CRITICAL REVIEW IN PHARMACEUTICAL SCIENCES

ISSN 2319-1082

Review Article

Medicinal properties and biosynthetic studies on Indigenous Medicinal Plant S*kimmia laureola*

Nighat Sultana

Pharmaceutical Research, Center, PCSIR Laboratories Complex, Karachi-75280, Pakistan

Abstract

This review covers the introduction, pharmacological activities, the spectral features, medicinal properties and biosynthesis of chemical constituents in *Skimmia laureola*. Besides this, ^{1}H and ^{13}C-NMR values of new compounds and their activity as the antifungal and anticholinesterases agent are also reviewed. The aim of the present study is to describe the pharmacological and spectral features of constituents of *Skimmia laureola.* The pharmacological properties of quinoline alkaloids have been investigated to a limited degree and as a result evidence of cytotoxic, phototoxic, mutagenic, antibacterial and anti-viral (HIV) activity has been observed. Quinoline alkaloids have not been screened for enzymatic activities for comparative studies of their constituents. The anticholinesterase activities of these compounds can be used with advantage in the screening of other quinoline compounds with structural variations.

KEY WORDS: *Skimmia laureola*,, biosynthetic studies, Medicinal properties

INTRODUCTION

In Pakistan some plants of family Rutaceae are found in Kashmir and in the mountains of Mansehra and Hazara in North West Frontier Province of Pakistan. The Rutaceae family has 150 genera and over 1500 species. *Skimmia laureola* Hook also belongs to the Rutaceae family and widely occurs in Kashmir and North West Frontier Province of the country.

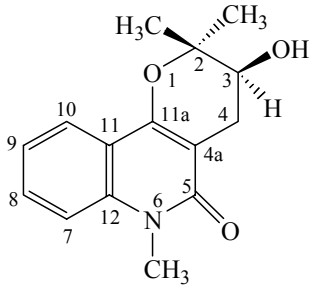
Skimmia laureola is a rich source of quinoline alkaloids, coumarins and triterpenes. The occurrence, chemistry and biosynthesis of quinoline alkaloids have been frequently reviewed in the Manske and later Brossi, series of the alkaloids [1,4-6] and regularly in the specialist periodical reports of the alkaloids, published by the Royal Society of Chemistry [7,8]. The latter have been carried on as Natural Product Reports [9]. Individual presentations on various aspects of quinoline alkaloids have also appeared as book chapters or articles in journals [10-18]. These constituents have attracted considerable interest due to their biological activity but only few publications have appeared on the spectral features of different constituents of the plant *S. laureola*.

Pharmacological Activities of *S. Laureola*

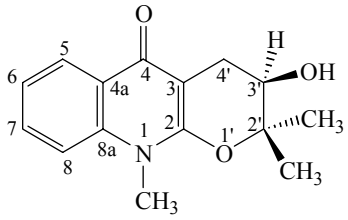
S. laureola is an ever green shrub. The leaves of this plant are commonly used in the indigenous system of medicine. The soot obtained from the burning of leaves is inhaled for the treatment of body pain, fever and flu by the local population of Hazara [19]. A poisonous crystalline alkaloid skimmianine has been found to be present in the leaves. The alkaloid has been found by experiments to have a direct action on the muscles of the heart, decreasing the pulsations and causing the

ISSN 2319-1082

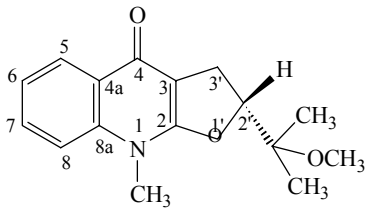
disturbances of the diastole [19]. Compound 3-hydroxy-2,2,6-trimethyl-3,4,5,6-tetrahydro-2*H*-pyrano-[3, 2-*c*] quinoline-5-one (**1**), ribalinine (**2**) and methyl isoplatydesmine (**3**) were screened for their enzyme inhibitory activity against acetylcholinesterase (AcChE) and butyrylcholinesterase (BuChE) by using modified Ellman method [20-23] were found to be potent cholinesterase inhibitors [2, 3].



2,2,2-Trimethyl-3,4,5,6-tetrahydro -2*H*-pyrano[3,2-*c*] quinoline 5-one (**1**)



Ribalinin (**2**)



Methyl isoplatydesmine (**3**)

Compound 4-methoxy-1-methyl-3-(2′*S*-hydroxy-3′-ene butyl)-2-quinolone (**134**) and ulopterol (**147**) were screened for antifungal activity [24].

Characteristic Features of the Constituents of *Skimmia laureola*

Spectral features, biosynthesis and characterization of some of the classes of compounds found in *S. laureola* is briefly described in following sections:

Spectral Features of Quinoline Alkaloids

UV and IR Spectroscopy

The UV spectra of furoquinoline-type alkaloids such as dictamnine showed an intense band at 235 nm and a broad band with fine structures (λ_{max} 308, 312 and 328 nm) in the region 290-335 nm was observed. The *N*-methyl-2-quinolone system showed UV maxima at 228, 260, 267 and 320 nm [25]. Ultraviolet and infrared spectroscopy can be used to differentiate the 2- and 4-quinolon-types of alkaloids.

2-Quinolinone alkaloids showed UV absorption maxima between 263-298 nm, while the 4-quinolinone alkaloids have slightly more intense absorption at longer waves length 290-340 nm.

In the IR spectra of 2-quinolinones, the carbonyl absorption commonly occurs between 1660-1640 cm^{-1}, whereas the carbonyl of 4-quinolinones absorbs at 1630-1620 cm^{-1}. The IR spectra of acridones (also vinylogous amides) are similar to the 4-quinolones with carbonyl absorption between 1640-1620 cm^{-1}.

Electron-Impact Mass Spectroscopy (ms)

This technique has been used extensively in the structure elucidation of quinoline alkaloids [25,28]. The methoxy-substituted furanoquinolines generally yield strong molecular ions, which in many cases are also the base peaks. Compounds with a methoxy group in position-8 such as □-fagarine (**Scheme 1.1-4**), give strong $[M-1]^+$ and $[M-29]^+$ ions (**5**) and **(7)** respectively [26] (**Scheme 1.1**), which are absent in compounds lacking in 8-methoxy group e.g. dictamnine (**Scheme 1.2**) [26]. The loss of

ISSN 2319-1082

CHO is the characteristic behaviour of quinoline compounds having furan ring.

Mass spectra of furanoquinoline alkaloids produce significant $[M-15]^+$ and $[M-43]^+$ ions due to the formation of fragments (**1.2-9** and **1.2-10**). These ions arise due to the loss of Me or the COMe from the 4-position respectively [26]. The common mass fragments of dictamnine are shown in (**Scheme 1.2**). The mass spectra of pyranoquinolinones like flindersine (**21**) and *N*-methyl flindersine (**22**) produce significant $[M-15]^+$ ion due to the formation of the benzopyrilium cation (**23**) [27]. The mass spectra of linear and angular dihydropyranoquinolines are very similar due to a common fragmentation route (**Scheme 1.3**). The mass spectra of 3-prenyl quinolinones such as **24** showed significant $[M-85]^+$ ions (**25**) due to the characteristic loss of the side chain [28] (**Scheme 1.4**).

^{13}C- and ^{1}H-NMR Spectroscopy

^{1}H-NMR spectroscopy has been particularly useful for distinguishing between 2- and 4- quinolinones, which are unsubstituted in position-5. The chemical shifts of H-5 are always at a lower frequency in 2-quinolinones, as compared to H-5 in 4-quinolinones.

The typical H-5 signals for quinolones, unsubstituted in the aromatic ring, appeared at □7.9-8.1 and 8.3-8.5 [29,30] for 2- and 4- quinolones, respectively. The C-8 proton is generally the most deshielded aromatic proton in acridone alkaloids [31]. In furanoquinoline alkaloids the furan ring protons appear as a pair of doublets (J = 3.0 Hz). The C-2 proton appears in the region of □ 7.5-7.6 and the C-3 proton resonates in the region □ 6.9-7.1. The C-5 proton is often the most downfield one (□ 7.5-8.1), and its multiplicity is a key to determine the substitution pattern of the benzenoid nucleus. The aromatic methoxy group appears at □ 4.0-4.2 ppm. Methoxy group shield the vicinal aromatic proton by 0.6 ppm (Table **1**) [32].

^{13}C-NMR spectroscopy has also been very informative in distinguishing between 2- and 4-quinolinones. The amidic carbonyls of 2-quinolinones resonate in between □160-165 e.g. in flindersine (**28**), C-5 appears at □162.9, whereas the carbonyls of the vinylogous amides normally occur at □171-176 [33].

The carbonyls of the acridones resonate at even higher frequency [31] i.e. □180-182. In furanoquinoline (**26**), the furan C-2 appears at □142.8 and C-3 appears at 104.6, respectively. These carbons chemical shift values are diagnostic feature of furanoquinoline compounds. The ^{13}C-NMR assignments for furanoquinoline e.g. skimmianine [32] are shown around structure **26** and for pyranoquinoline e.g. flindersine around structure **28**.

Biosynthesis of Quinoline Alkaloids

The quinoline nucleus is derived from anthranilic acid (**30**) and one molecule of acetate/malonate. Malonyl thioester (**31**) is formed by the addition of carbon dioxide to acetyl coenzyme. Thio coenzyme A (SCoA) stablizes the anions to the carbonyl group of malonyl thioester. Attack of this anion on carbonyl group of anthranilic acid yield the product **32** (**Scheme 1.5**). The elimination of thio coenzyme A (SCoA) yield the 4-hydroxy-1-methyl-2-quinolinone (**33**) [34,35]. The C-2 and C-3 of **33** are derived from C-1 and C-2 of acetate, respectively. Prenylation in C-3 (**33**) followed by oxidation of the requisite C-prenyl substituent (**34**) at C-2' and C-3' leads to the formation of **35**. The cyclization of the C-prenyl substituent (**38**) with an ortho oxygen function in C-2 or C-4 leads to the formation of the linear (**37**) or angular (**36**) dihydrofuranoquinolinones. Platydesmine (**37**) has been shown to be an intermediate

ISSN 2319-1082

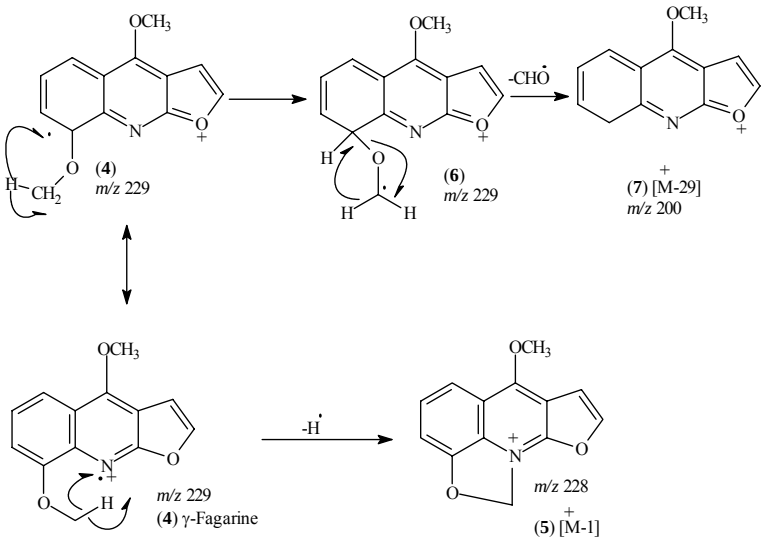
in the pathway from prenylquinolinone (**34**) to dictamnine (**38**) (**Scheme 1.5**) [38]. The removal of the isopropyl group from the linear dihydrofuranoquinoline (**37**) yields the common furanoquinoline dictamnine (**38**) [15]. This hypothesis further supported a more recent finding in the chemistry of unsubstituted furan ring arises by the fission of a three carbonfragment from the cyclized isopentane unit [36], whereas the C-2 furan ring was formed by the loss of a three carbon fragment from a mevalonate derived isoprenyl group [32,35,16]. The C-4 and C-5 of mevalonic acid are incorporated specifically into C-2 and C-3, respectively, of skimmianine (**50**) (**Scheme 1.7**).

