Review

Highly Oxygenated Cyclobutane Ring in Biomolecules: Insights into Structure and Activity

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Highly Oxygenated Cyclobutane Ring in Biomolecules: Insights into Structure and Activity

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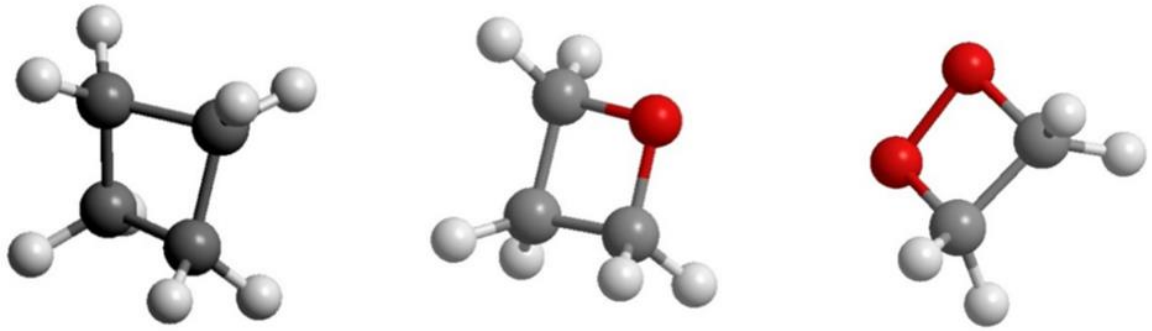
Abstract: This review explores the unique structural and functional characteristics of natural products featuring highly oxygenated cyclobutane rings, with a specific focus on oxetane and 1,2-dioxetane motifs. It presents the structures and biological activities of compounds containing these rings, highlighting their contribution to molecular stability and pharmacological potency. Through detailed case studies and recent research findings, it has been demonstrated that these oxygen-rich rings enhance the molecular diversity and biological efficacy of natural products, potentially offering new avenues for drug development. Notably, these compounds are predominantly synthesized by microorganisms and can also be found in extracts from fungi, plants, and certain marine invertebrates. Compounds with oxetane and 1,2-dioxetane rings are primarily noted for their strong antineoplastic properties, among other biological activities. In contrast, most 1,2-dioxetanes exhibit potent antiprotozoal effects. It is important to note that 1,2-dioxetanes often serve as intermediate products in oxidation reactions, characterized by their instability and propensity to decompose into new compounds.

Keywords: oxetane; 1,2-dioxetane; microorganisms; fungi; plants; antineoplastic; antiprotozoal effects

1. Introduction

Four-membered ring or cyclobutane is a cycloalkane that is widespread in nature and more than 2,600 compounds have been discovered containing a cyclobutane moiety [1]. In a chemical context, cyclobutane can be considered a unit or a fragment of a larger molecule. For example, it can be a substituent or a structural component in more complex organic compounds. It's not typically referred to as a "*group*" in the same way that functional groups like hydroxyl (-OH) or methyl (-CH_3) are [1–3]. The cyclobutane *moiety* occurs as a major structural unit in a wide range of naturally occurring metabolites in bacteria, fungi, plants and marine invertebrates [4–9]. While it is less stable than larger ring alkanes due to ring strain, it is relatively more stable compared to oxetane and 1,2-dioxetane (see Figure 1) because it does not contain any heteroatoms. Its synthesis in nature could be through various pathways, including photochemical reactions or as a byproduct of other biological processes.



A **B** **C**

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Figure 1. Comparative structures of cyclobutane (**A**), and their oxygenated derivatives, oxetane (**B**) and 1,2-dioxetane (**C**) molecules. Color of molecules: red is oxygen, gray is carbon, and white is hydrogen. Organic compounds containing one of these units are isolated from living organisms, as well as synthesized. The ratio of these organic compounds in nature is as follows: 2,600:700:20 [1]. The difference in the natural abundance of cyclobutane, oxetane, and 1,2-dioxetane molecules can be explained from a chemical perspective by considering their stability, reactivity, and the pathways through which they are formed in nature.

The relatively higher stability and simpler structure make it more abundant in nature. Oxetane is a four-membered ring containing one oxygen atom [10–12]. The presence of the oxygen atom increases the ring strain compared to cyclobutane, making it less stable. Additionally, the synthesis of oxetanes in nature is less common and typically requires specific enzymatic or photochemical reactions. This reduced stability and more complex synthesis pathway contribute to its lower abundance compared to cyclobutane. 1,2-Dioxetane contains two oxygen atoms in a four-membered ring, which significantly increases the ring strain and makes it highly unstable [13–16]. It is a highly reactive intermediate, often involved in chemiluminescence reactions [17–19], and is not typically isolated in nature due to its propensity to rapidly decompose. Its natural occurrence is rare, and when it does form, it quickly breaks down, leading to its very low abundance compared to cyclobutane and oxetane. In summary, the difference in the natural abundance of these molecules can be attributed to their relative stabilities and the complexity of the pathways through which they are formed in nature. Cyclobutane, being the most stable and simplest to form, is the most abundant, followed by oxetane and then the highly unstable 1,2-dioxetane [16,18].

In this review, we have tried to present information about natural metabolites bearing oxetane or dioxetane rings, as well as discuss their activity.

2. Oxetane Biomolecules Produced by Microorganisms

Oxetane biomolecules refer to biological molecules that contain an oxetane ring, which is a four-membered cyclic ether (C_3H_6O). Oxetane rings are of interest in medicinal chemistry and drug design due to their unique structural properties and ability to influence the biological activity of molecules [10–12]. The oxetane ring is characterized by its strained, small ring size, which can affect the conformation and reactivity of the molecule. This strain can be exploited in drug design to improve the stability or specificity of a molecule.Oxetane-containing compounds have been found to exhibit a range of biological activities, including antibacterial, antifungal, and anticancer properties [12]. The incorporation of an oxetane ring into drug molecules can also enhance their pharmacokinetic properties, such as solubility and permeability.

The synthesis of oxetane biomolecules can be challenging due to the ring strain. However, various synthetic strategies have been developed to incorporate oxetane rings into larger molecules, including biomolecules [20,21].

Oxetane biomolecules have potential applications in drug discovery and development. They are being explored as building blocks for the synthesis of more complex pharmaceutical compounds. Overall, oxetane biomolecules represent an interesting area of research in the field of medicinal chemistry, with potential implications for the development of new therapeutics [22,23].

Microorganisms produce significant quantities of metabolites containing an oxetane group [12]. Four β-lactones were isolated from the endophytic *Streptomyces* sp. T1B1, identified from the aged bast tissue of *Taxus yunnanensis* [24]: 4α-(3,5-dihydroxy hexyl)-3α-methyl-2-oxetanone (**1**, structures are shown in Figure 2 and activities are shown in Table 1), 4α-(3-methyl-4-formyloxy-hexyl)-3α-methyl-2-oxetanone (**2**), 4α-(3,5-dihydroxy-heptyl)-3α-methyl-2-oxetanone (**3**), and 4α-(3-methyl-4-formyloxy-heptyl)-3α-methyl-2-oxetanone (**4**). The fungal β-lactone hymeglusin (**5**, also known as antibiotic F 244), produced by *Fusarium* sp., inhibits HMG-CoA synthase (IC_{50} = 0.12 μM) by covalently modifying the enzyme's active Cys129 residue [25,26]. Ebelactone B (**6**), a potent β-lactone inhibitor of pancreatic lipase, is produced by *Streptomyces aburaviensis* [27,28]. Additionally, oxetin

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(**7**), a (2*R*,3*S*)-3-amino-2-oxetane carboxylic acid, was isolated from a fermentation broth of *Streptomyces* sp. OM-2317 [29].

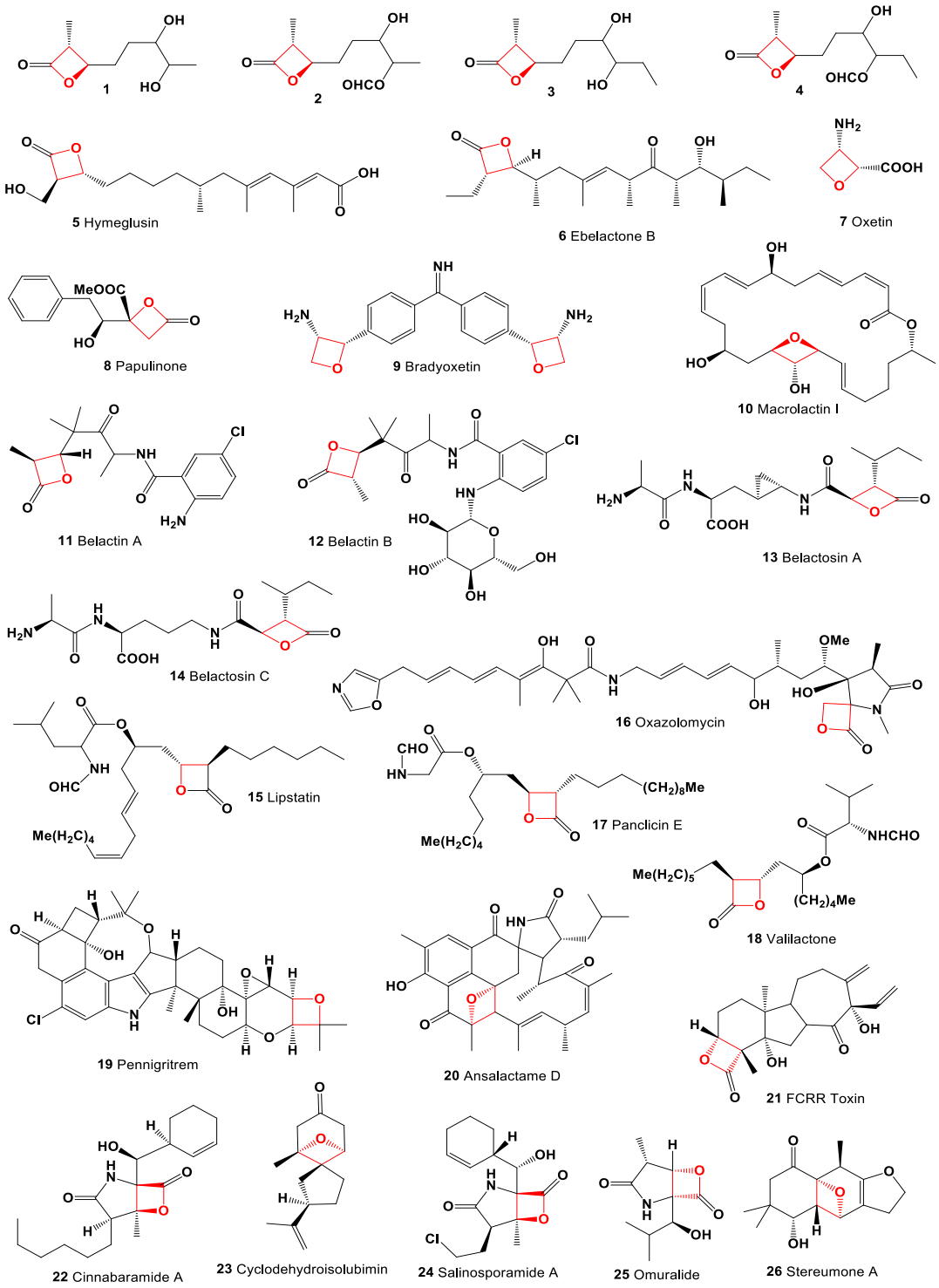

Figure 2. Oxetane biomolecules derived from microorganisms.

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Table 1. Biological activity of oxetanes produced by microorganisms, fungi and marine sources [10].

No.	Dominated predicted activity	No.	Dominated predicted activity
1	Anti-eczematic, strong	**25**	Autoimmune disorders treatment, strong
2	Anti-eczematic, moderate	**26**	Antidyskinetic, moderate
3	Anti-eczematic, strong	**27**	Angiogenesis stimulant, strong
4	General pump inhibitor, strong	**28**	Antineoplastic, strong
5	Antineoplastic, strong	**29**	Apoptosis agonist, strong
6	Antineoplastic, strong	**30**	Antineoplastic, moderate
7	Antibiotic glycopeptide-like, strong	**31**	Apoptosis agonist, strong
8	Antineoplastic, moderate	**32**	Respiratory analeptic, strong
9	Phobic disorders treatment, moderate	**33**	Antineoplastic, strong
10	Antineoplastic, strong	**34**	Antiprotozoal (Plasmodium), strong
11	Antihypertensive, strong	**35**	Respiratory analeptic, strong
12	Antihypertensive, strong	**36**	Antiprotozoal (Plasmodium), strong
13	Mucositis treatment, moderate	**37**	Respiratory analeptic, strong
14	Mucositis treatment, strong	**38**	Antineoplastic, strong
15	Anti-eczematic, strong	**39**	Antiprotozoal (Plasmodium), strong
16	Antineoplastic, strong	**40**	Apoptosis agonist, strong
17	Antidiabetic symptomatic, strong	**41**	Antineoplastic, strong
18	Antidiabetic symptomatic, moderate	**42**	Antineoplastic, strong
19	Antineoplastic, strong	**43**	Antineoplastic, moderate
20	Antineoplastic, strong	**44**	Antineoplastic, moderate
21	Genital warts treatment, strong	**45**	Antineoplastic, strong
22	Antineoplastic (multiple myeloma), strong	**46**	Antineoplastic, strong
23	Antineoplastic, strong	**47**	Angiogenesis stimulant, strong
24	Antineoplastic (multiple myeloma), strong	**48**	Antiarthritic, strong

Papulinone (**8**), a β-lactone with mild phytotoxic effects on apple and bean leaves, was isolated from the rod-shaped, Gram-negative bacterium *Pseudomonas syringae* [30]. Bradyoxetin (**9**) is a distinctive chemical component involved in the symbiotic regulation of genes, produced by the symbiotic bacterium *Bradyrhizobium japonicum* [31]. An ethyl acetate extract from marine *Bacillus* sp. bacteria, collected from sediments in Ieodo, South Korea, yielded a 24-membered antibacterial macrolactone called macrolactin I (**10**) [32].

