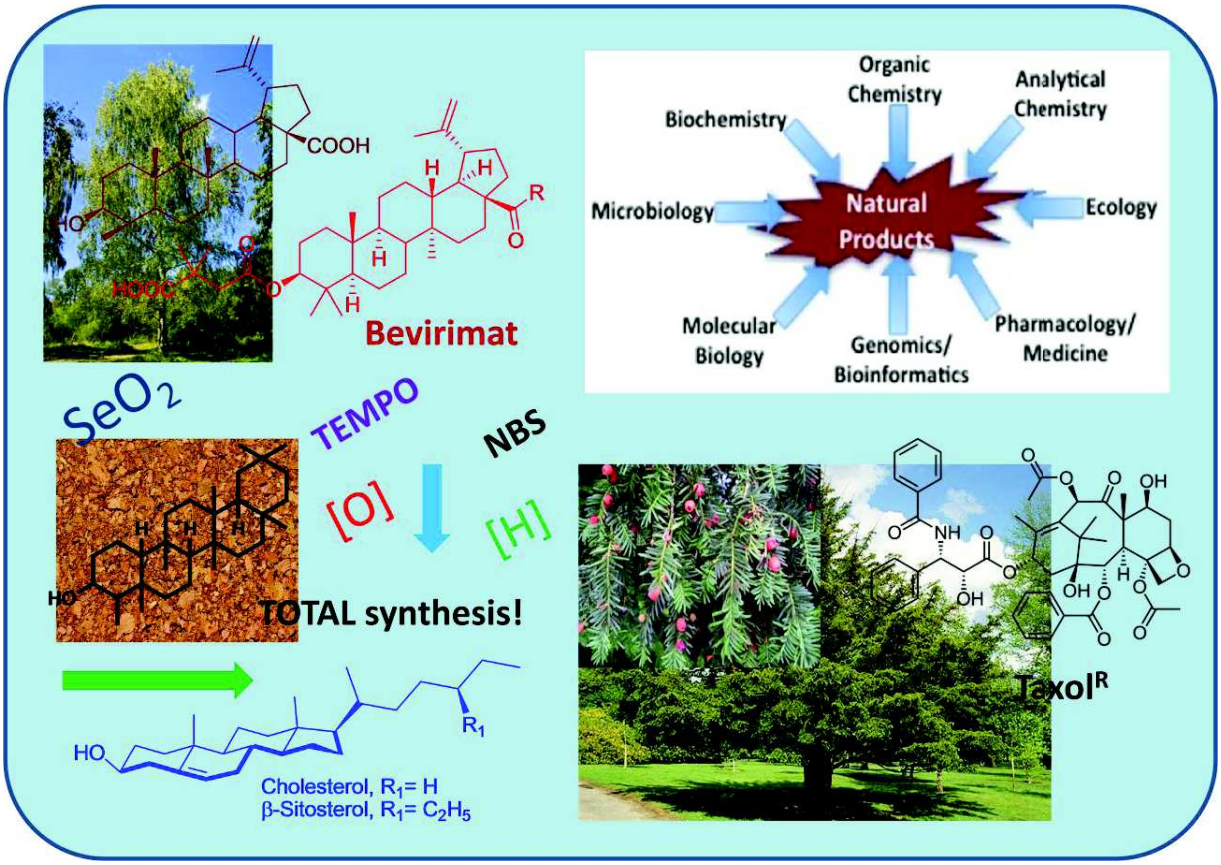
Chapter I

Carbocyclic compounds and their transformative reactions: A general perspective on natural products chemistry



I.1 Carbocyclic compounds

Chemistry, in its widespread periphery, is basically full of unlimited molecules with their novel interactions which lets human know Nature closer. And organic chemistry is based typically on the innumerous organic compounds which, on their structural aspect, can broadly be divided in two ways- acyclic and cyclic. As the cyclic molecules represent those which are a combination of both literally 'cyclic' and 'acyclic' molecules (e.g., hexyl cyclohexane (**1**) – a cyclic compound, **Figure 1.1**), the numbers of cyclic entities are thus more in nature.

In addition, cyclic molecules are classified into homocyclic and heterocyclic. The cyclic compounds where all the ring members are constituted by same element are termed as homocyclic compounds, e.g., cyclopropane (**2**), benzene (**3**), cholestane (5α: **4**, 5β: **5**), friedelane (**6**) pentazole (**7**) etc. And homocyclic compounds where all the ring members are carbon atoms, are termed as carbocyclic compounds (e.g., compounds **1**-**6**).[1] On the other hand, cyclic compounds where the ring is made by one or more different elements, the system is termed as heterocyclic, e.g., aziridine (**8**), thiophene (**9**), morpholine (**10**), benzothiooxazoline (**11**), etc (**Figure 1.1** and **Chart 1.1**).

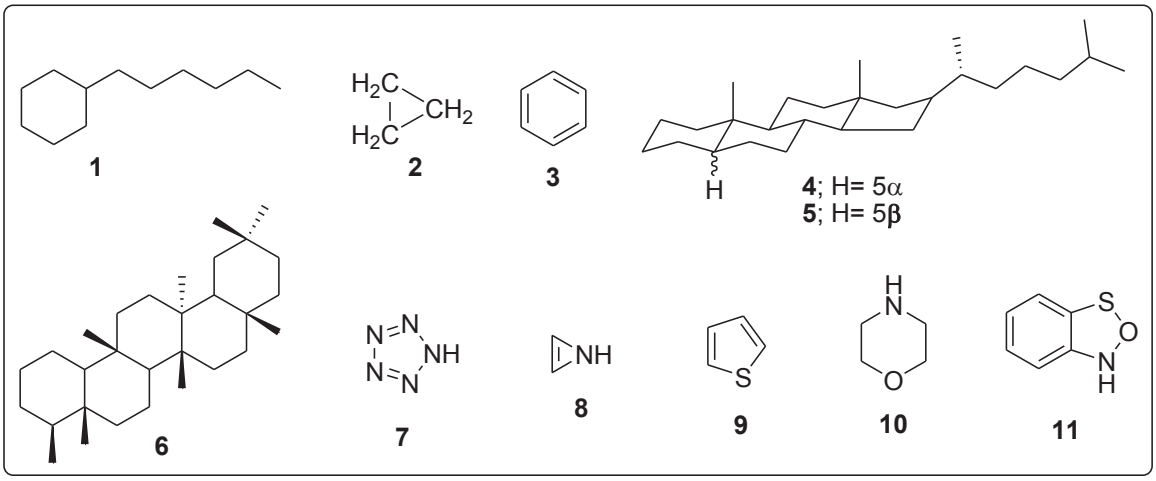


Figure 1.1 Some cyclic organic compounds (**1**-**6**: carbocyclic; **7**: nitrogen-based homocyclic; **8**-**11**: heterocyclic).

I.2 Natural products and carbocyclic compounds

Humans, throughout the ages, have bind them together with Nature to cater for their basic needs—starting from foods for survival, to medicines for healthy survival. And Nature always

has provided the materials to fight against a wide spectrum of diseases. Particularly, the plant kingdom has formed the basis of traditional medicine systems.

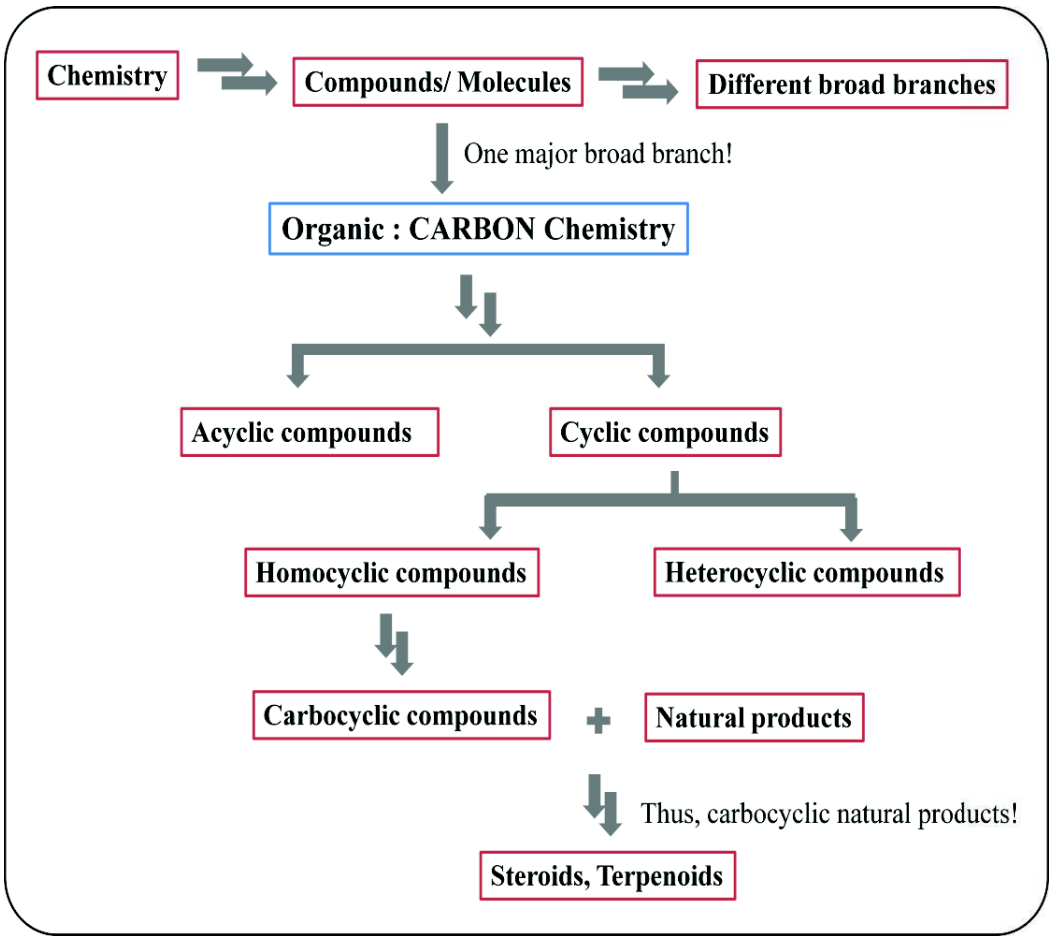


Chart 1.1

A chemical compound or substance produced by a living organism—thus found in nature, is termed as a natural product.[2, 3] Natural products thus include any substance produced by life.[4] The commercially available materials used for the aid of daily-life, viz., cosmetics, dietary supplements, some kind of medicines, foods etc., which are produced from natural sources without any artificial additives are also named as natural products.[5] As a consequence, to supply at a required amount, many of the natural compounds have been prepared in the laboratory by the process of chemical synthesis, which indeed has enriched organic chemistry enormously by following a huge number of challenging targets.

Within the periphery of organic chemistry, we consider natural products, typically, as pure organic compounds (thus pure molecules) isolated from natural sources related to lives, directly or indirectly. These natural compounds are produced mainly by the primary and secondary metabolism pathways.[6]

Primary metabolites are defined as the components of basic metabolic pathways that are essentially required for life. Cellular functions such as nutrient assimilation, energy production, and growth/ development are associated with the primary metabolites. In short, the basic building blocks of life are the primary metabolite-based natural products which include carbohydrates, lipids, amino acids, and nucleic acids.[7-9]

On the other hand, secondary metabolites, though have a broad range of functions, are not absolutely required for survival. Social signaling molecules (pheromones etc.), agents that solubilize and transport nutrients (siderophores etc.), competitive weapons which are used normally against competitors, prey, and predators (repellants, venoms, toxins etc.) and immune system developing components are basically under the secondary metabolite-based natural products.[10, 11] Alkaloids, phenylpropanoids, polyketides, and terpenoids are the general structural classes of secondary metabolites.

Natural products are prone to have pharmacological or biological activities and as a consequence, most traditional medicines as well as lots of modern medicines are based on them. The structural diversity of natural products exceeds that readily achievable by chemical synthesis, and on the other hand, synthetic analogs can be prepared with improved potency and safety. As a result, natural products are often inspirational and used as starting points for drug discovery. In fact, natural products are the inspiration for approximately one half of U.S. Food and Drug Administration-approved drugs.[12, 13]

Now, due to the large extent of catenation capability of carbon, it can produce a large number of molecules made solely by them which in turn, implies that nature provides a huge number of carbocyclic compounds. And in virtue, nature itself is the richest source of a variety of carbocyclic compounds.

Two or more carbocycles can be joined together in a number of different fashions to produce a number of different groups of carbocyclic compounds. And among the broad spectrum of all kinds of natural products, if we look for more common, easily available and highly useful carbocyclic natural products, we found mainly the steroids and terpenoids (**Chart 1.1**).

Thus, having the opportunity of working in the field of natural products chemistry, the author intended to work on the steroids (which belong, at majority, to the primary metabolites class) and pentacyclic triterpenoids (as our laboratory is actively engaged enriching this particular terpenoid chemistry), specially on friedelane triterpenoids (which belong to the secondary metabolites class) as these two areas are drawing the major increasing attention among the carbocyclic natural products.

I.3 Steroids

The important natural compounds which are constituted on the basis of 1,2-cyclopentenophenanthrene (**12**) skeleton with 17 carbon atoms are known as steroids (**Figure 1.2**). Besides the widespread distribution of the steroids in nature, marine plants and animals are the richest source which display interesting biocidal activities.[14]

Steroids include a large number of sterols, vitamin D, the bile acids, a number of sex hormones, the adrenal cortex hormones, some carcinogenic hydrocarbons, certain saponins, antibiotics, etc. Steroids can penetrate cells and bind to nuclear and membrane receptors. Nature has produced the steroid system to perform some selected fundamental biological functions and the fact directs to form the basis of new discoveries in this field which, in virtue, relates biology and chemistry with more practical applications.

Rigidity, permeability, conformational order, and phase behavior of phospholipid membranes in cells are highly regulated by the sterols, and particularly by cholesterol (**13**)[14] which is a major component (present up to 50 mole%) of eukaryotic cell plasma membranes.[15,16] The alteration of the acquired concentrations of sterols are associated with diseases.[17] For example, excess cholesterol results human atherosclerosis. Patients afflicted with sitosterolemia also suffer from atherosclerosis, for an accumulation of excess plant sterols, mainly β-sitosterol (**14**) and stigmasterol (**15**).[18] (**Figure 1.2**) In healthy and hypercholesterolemic (but non-sitosterolemic) subjects, plant sterols are found valued for their ability to lower plasma cholesterol levels[19,20] as well as their potential as anticancer compounds. [21]

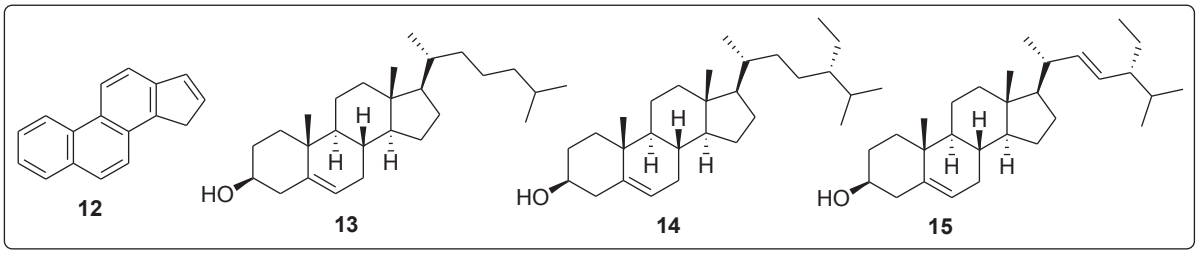


Figure 1.2 1,2-Cyclopentenophenanthrene (**12**), Cholesterol (**13**), β-sitosterol (**14**) and stigmasterol (**15**).

On the other hand, among the steroids, the compound considered as the most fundamental one is cholesterol (**13**) for the animals, and β-sitosterol (**14**, structurally, 24α-ethyl choleaterol) for the plants. As the author has the privilege to work with these molecules (and their derivatives), a brief general discussion about their recent advances in chemistry, giving emphasis especially on their transformative reactions, is provided below.

I.3.1 Recent selective transformative reactions on cholesterol and β-sitosterol

Within the family of steroids, an important branch of polycyclic compounds, cholesterol (**13**) is the most abundant member. The essential structural component of animal cell membranes required in order to maintain proper membrane permeability as well as fluidity is the lipid molecule- cholesterol, more precisely cholest-5-en-3β-ol (**13**) which originates from Ancient Greek chole- (i.e., bile) and stereos (i.e., solid) followed by the chemical suffix -ol for alcohol. Cholesterol is also the precursor for the biosynthesis of a number of essentially important compounds including steroid hormones, bile acids, vitamin D etc. Cholesterol (**13**) is synthesized by animals and, in vertebrates it is formed predominantly in the liver.

For more than a century, people have found it fascinating to work with the structure, biosynthetic pathway and metabolic regulation of cholesterol (**13**). Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to its study.[22]

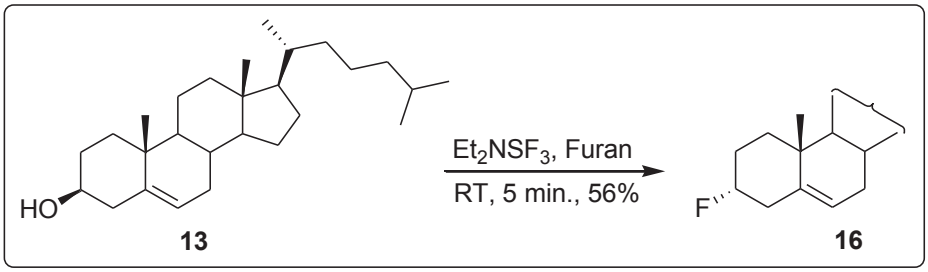
Cholesterol (**13**) was the first steroid ever isolated and was discovered by M.E. Chevreul in 1815. It was isolated from the non-saponifiable part of animal lipids. The structural elucidation of cholesterol was started in 1859 and its exact molecular formula ($C_{27}H_{46}O$) was established in 1888 by F. Reinitzer. Proof for its structure was obtained chiefly through the novel work of A. Windaus and H.O. Wieland. The structure of cholesterol as was suggested by Windaus and Wieland in the 1920s was not exactly correct, but their contribution in the field was really

unparalleled. Depending on the X-ray diffraction data, in the 1930s, the exact structure of cholesterol was established. Woodward et al., in 1951, reported a total synthesis of cholesterol.[23]

Thus, to start working with the transformative reactions of cholesterol and its derivatives, it was a bit essential to have a thorough study of the reports which are due to the various transformative reactions mainly. However, as the subject is an elaborative one, the major advances, excluding the simple derivatization reactions, since the last one and half decade is highlighted below.

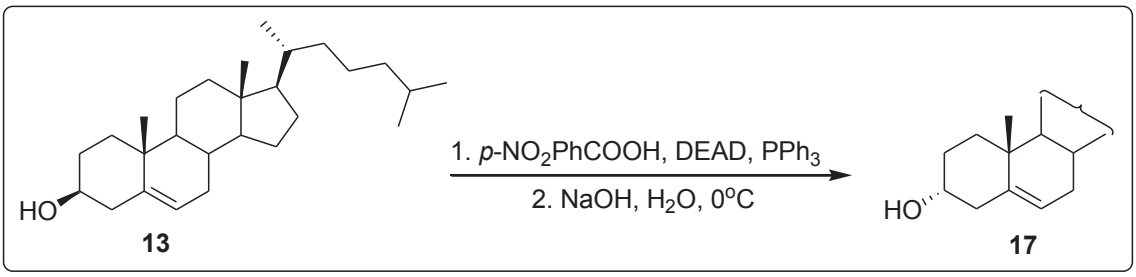
1.3.1.1 Recent transformative reactions on cholesterol

Diethylaminosulfur trifluoride (Et_2NSF_3, commonly abbreviated as DAST) generally reacts with alcohols to result the fluoro derivatives *via* an SN_2 or SN_i mechanism.[24] When cholesterol (**13**) was reacted with DAST, an SN_2 pathway furnished 3α-fluorocholesterol (**16**) as the only product (**Scheme 1.1**).[25]



Scheme 1.1 Synthesis of 3α-fluorocholest-5-ene (**16**).

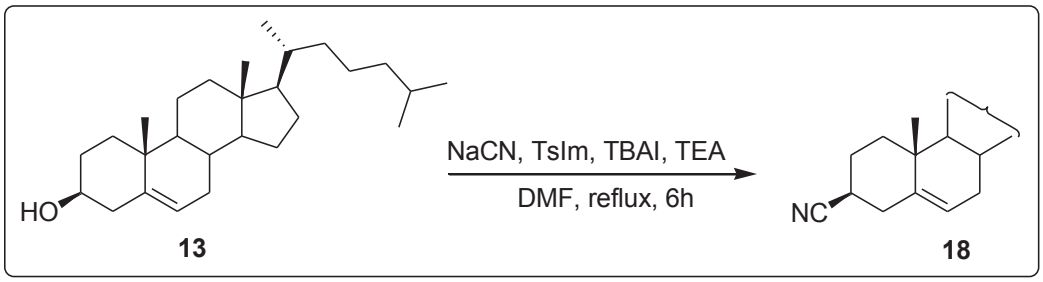
Cholesterol (**13**) was converted to its 3α-epimer **17** by following a two-step procedure *via p*-nitrobenzoate (**Scheme 1.2**).[26]



Scheme 1.2 A two-step synthesis of 3α-epimer of cholesterol (**17**).

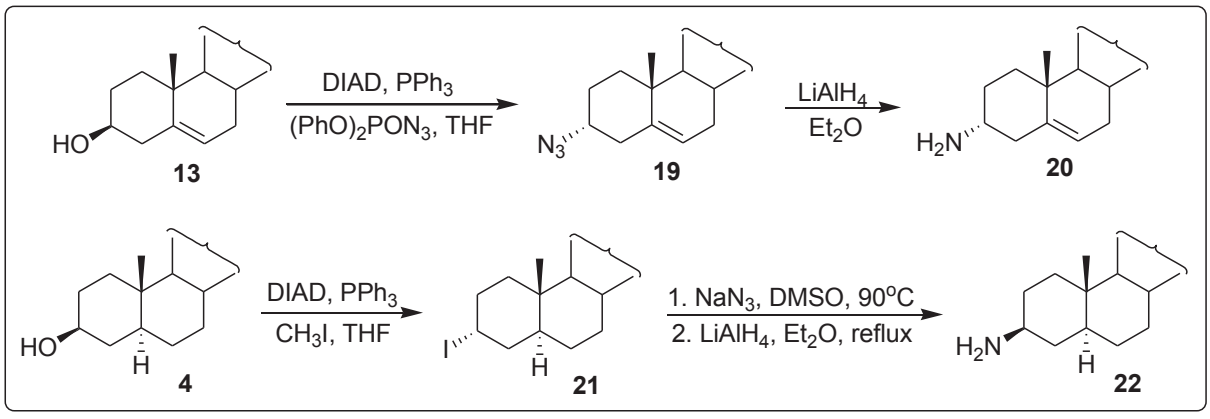
An established general method for the conversion of alcohols to the corresponding nitriles by using *N*-(*p*-toluenesulfonyl)imidazole (TsIm), was also applied to have 3β-nitrile derivative

18 of cholesterol at moderate yield. The method utilized NaCN, TsIm and triethylamine (TEA), and catalytic amounts of tetra-n-butylammonium iodide (TBAI) (**Scheme 1.3**).[27]



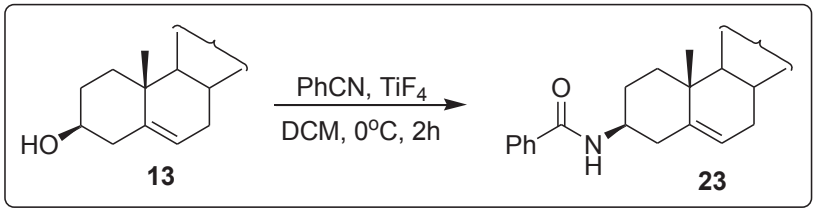
Scheme 1.3 Transformation of cholesterol into 3β-nitrile derivative (**18**).

The 3α-amino derivative of cholesterol and 3β-amino derivative of 5α-cholestane (**20** and **22** respectively) were prepared respectively from cholesterol (**13**) and 5α-cholestane (**4**) by following a two-step Mitsunobu procedure. A double inversion of configuration was utilized in the reaction sequences to afford ultimately the 3β-amino derivative (**22**) *via* 3α-iodide (**21**) and 3β-azide (not shown in the Scheme 1.) followed by $LiAlH_4$ reduction (**Scheme 1.4**).[28]



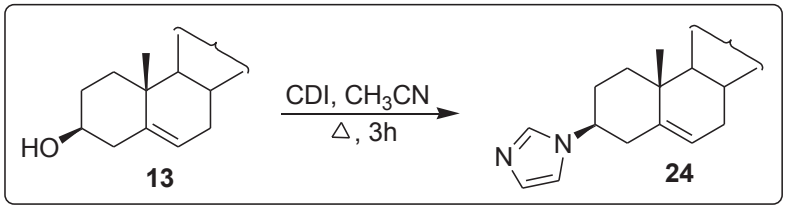
Scheme 1.4 Synthesis of 3α- and 3β-amino cholesterol (**20** and **22** respectively).

Mondal et al. found an interesting variation of the Ritter reaction where an inexpensive Ti(IV)/nitrile reagent was used for the transformation of cyclic secondary alcohols into the corresponding amides.[29] Retention of configuration was found to occur in the conversions e.g. cholesterol was converted into *N*-3β-cholesterylbenzamide (**23**) at a very good yield (**Scheme 1.5**).

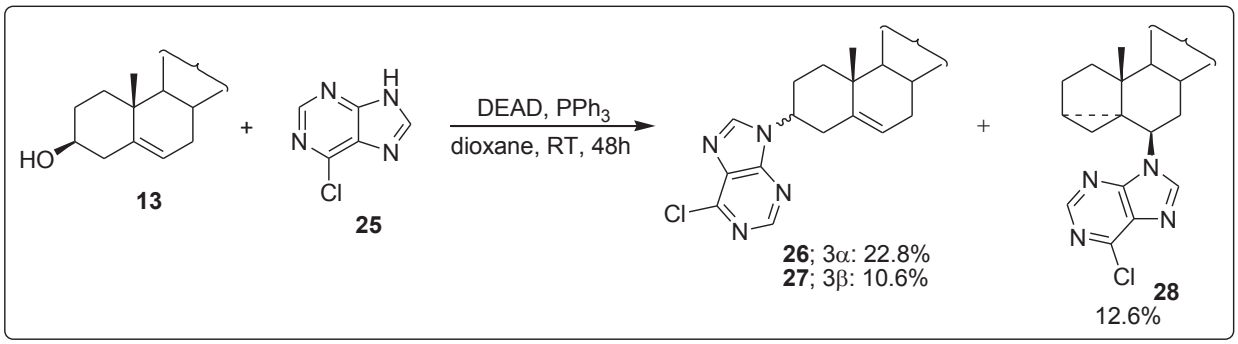


Scheme 1.5 Synthesis of *N*-3β-cholesterylbenzamide (**23**) by Ritter reaction.