Prenylation at C-3 of 4-hydroxy-1-methyl-2-quinolone (**33**) followed by cyclization of the requisite C-prenyl substituent [37] (as in **42**), with an *ortho* oxygen function at C-4 leads to the formation of angular pyranoquinolinone (**43**), while the epoxidation of **34** followed by cyclization of the oxygen at C-2 with the carbon at C-3' and methylation at C-4 oxygen leads to the formation of linear pyranoquinoline (**44**) while the cyclization of the oxygen at C-2 with the carbon at C-2' and methylation at C-4 oxygen leads to the formation of linear dihydrofuranoquinoline (**45**). Similarly the prenylation at C-4 oxygen function of (**33**) followed by Claisen-type rearrangement and then cyclization of the resulting product (**40**) leads to the formation of the angular furanoquinolinone (**41**) (**Scheme 1.6**). 2, 4-Dihydroxyquinoline (**46**) is known to be a precursor of kokusaginine (**52**). When [3-^{14}C]-2, 4-dihydroxy quinoline (**46**) was fed to *Skimmia japonica*, incorporation into dictamnine (**38**) and platydesminium salt (**49**) was observed [39]. The dimethyl allyl 2, 4-dihydroxy quinoline (**50**) (especially labelled with ^{14}C) was better incorporated (3.8% and 4.7% respectively) in accord with the biosynthetic route. Thus in skimmiannine hydroxylation of C-7 and C-8 probably occurs at a later stage in the biosynthesis [40]. Dictamnine (**38**) was efficiently incorporated into skimmianine (**50**) [40,41] indicating that dictamnine is an intermediate in skimmianine biosynthesis and that aromatic hydroxylation occurs after the formation of the furan ring [42] (**Scheme 1.7**). Dictamnine was a specific, although less efficient, precursor of choisyine (**51**) and evoxime (**48**) [43].

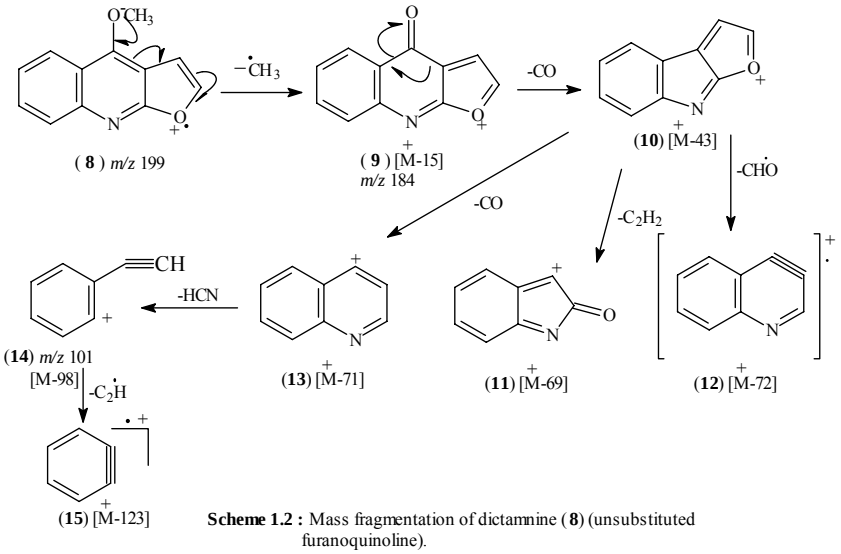
1.1.3.1 COUMARINS

The coumarins is a group of aromatic lactones derived from benzopyrone possessing a 2*H*-1-benzopyran-2-one nucleus (**53**). *Skimmia laureola* is a rich sourse of coumarins. A number of coumarins isogospherol, heraclenol, (+)-7-methoxy-6-(2'*R*-methoxy-3'-hydroxy-3'-methyl butyl)coumarin, 5,8-dimethoxy coumarin-2*H*-1-benzopyran-2-one, 7-methoxy-6-[2'-oxo-3'-methyl butyl) coumarin and (+)-ulopterol have been isolated from *Skimmia laureola*. Many coumarins contain a furan ring fused on to the aromatic ring, and these are known collectively as furanocoumarin such as psoralen (**54**). The main natural source of coumarin and furocoumarin are plants, especially members of Rutaceae, Umbelliferae and Leguminosae families [47]. Coumarins also serve several important functions in plants. They absorb a wide range of ultraviolet light and generate intense fluorescence (usually blue). The umbelliferone (**55**) is of commercial importance since it is the major UV-absorbing component of many sun-tan preparations. In addition they posses antibacterial, anticoagulant and cytotoxic activities. Some simple coumarins like scopoletin (**56**) isolated from various species of Rutaceae are a potent germination stimulant active at a concentration of 2-20 ppm [44].

ISSN 2319-1082



Scheme 1.1: Mass fragmentation (EI-MS) of γ-fagarine (**4**) (8-methoxy substituted furanoquinoline).

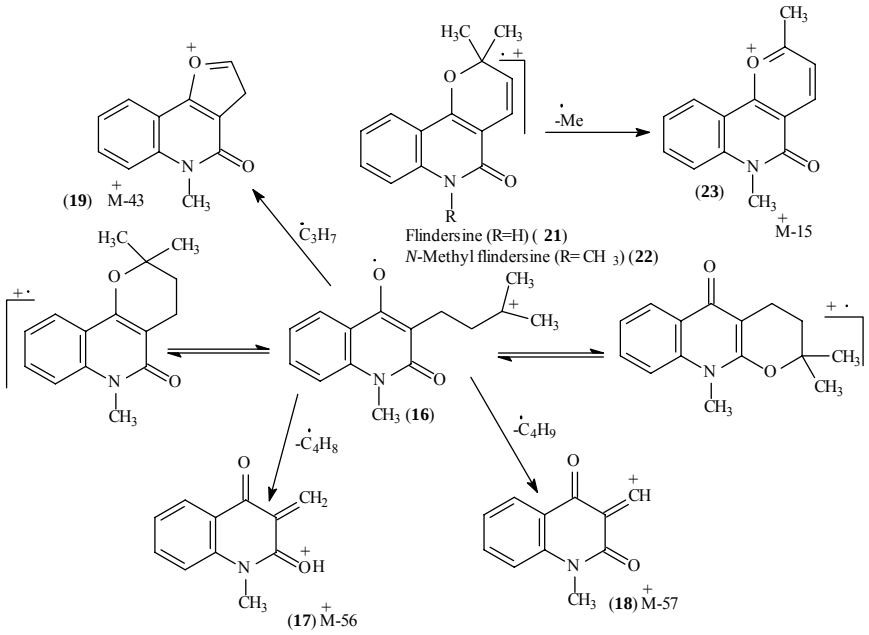


Scheme 1.2 : Mass fragmentation of dictamnine (**8**) (unsubstituted furanoquinoline).

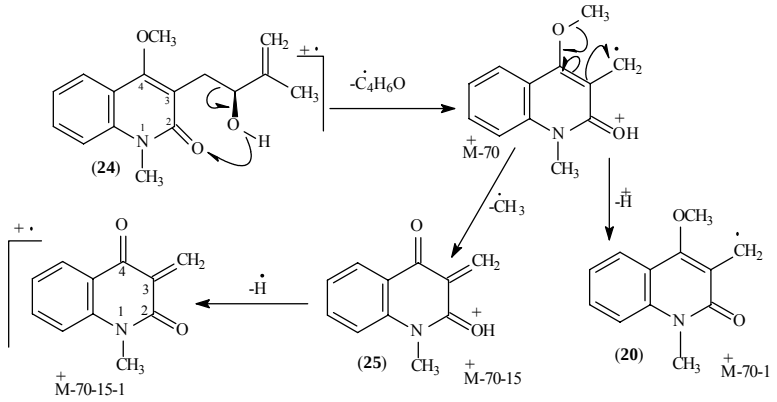
Table 1: Proton NMR data (in ppm) of furanoquinoline alkaloids.

Compounds	**H-2**	**H-3**	**4-OCH$_3$**	**H-5**	**H-6**	**H-7**	**H-8**
Dictamnine (**8**)	7.53	6.95	4.32	8.11	-	-	7.88
Robustine (**27**) (8-hydroxy)	7.50	7.13	4.13	-	-	-	-
6-Methoxy dictamnine	8.05	-	-	7.50	-	7.34	7.90
7-Methoxy dictamnine	7.95	-	-	8.10	7.10	-	7.25
Skimmianine (**26**)	7.58	7.07	4.42	8.05	7.25	-	-
6,7-Dimethoxy dictamnine	7.90	7.40	4.40	7.44	-	-	7.30

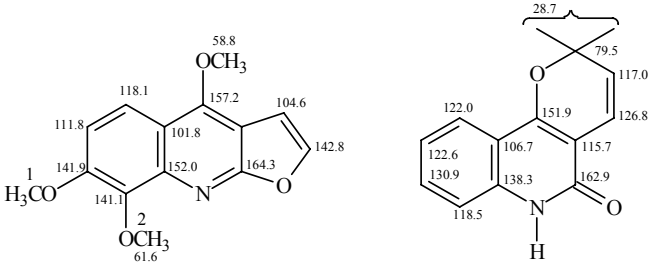
ISSN 2319-1082



Scheme 1.3: Mass fragmentation pattern of pyranoquinolinones.



Scheme 1.4: Mass spectra of 3-(2-hydroxy-3-methyl-but-3-enyl)-2-quinolones.

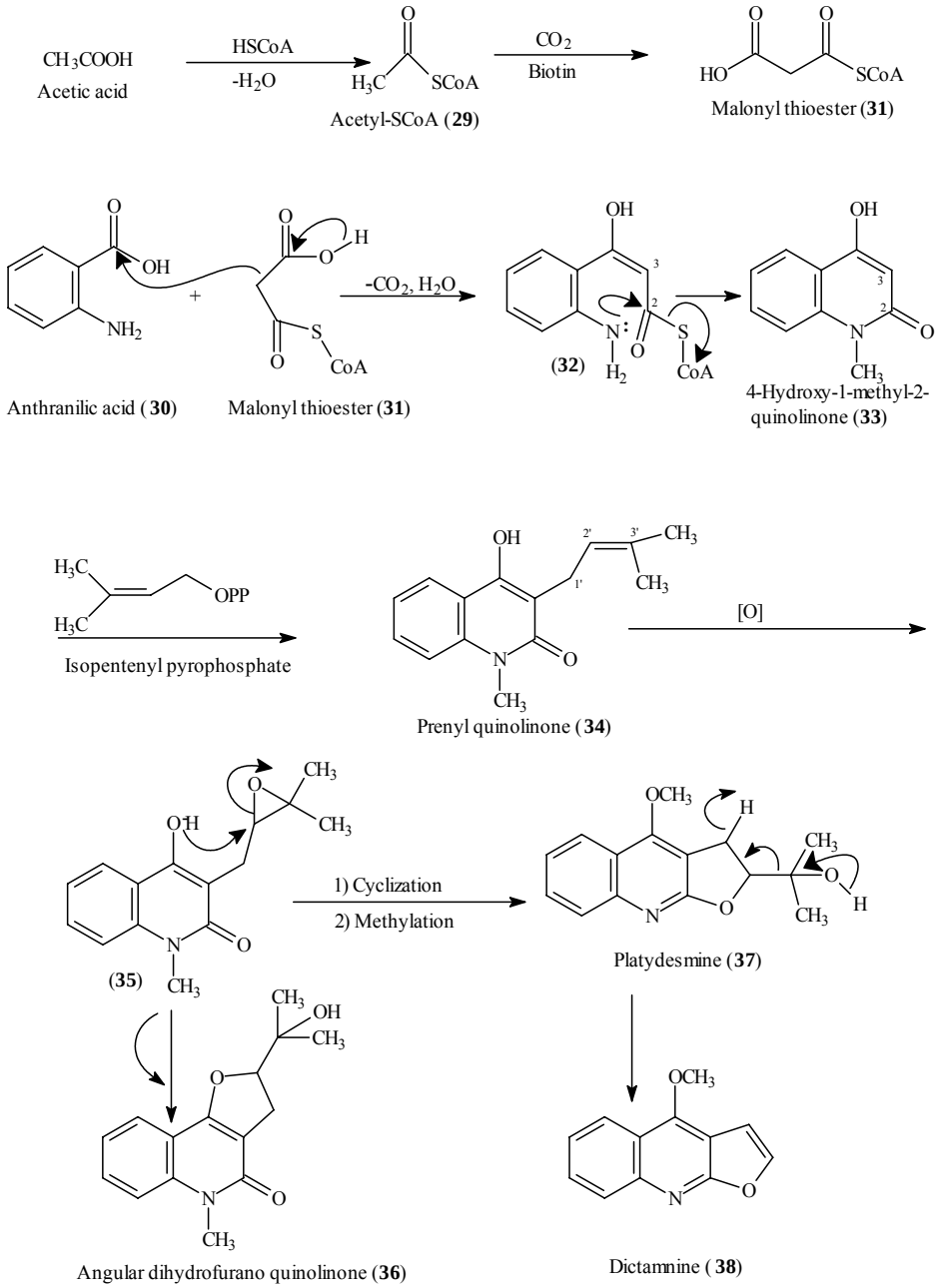


Skimmianine (**26**)

