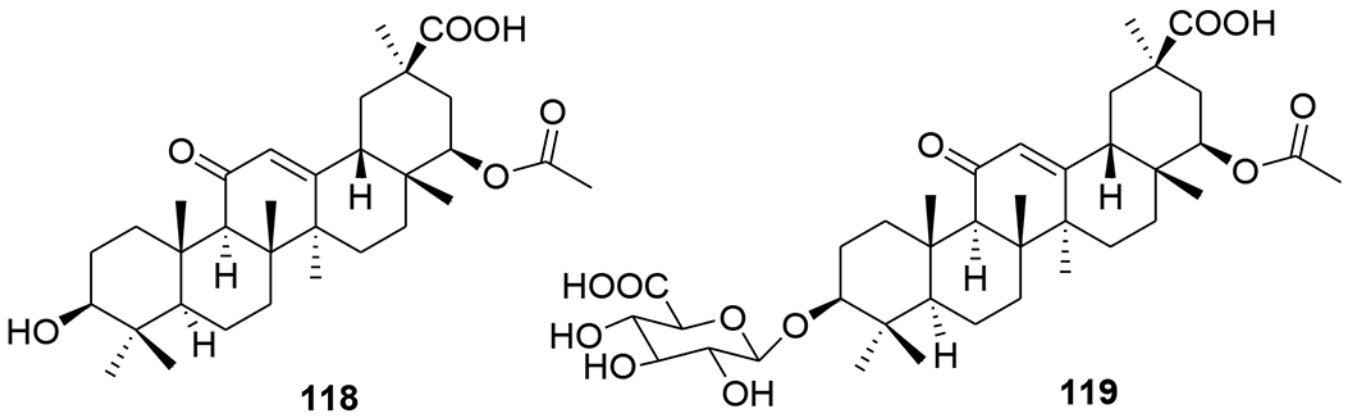


FIGURE 27.
Chemical structures of compounds **118** and **119**

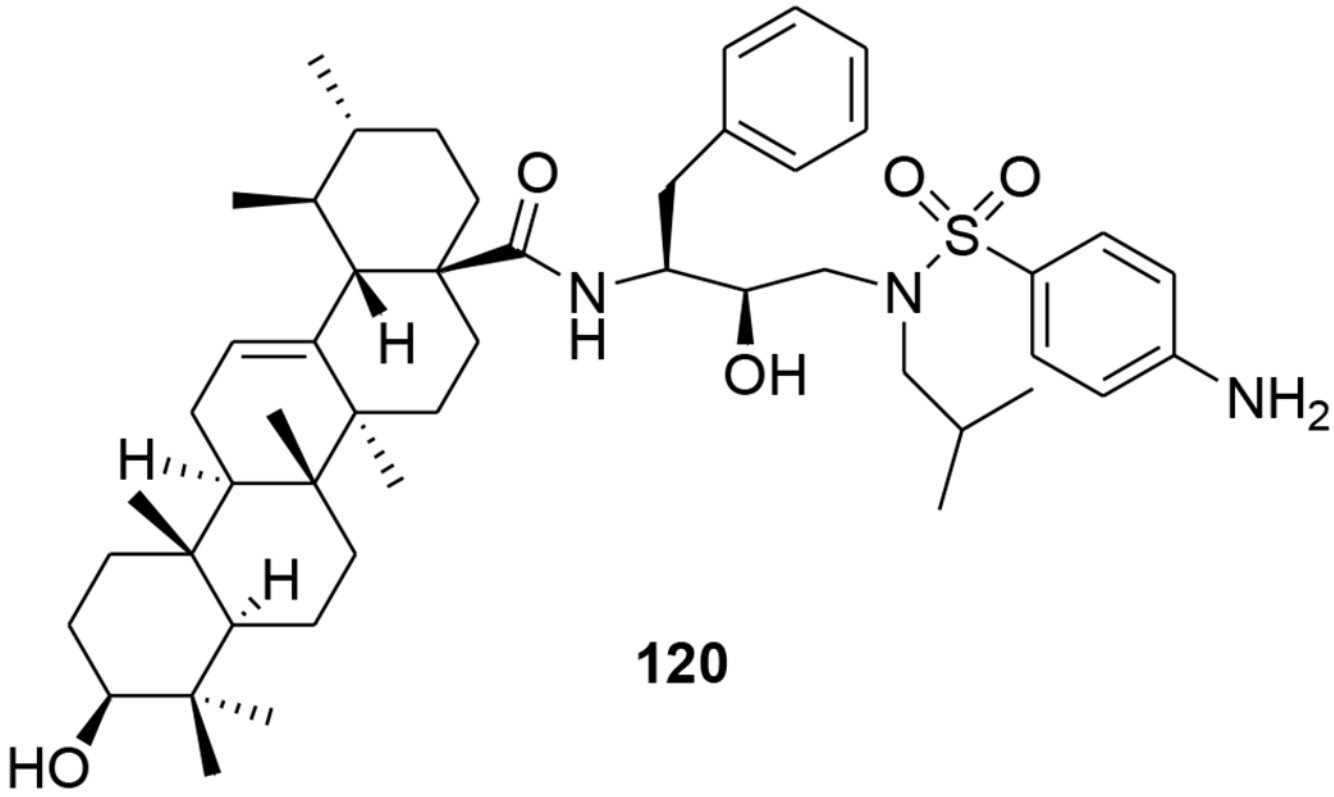


FIGURE 28.
Chemical structure of compound **120**

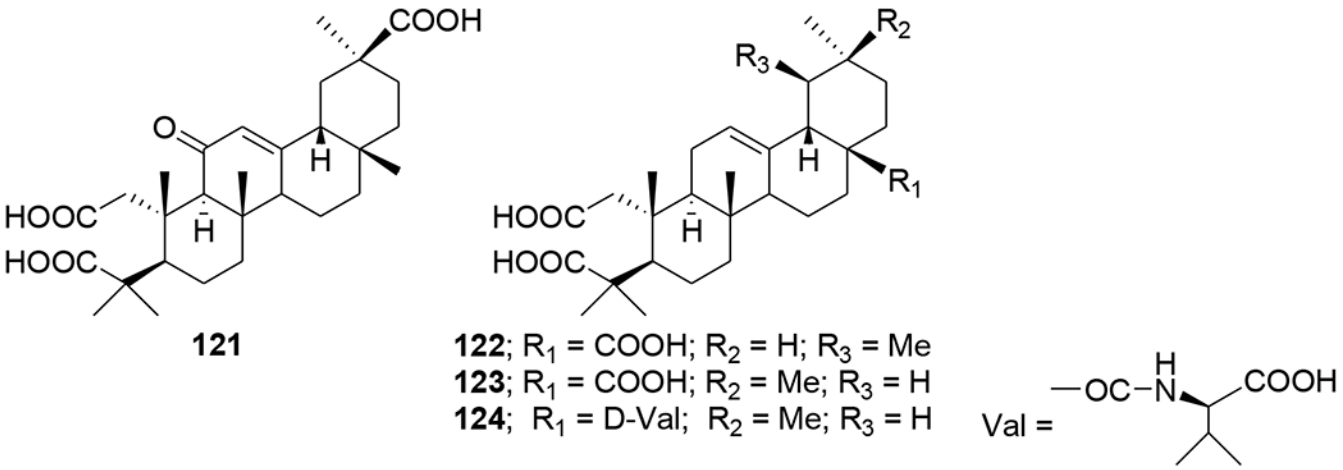


FIGURE 29.
Chemical structures of compounds **121**–**124**

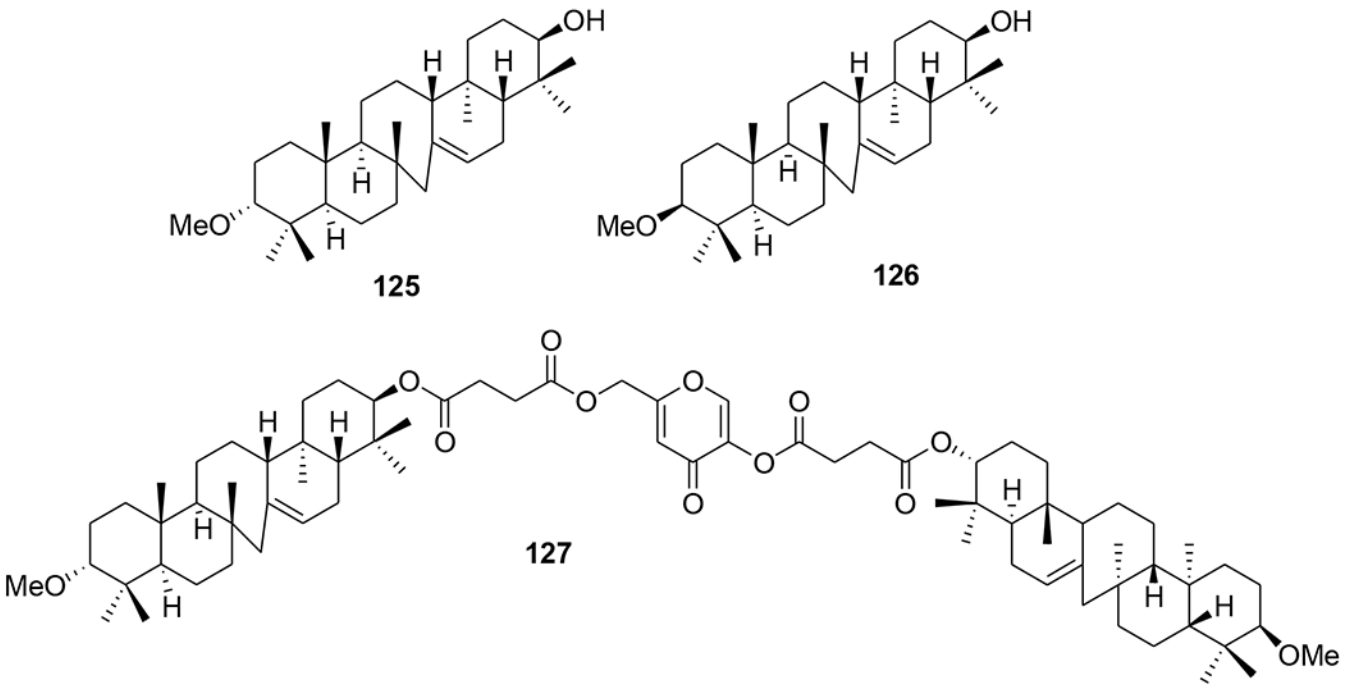


FIGURE 30.
Chemical structures of compounds **125–127**

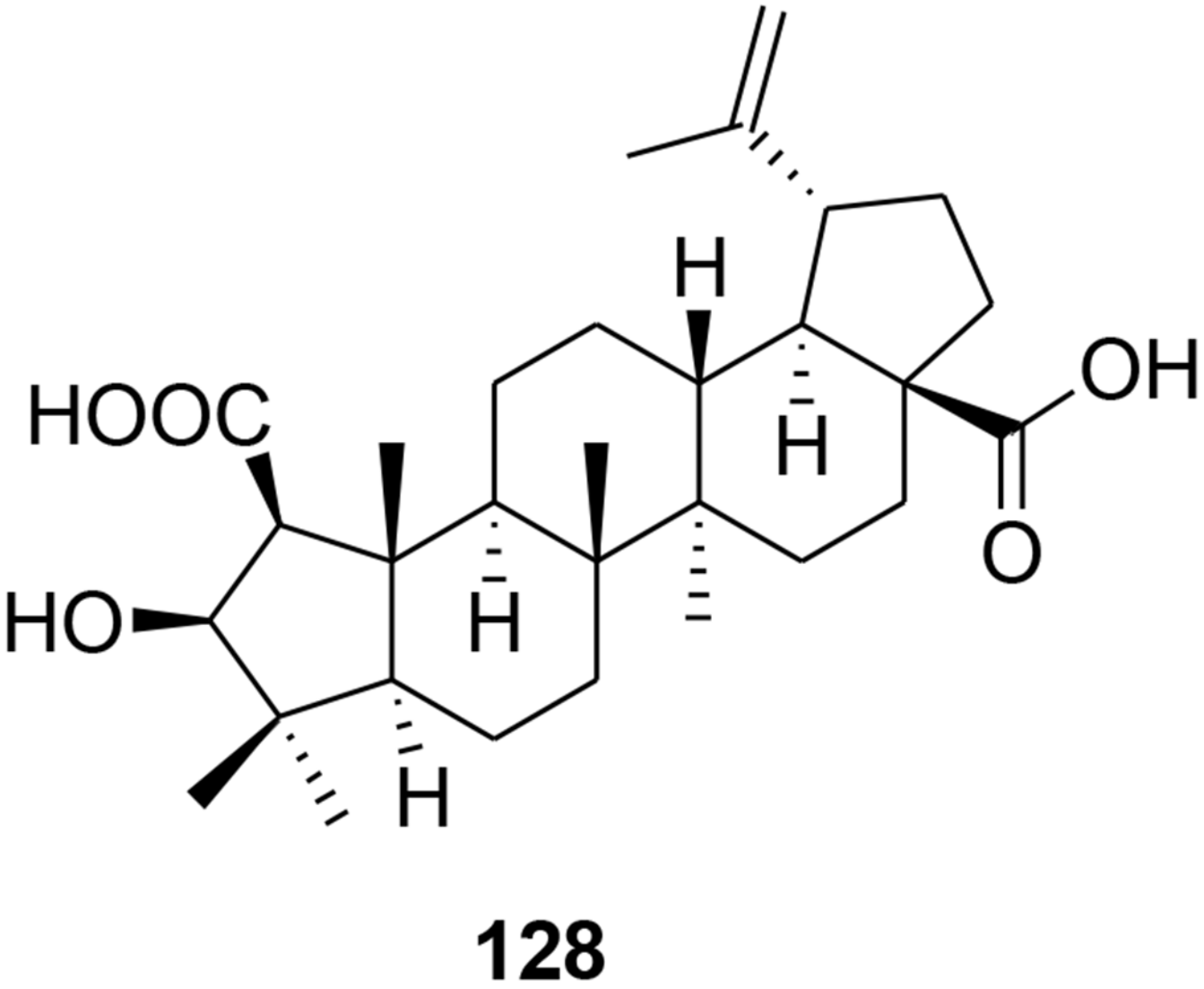


FIGURE 31.
