PART 2

TRANFORMATIVE REACTIONS OF TRITERPENOIDS AND THE BIOCIDAL ACTIVITY OF THE DERIVED COMPOUNDS

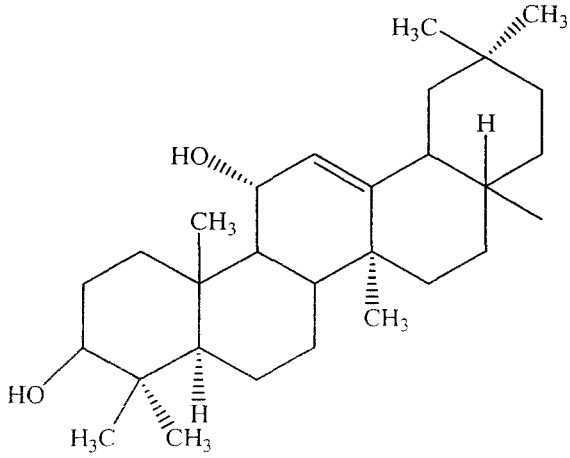
Chapter 1

SHORT REVIEW ON TRANFORMATIVE REACTION OF TRITERPENOIDS AND BIOCIDAL ACTIVITY OF THEIR PREPARED DERIVATIVES

Triterpenoids represent a varied class of natural products. Thousands of structures have been reported with hundreds of new derivatives discovering each year. Among these are included the pentacyclic lupane type triterpenes which are represented by a diverse assemblage of bioactive natural products. The author extracted several triterpenes from plants and studied their biological activities against different microorganisms and seeds and observed some interesting results (Part 1).

So the author interested to introduce some groups or atoms to triterpenes through transformative reactions including microwave assisted methodology. For this the author has undertaken these surveys to summarize the available literature. A number of computer based databases, journals, abstracts were utilized in literature search. Based on this search it was observed that more than 1000 publications were identified in which triterpenes were mentioned but very fewer publications mentioned the transformative reactions of triterpenoids and biocidal activities of the derived compounds. A short review of it is presented in this chapter.

Corey *et al.* [1] established that the 3α, 11β-dihydroxy pentacyclic triterpenoid (**4**) on treatment in methylene chloride with a solution of 30% hydrogen peroxide and p-toluene sulphonic acid in tertiary butanol forms an epoxide, 11α,12α-epoxide and undergoes a skeletal rearrangement by C_{14}-C_{13} methyl migration and shift of the double bond (**5**).



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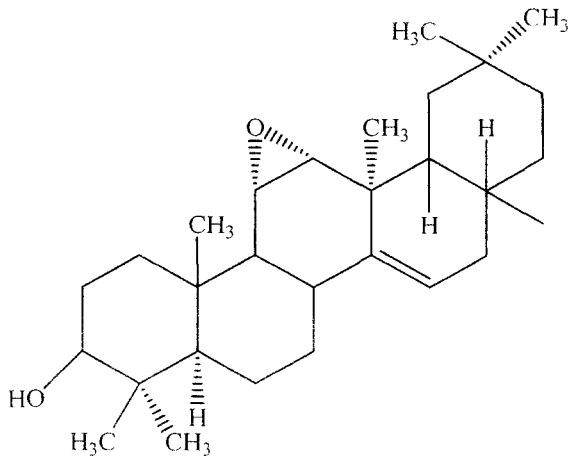

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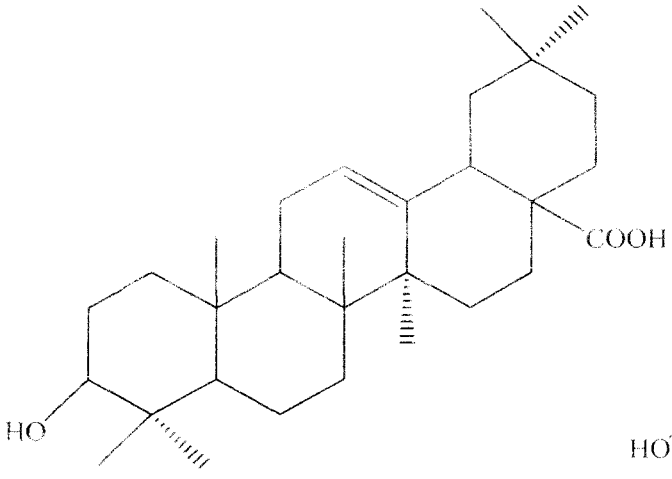
Kitagawa *et al.* [2] studied photooxidation of oleanolic acid and reported that irradiation of oleanolic acid **(6)** and reported that irradiation of the acidified ethanolic solution of 7 for 80 hours afforded products **8, 9** together with starting material.



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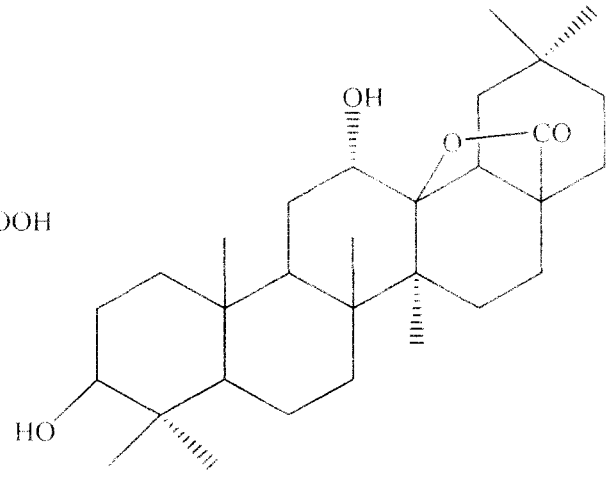

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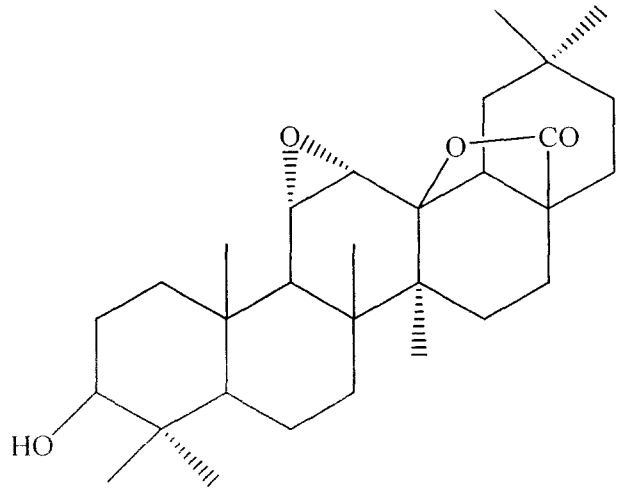

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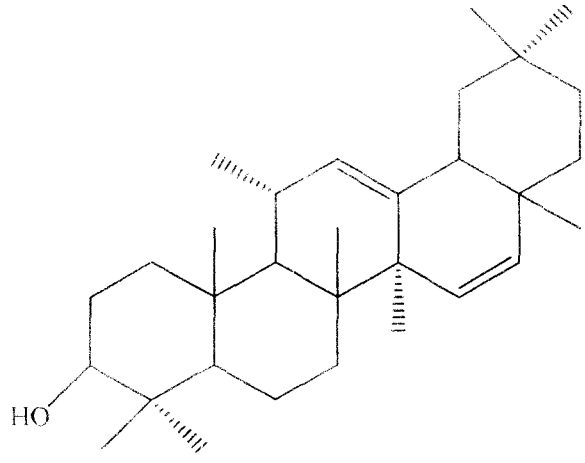
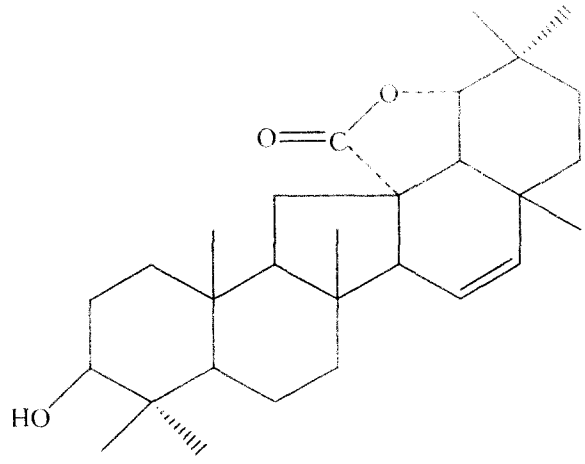
Pradhan *et al.* [3] carried out the reaction of olean-12, 15-dien-3, 11-diol **10** with hydrogen peroxide containing p-toluene sulphonic acid under identical conditions of corey *et al.*[1] with a view to producing the multiflorenol derivative **12**. But they isolated two isomeric γ-lactones identified as 3β–acetates of C-12-nor-olean-15-en-13α-carb— 19α-olide **12** and C-12-nor-olean-18(19)-en-13 -carb— 15 –olide **13**.