Robustine (**27**) $^{1}OCH_3$= H, $^{2}OCH_3$= OH

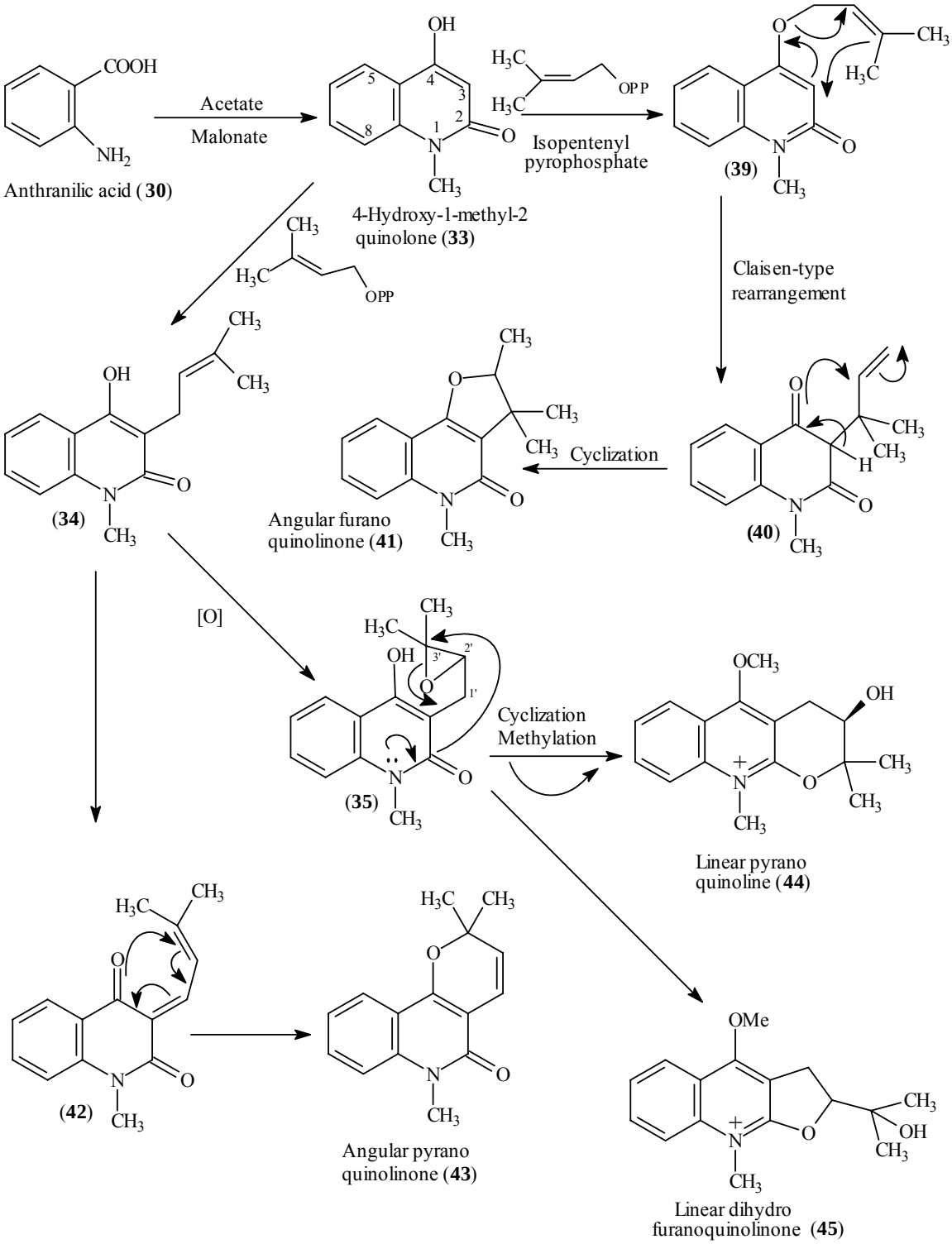
Flindersine (**28**)

ISSN 2319-1082



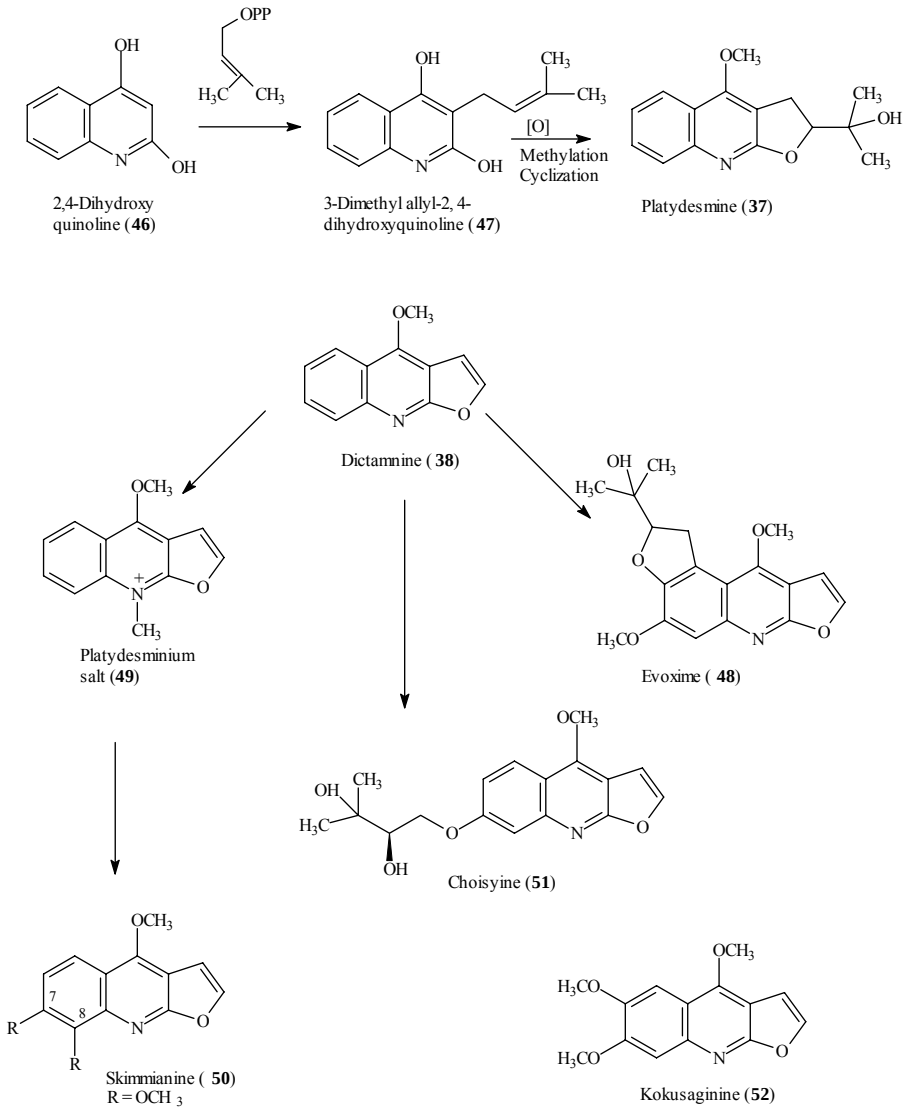
Scheme 1.5 : Biosynthesis of quinoline alkaloids.

ISSN 2319-1082



Scheme 1.6: Biosynthesis of linear pyranoquinoline (**44**), angular pyranoquinolinone (**43**) and linear dihydrofuranoquinoline (**45**).

ISSN 2319-1082



Scheme 1.7 : Biosynthesis of evoxime (**48**), choisyine (**51**) and kokusaginine (**52**).

Geiparvarin (**57**) has stimulated the development of a wide variety of interesting and practical synthesis due to its antitumor activity. The furano coumarin rutain (**58**) shows antibiotic activity against fungi [45]. Coumarins are physiologically active compounds [46] which have many and varied effects upon living cells. Aflatoxins, which are metabolites of *Aspergillus flavus* are intense liver poisons and are among the most potent known carcinogens. Coumarin exhibits a wide range of cytological and physiological effects on plants, some of which are shared by certain of its derivatives. It has been known for many years that contact of the skin with the juices of certain plants, followed by exposure to sunlight, can lead after a delay of some hours to development of erythema. Subsequently pigmentation of the effected areas occurs and in severe cases vesicle formation takes place. This effect is one of photosensitization of the skin [46].

Dicoumarol (**59**) has marked anticoagulant properties and does on occasion cause the death (from internal haemorrhage) of livestock that have consumed contaminated hay. The powerful rodenticide warfarin (**60**) was developed

ISSN 2319-1082

with these anticoagulant properties in mind and has proved to be very effective in controlling the rat population.

Most of the coumarins have eriobrucinol (**61**) and toddalenone (**62**) types skeletons. Many of the observed activities of coumarins appear attributable to the benzofuran system but simple coumarins are also toxic and are reported to deter some generalist herbivores. Some troublesome clinical cases have been reported in field workers handling plants infected with the fungus *Sclerotinia sclerotiorum* [48], which contains xanthotoxin and 4, 5, 8- trimethyl psoralen [48].

1.1.3.2.1 Characteristic Spectral Features of Coumarins

1.1.3.2.1.1 UV and IR Spectroscopy

The UV spectra of simple coumarin e.g. archetypal (**53**) showed absorption bands at 274 and 311 nm (log Σ 4.03 and 3.72), which have been attributed to the benzene and pyrone rings respectively [50]. Introduction of methyl group into the coumarin nucleus results in very small shifts of the absorption maxima. Substitution of a methyl group at C-3 causes a small hypsochromic shift of the 311 nm maximum, leaving the other maximum essentially unchanged. However, the methyl substitution at C-5, C-7 or C-8 leads to a bathochromic shift of the 274 nm maximum but leaves the 311 nm maximum practically unchanged [50].

In the IR spectra of coumarins the pyrone carbonyl stretching frequency is found in the region of 1700-1750 cm^{-1} [51,52]. When an alkoxyl group is attached to C-5 with C-8 unsubstituted, the carbonyl band shifts to a frequency higher than 1720 cm^{-1} but when the alkoxyl group is substituted at C-8, a frequency lower than 1720 cm^{-1} is obtained [53]. The IR spectra of pyranocoumarins showed a strong absorption band at 1717-1730 cm^{-1} which shifts to 1735-1750 cm^{-1} in dihydropyranocoumarins.

1.1.3.2.1.2 Electron Impact Mass Spectrometry (MS)

Electron-impact mass spectrometry of simple coumarin (**53**) gives a strong molecular ion at *m/z* **146** ($\mathbf{M^+}$) and a base peak at *m/z* 118. The later ion formed from the molecular ion by loss of carbon monoxide, a highly stable neutral particle [54] from the pyrone ring [55]. The benzofuran ion (**63**) decomposes further by consecutive loss of CO and a hydrogen atom yield, an ion at *m/z* 89 (**65**) (**Scheme 1.8**). Following sections summarize the mass fragmentation pattern in different classes of coumarins.

Hydroxy coumarins and Alkoxy coumarins

The mass spectra of hydroxy coumarins showed characteristic loss of C_2H_2O from the pyrone ring. This yields a base-peak which is 42 mass units lower than the molecular ion. This helps in the recognition of a 4-hydroxy coumarin [56] (**Scheme 1.9**). The molecular ion is also the base-peak in the mass spectrum of 7-methoxy coumarin (**69**). A strong $[M\text{-}CO]^+$ ion **(69a)** is also present in their mass spectra [55]. Loss of a methyl radical from the methoxy group yields a conjugated oxonium ion **73** (*m/z* 133), but this only occurs after the molecular ion has been converted to the 6-methoxy-benzofuran ion [56] (**69a)** (**Scheme 1.10**).

Furano coumarins

The ready elimination of CO from the pyrone ring is the characteristic feature for furanocoumarins [55,57]. However, in methoxy furanocoumarins such as xanthotoxin (**74**), loss of a methyl radical can give rise to a conjugated oxonium ion

ISSN 2319-1082

(**75**) and this process often predominates [55,56] (**Scheme 1.11**).

Pyranocoumarins

The ready elimination of methyl group from the pyrone ring and generation of a stable benzopyrylium ion (**75**), which is frequently the base-peak is the characteristic feature of pyranocoumarins [55,58]. The stable benzopyrylium ion (**75**), which is obtained from xanthyletin (**74**), is also obtained by the loss of 31 mass units from the 7-methoxy coumarin, suberenon (**76**) (**Scheme 1.12**).

1.1.3.2.1.3 ^{1}H-and ^{13}C-NMR Spectroscopy

In the ^{1}H-NMR spectra of coumarins, two characteristic doublets between 6.1-6.4 and 7.5-8.3 indicate a coumarin skeleton unsubstituted in the pyrone ring. These characteristic signals arise from the H-3 and H-4 olefinic protons respectively [59]. The majority of natural coumarins have an oxygen function at C-7 which cause H-3 to resonate to higher field as compared to unsubstituted coumarin (**53**) [60]. When a 7-oxygenated coumarin is substituted at C-5, the latter is invariably an oxygen function. The protons at C-6 and C-8 are now meta-related and give rise to a pair of close doublets (J = 2.0 Hz), when both are present and two singlets, when either C-6 or C-8 carries a carbon substituent. When only one aromatic proton is present as in 5-and 8-alkoxy psoralens, the position of substitution can still be clearly inferred. In the 8-alkoxy series (e.g. xanthotoxin (**71**), **Scheme 1.11**), the H-4 and H-2' signals overlap and H-5 appears at 7.3-7.4, whereas for 5-alkoxy psoralens, H-4 is shifted downfield, H-2' upfield and H-8 resonates at 7.0-7.2 [61,62].