Following a general reaction applicable to a variety of alcohols, cholesterol (**13**) was converted into the 3β-imidazolyl derivative (**24**) in high yields by using *N,N′*-carbonyldiimidazole (CDI) as the heterocycle donor substrate (**Scheme 1.6**). Similarly, *N,N′*-carbonylditriazole (CDT) was used to furnish the corresponding triazolyl derivative (Scheme not shown).[30] Some nucleo-cholesterols (**26-28**) was also prepared by the Mitsunobu coupling of 6-chloropurine (**25**) with cholesterol. The reaction resulted, besides the SN_2 major product **26**, two isomeric compounds (**27** and **28**) formed *via* the mesomeric homoallylic carbocation (**Scheme 1.7**).[31]



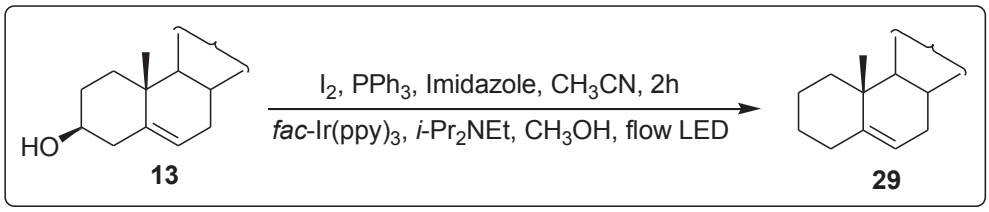
Scheme 1.6 Synthesis of *N*-3β-imidazolylcholesterol (**24**).



Scheme 1.7 Coupling of 6-chloropurine (**25**) with cholesterol by Mitsunobu reaction.

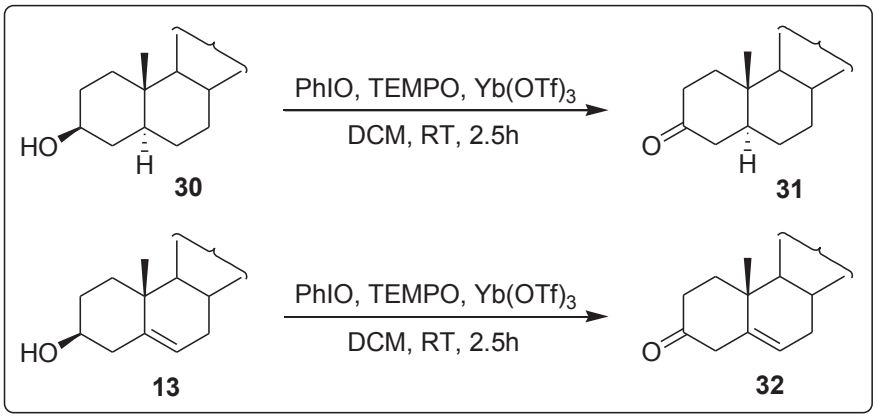
Primary and secondary alcohols were deoxygenated in one-pot *via* a combination of the Garegg–Samuelsson reaction, visible light-photoredox catalysis, and flow chemistry. The

reaction indeed attains importance due to the mild reaction condition, easy handling of the reagents, excellent functional group tolerance and good yield. Following the procedure, 5-cholestene (**29**) was obtained from cholesterol at 72% yield (**Scheme 1.8**).[32]



Scheme 1.8 A one-pot deoxygenation of cholesterol.

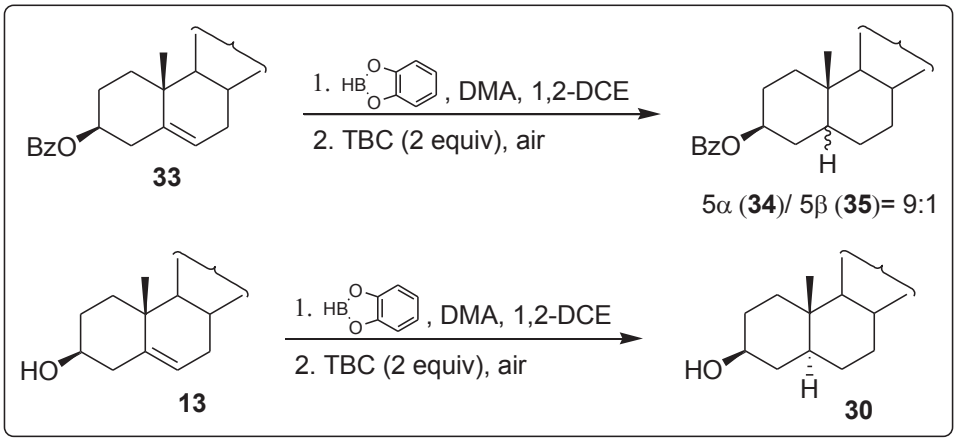
Rapid oxidation of alcohols into the corresponding carbonyl derivatives was achieved by using PhIO and catalytic amounts of TEMPO and $Yb(OTf)_3$. Following the oxidation protocol, 5α-cholestanol (**30**) furnished 5α-cholestanone (**31**) whereas cholesterol (**13**) afforded cholest-5-en-3-one (**32**) by maintaining the double bond position unaltered (**Scheme 1.9**).[33]



Scheme 1.9 One-step synthesis of 5α-cholestanone (**31**) and cholest-5-ene-3-one (**32**) respectively from 5α-cholestanol (**30**) and cholesterol (**13**).

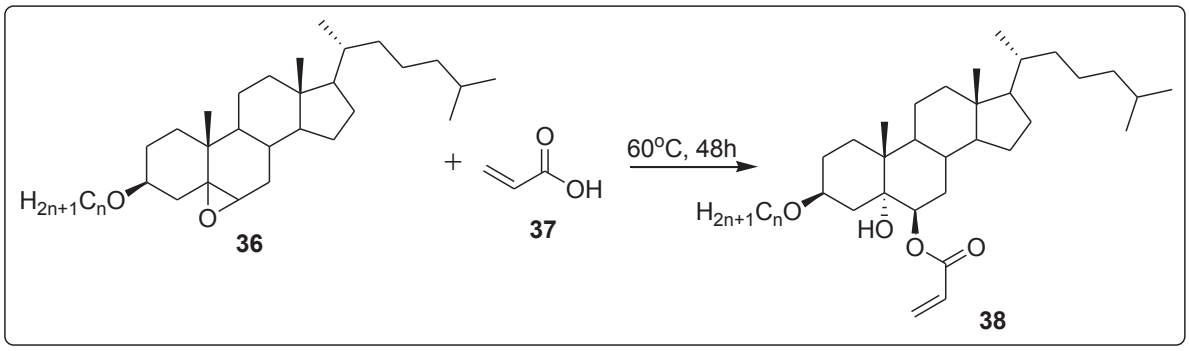
The organoborane derivative obtained from the reaction of cholesteryl benzoate (**33**) with two equivalents of catecholborane was treated with 4-*tert*-butylcatechol (TBC) in the presence of air to afford the reduced product 3β-benzoyloxycholestane in excellent yield having a 5α/5β = 9:1 mixture of diastereomers, **34** and **35**, respectively. Following the same reaction protocol,

however, cholesterol afforded 5α-cholestan-3β-ol (**30**) in 72% yield as a single diastereomer (**Scheme 1.10**).[34]



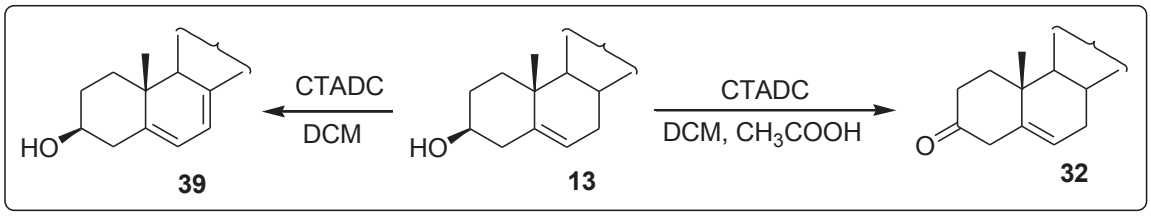
Scheme 1.10 Catecholborane mediated reduction of cholesterol (**13**) and cholesteryl benzoate (**33**).

5α-Hydroxy-6β-acrylate derivative of cholesterol, **38** was prepared from the reaction of 3-alkoxy-5,6-epoxycholestane (**36**) with acrylic acid (**37**). (**Scheme 1.11**) Free radical polymerization was then carried out with the acrylate derivative which was studied thoroughly with the use of different methods.[35,36]



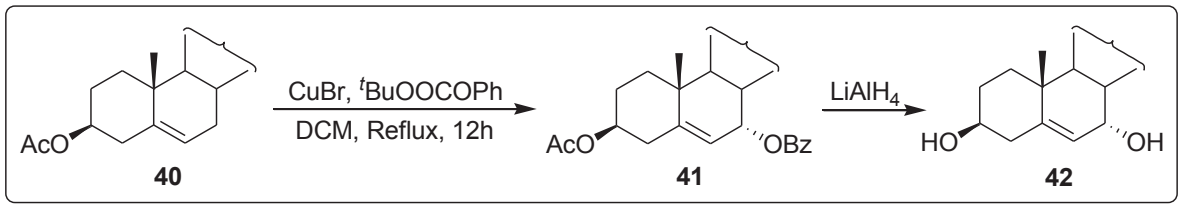
Scheme 1.11 Synthesis of cholesterol-based monomer **38** for radical polymerization.

Cetyltrimethylammonium dichromate (CTADC), when was applied on cholesterol (**13**) in dichloromethane (DCM), 7-dehydrocholesterol (**39**) was the isolated product whereas addition of acetic acid in DCM produced 5-cholesten-3-one (**32**, **Scheme 1.12**).[37] The kinetics of the oxidation reaction suggests to follow the reversed micellar system and, involves the formation of an intermediate ester complex which ultimately was decomposed into the products.



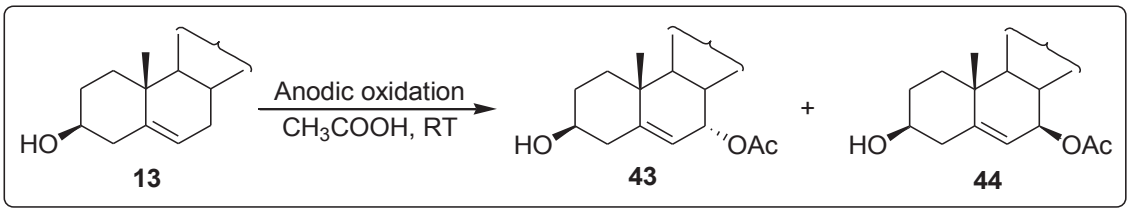
Scheme 1.12 Oxidative transformation of cholesterol (**13**) with cetyltrimethylammonium dichromate.

A copper-catalyzed, stereoselective allylic benzoyloxylation of sterol derivatives was developed by Brunel et al.[38] The complete stereoselectivity was justified through a rationale mechanism. Thus, following the reaction protocol, 7α-hydroxycholesterol (**42**) was obtained in a two-step process from cholesteryl acetate (**40**) in 61% overall yield *via* the 7α-benzoyloxy cholesteryl acetate **41**. (**Scheme 1.13**).



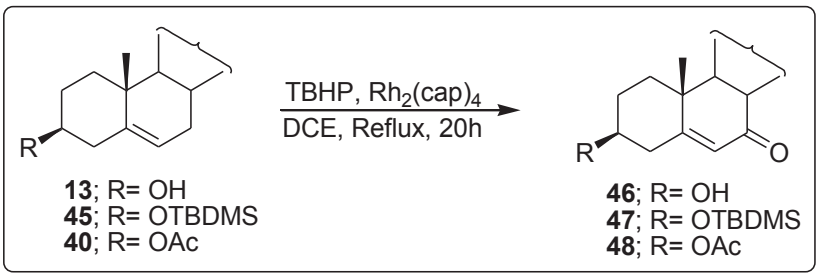
Scheme 1.13 A copper-catalyzed allylic benzoyloxylation.

Cholesterol (**13**), on electrochemical oxidation on a platinum electrode in glacial acetic acid furnished two major products: 7α-acetoxycholesterol (**43**) and 7β-acetoxycholesterol (**44**) in a ratio of 10:3. In the oxidation reaction, sodium perchlorate and sodium acetate was also used as the supporting electrolytes (**Scheme 1.14**).[39]

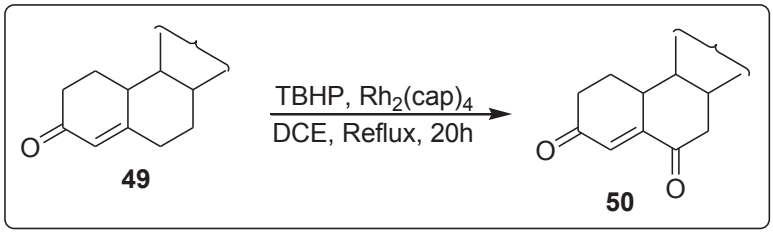


Scheme 1.14 Electrochemical allylic acetoxylation of cholesterol (**13**).

Dirhodium caprolactamate with *t*-butyl hydroperoxide (TBHP) was used to oxidize cholesterol (**13**), its OTBDMS (**45**), 3β-acetoxycholesterol (**40**) into their respective 7-oxo derivatives **46-48** (**Scheme 1.15**).[40,41] It was observed that oxygen-protected steroids provide yields better. This oxidizing system was also used for the allylic oxidations of steroidal enones into the corresponding enediones in moderate to high yields, e.g. cholest-4-en-3-one (**49**) was oxidized into cholest- 4-ene-3,6-dione (**50**) at 50% yield.[42] (**Scheme 1.16**).

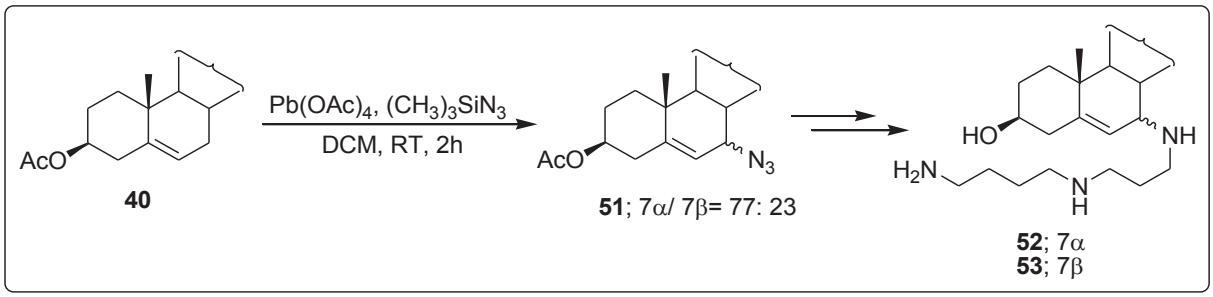


Scheme 1.15 Rhodium-catalyzed allylic oxidation of cholesterol and its derivatives.



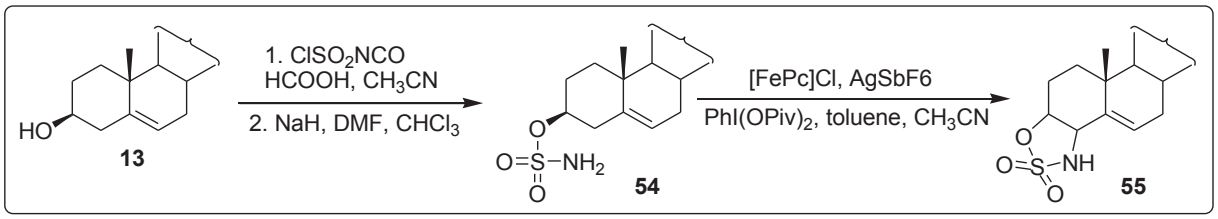
Scheme 1.16 Rhodium-catalyzed allylic oxidation of cholestenone (**49**) into cholest- 4-ene-3,6-dione (**50**).

A number of squalamine-related polyaminosterols were synthesized from cholesterol.[43] In the key-step of the transformations, the azido group was introduced on the allylic C-7 position of cholesteryl acetate (**40**) with the treatment of trimethylsilyl azide in the presence of Pb(IV) acetate (**Scheme 1.17**). The yield of the 7-azido cholesteryl acetate (**51**) was obtained at 68% with the epimeric ratio of 7α/7β = 77:23. The epimers were separated and transformed into the corresponding squalamine analogs (**52**, **53**) which were evaluated with their biological activities.



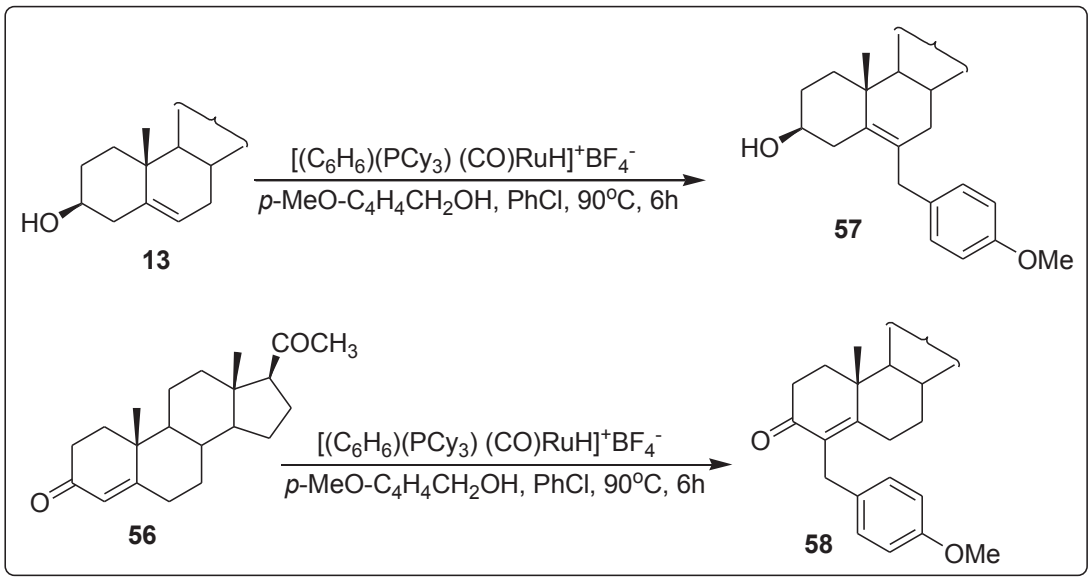
Scheme 1.17 Synthesis of squalamine-related polyaminocholesterol derivatives (**52** and **53**).

An intramolecular allylic C-H amination catalyzed by iron(III) has recently been reported.[44] The inexpensive commercial compound, [Fe(III)pc]Cl (pc = phthalocyaninato), typically used as an industrial additive in ink and rubber manufacturing, was employed as the iron-catalyst. In the reaction protocol, allylic C-H amination was found to be favored to the aziridination and amination at other C-H bond types. Employing the reaction, cholesteryl sulfamate (**54**) furnished a single diastereomer of the allylic intramolecular amination product **55** at 58% yield. (**Scheme 1.18**)

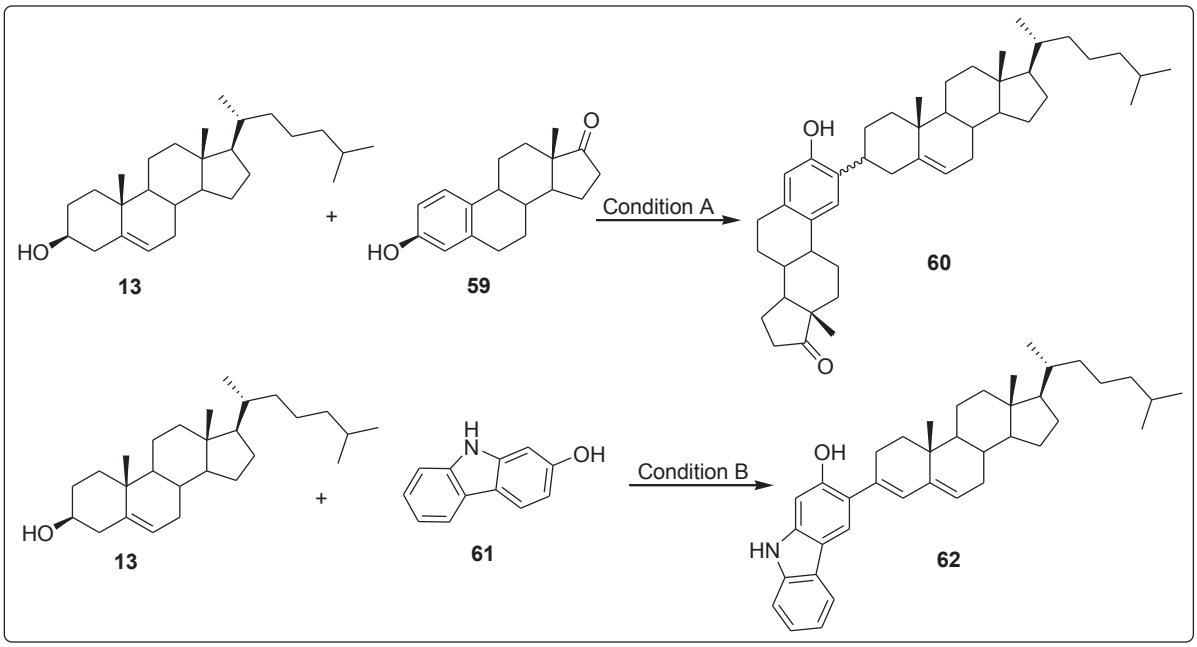


Scheme 1.18 Iron-catalyzed intramolecular allylic amination in cholesteryl sulfamate (**54**).

Catalytic selective alkylation of alkenes with the alcohols to form a C-C bond between vinyl C–H and C-OH centers with the concomitant loss of H_2O was reported.[45] The catalyst used for the transformation was a cationic ruthenium complex and a broad range of substrate functionality including amines and carbonyls were found to be tolerated. With *p*-methoxybenzyl alcohol, both cholesterol (**13**) and progesterone (**56**) under the optimum reaction conditions, afforded the corresponding 6- and 4-*p*-methoxybenzylated products (**57** and **58** respectively), without affecting either the alcohol or carbonyl functional groups. (**Scheme 1.19**)



Scheme 1.19 Ruthenium-catalyzed alkylation of steroidal alkenes (**30** and **56**) with alcohols.



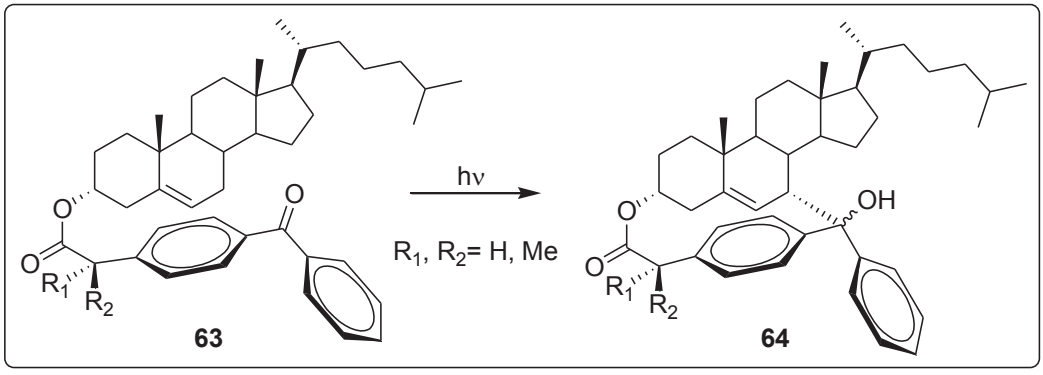
Scheme 1.20 Ruthenium-catalyzed dehydrative C-H alkylation of phenols with cholesterol: Condition A: $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$, cyclopentene (0.15 equiv), toluene/ DMSO 9:1, 100°C, 10h; Condition B: $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$, cyclopentene (1.5 equiv), toluene/ C_6H_5Cl= 1:1, 100°C, 8h.

Another interesting dehydrative C–H alkylation reaction of phenols with alcohols to produce *ortho*-substituted phenol derivatives was also reported by using the same cationic ruthenium

complex.[46] And utilizing this transformation, C-H alkylation of estrone (**59**) with cholesterol (**13**) was carried out to form a 1:1 diastereomeric mixture of the coupling product **60**. On the other hand, the analogous C-H alkenylation of 2-hydroxycarbazole (**61**) with cholesterol (**13**) resulted the desired oxidative coupling product **62** only. (**Scheme 1.20**)

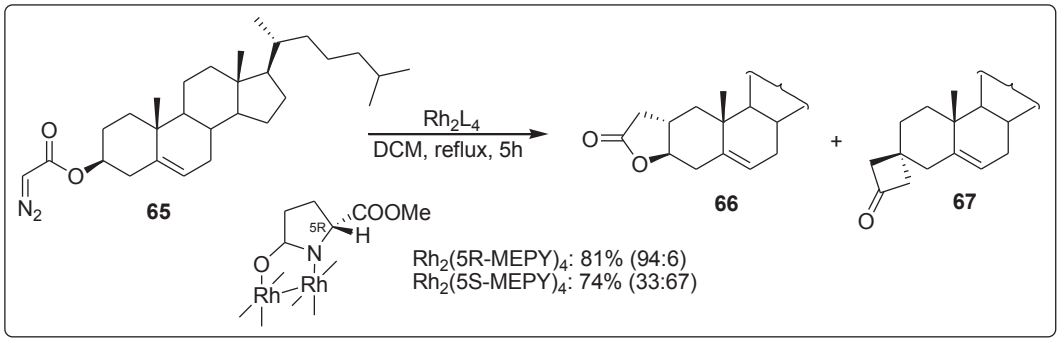
Employing the triplet excited benzophenone, abstraction of the allylic hydrogen from C-7 of cholesterol was studied.[47] When the reaction was considered for intramolecular transformation (e.g., from **63** to **64)**, very high diastereoselectivity (7β-H was abstracted only) was found to occur (**Scheme 1.21**).[48,49]

Cholest-5-en-3b-yl diazoacetate (**65**) was designed and prepared at a good yield (68%) from cholesterol (**13**) by diketene condensation following by diazo transfer and deacetylation. The diazoacetate derivative of cholesterol, **65** was then subjected to standard conditions for diazo decomposition with a series of chiral dirhodium(II) carboxamidate catalysts (**Scheme 1.22**).[50] The products (**66** and **67**) from C–H insertion were found in high yields and selectivities. Intereatingly, insertion into the 3-position to form β-lactone derivatives was preferred by the S-configured catalysts whereas insertion to the equatorial C_2-H bond took place preferentially by the R-configured catalysts. However, present of substituents or functional groups at the 5/6-position were found to prevent C–H insertion at the 4-position.



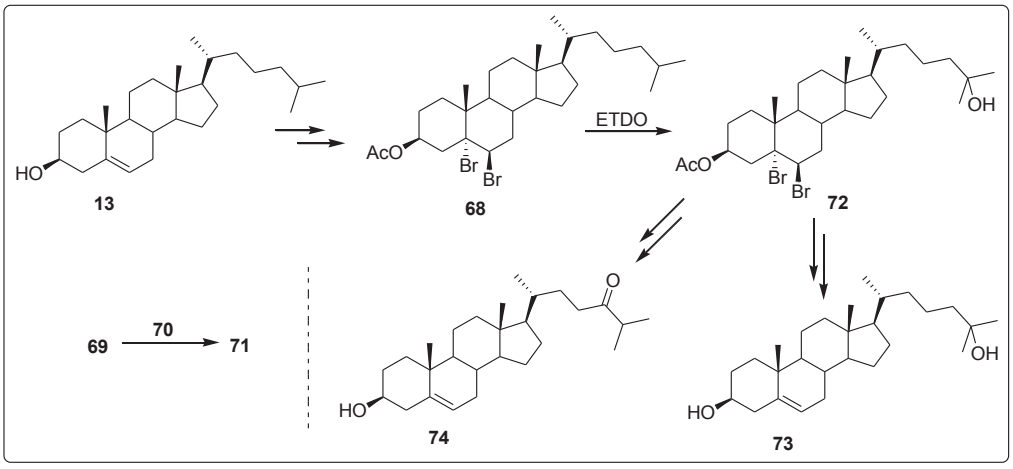
Scheme 1.21 Intramolecular allylic hydrogen abstraction by triplet benzophenone.