Belactins A (**11**), inhibitors of serine carboxypeptidase, was discovered in the fermentation broth of *Saccharopolyspora* sp. MK19-42F6, also known as *Streptomyces erythraeus* [33]. Similarly, belactins B (**12**), also serine carboxypeptidase inhibitors, were identified in the same strain [33,34]. Two antitumor peptide antibiotics, belactosin A (**13**) and belactosin C (**14**), which act on cyclin/CDK-mediated cell cycle regulation, were produced by the soil-dwelling *Streptomyces* sp. KYI 1780 from Kanagawa Prefecture, Japan [35].

The β-lactone antibiotic lipstatin (**15**), derived from *Streptomyces albus*, exhibits antibacterial properties [36]. The same compound, known as oxazolomycin (**16**), is produced by *Streptomyces* sp. KBFP-2025 and has been shown to possess antiviral activity as well, according to research by Tonew and co-authors [37,38]. Additionally, a series of pancreatic lipase inhibitors featuring an oxetane ring, named panclicins A, B, C, D, and E (**17**), are produced by *Streptomyces* sp. NR0619 [39].

The actinomycete *Streptomyces albolongus* MG147-CF2, isolated from a soil sample from Shirane Mountain in Gunma Prefecture, produces the antibiotic valilactone (**18**). This compound inhibits hog liver esterase and hog pancreas lipase with IC_{50} values of 29 ng/mL and 0.14 ng/mL, respectively. It also inhibits fatty acid synthase with an IC_{50} value of 0.3 μM and demonstrates selective toxicity towards MDA-MB-231 breast cancer cells with an IC_{50} value of 10 μM [40].

A fungal indole-diterpenoid with an oxetane ring, known as pennigritrem (**19**), was isolated from *Penicillium nigricans* [41]. Ansalactam D (**20**), another compound, was isolated from a marine-

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derived *Streptomyces* sp. [42]. The phytotoxin FCRR-Toxin (**21**) was isolated from the culture filtrate of *Fusarium oxysporum* f. sp. *radicis-lycopersici* [43]. Cinnabaramide A (**22**), a proteasome inhibitor, was detected in the fermentation broth of *Streptomyces* sp. JS360 [44]. Lastly, a tricyclic sesquiterpene known as cyclodehydroisolubimin (**23**) has been isolated from potato tubers inoculated with the oomycete *Phytophthora infestans* [45].

The marine *Salinispora tropica* produced antibiotics, salinosporamide A (**24**) and omuralide (**25**) [46]. Sesquiterpene called stereumone A (**26**) was isolated from a culture broth of the fungus *Stereum* sp. [47] which showed nematicidal activity against nematode *Panagrellus redivivus*.

3. Oxetane Biomolecules Derived from Fungi and Marine Sources

Butenolide, known as ramariolide B (**27**), has been isolated from the fruiting bodies of the coral mushroom *Ramaria cystidiophora*. Its structure and activity are detailed in Figure 3 and Table 1, respectively [48].

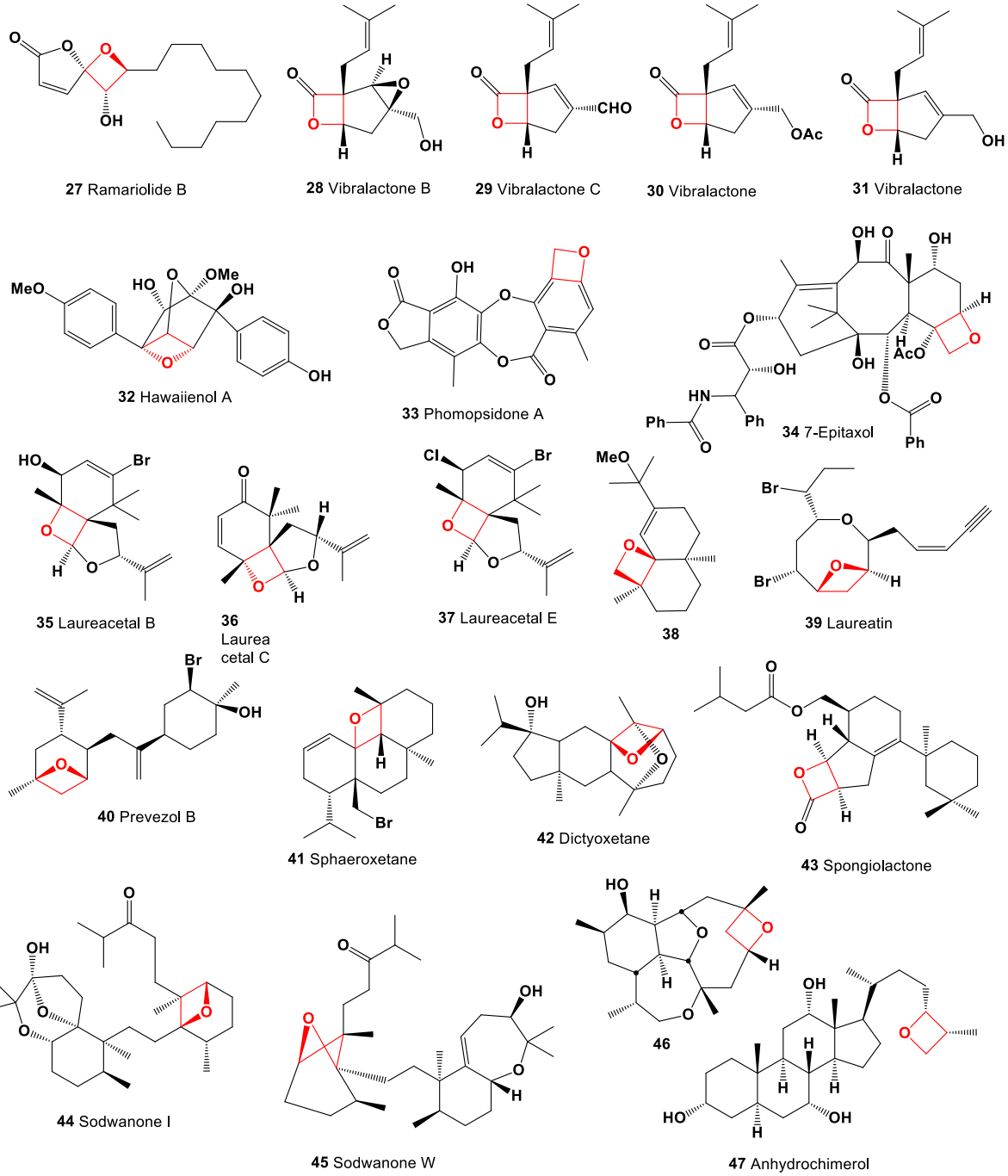

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Figure 3. Oxetane biomolecules derived from fungi, and marine sources.

Several natural products featuring a vibralactone skeleton have been isolated from cultures of the basidiomycete *Boreostereum vibrans* (see Figure 4). These include vibralactone B (**28**), vibralactone C (**29**); and acetylated vibralactone (**30**) [49]. Additionally, vibralactone (**31**) was isolated from the same fungal source [50].

Figure 4. a, The coral mushroom Ramaria cystidiophora; **b**, Basidiomycete Boreostereum vibrans; **c**, Japanese red algae Laurencia nipponica; **d**, Red alga Sphaerococcus coronopifolius; **e**, Octocoral Briareum asbestinum; **f**, Marine sponge *Axinella* sp. Pictures of samples of plants, fungi or marine organisms presented in the review were taken from sites that allow their use for non-commercial purposes.

A highly oxygenated *p*-terphenyl, hawaiienol A (**32**), has been isolated from cultures of *Paraconiothyrium hawaiiense*, a fungus associated with the Septobasidium-infected insect *Diaspidiotus* sp. Another compound, a pentacyclic depsidone with an oxetane unit called phomopsidone A (**33**), was isolated from the mangrove endophytic fungus *Phomopsis* sp. A123. Bioactivity assays demonstrate that this compound possesses cytotoxic, antioxidant, and antifungal activities [51].

A taxol derivative, 7-epi-10-deacetyltaxol (**34**), was detected in the culture of the endophytic fungus *Pestalotiopsis microspora*, which was isolated from the bark of *Taxodium mucronatum* [52].

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Several secochamigranes, namely laureacetal B (**35**), C (**36**), and E (**37**), were identified from the Japanese red algae *Laurencia nipponica* [53,54]. An organic extract from the Formosan soft coral *Nephthea erecta* led to the isolation of a sesquiterpene (**38**) [55].

A brominated compound, laureatin (**39**), was also isolated from *Laurencia nipponica* [56]. A diterpene with anticancer activity, known as prevezol B (**40**), was found in the red algae *Laurencia rigida* [57]. The diterpenoid sphaeroxetane (**41**) was detected in the red alga *Sphaerococcus coronopifolius*, collected in the north Adriatic Sea [58]. Dictyoxetane (**42**), a diterpene with a 2,7-dioxa-tricyclo[4.2.1.0]nonane ring subunit, was isolated from the brown alga *Dictyota dichotoma* collected from the Indian Ocean [59].

Diterpene isovalerate, spongiolactone (**43**), was isolated from the Mediterranean sponge *Spongionella gracilis* [60]. A series of anti-cancer triterpenoids, including sodwanone I (**44**) and sodwanone W (**45**) were yielded from a South African marine sponge, *Axinella* sp. [61]. An unusual asbestinane diterpene (**46**) has been isolated from the octocoral *Briareum asbestinum*, collected off the coast of Tobago, West Indies [62].

Anhydrochimerol (**47**), a 24,26-epoxy-5β-cholestane-3α,7α,12α-triol, was obtained from the hydrolysis of bile salts of the rabbit fish *Chimaera monstrosa* [63].

4. Oxetane Biomolecules Derived from Plants

An acetone extract from the leaves of the Indian herb *Acalypha indica*, particularly from Tamil Nadu, contains a compound with an oxetane ring (**48**) [64]. A β-lactone called vittatalactone (**49**, structures are shown in Figure 5 and activities are shown in Table 2) was isolated from collections of airborne volatile compounds emitted by feeding male striped cucumber beetles, *Acalymma vittatum* [65].

Table 2. Biological activity of oxetanes derived from fungi and plants [10].

No.	Dominated predicted activity	No.	Dominated predicted activity
49	Anti-eczematic, strong	**73**	Antineoplastic, strong
50	Respiratory analeptic, strong	**74**	Antineoplastic, strong
51	Antineoplastic, strong	**75**	Antineoplastic, strong
52	Antineoplastic, moderate	**76**	Antineoplastic, strong
53	Genital warts treatment, strong	**77**	Cardiovascular analeptic, strong
54	Genital warts treatment, strong	**78**	Renin release stimulant, strong
55	Genital warts treatment, strong	**79**	Genital warts treatment, moderate
56	Antineoplastic, moderate	**80**	Apoptosis agonist, strong
57	Antineoplastic, strong	**81**	Antineoplastic enhancer, strong
58	Antineoplastic, strong	**82**	Anti-eczematic, moderate
59	Anti-eczematic, strong	**83**	Apoptosis agonist, strong
60	Expectorant, strong	**84**	Antineoplastic, strong
61	Wound healing agent, strong	**85**	Antineoplastic, strong
62	Antineoplastic, strong	**86**	Antineoplastic, strong
63	Antineoplastic, strong	**87**	Respiratory analeptic, strong
64	Antineoplastic, strong	**88**	Respiratory analeptic, strong
65	Antineoplastic, strong	**89**	Respiratory analeptic, strong
66	Antineoplastic, strong	**90**	Respiratory analeptic, strong
67	Genital warts treatment, moderate	**91**	Respiratory analeptic, strong
68	Antineoplastic, weak	**92**	Respiratory analeptic, strong
69	Genital warts treatment, moderate	**93**	Respiratory analeptic, strong
70	Genital warts treatment, moderate	**94**	Respiratory analeptic, strong
71	Stroke treatment, strong	**95**	Antineoplastic, strong
72	Genital warts treatment, moderate	**96**	Antineoplastic, strong