Chemical structure of compound **128**

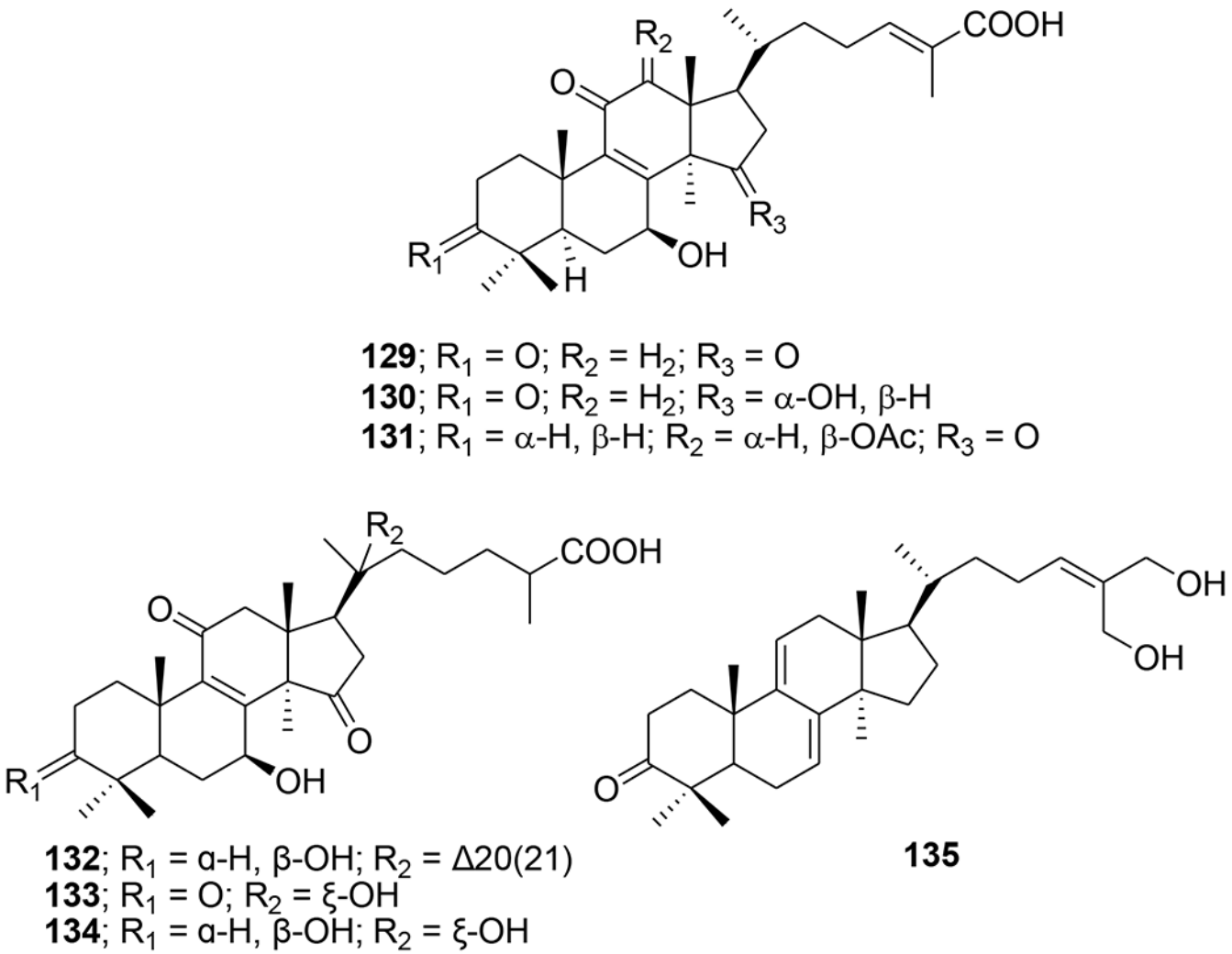


FIGURE 32.
Chemical structures of compounds **129**–**135**

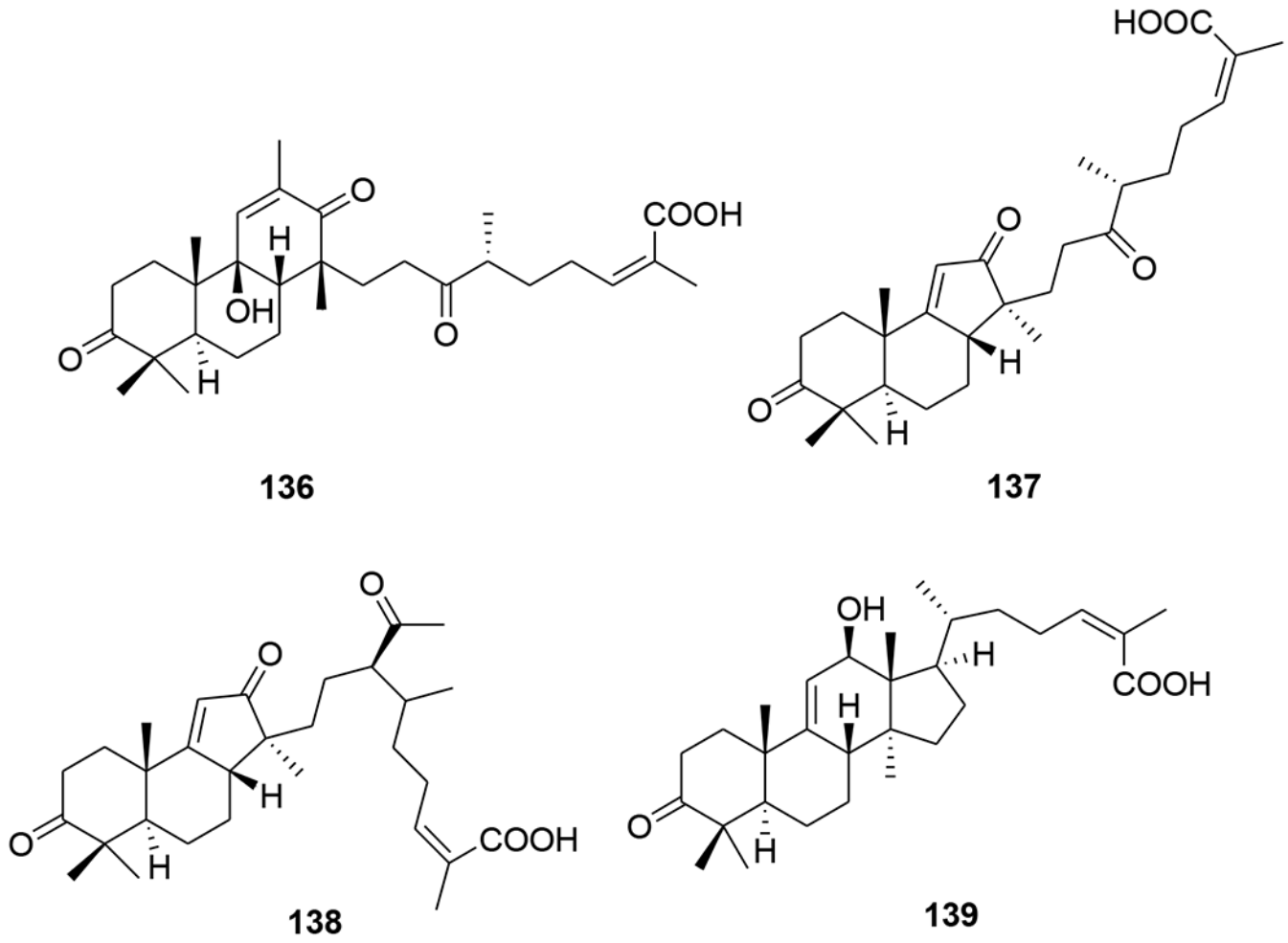


FIGURE 33.
Chemical structures of compounds **136–139**

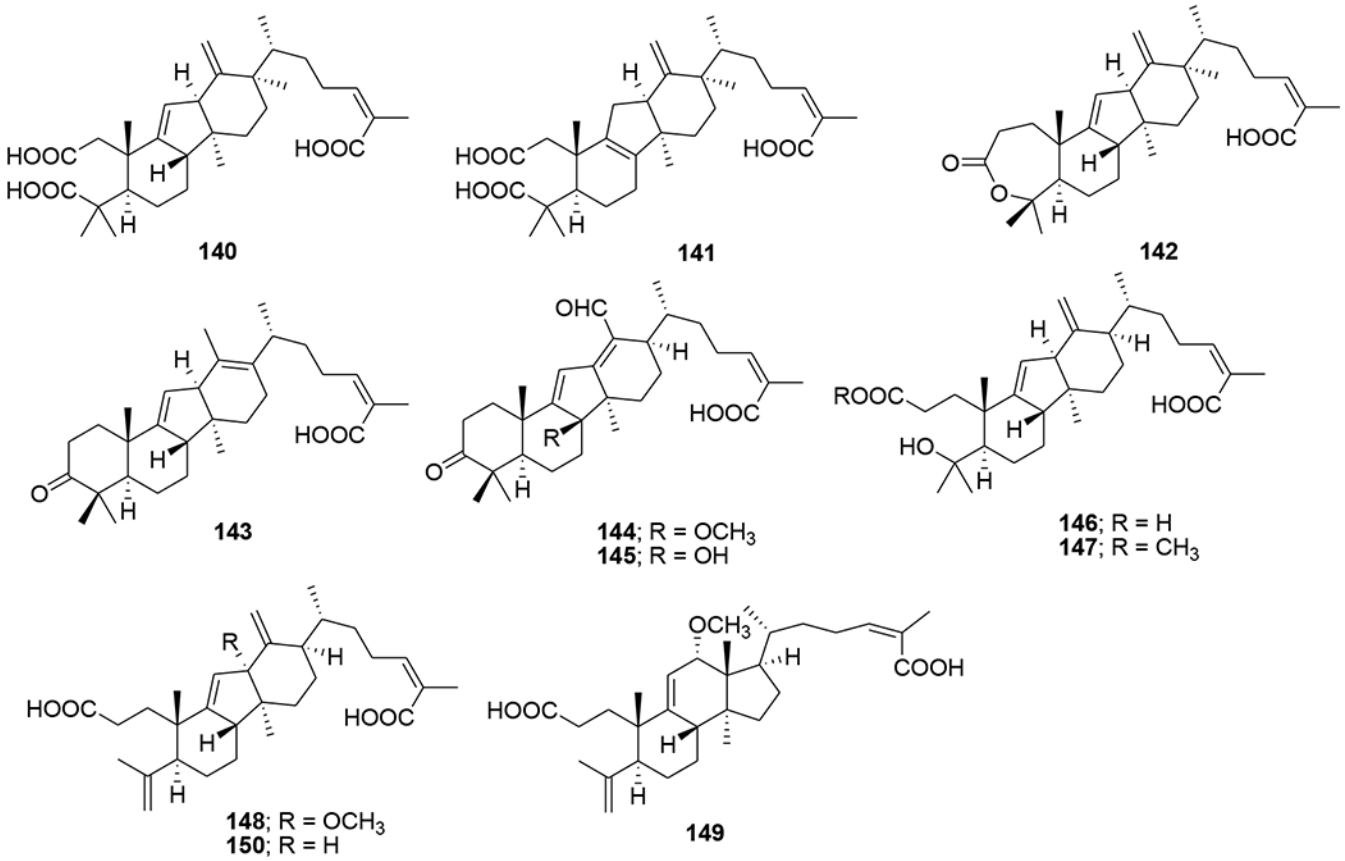


FIGURE 34.
Chemical structures of compounds **140**–**150**

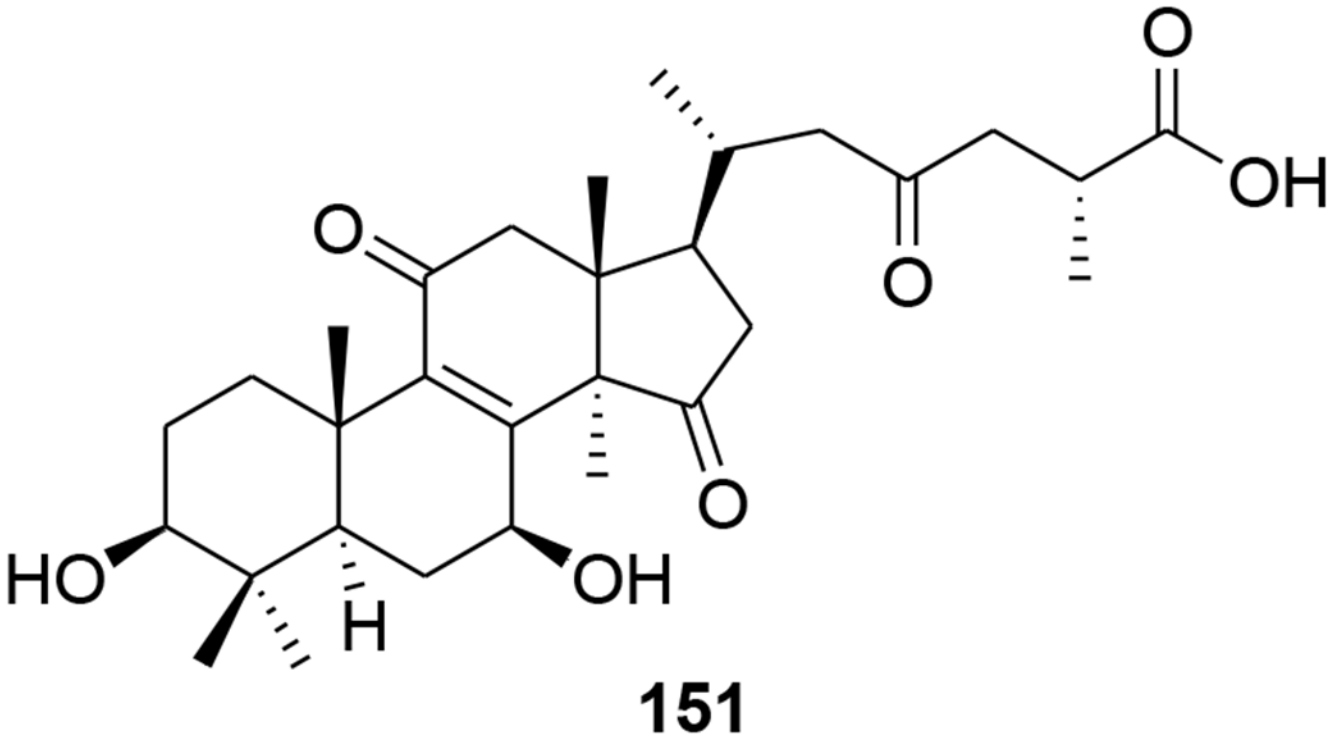


FIGURE 35.
Chemical structure of compound **151**

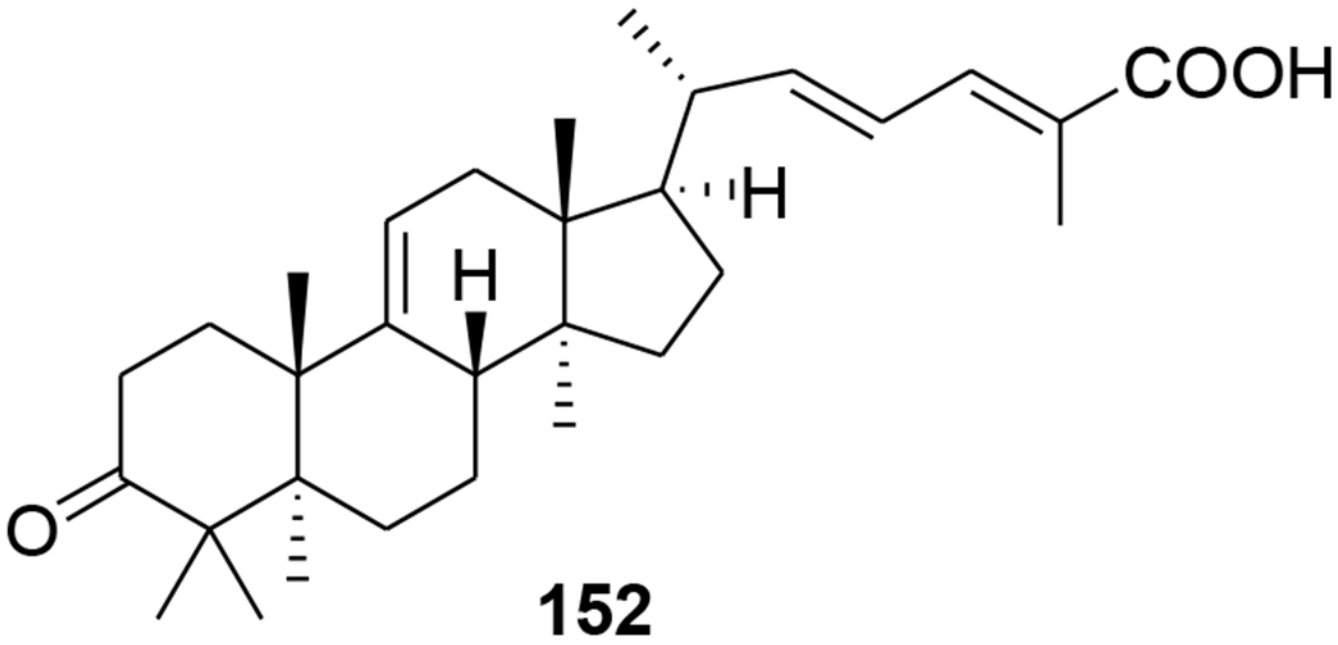