Cholest-5-en-3b-yl diazoacetate (**65**) was designed and prepared at a good yield (68%) from cholesterol (**13**) by diketene condensation following by diazo transfer and deacetylation. The diazoacetate derivative of cholesterol, **65** was then subjected to standard conditions for diazo decomposition with a series of chiral dirhodium(II) carboxamidate catalysts (**Scheme 1.22**).[50]



Scheme 1.22 Rhodium-catalyzed decomposition of cholesteryl diazoacetate (**65**).

A regioselective hydroxylation at the tertiary C_{25}–H bond in cholesterol derivatives such as in 5α,6β-dibromocholestan-3β-yl acetate (**68**) was found to occur by ethyl(trifluoromethyl) dioxirane (ETDO, **71**), generated *in situ* from the treatment of 1,1,1-trifluorobutan-2-one (**69**) with potassium peroxymonosulfate (**70**) (**Scheme 1.23**).[51] Thus following the key-step of selective hydroxylation (by forming **72**), concise syntheses of naturally occurring alkyl chain-based oxysterols, *viz.*, 25-hydroxycholesterol (**73**) and 24-oxocholesterol (**74**) were achieved starting from cholesterol (**13**).



Scheme 1.23 Regioselective oxygenation in cholesterol side-chain.

1.3.1.2 Recent advances in the β-sitosterol chemistry

The sterols synthesized in plants are termed as phytosterols, of which the most prevalent are β-sitosterol (**14**) and campesterol (**75**) (**Figure 1.3**) (comprising 95% of total plant sterols).

Recently, in the direction to lower cholesterol levels, incorporation of phytosterol esters into foodstuffs has increased which in turn has increased the interest in phytosterols (and β-sitosterol!).[52,53] Dietary intake of phytosterols is projected to increase in Western countries as consumers respond to health messages to increase vegetable oil consumption at the expense of animal fats.[54]

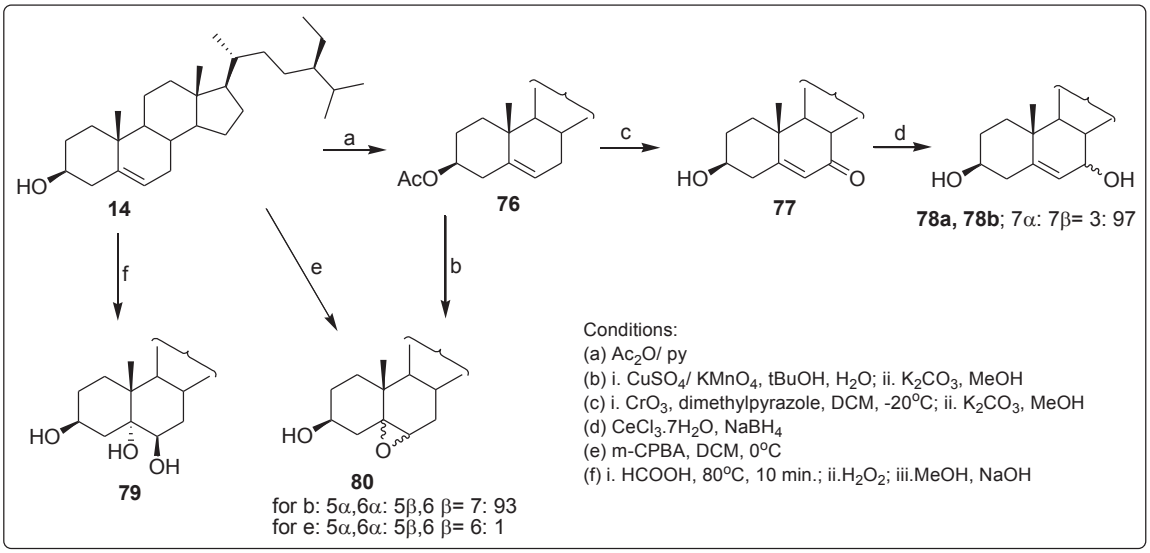
β-Sitosterol is structurally 24α-ethyl cholesterol, and hence it may undergo similar oxidation processes and products to cholesterol. The adverse effects of cholesterol oxidation products is well documented which also include the harmful role in the development of atherosclerosis.[55-57] The consumption of dietary phytosterols in increased quantities has lead to the possibility of increased levels of phytosterol oxides in the blood.

It is assumed, generally, that the absorption of the phytosterols as well as the phytosterol oxidation products (POPs) occurs poorly from the diet, however, the oxidation products have been isolated recently from the plasma of healthy human subjects.[58] Discussion continues as to whether these POPs are absorbed as such or transformed into, *in vivo,* from the parent phytosterols.[59]

The mutation of the ATP-binding cassette transporter G5 (ABCG5) or ABCG8 gene causes an autosomal recessive disease termed as phytosterolemia (or, β-sitosterolemia).[60] ABCG5/ ABCG8 proteins are important to regulate the intestinal absorption as well as the biliary excretion of phytosterols. And, a defect in the protein leads to increased absorption and decreased excretion of the phytosterols, derived from the diet. As a result, an accumulation of the phytosterols occurs in serum and tissues except for the brain, thereby inducing tendon and tuberous xanthomas and premature coronary atherosclerosis.[61] Hence, for the diagnosis of phytosterolemia it is required to determine the serum phytosterols, such as β-sitosterol and campesterol.[62]

Recently, *British Journal of Nutrition* has found it important to conclude that, "the development of accurate and sensitive methods for qualitative and quantitative analyses of oxysterols and oxyphytosterols in food, dietary products and biological samples has become a new challenge."[63]

Synthesis of multi-gram quantities of pure β-sitosterol (**14**) along with its oxygenated derivatives (**76-80**) are reported in the literature (**Scheme 1.24**).[64,65]



Scheme 1.24 Synthetic routes to some oxygenated β-sitosterol (**14**) derivatives.

High-performance liquid chromatography with electrochemical detection (HPLC-ECD) has been reported, by Hakamata et al., to use successfully in the determination of the phytosterols such as β-sitosterol (**14**), stigmasterol (**15**), campesterol (**75**), and brassicasterol (**81**) (**Figure 1.3**).[66]

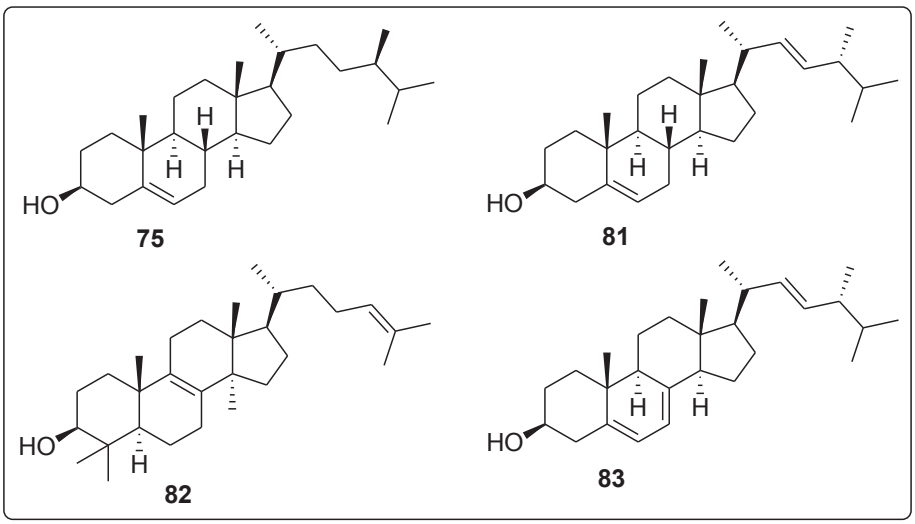


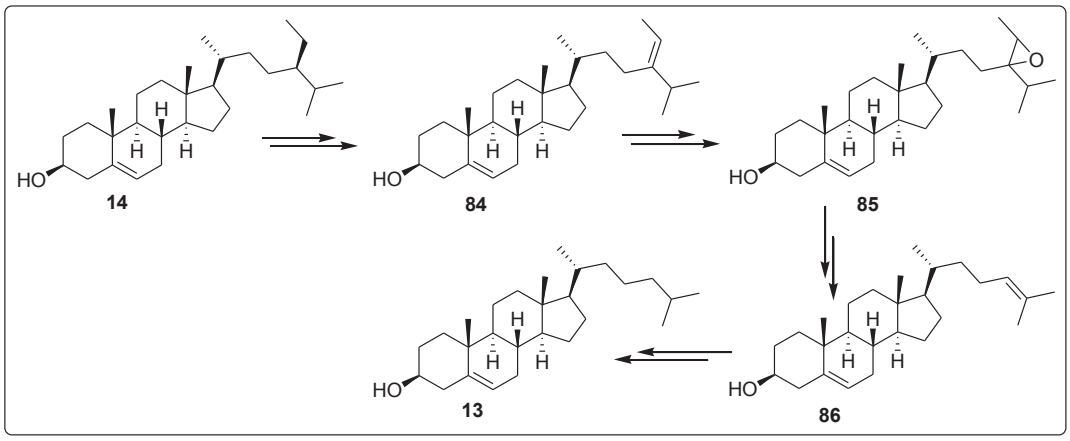
Figure 1.3 Some natural phytosterols (**75**, **81-83**).

People have used NMR spectroscopy also as an useful tool to measure the solubility limit of a number of biologically relevant sterols in electroformed giant unilamellar vesicle membranes containing phosphatidylcholine (PC) lipids in different sterol ratios. The findings conclude the solubility limits of cholesterol (**13**), lanosterol (**82**), ergosterol (**83**), (**Figure 1.3**) stigmasterol

(**15**), and β-sitosterol (**14**) to be 65–70 mol%, ~35 mol%, 30–35 mol%, 20–25 mol%, and ~40 mol%, respectively. Clearly, cholesterol possessed, in the experimental model, highest solubility in comparison to the similar sterols *viz.*, stigmasterol and β-sitosterol, which differ from cholesterol only in their alkyl tails. Thus, subtle differences in alkyl chain structure could strongly affect sterol solubility.[67]

In accordance with the experimental results, Mancera et al. showed, with a series of molecular dynamics simulations, the effect of β-sitosterol (**14**) on some important bio-membranes containing DMSO. As DMSO is one of the most widely used and important cryoprotective agents, the group considered it valuable to determine the nature of the interactions of DMSO with cell membranes at the molecular level and they found that β-sitosterol (**14**) was more effective, at ordering the bilayer, than stigmasterol (**15**).[68]

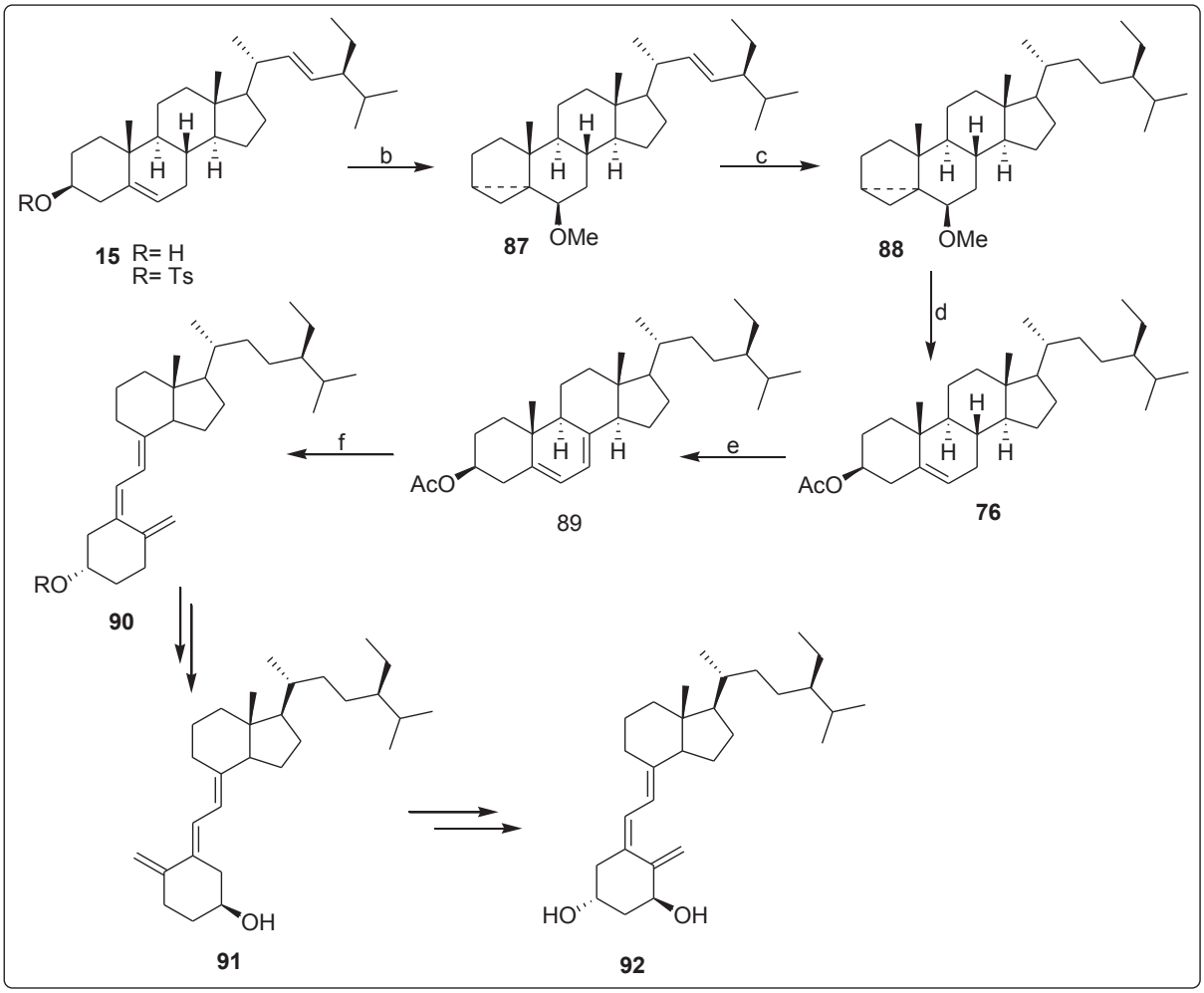
In the conversion of β-sitosterol (**14**) to cholesterol (**13**) in Silkworm, Ikekawa et al. proposed fucosterol-24,28-epoxide (**85**) to be a probable intermediate. Through some valuable experiments and with the comparison of corresponding *in vivo* findings, the group proposed that β-sitosterol (**14**) was first transformed into fucosterol (**84**) followed by epoxidation to form **85**. This Fucosterol-24,28-epoxide (**85**) was then dealkylated to furnish desmosterol (**86**) which produced finally cholesterol (**13**) (**Scheme 1.25**).[69]



Scheme 1.25 Proposed route for the conversion of β-sitosterol (**14**) to cholesterol (**13**) in Silkworm.

Moriarty and Albinescu synthesized (overall yield 1.2%) 1α-Hydroxyvitamin D5 (**92, Scheme 1.26**), a promising chemopreventive agent for breast cancer which is under development as a drug, by utilizing 7-dehydrositosteryl acetate (**90**) as the precursor. They started with

stigmasterol (**15**) to result **89** which furnished finally the potential compound **92** by following the photochemical step (from **89** to **90,** condition f, **Scheme 1.26**) as the key step for the B-ring opening.[70]



Scheme 1.26 Synthesis of promising chemopreventive agent 1α-Hydroxyvitamin D5 (**92**) starting from β-sitosterol (**14**). Conditions: (a) TsCl, DMAP, py, CH_2Cl_2, RT; (b) CH_3COOK, MeOH, reflux; (c) H_2, 10%, Pd/C, CH_3COOEt, RT; (d) $(OAc)_2Zn$, CH_3COOH, reflux; (e) i. dibromantin, hexane, $NaHCO_3$, reflux; ii. LiBr, acetone, toluene, 0^oC; iii. PhSH, Et_3N, RT; iv. *m*-CPBA, CH_3COOH, 0^oC; v. PhMe, Et_3N, 70^oC;(f) i. hn, ^{t}BuOMe, ethyl 4-(dimethylamino)benzoate, -20^oC to 0^oC, ii. uranium glass filter, 9-acetylanthracene, -20^oC to 0^oC; iii. CH_3COOH, reflux.

β-Sitosterol (**14**) has recently been utilized to synthesize a novel third-generation designer amphiphile/surfactant, named as "Nok" (i.e., SPGS-550-M; structurally, β-sitosterol methoxypolyethyleneglycol succinate, **93, Figure 1.4**) by Lipshutz and Klumphu. In water, it

readily forms nanomicelles which serve as nanoreactors. This comparatively far less costly material has been evaluated as highly potential catalyst for a number of transition-metal-catalyzed reactions run under micellar conditions. Two other amphiphiles (named as CPGS-750-M, **94** and PSS, **95**; **Figure 1.4**) were also prepared and studied. The novel surfactant "Nok" has also been comertialized recently (Aldrich catalog number 776033).[71]

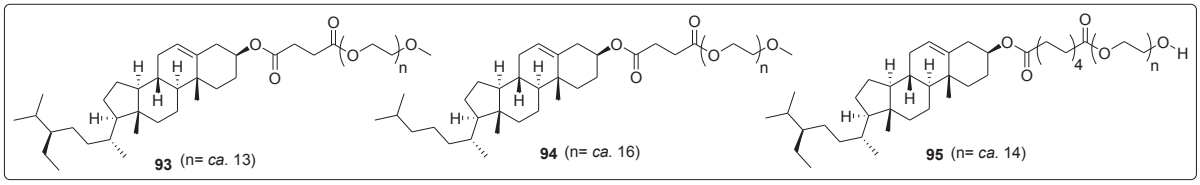
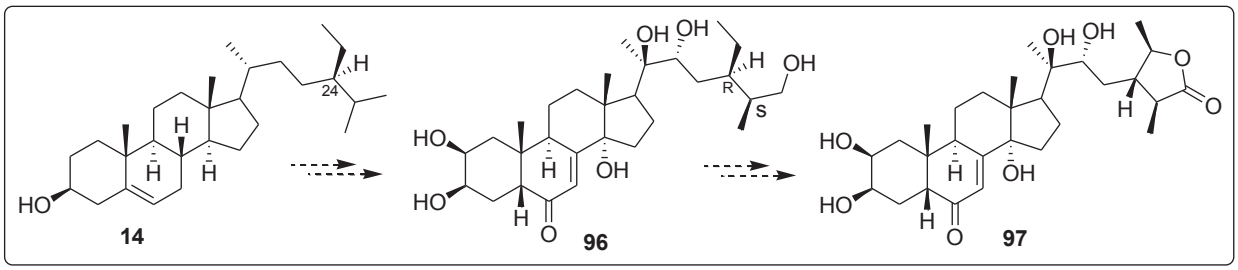


Figure 1.4 β-Sitosterol and cholesterol-based amphiphiles.

Recently, Fujimoto et al. proposed β-sitosterol (**14**) as the biosynthetic precursor for other phytosteroids amarasterone A (**96**) and cyasterone (**97**). The C-24 configuration of the recently isolated phytosteroids was also found identical with β-sitosterol (**14**) (**Scheme 1.27**).[72]



Scheme 1.27 Configurational assignment of amarasterone A (**96**) and cyasterone (**97**) based on β-sitosterol (**14**).

β-Sitosterol (**14**) together with γ-oryzanol component (actually a fraction containing ferulate esters of triterpene alcohols and plant sterols[73], and *ca* 80% of this is constituted by cycloartenyl ferulate (**98a**), 24-methylenecycloartanyl ferulate (**98b**) and campesteryl ferulate (**98c**)[74]; **Figure 1.5**) were found to be self-assembled to produce organogel systems. The influence of the type of oil-phase on the gelation was also studied. A decreasing polarity of the oil was found to promote the self-assembly leading to formation of nano-tubules at higher temperatures and at lower structurant concentrations.[75]

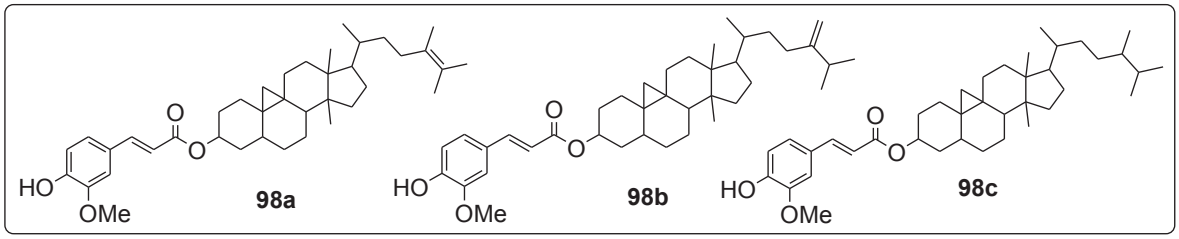
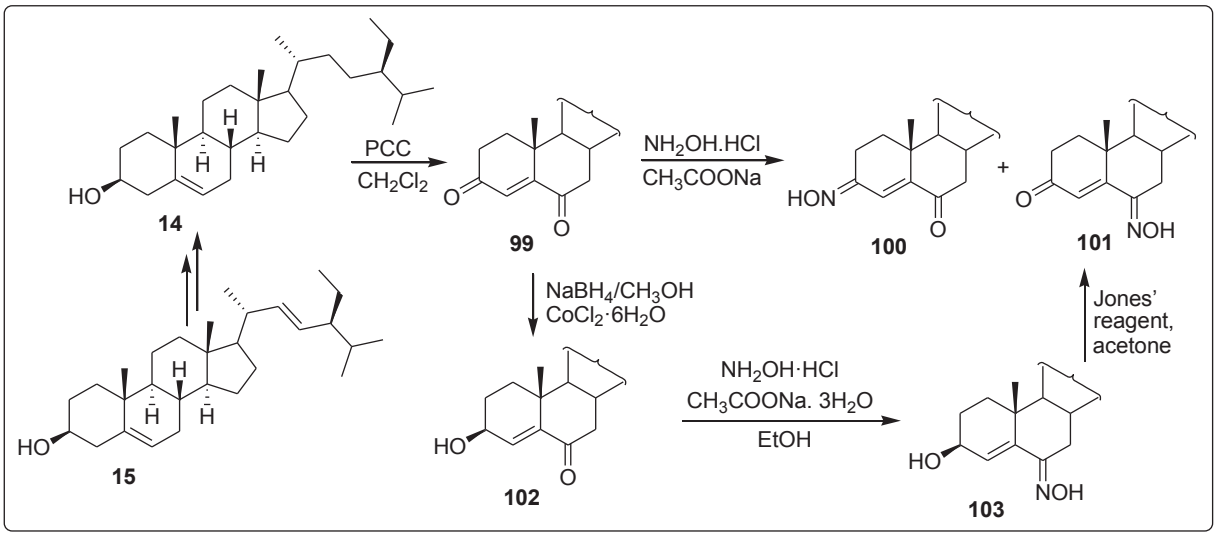


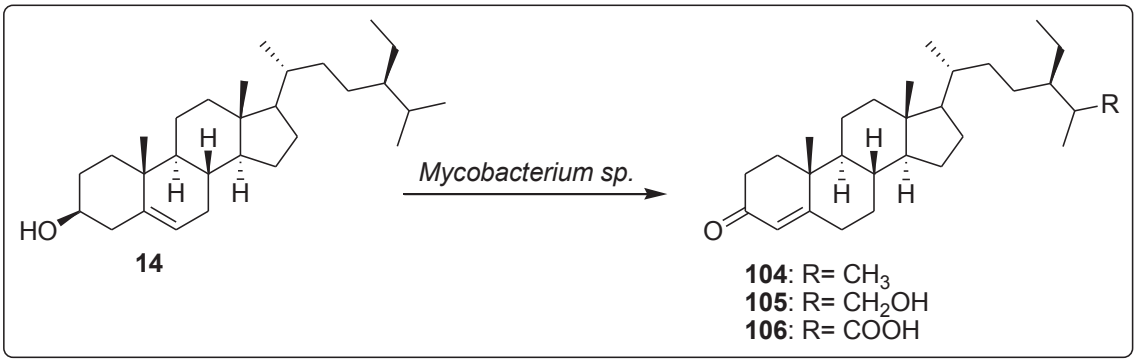
Figure 1.5 Major constituents of γ-oryzanol.

(6*E*)-Hydroximino-24-ethylcholest-4-en-3-one (**101**), a natural steroidal oxime isolated from *Cinachyrella alloclada* and *C. apion*, was synthesized from β-sitosterol.[76,77] Synthesis of a number of oxyphytosterols (**99-103**) was also reported from stigmasterol (**15**) (**Scheme 1.28**).[78]



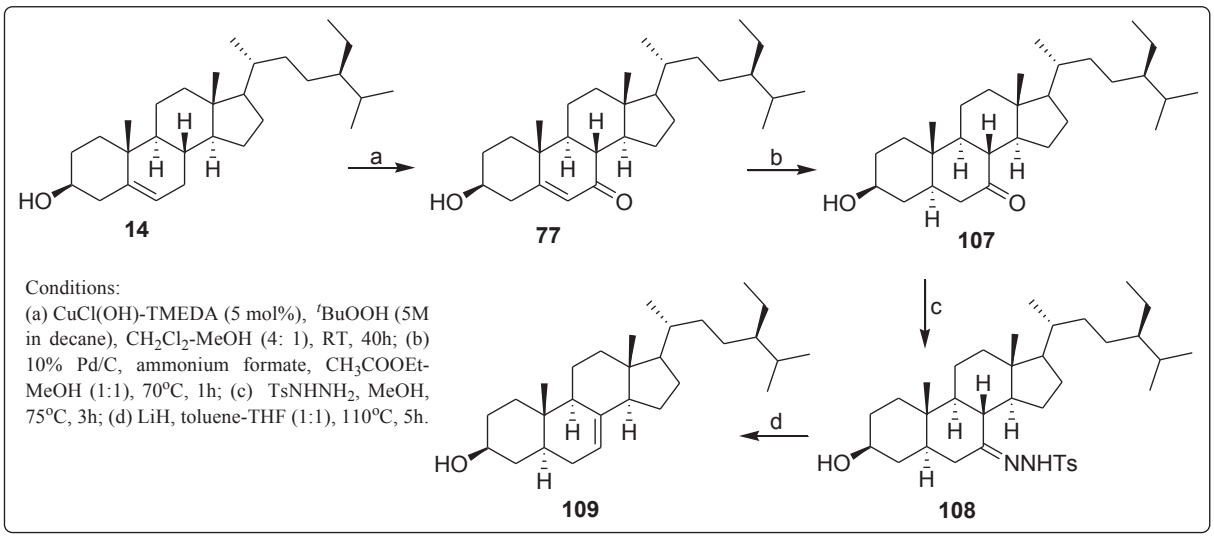
Scheme 1.28 Synthesis of natural β-sitosteryl mono-oxime derivatives (**100-103**).