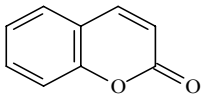
^{13}C-NMR spectroscopy is also an important technique for the structural studies of coumarins. For most coumarins the chemical shift of the carbonyl carbon atom has been found generally at 160 ppm. The chemical shifts of C-3 and C-4 of ,-unsaturated lactone ring of coumarin generally appear at 114 and 143 respectively. For a simple coumarin e.g. archetypal (**53**) the following chemical shifts have been observed, [63] C-2, (160.4), C-3, (116.4); C-4, (143.6); C-4a, (118.8), C-5, (128.1); C-6, (124.4); C-7, (131.8); C-8, (116.4) and C-8a, (153.9) are characteristic of the coumarin ring system.

Cinnamic acid is generated by the conversion of 3-dehydro-shikimate (**77**). Formation of shikimic acid 3-phosphate (**78**) followed by reaction with phosphoenol pyruvate (**79**) and after subsequent elimination and rearrangement of chorismate (**81**) produces prephenate (**82**). (This [3,3] sigmatropic rearrangement is a symmetry allowed pericyclic process) (**Scheme 1.13**). Decarboxylation of prephenate (**82**) is followed by aromatization and amination to produce the amino acid phenylalanine (**83**). An alternative route provides the tyrosine (**84**) and involves reductive amination of prephenate (**82**). The stereospecific anti elimination of ammonia from either phenyl alanine (**83**) or tyrosine (**84**) yields cinnamic acid (**85**) or para coumaric acid (**86**) respectively (**Scheme 1.13**). Trans cinnamic acid formed from the enzyme mediated deamination of phenylalanine (**83**), and subseuently undergoes ortho oxidation. The ortho coumarinyl glucoside are probable intermediates as is confirmed by the high incorporation of the former (^{14}C-labelled) into coumarin. *O*-Coumaric acid glucoside (**88**) undergoes isomerization to the corresponding cis acid (**90**) by the action of phenyl alanine ammonia lyase. This enzyme is liberated on crushing the cells, affording the unstable cis 2-hydroxy cinnamic acid which spontaneously lactonizes to coumarin (8**9a**). Substitution to yield simple substituted coumarins occurs only after cyclization, while prenylation occurs at the umbelliferone

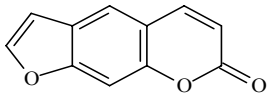
ISSN 2319-1082

stage [65]. The mechanism of prenylation of umbelliferone is visualized as involving the formation of the stable anion (**91a-91c**). The electrophilic attack of a prenyl carbonium ion can occur at either C-6 or C-8 to yield C-prenyl coumarins (**93**, **94**) or can occur on the phenoxide to give *O*-prenyl compounds (**92**) (Scheme **1.14**).

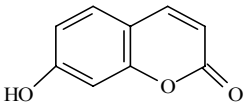
The addition of the dimethyl-allyl unit at C-6 appears to be stereospecifically controlled by the enzyme dimethyl allyl phosphate umbelliferone transferase [65,66]. The role of prenylating enzymes is to localize the charge on the anion and thereby directing the attack of the prenyl unit (**Scheme 1.14**).



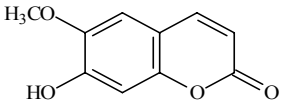
Archetypal (**53**)



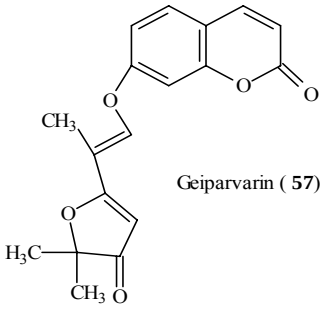
Psoralen (**54**)



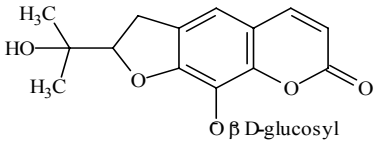
Umbelliferone (**55**)



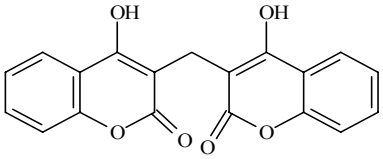
Scopoletin (**56**)



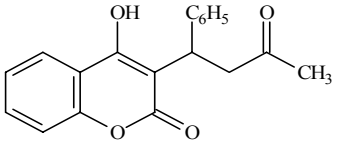
Geiparvarin (**57**)



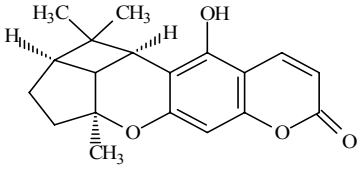
Rutarin (**58**)



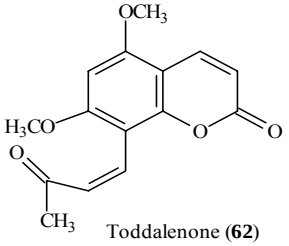
Dicoumarol (**59**)



Warfarin (**60**)

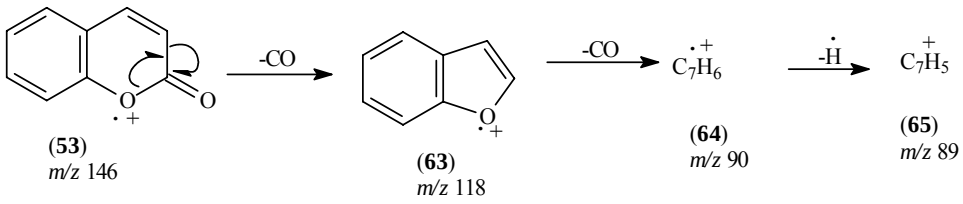


Eriobrucinol (**61**)



Toddalenone (**62**)

ISSN 2319-1082



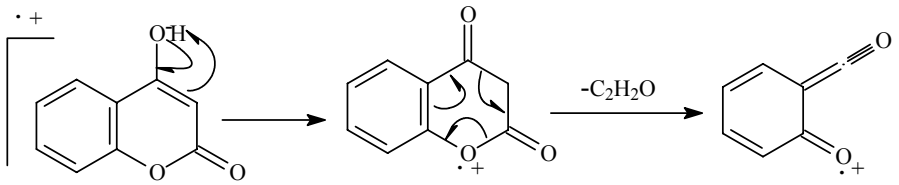
(**53**)
m/z 146

(**63**)
m/z 118

(**64**)
m/z 90

(**65**)
m/z 89

Scheme 1.8

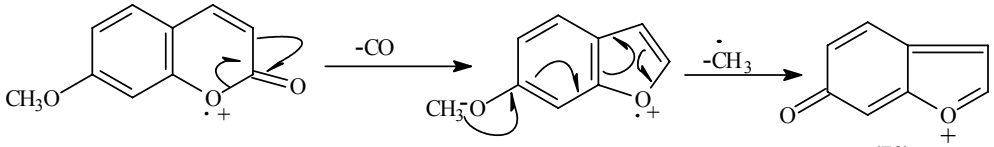


(**66**)

(**67**)
m/z 162

(**68**)
m/z 120

Scheme 1.9

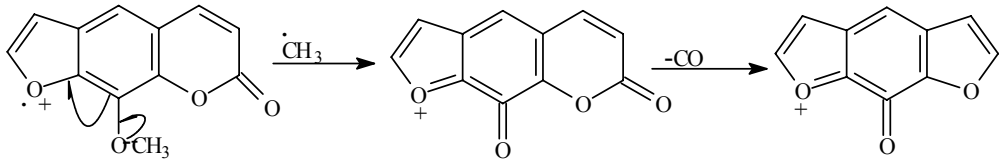


(**69**)
m/z 176

(**69a**)
m/z 148

(**70**)
m/z 133

Scheme 1.10

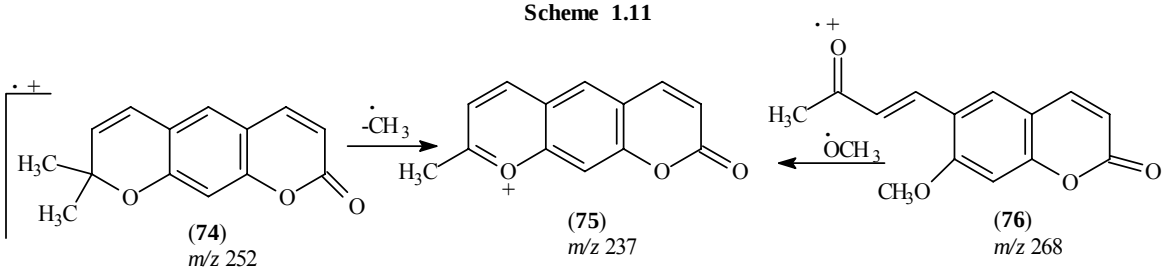


(**71**)
m/z 216

(**72**)
m/z 201

(**73**)
m/z 173

Scheme 1.11



(**74**)
m/z 252

(**75**)
m/z 237

(**76**)
m/z 268

Scheme 1.12

ISSN 2319-1082

1.1.3.2.2 Biosynthesis of Coumarins

Biogenetically coumarins are formed from cinnamic acid. Mate

The secondary modification takes place on the prenyl side-chain, *via* the initial epoxidation of the olefinic double bond. The *O*-prenylation and *C*-prenylation process is controlled by two distinct mono-oxygenases, probably because of differing stereo-electronic requirements of the two prenyl types [67]. The intermediate appears to be either the prenyl epoxide (**96**) or the diol (**100**) for the linear type or their C-8 prenyl equivalents for the angular type [67]. The furanocoumarins marmesin (**98**) and columbianetin (**104**) contain a coumarin and a C-5 sub-units. Biosynthetic pathways *via* 7-demethyl suberosin (**95**) and osthenol (**103**) to marmesin (**98**) and columbianetin (**104**) is analogous (**Scheme 1.15**). Further metabolism of marmesin produces psoralen, (**99**) in which three of the original carbon atoms have been lost. Hydroxylation at C-5 then yields bergaptol (**100**) and methylation yields bergapten (**101**). Subsequent hydroxylation at C-8 and methylation finally produces isopimpinellin (**102**) (**Scheme 1.15**).

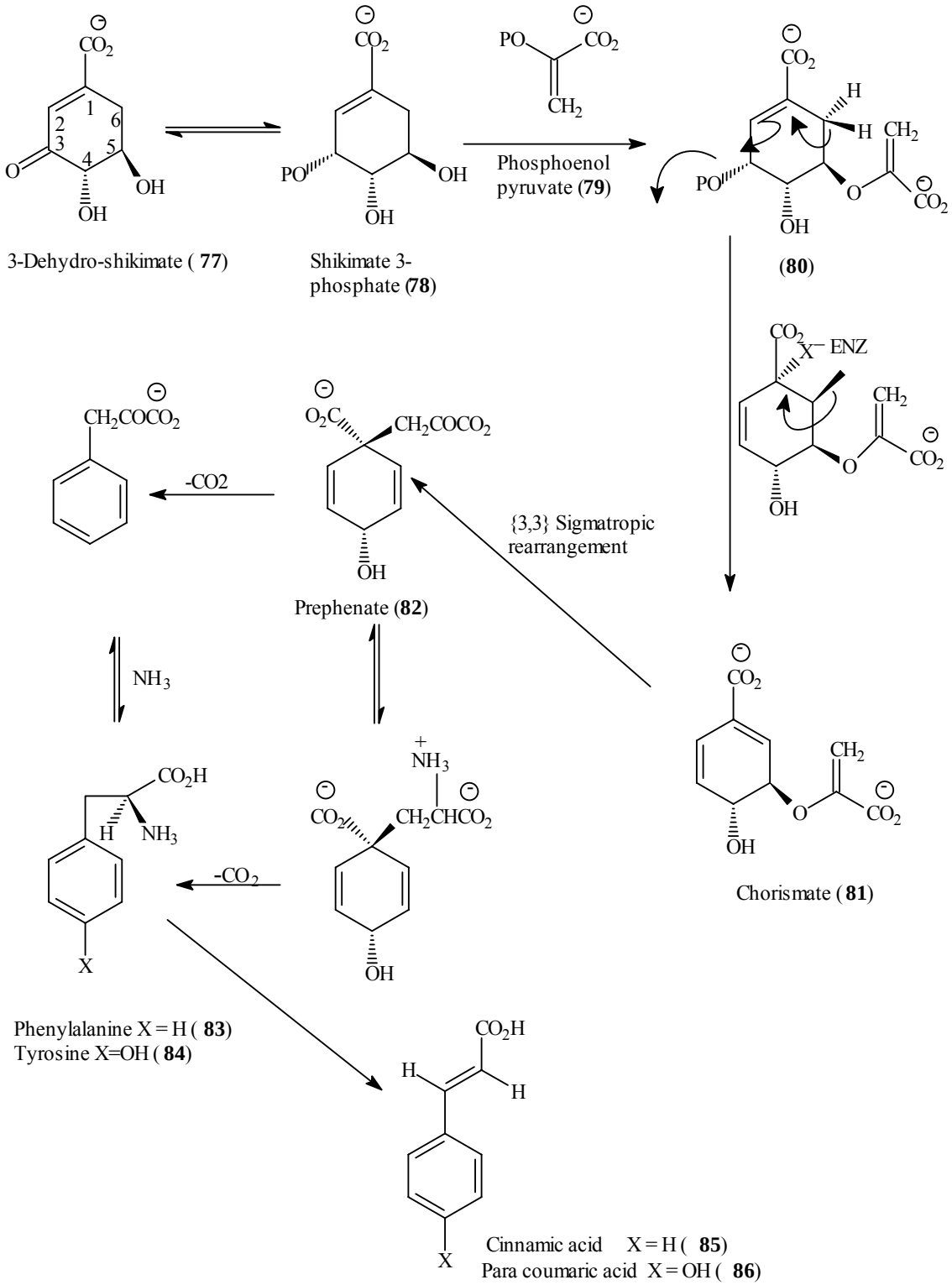
1.1.3.3 TRITERPENOIDS AND STEROIDS

Triterpenoids and steroids are a naturally occurring group of compounds whose structures comprise six isoprene units. Terpenes and terpenoids constitute one of the most numerous and varied classes of organic compounds, embracing a wide range of substances from simple monoterpenes to the highly complex triterpenes. A number of triterpenes have been isolated from *Skimmia laureola* [3]. Like alkaloids, terpenes also serve important functions. In daily life, volatile terpenes are used as perfumes and fragrances. In addition they possess antibiotic, cytotoxic and antifeedant activities and are commonly used as drugs and pesticides. The chief natural source of terpenes, marine and triterpenoids are plants but terpenoids are also reported from other sources, such as microorganisms and sex hormones of insects and from fungi.