FIGURE 36.
Chemical structure of compound **152**

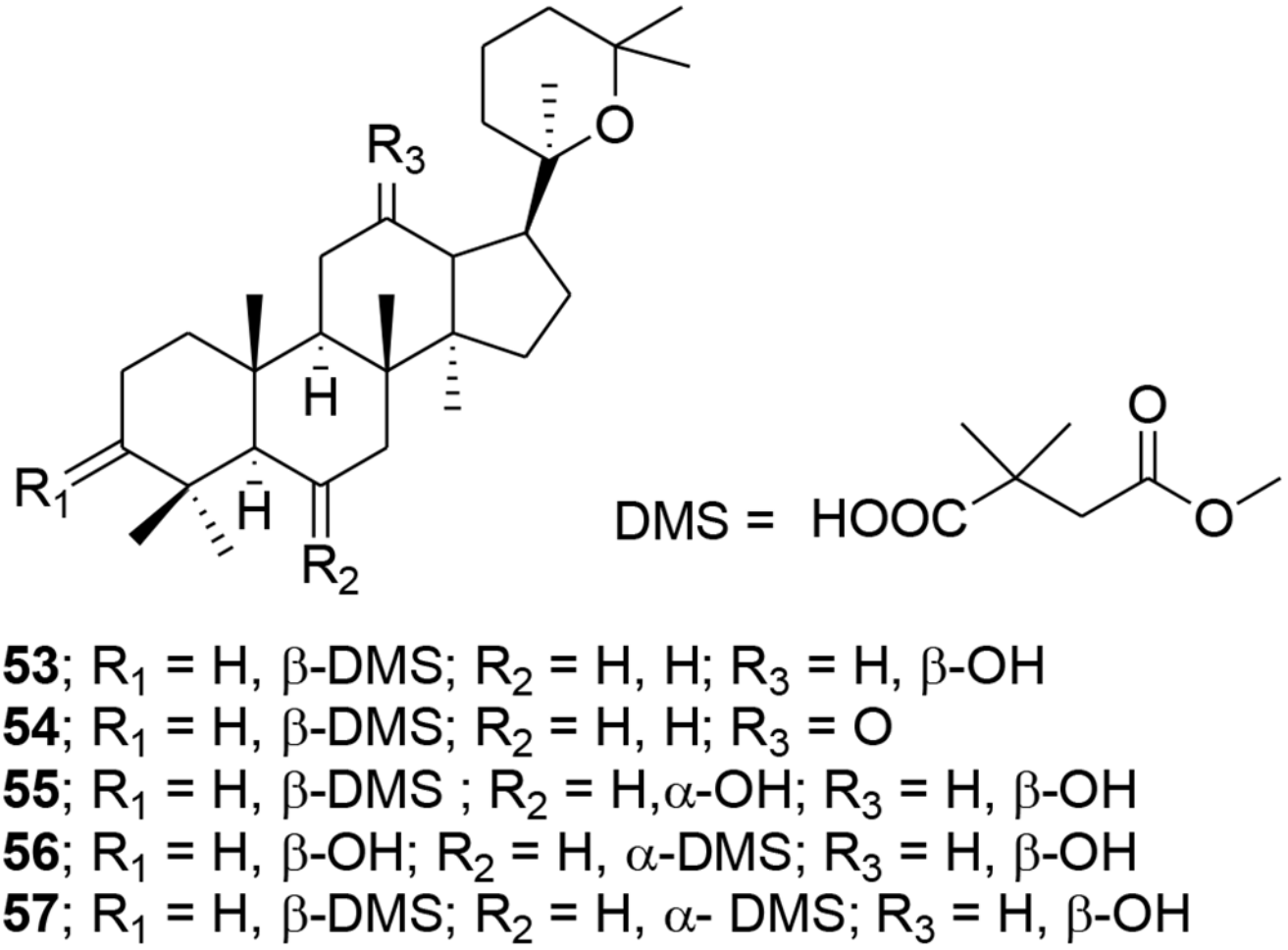


FIGURE 37.
Chemical structures of compounds **153–157**

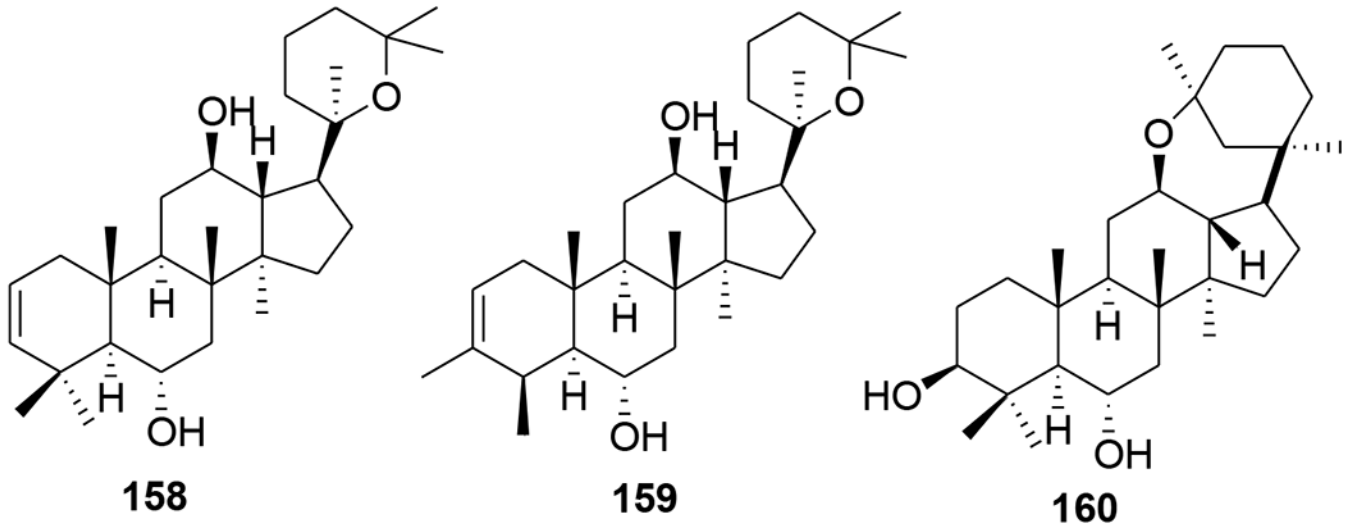


FIGURE 38.
Chemical structures of compounds **158**–**160**

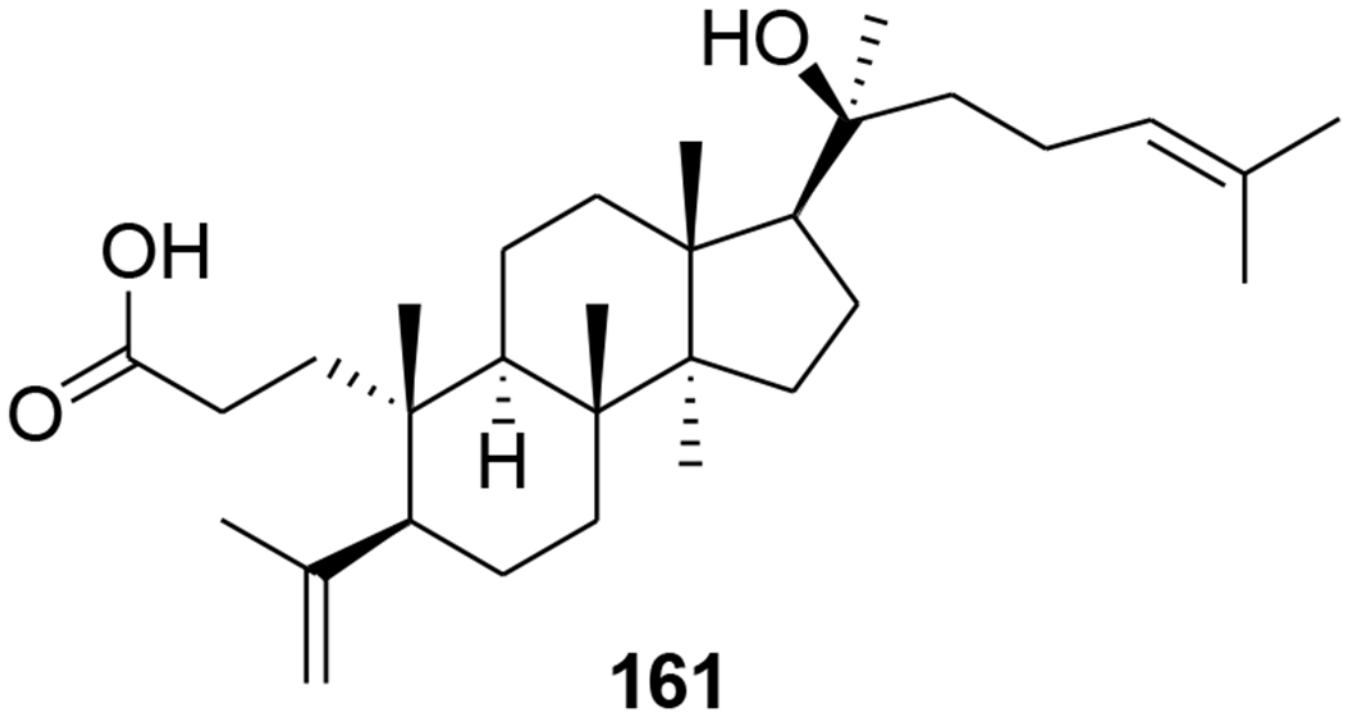


FIGURE 39.
Chemical structure of compound **161**

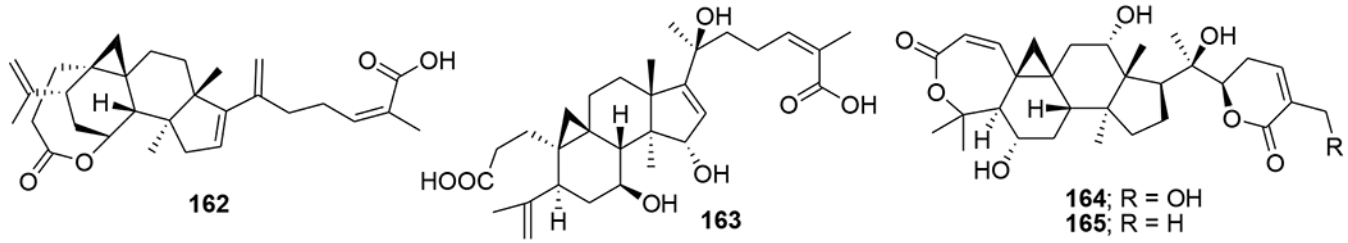
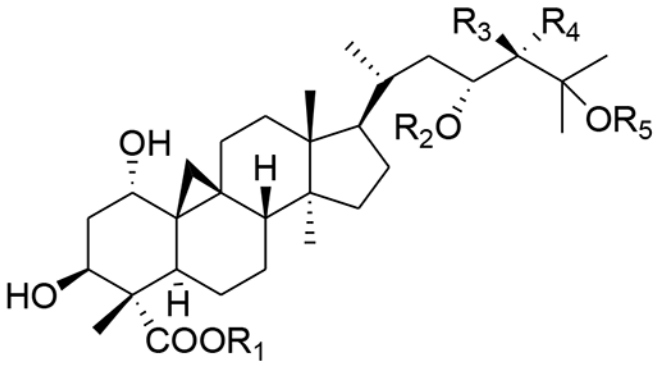
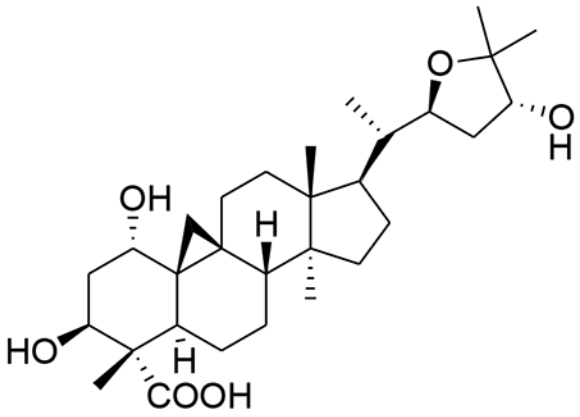