Biotransformation of β-sitosterol by *Mycobacterium sp.* was found to result 4-stigmasten-3-one (**104**), 26-hydroxy-4-stigmasten-3-one (**105**) and 3-oxo-4-stigmasten-26-oic acid (**106**) (**Scheme 1.29**).[79]



Scheme 1.29 Biotransformation of β-sitosterol (**14**) by *Mycobacterium sp.*

Very recently, Schottenol (**109**), a phytosterol present in argan oil and in cactus pear seed oil, and which revealed reduced mitochondrial activity on 158N murine oligodendrocytes (50%) and C6 rat glioma cells (10–20%), was synthesized from β-sitosterol (**14**) (**Scheme 1.30**).[80]



Scheme 1.30 Synthesis of schottenol (**109**) starting from β-sitosterol (**14**).

I.4 Pentacyclic Triterpenoids

When five carbocyclic rings are fused one-by-one to produce some 6-6-6-6-6, 6-6-6-6-5 or 6-6-7-6-6 type of structure along with some other functional groups (not must) and few –Me groups, to have altogether 30 carbon atoms obeying isoprene rule is known as pentacyclic triterpenoid (PT, **Figure 1.6**).[81] These are the secondary metabolites which are widely distributed in plants and are traditionally used as medicines.[82] Natural PTs are found to possess unique biological activities. A number of important pharmacological and related mechanistic studies including

antitumor, antiviral, anti-inflammatory, antimicrobial, antidiabetic, antiparasitic, cardio-hepato- and gastro-protective, analgesic and wound-healing effects have been carried out. Several PTs are now being marketed as therapeutic agents, and some synthetic PT derivatives are now under clinical trials.[83] The large number of continuous research works in the field, with the evaluation of their practical utilization, implies the increasing interest of the chemical as well as pharmacological research of the pentacyclic triterpenoids.

I.4.1 Different groups of pentacyclic triterpenoids

Pentacyclic triterpenoids are an widespread group of compounds which altogether, depending on their basic structural skeletons, can be divided into six broad classes- 1) friedelane (**6**), 2) lupane (**110**), 3) ursane (**111**), 4) oleanane (**112**), 5) serratane (**113**) and 6) Ψ-taraxastane (**114**) (**Figure 1.6**). Very brief discussion on these classes of compounds are provided below.

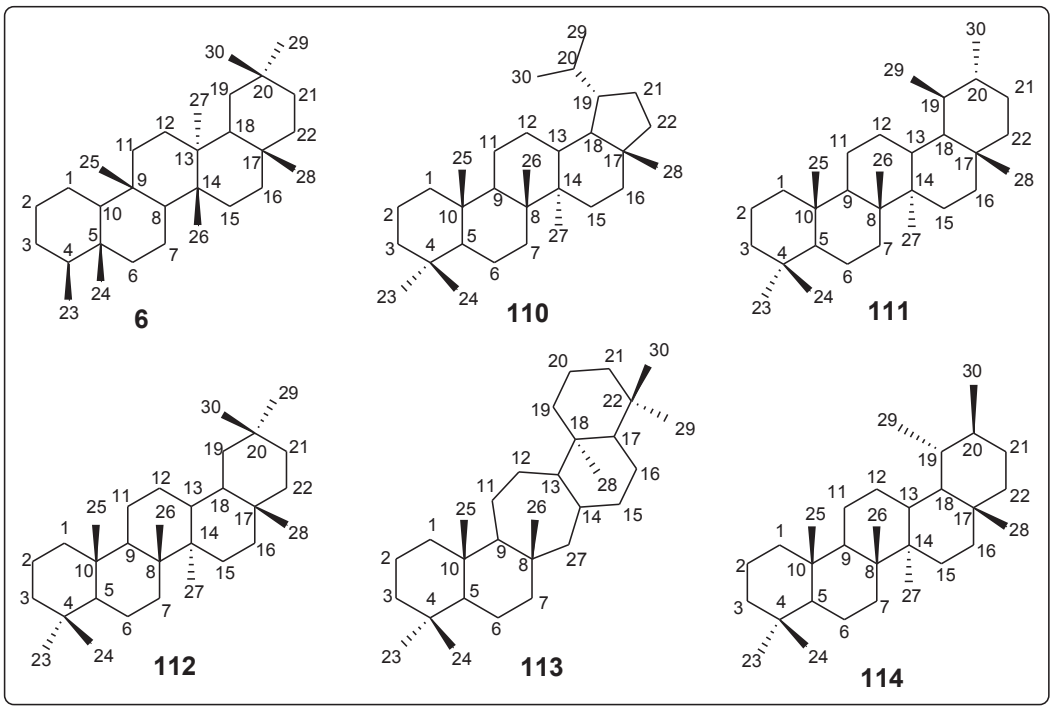


Figure 1.6 Structural skeletons with carbon-numbering of various pentacyclic triterpenoids.

I.4.1.1 Friedelane triterpenoids

Friedelane triterpenoids possess [6-6-6-6-6]-fused pentacyclic basic skeleton with eight -Me groups situated at C(4), C(5), C(9), C(13), C(14), C(17), and C(20) (a geminal-dimethyl), respectively. The most fundamental compounds of the class are friedelin (**115**) and cerin (**116**)

(**Figure 1.6**) which are obtained, at major amount, from the cork smoker washed solids. A large number of friedelanes with different functional/ active groups[84] and their potential biological activities have been reported.[85] Recently, Zhan et al. have reviewed the family of friedelane triterpenoids beautifully by giving emphasis on the fascinating structure and their interesting bioactivities. This review essentially concludes friedelane triterpenoids as 'prime candidates for developing new drugs.'[86] Some very active compounds of the group, such as celastrol (**117**) and correolide (**118**), are being used in pharmacy or in further drug development (**Figure 1.7**).[86]

As the author worked with friedelane triterpenoids giving emphasis on their transformative reactions, a brief review on their bio-availability as well as their transformative reactions are produced separately in **Chapter IV** which describes the syntheses of new friedelane triterpenoids focusing on A-ring modifications including 2-*homo*derivatives.

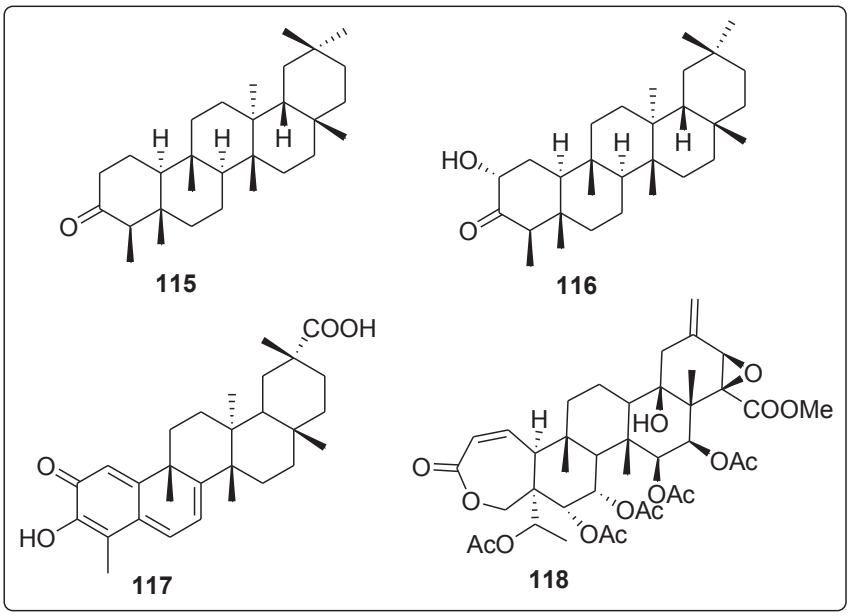


Figure 1.7 Friedelin (**115**), cerin (**116**), celastrol (**117**) and correolide (**118**).

I.4.1.2 Lupane triterpenoids

The pentacyclic triterpenoids having [6-6-6-6-5]-fused carbocyclic rings with six -Me groups situated as C(4) (geminal-dimethyl), C(8), C(10), C(14), C(17), and an isopropyl group at C(20) are known as lupane triterpenoids.

Betulinic acid (BA, **119**), a naturally occurring plant-derived pentacyclic triterpenoid found in many fruits and vegetables[87-88] is the most important member of this group (**Figure 1.8**). It exhibits a wide spectrum of pharmacological and biochemical activities including anti-inflammatory and anticancer,[87-89] anti-HIV[90-93] activities, with low toxicity to normal cells.[94] The natural compound BA shows potential anticancer effects through the activation of mitochondrial pathway of apoptosis in cancer cells. To enhance its antitumor effects through combination protocols, in chemo- or radiotherapy, or in the death receptor ligand TRAIL, BA was found to result as a potential additive.[95] BA is a promisingly new experimental anticancer agent for the treatment of human cancer due to its relative selectivity towards the cytotoxicity against malignant cells compared to normal cells.[96] Currently, BA is in second phase of clinical trials for dysplastic nervus treatment.[97] Again, a number of betulinic acid derivatives were prepared and evaluated for their bio-activities.[98-100] Among the other important lupane triterpenoids, lupeol (**120**) (**Figure 1.8**) and its derivatves were found to have a broad spectrum of biological activities including but not limited to, antiurolithic,[101] antioxidative,[102] anti-inflammatory,[103] hepatoprotective,[104] and antilipidemic activities.[105,106]

I.4.1.3 Ursane and oleanane triterpenoids

Both the ursane and oleanane group of pentacyclic triterpenoids contain a [6-6-6-6-6]-fused carbocyclic skeleton along with eight methyl groups. Thus, these are structurally isomeric. In ursane PTs, the methyl groups are situated at C(4) (geminal-dimethyl), C(8), C(10), C(14), C(17), C(20) and C(21) whereas in the oleanane PTs, no methyl group is there at C(21) and geminal dimethyls are present at C(20). The most fundamental compounds of the group are ursolic acid (UA, **121**) and oleanolic acid (OA, **122**) (**Figure 1.8**). Oleanolic acid, ursolic acid, and their derivatives along with some other PTs of the group are also found to possess useful bioactivities such as anti-inflammatory,[107-110] diuretic and anti-tumor,[111-112] hepatoprotective[113-114] and anti-HIV[115-116] activities. Ursolic acid itself is cytotoxic against A-549, L-1210 and KB tumor cells.[117] There are useful reviews highlighting also the broad spectrum of biological activities including phytotoxic[118] and photosynthesis inhibition activities[89] and low toxicities of oleanane and ursane triterpenoids.[119-123]

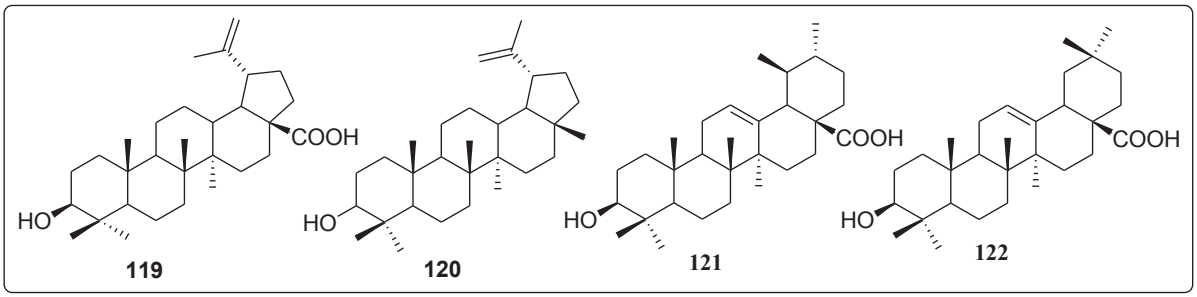


Figure 1.8 Betulinic acid (**119**), lupeol (**120**), ursolic acid (**121**) and oleanolic acid (**122**).

I.4.1.4 Serratane and Ψ-taraxastane triterpenoids

A [6-6-7-6-6]-fused carbocyclic skeleton having seven -Me groups at C(4) (geminal-dimethyl), C(8), C(10), C(18), and C(22) (geminal-dimethyl) to result a pentacyclic triterpenoid is known as serratane triterpenoids. On the other hand, the ursane skeletal-based groups of PTs where the stereochemistry of the methyl groups at C-20 and C-21 are just the reverse to that of ursane itself, is known as Ψ-taraxastane triterpenoids. However, these PTs are somehow limited in their reports so far. Few of the members of these groups are phlegmanol A (**123**),[124] faradiol, heliantriol B_o, heliantriol C, arnidiol (**124**) and many of them are found to be cytotoxic (**Figure 1.9**).[125]

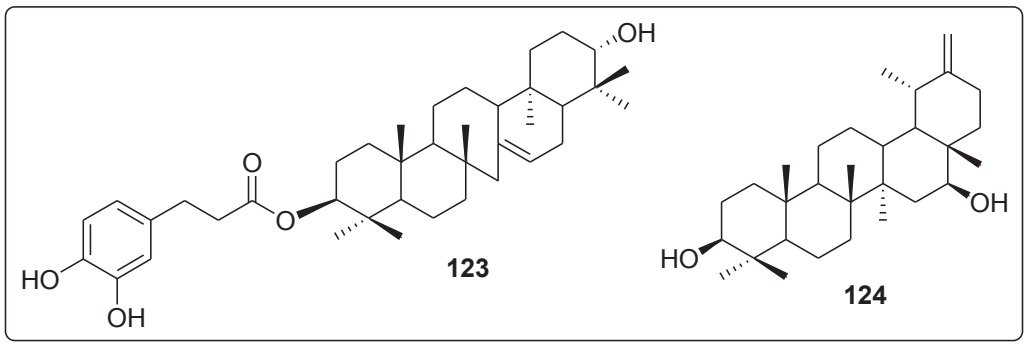


Figure 1.9 Phlegmanol A (**123**) and arnidiol (**124**).

1.4.2 Recent advances in the transformative reactions on pentacyclic triterpenoids

Though this is a very broad and elaborate subject, the present title is an effort to summarize, in very brief, the different transformative scopes on some major and selective pentacyclic triterpenoids. Again, as all of these are associated with some useful/ probable biological importance, the bioactivities are also mentioned. Of note, most of the derivatization processes are consist of a number of steps as well as a number of different transformative protocols. Thus, in

most of the instances the major derivatization step(s) or the skeletal presentation of the resultant compound(s) is provided below to have a very brief overview.

Betulinic acid (BA), a natural pentacyclic triterpene exhibits a variety of biological activities including antitumor properties.[126] Betulinic acid was also found to show selective cytotoxicity on tumor cell lines, but not on normal cells.[127] BA (3β-hydroxy-lup-20(29)-en-28-oic acid) is widely distributed in the plant kingdom throughout the world.[124] And these two factors, easy availability and promising bioactivity render the compound very much suitable for a number of chemical transformative reactions. The cooperative effect of betulinic acid for the sensitization of anticancer drug-induced apoptosis was also studied by Fulda et al.[128] Aiken et al. reviewed BA derivatives as HIV-1 antivirals[129] and Fulda reviewed the anticancer potential of betulinic acid.[130]

A number of modified betulinic acid derivatives were achived which include cytotoxic A-seco derivatives,[131] C28-modified HIV-2 inhibitors,[132] C28-modified alphavirus replication inhibitors,[133] C3-modified BA derivatives for anti-AIDS agents.[100] A-ring modifications including the synthesis of betulin amine dimer (**126**) (**Figure 1.10**),[134] C3-neoglycosylation (**128**)[135] are reported (**Figure 1.11**). Synthetic routes for C28,C30-disubstituted derivatives, C3,C28-disubstituted 3β-amino derivatives and C3,C28-disubstituted C28-piperidine derivatives were found useful to result ultimately a number of potent anti-HIV betulinic acid triterpenoids.[136] After having a library of these derivatives, SAR were revealed to be used efficiently for further designed transformations.[100] Simple modifications at C3, C20, C28 and C30 in betulinic acid lead the derivatives towards potent Topoisomerase inhibitors.[137] Some natural C3 modified BA derivatives were also found to show DNA topoisimerase II inhibitory activity.[138] C3 and C28-modified BA derivatives showed anticancer activities[139] as well as activation and inhibition of the proteasome.[140] C3, C20 and C29- Modified derivatives of BA were synthesized and were found to be anti-diabetec.[141] Bidesmosidic betulin and betulinic acid saponins were also synthesized and were evaluated for their cytotoxicity.[142] C28 and/ or C3-Modified derivatives were found active as antitumor agents.[143, 144] A number of heterocyclic ring-fused betulinic acid derivatives were also synthesized and evaluated for their biological activities.[145]

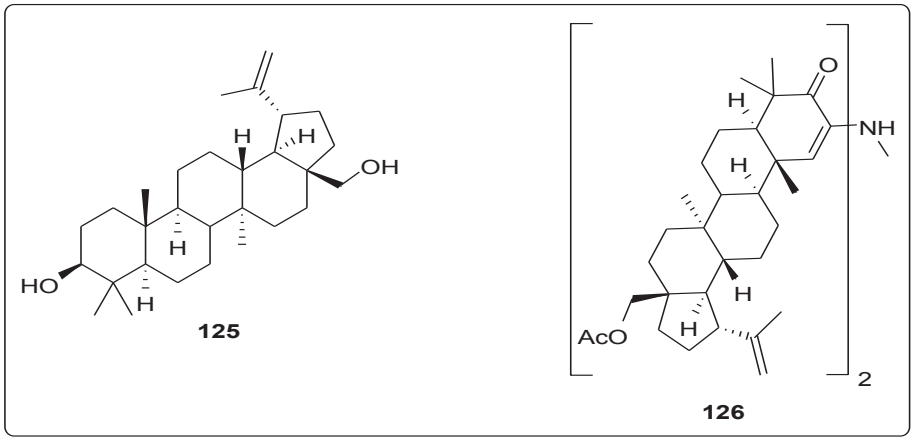


Figure 1.10 Betulin (**125**) and its amine dimer (**126**).

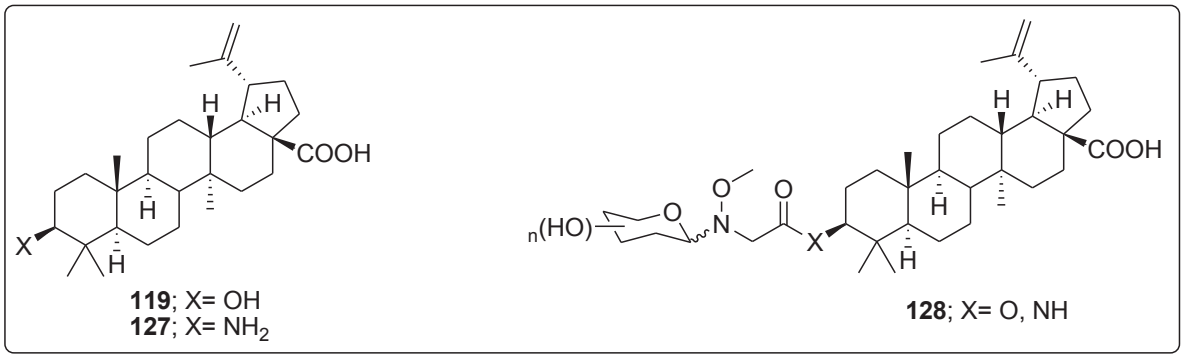


Figure 1.11 C3-Neoglycosylation of betulinic acid and its 3β-amino derivative.

Mayaux et al. reported a betulinic acid derivative RPR103611 (**129**, **Figure 1.11**) which was found to be a fusion inhibitor active at a submicromolar level.[146] Results also showed that epimeric IC9564 (**130**, **Figure 1.12**) inhibits HIV-1 at the membrane fusion step[145] and further analysis showed that HIV-1 gp120 was the molecular target for IC9564. In analogy, Lee and his group discovered more potent anti-fusion derivatives of betulinic acid where the modifications were carried out in the isopropylene and C-28 side chain.[99]

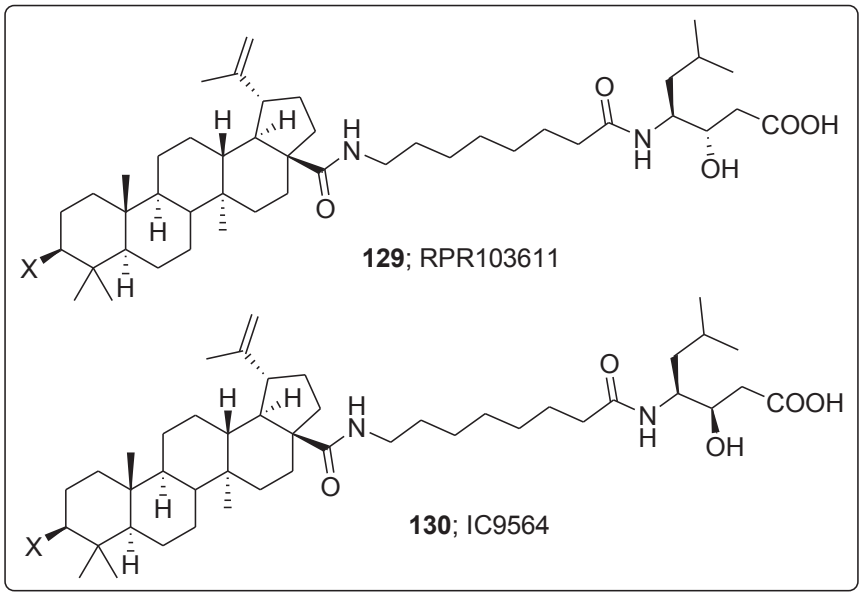
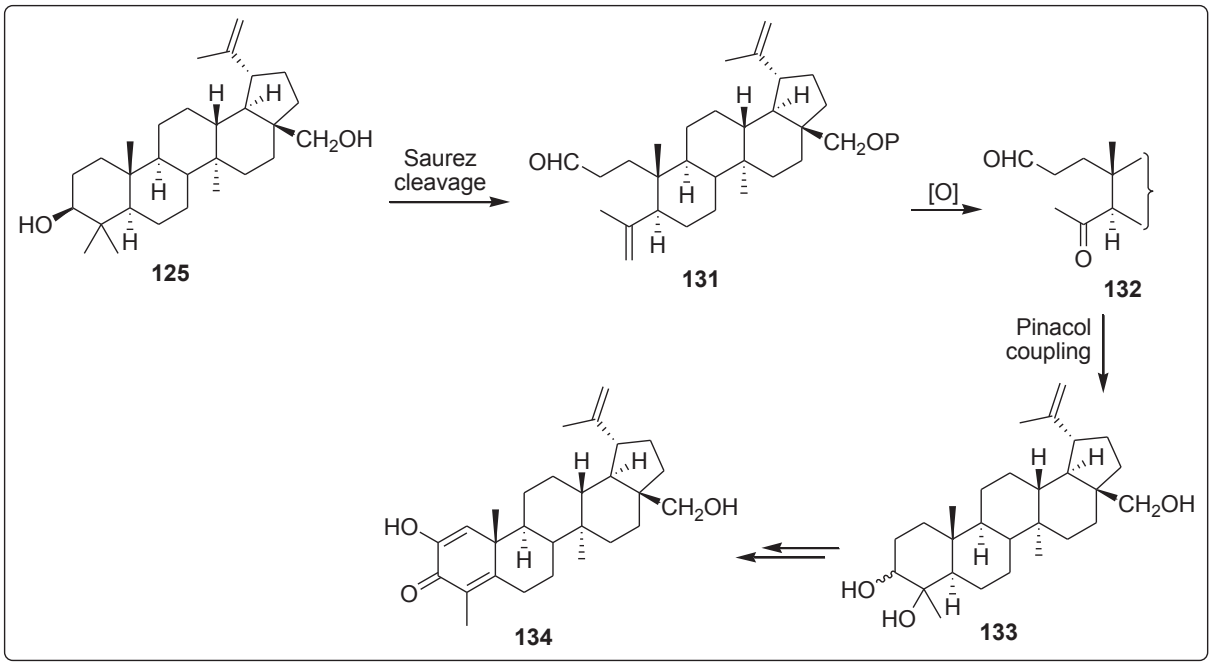


Figure 1.12 RPR103611 (**129**) and IC9564 (**130**).

Betulin (**125**) was utilized to furnish a number of 24-nortriterpene derivatives. The key steps in the transformation were a Sua´rez cleavage of the A-ring followed by SmI_2-mediated pinacol-type coupling to reclose the A-ring. The derivatives were then screened for their anticancer activities.[147] (**Scheme 1.31**)

Bevirimat (**135**, BVM, also known as PA-457, DSB, and MPC- 4326, **Figure 1.13**) is an anti-HIV agent that blocks HIV-1 replication by interfering with HIV-1 Gag-SP1 processing at a late stage of viral maturation. However, clinical trials of **135** have revealed a high baseline drug resistance that is attributed to naturally occurring polymorphisms in HIV-1 Gag.[129,148-155]

Modification of the structure of **135** was thus essential to overcome the resistance. Improved activity of the compound was found by attaching a side chain at the C28 position of **135**.[156] In analogy, C28-modified derivative, compound **136** was found to be at least 20-fold more potent than **135** against the replication of NL4-3/V370A. Later on though it was found to be inactive against BVM-R viruses, its improved anti-HIV-1 activity against NL4-3 strain suggested that C28 modifications could impact drug-target interaction. Thus, a library of compounds of **135** analogues were synthesized systematically focusing C28 modifications.[157]



Scheme 1.31 Key step for the synthesis of 24-nortriterpene derivatives from betulin (**125**).

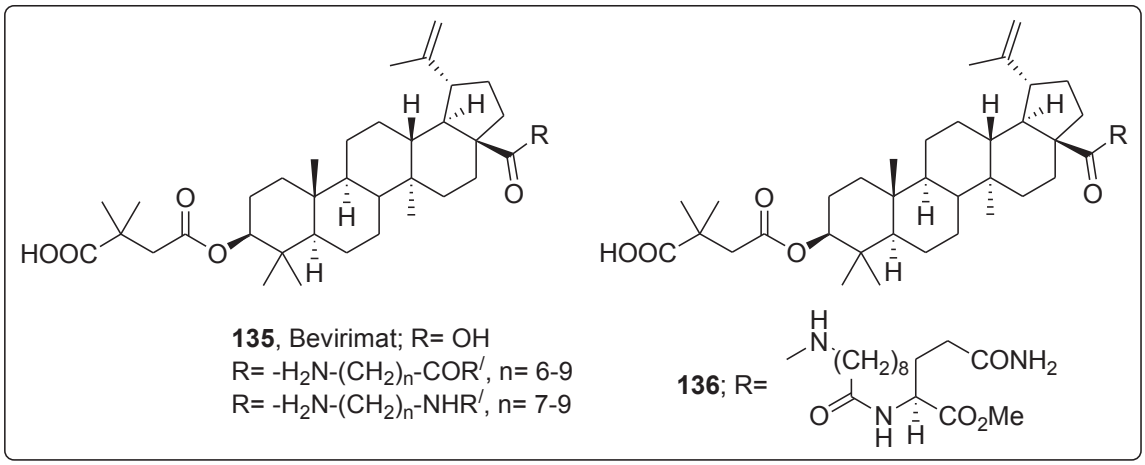


Figure 1.13 Bevirimat (**135**) and C28-modified derivative **136**.