olean-12, 15-dien-3, 11-diol (11)



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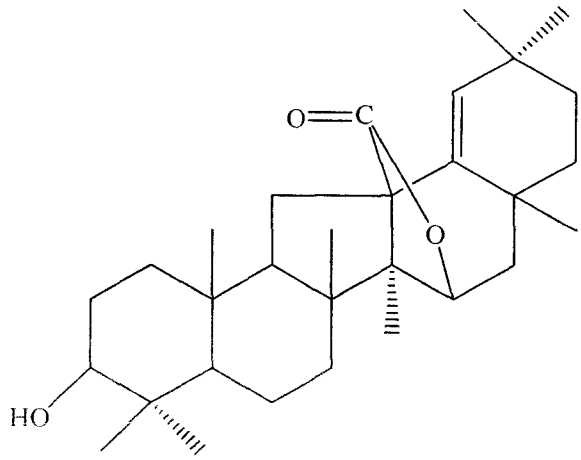

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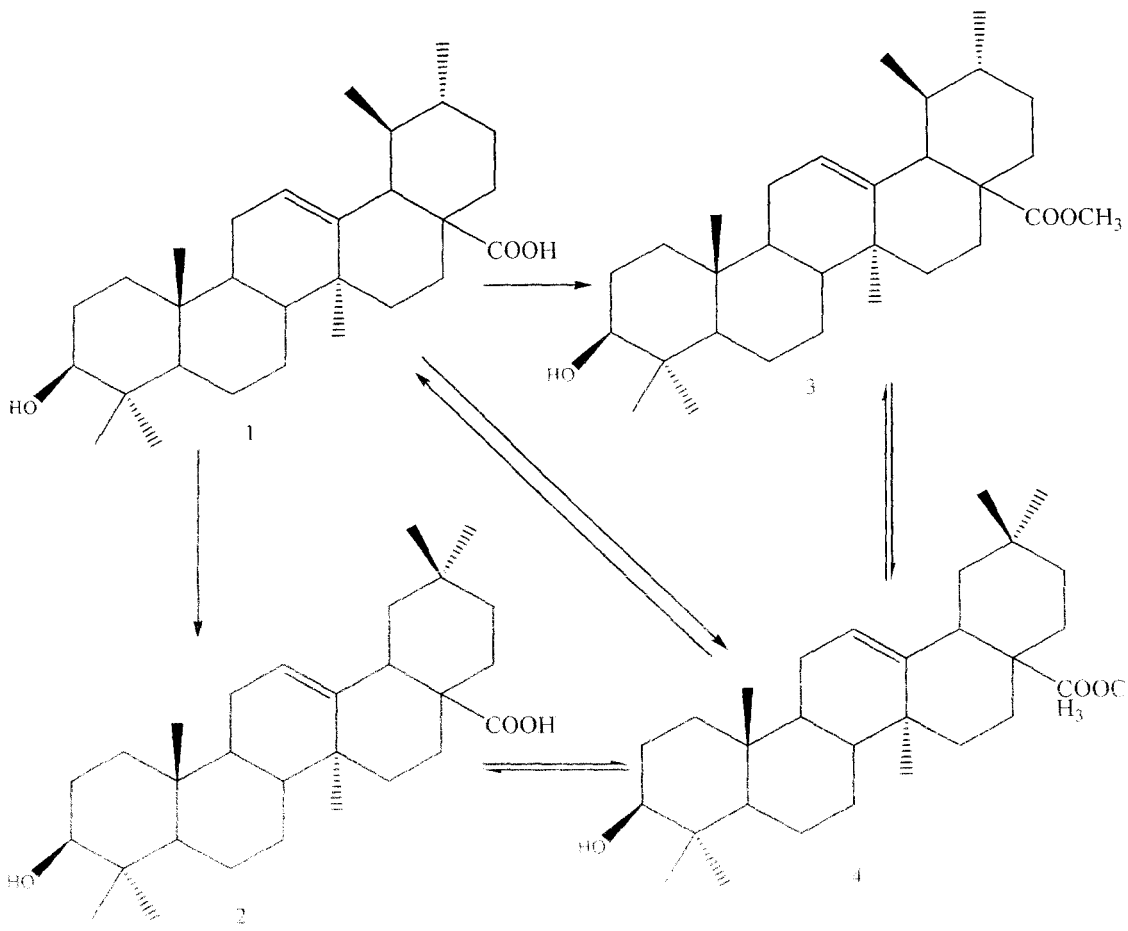
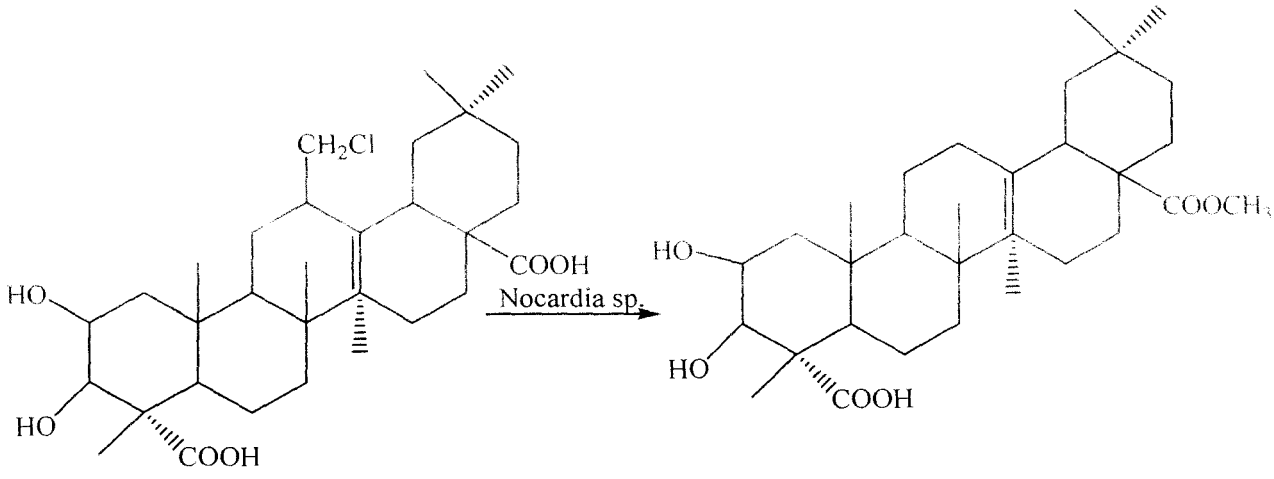
Yadava and Chakravarti [4] isolated a new bioactive triterpenoid saponin 3β-O-[β-D-xylopyranosyl(1 → 3)-O-β-D-galactopyranosyl]-lup-12-ene-28 oic acid-28-O-α-L-rhamnopyranosyl ester compound (**A**) from the methanolic fraction of the roots of *carthamus tinctorius* linn by various colour reactions, chemical degradations and spectral analysis. They reported that compound (**A**) showed anti-inflammatory activity.