Some simple terpenes like santonin isolated from various species of *Artemesia* and *Ascaridole* as well as from the oil of *Chenopodium,* are used in the treatment of round worms [68]. The biological activity of cyclic terpenes is due to their oxygenated nature e.g. the fungal antibiotic ovalicin is highly oxygenated. Other compounds having similar basic skeleton to ovalicin are reported to possess antimicrobial activity [69].

Monoterpene glycosides play an important role in the storage and transportation [70] of different essential constituents in the plant. Cyclic monoterpenoids are surprisingly quite rare as fungal metabolites, however, a *p*-menthanetriol has been isolated from the fungus *Fusicoccum amygdali*. The search for biologically active natural products has afforded a number of new triterpenoids. A number of tumor-inhibitory derivatives exemplified by isocucurbitacin D have also been isolated. The highly oxidized triterpenoid such as azadirachtin from *Melia azadrach* is of interest because of its insect antifeedant activity.

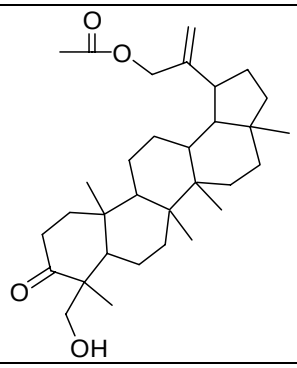
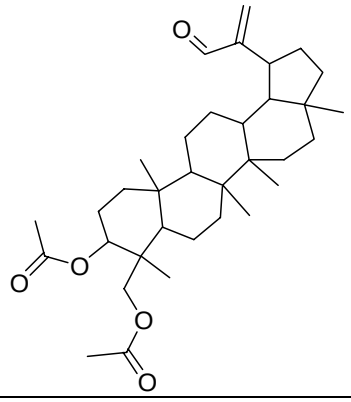
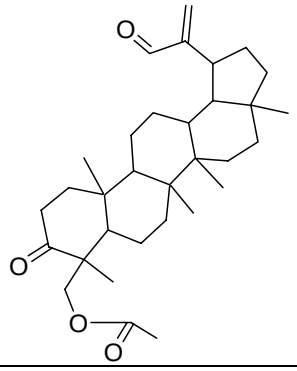
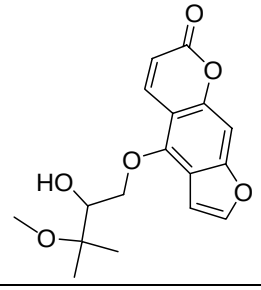
ISSN 2319-1082



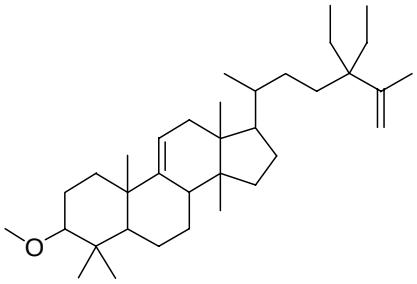
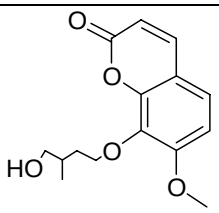
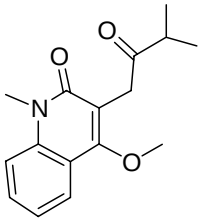
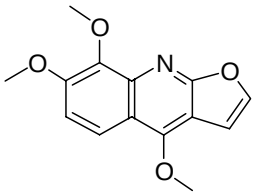
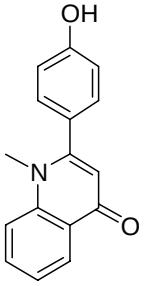
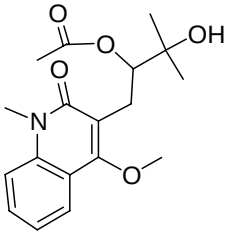
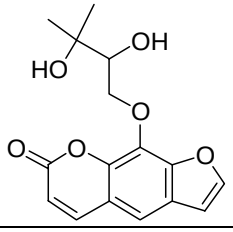
Scheme 1.13: Biosynthesis of coumaric acid.

ISSN 2319-1082

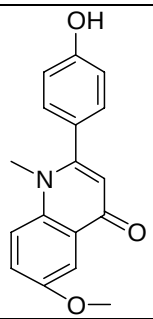
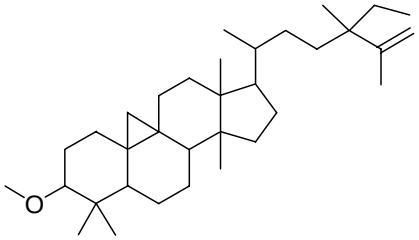
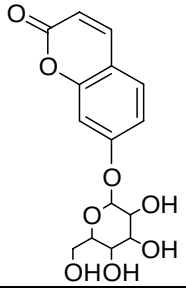
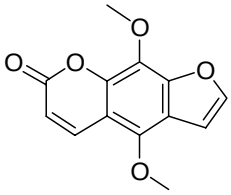
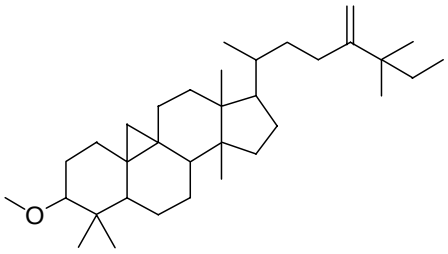
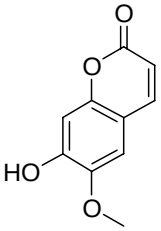
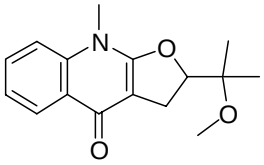
Table **2**: Reported Compounds from *Skimmia laureola*

1.	3,23-Dihydroxy-20 (30)- 29-al, -29-alcohol, 29-Ac, 3-ketone lupen: (3□ form) [71]	$C_{32}H_{50}O_4$	
2.	3, 23-Dihydroxy-20 (30)- 29-al, Di-Ac lupen: (3□ form) [71]	$C_{34}H_{52}O_5$	
3.	3,23-Dihydroxy-20-(30)-29-al,Ac, 3-ketone, lup: (3□ form) [71]	$C_{32}H_{48}O_4$	
4.	Aviprin : (*R* form) [72-90]	$C_{17}H_{18}O_6$	

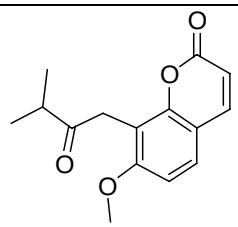
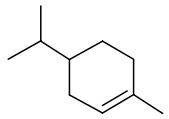
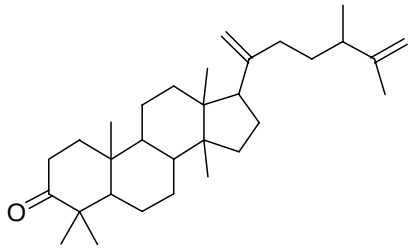
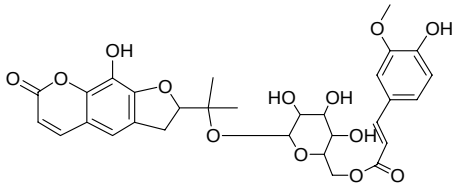
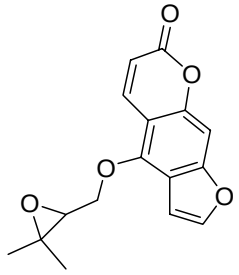
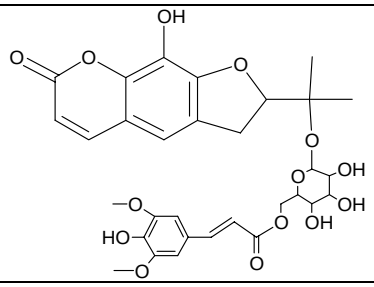
ISSN 2319-1082

5.	24, 24-diethyllanosta-9 (11), 25-dien-3-ol: (3□-form) [911-92]	$C_{35}H_{60}O$	
6.	7,8-Dihydroxy-2*H*-1-benzopyran-2-one [93-130]	$C_{15}H_{18}O_5$	
7.	Edulinine (*R* form) [131-136]	$C_{16}H_{10}NO_3$	
8.	Furo [2,3-b] -4, 7, 8-teiol; ri-me-ether quinoline [137-158]	$C_{14}H_{13}NO_4$	
9.	2- (4-hydroxy phenyl)-1- methyl-4 (1*H*) –quinolinone [159-161]	$C_{16}H_{13}NO_2$	
10.	Edulinine : (*S* form) [131-136]	$C_{18}H_{23}NO_5$	
11.	Heraclenol (*S* form) [75, 91, 165-166,175- 169]		

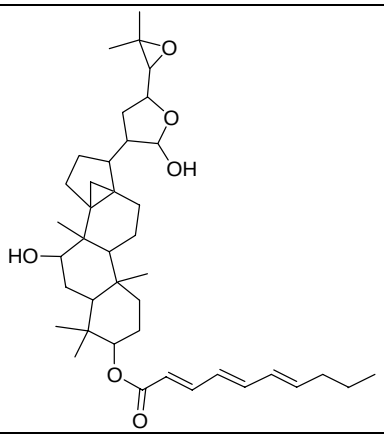
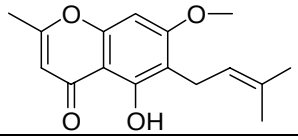
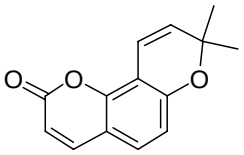
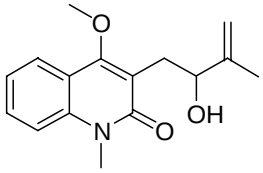
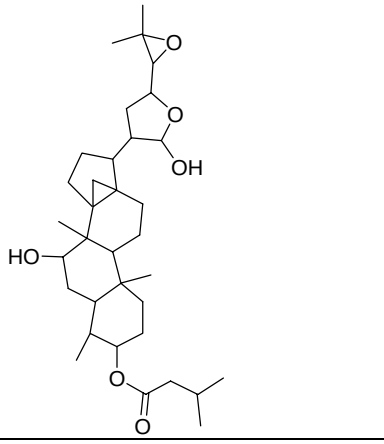
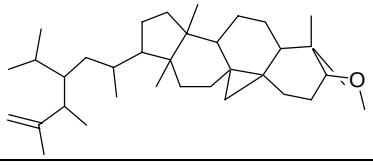
ISSN 2319-1082

12.	2 (4-Hydroxy pheny)-1-methyl-6-methoxy -4 (1*H*) quinolinone [165-167]	$C_{17}H_{15}NO_3$	
13.	24-Ethyl-24-methylcyclo-art-25-en-3-ol (3□, 24 E form) [170]	$C_{34}H_{58}O$	
14.	7-Hydroxy-2 *H*-1-benzopyran-2-one; *O*-□-D-glucopyranoside [57, 107-108, 171-199]	$C_{15}H_{16}O_8$	
15.	Isopimpinellin [98, 200-201]	$C_{13}H_{10}O_5$	
16.	25-Ethyl-24-methylene cycloartan-3-ol : me ether (3□ form) [189]	$C_{34}H_{58}O$	
17.	7-Hydroxy-6-methoxy-2*H*-1-benzopyran-2-one [199, 207-239]	$C_{10}H_8O_4$	
18.	Isoplatydesmine (*R* form) [240-245]	$C_{16}H_{19}NO_3$	