Very recently, a fluorescent cancer cell detector as well as potent anticancer agent has been synthesized based on betulinic acid (**119**). The compound **137** (**Figure 1.14**) is actually an example and use of isatins as betulinic acid conjugate for selective detection of cancer and subsequent killing of cancer cells *via* apoptosis.[158]

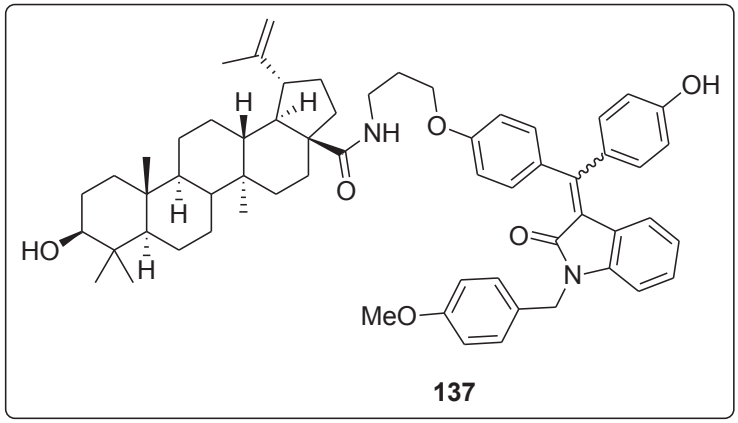


Figure 1.14 A fluorescent cancer cell detector **137**.

Recently, self-assembled targeted folate-conjugated eight-arm-polyethylene glycol–betulinic acid nanoparticles **138** were synthesized for the co-delivery of anticancer drugs.[159] (**Figure 1.15**)

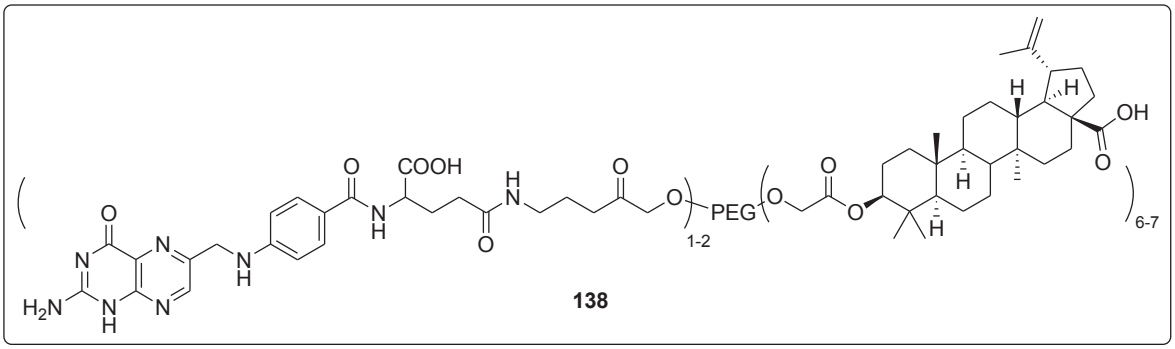
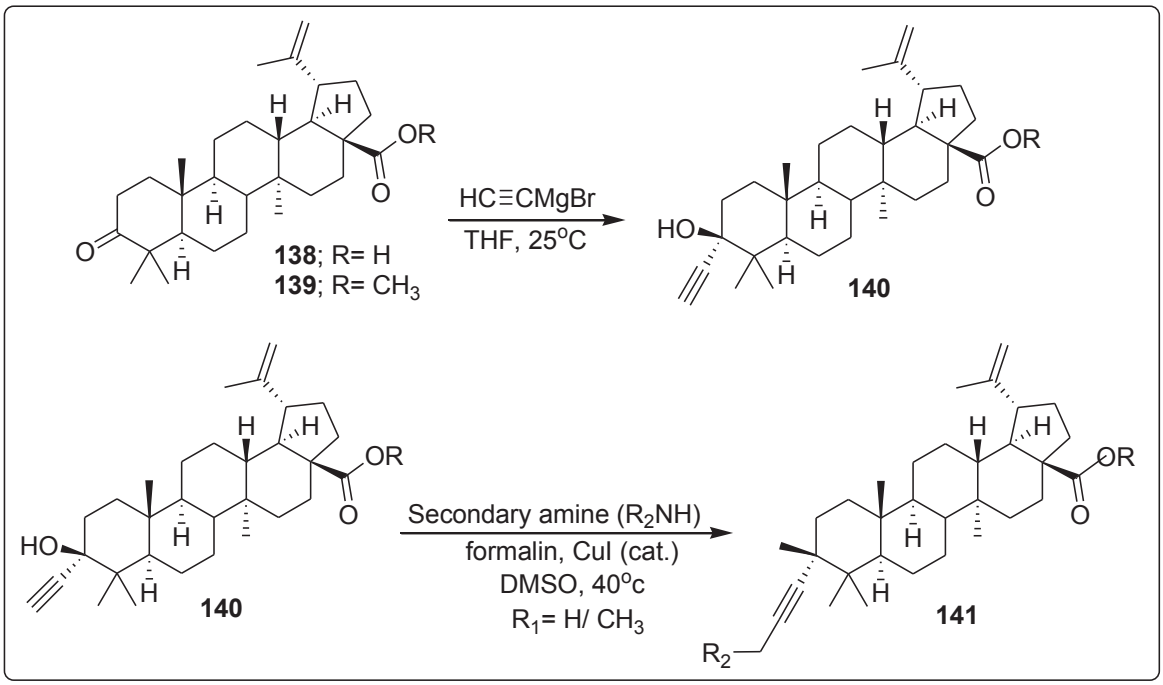


Figure 1.15 Compound **138** for the co-delivery of anticancer drugs.

Biotransformation of betulinic acid (**119**) and its derivatives were also achieved. Microbial transformations of betulinic and betulonic acids are reported.[160, 161] Liu et al. optimized the biotransformation process of betulin (**125**) into betulinic acid (**119**) catalysed by fungus *Armillaria luteo-virens* Sacc ZJUQH100-6.[162]

Following copper-catalyzed Mannich reactions, Csuk et al. synthesized a library of C3-hydroxypropargylamine derivatives of betulinic acid (**141**, as the general skeleton), some of which showed significant cytotoxicity.[163] (**Scheme 1.32**)



Scheme 1.32 C3- Hydroxypropargylamine derivatives of betulinic acid.

The semisynthesis of piperazine derivatives **142-143** of betulinic acid are described recently and these were evaluated biologically for their antimalarial activity, cytotoxicity and the mechanism of their action.[164] (**Figure 1.16**)

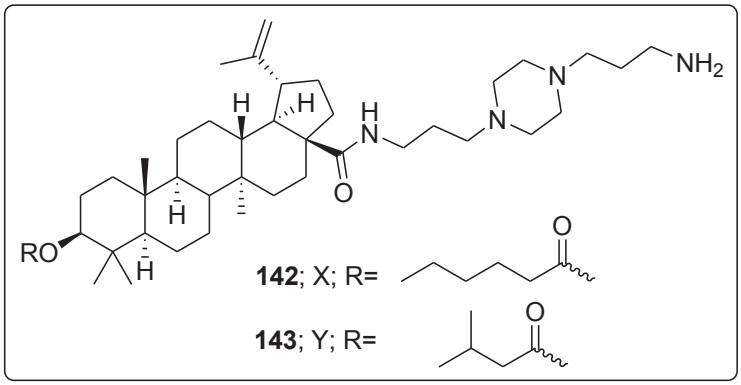
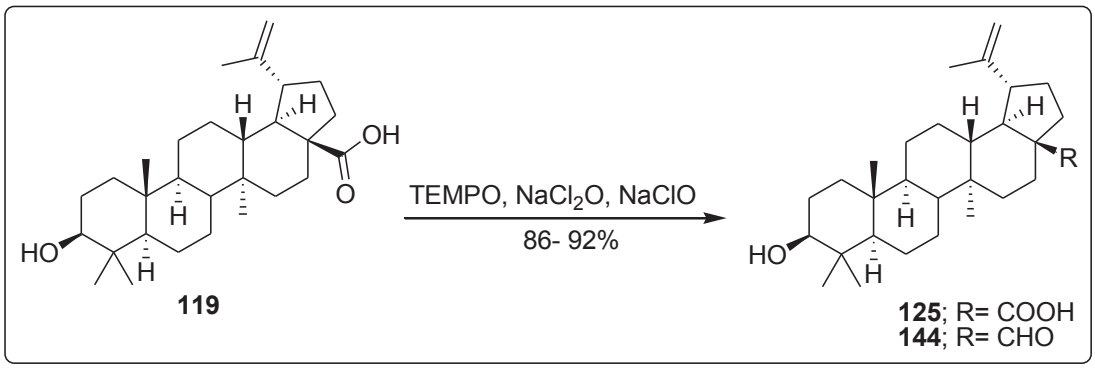


Figure 1.16 Piperazine derivatives of betulinic acid **142-143**.

Synthetic route for the synthesis of betulinic acid (**119**) from betulin (**125**) was developed by utilizing the selective oxidation of the primary alcohol function of betulin (**125**) without affecting

the secondary hydroxyl group. The corresponding aldehyde, betulinal (**144**) was also achieved exclusively by applying shorter reaction times and lower temperatures.[165] (**Scheme 1.33**)



Scheme 1.33 Synthesis of betulin (**125**) and betulinal (**144**).

C-20 Modified betulinic acid derivatives were prepared and were evaluated for structure–activity relationship study which revealed that the C-20 position was found to be sensitive to the size and the electron density of the substituents in retaining the cytotoxicity of betulinic acid and was found to be undesirable position for derivatization.[166]

Betulinic acid and its derivatives (modified at C3 and C20), as anticipated earlier, were found to possess anti-angiogenic effects and cytotoxic activity of 3-O-acyl/3-hydrazine/2-bromo/20,29-dibromo betulinic acid derivatives were also studied by Mukherjee et al.[167, 168] Some other A-ring modified betulinic acid derivatives were synthesized and evaluated for their cytotoxic activities.[169] 3β-*O*-Phthalic esters of betulinic acid and its esters were also synthesized. The evaluation of cytotoxicity of the prepared compounds revealed that hemiphthalic esters possess better cytotoxicity in comparison to the starting materials.[170]

Betulinic acid derivatives with a side chain at C-3 were found to inhibit HIV-1 maturation. On the other hand, BA derivatives with a side chain at C-28 were active to block HIV-1 entry. In order to combine the anti-maturation and anti-entry activities in a single molecule, bi-functional BA derivatives (**147**) containing side chains at C-3 and C-28 were synthesized by Lee and his coworkers. Screening resulted compound ([[N-[3b-O-(30,30-dimethylsuccinyl)-lup-20(29)-en-28-oyl]-7-aminoheptyl]-carbamoyl]methane, **148**) to be the most potent which inhibited HIV-1 at an EC_{50} of 0.0026 μM and was at least 20 times more potent than either the anti-maturation

lead compound DSB (**145**) or the anti-entry lead compound IC9564 (**146**). This bi-functional BA derivative was active against both HIV entry and maturation.[171] (**Figure 1.17**)

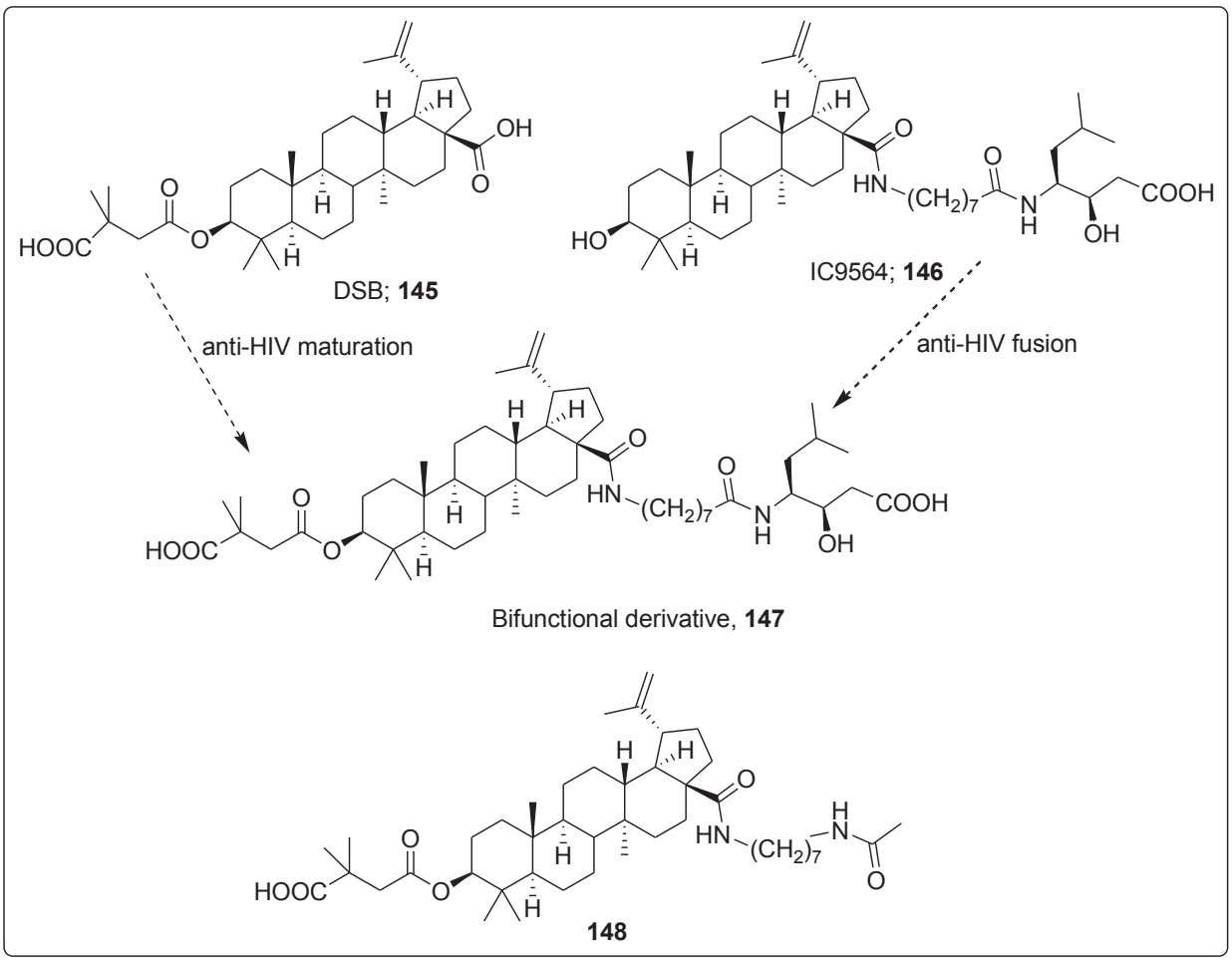


Figure 1.17 BA derivatives **145-148**.

Natural betulinic acid saponins (**149-150**) which were isolated from *Pulsatilla koreana* and *Schefflera rotundifolia*, were synthesized using a stepwise glycosidation approach involving eight linear steps.[172] (**Figure 1.18**)

Sulfur derivatives of lupane and oleanane triterpenoids were also achieved[173] by using the Lawesson's reagent (**151**),[174] (**Figure 1.19**) a widely used thionation reagent.[175]

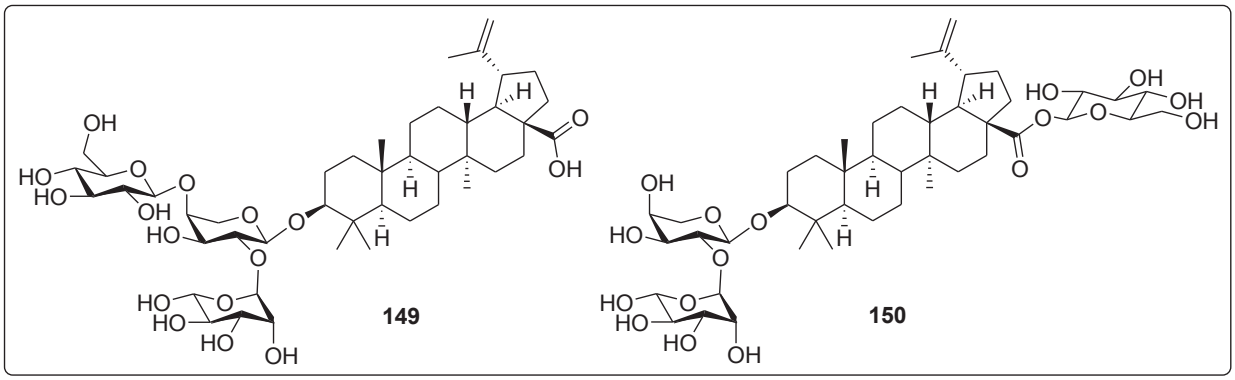


Figure 1.18 Natural betulinic acid saponins (**149-150**).

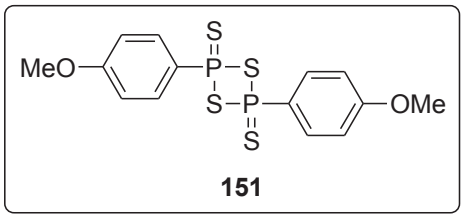
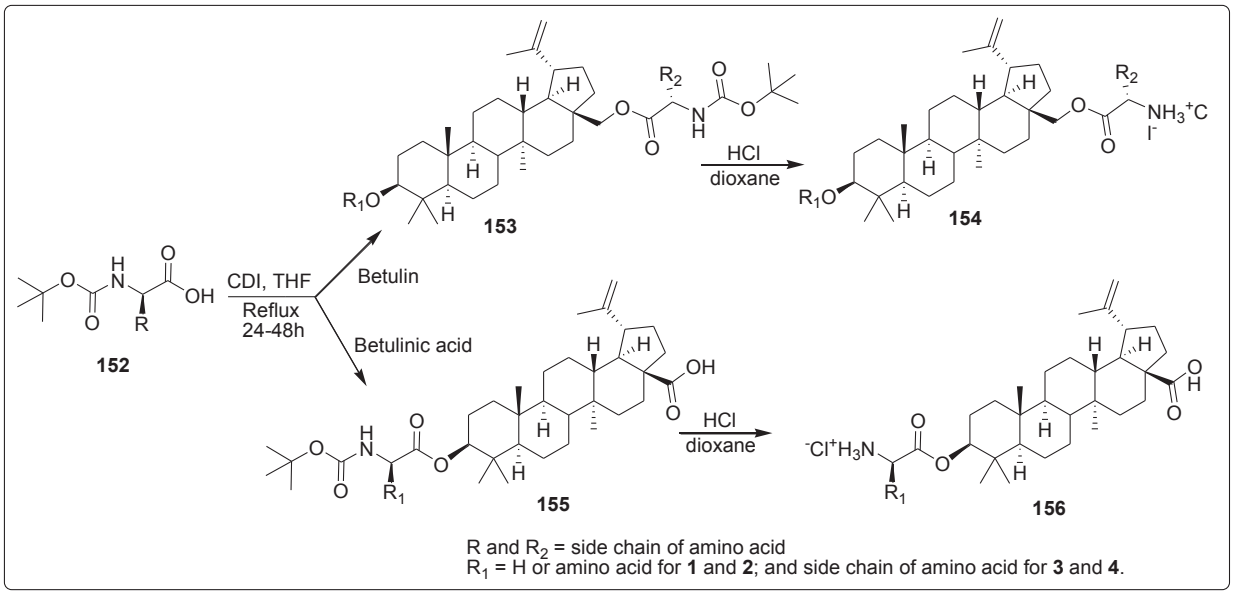


Figure 1.19 Lawesson's reagent (**151**).

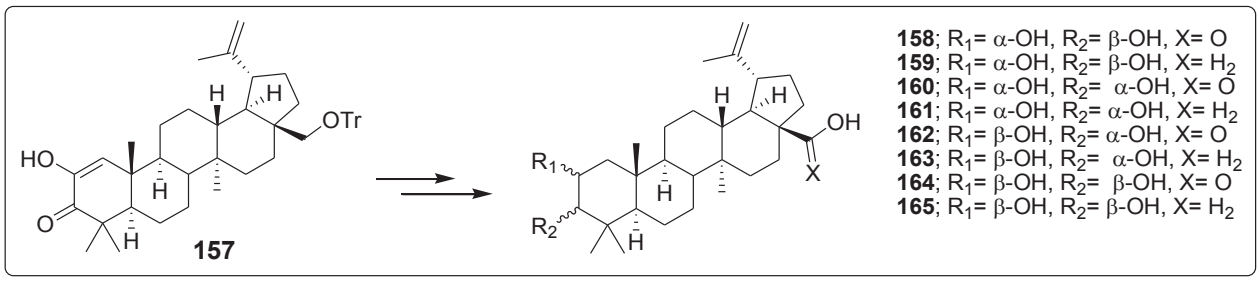
Nitrogen-containing derivatives of betulin and betulinic acid, such as amine derivatives,[169,176,177] oxime derivatives,[169,170,176] amino acid conjugates,[178] amide derivatives,[179-180] hydrazine[181] and hydrazone derivatives,[170-171,177,181] imidazolide derivatives,[182] and other *N*-heterocyclic derivatives[183-188] have been reported to possess antiproliferative effect against tumour cell lines. Imidazole carboxylic esters (carbamates) and *N*-acylimidazole derivatives of betulin and betulinic acid were also synthesized and were evaluated for their cytotoxic activities.[189]

To achieve better water solubility without the loss of the observed earlier anticancer properties, betulin and betulinic acid were undergone simple transformation to mono- and disubstituted esters of *L*-amino acids (**153-156**).[190] (**Scheme 1.34**)

Alphitolic acid (**158**), a naturally occurring lupane type pentacyclic triterpene with various pharmacological properties, was synthesized in 10 steps with an overall yield of 19% starting from the readily available diketone **157**. Seven other isomeric 2,3-dihydroxy lupanes **159-165** were also synthesized. The synthesized triterpenes **158-165** were also evaluated for their bio-activities.[191] (**Scheme 1.35**)



Scheme 1.34 Esters of L-amino acids **153-156.**



Scheme 1.35 Synthesis of lupane derivatives **(158-165).**

Stereoselective synthesis of 28-*O*-β-D-glucuronide betulinic acid (**166**) was carried out under phase-transfer conditions. The methodology was also applicable for the preparation of the major acyl glucuronide metabolite of bevirimat (**167**) or other carboxylic acid-containing drug metabolites.[192] (**Figure 1.20**)

C3- and C28-Modified carbamate derivatives of betulinic acid and betulin possessing selective cytotoxic activity were also achieved by Kommera et al.[193]

Semisynthesis of betulinic acid derivatives RS01 (**168**), RS02 (**169**) and RS03 (**170**) were carried out, which showed 18-45 times improved cytotoxic activity against HepG2 cells.[194] (**Scheme 1.36**)

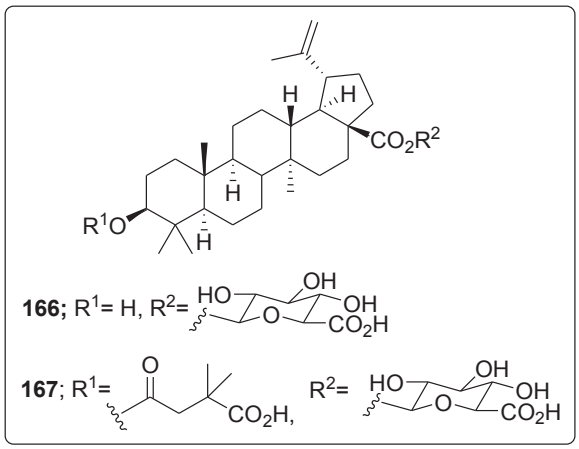
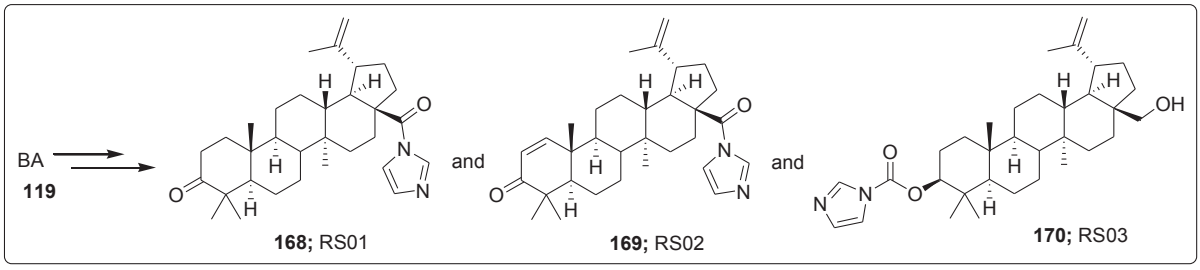


Figure 1.20 28-*O*-β-D-glucuronide betulinic acid and bevirimat (**166** and **167**).



Scheme 1.36 Semisynthesis of betulinic acid derivatives RS01 (**168**), RS02 (**169**) and RS03 (**170**).

Bevirimat, a C3-modified BA derivative exhibited promising pharmacokinetic profiles in clinical trials, but its effectiveness was compromised by the high baseline drug resistance of HIV-1 variants with polymorphism in the putative drug binding site. Towards the improvement of the drug, a library of C28-modified derivatives were synthesized and among them, comp **171**, **172** and **173** were found to improve markedly the microsomal stability compared to A43D, a C28-modified HIV-1 entry inhibitors.[195] (**Figure 1.21**)

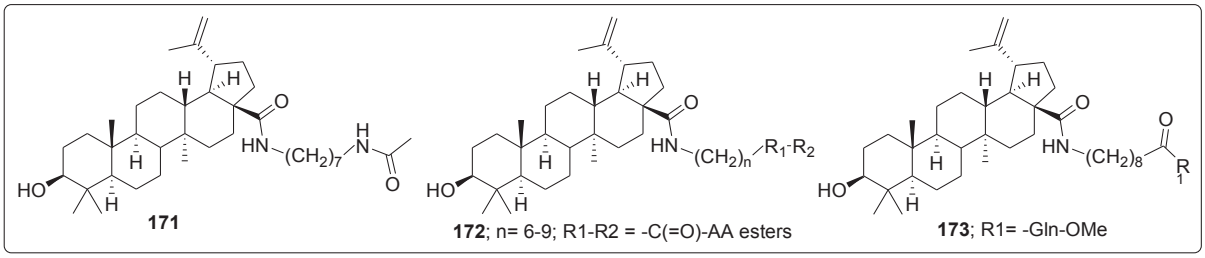


Figure 1.21 C28-modified derivatives **171-173**.