Haytsu *et al.* [5] elucidated the possible natural evolutionary pathways for the transformation of pentacyclic triterpenoids. They heated three terpenoids samples, Δ^2-allobetulene, tetranormethylallobetulheptaene and fernenes independently at 150°C for 7 weeks with montmorillonite clay. As a result of this transformation they obtained di, tri-, tetra-, and pentacyclic hydroaromatic and aromatic hydrocarbons, which are commonly found in higher rank coals.

Zhang *et al.* [6] converted six pentacyclic triterpene acids, ursolic acid, oleanolic acid, betulinic acid, 23-hydroxybetulinic acid, glycyrrhetinic acid, and senegenin to their corresponding 28-methyl esters through novel biotransformation by the microbe *Nocardia* sp. NRRL 5646. They reported that notably, ursolic acid (**1**) was converted to oleanolic acid methyl ester (**4**) via two intermediates, oleanolic acid (**2**), and ursolic acid methyl ester (**3**), which are formed by participation of 'retro-biosynthetic' methyl migration from C-19 to C-20. They also reported that senegenin (**11**) was selectively converted to a

nortriterpene methyl ester, senegenic acid methyl ester (**12**), via an unprecedented C–C bond cleavage.





senegenin (**11**)

senegenic acid methyl ester (**12**)

Chatterjee *et al.* [7] studied the microbial transformation of the antimelanoma agent betulinic acid. The main objective of this study was to utilize microorganisms as in vitro models to predict and prepare potential mammalian metabolites of the compound. The resultant product obtained of this biotransformation with resting-cell suspensions of *Bacillus megaterium* ATCC 13368 identified as 3-oxo-lup-20(29)-en-28-oic acid, 3-oxo-11α-hydroxy-lup-20(29)-en-28-oic acid, 1β-hydroxy-3-oxo-lup-20(29)-en-28-oic acid, and 3β,7β,15α-trihydroxy-lup-20(29)-en-28-oic acid based on nuclear magnetic resonance and high-resolution mass spectral analyses.

Guirado *et al.* [8] established an efficient synthetic method for dichloromethylated pyrazolines. They efficiently prepared aryl-4,4-dichlorobut-3-en-1-ones **4** by treatment of acetophenones with anhydrous chloral, followed by dehydration and reductive dechlorination. They reported that compounds 4 reacted with hydrazine hydrate and methylhydrazine to give the respective 5-dichloromethyl-2-pyrazolines in high to quantitative yields and determined the molecular structure of 5-dichoromethyl-1-methyl-3-(2-naphthyl)-2-pyrazoline by X-ray crystallography.

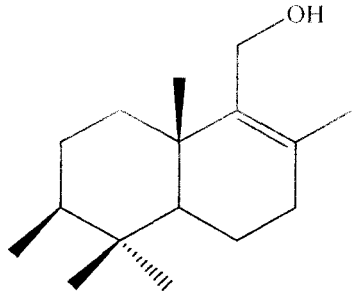
Wael *et al.* [9] has been designed a dual action prodrug based on the imidazo-[1, 2-a]-pyrazin-3-(7H)-one scaffold for combining antioxidant and anti-inflammatory activities, possibly unmasked upon oxidation. The construction of the target-molecule requires two building blocks, namely a 2-amino-1, 4-pyrazine and a 2-ketoaldehyde. They reported that attempts to synthesize the 2-ketoaldehyde (**5a**) derived from ibuprofen failed, but led to the corresponding 2-ketoaldoxime (**7a**) which could not be condensed with the pyrazine synthons. They observed that a model compound, i.e. phenylglyoxal aldoxime, reacted well under microwave activation to furnish novel imidazo [1, 2-a]-pyrazine-3-(7H)-imine derivatives (**18a,b**) and this heterobicycles behave as antioxidants by inhibiting the lipid peroxidation, and one compound (**18b**) is endowed with a significant anti-inflammatory effect in a cellular test.

Neto *et al.* [10] performed Retro-Michael reactions by super-heated steam distillation of 1, 5-diketones with a basic catalyst. They observed that dammarane, hopane and lupane derivatives gave yields in the range of 85 to 100% using sodium hydroxide deposited on glass wool as a catalyst.

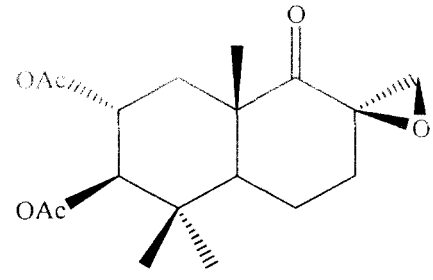
Parra et al. [11] obtained new derivatives of triterpenoids that are potentially useful for pharmacological studies by microbial transformation. They reported that In these biotransformation processes, several reactions that are difficult to achieve by chemical means have been accomplished, such as: introduction of hydroxyl groups into remote positions of the molecules; selective cleavage of the side chains of tetra-cyclic terpenoids to produce C19 steroids; regioselective glycosidic transfer reactions; selective ring cleavage through a Baeyer-Villiger-type oxidation to render *seco*-triterpenoids; and carbon skeleton rearrangements involving a methyl group migration. They observed that these biotransformations have been used as *in vitro* models to mimic and predict the mammalian metabolism of biologically active triterpenoids.

Yogeeswari *et al.*[12] reported that a naturally occurring pentacyclic triterpenoid betulinic acid exhibit a variety of biological activities including inhibition of human immunodeficiency virus (HIV), antibacterial, antimalarial, antiinflammatory, anthelmintic and antioxidant properties. They carried out various structural modifications and their biological and pharmacokinetic profiles are also incorporated.

Garcı a-Granados *et al.* [13] obtained three *seco*-C-ring triterpenic compounds from oleanolic or maslinic acids from olive-mill solid wastes by photochemical and chemical reactions. They also obtained different remarkable sesquiterpene and *nor*-sesquiterpene fragments such as 3β- hydroxydrimenol (**13**) and epoxydecalone (**16**) from these oleantriene compounds through oxidative cleavages of the double bonds in the opened C-ring.



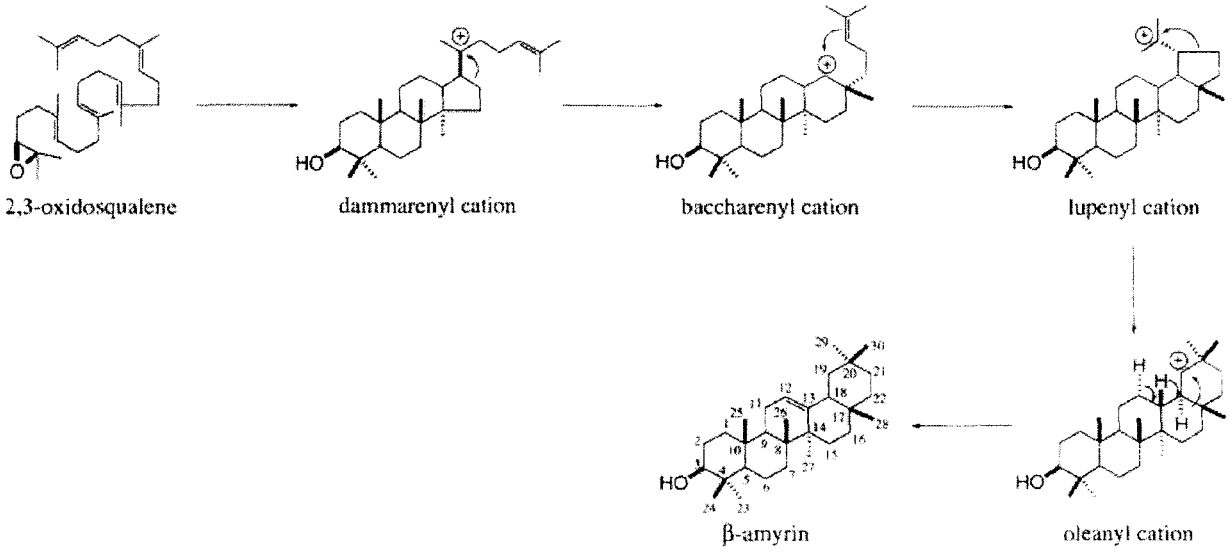
3β-hydroxydrimenol (13)



epoxydecalone (16)

Kushiro *et al.* [14] biosynthesised β-amyrin, a typical pentacyclic triterpene having an oleanane skeleton from (3*S*)- 2, 3-oxidosqualene. The enzyme, β-amyrinsynthase,

catalyzing the cyclization of oxidosqualene into β-amyrin, generates five rings and eight asymmetric centers in a single transformation.