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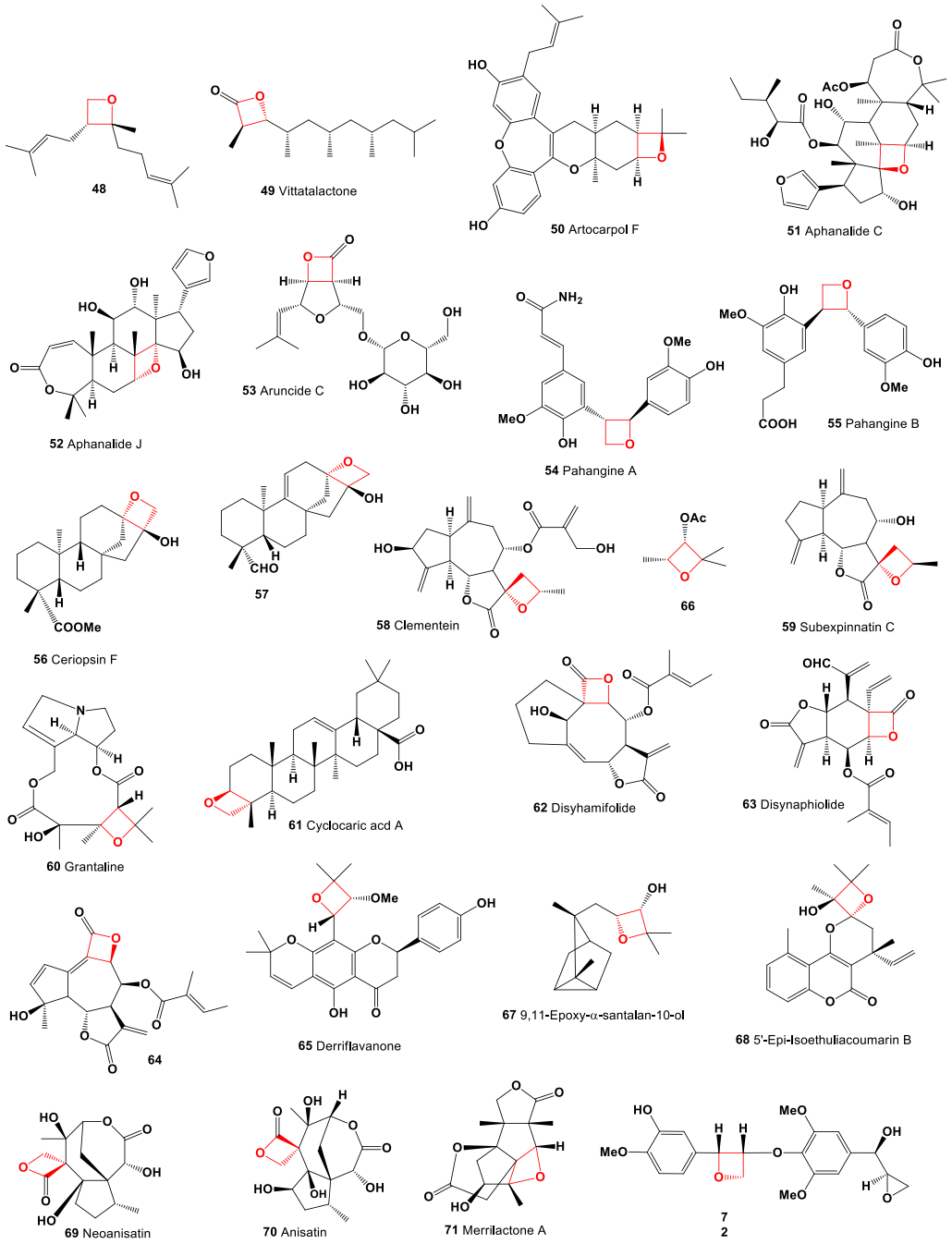

Figure 5. Oxetane biomolecules derived from plants.

Artocarpol F (**50**), a phenolic compound containing an oxepine ring, was isolated from the root bark of *Artocarpus rigida* [66]. From the fruits of *Aphanamixis polystachya*, two A-secolimonoids were isolated: aphanalide C (**51**) and aphanalide J (**52**), the latter featuring an unusual oxetane ring between C-7 and C-14 [67]. The aerial parts of *Aruncus dioicus* var. *kamtschaticus* yielded a monoterpenoid-O-β-D-glucopyranoside known as aruncide C (**53**) [68]. Two oxetane-containing neolignans, pahangine A (**54**) and B (**55**), were discovered in the bark extract of *Beilschmiedia glabra* [69].

A methanol-chloroform extract from the roots of *Ceriops decandra*, collected from the Kauvery estuary, resulted in the isolation of a diterpenoid, ceriopsin F (**56**) [70]. Additionally, 17-hydroxy-16-oxobeyer-9(11)-en-19-al (**57**) was found in the stems of *Bruguiera sexangula* var. *rhynchopetala* [71].

Clementein (**58**), a guaianolide, was isolated from *Centaurea clementei* [71], and an oxetane lactone called subexpinnatin C (**59**) was isolated from *Centaurea canariensis* [73]. In Australia, the plant *Crotalaria virgulata* subsp. *grantiana* contains the alkaloid grantaline (**60**) [74], and cyclocaric acid A (**61**) was detected in the ethanol extract of *Cyclocarya paliurus* [75].

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The South American flowering plant *Disynaphia halimifolia* produced sesquiterpene lactones, disyhamifolide (**62**) and disynaphiolide (**63**) [76], while the flowers and leaves of *Disynaphia multicrenulata* from Argentina contained a sesquiterpene dilactone (**64**) [77].

A flavonoid named derriflavanone (**65**) was discovered in Chinese lianas *Derris laxiflora*. The stem bark of *Duguetia glabriuscula*, collected in Jardim, Brazil, yielded two oxetane-containing metabolites, (**66**) and (+)-α-santalan-9,11-epoxy-10-ol (**67**) [78]. The aerial parts of *Ethulia conyzoides* from Egypt afforded a monoterpene 5-methyl-coumarin, named 5′-epi-isoethuliacoumarin B (**68**) [79]. Toxic metabolites, neoanisatin (**69**) and anisatin (**70**), were isolated from Japanese star anise *Illicium anisatum* [80]. A unique sesquiterpene bearing two γ-lactones and an oxetane ring, merrilactone A (71), was isolated from the pericarps of *Illicium merrillianum* and shows neurotrophic activity in cultures of fetal rat cortical neurons [81]. Neolignane (**72**) was detected in the aerial parts of *Isodon coetsa* [82].

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Figure 6. a, *Artocarpus lacucha,* also known as monkey jack or monkey fruit, is a tropical evergreen tree species of the family Moraceae from the Indian Subcontinent and Southeast Asia. The tree is valued for its wood; its fruit is edible and is believed to have medicinal value; **b**, *Centaurea clementei* is a native of southern Spain where it grows on the limestone cliffs and rarely seen in cultivation. The flowers are very thistle like, the hairy bracts form a tight urn above which the pale yellow flower opens; **c**, *Crotalaria virgulata*, garden plant; **d**, *Derris laxiflora*, is native to Taiwan and grows primarily in the humid tropical biome; **e**, *Ethulia conyzoides* is an erect or lodging annual aromatic plant that is collected from the wild, mainly for local medicinal purposes in Myanmar, Thailand, Laos, and Vietnam; **f**, *Illicium anisatum*, with common names Japanese star anise, Aniseed tree, and sacred Anise tree, known in Japanese as shikimi, is an evergreen shrub or small tree closely related to the Chinese star anise; **g**, *Isodon coetsa*, plant from tropical and subtropical Asia; **h**, The sausage tree *Kigelia africana* (also *Kigelia pinnata*), with its distinctive sausage-shaped fruits and blood-red tulip-shaped flowers, is a colorful standout plant native to tropical Africa, where it grows in open forests, along river and stream banks, and in floodplains.

An unusual metabolite, maoyecrystal I (**73**) with a 11,20:1,20-diepoxy-ent-kaurane skeleton, exhibiting cytotoxic activity against K562 cells, was found in the extract of *Isodon japonicus*. The presence of the oxetane group in maoyecrystal I is believed to determine its biological activity [83].

Guaiagrazielolide (**74**, structures are shown in Figure 7 and activities are shown in Table 2), a guaianolide with a β-lactone and an oxetane ring, was obtained from the leaves of the South American flowering plant *Grazielia* sp., along with 8-hydroxygrazielolide (**75**) [84]. *cis*-Himachalane-type sesquiterpenes, 2α,6α-epoxy-3-himachalene (**76**) and 2α,6α-epoxyhimachalan-3β-ol (**77**) were isolated from the heartwood of *Juniperus chinensis* var. *tsukusiensis* [85].

A limonoid named kigelianolide (**78**) was isolated from the ethyl acetate-soluble fraction of the methanolic extract of the African plant *Kigelia africana*, showing weak inhibitory activities against acetylcholinesterase, butyrylcholinesterase, and lipoxygenase [86].

Phenolic amide, lyciumamide C (**79**), identified from the stem of *Lycium barbarum*, exhibited moderate anti-cancer activity against human glioma stem cell lines [87,88].

Norfriedelane A, possessing an α-oxo-β-lactone group (**80**) and showing acetylcholinesterase inhibitory effects with an IC_{50} value of 10.3 μM, was isolated from the branches and roots of *Malpighia emarginata* [89]. An ent-Trachylobane diterpenoid, mitrephorone A (**81**), which possesses a hexacyclic ring system with adjacent ketone moieties and an oxetane ring, was detected in the stem bark of *Mitrephora glabra* [90].

Parthoxetin (**82**) was detected in the flowering plant *Parthenium fruticosum*, which belongs to the Chrysanthemum family. A triterpenoid carbon framework, named petatrichol B (**83**), was isolated from the rhizome of *Petasites tricholobus* and exhibited significant antibacterial activity against *Bacillus subtilis* [91]. A series of ergostane-type steroids, including petuniasterone P1 (**84**), were isolated from the leaves and stems of *Petunia hybrida* [92,93]. A limonoid, 7,14-epoxy-azedarachin B (**85**), was detected in a methanol extract of the roots of *Melia azedarach* [94]. An alkaloid, 1,9-epoxy-9α-hydroxystenine (**86**), has been isolated from the roots of *Stemona tuberosa* [95].

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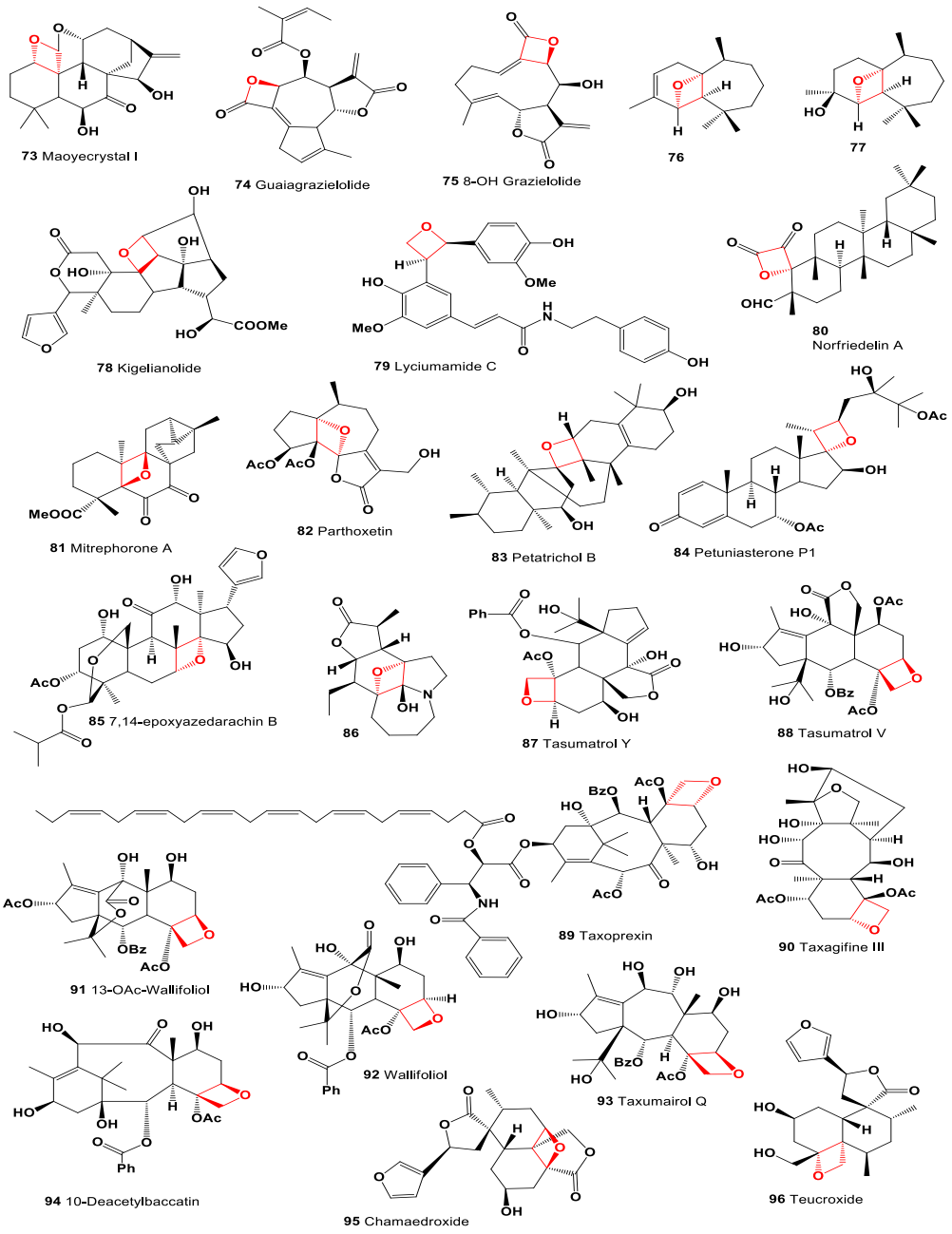

Figure 7. Oxetane biomolecules derived from plant species.