Chemical transformation of betulinic acid, through concise 1,2,3-triazole synthesis *via* click chemistry approach at C-3 position in ring A, was achieved to result 3-*O*-propargylated betulinic acid and its 1,2,3-triazoles which were found to be potential apoptotic agents.[196]

A number of DMAP derivatives of BA (**174-180**) were synthesized and the compounds were active for promoting cell death through directly targeting mitochondria of breast cancer cells.[197] (**Figure 1.22**)

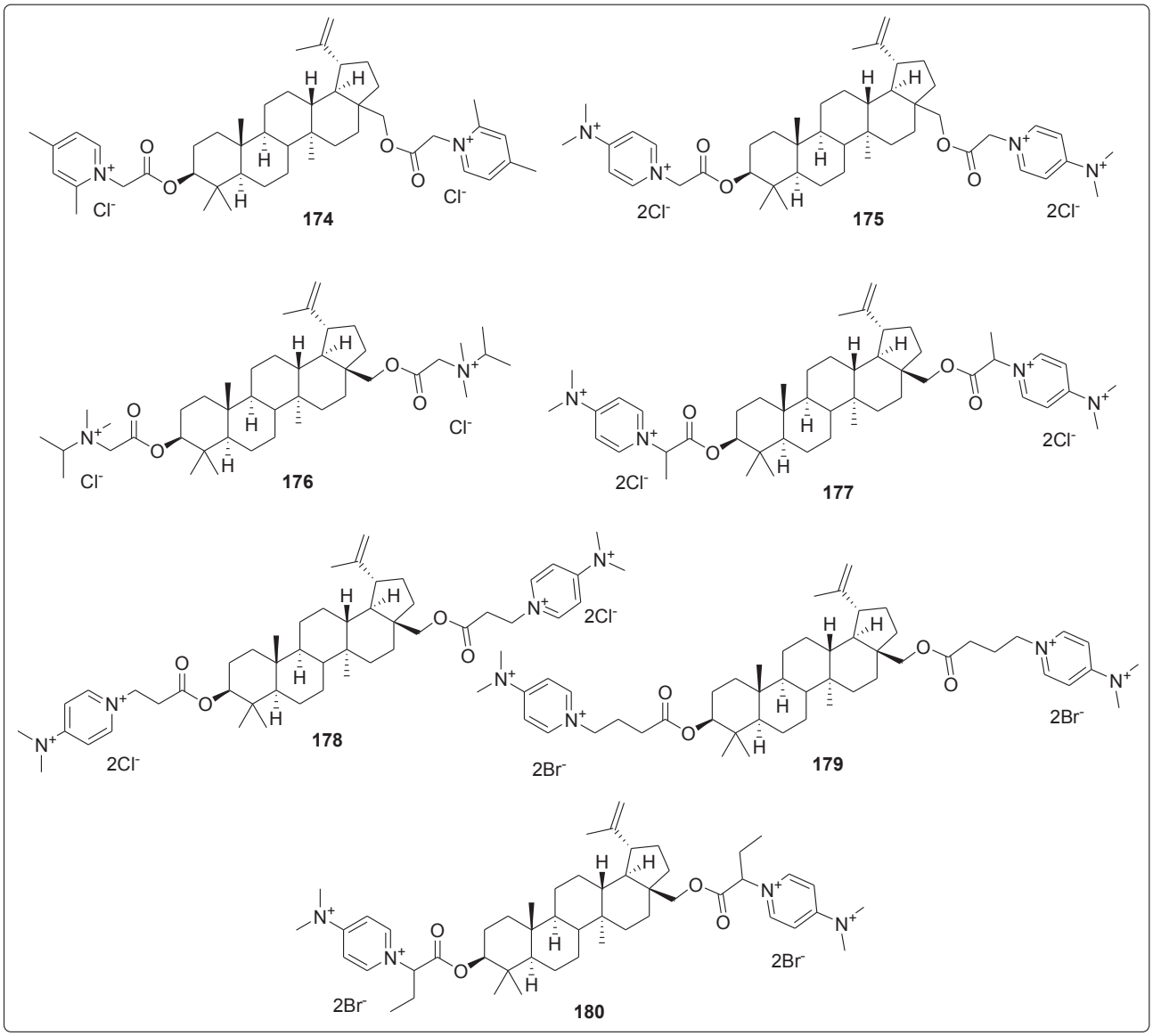


Figure 1.22 DMAP derivatives (**174-180**) of BA.

Synthesis of triphenylphosphonium derivatives (**181-189**) of betulin and betulinic acid, characterized by a covalently linkage of the hydrophobic fragment of the triterpenoid at C2- or C30-position with the triphenylphosphonium moiety *via* a hydrocarbon bridge, were achieved and found potent against *Schistosoma mansoni*, *in vitro* and *in vivo*.[198] (**Figure 1.23**)

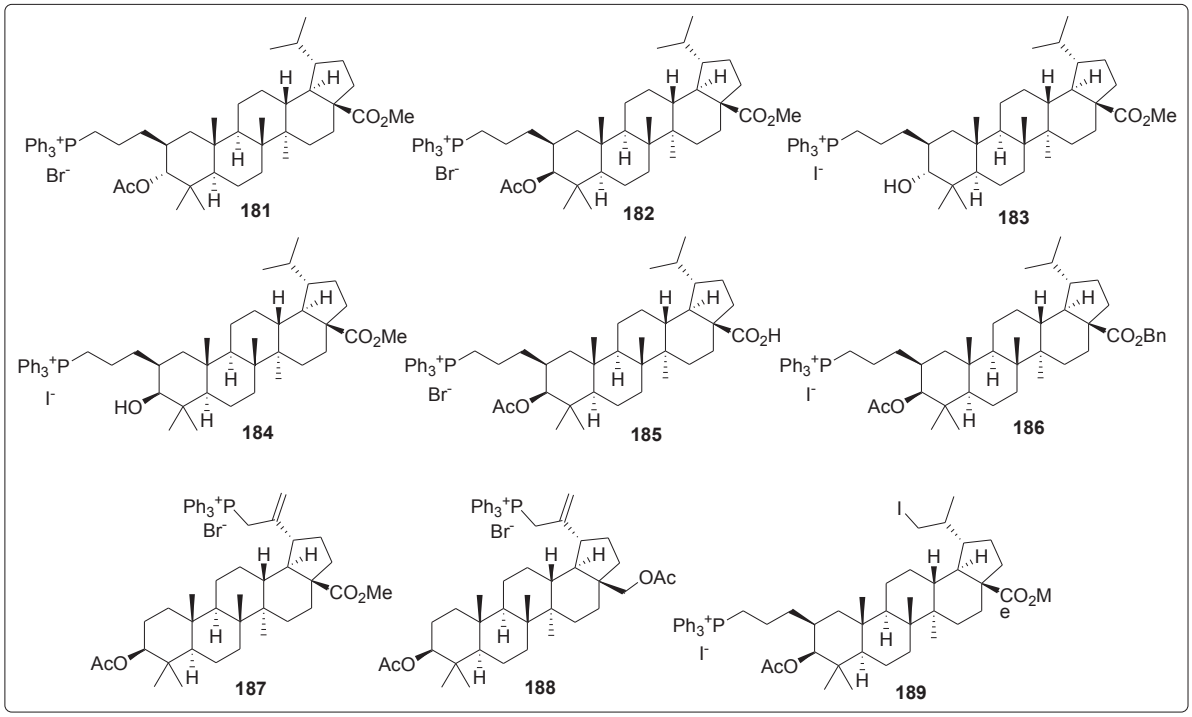
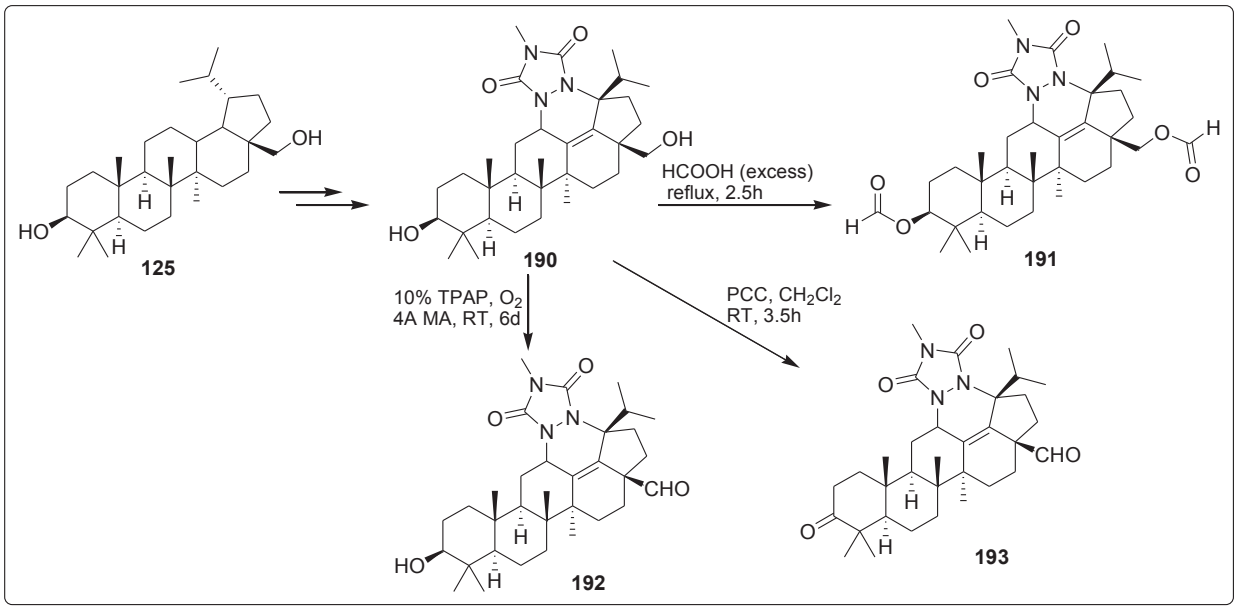


Figure 1.23 Triphenylphosphonium derivatives (**181-189**) of betulin and betulinic acid.

Simultaneous C, D and E-ring-fused heterocyclic derivatives (**190-193**) of betulin (**125**) were synthesized and found to impair *Leishmania braziliensis* viability and host–parasite interaction.[199] (**Scheme 1.37**)

Novel ester-triazole-linked triterpenoid–AZT conjugates (**194-205**) were synthesized by transforming the triterpenoid first into the corresponding propargyl esters and subsequently deployed as substrates for a click chemistry-mediated coupling with azidothymidine (AZT) *en route* and the derivatives were evaluated for their useful cytotoxicity.[200] (**Figure 1.24**)

3,4-*Seco*betulinic acid (BA) derivatives (**206-215**) were synthesized and some derivatives exhibited enhanced chemopreventive ability.[201] (**Figure 1.25**)



Scheme 1.37 C, D and E-Ring-fused heterocyclic derivatives (**190-193**) of betulin**.**

A series of novel 3-oxo-23-hydroxybetulinic acid derivatives were synthesized and evaluated for their SAR-based antitumor activities.[202]

Lupane-type 3β-*O*-monodesmosidic saponins with an extended C-28 side chain, were synthesized and structure-activity relationship study of their cytotoxic activities were evaluated.[203]

Ionic derivatives (**216-219**) of betulinic acid were synthesized and were found to exhibit antiviral activity against herpes simplex virus type-2 (HSV-2), but not HIV-1 reverse transcriptase.[204] (**Figure 1.26**)

Pentacyclic triterpenes (**220-223**) bearing *O*-[4-(1-piperazinyl)-4-oxo-butyryl moiety were synthesized and biofunctional evaluation was carried out as their antiproliferative activities. Compounds OA-4 (**222**) and AA-5 (**221**) showed potentiality for further optimization as antitumor drugs.[205] (**Figure 1.27**)

NO-releasing derivatives of betulinic acid (BA) bearing two types of NO-donors [nitrates (**225-226**) (**Scheme 1.38**) and furoxans (**227-229**) (**Figure 1.28**)] were synthesized and evaluated for their antitumor activity. Both C3 and C28-positions were modified beautifully to result the bioactive derivatives.[206]

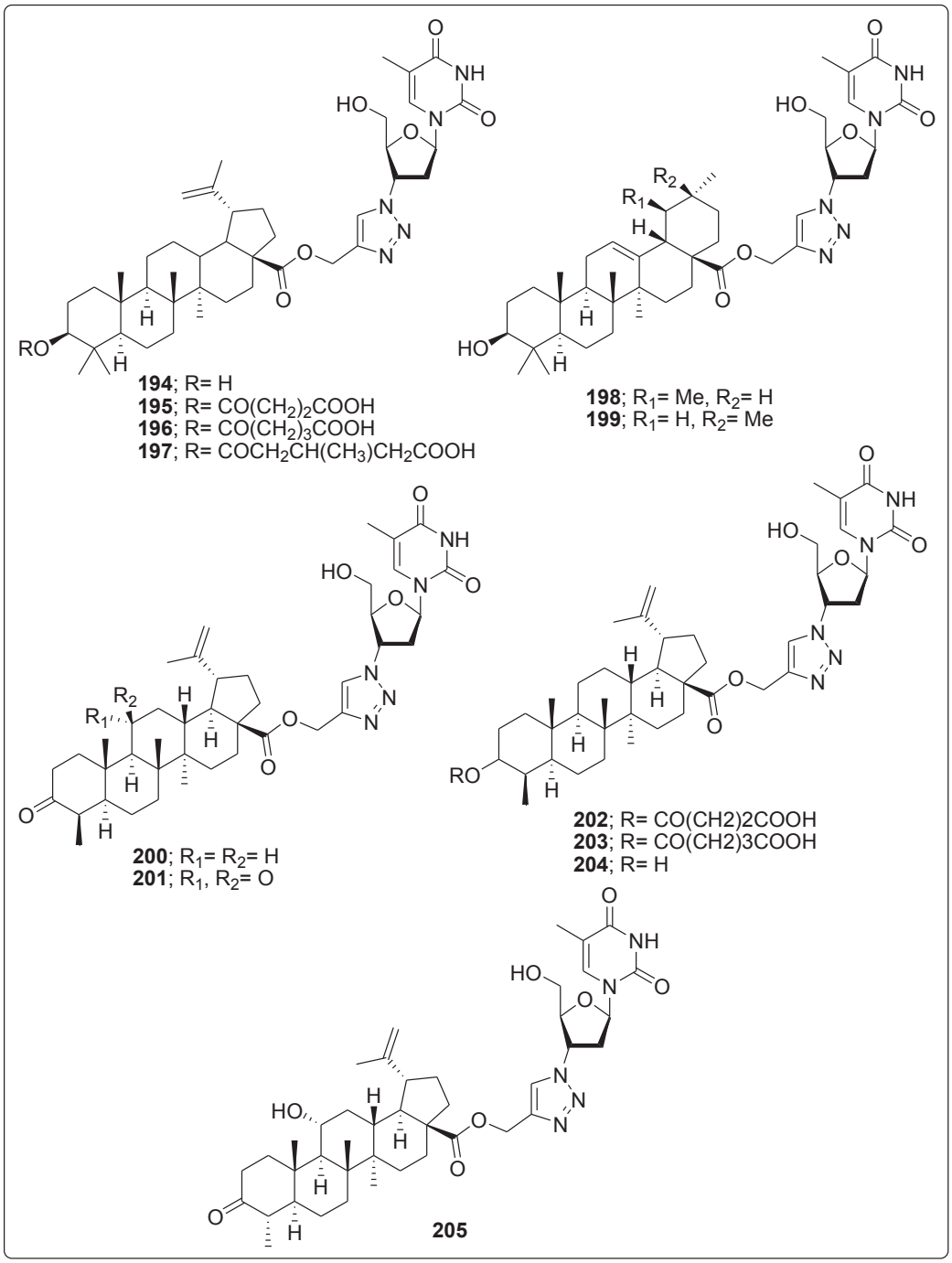


Figure 1.24 Novel ester-triazole-linked triterpenoid–AZT conjugates (**194-205**).

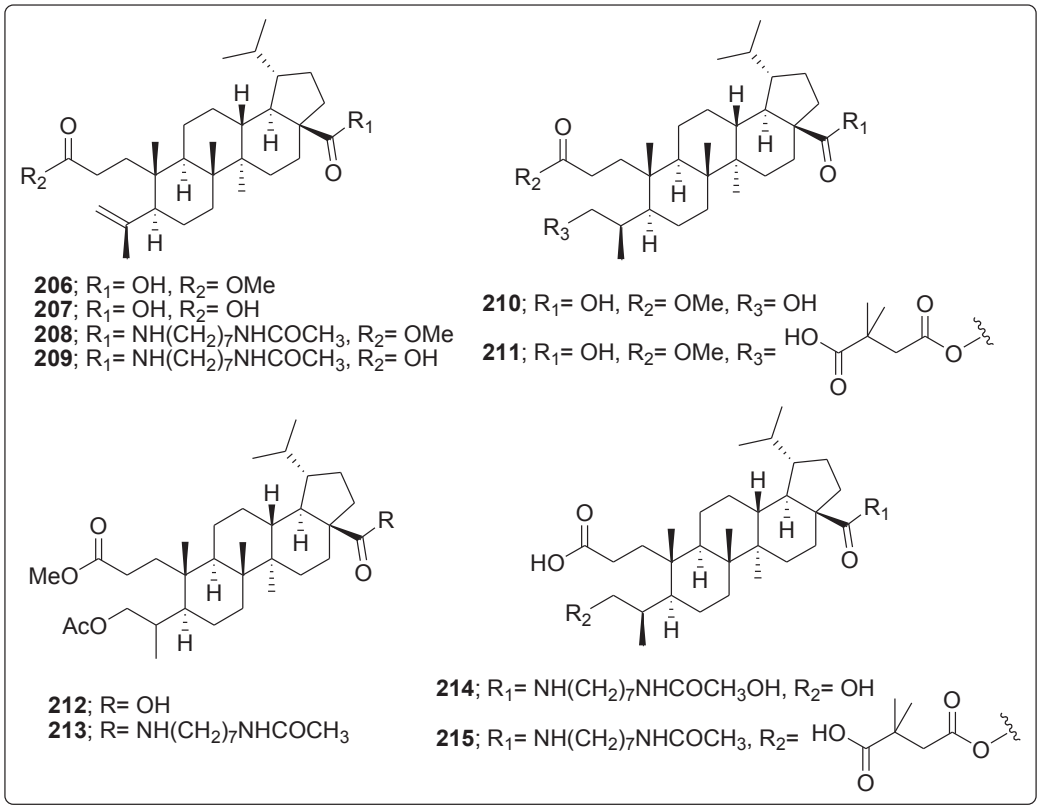


Figure 1.25 3,4-*Seco* betulinic acid (BA) derivatives (**206-215**).

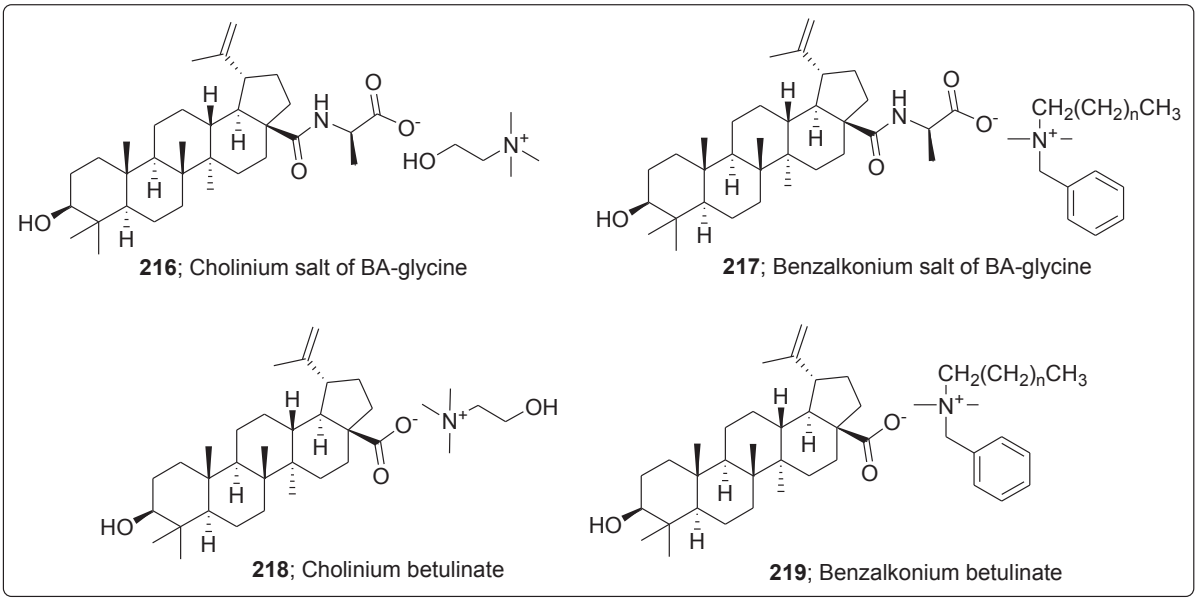


Figure 1.26 Ionic derivatives (**216-219**) of betulinic acid.

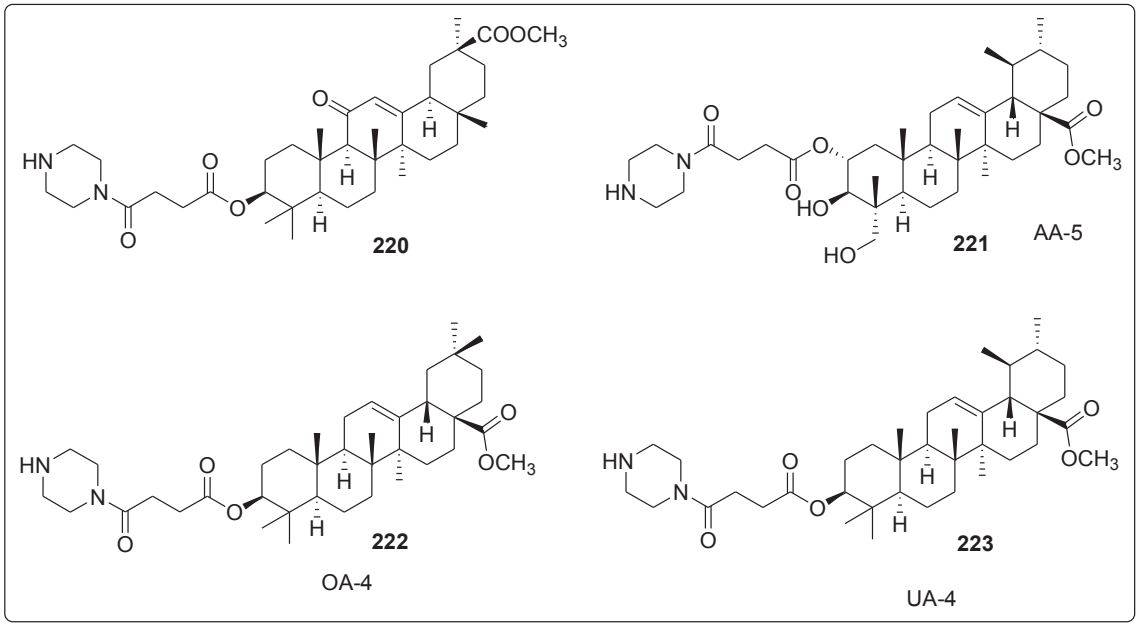
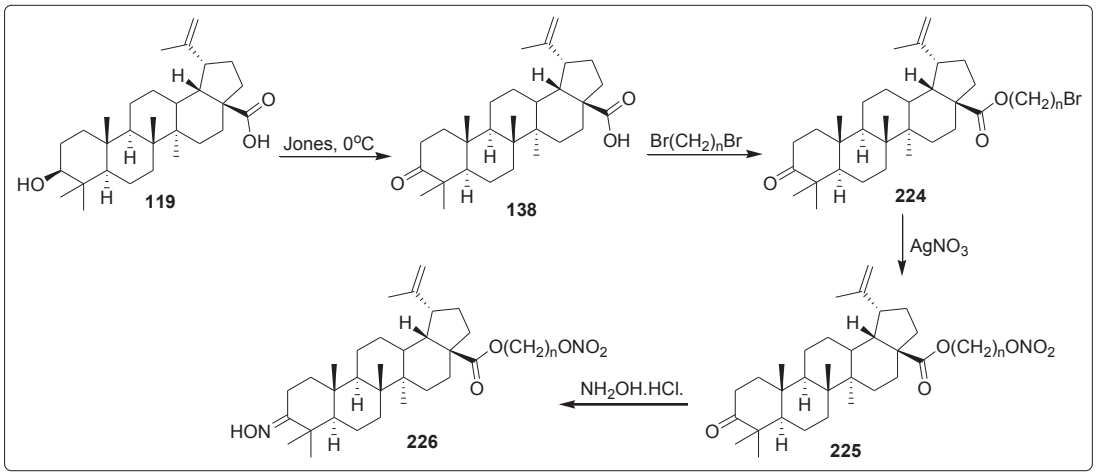


Figure 1.27 Pentacyclic triterpenes (**220-223**) bearing *O*-[4-(1-piperazinyl)-4-oxo-butyryl moiety.



Scheme 1.38 NO-releasing nitrate derivatives of betulinic acid (**225-226**).

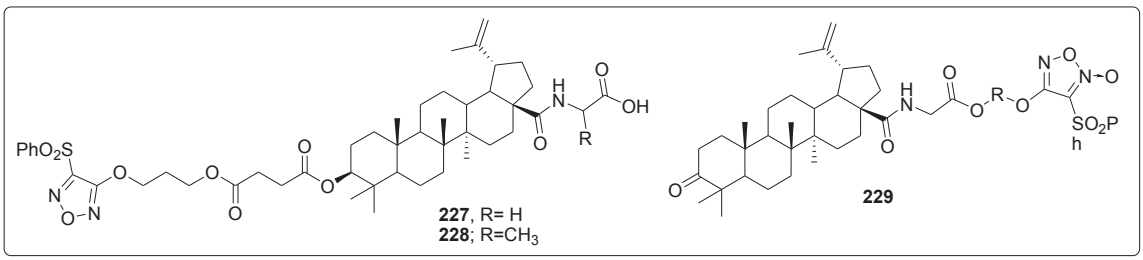


Figure 1.28 NO-releasing furoxan derivatives of betulinic acid (BA) (**227-229**).

A family of betulinic acid analogues, carrying a triazole unit at C-3 attached through a linker (**230**, **Figure 1.29**) was synthesized by the application of azide-alkyne "click reaction." The derivatives (follow structural skeleton, **Figure 1.29**) were evaluated biologically as inducers of apoptosis in human colon carcinoma cells (HT-29).[207]

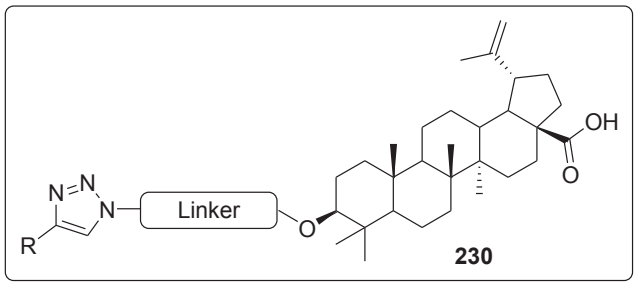


Figure 1.29 General skeleton of triazole-attached to BA at C3 through a linker (**230**).