Ahmad *et al.* [15] isolated a new *C*-glycoside, symcososide (**1**) along with one known compound β-sito-glycoside (**2**) from the re-investigation of the chemical constituents of *Symplocos racemosa* Roxb. They observed that the glycoside **1** displayed *in vitro* inhibitory activity against butyrylcholinesterase (BChE) enzyme with *IC*50 value of 21.2 ± 0.01 M.

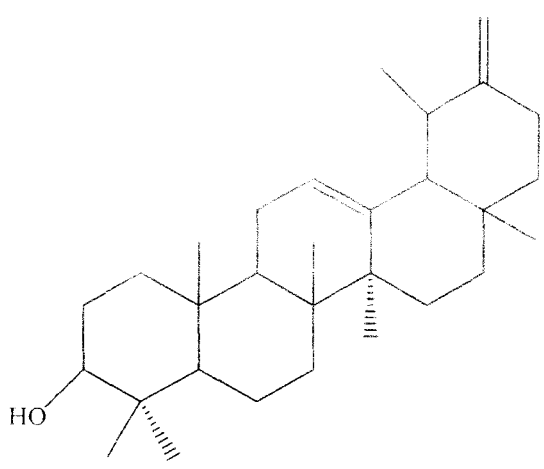
Pomarnacka *et al.* [16] were synthesized of 1-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)-4-hydroxysemicarbazides **11–19**, hydroxybenzaldehyde *N*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl) hydrazones **21–24** and 8-chloro-2-(1-naphthylamino)-5,5-dioxo[1,2,4] triazolo[2,3-*b*][1,4,2]benzodithiazine-7-carbonitrile (**26**). All compounds were tested for their *in vitro* cytotoxic potency against 12 human cancer cell lines at the Institute of Pharmacy, University of Greifswald. They observed that compounds **11–19** were inactive, whereas **22** and **24** exhibited weak tumor growth inhibitory properties. The compound **26** was screened at the National Cancer Institute and showed reasonable anticancer activity.

Sahaa *et al.* [17] extracted compounds from the leaves of *Mimusops elengi* Linn. and evaluated reducing power and total antioxidant capacity by using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) scavenging assay. They reported that the extract showed significant

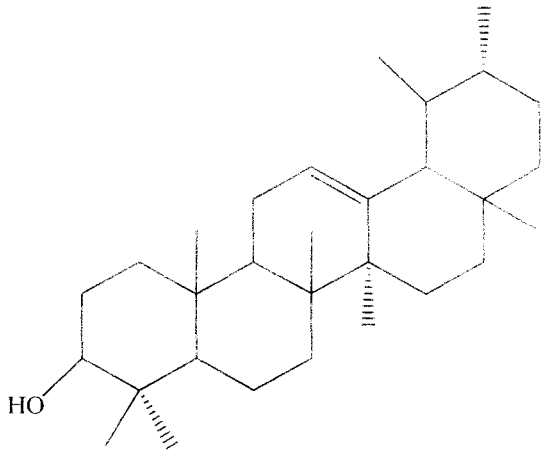
activities in all antioxidant assays compared to the reference antioxidant ascorbic acid in a dose dependent manner. They also reported that DPPH scavenging assay the IC50 value of the extract was found to be 43.26μg/ml while the IC50 value of the reference standard ascorbic acid was 58.92 μg/ml. Total antioxidant activity was also found to increase in a dose dependent manner. Moreover, *M. elengi* extract showed strong reducing power. These results suggest that *Mimusops elengi* may act as a chemopreventative agent, providing antioxidant properties and offering effective protection from free radicals.

Nishikawa *et al.* [18] efficiently synthesized of L-α-phosphatidyl-D-*myo*-inositol 3,5-bisphosphate from 1,2,5,6-diisopropylidene-D-glucose by utilizing ring-closing metathesis and catalytic OsO_4 dihydroxylation.

Corey *et al.* [19] used Li in presence of ethylene diamine for selective reduction of Olefinic double bond on triterpenoid. They obtained α-amyrin (1) from ursa-12:20(30)-dien-3β-ol (1a).



α-amyrin



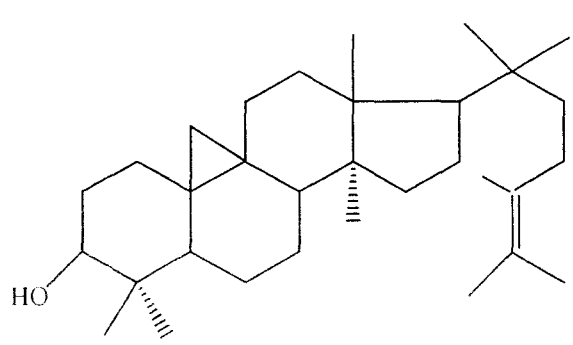
ursa-12:20 (30)-dien-3β-ol

Reggel *et al.* [20] also studied the isomerisation of olefins and dehydrogenation of cyclic dienes with Li in presence of ethylenediamine.

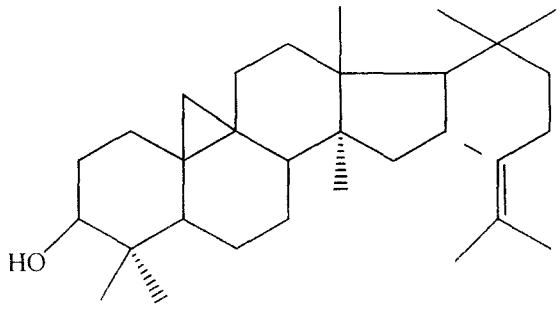
Tyagi *et al.* [21] studied the behavior of cyclopropane and cyclobutane rings on many triterpenoids towards the Li-ethylenediamine.

Smith *et al.* [22] reported that primary and secondary alcohols were dehydrogenated to carbonyl compounds in presence of Li metal in ethylene diamine.

Sukhdev *et al.* [23] reported that cyclolaudenol 2 on exposure to N-lithioethylenediamine at 120-125oC gave the isopropylidene isomer 2a in 92% yield.