The genus *Taxus* is known for containing over 450 taxane diterpenes, many of which have an oxetane ring. An acetone extract from the leaves and twigs of *Taxus sumatrana* resulted in the isolation of bicyclic taxoids tasumatrol Y (**87**) and tasumatrol V (**88**) [97]. The anticancer agent taxoprexin (**89**) was first isolated from the bark of *Taxus brevifolia* [98,99]. A taxane diterpene, taxagifine III (**90**), was isolated from the leaves and stems of *Taxus chinensis* [100], and the taxoid 13-O-acetyl wallifoliol (**91**) has been isolated from extracts of the needles of Himalayan *Taxus wallichiana* [101]. A diterpene with a 5/6/6/6/4 ring system called wallifoliol (**92**) was also isolated from Himalayan *T. wallichiana* [101]. Taxumairol Q (**93**) was isolated from the leaves and twigs of *T. sumatrana* and exhibited significant cytotoxicities against both Hepa 59 T/VGH (human liver carcinoma) and KB (human oral epidermoid carcinoma) tumor cells [102]. An anti-*Leishmania donovani* agent called 10-deacetylbaccatin (**94**) and a series of closely related compounds have been isolated from the yew tree *Taxus* sp. [103]. A neo-clerodane diterpenoid, chamaedroxide (**95**), containing an oxetane ring was found in *Teucrium chamaedrys* [104], and the aerial parts of *Teucrium salviastrum* contain diterpene teucroxide (**96**) and teusandrin E (**97**, structures are shown in Figure 8 and activities are shown in Table 3) [105].

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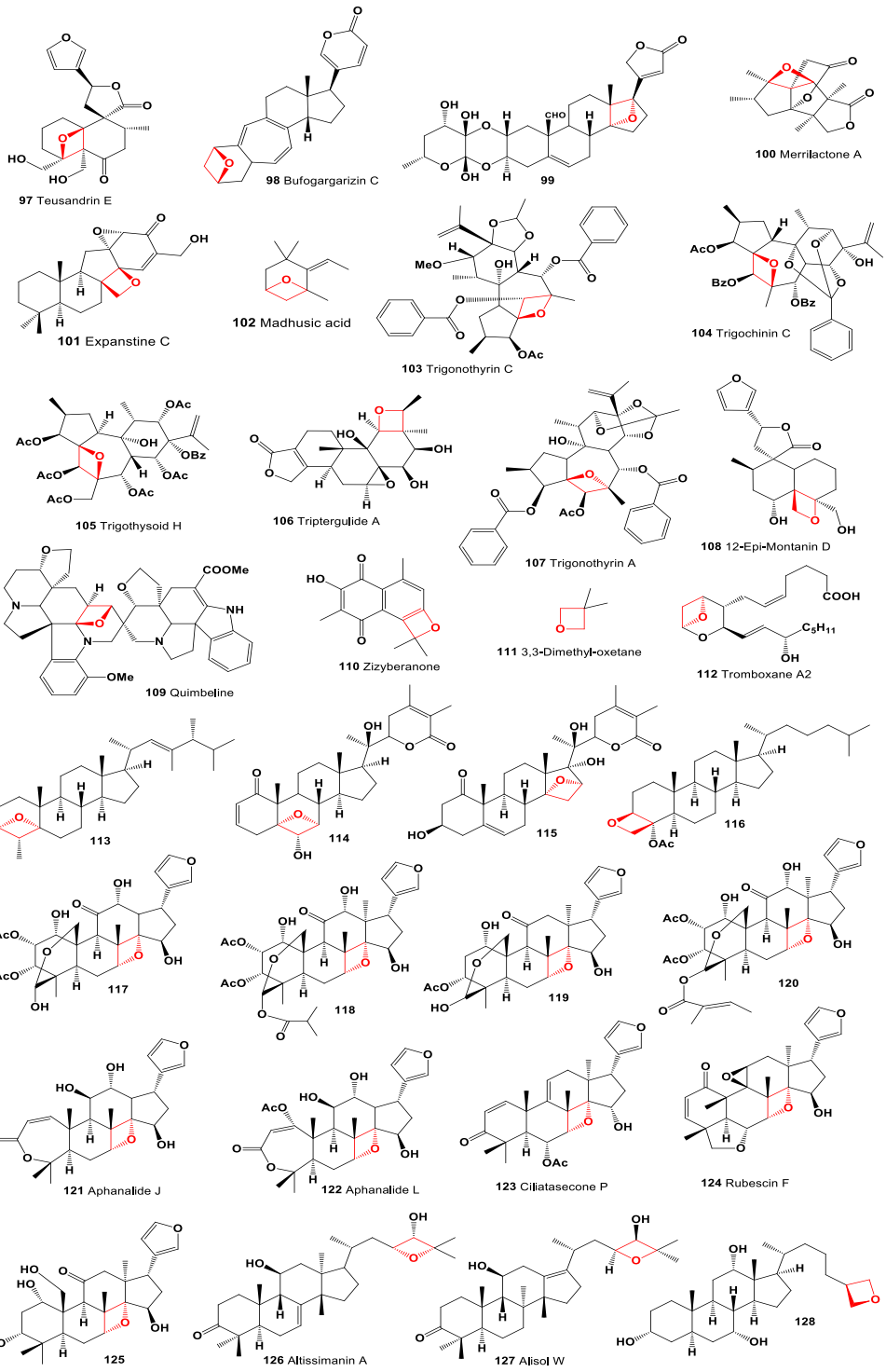

Figure 8. Oxetane biomolecules derived from terrestrial and aquatic biotopes.

Table 3. Biological activity of oxetanes derived from fungi and plants [10].

No.	Dominated predicted activity	No.	Dominated predicted activity
97	Antineoplastic, strong	**113**	Antineoplastic, moderate
98	Antineoplastic, strong	**114**	Antiviral, moderate
99	Cytotoxic, strong	**115**	Antiviral, moderate
100	Neurotrophic, moderate	**116**	Antiviral, strong
101	Antibacterial, strong	**117**	Antineoplastic, weak
102	Anti-inflammatory, weak	**118**	Antineoplastic, weak

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103	Tyrosine kinase inhibitor, strong	**119**	Antineoplastic, weak
104	Tyrosine kinase inhibitor, strong	**120**	Antineoplastic, moderate
105	Anti-HIV-1, strong	**121**	Anti-feedant, moderate
106	Antibacterial, moderate	**122**	Anti-feedant, moderate
107	Antibacterial, moderate	**123**	Cytotoxic, moderate
108	Cytotoxic, moderate	**124**	Cytotoxic, moderate
109	Antibacterial, moderate	**125**	Cytotoxic, moderate
110	Antibacterial, moderate	**126**	Cytotoxic, strong
111	Antifungal, moderate	**127**	Antitumor, strong
112	Cytotoxic, moderate	**128**	Antitumor, moderate

Bufogargarizin C (**98**), a steroid with rearranged A/B rings and an unusual bufadienolide with a cycloheptatriene B ring, was isolated from the toad *Bufo bufo gargarizans* [106]. A cardenolide glycoside (**99**) was isolated from the aerial parts of the milkweed, Gomphocarpus sinaicus [107]. Merrilactone A (**100**), isolated from the pericarps of *Illicium merrillianum*, shows intriguing neurotrophic activity in the cultures of fetal rat cortical neurons [81].

An isoprenoid epoxycyclohexenone, expanstine C (**101**), featuring an unusual oxetane ring, was isolated from *Penicillium expansum* YJ-15. This compound exhibited potent antibacterial activities against *B. subtilis* [108].

A homomonoterpene, 1,3,3-trimethyl-7-oxabicyclo[3.1.1]hexa-9-en-10-oic acid, named madhusic acid A (**102**), was isolated from the methanolic extract of the dried leaves of *Madhuca pasquieri* [109].

Highly oxygenated diterpenes, trigochinin C (**103**) and trigonothyrin C (**104**), were isolated from *Trigonostemon chinensis* and showed significant inhibition against MET tyrosine kinase activity with an IC_{50} value of 2 μM [110]. A daphnane diterpenoid, trigothysoid H (**105**), was isolated from the methanol extract of the twigs and leaves of *Trigonostemon thyrsoideum*; this compound demonstrated potent anti-HIV-1 activity, with an EC_{50} value of 0.001 nM and a TI value of 1618 [112].

An abietane diterpene, triptergulide A (**106**), containing a fused 5/6/6/3/6/4 hexacyclic system, was isolated from the leaves of *Tripterygium wilfordii* [113]. A highly functionalized daphnane diterpenoid, trigonothyrin A (**107**), was found in the extract of the stems of *Trigonostemon thyrsoideum* [114]. A furanoid diterpene of the clerodane type, 12-epi-montanin D (**108**), was isolated from the bitter fraction of the aerial parts of the Mediterranean tree, *Teucrium montanum* (syn. *Chamaedrys montana*) [115].

A bisindole alkaloid, quimbeline (**109**), was found in the root bark of *Voacanga chalotiana* [116], and a sesquiterpene, zizyberanone (**110**), was isolated from the fruits of the thorny rhamnaceous plant *Ziziphus jujuba* [117].

Approximately 300 compounds, including 3,3-dimethyl-oxetane (**111**), contributing to apple flavor and aroma from different cultivars Cortland and Empire, have been reviewed [118]. The hormone thromboxane A2 (**112**) has been discovered in blood platelets [119,120].

An unusual 3,5-epoxysterol (**113**) was derived from the octocoral *Plexaura flexuosa*, located in Mochima Bay, Venezuela [121].

Two withanolide derivatives (**114** and **115**) were found in leaf extracts of plants belonging to the genus *Solanum* [122]. The antiviral activity of oxetane (**116**) obtained from 23,3α-dihydroxy-5α-cholestane has been described [123]. Highly oxygenated trichilin-type limonoids (**117**-**120**) were isolated from the desiccative ripe fruits of *Trichilia sinensis*, which showed weak inhibitory activity in the Hela cell line [124]. From the fruits of the tropical tree *Aphanamixis grandifolia*, two oxetane limonoids, aphanalide J (**121**) and L (**122**), were isolated and demonstrated anti-feedant activity [125].

A limonoid named ciliatasecone (**123**) was detected in the barks of *Toona ciliata*, belonging to the Meliaceae family. This tree is cultivated throughout the tropics for its colored wood hearts suitable for architecture and furniture. Large amounts of *T. ciliata* barks, a by-product of wood first-stage processing, have also been used as Chinese folk medicine to treat diarrhea, dysentery, and ringworm [126]. Rubescin F (**124**), a vilasinin-type limonoid, and another compound (**125**) were obtained from

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the leaves of *Trichilia rubescens* (Meliaceae) [127]. A cytotoxic triterpenoid named altissimanin A (**126**), a tirucallane-type triterpenoid bearing an uncommon oxetane ring in the side-chain, was isolated from the bark of *Ailanthus altissima* [128].

A protostane-type triterpenoid bearing an oxetane ring in the side-chain, named alisol W (**127**), has been obtained from the dried rhizome of *Alisma plantago-aquatica* subsp. *orientale* [129]. Bile sterol, 3α,7α,12α-trihydroxy-26,27-epoxycholestane (**128**), from carp bile was reported by Hoshita [130].

5. Dioxetane Biomolecules Derived from Natural Sources

1,2-Dioxetanes, characterized by a four-membered ring containing two oxygen and two carbon atoms ($C_2H_4O_2$), are a class of cyclic peroxides known for their instability and tendency to release energy as light [14–16,20]. These high-energy, non-aromatic heterocycles are of interest due to their potential as novel pharmacophores with a broad spectrum of biological activities. Due to their strained structure and relatively weak peroxide bond (-O-O-) ranging from 190–210 kJ/M, 1,2-dioxetanes are highly unstable. These compounds have been found, isolated, and identified as intermediate products in natural and synthetic contexts [131].

1,2-Dioxetane units are found in extracts from various plants, marine invertebrates, and are produced by certain fungi and fungal endophytes (samples of fungi and plants are shown in Figure 9), For example, a solubilized enzyme fraction from the mycelium lyophilisate of the oyster mushroom *Pleurotus sapidus* converts β-myrcene into furanoterpenoids through 1,4-endoperoxides, with compound (**129**) isolated as a stable intermediate [132].

Figure 9. Samples of fungi and plants in which stable 1,2-dioxetanes were discovered and isolated. **a**, the oyster mushroom *Pleurotus sapidus;* **b**, wormwood *Artemisia* spp.; **c**, *Pongamia pinnata* is a species of tree in the pea family, Fabaceae, native to eastern and tropical Asia, Australia, and the Pacific islands; d, *Dendrobium nobile*, commonly known as the noble dendrobium, is a member of the family Orchidaceae.

Several mono- and diterpenoids (**129a-g**, structures are shown in Figure 10 and activities are shown in Table 4) have been isolated from terreastial and marine species, and showed antimalarial activity. Tinctures made from wormwood have always enjoyed panacea status in folk medicine,

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especially as thermogenics and remedies for fatigue, dyspepsia, and respiratory tract infections. Some representatives of this group of plants (*Artemisia* spp., *Angelica keiskei*, *Melaleuca alternifolia*) contain a number of bioactive substances such as 1,2-dioxetanes (**129a**-**f**). Studies have shown that these compounds demonstrate strong antimalarial activity against *Plasmodium falciparum* [16,20,133,134].