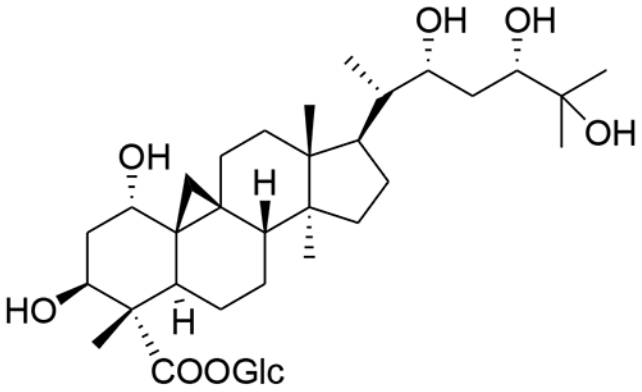
FIGURE 40.
Chemical structures of compounds **162**–**165**



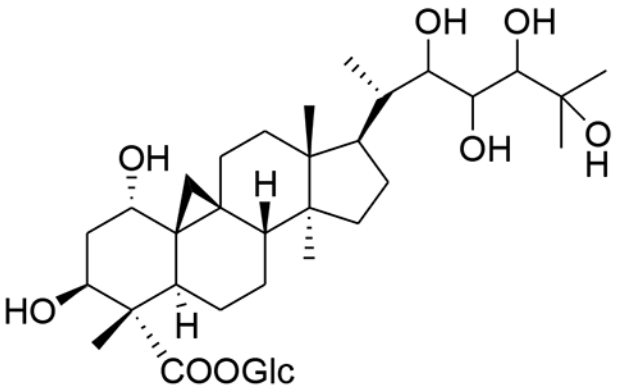


166; $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = OH$
168; $R_1 = Glc$; $R_2 = R_4 = R_5 = H$; $R_3 = OH$
169; $R_1 = R_4 = R_5 = H$; $R_2 = Glc$; $R_3 = OH$
170; $R_1 = Glc$; $R_2 = R_3 = H$; $R_4 = OH$; $R_5 = CH_3$