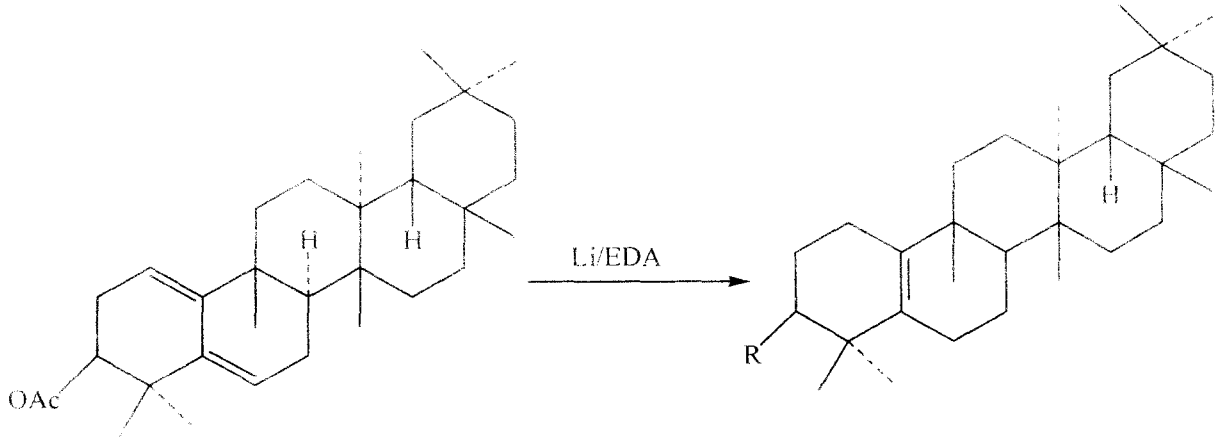


Cyclolaudenol



isopropylidene

Sengupta *et al.* [24] studied the reaction of Li in ethylene diamine on triterpenoid heteroannular 1,3-dienes and observed that gluto-1(**10**), 5-dienyl-3β–acetate **4** gave a mixture of deoxygenated product, glut-5(10)-ene **5a** and hydrolysed product, glut-5(10)-en-3β-ol **5b.**

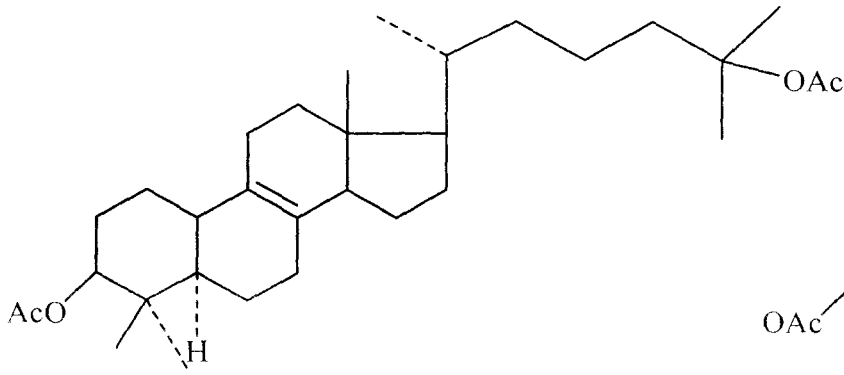


4

5a. R=H
5b. R=OH

Barton *et al.* [25] studied the reduction on sterol system contained two ester groups in sterically different environments. The compounds **6** and **7** when treated with Li in

ethylene diamine the products **8, 9, 10** were obtained respectively



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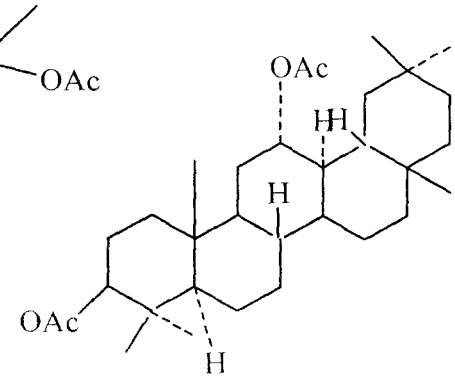

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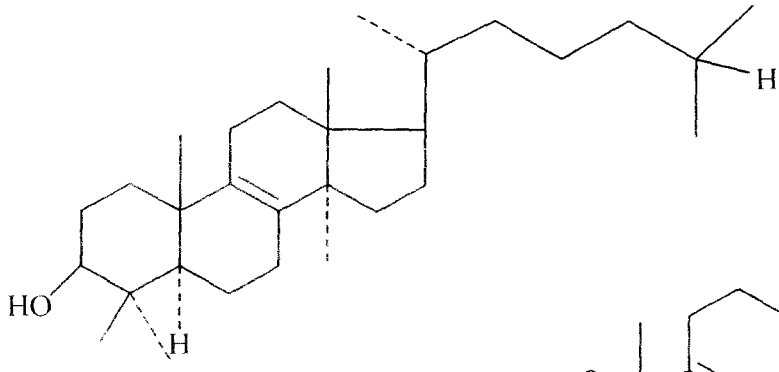

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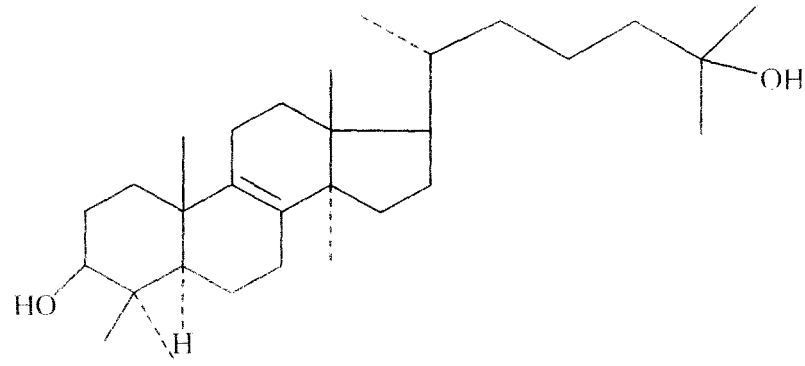

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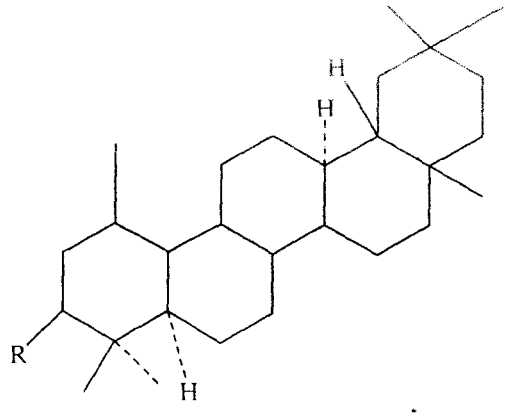


10

From the above literature work it appears that limited chemical work has so far been attempted both on the transformative reaction of triterpenoids as well as on the systematic studies of the biological activities of the derived compounds. Hence, there exists an ample opportunity to study the transformative reactions on the isolated triterpenoids using various reagents and also the biocidal activities of each of them in comparison to the parent compound. These investigations will not only enrich the little known triterpenoid chemistry but at the same time may yield a number of very useful pharmacologically important derivatives.

Chemical transformations using MW irradiation has been used extensively by various groups of researchers and a short review of which is described below.

Ma *et al.* [26] has been developed an efficient one-pot method to generate structurally diverse and medicinally interesting pyrazolone derivatives in good to excellent yields of 51–98% under microwave irradiation and solvent-free conditions.

Gaina *et al.* [27] applied a dynamic microwave power system in the chemical synthesis ofsome phenothiazine and quinoline derivatives is described. They compared the microwave-assisted synthesis with the conventional synthetic methods and found advantages related to shorter reaction time and in some cases better reaction yields in the case of microwave-assisted system.

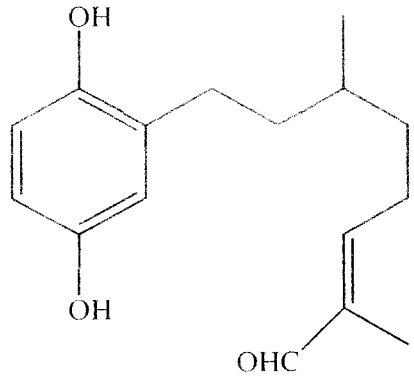
Chen and Hu [28] were synthesized a series of 1,2,3,4-tetrahydrocarbazoles by the reaction of substituted 2-bromocyclohexanones with appropriate anilines under microwave irradiation without any other catalysts.

Wu *et al.* [29] was developed a microwave-assisted reaction to facilitate the construction of 4,5-disubstituted pyrazolopyrimidines and reported that using microwave irradiation leads to high product conversion, low side product formation, and shorter reaction.