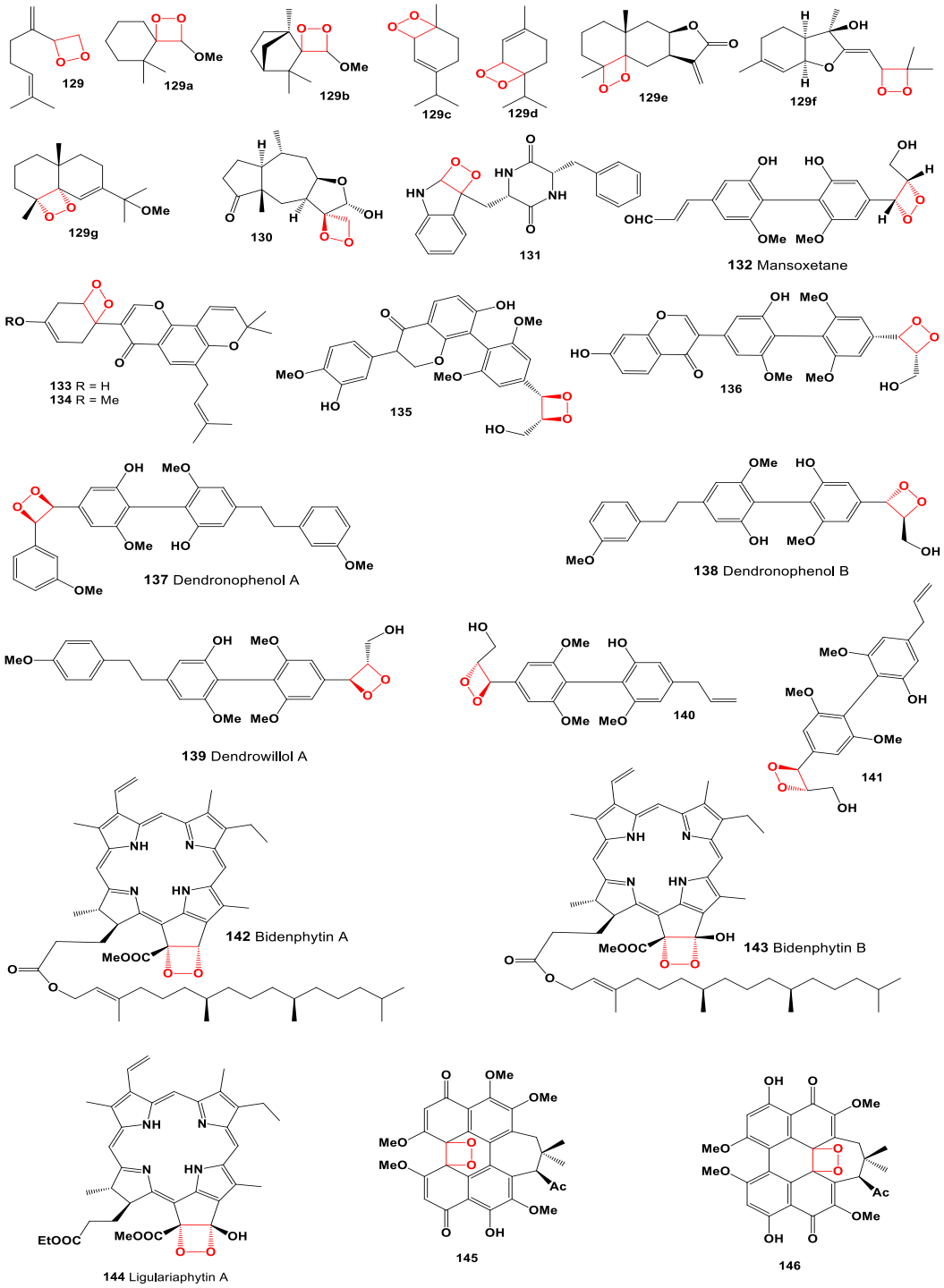

Figure 10. Stable 1,2-Dioxetane Biomolecules Derived from Natural Sources.

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Table 4. Biological activity of oxetanes derived from fungi and plants [16,141–144].

No.	Dominated activity	No.	Dominated activity
129	Antiprotozoal (Plasmodium), moderate	**135**	Neuroprotective effect, strong
129a	Antiprotozoal (Plasmodium), strong	**136**	Antiprotozoal (Plasmodium), strong
129b	Antiprotozoal (Plasmodium), strong	**137**	Antiprotozoal (Plasmodium), strong
129c	Antiprotozoal (Plasmodium), strong	**138**	Antiprotozoal (Plasmodium), strong
129d	Antiprotozoal (Plasmodium), strong	**139**	Antiprotozoal (Plasmodium), strong
129e	Antiprotozoal (Plasmodium), strong	**140**	Antiprotozoal (Plasmodium), strong
129f	Antiprotozoal (Plasmodium), moderate	**141**	Antiprotozoal (Plasmodium), strong
129g	Antiprotozoal (Plasmodium), moderate	**142**	Photosensitizer, strong
130	Antiprotozoal (Plasmodium), moderate	**143**	Photosensitizer, strong
131	Anticancer, weak	**144**	Cytotoxic, weak
132	Antiprotozoal (Plasmodium), weak	**145**	Antineoplastic, strong
133	Antiprotozoal (Plasmodium), moderate	**146**	Antineoplastic, strong
134	Neuroprotective effect, strong		

The sesquiterpenoid (6*E*,10*R*)-4,5-dioxo-11-methoxy-eudesm-6-ene (**129g**) isolated from the organic extract of the Formosan soft coral *Nephthea erecta* demonstrated anti-inflammatory and cytotoxic activities [55].

An unusual sesquiterpene lactone, 11,13-Epidioxy-10-hydroxy-4-oxo-12,8-pseudo-guaianolide (**130**), was isolated from the methanol extract of the Ambrosia species [134]. A dipeptide, diketopiperazine (**131**), isolated from a static culture of the Antarctic fungus *Penicillium citreonigrum* SP-6, showed weak inhibition against the HCT116 cancer cell line.

Neolignan mansoxetane (**132**) was obtained from dichloromethane extracts of the heartwood stem of *Mansonia gagei* (Stercullariaceae) and also isolated from the roots of *Pongamia pinnata* alongside compounds **133**, **134**, phenylisoflavone (**135**), and (**136**) [136–138]. Compounds possessing a bis(bibenzyl) skeleton, dendronophenol A (**137**) and B (**138**), were isolated from the stems of *Dendrobium nobile* (Orchidaceae) [139]. Dendrowillol A (**139**), a 9,10-dihydrophenanthrene, was identified in the whole plants of *Dendrobium moniliforme* [140]. Neolignans (**140** and **141**) featuring a 1,2-dioxetane moiety were isolated from the twigs of *Cinnamomum cassia* [139].

Two pheophytins, bidenphytins A (**142**) and B (**143**), with peroxide functionalities on ring E were discovered over 20 years ago in crushed leaves of *Biden pilosa* var. *radiata* [141]. More recently, an unusual phaeophytin, 131-hydroxy-131,132-peroxyphaeophorbide an ethyl ester known as ligulariaphytin A (**144**), was isolated from the aerial parts of *Ligularia knorringiana*, displaying weak cytotoxicity [142].

Hypocrellin A, an effective photosensitizer known for its light-induced antitumor, antifungal, and antiviral activities, has gained attention for its ability to generate reactive oxygen species and inhibit protein kinase C activity, along with antimicrobial and anti-leishmanial activities *in vitro* [143]. Photooxidation of hypocrellin A yielded two cytotoxic peroxyhypocrellins (**145** and **146**) [144].

The data presented in Table 4 are of great interest, since more than 75 percent of stable 1,2-dioxetanes demonstrate strong antimalarial activity against *Plasmodium falciparum*, although others compounds show strong neuroprotective or antineoplastic effects.

5.1. Stable and Unstable 1,2-Dioxetanes of Natural Products

Research in recent years has shown that 1,2-dioxetanes are intermediates in synthesis or biosynthesis in reactions that form new molecules [14–16]. Currently, more than 150 reactions are

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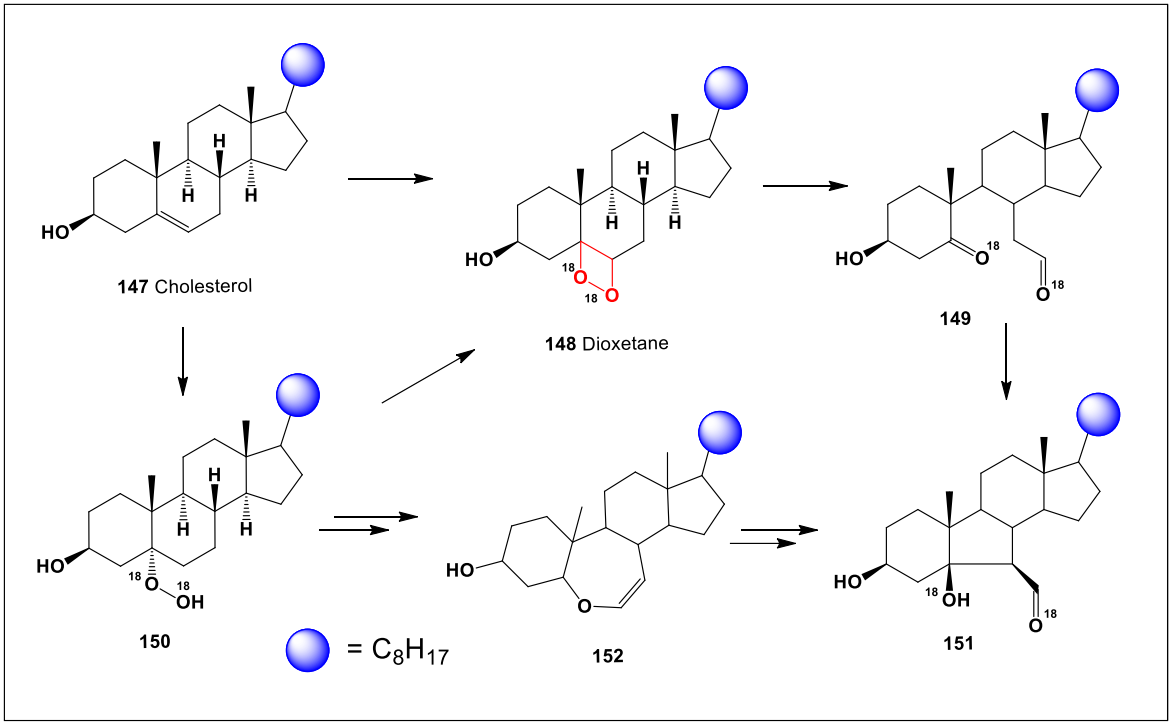
known in which, as a result of oxidation, unstable intermediate products are formed in the form of 1,2-dioxetanes. Below are some oxidation reactions of various natural products, the oxidation of which produces 1,2-dioxetanes.

The biological activity of the unstable 1,2-dioxetanes presented below has not been determined and has not been found in published studies. However, based on published data, these peroxides should exhibit antiprotozoal or anticancer activity.

5.1.1. Cholesterol Oxidation by Singlet Molecular Oxygen

Cholesterol (**147**) is a crucial lipid molecule necessary for the structure and function of animal cell membranes. It is a waxy, fat-like substance produced in the liver and obtained from dietary sources [145,146]. Cholesterol plays a vital role in maintaining the fluidity and integrity of cell membranes and serves as a precursor for the synthesis of various steroid hormones, including sex hormones like estrogen and testosterone, as well as corticosteroids such as cortisol and aldosterone [147]. It also contributes to the synthesis of vitamin D in the skin when exposed to sunlight [148] and is used in the liver to produce bile acids, which are essential for digesting and absorbing dietary fats [149].

Paolo Di Mascio and colleagues recently published a review focusing on the use of [^{18}O] labeled endoperoxides and hydroperoxides to investigate the mechanistic aspects of the formation of singlet molecular oxygen and its reactions in biological systems. The review highlights the synthesis and primary uses of [^{18}O]-labeled compounds, particularly peroxides and singlet oxygen ($^1O_2$), to elucidate reaction mechanisms. It also summarizes the peroxidation reactions of major cellular targets like steroids, unsaturated lipids, proteins, and nucleic acids published over the last three decades [150]. The review reports cholesterol oxidation by singlet molecular oxygen and the decomposition of the 1,2-dioxetane intermediate (Scheme 1).



Scheme 1. Cholesterol oxidation by singlet molecular oxygen. 5β-Cholesterol-hydroperoxide (**150**) and secosteroids (**149**, **151** and **152**) can be formed by either the Hock-cleavage of 5α-OOH or the decomposition of the 1,2-dioxetane intermediate (**148**).

Additionally, the formation of endogenous ozone has been linked to the oxidation of water catalyzed by antibodies, with the formation of dihydrogen trioxide as a primary intermediate product. A specific product of cholesterol's reaction with singlet molecular oxygen ($^1O_2$) is 3β-

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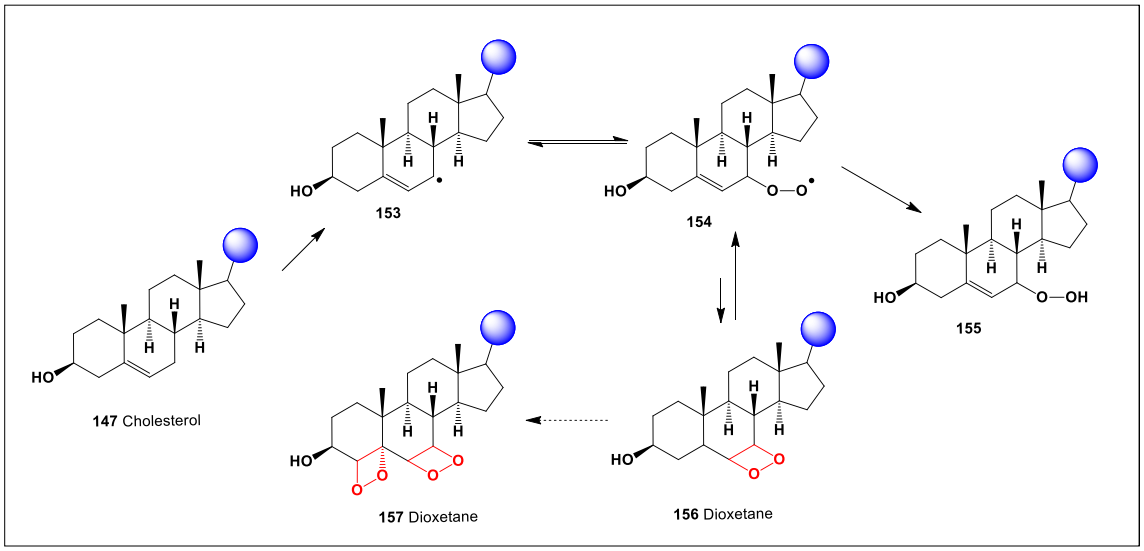
hydroxy-5β-hydroxypseudo-B-norcholestane-6β-carboxaldehyde, generated from photodynamic exposure or thermal decomposition of 1,4-dimethylnaphthalene endoperoxide as an oxygen source. The mechanism for generating this product (**151**) involves forming well-known 5α-cholesterol hydroperoxide (5α-OOH) (**150**, main product) and a 1,2-dioxetane intermediate (**148**). The unstable decomposition of this dioxetane yields an intermediate compound of 5,6-secosterol (**149**), which undergoes intramolecular aldolization to form the compound (**152**) [151].