167



171



172

FIGURE 41.
Chemical structures of compounds **166**–**172**

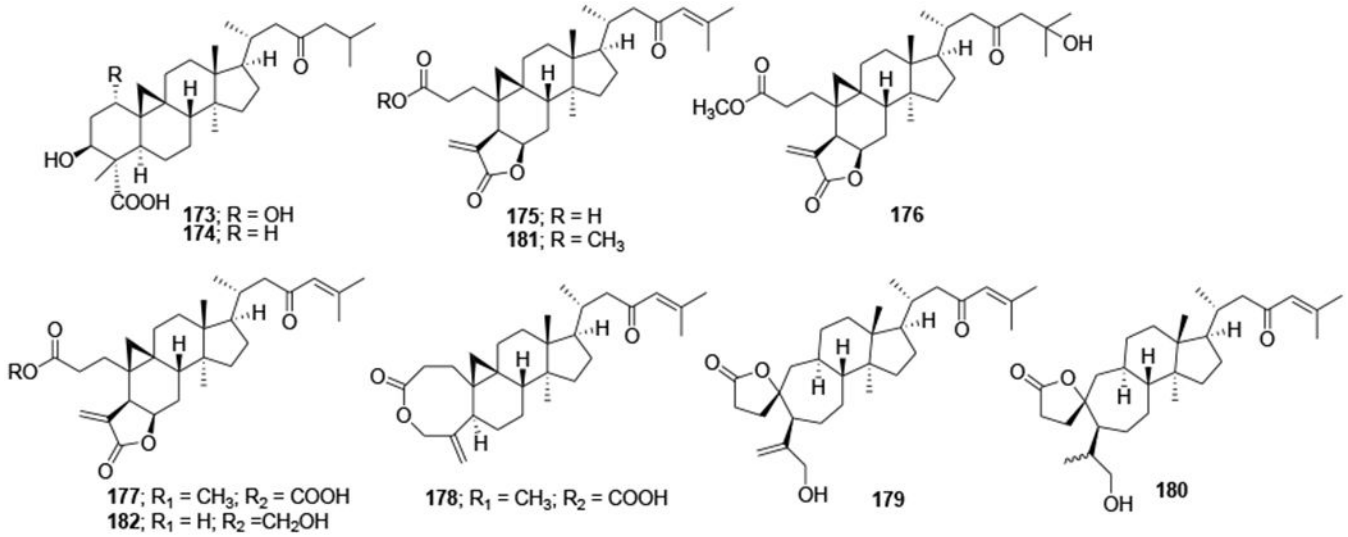


FIGURE 42.
Chemical structures of compounds **173**–**182**

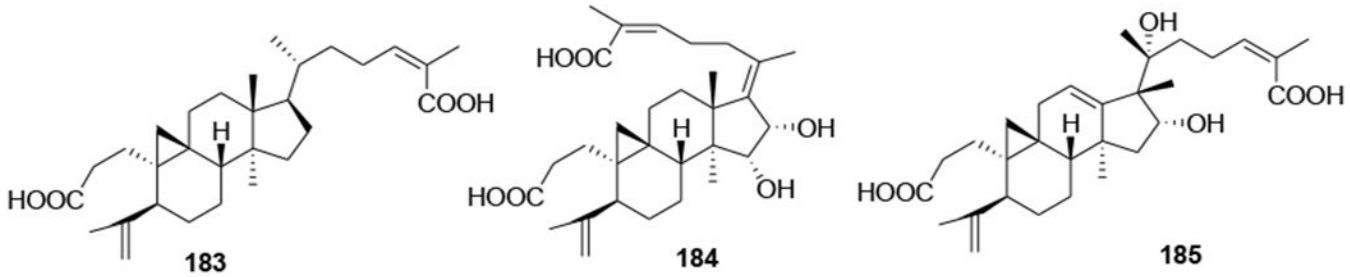


FIGURE 43.
Chemical structures of compounds **183**–**185**

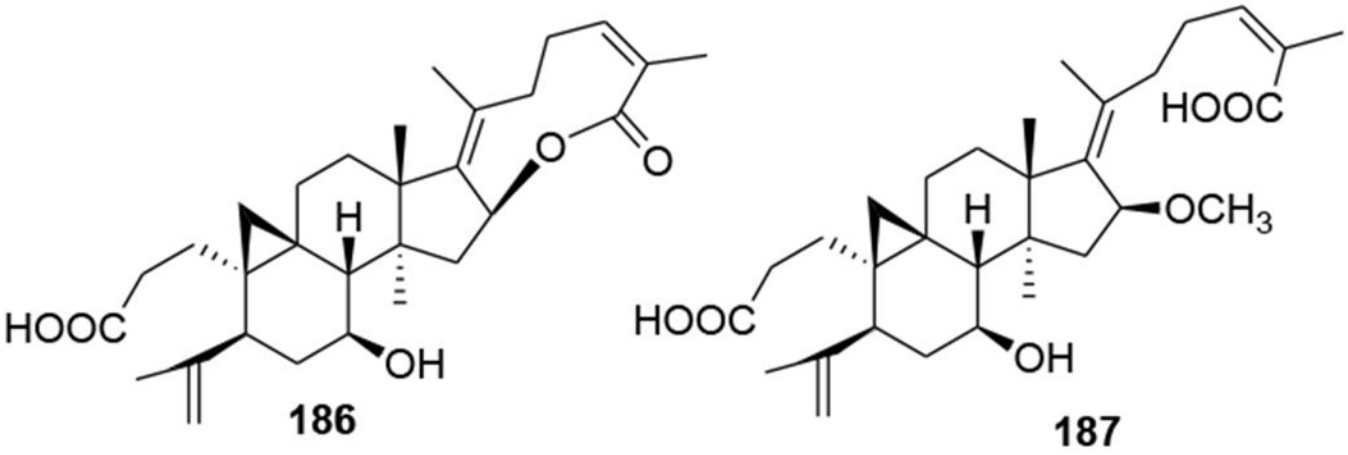


FIGURE 44.
Chemical structures of compounds **186** and **187**

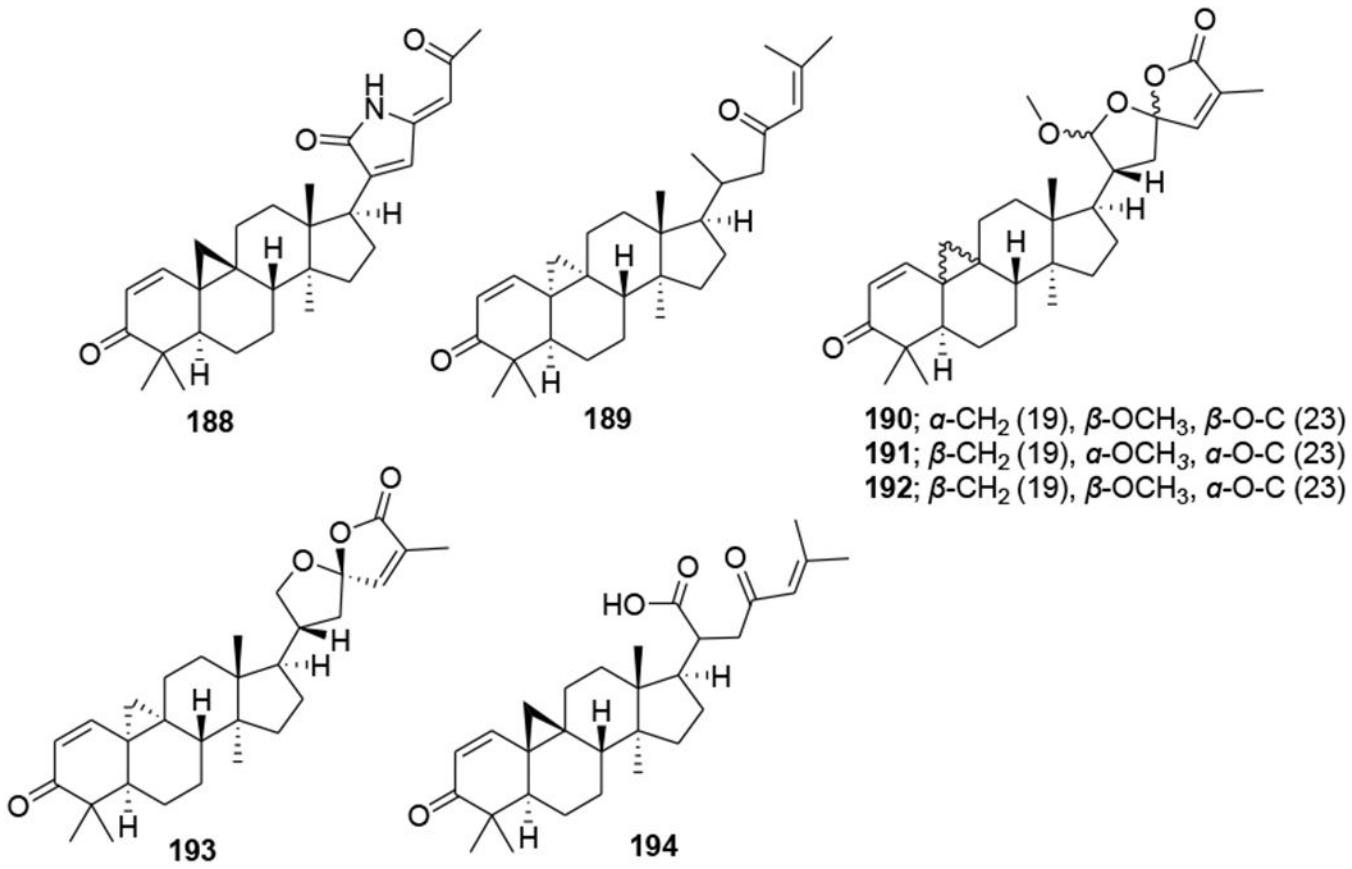


FIGURE 45.
Chemical structures of compounds **188**–**194**

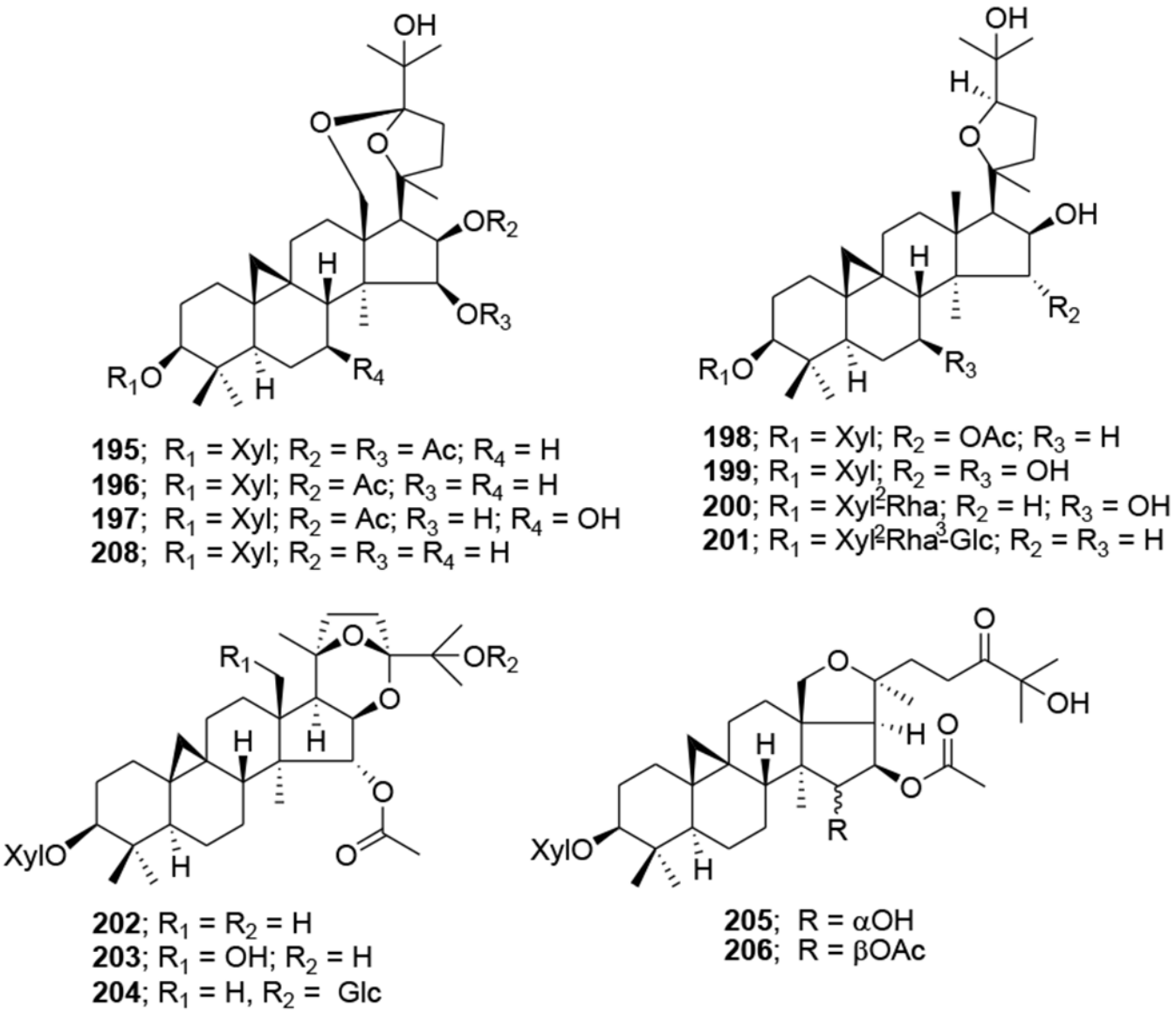


FIGURE 46.