Raghunandan *et al.* [30] synthesized bio functionalized silver nanoparticles from guava (*Psidium guajava*) leaf by microwave-assisted process. The reaction was completed within 90 s. They selected the microwave-assisted route for synthesis to carry out the reaction fast, suppress the enzymatic action and to keep the process environmentally clean and green.

Bai *et al.* [31] has been developed a simple and rapid microwave-assisted extraction (MAE) procedure optimized for extracting triterpenoids (TTP) from the *Actinidia deliciosa* root. They reported that several variables that could potentially affect the extraction efficiency, namely extraction time (min), ethanol fraction (%), liquid: solid ratio (volume per mass) and microwave power. They also reported that under the optimum operating conditions (ethanol fraction 72.67 %, microwave power 362.12 W, liquid: solid ratio 15:1 and extraction time 30 min) the percentage of extracted TTP was 84.96 %, and MAE showed significantly higher recoveries than those obtained by the conventional extraction methods

Kad *et al.*[32] readily synthesized terpenoids **1** and **2** from readily available starting materials using Li_2CuCl_4-catalyzed coupling of Grignard reagents with alkyl/aryl bromides and microwave assisted oxidation of allylic methyl groups using SeO_2/ BuOOH adsorbed over SiO_2 as key steps.



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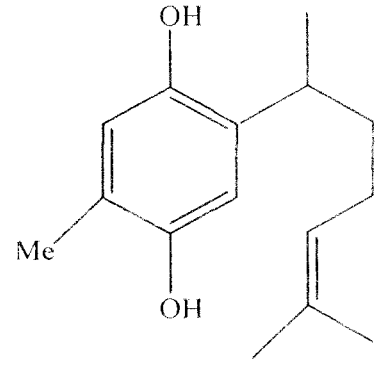


2

More *et al.* [33] have been synthesized various thymyl ethers and esters by reactions of thymol with alkyl halides and acid chlorides, respectively, in aqueous medium using microwave irradiation and reported that the products are important as potent pest managing agents.

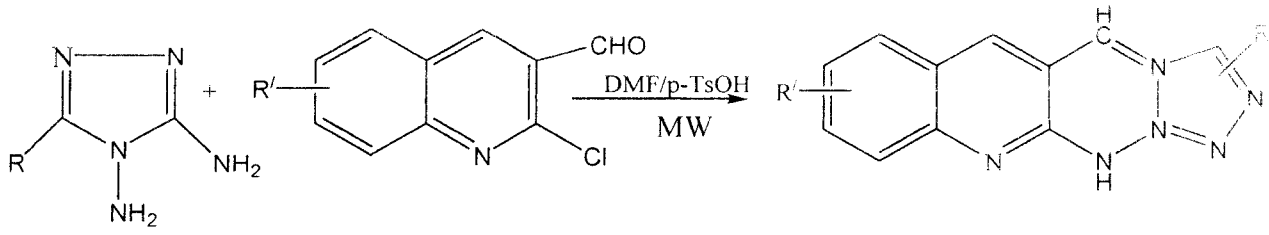
Gopalakrishnan *et al.* [34] oxidized Tetranortriterpenoids from *Azadirachta indica* A. Juss and *Soymida febrifuga* (Meliaceae) to single major products which exhibited bioactivity higher than the parent compound azadirachtin A. They reported that the reaction completed in less than 15 min and 1 min on being assisted by ultrasound and

microwave irradiation, respectively. They also reported a rapid and selective oxidation of the furan moiety of some limonoids employing microwave and ultrasound irradiations.

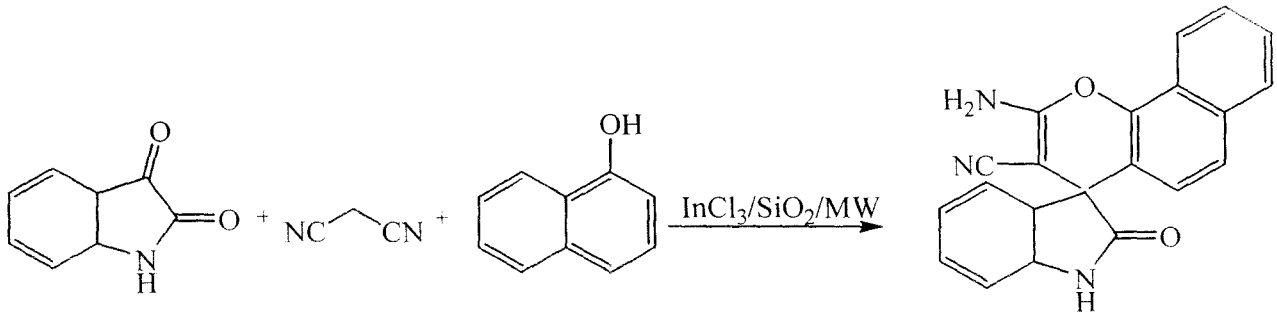
Yan *et al.* [35] were obtained volatile oils from *Marchantia convolute* by microwave extraction (ME) and phytosol extraction (PE) methods. The attained extracts were analyzed by gas chromatography with mass spectrometric detector. They identified a total of fourteen compounds in ME extract accounting for 80.72% of total peak area. Isolongifolene (24.588%), 1, 2-benzenedicarboxylic acid, butyl cyclohexyl ester (10.768%), pyrene (9.328%) and hexadecanoic acid, ethyl ester (8.570%) were the major compounds identified from ME extract.

Azizian *et al.* [36] introduced a microwave assisted one-pot three-component procedure for preparation of some dicyanomethylene derivatives of indenoquinoxaline and tryptanthrin under solvent free conditions.

Gupta *et al.* [37] synthesized 9-substituted -3-aryl-5H, 13 aH-quino-linol[3,2-f]triazolo[4,3-b][1,2,4]triazepines **8** from 5-aryl-3,4-diamino-1,2,4-triazoles **5** and 2-chloro-3-formyl quinolines **7** using catalytic amount of p-TsOH and N,N-dimethyl formamide as an energy transfer medium using microwave heating as well as solvent using oil bath heating at 80°C. The product were obtained in the good to moderate yield and in the state of high purity.



Shanthi *et al.* [38] described a simple and efficient method for the one-pot three-component synthesis of new spirooxindoles under conventional and solvent free microwave irradiation is described.



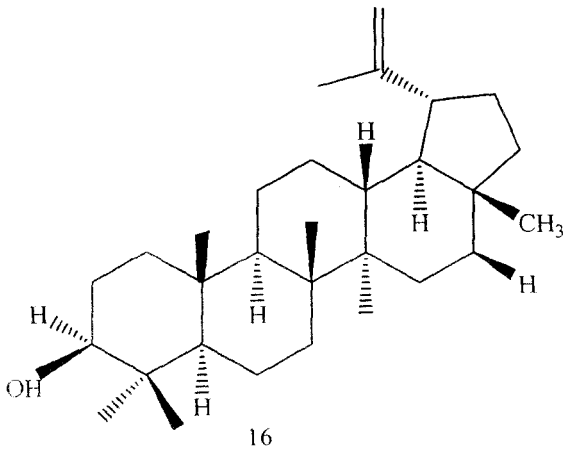
More *et al.* [39] have been synthesized various thymyl ethers and esters by reactions of thymol with alkyl halides and acid chlorides, respectively, in aqueous medium using microwave irradiation and reported that the products are important as potent pest managing agents.

It appears from the above that transformation under microwave irradiation has not yet been attempted on terpenoids and more precisely on pentacyclic triterpenoids. This encouraged the author to carry out the microwave assisted transformation of some of the isolated triterpenoids.