5.1.2. The Autoxidation of Cholesterol

Autoxidation of cholesterol is a chemical process where cholesterol undergoes oxidation, typically in the presence of oxygen from the air. This reaction can occur under normal atmospheric conditions, without the need for enzymes or other biological catalysts. The autoxidation process generally involves the formation of reactive oxygen species (ROS) which then attack the cholesterol molecule. This leads to the formation of various oxidized products. The primary sites of oxidation in cholesterol are the double bond in the ring structure and the allylic methyl groups [152–154].

The autoxidation of cholesterol (**147**) involves a carbon-centered radical (**153**) and a peroxyl radical (**154**), leading to the formation of cholesterol-7-hydroperoxide (**155**) as the major product [152,153]. During this process, the unstable peroxyl radical (**154**) further reacts to produce cholesterol dioxetane (**156**) and cholesterol 5-hydroperoxide dioxetane (**157**) as shown in Scheme 2 [153,154].



Scheme 2. Cholesterol oxidation pathways during auto-oxidation process.

5.1.3. Oxidation of Cholesterol with Singlet Oxygen

Singlet oxygen is a highly reactive form of oxygen. Normally, molecular oxygen (O_2) is in a triplet state, which is its most stable form, with two unpaired electrons that have parallel spins. In contrast, singlet oxygen has both electrons paired and opposite spins, making it energetically excited and more reactive than the ground-state triplet oxygen. Singlet oxygen is a powerful oxidizing agent. It reacts with a wide range of organic and inorganic substances, often altering their chemical structure. Notably, it can add to double bonds in unsaturated organic compounds, leading to the formation of peroxides or other oxidation products [155–161].

Singlet oxygen ($^1O_2$), a crucial non-radical molecule, plays a significant role in the oxidation of cholesterol. It is formed when molecular oxygen receives an energy input, such as through photoactivation [155]. Due to its extremely short half-life, singlet oxygen reacts rapidly with cholesterol, resulting in the formation of four primary oxysterols: 5α-cholesterol-hydroperoxide (**150**), preferentially formed, along with 6α-cholesterol-hydroperoxide (**152**), 6β-cholesterol-hydroperoxide (**158**), and dioxetane (**148**). Additionally, ozone's interaction with cholesterol (**147**)

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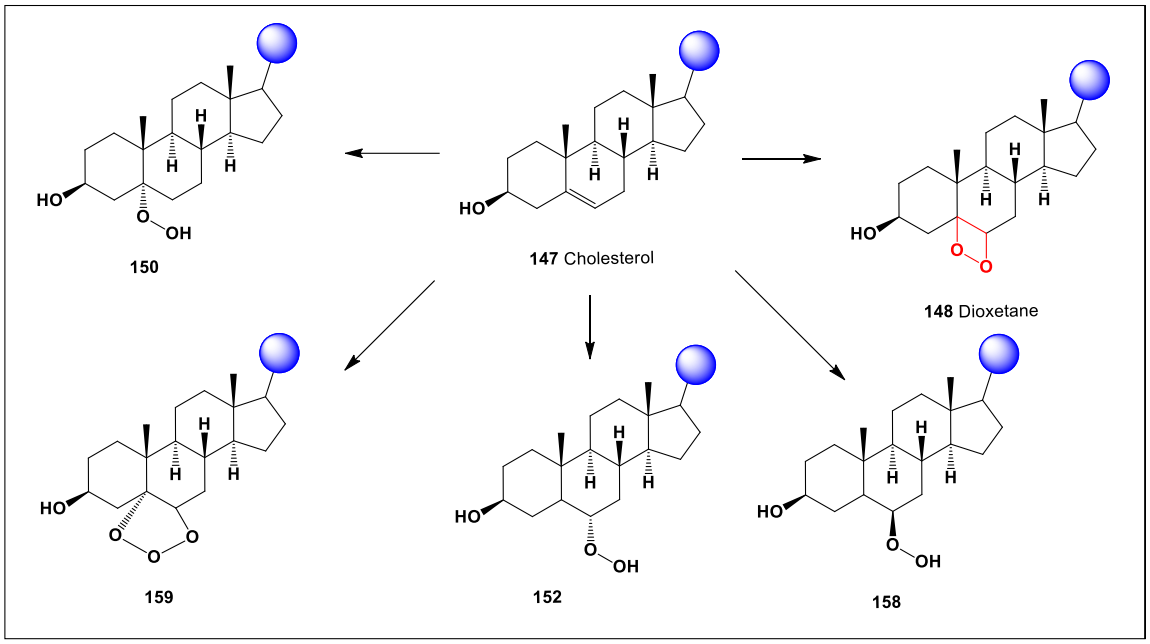
results in the formation of an unstable cholesterol-trioxolane (**159**) [156–161]. These cholesterol oxidation products are detailed in Scheme 3.



Scheme 3. The non-radical mediated cholesterol oxidation pathways. Cholesterol is oxidized by singlet oxygen to result in four different oxysterol species: dioxetane (**148**), 5α-cholesterol-hydroperoxide (**150**), 6α-cholesterol-hydroperoxide (**152**), 6β-cholesterol-hydroperoxide (**158**), and the unstable cholesterol-trioxolane (**159**).

5.1.4. Oxidation of 6,7-Dehydrocarnosic Acid

6,7-dehydrocarnosic acid is a diterpene compound that is chemically related to carnosic acid. Both of these compounds are found in rosemary (*Rosmarinus officinalis*) and are highly valued for their antioxidant properties. These compounds are part of a class of chemicals known as phenolic diterpenes, which are known for their ability to scavenge free radicals and contribute to the stability and health benefits of rosemary extract [162–164].

The oxidation of 6,7-dehydrocarnosic acid, a derivative of carnosic acid found in rosemary, involves its transformation into various oxidized products. Carnosic acid and its derivatives are known for their antioxidant properties, but under certain conditions, they can undergo oxidation. Carnosic acid (**160**, (4α*R*,10α*S*)-5,6-dihydroxy-1,1-dimethyl-7-propan-2-yl-2,3,4,9,10,10α-hexahydrophenanthrene-4α-carboxylic acid) and carnosol (**164**) are potent antioxidant compounds naturally found in *Salvia officinalis*. These compounds have demonstrated antimicrobial properties against pathogens such as *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis*, and *Staphylococcus aureus* [162–164].

In the presence of oxygen, 6,7-dehydrocarnosic acid can be oxidized to form several products. This process may involve the formation of radical species, which then react further with oxygen. The oxidation typically occurs at the double bond between the 6th and 7th carbons, which is part of a larger ring structure in the molecule. Additionally, these compounds, along with rosmanol (**165**), were identified in extracts from *Rosmarinus officinalis* [165]. Carnosic acid is also known for its anti-obesity [166], neuroprotective [167], anti-inflammatory [163], anticancer [168,169], and other biological activities [170–172]. The oxidation of 6,7-dehydrocarnosic acid (**160**) along with its oxidation products (**161**-**165**) are illustrated in Scheme 4 [173–175].

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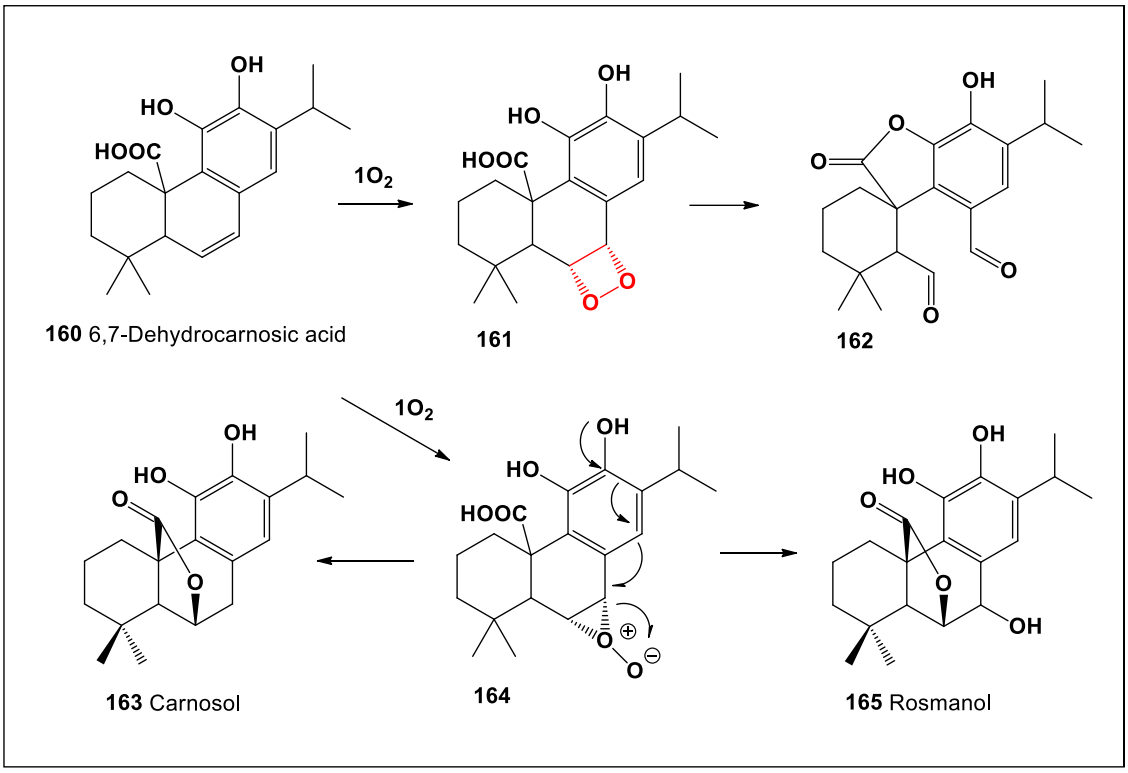

Scheme 4. The oxidation of 6,7-dehydrocarnosic acid to form dioxetane.

5.1.5. Oxidation of Vitamin D

Vitamin D is a fat-soluble vitamin that plays a crucial role in several important body functions, particularly in the regulation of calcium and phosphorus absorption, making it essential for maintaining healthy bones and teeth. Unlike many other vitamins, vitamin D functions like a hormone, and every cell in your body has a receptor for it. Oxidation of vitamin D refers to the chemical process where vitamin D reacts with oxygen, leading to the alteration of its molecular structure and potentially affecting its biological activity. This process can occur under various conditions, including exposure to air, light, or heat, and can impact the stability and efficacy of vitamin D [176–179]

Vitamin D (**166**) possesses a standard reduction potential of 650 mV and is readily oxidized by reactive oxygen species (ROS) [176]. The oxidation of vitamin D by singlet oxygen results in the formation of 5,6-epoxide (**167**) [177]. Notably, this oxidation process is independent of temperature [178] and occurs at a high reaction rate [179]. The cleavage of 5,6-epoxide or dioxetane (**167**) ultimately leads to the formation of 4-methylcyclohex-3-ene-1,3-diol (**170**) and compound (**169**) through the intermediate (**168**), as detailed in Scheme 5.

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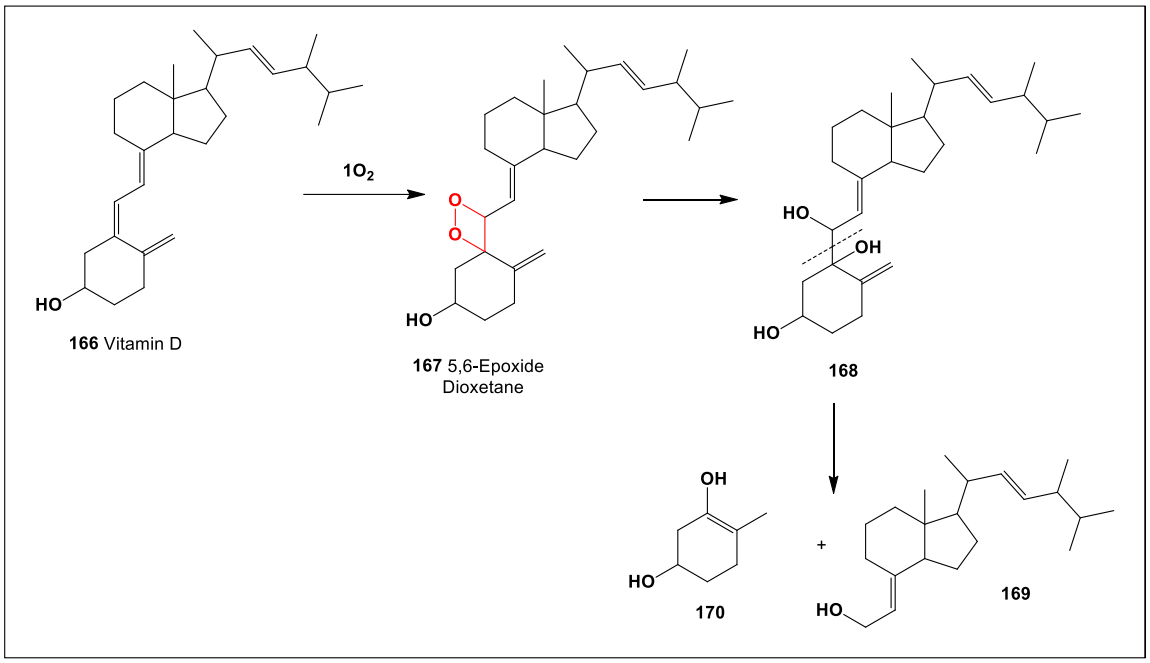

Scheme 5. Singlet oxygen oxidation of vitamin D.