Chemical structures of compounds **195**–**206** and **208**

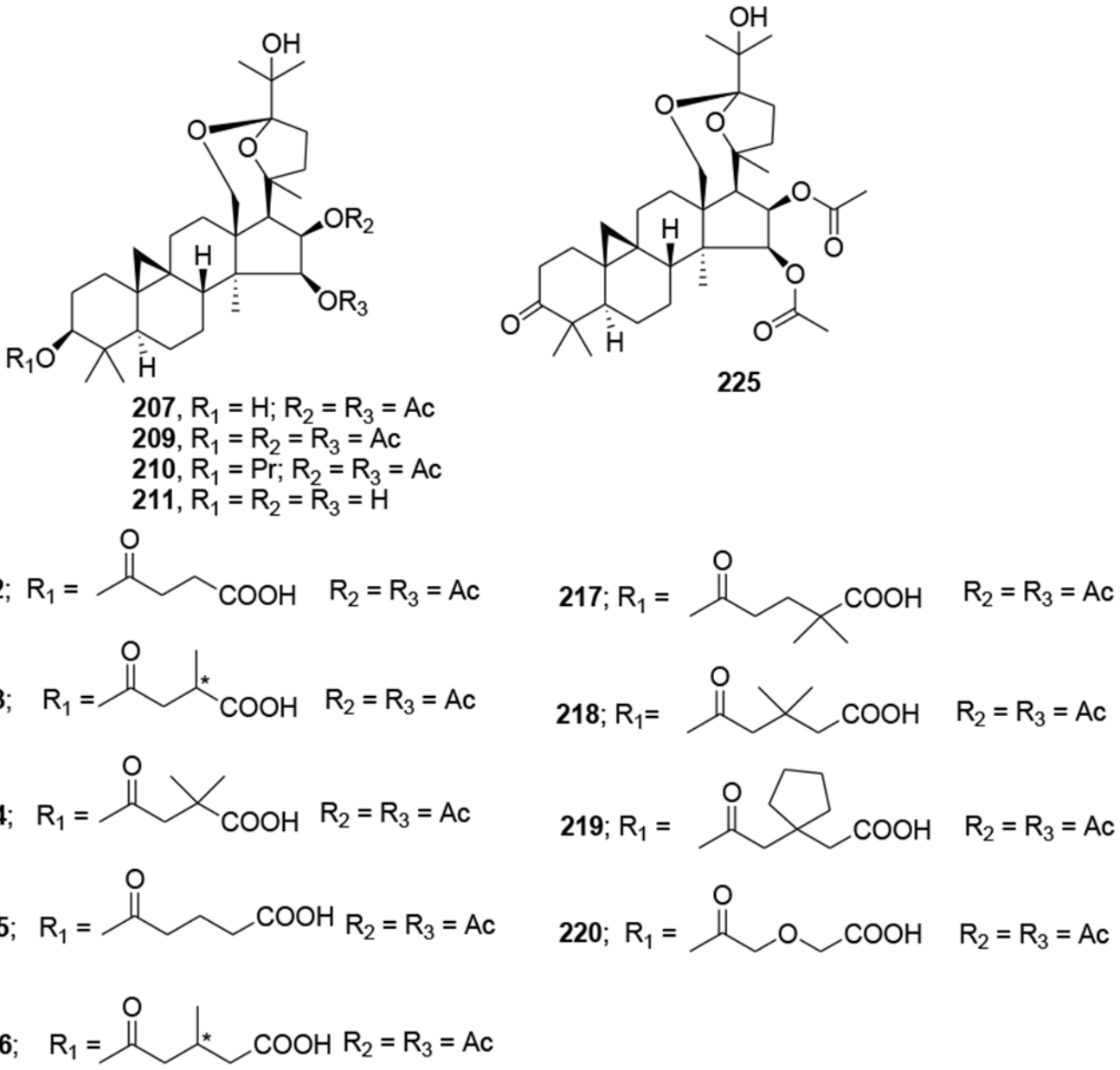


FIGURE 47.
Chemical structures of compounds **207** and **209**–**221**

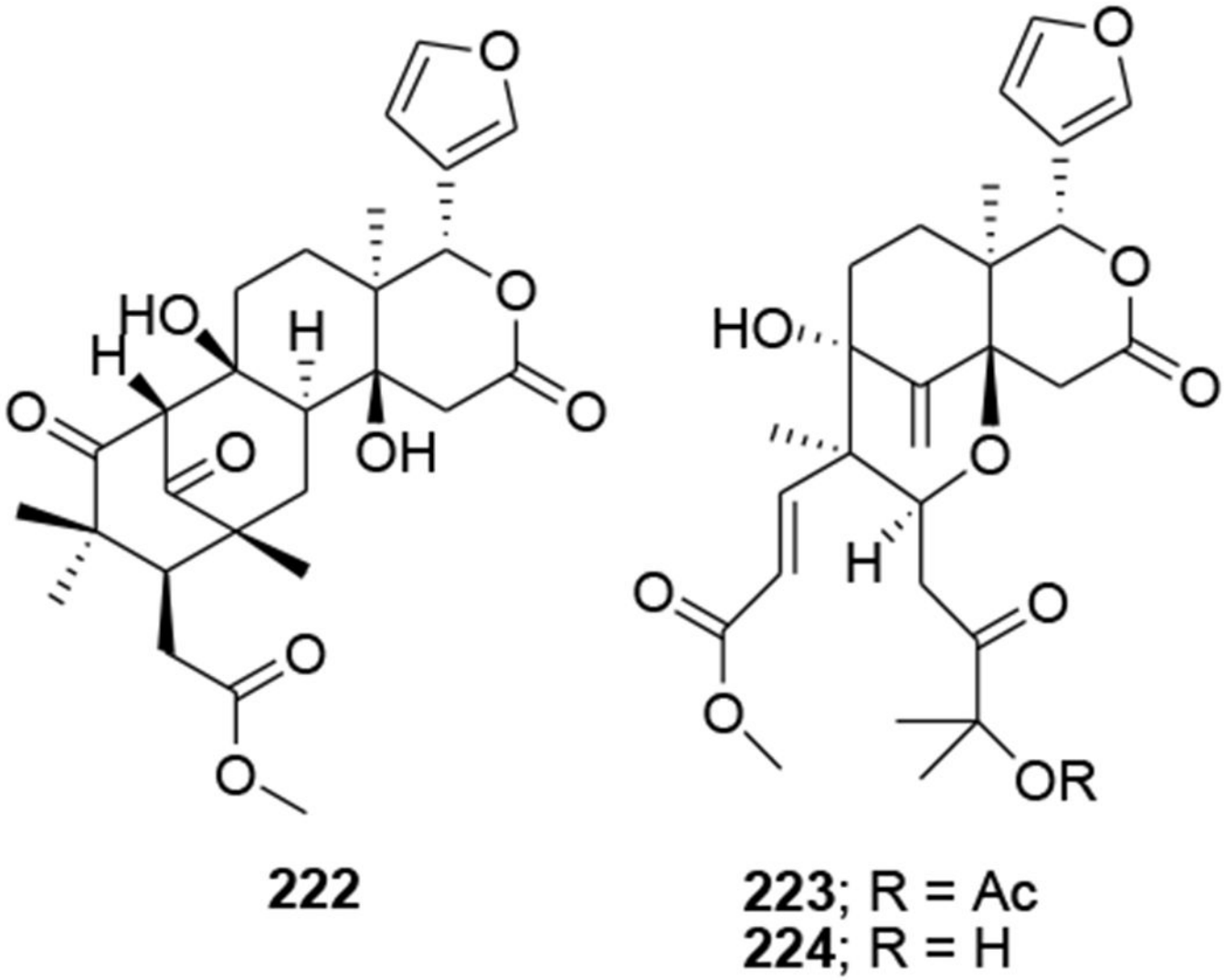


FIGURE 48.
Chemical structures of compounds **222–224**

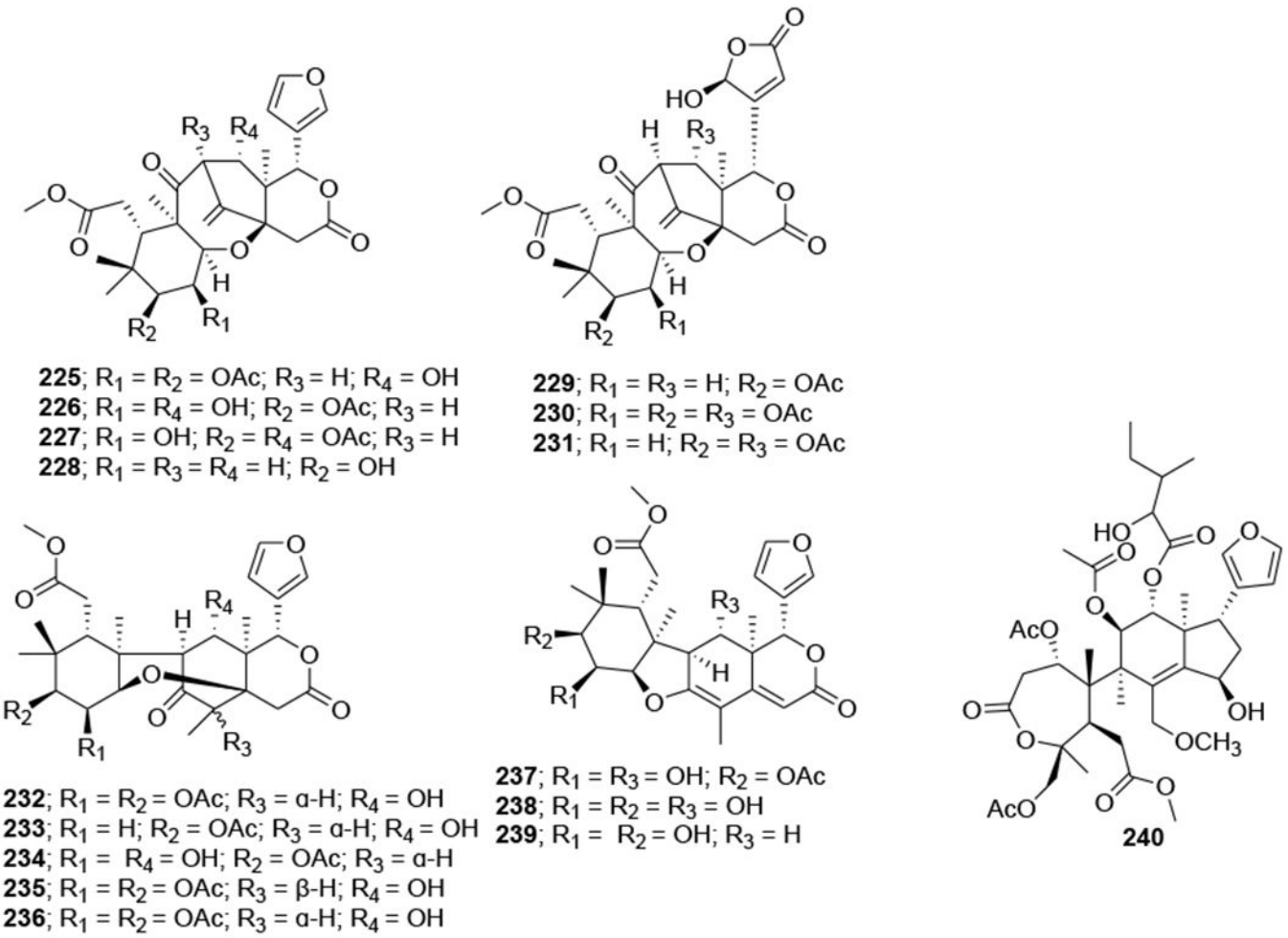


FIGURE 49.
Chemical structures of compounds **225**–**240**

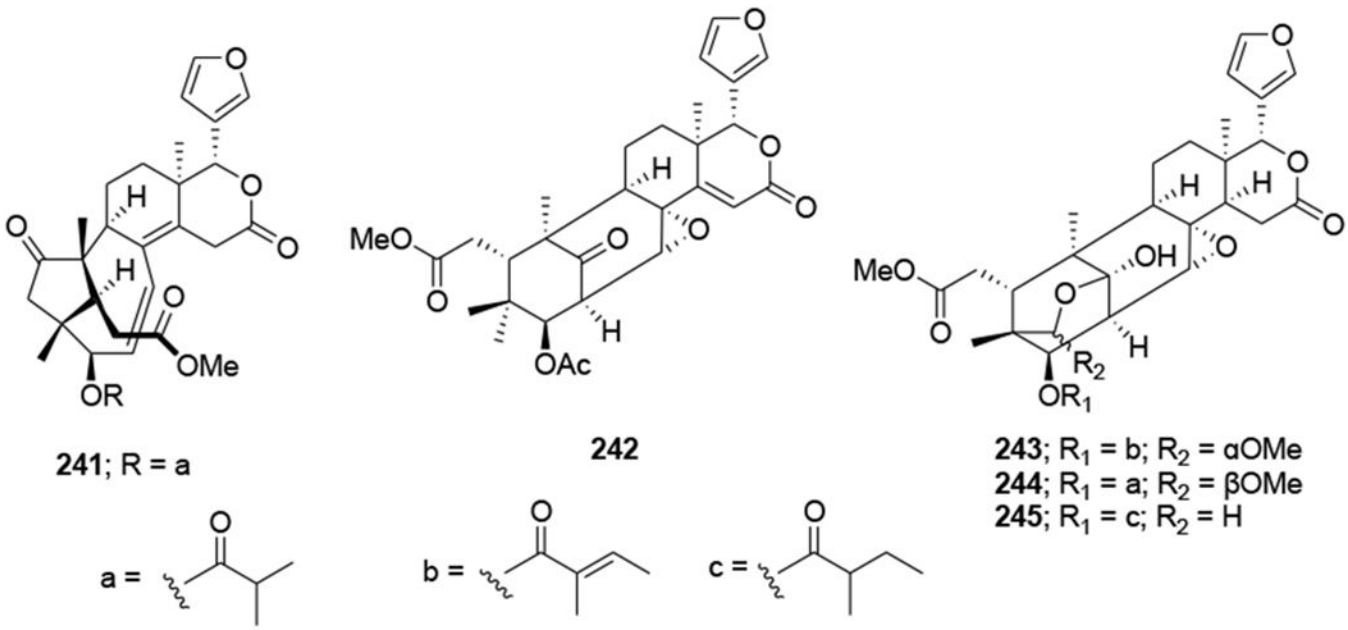


FIGURE 50.