REVIEW ON BIOCIDAL ACTIVITY OF THE DERIVATIVES OF PENTACYCLIC TRITERPENOIDS

Akihisa *et al.* [40] isolated twenty-eight 3-hydroxy triterpenoids from the non-saponifiable lipid fraction of the flower extract of *chrysanthemum* (*Chrysanthemum morifolium*) and one lupane-type 3 alpha-hydroxy triterpenoid (**17**) derived from **16** were tested for their antitubercular activity against Mycobacterium tuberculosis strain H37Rv using the Microplate Alamar Blue Assay (MABA). They observed that Cytotoxicity of compound **17** against Vero cells gave an IC50 value of over 62.5 microg/ml, suggesting some degree of selectivity for M.

tuberculosis.



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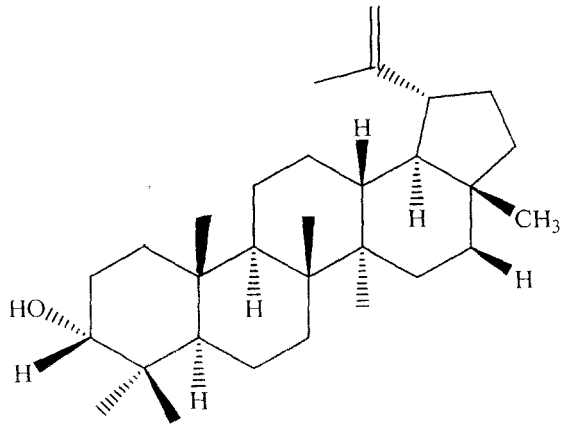


17

Ryu *et al.* [41] studied antiviral activity of triterpenoid derivatives and observed that 3-*oxo* or/and 11-oxo derivatives of natural 3-*hydroxy* triterpenes *i.e.*, 3-oxoursolic acid I a, 11-oxoursolic acid I b, 3,11-dioxoursolic acid I c, 3-oxobetulinic acid II a and 3-oxopomolic acid VI a were exhibited to show an increased anti-HSV-1 activity *in vitro*, four to ten times with respect to corresponding parent 3-*hydroxy* compounds.

Liby *et al.* [42] observed that synthetic oleanane triterpenoids have profound effects on inflammation and the redox state of cells and tissues, as well as being potent anti-proliferative and pro-apoptotic agents. Rexinoids are ligands for the nuclear receptor transcription factors known as retinoid X receptors. They found that both classes of agents can prevent and treat cancer in experimental animals and these drugs have unique molecular and cellular mechanisms of action and might prove to be synergistic with standard anti-cancer treatments.

Tamura *et al.* [43] reported that the leaf beetle *Ophraella communa* infests almost exclusively *Ambrosia artemisiifolia* in the fields of Japan and a filter paper bioassay showed that the feeding of *O. communa* is strongly stimulated by methanolic extracts of *A. artemisiifolia.* They also reported that triterpenoid derivatives (α-amyrin acetate or β-amyrin acetate) and caffeic acid derivatives (3, 5-dicaffoylquinic acid or 5-caffeoylquinic acid) showed feeding stimulant activity when mixed together.

Reddy *et al.* [44] isolated lupeol from the leaves extract of *Aegle marmelos* and synthesized few novel derivatives (**2–13**) from the naturally occurring lupeol (**1**) and

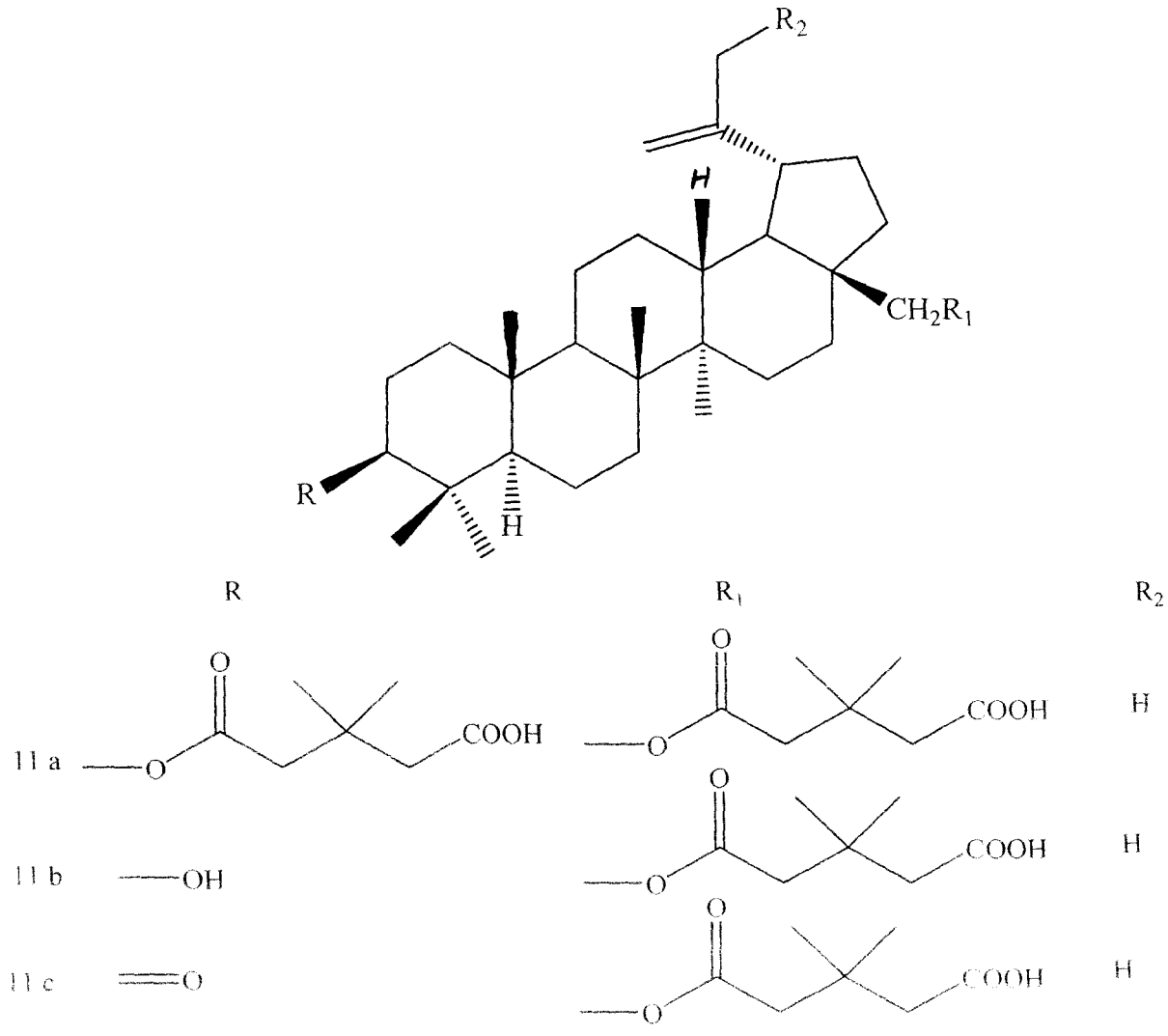
screened for their antihyperglycemic activity (**2–11**) and antidyslipidemic activity (**2–4** and **12–13**). They found that derivative **4** lowered the blood glucose levels by 18.2% and 25.0% at 5 h and 24 h, respectively, in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model at the dose of 100 mg/kg body weight and the compound **4** also significantly lowered 40% (P <0.001) in triglycerides, 30% (P <0.05) in glycerol, 24% (P <0.05) in cholesterol quantity and also improved the HDL–cholesterol by 5% in dyslipidemic hamster.

Meng *et al.* [45] were synthesized and designed a series of boswellic acid derivatives in order to search for new potent anti cancer agents and six of them were identified by IR, NMR and MS.

Woldmichael *et al.* [46] detected at least 16 saponins in the seeds of *Chenopodium quinoa*. They studied antifungal activity and hemolytic activity on erythrocytes of these compounds and derived monodesmosides against *Candida albicans*. They found that both bidesmosides and derived monodesmosides showed little antifungal activity whereas a comparatively higher degree of hemolytic activity could be determined for monodesmosides.