5.1.6. Reaction of 17α-Hydroperoxy Steroids with P450 17A Enzymes

Cytochrome P450 enzymes are a diverse group of proteins known for catalyzing the oxidation of various substances, including aliphatic, aromatic, and heteroatomic compounds, involving both ring formation and cleavage reactions [180–182]. These enzymes play a crucial role in the biosynthesis and degradation of steroids, including critical C–C bond cleavage reactions [183].

Guengerich and colleagues explored the reactions of 17α-hydroxypregnenolone (**171**) and 17α-hydroxyprogesterone (**172**) catalyzed by human P450 17A1, specifically focusing on the 17α,20-lyase reactions. They discovered that one of the reaction products for each steroid contained a 17,20-dioxetane unit, labeled as compounds (**173**) and (**174**) in Scheme 6 [184,185]. The team also synthesized biomimetic reagents, 17α-OOH pregnenolone (**175**) and 17α-OOH progesterone (**176**), and introduced these to P450 17A enzymes without NADPH or reductase, leading to the suggested formation of steroids with the 17,20-dioxetane unit (**177** and **178**). The oxidation pathway is depicted in Scheme 7.

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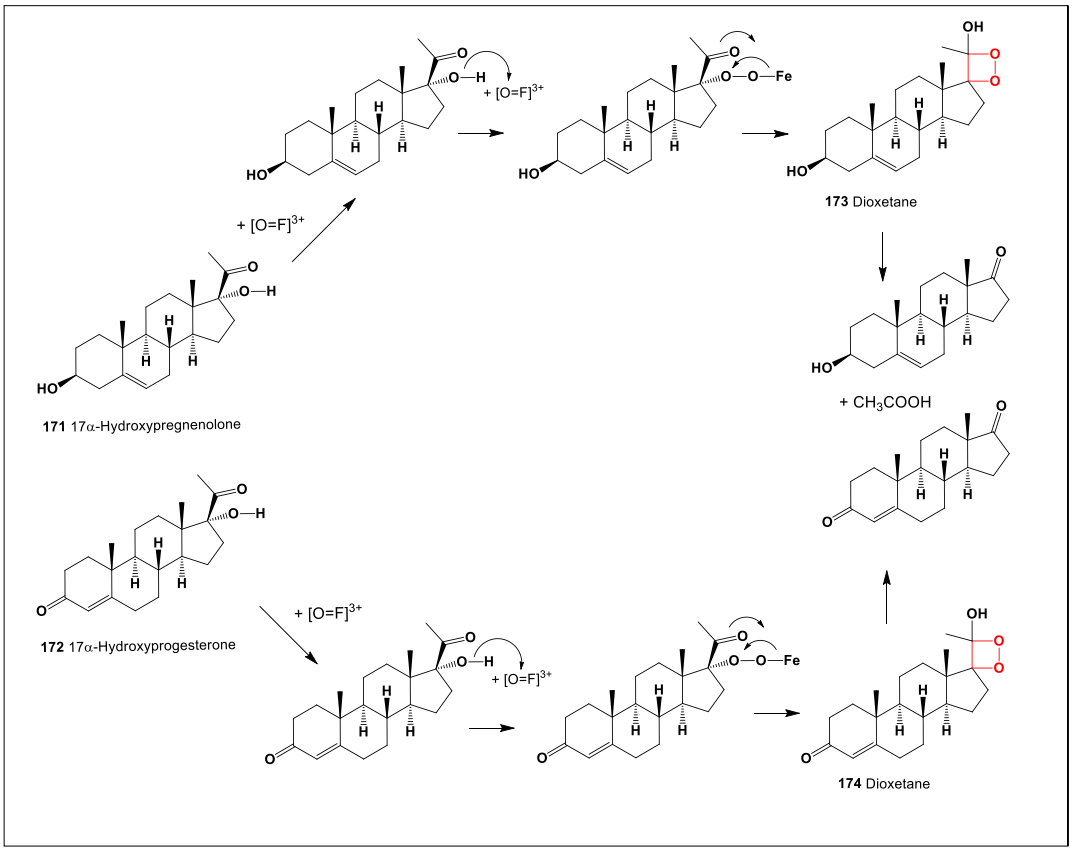
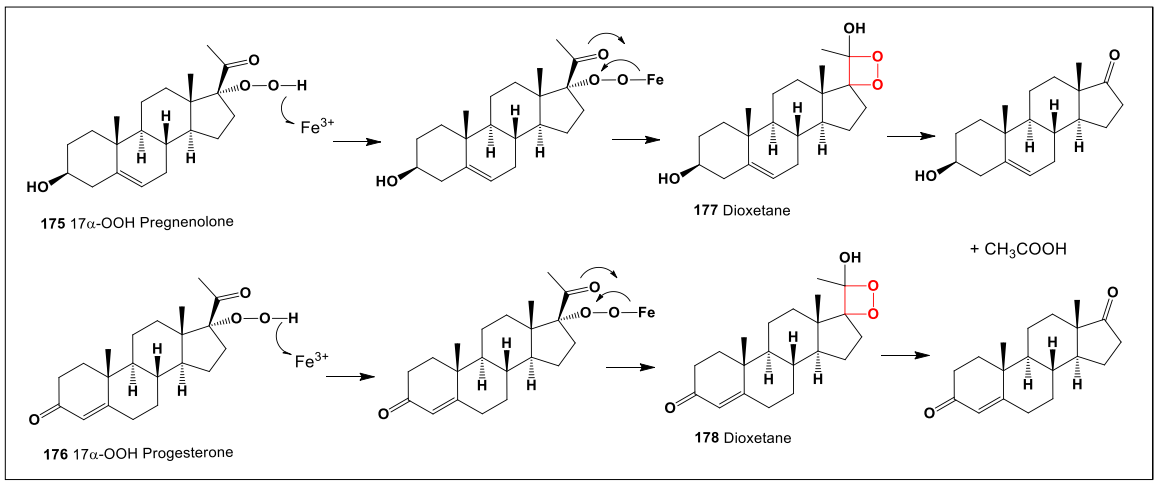


Scheme 6. Conversion of 17α-OH pregnenolone and 17α-OH progesterone to lyase products.



Scheme 7. Conversion of 17α-OOH pregnenolone and 17α-OOH progesterone to lyase products.

5.1.7. Formation of Vitamin K 2,3-Epoxide from Vitamin KH2

Vitamin K is a group of fat-soluble vitamins that play a crucial role in blood clotting, bone metabolism, and regulating blood calcium levels. The vitamin K family consists of structurally similar compounds that are divided into two main types [186–188]. Vitamin K1 (phylloquinone), found predominantly in green leafy vegetables like spinach, kale, and broccoli, as well as in some plant oils. Vitamin K1 is the primary form of vitamin K consumed in the human diet and is particularly important for its role in the blood clotting process. Vitamin K2 (menaquinones), this type of vitamin K is primarily found in fermented foods and animal products. It is also produced by bacteria in the human gut. Menaquinones have several subtypes, which differ in their side chain lengths, known as

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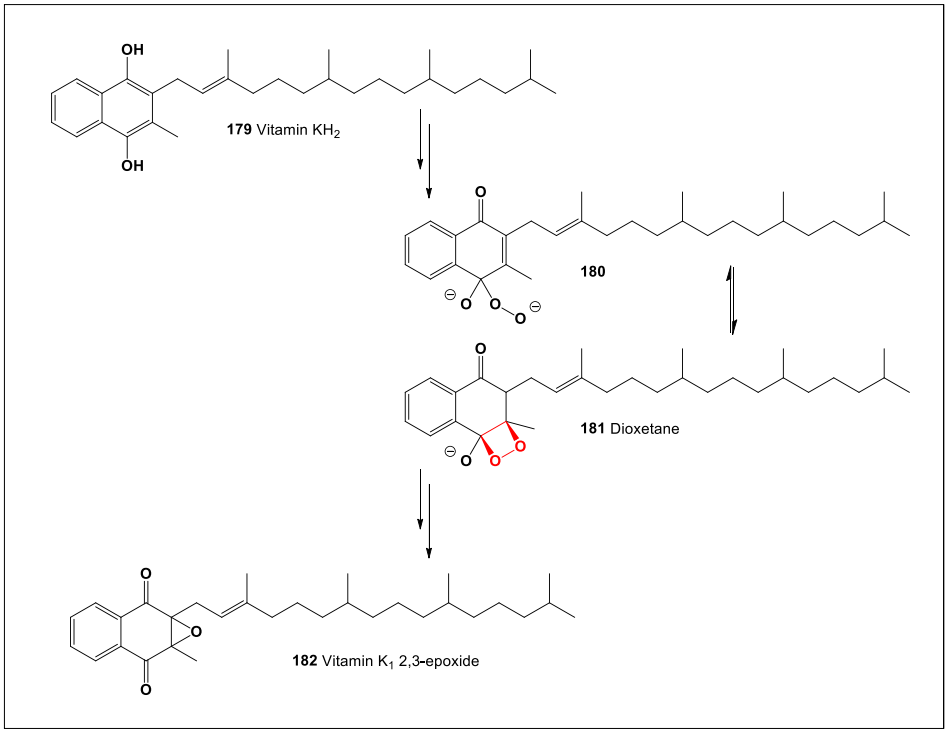
MK-4, MK-7, MK-8, etc. Vitamin K2 is especially important for bone health and cardiovascular health, as it helps regulate calcium deposition.

Vitamin K is crucial for the normal biosynthesis of clotting factors and is known to inhibit cell growth. Vitamin K1 2,3-epoxide (**182**, or 2,3-epoxyphylloquinone) is a derivative and inactive metabolite of vitamin K1. During the clotting process, vitamin K1 is converted into this epoxy form and then rapidly converted back to vitamin K1 by microsomal epoxide reductase. This conversion involves vitamin K hydroquinone and an unstable intermediate such as (**180**) and dioxetane (**181**), as outlined in Scheme 8. This cyclical process, known as the vitamin K1 epoxide cycle, allows for the transition of vitamin K1 between active and reserve states [186–188].



Scheme 8. Proposed mechanism of epoxidation vitamin KH2.

5.1.8. Synthesis of a Phosphodiesterase-4 Inhibitor Called Moracin M

Moracin M (**188**), a phosphodiesterase-4 inhibitor, was isolated from the leaves of plants within the *Morus* genus. Leaf fractions from *Morus insignis*, soluble in ethyl acetate and *n*-butanol, exhibited significant hypoglycemic activity in hyperglycemic streptozotocin-induced (STZ) rats. Both fractions contained moracin M (**188**) and mulberroside F (known as moracin M-3-O-beta-D-glucopyranoside) [189]. Mulberroside F, isolated from the leaves of *Morus alba*, is known to inhibit melanin biosynthesis [190]. Moracin M has also been isolated from the bark of Morus nigra [191].

Resveratrol (**183**), a natural phenolic stilbenoid, undergoes oxidation with singlet oxygen along two major pathways. Pathway A, which is a [2+2] cycloaddition, forms a transient dioxetane (**184**) that subsequently cleaves into the corresponding aldehydes (**185**) and (**186**). Pathway B, a [4+2] cycloaddition, results in the formation of an endoperoxide (**187**). Under heating, this endoperoxide undergoes a rearrangement to yield moracin M (**188**), as illustrated in Scheme 9 [192].