Chemical structures of compounds **241**–**245**

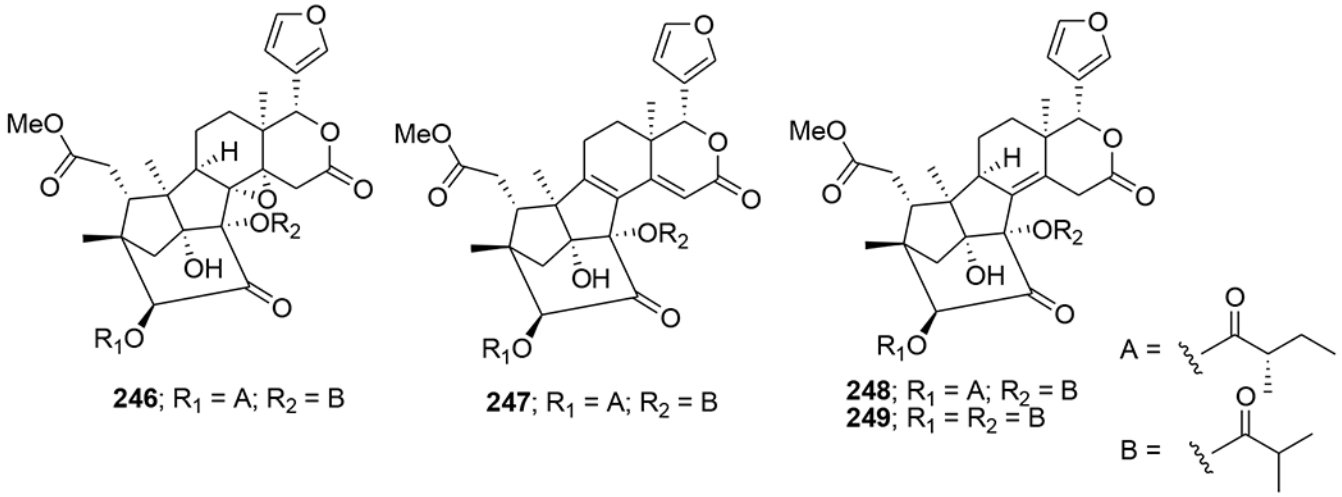


FIGURE 51.
Chemical structures of compounds **246**–**249**

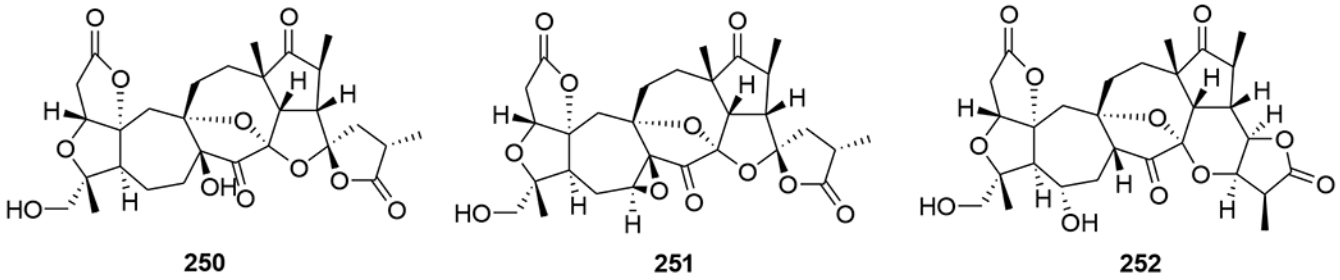


FIGURE 52.
Chemical structures of compounds **250**–**252**

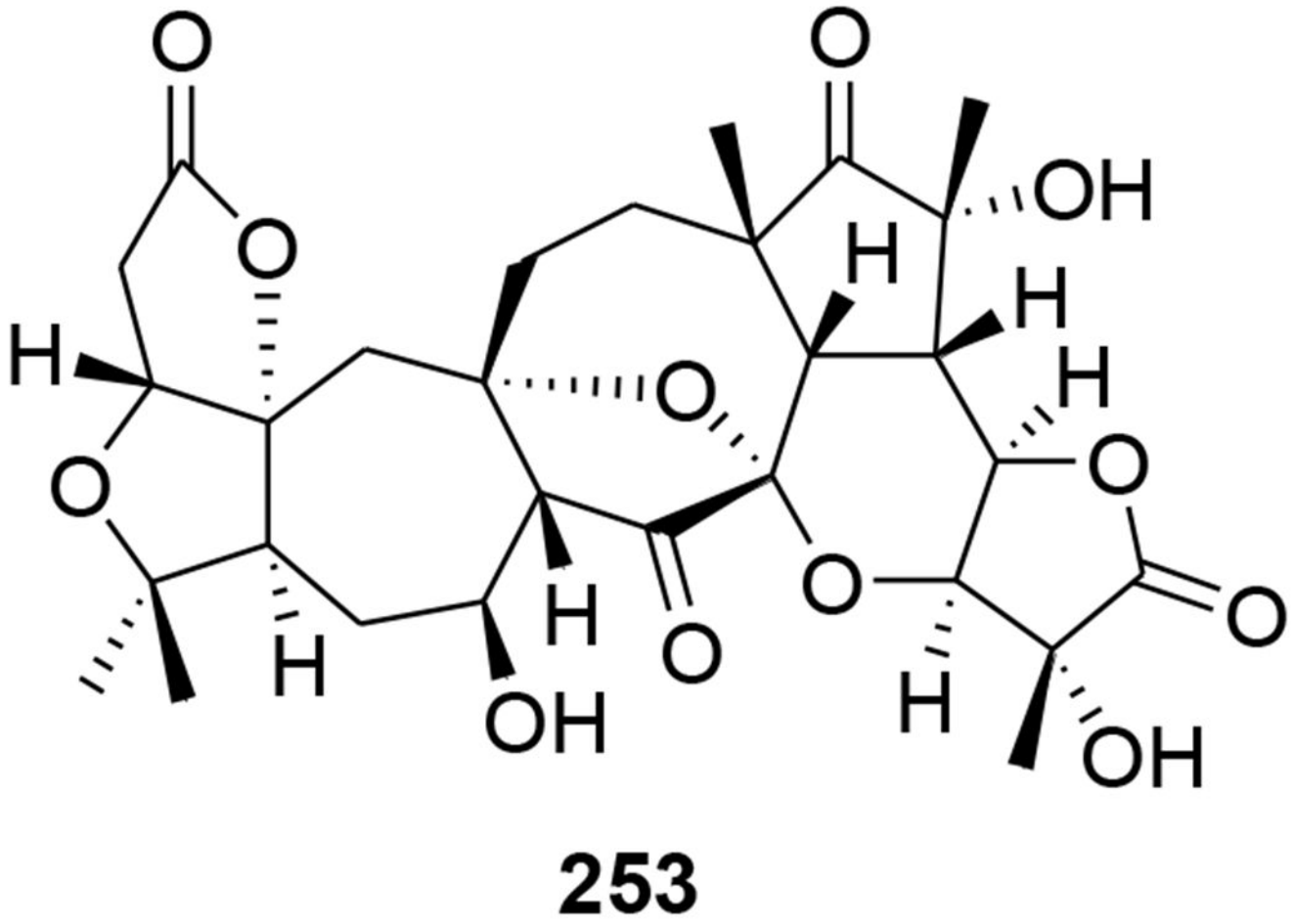


FIGURE 53.
Chemical structure of compound **253**

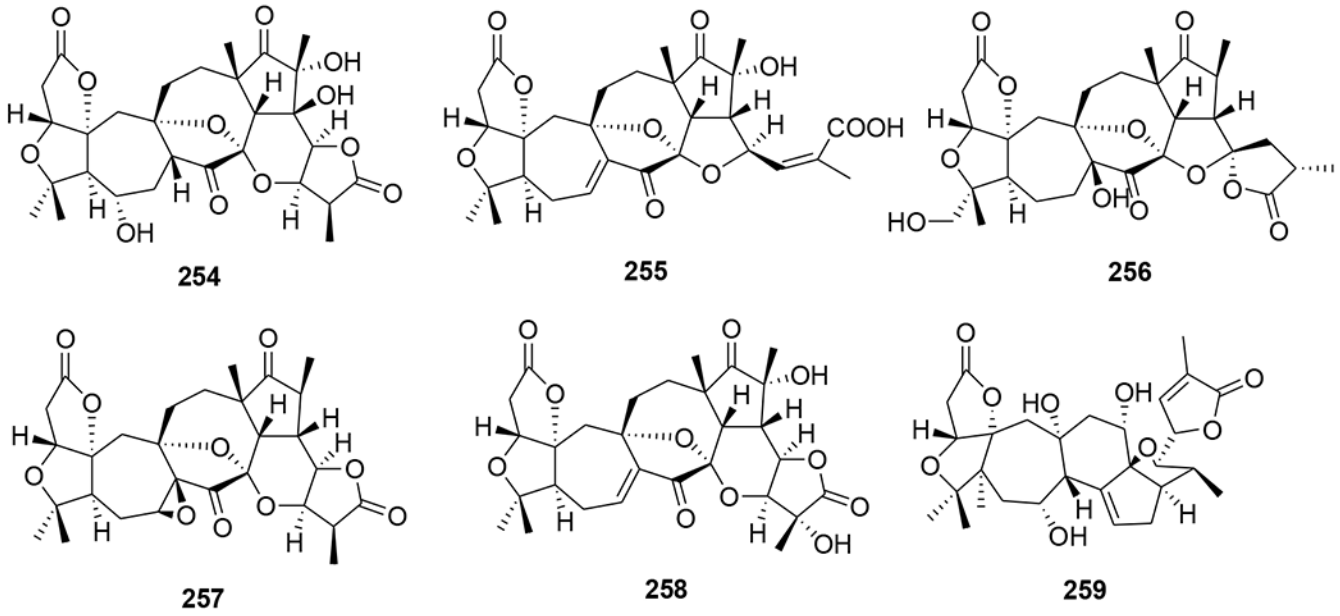
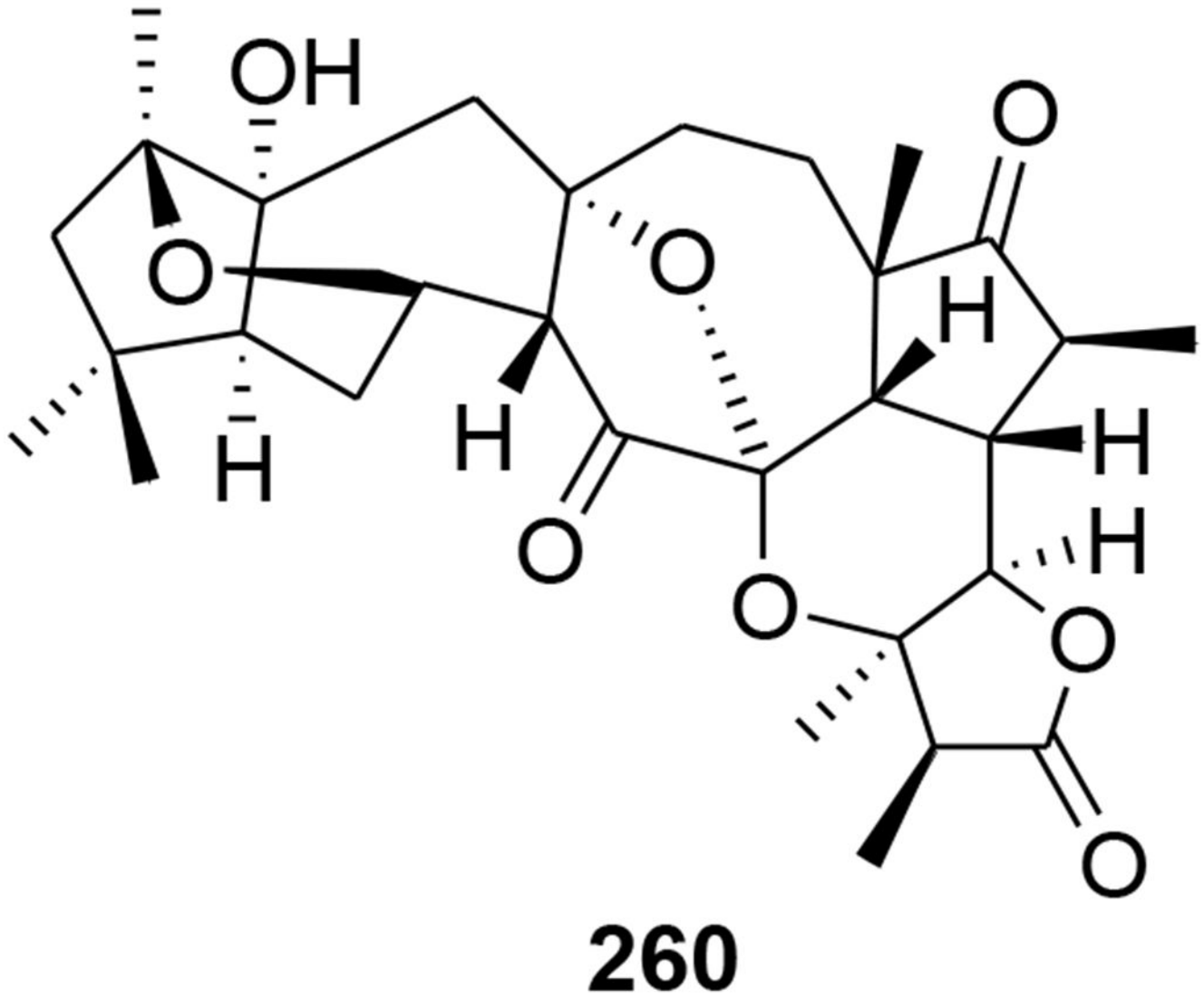