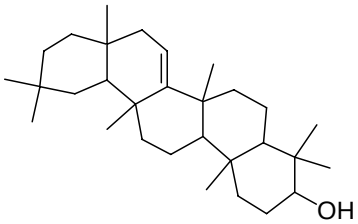
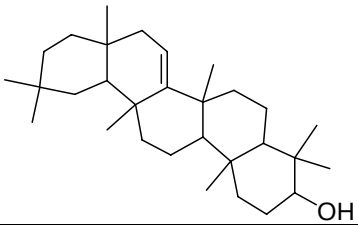
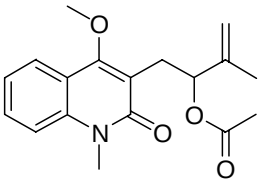
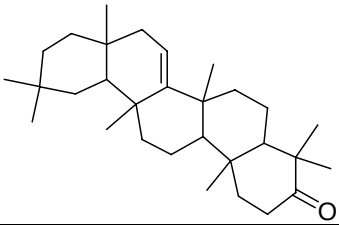
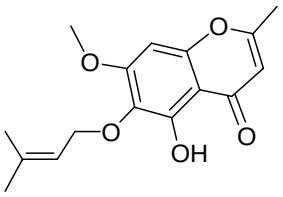
ISSN 2319-1082

19.	7-Hydroxy-8-(3-oxo-2-methyl butyl)-2*H*-1-benzopyrane-one-me- ether [82, 246-249]	$C_{15}H_{16}O_4$	
20.	p- Menth-1-ene: (*S* form) [250-255]	$C_{10}H_{18}$	
21.	24-Methyl lanosta-20,25-diene-(24 R)-3-one [245]	$C_{31}H_{50}O$	
22.	Rutarin [256-271]	$C_{30}H_{32}O_{13}$	
23.	Oxypencedanin: (*R* fom) [80,82,272-279]		
24.	Rutaretin : (*R* form) [256-271]	$C_{31}H_{34}O_{14}$	

ISSN 2319-1082

25.	3-Deacyl, 3- (2z, 4E, 6E decatrienoyl) Skimmiarepin A[280-281]	$C_{40}H_{60}O_6$	
26.	Pencenin [282-287]	$C_{16}H_{18}O_4$	
27.	Seselin [288-297]	$C_{14}H_{12}O_3$	
28.	Ptelefoliarine [136]	$C_{18}H_{21}NO_4$	 Structure under review.
29.	Skimmiarepin A [280,281]	$C_{35}H_{56}O_6$	
30.	Skimmiwallichin [298, 170]	$C_{35}H_{60}O$	

ISSN 2319-1082

31.	14- Taraxeren-3-ol : (3□ – form) [299-313]		
32.	14-Taraxeren-3-ol: (3□- form) [136]		
33.	Ptelefoliarine (*S* form) [299]	$C_{18}H_{21}NO_4$	 Structure under review.
34.	14- Taraxeren-3-one : (3□-form) [300-313]	$C_{30}H_{48}O$	
35.	5, 6, 7- Irihydroxy-2- methyl-4*H*-1-benzopyran-4-one [314-317]	$C_{16}H_{18}O_5$	

REFERENCES

1. M. F. Grundon, "*The Alkaloids*", (A. Brossi, Eds), Academic Press, New York, **32**, 341 (1988a).
2. J. P. Michael, *Nat. Prod. Rep*., **61**, 595 (1998).
3. N. Sultana, "Phytochemical and Structural Studies on the Chemical Constituents of *Adhatoda vasica, Sarcococca saligna* and *Skimmia laureola*", Ph.D. Dissertation, H. E. J. Research Institute of Chemistry, University of Karachi, Karachi-75270, Pakistan, (2000).
4. H. T. Openshaw, "The Alkaloids", (R. H. F. Manske, Ed.), Academic Press, New York, **7**, 229 (1960).
5. H. T. Openshaw, "The Alkaloids", (R. H. F. Manske, Ed.), *Academic Press*, New **7**, 223 (1971).
6. M. F. Grundon, "The Alkaloids", (R. H. F. Manske, and R. Rodrigo, Eds), *Academic Press*, New York, **17**, 105 (1979).
7. V. A. Sneickus, "*The Alkaloids, Special Reports of the Chemical Society*", The Royal Society of Chemistry, London, vol 1–5 (1971).
8. M. F. Grundon, "*The Alkaloids, Specialist Periodical*", (M. F.Grundon, Ed.), The Royal Society of Chemistry, London,vol 6–13 (1971).

ISSN 2319-1082

9. M. F. Grundon, *Nat. Prod. Rep.*, **1**, 195; **2**, 393; **4**, 225; **5**, 293; **7**, 131 (1984-1990).

10. I. Mester, *Fitoterapia*, **44**, 123 (1973).

11. I. Mester, *Fitoterapia*, **48**, 168 (1977).

12. I. Mester, "Chemistry and Chemotaxonomy of the Rutales", (P.G. Waterman, and M. F. Grundon, Eds), Academic Press, London, 31 (1983).

13. J. E. Saxton, "Chemistry of Heterocyclic Compounds", 2nd edn, (A. Weissberger, and E.C. Taylor, Eds), Wiley-Interscience, New York, vol. **9** (1973).

14. M. Sainsbury, Rodd's "*Chemistry of Carbon Compounds*" supplement to 2nd edn, Elsevier, Amsterdam, vol. $1V^G$, a; p.171, b; p. 209 (1978).

15. G. A. Cordell, "Introduction to Alkaloids; A Biogenetic Approach", Wiley-Interscience, New York (1981).

16. M. F. Grundon, "*Chemistry and Chemotaxonomy of the Rutales*", (P.G. Waterman, and M. F. Grundon, Eds), *Academic Press,* London, 9 (1983).

17. M. F. Grundon, "Alkaloids Chemical and Biological Perspectives", (S. W. Pelletier, Eds), *Wiley-Interscience,* New York, 339 (1988b).

18. P. G. Waterman, "*Alkaloids",Chemical and Biological Perspectives*" (S. W. Pelletier, Eds), Wiley-Interscience, New York, , 331 (1986).

19. K. M. Nadkarni, "*The Indian Materia Medica 1*" edited by A.Nadkarni, 1976, K. Popular Prakashan, Bombay, **1**, 1142 (1976).

20. G. Ellman, K. D. Courtney, V. Andrews, and R. M. Featherstone, *Biochem. Pharmacol*., **7**, 88 (1961).

21. W. Tong, E. R. Collantes, Y. Chen, and W. J. Welsh, *J. Med. Chem.*, **39**, 380 (1996).

22. Q. Yu, H. W. Holloway, T. Utsuki, A. Brossi, and N. H Greig, *J. Med. Chem.*, **42,** 1855, (1999).

23. Atta-ur-Rahman, S. Parveen, A. Khalid, A. Farooq, S. A. M. Ayattollahi, and M. I., Choudhary, *Heterocycles*, **49**, 481 (1998).

24. K. Fatima, and N. Sultana, *J. Chem. Soc. Pakistan*, **25**(4),328 (2003).

25. M. F. Grundon, *Nat. Prod. Rep.*, 195 (1984–1990).

26. D. M. Clugston, *Can. J. Chem*., **43**, 2516 (1965).

27. A. Sturaro, P. Traldi, P. Bravo, F. Viani, and G. Rasnati, *Org. Mass Spectrum,* **22**, 462 (1987).

28. J. Reish, K. Szendrei, V. Papay, E. Minker, and I. Novak, *Tet. Lett.*, 1945 (1970).

29. M. F. Grundon, in "The Alkaloids", (R. H. F. Manske, and R. Rodrigo, Eds), *Academic Press,* New York,**17,** 105 (1979).

30. A. V. Robertson, *Austral. J. Chem.*, **16**, 451 (1963).

31. J. Reisch, K. Szendrei, E. Minker, and I. Novak, *Pharmazie*, **27**, 208 (1972).

32. G. A. Cordell, "*Introduction to Alkaloids*", (John Wiley & Sons, Eds), New York, 2 (1981).

33. N. M. D. Brown, M. F. Grundon, D. M. Harrison, and S. A. Surgenor, *Tetrahedron*, **36**, 3579 (1980).

34. J. Monkovic, and I. D. Spenser, *Chem. Commun.*, 204 (1966).

35. J. Monkovic, I. D. Spenser, and A.D. Plunkett, *Can. J. Chem.,* **45**, 1935 (1967).

36. R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron*, **4**, 256 (1958).

37. A. O. Colonna, and E. G. Gros, *Chem.Commun.*, 1970, pp.674; *Phytochemistry*, **10**, 1515 (1971).

38. J. A. Diment, E. Ritchie, and W. C. Taylor, *Aust. J . Chem.,* **22**, 1797 (1969).

39. J. F. Collins, and M. F. Grundon, *Chem. Commun.,* 622 (1969).

ISSN 2319-1082

40. M. Cobet, and M. I. Luckner, *Eur. J. Biochem.,* **4**, 76 (1968).

41. J. F. Collins, M F. Grundon,. D. M. Harrison, C. G. Spyropoulos, *Chem. Commun.,* 1029 (1972).

42. D. J. Austin, and S. A. Brown, *Phytochemistry,* **12**, 1657 (1973).

43. M. F. Grundon, D. M. Harrison and C. G. Spyropouios, *J. Chem. Soc. Perkin Trans.*, **1**, 2181 (1974).

44. J. Mann, *Secondary Metabolism* (2nd edition), 178.

45. B. Wolters, *Planta Med.*, **43**, 166 (1981).

46. H. Kuske, *Furo Coumarin*, *Arch. Derm. Syph.,* Berlin, **178**, 112 (1983).

47. R. D. H. Murray, *Nat. Prod. Rep.*, 591 (1989).

48. L. D. Scheel, V. B. Perone, "*The Natural Occurrence and Uses of the Toxic Coumarins. Microb Toxins",* **8**, 67 (1972).

49. L. D. Scheel, V.B. Perone, R.L. Larkin, R. E. Kupel, "*The Isolation and Characterization of two Photo Toxic Furano-Coumarins (Psoralens) from diseased Celery*", *Biochemistry,* **2**, 1127 (1963).

50. K. V. Masrani, H. S. Rama, and S. L. J. Bafna, *J. Appl. Chem. Biotechnol.*, **24**, 331 (1974).

51. K. H. Lee, and T. O. Srine, *J. Pharm. Sci.,* **58**, 681 (1969).

52. B. E. Nielsen, and Lemmich, *J. Acta. Chem . Scand*., **18**, 932 (1964).

53. B. E. Nielsen, and Lemmich, *J. Acta. Chem. Scand.,* **19**, 601 (1965).

54. H. Budzikiewiez, C. Djerassi, and D.H Williams, "*Structure Elucidation of Natural Products by Mass Spectrometry*", Holden-Day, San Francisco, **2** (1964).

55. C. S. Barnes, and J.L. Occolowitz, *Aust. J. Chem.,* **17**, 75 (1964).

56. J. P. Kutney, G. Eigendorf, T. Inaba, and D.L. Dreyer, *Org. Mass Spectrum*, **5**, 249 (1971).

57. T. Furuya, H. Kojima, and H. Sato, *Chem. Pharm. Bull*., **15**, 362 (1967).

58. R. T. Aplin, and C.B. Page, *J. Chem. Soc.,* 2593 (1967).

59. S. P. Gunasekera, G. S. Jayatilake, S. S. Selliah, and M. U. S. Sultanbawa, *J. Chem. Soc. Perkin Trans.* **1**,1505 (1977).

60. F. M. Dean, A.M.B.S.R.C.S. Costa, J. B. Harborne, and D. M. Smith, *Phytochemistry*, **17**, 505 (1978).

61. J. F. Fisher, and H.E. Nordby, *J. Food Sci.,* **30**, 869 (1965).

62. S. I. Kapoor, Y.N. Sharma, and A. Zaman, *Phytochemistry*, **11**, 475 (1972).

63. M. H. A. Elgamal, N.H. Elewa, E. A. M. Elkhrisy, and H. Duddek, *Phytochemistry*, **18**,139 (1979).

64. S. A. Brown, M. Dakhakhny, and W. Steck, *Can. J. Biochem.,* **48**, 63 (1970).

65. B. E. Ellis, and S. A. Brown, *Can. J. Biochem.,* **52**, 34 (1974).

66. D. S. Dhillon, and S. A. Brown, *Arch. Biochem . Biophys.,* **74**, 177 (1976).

67. M. F. Grundon, and I. S. Mccoll, *Phytochemistry*, **14**, 143 (1975).

68. L. B. Desilva, "*Essay on Science*", Hamdard Foundation Pakistan, Nazimabad Karachi (Ed. by Hakim Muhammed Said), 100 (1986).