Pyrazine-fused 23-hydroxybetulinic acid derivatives were synthesized by introducing a pyrazine ring between C-2 and C-3 position and further modifications were carried out by substitution of C-28 carboxyl group by ester and amide linkage to enhance the antitumor activity.[208] Cytotoxic 2,2-difluoroderivatives of dihydrobetulinic acid and allobetulin were also synthesized.[209]

Polyamine derivatives (**231-236**) of betulinic acid were synthesized and evaluated for their cytotoxic and antimicrobial activities.[210] (**Figure 1.30**)

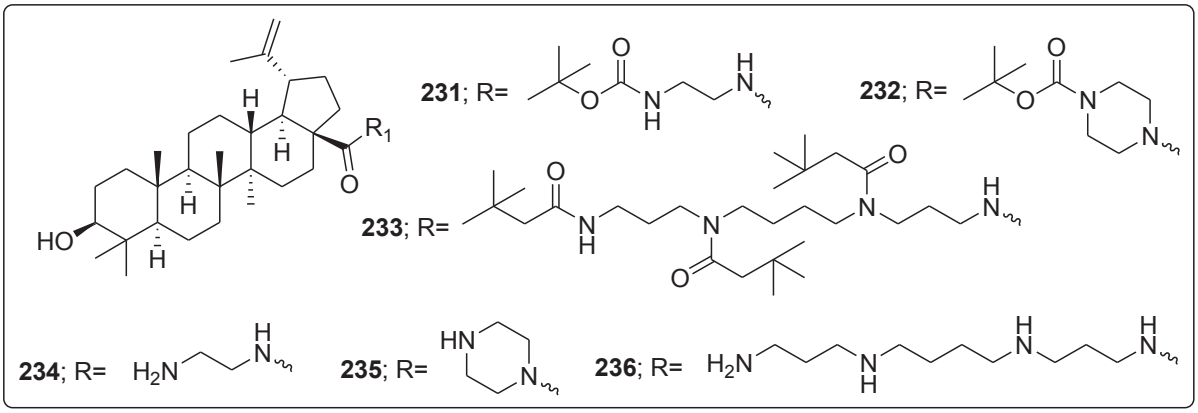
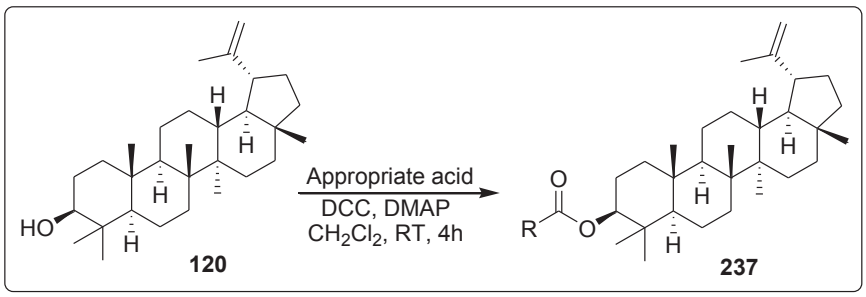


Figure 1.30 Polyamine derivatives **231-236** of betulinic acid.

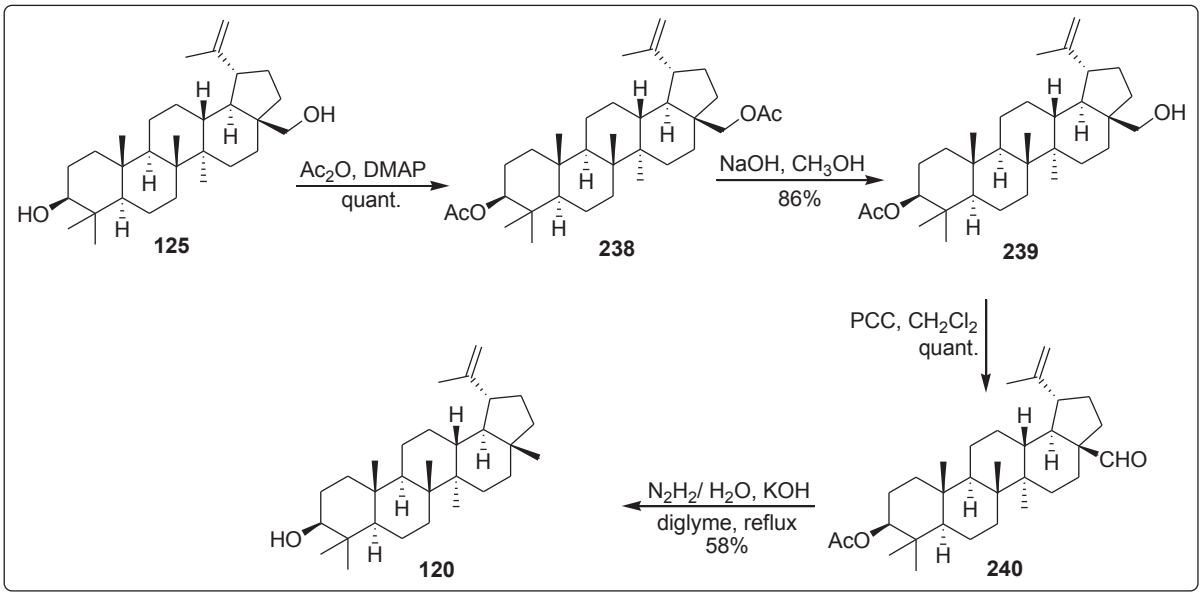
Synthesis of 28α-homolupane triterpenes and the corresponding saponins containing D-mannose, D-idose, D-arabinose, and L-rhamnose moieties was elaborated and the results indeed were found to correlate the synthesis of various lupane-type triterpene and saponin derivatives as potential anticancer compounds.[211]

Lupeol, a lupane series of natural pentacyclic triterpenoid with potential pharmaceutical activities, has been reviewed.[212-213] A concise enantioselective total synthesis of lupeol was accomplished recently by Corey et al.[214] Long-chain fatty acid esters of the pentacyclic triterpenoid were found to exhibit antimalarial activities.[215] A-ring modifications as well as A-ring-fused heterocyclic derivatives of lupeol were synthesized and found to be nitric oxide and pro-inflammatory cytokine inhibitors.[216] Structure modifications of lupeol at the isopropylene moiety was described *via* allylic oxidation using selenium dioxide and the derivatives were evaluated for their glucose uptake stimulatory effect.[217] A variety of lupeol esters (**237**) were synthesized by using the appropriate acids and the derivatives were evaluated for their *in vivo* antihyperglycemic and antidyslipidemic activity.[218] (**Scheme 1.39**)



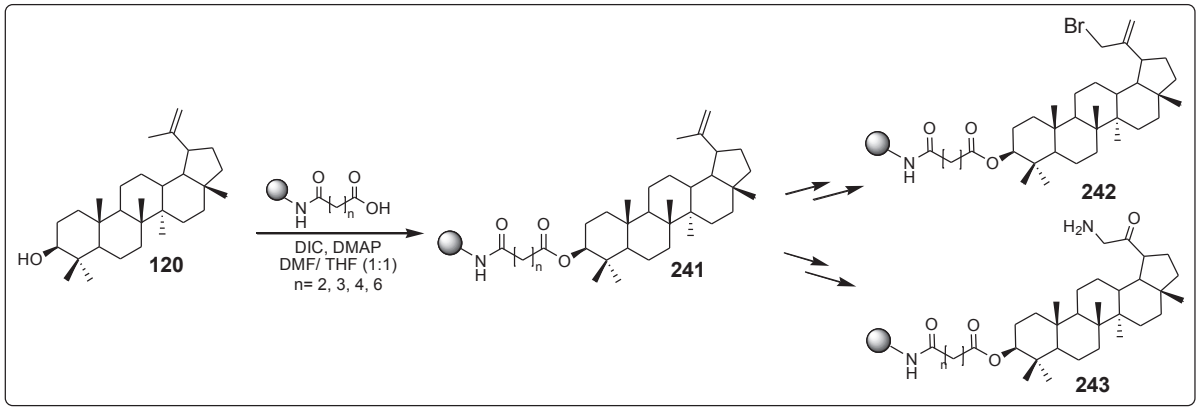
Scheme 1.39 Synthesis of lupeol esters (**237**).

A convenient synthesis of lupeol (**120**) from betulin (**125**) isolated from white birch species, was also established with an overall yield of 50% in 4 steps, which indeed enriched the natural availability of lupeol.[219] (**Scheme 1.40**)



Scheme 1.40 Synthesis of lupeol (**120**) from betulin (**125**).

Lupeol-based libraries of antimalarial agents were synthesized under solid-phase synthesis methodology. Lupeol (**120**) was first anchored to a solid support (Rink amide/ Sieber Amide) through aliphatic dicarboxylic acid moieties. The resulting polymer linked 3β-*O* (resin-alkanoyl)-lup-20(29)-ene **241** was then used to generate the key intermediates 3β-*O* (resin-alkanoyl)-30-bromo-lup-20(29)-ene **242** and 3β-*O* (resin-alkanoyl)-30-amino-lup-20(29)-ene **243** for the generation of a large library based on disubstituted lupeol derivatives (**244-248**).[220] (**Scheme 1.41** and **Figure 1.31**)



Scheme 1.41 Synthesis of lupol-based precursors for antimalarial agents (**241-243**).

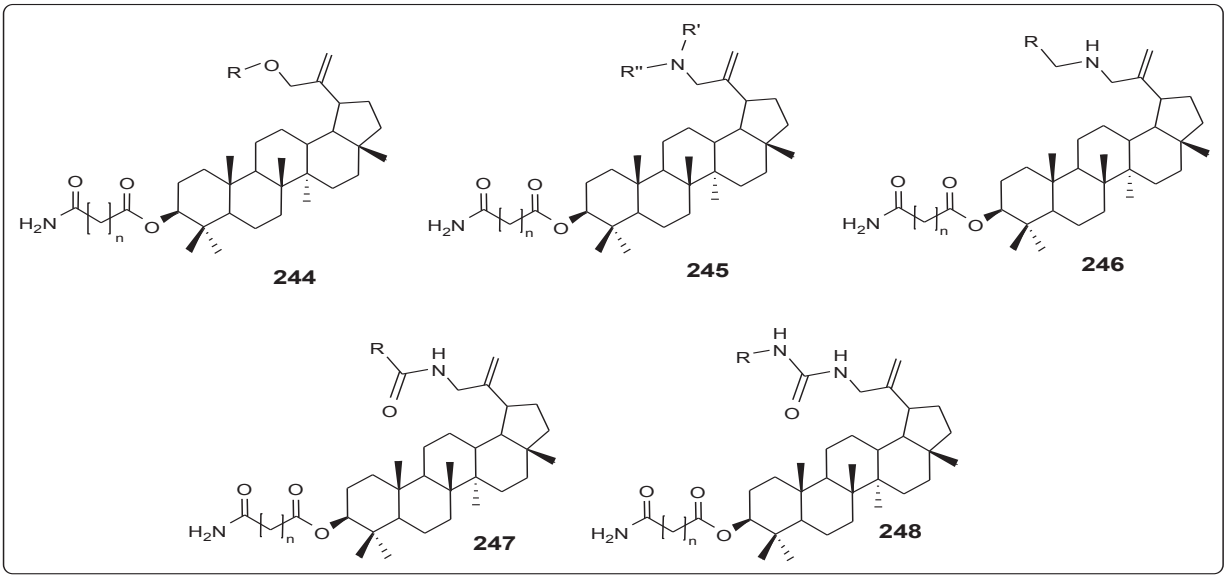


Figure 1.31 Disubstituted lupeol derivatives (**244-248**) for antimalarial agents.

Oleanolic acid (OA) and ursolic acid (UA) are ubiquitous pentacyclic triterpene compounds in plants with great interest as anti-inflammatory therapeutics.[115,221-226] Recently Shanmugam et al. have reviewed oleanolic acid and its synthetic derivatives for the prevention and therapy of cancer.[227]

A number of oleanolic acid derivatives are synthesized and evaluated for their biological activities. The transformative modifications include glycosyl derivatives,[228] glycosylated diazeniumdiolate-based derivatives,[229] synthesis of heterocyclic derivatives,[230-232] oleanolic acid derivative–chalcone conjugates,[233] furoxan-based nitric oxide (NO) releasing derivatives etc.[234] Besides, a large number of derivatives were synthesized depending on the transformative access to C3, C28 and C12-C13 positions.[235-248]

The semi-syntheses of taraxerane triterpenoids by diverse bromination processes and other reactions, from oleanolic acid and some closely related derivatives, was also performed.[249] Biotransformation of oleanolic and maslinic acids by *Rhizomucor miehei* is also reported.[250] Ursolic acid has also been modified suitably to produce a number of pharmaceutically active derivatives. [247,250-252]

Methyl 2-cyano-3,12-dioxoursol-1,9-dien-28-oate (CDDU-methyl ester, **249**) was synthesized from commercially available ursolic acid (**121**) which was based on an oxidative ozonolysis-mediated C-ring enone formation, and the route provided the access to ursolic acid-

derived cyano enone analogues (**250-252**) with C-ring activation. The biological activities were found approximately five-fold less than the corresponding oleanolic acid (**122**) derivatives (**253-257**).[253] (**Figure 1.32**)

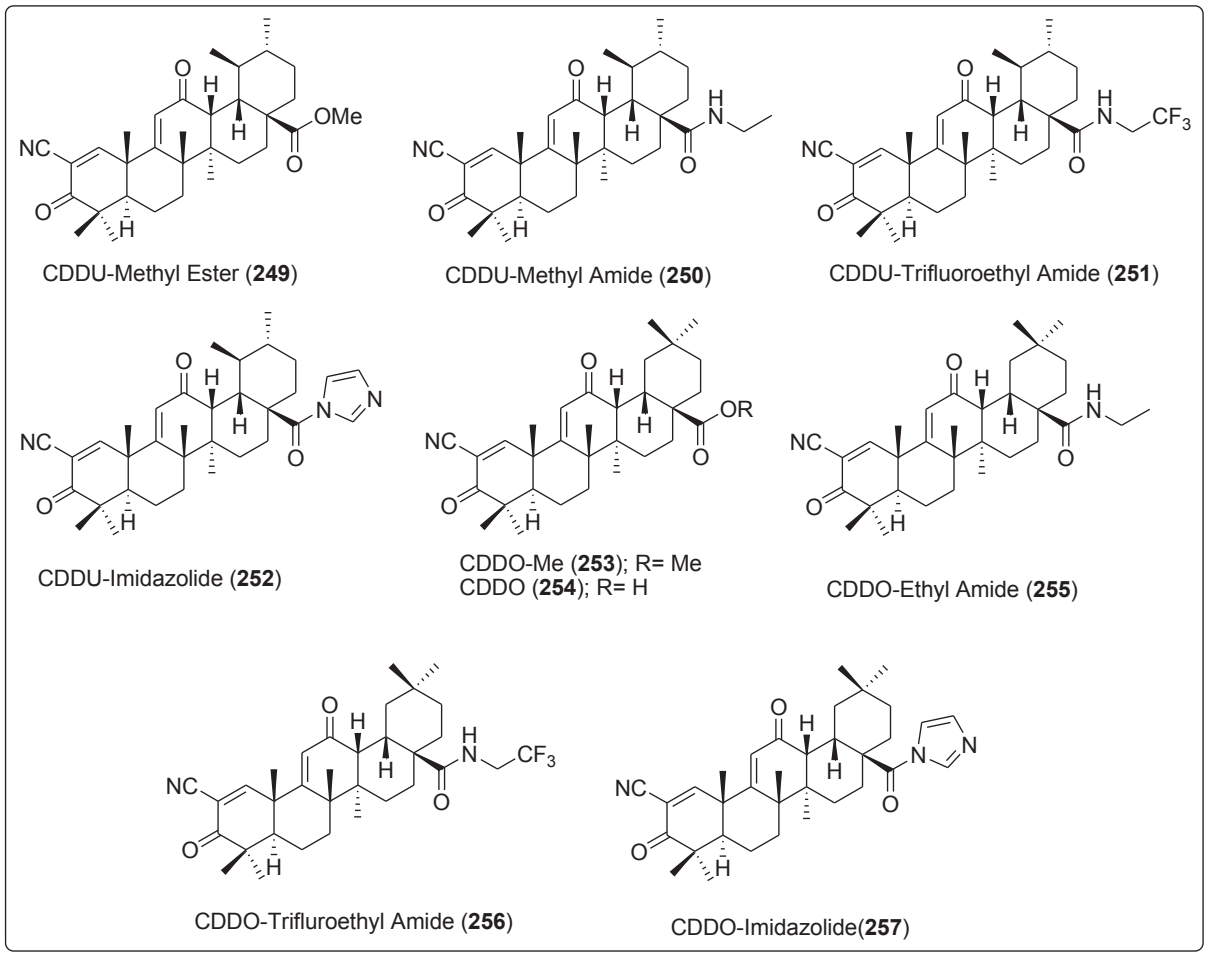


Figure 1.32 CDDU- (**249-252**) and CDDO-(**253-257**) esters**.**

C3- and C28-Modified nitric oxide-releasing derivatives (**258-259**) of oleanolic acid were synthesized and were found to be potential anti-colon cancer agents.[254] (**Figure 1.33**)

Synthesis of oleanolic acid dimmers (**260-264**) were also accomplished and were biologically evaluated as glycogen phosphorylase inhibitors.[255] (**Figure 1.34**)

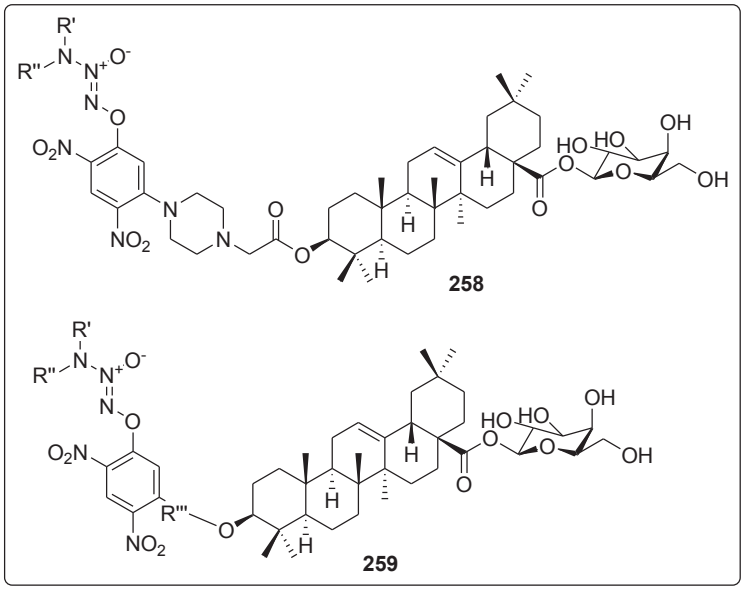


Figure 1.33 C3 and C28-Modified nitric oxide-releasing derivatives (**258-259**) of oleanolic acid.

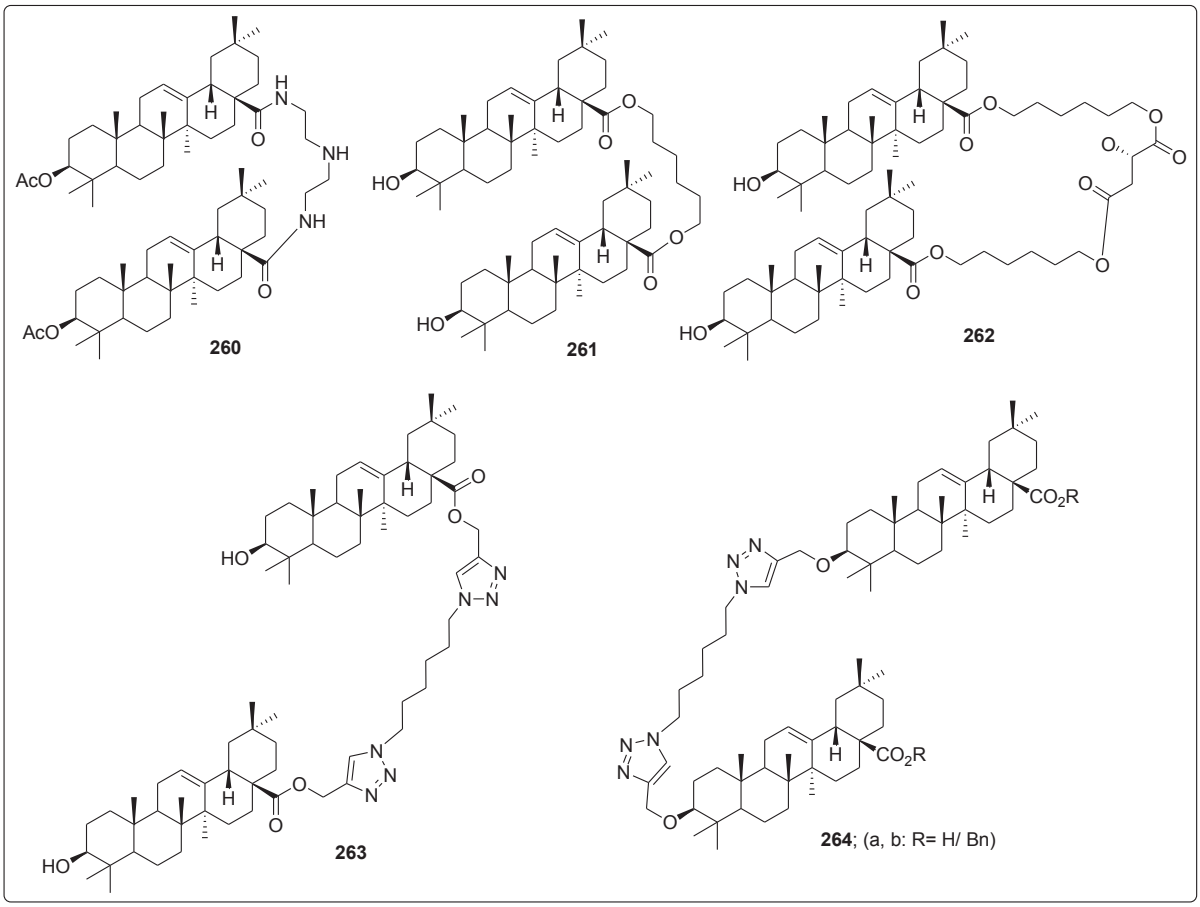


Figure 1.34 Oleanolic acid dimers (**260-264**).

A series of oleanolic acid saponins (**265-273**) were synthesized and found to be α-glucosidase and α-amylase inhibitors.[256] (**Figure 1.35**)

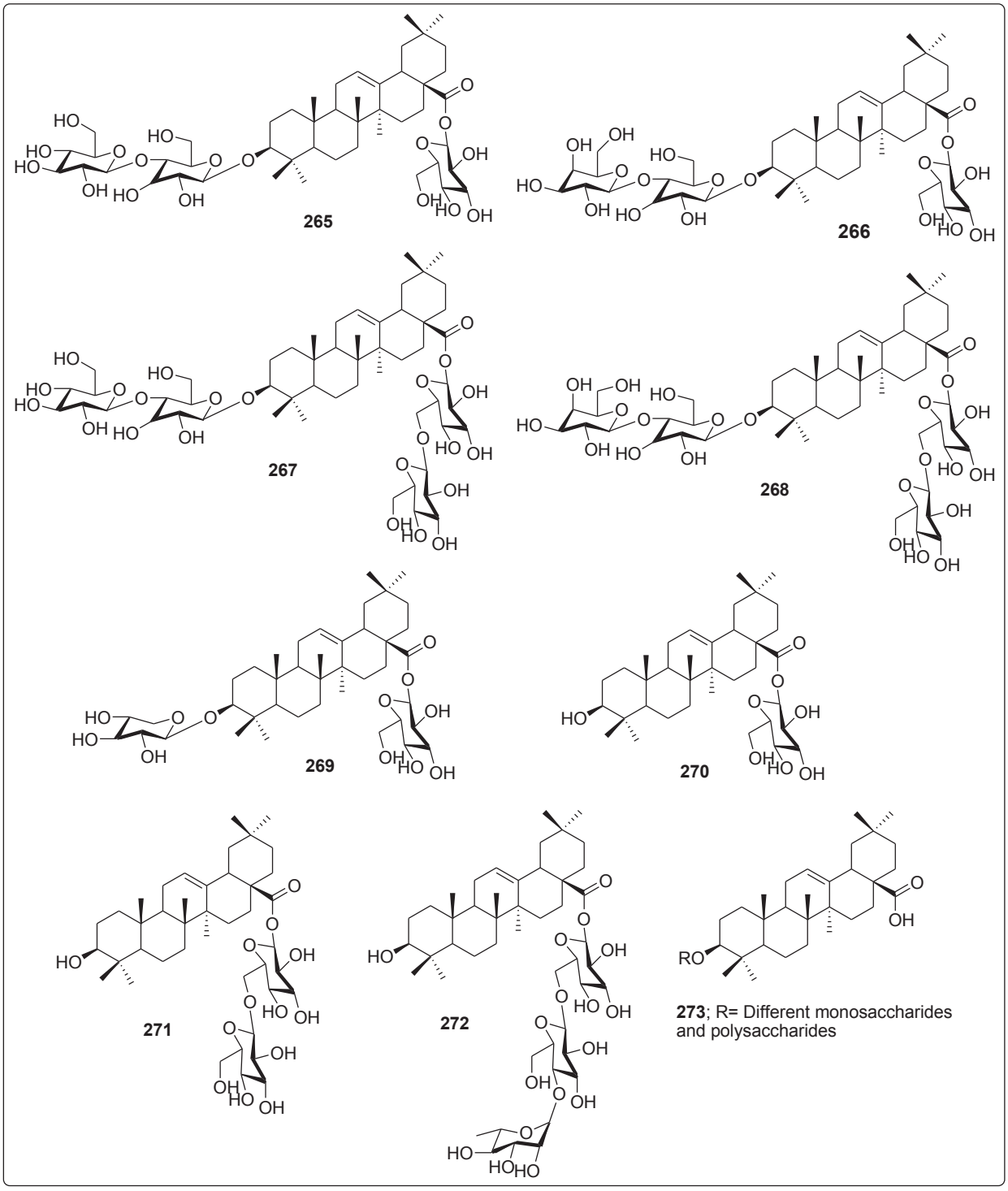


Figure 1.35 Oleanolic acid saponins (**265-273**).