Tolstikov *et al.* [47] systematized the data on natural source of betulin and methods of its extraction, transformation and its available derivatives. They presented the data on the biological activity of betulin, its natural and synthetic analogs. The reported the promising character of the compounds based on betulin for creation of antiviral and antitumour agents.

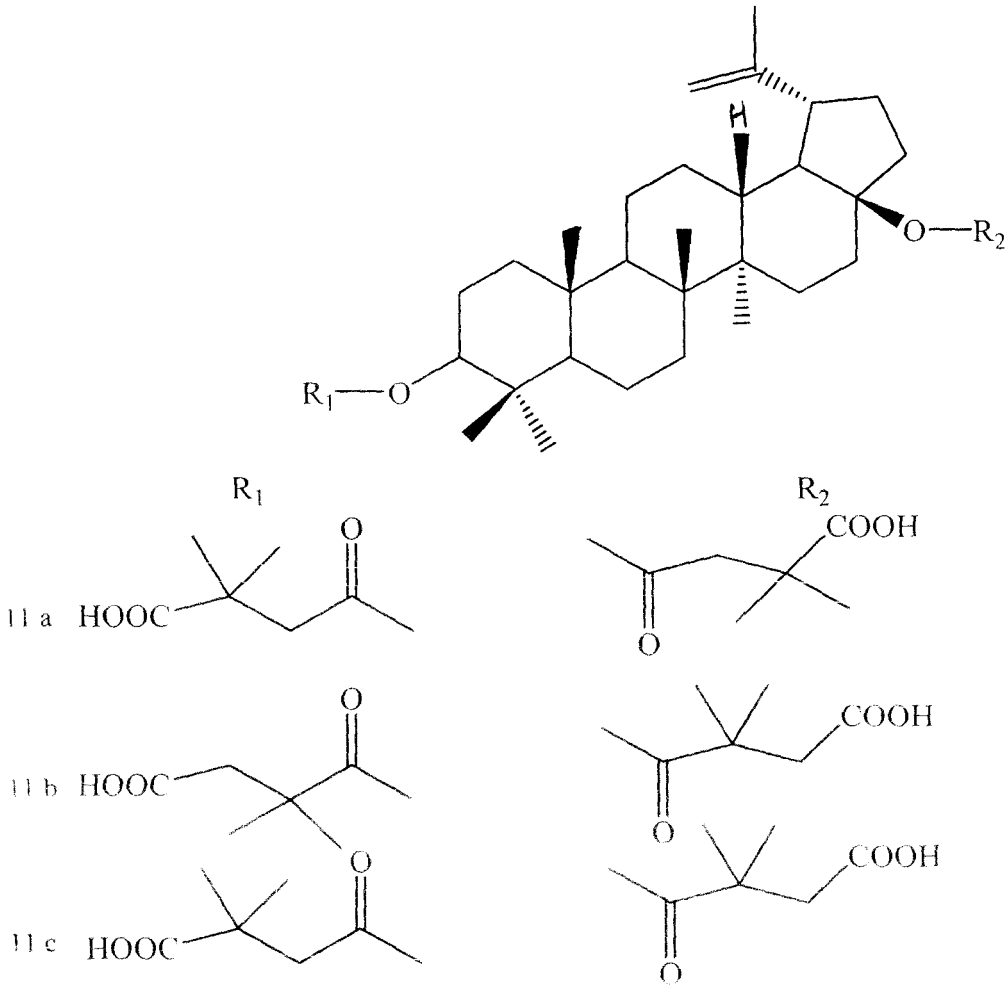
Su *et al.* [48] synthesized various o-acyl betulinic and dihydro betulin derivatives. Among them the most potent compound **11a** with two 3′, 3′-dimethyl glutaryl groups displayed anti-HIV activity with an EC_{50} value of 0.66 nM and SI of 21,515. The dihydro betulin derivative of **11a** showed a SI of 2253. Monoacyl betulin (**11b**), containing a substitutd glutaryl group only at C_{28} position, had an EC_{50} value of 36 μM and SI of 7.8. Conversion of the 3β-hydroxy gr. of **11b** to the mono keto derivative led to the **11c** and 0.46 μM respectively.



Schuhly *et al.* [49] isolated betulinic acid from the stem bark of Brazilian medicinal plant Zizypus jaazerio and its three new derivatives namely 7β-(4-hydroxybenzoyloxy) betulinic acid and 27-(4-hydroxy-3-methoxybenzoyloxy) betulinic acid and 27-(4-hydroxy-3-methoxybenzoyloxy) showed considerable activity against Gram-positive bacteria.

Kashiwada *et al.* [50] prepared four isomeric 3, 28-di-O-(dimethylsuccinyl) betulin derivatives and evaluated their anti-HIV potency. Among these derivatives, **11c** demonstrated the highest activity in acutely infected H9 cells with an EC_{50} value of 0.87 nM and inhibited uninfected H_9 cell growth with an IC_{50} value of 36.9 μM. Its calculated SI value (42,400) was comparable to that of zidovudine (41,622). Compound **11a** was also

extremely potent with an EC_{50} value of 0.02 μM and SI of 1680. Compound 11**b** displayed fair activity (EC_{50}=0.4 μM; SI=96.5) while 12**b** was toxic.

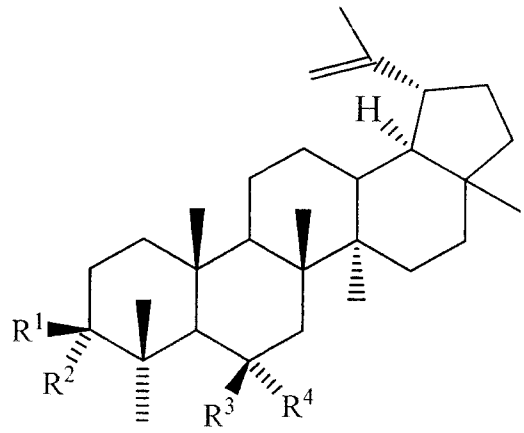


Su *et al.* [51] studied a series of triterpene derivatives for quantitative structure-activity relationship with multiple linear regression (MLR) and artificial neural networks (ANN). They observed that the linear model with MLR performed poorly while the nonlinear model with ANN preformed well. For the ANN model with architecture of 5-6-1, the root mean square error for the training set, validation set and the prediction set were 0.2019, 0.2214 and 0.2883, respectively. In this study they used different methods to select the most relevant descriptors for MLR and ANN and the result indicates these descriptors are playing an important role on the anti-HIV activity of triterpene derivatives.

Suh *et al.* [52] reported that the new synthetic oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) is a potent, multifunctional molecule. It induces monocytic differentiation of human myeloid leukemia cells and adipogenic differentiation of mouse 3T3-L1 fibroblasts and enhances the neuronal differentiation of rat PC12 pheochromocytoma cells caused by nerve growth factor. They found that CDDO inhibited proliferation of many human tumor cell lines, including those derived from estrogen receptor-positive and -negative breast carcinomas, myeloid leukemias, and several carcinomas bearing a *Smad4* mutation and suppresses the abilities of various inflammatory cytokines.

Baltina *et al.* [53] modified betulin and betulinic acid at the C-3 and C-28 positions and evaluated in vitro for antiviral activity. It was found that simple modifications of the parent structure of lupane triterpenes produced highly effective agents against influenza A and herpes simple type 1 viruses.

Mustafa *et al.* [54] reported that lupeol derivatives **(III-V)** containing functional groups in the ring B displayed a high inhibiting activity toward α-glucosidase and a moderate antibacterial activity. Lupeol ester **(VI)** was found to display cytostatic activity against JB6 cells Gao *et al.* [55].



	R^1	R^2	R^3	R^4
III	OH	H	OH	H
IV	–	O –	–	O –
V	$COC_{17}H_{35}$	H	H	OH
VI	$OCOCHCHC_6H_{13}(OH)_2$	H	H	H