69. P. W. Atkin, J. S. E. Holker, and A. K. Holliday, "*Secondary Metabolism*", *Clarendon Press*, Oxford, 125 (1987).

70. R. H. Thomas, "*The Chemistry of Natural Products*", Blackie and Sons Ltd., 156 (1985).

71. T. K. Razdan, *Phytochemistry,* **27**, 890 (1978).

72. B. E. Nielsen, *J. Acta Chem. Scand.*, **18**, 1379 (1964); **23**, 962 (1969).

73. B. D. Gupta, *Indian J. Chem.*, **2**, 64 (1964).

74. G. K. Nikonov, *Zh.Obshch. Khim.*,1353; *J. Gen. Chem.* USSR (Engl. Transl.), **34**, 1353 (1964).

ISSN 2319-1082

75. A. Chatterjee, *Indian J. Chem.*, **6**, 415 (1968).

76. L. G. Avramenko, *Khim. Prir. Soedin.*, 1971, **7**, 830; *Chem. Nat. Compd.* (Engl. Transl.), *7*, 804 (1971).

77. N. S. Ignat'eva, *Khim. Prir. Soedin.,* 1972, **8**, 388; *Chem. Nat. Compd.*, (Engl. Transl), **8**, 381 (1972).

78. J. Meacutendez, *Experientia,* **29**, 371 (1973).

79. A. Z. Abyshev, *Khim. Prir. Soedin*., 722; *Chem. Nat. Compd*., (Engl. Transl.), **9**, 692 (1973).

80. E. Atkinson, D.R. Boyd, M.F. Grundon *Phytochemistry*, **13**, 853 (1974).

81. S. A. Khaled, *Phytochemistry*, **14**, 461 (1975).

82. J. Reisch, *Phytochemistry*, **14**, 889 (1975).

83. G. W. Ivie, *J. Agric. Food Chem*., **26**,1394 (1978).

84. S. S. Kerimov, *Khim. Prir. Soedin*., 1978, **14**,396; 1979, **15**, 92; 1978, *Chem. Nat. Compd*., (Engl. Transl.), **14**, 331; 15, 77 (1979).

85. A. Z. Abyshev, *Khim. Prir. Soedin*., 1979, 15, 847; *Chem. Nat. Compd*., (Engl. Transl.), 15, 50 (1979).

86. S. K. Koul, *Phytochemistry*, **18**, 762 (1979).

87. S. Harkar, *Phytochemistry*, **23**, 419 (1984).

88. A. Hiermann, *Phytochemistry*, **43**, 881 (1996).

89. P. Zhou, *Phytochemistry*, **53**, 689 (2000).

90. B. Jimenez, *Phytochemistry*, **53**, 1025 (2000).

91. H. J. Zhang, *Chin. Chem. Lett.*, **6**, 873 (1995).

92. H. J. Zhang, *Magn. Reson. Chem.*, **35**, 410; 413 (1997).

93. R. F. C. Brown, *Aust. J. Chem.*, **7**, 181 (1954).

94. B. A. Bohm, *Can. J. Biochem.*, **39**, 1389 (1961).

95. G. Billek, *Monatsh. Chem.*, **93**, 85 (1962).

96. S. A. Brown, *Phytochemistry*, 469 (1964).

97. B. D. Jain, *Anal. Chim. Acta.*, **37**, 358 (1967).

98. J. Mendeacutez, *Microchem. J.*, **14**, 67 (1969).

99. W. Wildenhaim, *J. Prakt. Chem.*, **312**, 90 (1970).

100. W. Herz, *Phytochemistry*, **9**, 891 (1970).

101. M. Sato, *Phytochemistry*, **11,** 657; 2367 (1972).

102. L. Jurd, *Aust. J. Chem.*, **27**, 697 (1974).

103. A. Z. Abyshev, *Khim. Prir. Soedin.*, 1974, **10**, 568; *Chem. Nat. Compd.,* (Engl. Transl.), **10**, 81 (1974).

104. H. G. Uuml, *Org. Magn. Reson.*, **7**, 339 (1975).

105. N. J. Cussans, *Tetrahedron,* **31**, 719 (1975).

106. K. Ueno, *Acta Cryst. B.*, **31**, 46 (1976).

107. K. S. Rybalko, *Khim. Prir. Soedin.*, 1976, **12**, 94; *Chem. Nat. Compd.*, (Engl. Transl.), **12**, 262 (1976).

108. J. K. MacLeod, *Aust. J. Chem.*, **31**, 1545 (1978).

109. H. Shimomura, *Chem. Pharm. Bull.*, 347 (1980).

110. A. Z. Abyshev, *Khim.Prir.Soedin.*, **16**, pp.800 (1980); *Chem. Nat. Compd.* (Engl. Transl.), **16**, 571 (1980).

111. N. C. Barua, *Phytochemistry*, **19**, 2217 (1980).

112. A. I. Gray, *Phytochemistry*, **26,** 1171; 1987, 257 (1981).

113. P. Joseph-Nathan, *J. Het. Chem.*, **21**, 141 (1984).

114. J. Borges del Castillo, *Phytochemistry*, **23**, 59 (1984).

ISSN 2319-1082

115. G. Szabo, *Phytochemistry*, **24,** 537 (1985).

116. M. M Singh, *Planta Med.*, 268 (1985).

117. O. Hofer, *Annalen***.,** 2142 (1986).

118. S. A. Brown, *Z. Naturforsch,* C., **41**, 247 (1986).

119. R. E. Pastor, *Can. J. Chem.*, **65**, 1356 (1987).

120. J. Reisch, *Monatsh. Chem.*, **119,** 1333 (1988).

121. M. Niwa, *Chem. Pharm. Bull.*, **39**, 2422 (1991).

122. M .Hong, *J. Chin. Pharm. Sci.*, **1**, 13 (1992).

123. T. Harayama, *Chem. Pharm. Bull.*, **42**,1550 (1994).

124. M. Jung, *Z. Naturforsch.*, C., **49**, 697 (1994).

125. I. S. Chen, *Phytochemistry*, **39**,1091; 1997, **45**, 1419 (1995).

126. A. U. Rahman, *Phytochemistry* , **44** , 683 (1997).

127. Atta-ur-Rahman, M. I. Choudhary, **N. Ullah** and M. N. G. James, **...** *Fitoterapia*, **69**, 280 (1998).

128. I. L. Tsai, *J. Chin. Chem. Soc.*, (Taipei), **45**, 99 (1998).

129. I. L. Tsai, *Planta Med.*, **66,** 618 (2000).

130. Takeuchi, K. Azuma, K. Takakura, H. Abe, H. -S. Kim, Y. Wataya and T. Harayama, *Heterocycles*, **54**, 319 (2001).

131. J. Iriarte, F. A. Kincl, J. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 4170 (1956).

132. T. P. Toube, *Tetrahedron*, **23**, 061 (1967).

133. D. R Boyd, *J. Chem. Soc.*(C), 56 (1970).

134. T. Naito, *Chem. Pharm. Bull.*, **31**, 66 (1983).

135. S. A. Barr, *Chem. Comm.*, 53 (1994).

136. A. U. Rahman, *J. Nat. Prod.*, **61**, 713 (1998).

137. V. Delofeu, *J. Am. Chem. Soc.*, **64**, 2326 (1942).

138. F. W. Eastwood, *Aust. J. Chem.*, **7**, 87 (1954).

139. L. H. Briggs, *J. Chem. Soc.*, 2458 (1960).

140. R. H. Prager, *Aust. J. Chem.*, **15**, 301 (1962).

141. G. P. Sidyakin, *Dokl.Akad. Nauk SSSR, Ser. Khim.*, **19**, 39 (Chem. Abstr., **57**,15170) (1962).

142. D. L .Dreyer, *Phytochemistry* , **8**, 013 (1969).

143. D. L .Dreyer, *J. Org. Chem.*, **35**, 2420 (1970).

144. A. G. Gonzalez, *An. Quim.*, **68**, 1133 (1972).

145. V. I. Akhmedzhanova, *Khim. Prir. Soedin.*, **10**, 680 (1974); **11**, 272 (1975); *Chem. Nat. Compd.* (Engl. Transl.), **10**, 706 (1974); **11**, 291 (1975).

146. E. F. Nesmelova, *Khim. Prir. Soedin.*, **11**, 666 (1975); *Chem. Nat. Compd.* (Engl. Transl.), **11**, 706 (1975).

147. K. A. Abdullaeva, *Khim. Prir. Soedin.*, **13**, 425 (1977); **14,** 219 (1978); **15,** 873 (1979); *Chem. Nat. Compd.* (Engl. Transl.), **13,** 363 (1977); **14**, 179 (1978); **15**, 782 (1979).

148. C. Moulis, *Planta Med.*, **42**, 400 (1981).

149. F. Tillequin, *J. Nat. Prod.*, **45**, 486 (1982).

150. J.A.Grina, M.R.Ratcliff, and F.R.Stermitz, *J. Org. Chem.*, **47**, 2648 (1982).

151. R. Shakirov, M. V. Telezhenetskaya, Ametova t.F., Yunusov M.S., Tel'nov V.A., I. A. Bessonova, *Khim. Prir. Soedin.*, 529; **18,** 504 (1982); **20**, 124 (1984); *Chem. Nat. Compd.* (Engl. Transl.), **20**, 125 (1984).

152. D. M. Razakova, *Khim. Prir. Soedin.*, **21**, 273 (1985); *Chem. Nat. Compd.* (Engl. Transl.), **21**, 259 (Chem. Abstr., **103**, 34907m,1985).

ISSN 2319-1082

153. T. P. Lin (Chem. Abst., **106**, 30033n, 1987).

154. K. A. Razulova, *Khim. Prir. Soedin.*, **23**, 876 (1987); **24**, 94 (1988); *Chem. Nat. Compd.* (Engl. Transl.), **23**, 731 (1987); **24**, 82 (1988).

155. A. Wondimu, *Phytochemistry*, **27**, 959 (1988).

156. O. Cox, *Acta Cryst.* C., **45**, 1263 (1989).

157. G. E. Jackson, *Spectrosc. Lett.*, **23**, 971 (1990).

158. A. K. Chakravarty, *Phytochemistry*, **50**, 1263 (1999).

159. T. S. Wu, *Phytochemistry*, **26**, 873 (1987).

160. S. C. Kuo, *J. Med. Chem.*, **36**, 1146 (1993).

161. J. Koyama, *Chem. Pharm. Bull.*, **47**, 1038 (1999).

162. Y. N. Sharma, *Naturwissenschaften*, **51**, 37 (1964).

163. B. E. Nielsen, *Acta Chem. Scand.*, **23**, 62 (1969).

164. I. Sokolova, *Khim. Prir. Soedin.*, **5**, 359 (1969); *Chem. Nat. Compd.* (Engl. Transl.), **5**, 299 (1969).

165. M. Bandopadhyay, *Indian J. Chem.*, **8**, 855 (1970); 1146; **11**, 530 (1973).

166. G. Gonzaacutelez, *An. Quim.*, **70**, 856 (1974); **72**, 584 (1976); **73**, 858 (1977).

167. T. K. Razdan, *Phytochemistry*, **21**, 23 (1982).

168. H. Sun, *Pharmazie*, 1986, **41**, M.H. A. Elgamal, *Phytochemistry*, **34**, 819 (1993).

169. M. Trani, *Gazz. Chim. Ital.*, **127**, 415 (1997).

170. I. Kostova, *Phytochemistry*, **43**, 643 (1996).

171. Aldrich Library of FT-IR Spectra, 1st edn., **2**, 323A; 323C; 325B (1985).

172. Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra, **2,** 1312C; 1313C; 1315C (1992).

173. S. Sethna, *Org. React.*, (N.Y.), **7**, 0 (1953).

174. K. Sen, *J. Org. Chem.*, **24**, 16 (1959).

175. K. D. Gupta, *J. Chem. Soc.* (C), 29 (1969).

176. K. Hata, *Chem. Pharm. Bull.*, **19**, 640 (1971).

177. E. V. Lassak, *Aust. J. Chem.*, **25**, 2491 (1972).

178. W. Karrer, "*Konstitution und Vorkommen der Organischen Pflanzenstoffe*", 2nd edn., *Birkhaumluser Verlag*, Basel, nos. 1320; 132; 1321 (1972).