A series of hybrids (**274-277**) from O^2-(2,4-dinitrophenyl)-diazeniumdiolate and oleanolic acid (OA) were synthesized, and biologically evaluated as novel nitric oxide (NO)-releasing prodrugs.[257] (**Figure 1.36**)

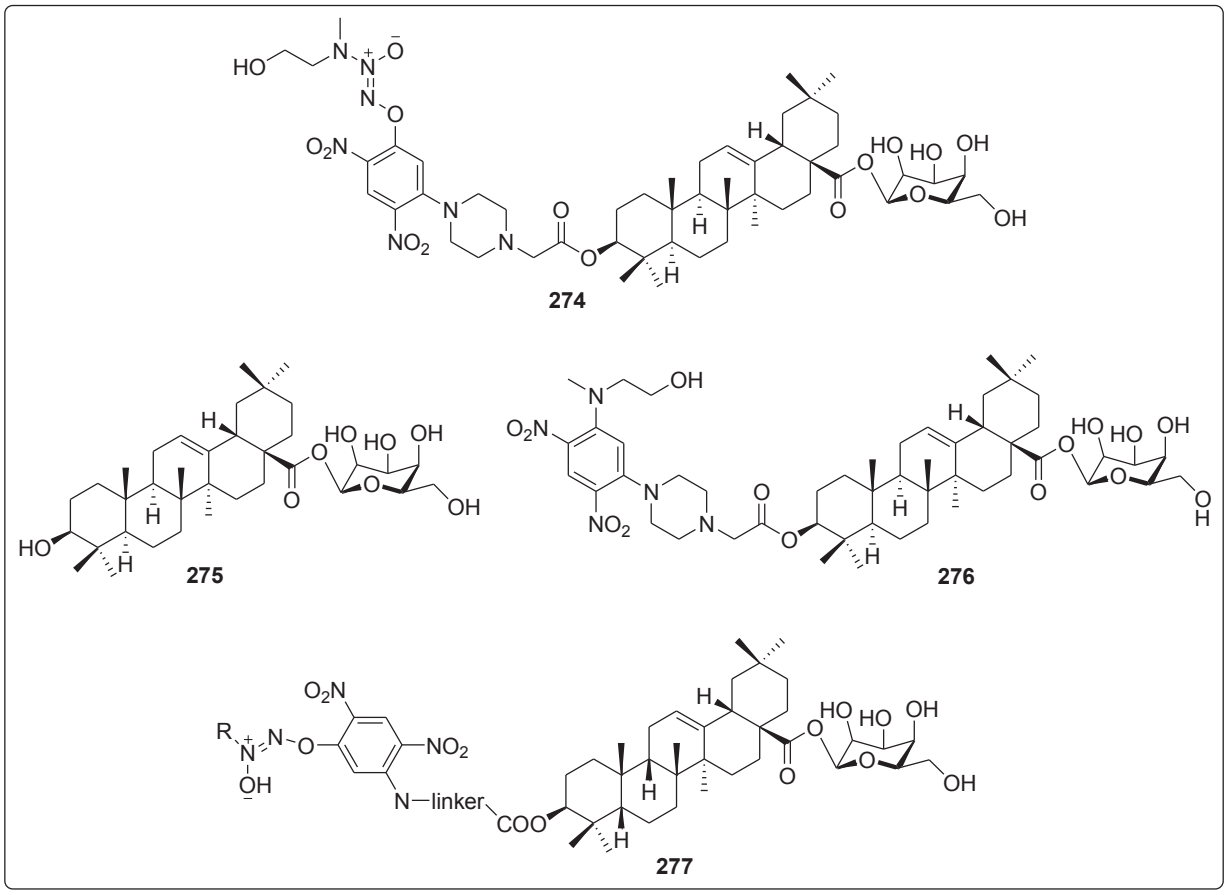
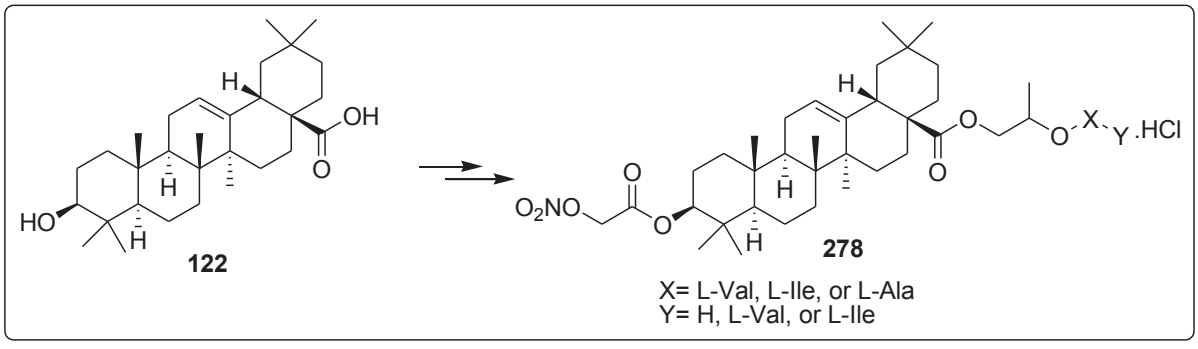


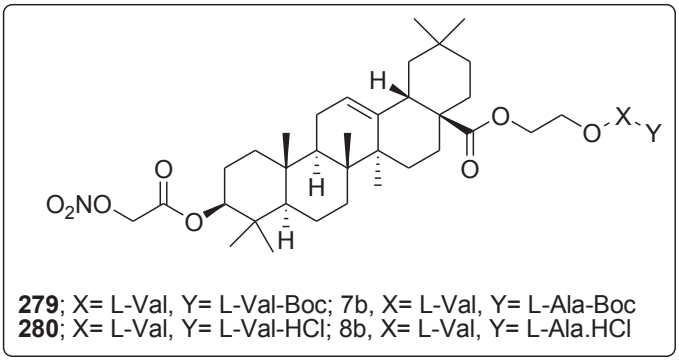
Figure 1.36 Hybrids (**274-277**) of O^2-(2,4-dinitrophenyl)-diazeniumdiolate with oleanolic acid.



Scheme 1.42 Synthesis of NO-donating oleanolic acid derivative (**278**).

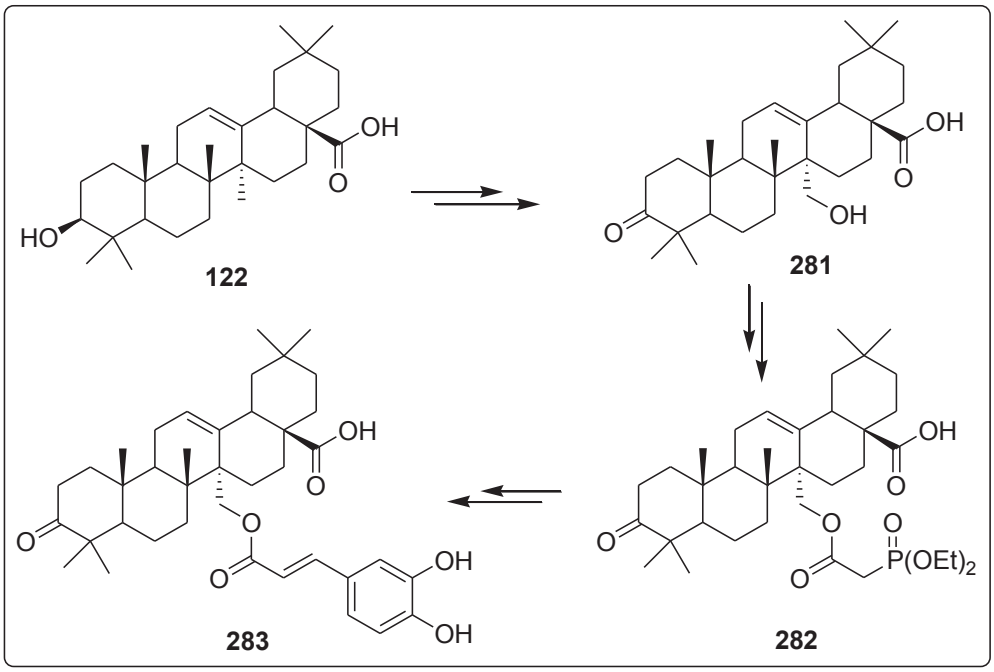
A series of amino acid/ dipeptide diester prodrugs of NO-donating oleanolic acid derivatives (**278-280**) were synthesized and evaluated biologically as PepT1 targeting antitumor prodrugs.[116] (**Scheme 1.42** and **Figure 1.37**)

A partial large-scale synthesis (14 steps, 31% yield) of myriceric acid A (**283**), an endothelin receptor antagonist, from oleanolic acid (**122**) was accomplished.[258] (**Scheme 1.43**)



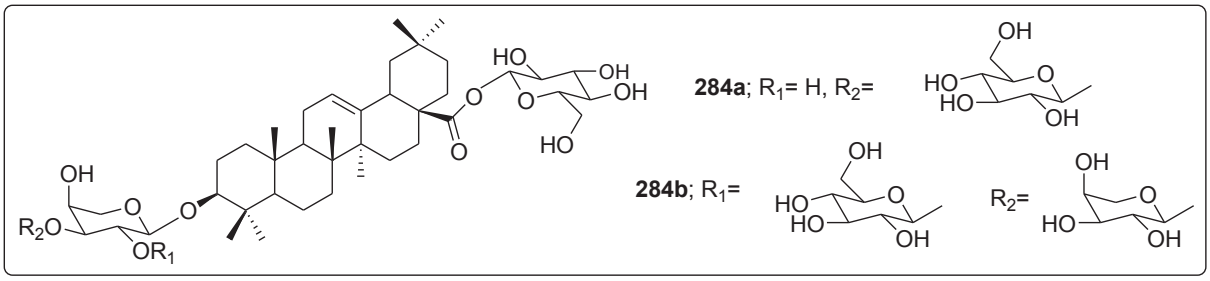
279; X= L-Val, Y= L-Val-Boc; 7b, X= L-Val, Y= L-Ala-Boc
280; X= L-Val, Y= L-Val-HCl; 8b, X= L-Val, Y= L-Ala.HCl

Figure 1.37 NO-donating oleanolic acid derivative (**279-280**).



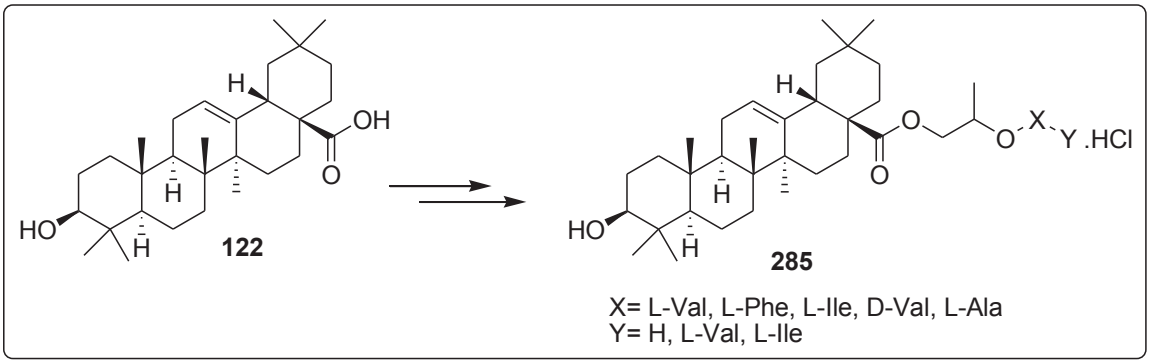
Scheme 1.43 Synthetic route of myriceric acid A (**283**) from oleanolic acid (**122**).

A number of natural oleanolic acid saponins (**284**) were also synthesized.[259] (**Scheme 1.44**)



Scheme 1.44 Synthesis of natural oleanolic acid saponins (**284**).

Propylene glycol-linked amino acid/ dipeptide diester prodrugs of oleanolic acid (**285**) for PepT1-mediated transport were also synthesized.[260] (**Scheme 1.45**)



Scheme 1.45 Synthesis of prodrugs of oleanolic acid (**285**).

A number of 3-*O*-acyl ursolic acid derivatives (**286-294**) were prepared and were then evaluated as anti-AIDS agents.[116] (**Figure 1.38**)

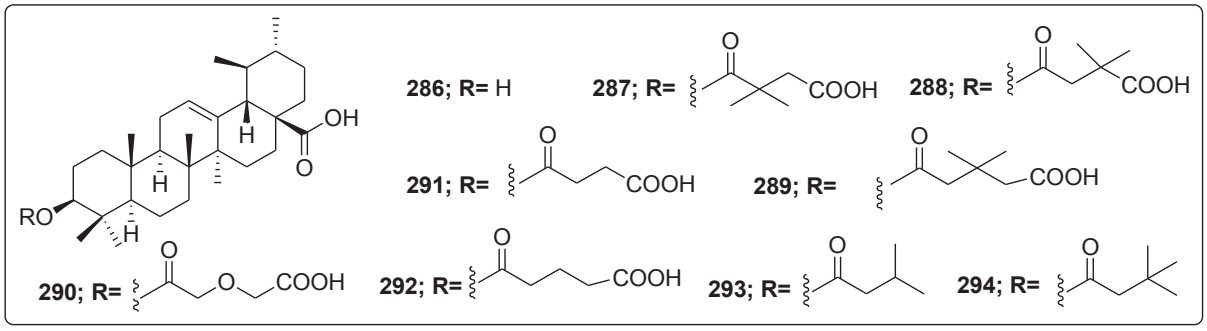
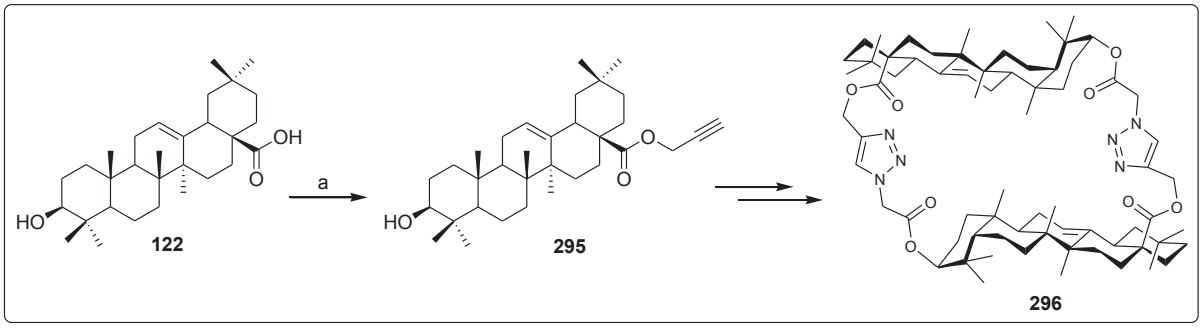


Figure 1.38 3-*O*-acyl ursolic acid derivatives (**286-294**).

One oleanolic acid-based cyclic dimer (**296**) was synthesized using click chemistry approach and it showed remarkable selectivity and affinity to bind fluoride ion.[261] (**Scheme 1.46**)



Scheme 1.46 Synthesis of oleanolic acid-based cyclic dimer (**296**).

Synthesis of glucoconjugates (**297-300**) of oleanolic acid, linked by either a triazole moiety or an ester function, as inhibitors of glycogen phosphorylase were accomplished by Cheng et al.[262] (**Figure 1.39**)

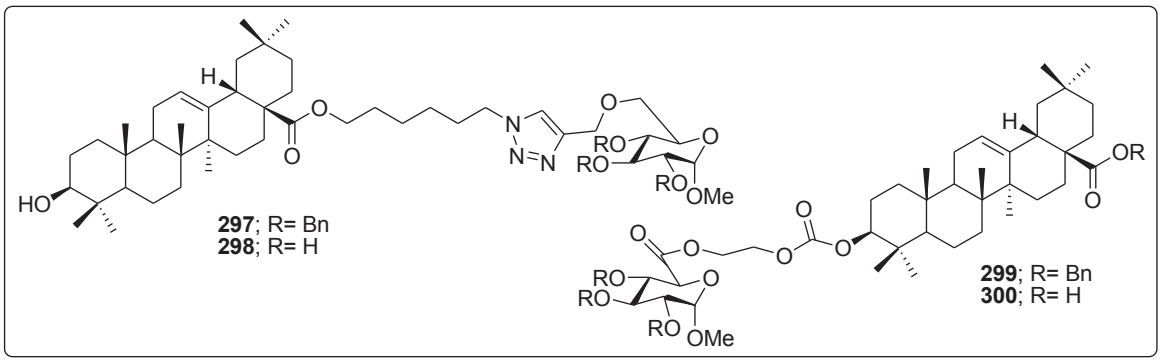


Figure 1.39 Glucoconjugates (**297-300**) of oleanolic acid.

Synthesis of oleanolic acid saponins (**301-306**) were also achieved by Huang et al.[263] (**Figure 1.40**)

Concise synthesis of bidesmosidic oleanolic acid saponins (**307-309**) with strong inhibitory activity on pancreatic lipase were also accomplished.[264] (**Figure 1.41**)

A convenient transformative reaction-based separation technique for ursolic acid (**121**) from oleanolic acid (**122**) were also achieved by Csuk et al.[265] (**Scheme 1.47**)

A series of oleanolic acid dimers (**313, 315**) linked at C-28 by 1,6-hexanediamine, or built around the carbon chains of varying lengths between two carboxyl groups were synthesized and biologically evaluated as their anti-tumor activities.[266] (**Scheme 1.48**)

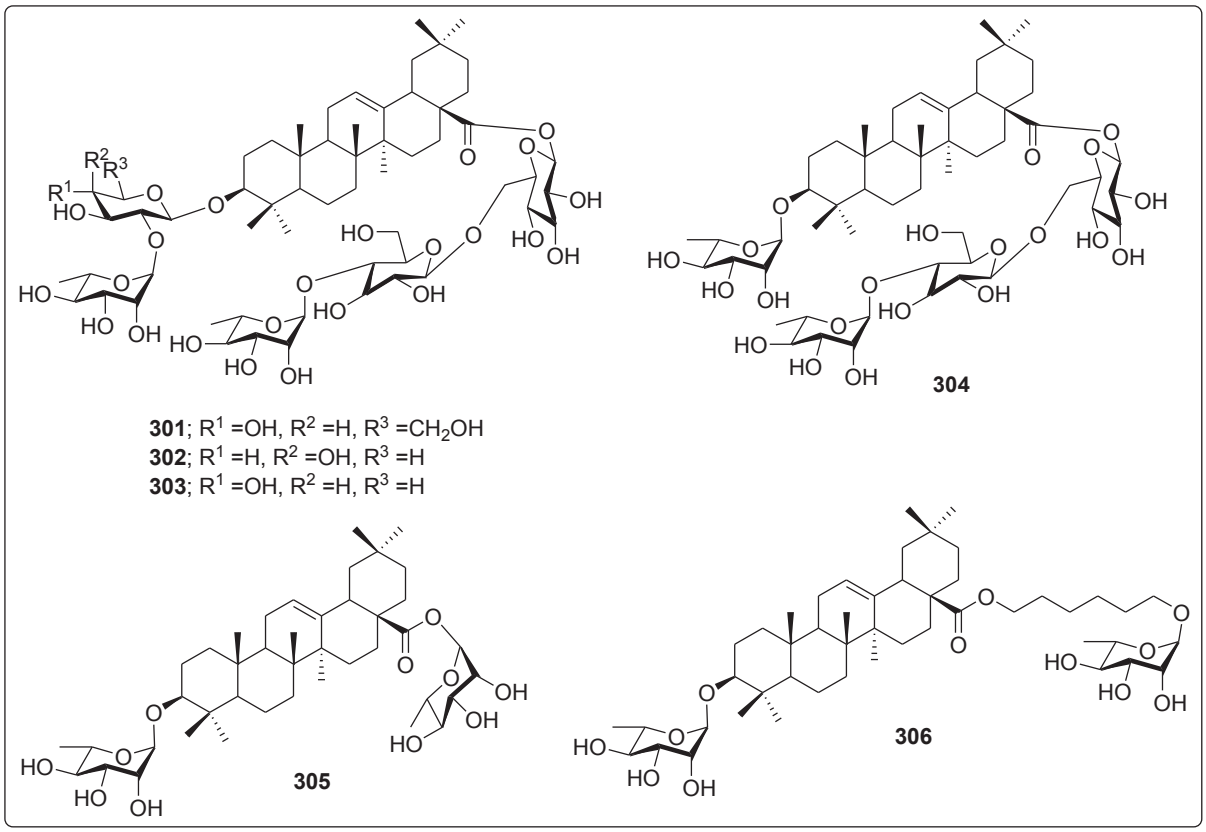


Figure 1.40 Oleanolic acid saponins (**301-306**).

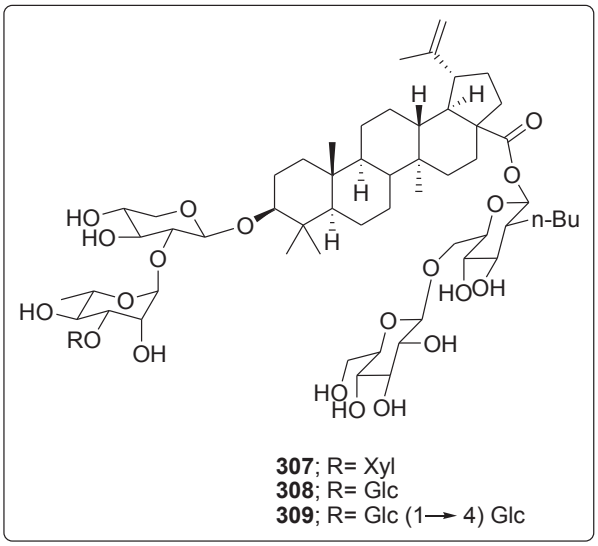
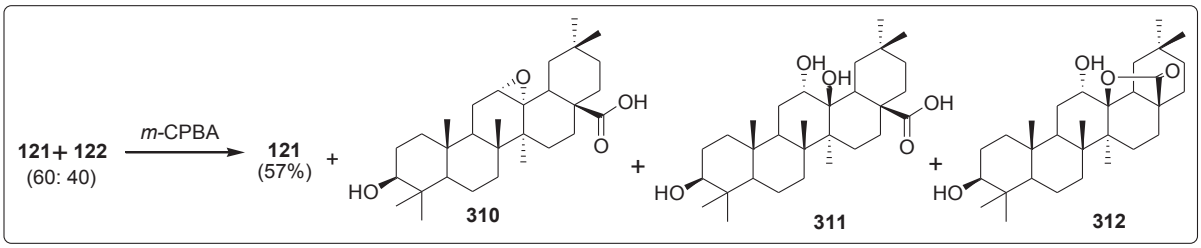
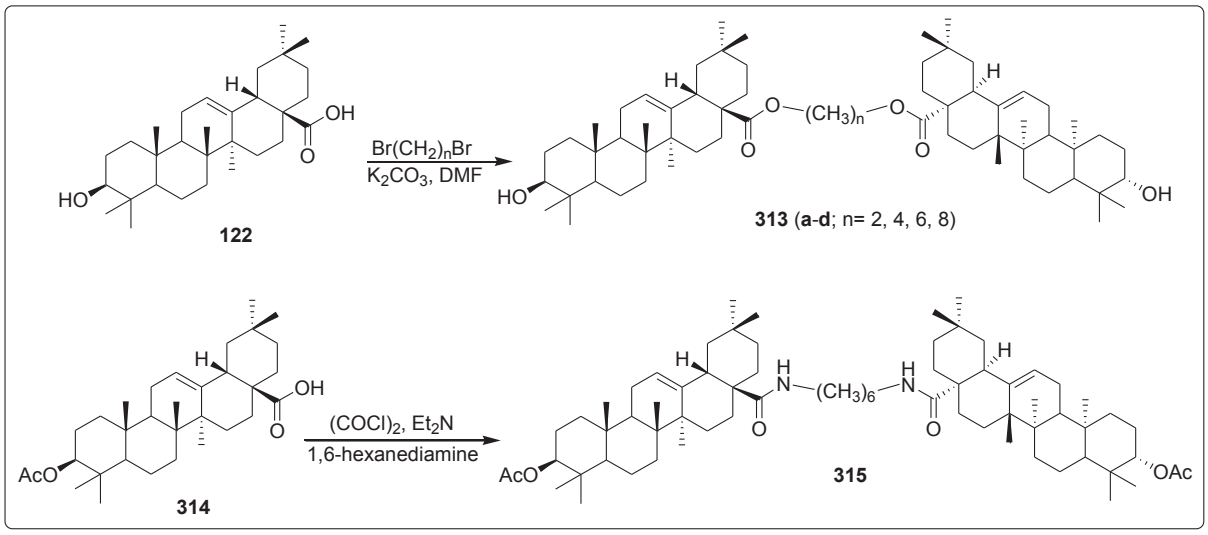


Figure 1.41 Bidesmosidic oleanolic acid saponins (**307-309**).



Scheme 1.47 Seperation for ursolic acid (**121**) from oleanolic acid (**122**).



Scheme 1.48 Synthesis of oleanolic acid dimers (**313**, **315**).

I.5 Some steroid- and PT-based marketed drugs

There are many steroid- and PT-based drugs known globally for their diversified therapeutic applications. For example, to treat the acute leukemia in children a steroidal drug named prednisone (**316**) is used with combination of the other antineoplastic agents.[267-270] To treat postmenopausal breast cancer, a steroidal drug exemestane (**317**) is used as aromatase inhibitors.[271] Steroids dutasteride (**318**), is used in clinic for the treatment of androgen-dependent prostate cancer and fluoxymesterone (**319**) is used to treat advance- and metastatic neoplasm of the breast (**Figure 1.42**).[272-275]

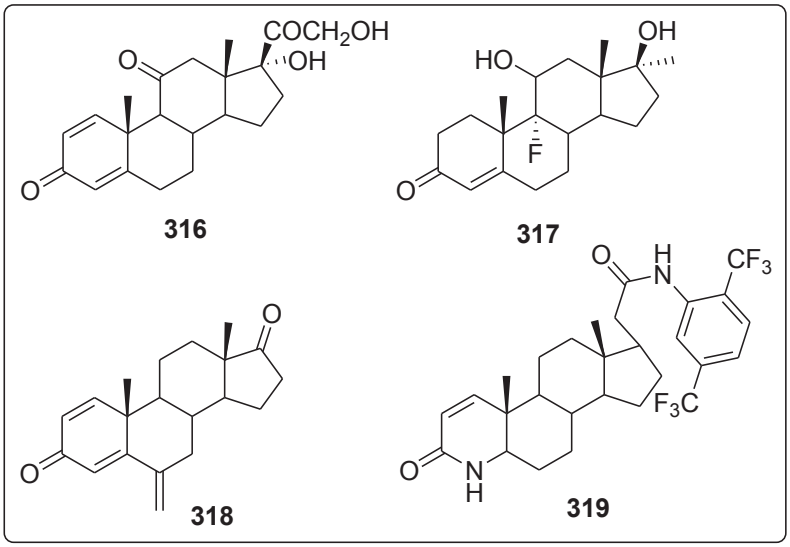


Figure 1.42 Some steroid-based marketed drugs.

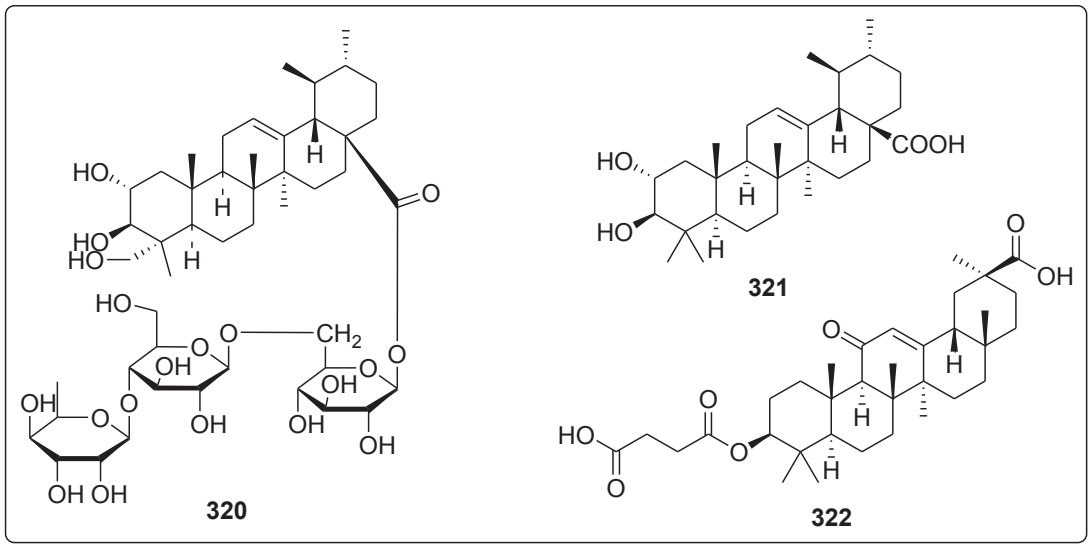


Figure 1.43 Some of the PT-based marketed drugs (**320-322**).

A number of PT-based drugs are also available in the market e.g., oleanolic acid (**122**) for lever disease, asiaticoside (**320**) for wound healing and Perkinson's disease, corosolic acid (**321**) for diabetes and obesity, carbenoxolone (**322**) for oesophageal ulceration and inflammation, etc. (**Figure 1.43**)