FIGURE 54.
Chemical structures of compounds **254**–**259**



260

FIGURE 55.
Chemical structure of compound **260**

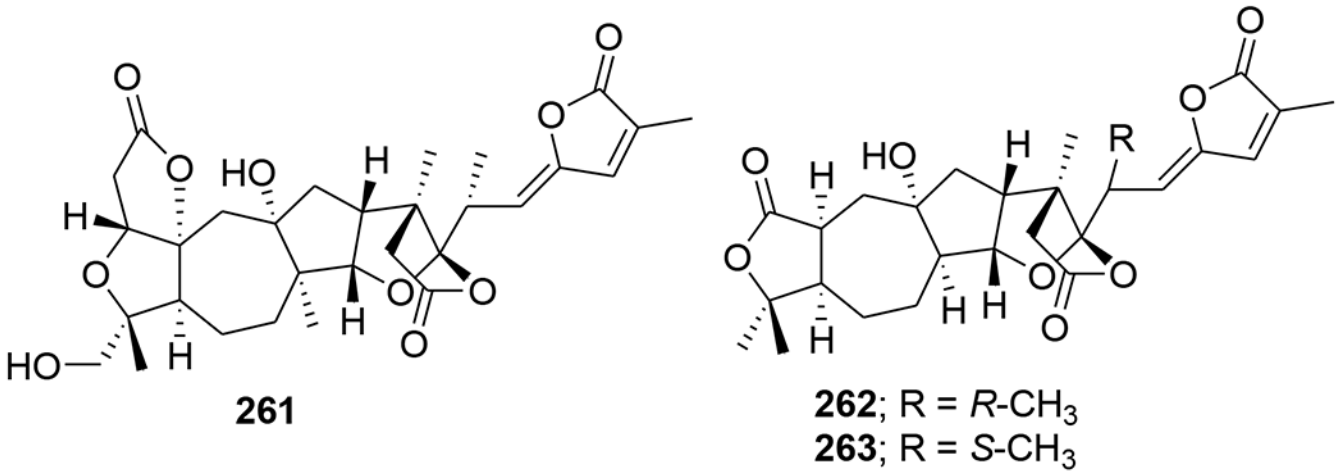


FIGURE 56.
Chemical structures of compounds **261**–**263**

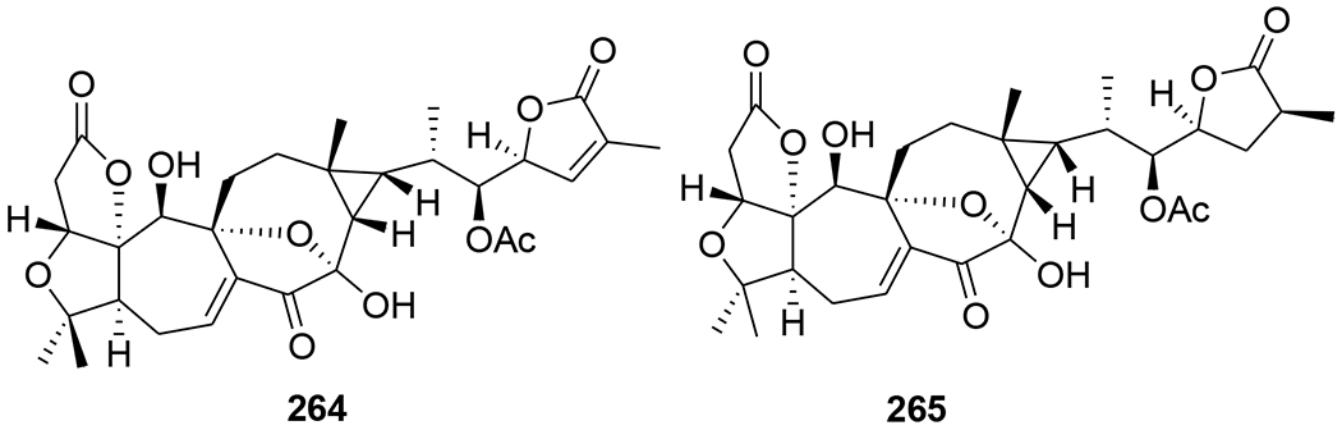


FIGURE 57.
Chemical structures of compounds **264** and **265**

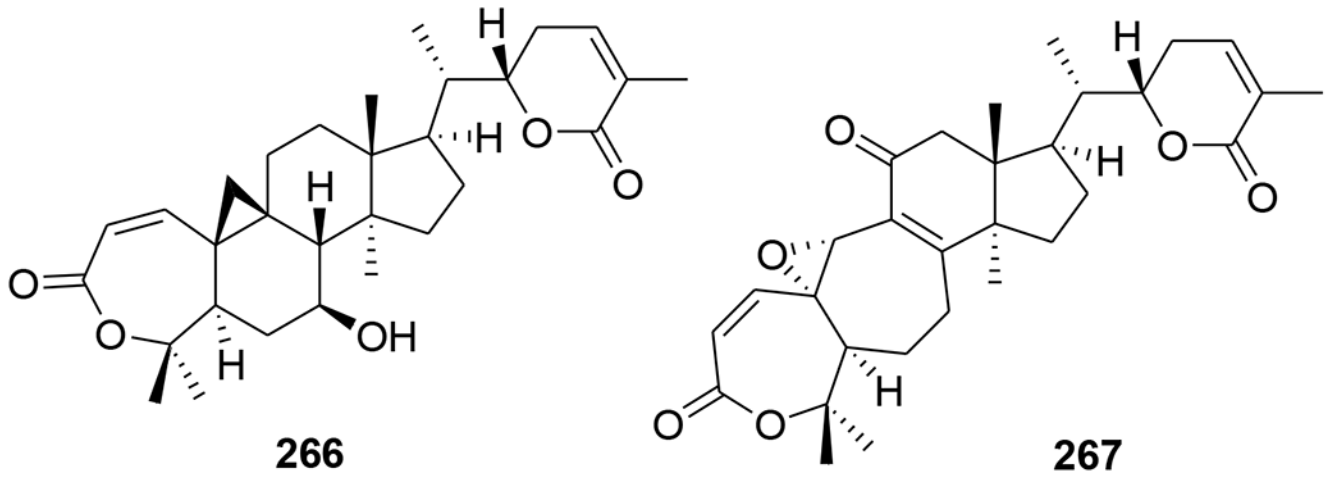


FIGURE 58.
Chemical structures of compounds **266** and **267**

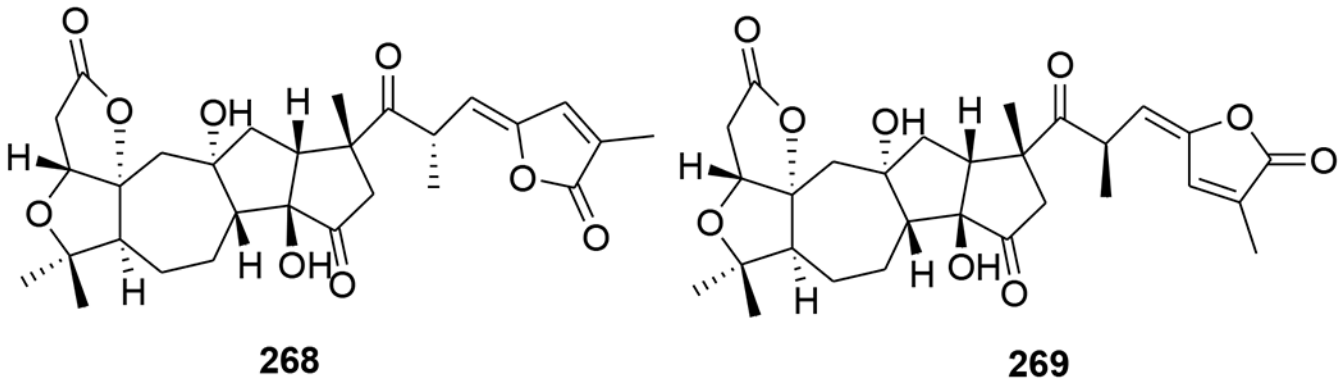


FIGURE 59.
Chemical structures of compounds **268** and **269**

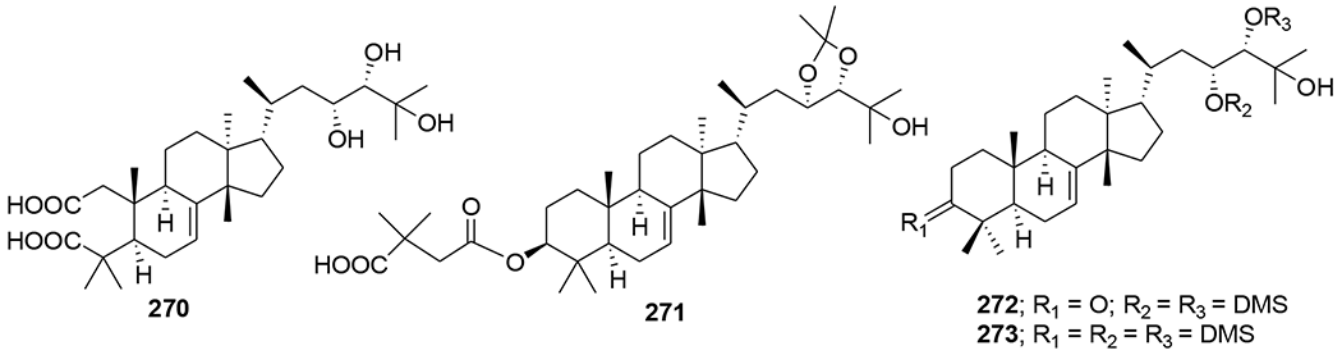


FIGURE 60.
Chemical structures of compounds **270**–**273**

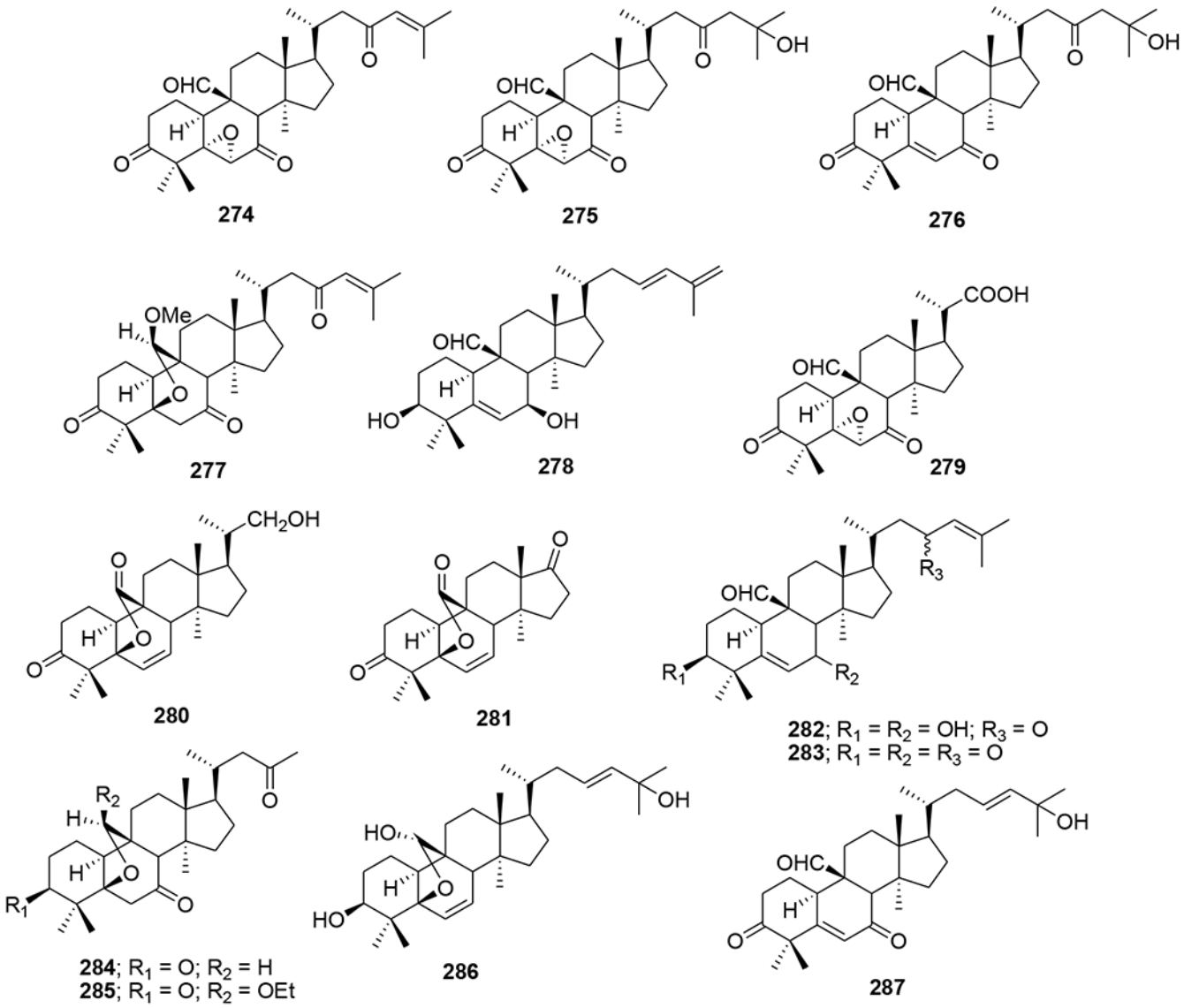


FIGURE 61.
Chemical structures of compounds **274**–**287**

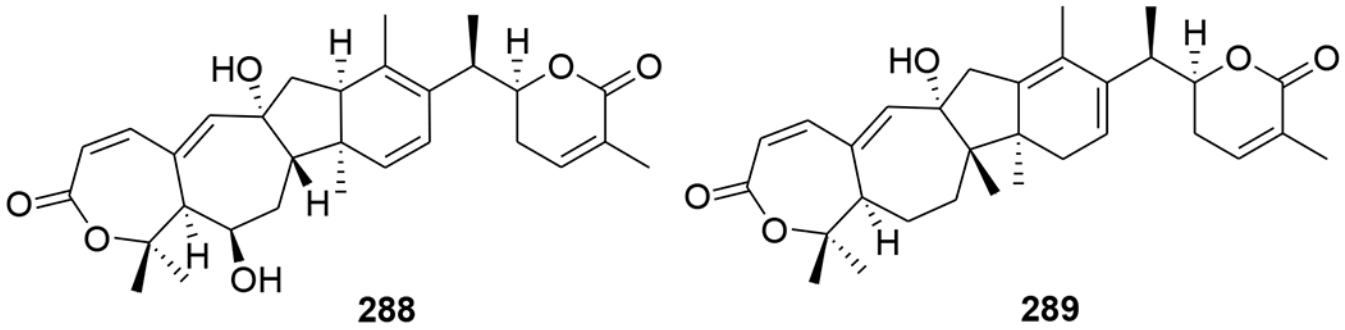


FIGURE 62.
Chemical structures of compounds **288** and **289**

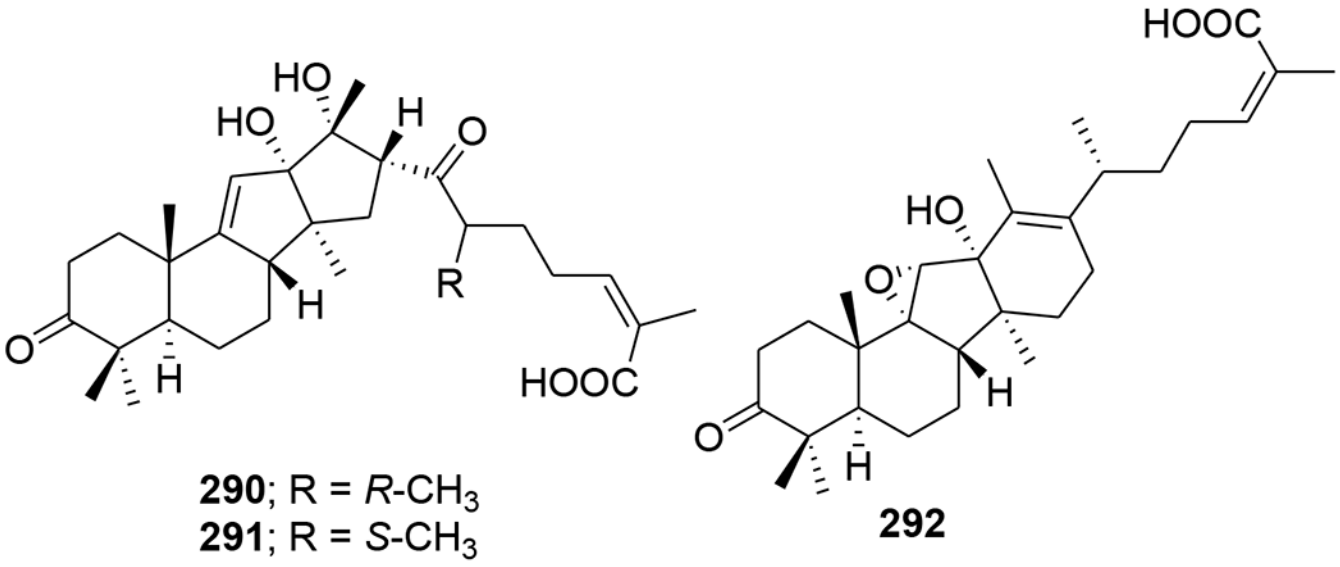
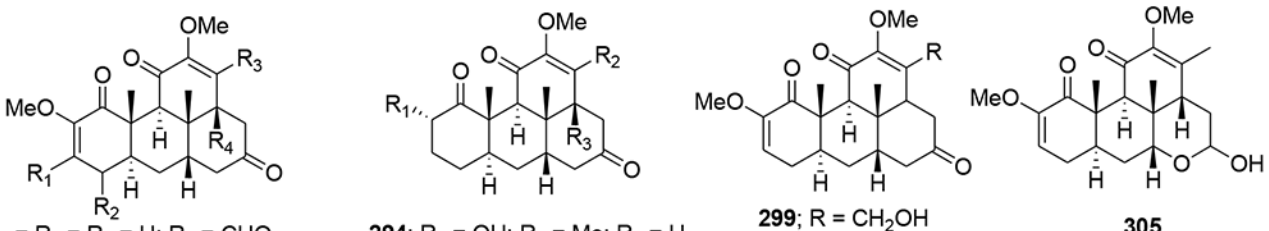


FIGURE 63.
Chemical structures of compounds **290**–**292**

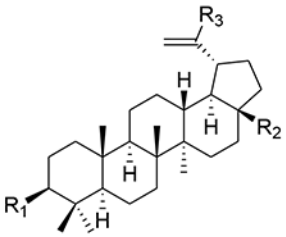


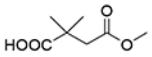
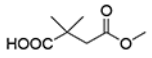
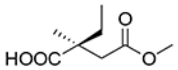
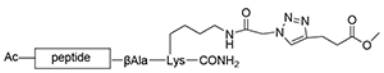
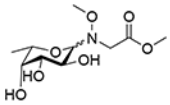
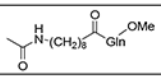
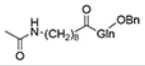
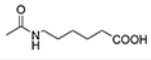
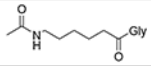
293; $R_1 = R_2 = R_4 = H$; $R_3 = CHO$
294; $R_1 = OH$; $R_2 = Me$; $R_3 = H$
295; $R_1 = OMe$; $R_2 = Me$; $R_3 = H$
296; $R_1 = OH$; $R_2 = Me$; $R_3 = OH$
297; $R_1 = OMe$; $R_2 = R_4 = H$; $R_3 = Me$
298; $R_1 = OMe$; $R_2 = H$; $R_3 = Me$; $R_4 = OH$
299; $R = CH_2OH$
300; $R_1 = R_2 = R_4 = H$; $R_3 = CH_2OH$
301; $R_1 = OH$; $R_2 = CH_2OH$; $R_3 = H$
302; $R_1 = OMe$; $R_2 = R_4 = H$; $R_3 = CH_2OH$
303; $R_1 = R_4 = H$; $R_2 = O$; $R_3 = Me$
304; $R_1 = R_4 = H$; $R_2 = \alpha$-OH; $R_4 = Me$
305
306; $R_1 = R_2 = R_4 = H$; $R_3 = Me$
307; $R = Me$

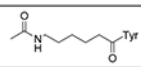
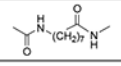
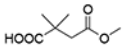
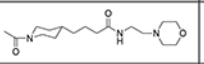
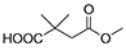
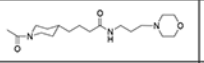
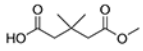
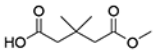
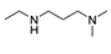
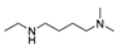
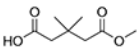
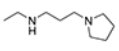
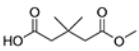
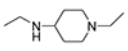
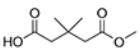
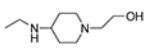
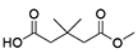
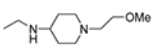
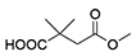
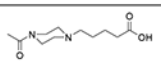
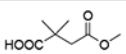
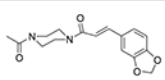
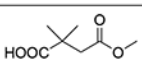
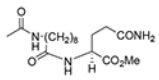
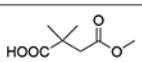
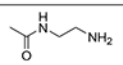
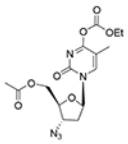
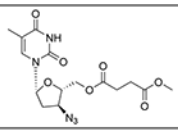
FIGURE 64.
Chemical structures of compounds **293**–**307**

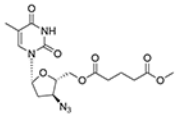
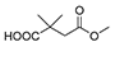
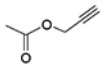
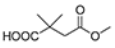
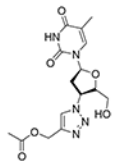
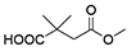
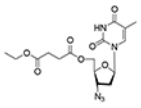
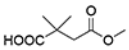
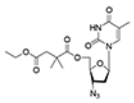
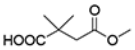
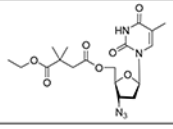
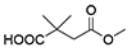
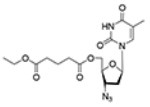
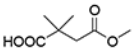
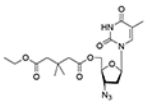
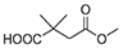
TABLE 1

Structures and anti-HIV activity of betulinic acid and betulin derivatives and analogues



Compound	R_1	R_2	R_3	EC_{50} (μM)
8	O	CH_2OH	H	3.40
9	O	CHO	H	4.08
10	OH		H	1.66
11		CN	H	1.5
13		CHO	H	1.2
16		COOH	H	0.0006
17[a]		COOH	H	4.28 ($HIV\text{-}1_{IIIB}$); 6.9 ($HIV\text{-}1_{BaL}$)
18		COOH	H	61 %[b]
21	OH		H	0.09
22	OH		H	0.12
24	OH		H	0.15[c]
25	OH		H	0.35[c]

26	OH		H	0.23[c]
29	OH			0.09
30			H	0.007
31			H	0.006
32			H	0.003
33			H	0.007
34			H	0.009
35			H	0.003
36			H	0.005
37			H	0.005
38			H	0.021
39			H	0.002
40			H	0.0059
41			H	0.019
42			H	0.01
43			H	0.016
46	OH		H	0.017
47		COOH	H	0.015

48		COOH	H	0.012
49			H	0.067
50			H	0.10
51			H	0.045
52			H	0.098
53			H	0.040
54			H	0.060
55			H	0.063
60				0.097
70	OAc	CH_3	H	-
71	OAc	CH_3	CHO	-
73	NOH	CH_3	H	-
75	OH	CH_2OH	CHO	-
78	OH	CH_2OAc	CHO	1.70

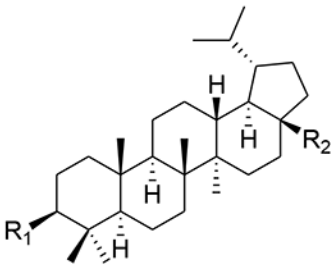
a: Peptide: NNYTSLIHSLIEESQNQQEKNEQELL;

b: Antiviral activity was assessed by the percent increase of cytoprotective effect over untreated HIV-1-infected cells

c: anti-HIV-2 activity.

TABLE 2

Structures and anti-HIV activity of dihydrobetulinic acid derivatives and analogues



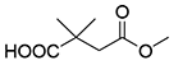
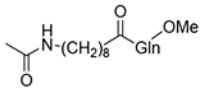
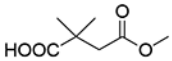
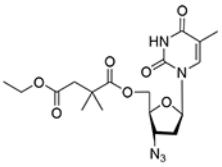
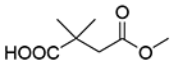
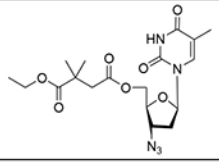
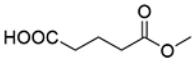
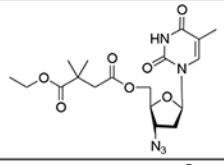
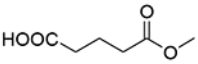
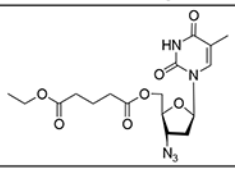
Compound	R_1	R_2	IC_{50} (μM)
12		CHO	1.8
23	OH		0.05
56			0.087
57			0.056
58			0.073
59			0.093

TABLE 3

Antiviral activity of compounds **21**–**23** toward BVM-resistant virus

Compound	**21**	**22**	**23**
V370A/EC_{50} (μM)	0.02	0.05	0.02

TABLE 4

Antiviral activity of compounds **32**–**39** toward BVM-resistant virus

Compound	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**
V7A/EC_{50} (μM)	0.009	0.014	0.022	0.026	0.022	0.010	0.008	0.019

TABLE 5

Antiviral activity of compound **42** toward BVM-resistant viruses

Compound	EC_{50} (μM)			
	V370A	**V370Δ**	**T371Δ**	**V362I**
42	0.16	0.32	0.067	0.016

TABLE 6

Antiviral activity of compounds **61** and **62** toward BVM-resistant viruses

Compound	EC_{50} (μM)	
	V370A	**ΔV370**
61	0.008	0.031
62	0.038	0.025

TABLE 7

Antiviral activity of compounds **63** and **64** toward BVM-resistant viruses

Compound	EC_{50} (μM)							
	V370A	**ΔV370**	**Q369H**	**T371A**	**V362I**	**V370M**	**V370A/ΔT371**	**ΔV371**
63	0.0025	0.014	-	0.0017	0.00094	-	-	-
64	0.0027	0.013	0.0019	0.002	0.0045	0.0028	0.0036	0.0073

-: Not determined