179. G. Gonzaacutelez, *An. Quim.*, **69**, 1013 (1973).

180. G. M. Huitnik,*Talanta.*, **21**, 1193 (1974).

181. D. Brown, *Phytochemistry*, **14**, 1083 (1975).

182. Z. Holzbecher, "Handbook of Organic Reagents in Inorganic Analysis", Horwood, Chichester (1976).

183. R. D. H. Murray, *Prog. Chem.Org. Nat. Prod.*, **35**, 200 (1978).

184. Chatterjee, *Phytochemistry*, **19**, 2219 (1980).

185. T. J. Hardt, *Diss. Abstr. Int.*, B, **43**, 1445 (1982).

186. W. A. Ritschel, *Arzneim.-Forsch.*, **33**, 836 (1983).

187. D. Batsuren, *Khim. Prir. Soedin.*, **19**, 142 (1983).

188. K.Ueno, *Acta Cryst. C.*, **41**, 1786 (1985).

189. R. H. A. Eittah, *Can. J. Chem.*, **63**, 1173 (1985).

190. Y. Asheervadam, *Fitoterapia*, **57**, 231 (1986).

191. B. Talapatra, *Indian J. Chem.*, Sect.B, **25**,1122 (1986).

192. Ulubelen, *J. Nat. Prod.*, **49**, 692 (1986).

ISSN 2319-1082

193. R. A. Ford, *Food Chem. Toxicol.*, **26**, 375 (1988).

194. K. Jain, *Indian J. Pharm. Sci.*, **51**, 32 (1989).

195. H. Ishii, *Chem. Pharm. Bull.*, **39**, 3100 (1991).

196. K. Machida, *Chem. Pharm. Bull.*, **41**, 248 (1993).

197. L. Yang, *Indian J. Chem.*, Sect. B, **34**, 975 (1995).

198. X. Yang, H. Masao and N. Tsuneo *J. Chin. Pharm. Sci.*, **5**, 68 (1996).

199. J. Latip, TG HARTLEY, PG WATERMAN *Phytochemistry*, **51**, 107 (1999).

200. Y. N. Sheinker, A. Dokl. Akad. Nauk SSSR, *Ser. Khim*., **158**,1382 (1964).

201. V. K. Ahluwalia, *Indian J. Chem.*, **9**,194 (1971).

202. W. Karrer, "*Konstitution und Vorkommen der Organischen Pflanzenstoffe*" , 2nd edn., *Birkhaumluser Verlag*, Basel, no. 1378 (1972).

203. S. K. Talapatra, *Phytochemistry*, **12**, 236 (1973); D. J. Austin, *Phytochemistry*, **12**, 1657 (1973).

204. J. P. Kutney, *Tetrahedron*, **29**, 2645; 2661; 2673 (1973).

205. D. Voigt, *J. Prakt. Chem.*, **319**, 767 (1977).

206. G. Innocenti, F. Dall'Acqua, G. Caporale *Phytochemistry*, **22**, 2207 (1983).

207. Aldrich Library of FT-IR Spectra, 1st edn., **2**, 324B (1985).

208. Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra, **2**, 1314B (1992).

209. R. Seka, Ber., pp.64 (1931), F.G.H. Head, *J. Chem. Soc.*, 1241 (1931).

210. P. H. McCabe, *J. Chem. Soc.* (C), 145 (1967).

211. P. K. Larsen, *Acta. Chem. Scand.*, **24**,1113 (1970).

212. W. Karrer, "*Konstitution und Vorkommen der Organischen Pflanzenstoffe*", 2nd edn., Birkhaumluser Verlag, Basel, nos. 1328; 1329 (1972).

213. V. B. Andrianova, *Khim. Prir. Soedin.*, 1975**,** **11**, 89; *Chem. Nat. Compd.* (Engl. Transl.), **11**, 91 (1975).

214. S. Tanaka, *Arzneim.-Forsch.*, **27**, 2039 (1977).

215. W. H. M. Herath, *Phytochemistry*, **17**, 1007 (1978).

216. F. Bohlmann, *Phytochemistry*, **18**, 1367 (1979).

217. N. Ishibura, *Z. Naturforsch.*, C., **34** (1979); A.D. Matkarimov, *Khim. Prir. Soedin.*, **16**, 328; 785 (1980); *Chem. Nat. Compd.* (Engl. Transl.), **16**, 240; 558 (1980).

218. E. K. Batirov, *Khim. Prir. Soedin.*, **18**, 691 (1982); *Chem. Nat. Compd.* (Engl. Transl.), **18**, 654 (1982).

219. V. K. Ahluwalia, *Monatsh. Chem.*, **113**, 197 (1982).

220. R. D. H. Murray, "The Natural Coumarins", J. Wiley (1982).

221. E. K. Batirov, *Khim. Prir. Soedin.*, 1984, **20**, 244; *Chem. Nat. Compd.* (Engl. Transl.), **20**, 226 (1984).

222. O. Hofer, *Phytochemistry*, **23**,181 (1984).

223. T. Iwagawa, *Phytochemistry*, **23**, 467 (1984).

224. M. P. Yuldashev, *Khim. Prir. Soedin.*, 1985**,** **21**, 27; *Chem. Nat .Compd.* (Engl. Transl.), **21**, 25 (1985).

225. M. Kuroyanagi, *Chem. Pharm. Bull.*, **34**, 4012 (1986).

226. S. Narantuyaa, *Khim. Prir. Soedin.*, **22**, 288; *Chem. Nat. Compd.* (Engl. Transl.), **22**, 267 (1986).

227. E. Wollenweber, *Fitoterapia* , **58**, 133 (1987).

228. S. K. Koul, *Indian J. Chem.*, Sect. B, **26**, 574 (1987).

229. D. Udovin, *Khim. Prir. Soedin.*, **23**, 796; *Chem. Nat. Compd.* (Engl. Transl.), **23**, 660 (1987).
230. K. L. A. Khayat, *Tetrahedron*, **43**, 4649 (1987).
231. P. S. Rao, *J. Nat. Prod.*, **51**, 959 (1988).
232. Jakupovic, *Phytochemistry*, **27**, 3831 (1988).
233. E. Wollenweber, *Fitoterapia*, **60**, 460 (1989).
234. S. Sibanda, *Phytochemistry*, **28**, 1550 (1989).
235. M. Mizuno, *Phytochemistry*, **31**, 717 (1992).
236. H. Hauer, *Arch. Pharm.* (Weinheim, Ger.), **328**, 737 (1995).
237. Pistelli, *Phytochemistry*, **41**, 1579 (1996).
238. J. H. Kwak, *Planta Med.*, **63**, 474 (1997).
239. S. L. Debenedetti, *Phytochemistry*, **48**, 707 (1998).
240. R. M. Bowman, *J. Chem. Soc.* (C), 504 (1966).
241. A. Bessonova, *Khim. Prir. Soedin.*, **7**, 629; *Chem. Nat. Compd*. (Engl. Transl.), **7**, 608 (1971).
242. T. Higa, *Phytochemistry*, **13**, 1269 (1974).
243. Vaquette, *Phytochemistry*, **15**, 743 (1976).
244. G. M. Coppola, *J. Het. Chem.*, **20**,1589 (1983).
245. Atta-ur-Rahman, and N. Sultana, *Nat. Prod. Lett*., **12**, 223 (1998).
246. Guiotto, *Phytochemistry*, 1976, **15**, 348 (1976); **16**, 1257 (1977).
247. B. De Silva, *Phytochemistry*, **20**, 2776 (1981).
248. T. Ngadjui, *J. Nat. Prod.*, **52**, 243 (1989).
249. J. Abaul, *J. Nat. Prod.*, **57**, 846 (1994).
250. W. F. Newhall, *J.Org.Chem.*, **23**, 1274 (1958).
251. T. Sakai, *Nippon Kagaku Kaishi*, **83**, 745 (1962).
252. F. Thomas, *Helv. Chim. Acta.*, **47**, 475 (1964).
253. F. J. Schnelle, *Planta Med.*, **16**, 48 (1968).
254. N. Sakota, *Bull.Chem. Soc. Jpn.*, **44**, 485 (1971).
255. J. Choi, *Synthesis*, **26**, 597 (1996).
256. G. Schneider, *Arch. Pharm.* (Weinheim, Ger.), **300**, 73; 913 (1967).
257. I. Shagova, *Khim. Prir. Soedin.*, **9**, 665; *Chem. Nat. Compd.* (Engl. Transl.), **9**, 631 (1973).
258. E. Varga, *Acta Pharm. Hung.*, Suppl. No.36, **44** (Chem. Abstr., 82, 13996) (1974).
259. P. Sharma, *Indian J. Chem.*, Sect. B, **16**, 563 (1978).
260. S. K. Garg, *Phytochemistry*, **17**, 2135 (1978); **18**, 1769 (1979).
261. R. Sharma, *Indian J. Chem.*, Sect. B, **17**, 647 (1979).
262. B. R. Sharma, *Phytochemistry*, 19 (1980).
263. J. Lemmich, *Phytochemistry*, **23**, 863 (1984).
264. H. Ishii, *Tetrahedron*, **37**, 285 (1986).
265. V. G. Thailambal, *Acta Cryst.* C, **43**, 2369 (1987).
266. V. K. Ahluwalia, *Phytochemistry*, **27**, 1181 (1988).
267. T. Okuyama, *Planta Med.*, **55**, 64 (1989).
268. J. Reischet, *Phytochemistry*, **31**, 4376 (1992).
269. C. Kong, *Chem. Lett.*, **4**, 37 (1993).
270. S. K. Srivastava, *Fitoterapia*, **65**, 301 (1994).
271. J. Reisch, *J. Chem. Soc. Perkin 1*, 3251 (1994).

ISSN 2319-1082

272. Spaumlth, *Ber.*, **66**, 914 (1933); **72**, 52 (1939).

273. C. R. Ghosal, *Chem. Ind.* (London), 1430 (1963).

274. S. Vulfson, *Dokl. Akad. Nauk* SSSR, Ser. Khim., **155**, pp.1104 (1964).

275. J. Lemmich, *Phytochemistry*, **10**, 3333 (1971).

276. W. Karrer, "*Konstitution und Vorkommen der Organischen Pflanzenstoffe*", 2nd edn., *Birkhaumluser Verlag*, Basel, no.1372 (1972).

277. G. Gonzaacuteles, *An.Quim.*, **69**,1141 (1973).

278. S. V. Serkerov, *Khim. Prir. Soedin.*, 94 (1976).

279. G. S Yost, *Phytochemistry*, **16**,1097 (1977).

280. B. Ochi, *Chem. Soc. Jpn.*, 61 (1988).

281. S. P. Arruda, *Phytochemistry*, **36**,1303 (1994).

282. A. Bolleter, *Helv. Chim. Acta.*, **34**, 186 (1951).

283. Bohlmann, *Phytochemistry*, **19**, 1815 (1980).

284. K. Baba, *Shoyakugaku Zasshi*, **39**, 282 (Chem. Abstr., **105**, 85018w) (1985).

285. W. Cisowski, *Pol. J. Chem.* (Rocz.Chem.), **62**,135 (1988).

286. K. Baba, *Phytochemistry*, **31**, 1367 (1994).

287. K. Baba, *Phytochemistry*, **35**, 221 (1994).

288. E. Spaumlth, *Ber.*, **72**, 821; **963**, 2093 (1939).

289. S. N. Shanbhag, *Tetrahedron*, **20**, 2605 (1964).

290. K. Kato, *Acta Cryst.* B, **26**, 2022 (1970).

291. J. Hlubucek, *Aust. J. Chem.*, **24**, 2347 (1971).

292. S. Gupta, *J. Indian Chem. Soc.*, **51**, 904 (1974).

293. B. F. Bowden, *Aust. J. Chem.*, **28**, 1393 (1975).

294. I. Gray, *J. Chem. Soc. Perkin 2*, 391 (1978).

295. Sattar, *Phytochemistry*, **17**, 559 (1978).

296. X. A. Dominguez, *Rev. Latinoam. Quim.*, **16**, 52 (1985).

297. D. D. Narkhede, *Tetrahedron*, **46**, 2031 (1990).

298. Kostova, *Indian J. Chem.*, Sect. B, 158 (1977).

299. J. W. Brooks, *Chem. Ind.* (London), 1178 (1953).

300. Budzikiewicz, *J. Am. Chem. Soc.*, **85**, 3688 (1963).

301. T. A. Bryce, *Tetrahedron*, **23**, 1283 (1967).

302. R. E. Corbett, *J. Chem. Soc. Perkin 1*, 2827 (1972).

303. W. Karrer, "*Konstitution und Vorkommen der Organischen Pflanzenstoffe*", 2nd edn., *Birkhaumluser Verlag*, Basel, no. 1970 (1972).

304. S. R. Anjaneyulu, *Curr. Sci.*, **43**, 10 (1974).

305. W. Hui, *Phytochemistry*, **15**, 563 (1976).

306. R. Banerji (Chem. Abstr., **87**, 114605c) (1977).

307. Talapatra, *J. Indian Chem. Soc.*, **58**, 814 (1981).

308. S. Huneck, *Phytochemistry*, **25**, 453 (1986).

309. Sakuri, *Phytochemistry*, **26**, 217 (1987).

310. U. Kokpol, *J. Nat. Prod.*, **53**, 953 (1990).

311. Atta-ur-Rahman, *Nat. Prod. Lett.*, **10**, 249 (1997).

312. M. Parvez, *Acta Cryst. C*, **55**, 213 (1999).

313. R. Billodeaux, *Acta Cryst. C*, **55**, 2129 (1999).

ISSN 2319-1082

314. B. S. Joshi, *J. Chem. Soc. Perkin 1*, 433 (1977).

315. S. Ghosal, *Phytochemistry*, 21 (1982).

316. B. Nanda, *Indian J. Chem.*, Sect. B., **22**, 185 (1983).

317. T. K. Razdan, *Phytochemistry*, **26**, 2063 (1987).