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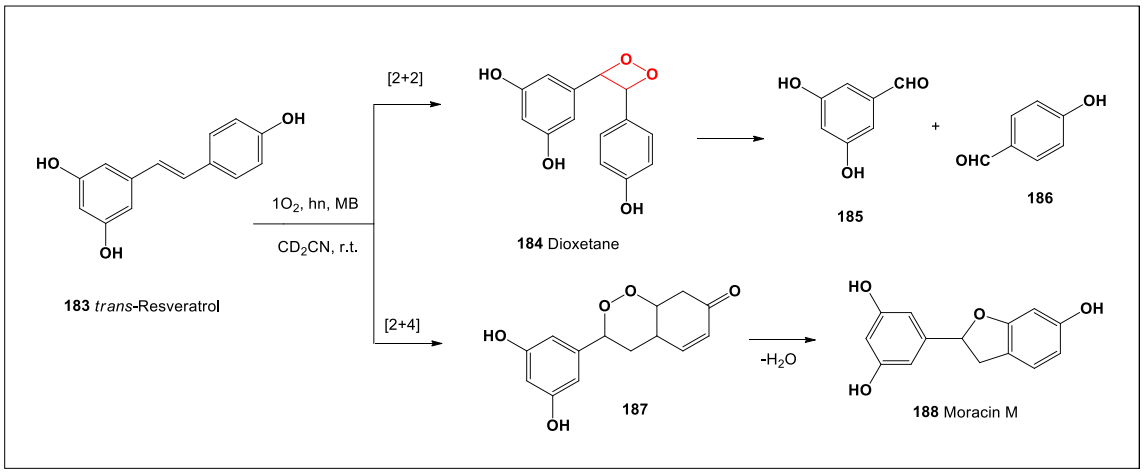
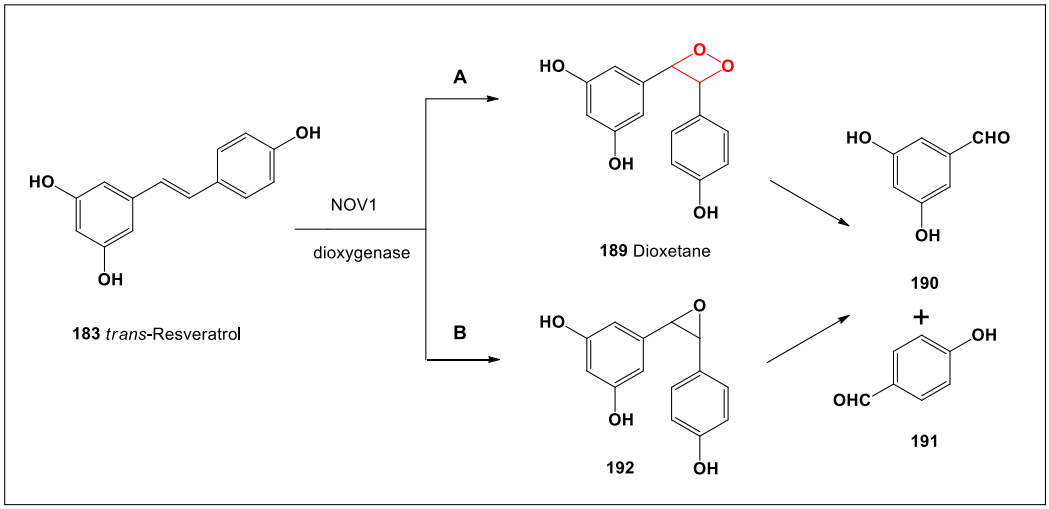


Scheme 9. Synthesis of a phosphodiesterase-4 inhibitor called moracin M.

5.1.9. Oxidation of Resveratrol Catalyzed by Dioxygenase NOV1

Bai and co-authors [193] investigated the oxidative cleavage of resveratrol (**183**) catalyzed by the dioxygenase enzyme NOV1 from the Gram-negative bacterium *Novosphingobium aromaticivorans*. NOV1, identified as a stilbene cleavage oxygenase, is responsible for the oxidative cleavage of the central double bond in stilbenes, resulting in the formation of two phenolic aldehydes (**190** and **191**).

The research outlined two distinct pathways for this reaction, differing only in the sequence of forming the first [C-O] bond. The first pathway involves a dioxetane intermediate (**189**), while the second pathway involves an epoxy intermediate (**192**). Each pathway encounters high energy barriers for the formation of the second [C-O] bond, as depicted in Scheme 10 [193]. These pathways highlight the complex mechanisms involved in the biochemical transformation of stilbene compounds by microbial enzymes.



Scheme 10. Oxidation of resveratrol by dioxygenase NOV1.

Mazzone and co-authors also studied the *trans*-resveratrol (**183**) and $^1O_2$ interaction mechanism and concluded that the oxidation of *trans*-resveratrol resulted in a resveratrol-quinone (**194**) product *via* an endoperoxide intermediate (**193**) through the action of $^1O_2$ on the resorcin ring. The second mechanism, in which singlet oxygen reacts with a double bond connecting two resveratrol rings, resulting in benzaldehyde products (**190** and **191**), involves the formation of dioxetane intermediate (**189**) (Scheme 11) [194].

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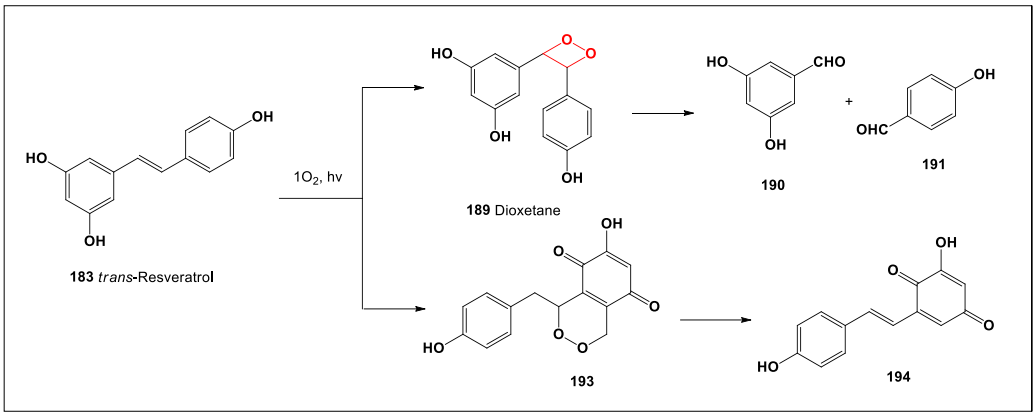

Scheme 11. The oxidation of *trans*-resveratrol and the formation of dioxetane intermediate.

5.1.10. Oxidation of Natural Unsaturated Products by Dioxygenases

Dioxygenases, a class of oxidoreductase enzymes, are found across a wide range of organisms from simple unicellular species and bacteria to complex eukaryotic organisms [194]. These enzymes are distinguished by their ability to incorporate both atoms of molecular oxygen into substrates during various metabolic pathways. Dioxygenases frequently participate in the cleavage of bonds, including aromatic rings, making them essential in biochemical transformations [195].

Dioxetanes (four-membered peroxides, labeled **195-198**) are often intermediates in these reactions (Figure 12). The oxidative cleavage of aromatic rings typically involves substrates such as catechol (1,2-dihydroxy) or quinol (1,4-dihydroxy). In the case of catechols, cleavage usually occurs between the two hydroxyl groups, resulting in products that contain aldehyde and/or carboxylic acid(s) (Figure 12). This enzymatic action underscores the critical role of dioxygenases in the degradation and transformation of aromatic compounds in nature.

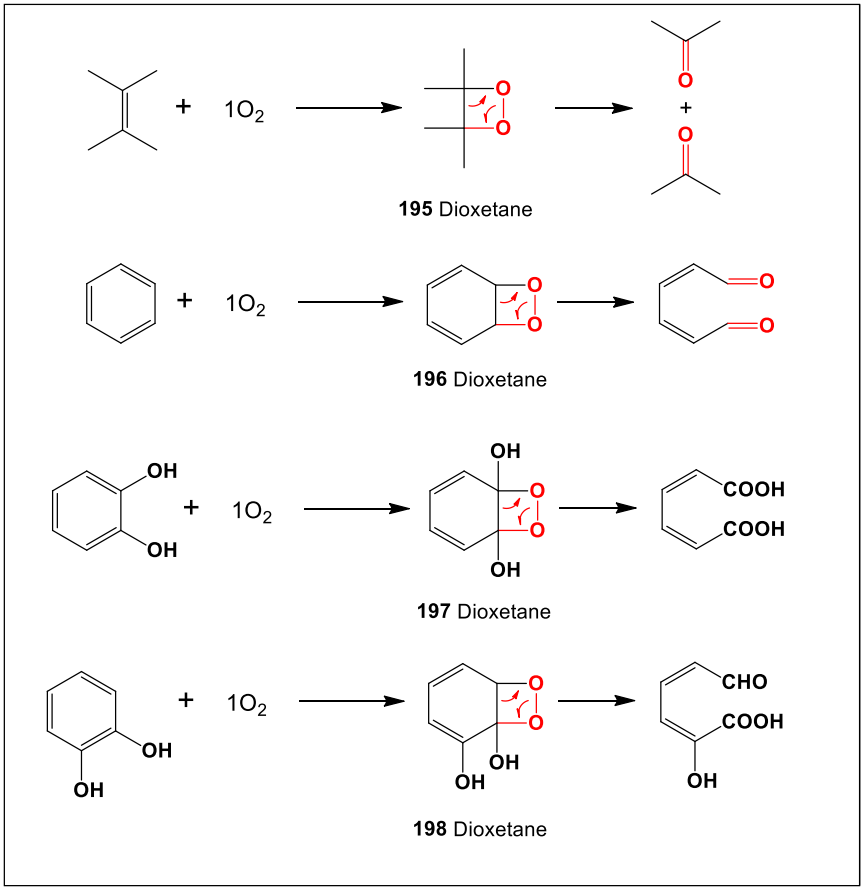

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Figure 12. Oxidation of unsaturated compounds.

5.1.11. Oxidation of Unsaturated Fatty Acids with Formation of Dioxetanes

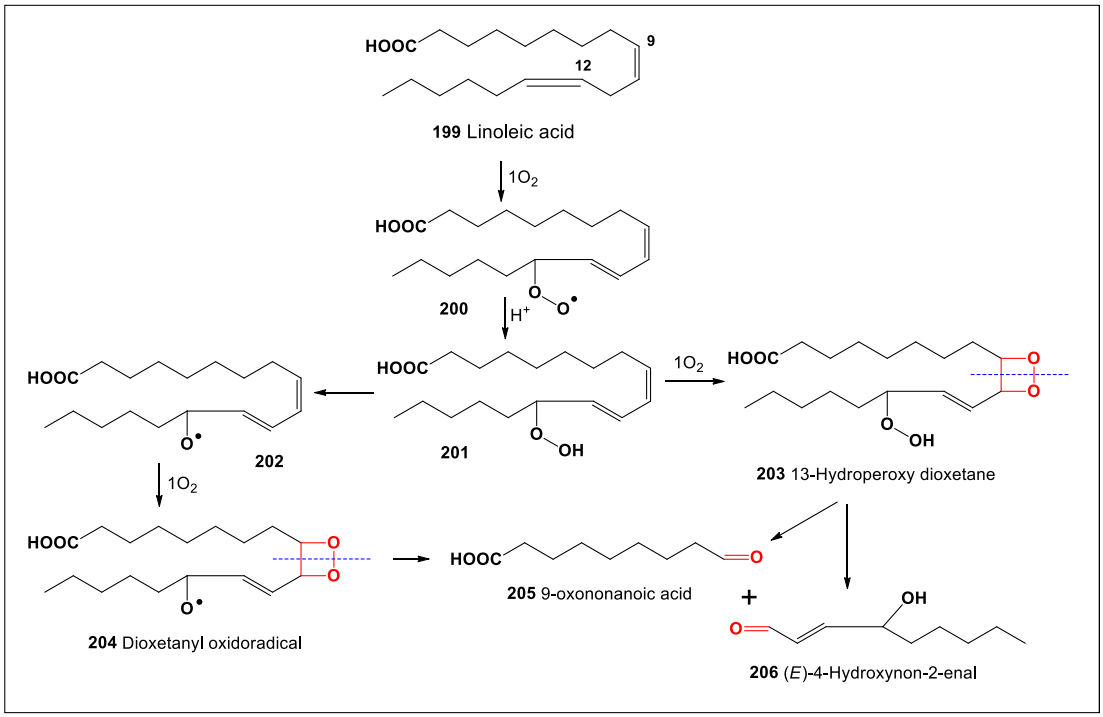
Over the past four decades, numerous mechanisms have been proposed for the oxidation of fatty acids [196–207]. These oxidative processes generally produce biologically active fatty aldehydes, such as (*E*)-4-hydroxynon-2-enal (**206**), 4-hydroxyhexenal, malonaldehyde, and 9-oxononanoic acid (**205**). The fatty aldehydes formed are highly reactive and have been shown to promote various diseases due to their cytotoxic, genotoxic, chemotactic activities, and influences on cell proliferation and gene expression [208–210].

One specific pathway of interest is the *Esterbauer Dioxetane Mechanism* [211,212], which involves the fragmentation of fatty acids and the formation of intermediate dioxetanes (**203** and **204**). A notable limitation of this mechanism, however, is that the specific process of dioxetane generation, which presumably involves singlet oxygen cyclo-additions to the C=C bond, is not fully elucidated.

Linoleic acid, an essential fatty acid with two cis-configured double bonds at positions 9 and 12 (**199**, *cis*-9,12-18:2), is primarily found in vegetable oils as triglyceride esters. It plays a crucial role in mammalian nutrition and is used in the biosynthesis of prostaglandins and cell membranes [213–217]. Linoleic acid's biological activities, studied for over 90 years, include antibacterial, antimicrobial, antiviral, and antifungal properties [218–222].

Conjugated linoleic acid (CLA) has been extensively researched for its health-promoting benefits. Recent in vivo and in vitro studies have demonstrated that CLA inhibits the development of multistage carcinogenesis at various sites. These studies have provided significant insights into CLA's mechanisms of action in cancer prevention [223–226].

The oxidation of linoleic acid has been the subject of research for over 50 years, with numerous reviews summarizing these findings [227–232]. Overall, the mechanism of linoleic acid oxidation presents an interesting and plausible scenario, as depicted in Scheme 13.



Scheme 13. The scheme shows an example of the Esterbauer mechanism for the synthesis of dioxetanes in the breakdown of unsaturated fatty acids using singlet oxygen. The scheme shows a special case of the oxidation of linoleic acid (**199**). The formation of two dioxetans (**203** and **204**) is the most interesting point in the oxidation of linoleic acid, which flows through the intermediate products (**200**, **201** and **202**) and the final products (*E*) -4-hydroxynon-2-enal (**206**) and 9-oxononanoic acid (**205**).

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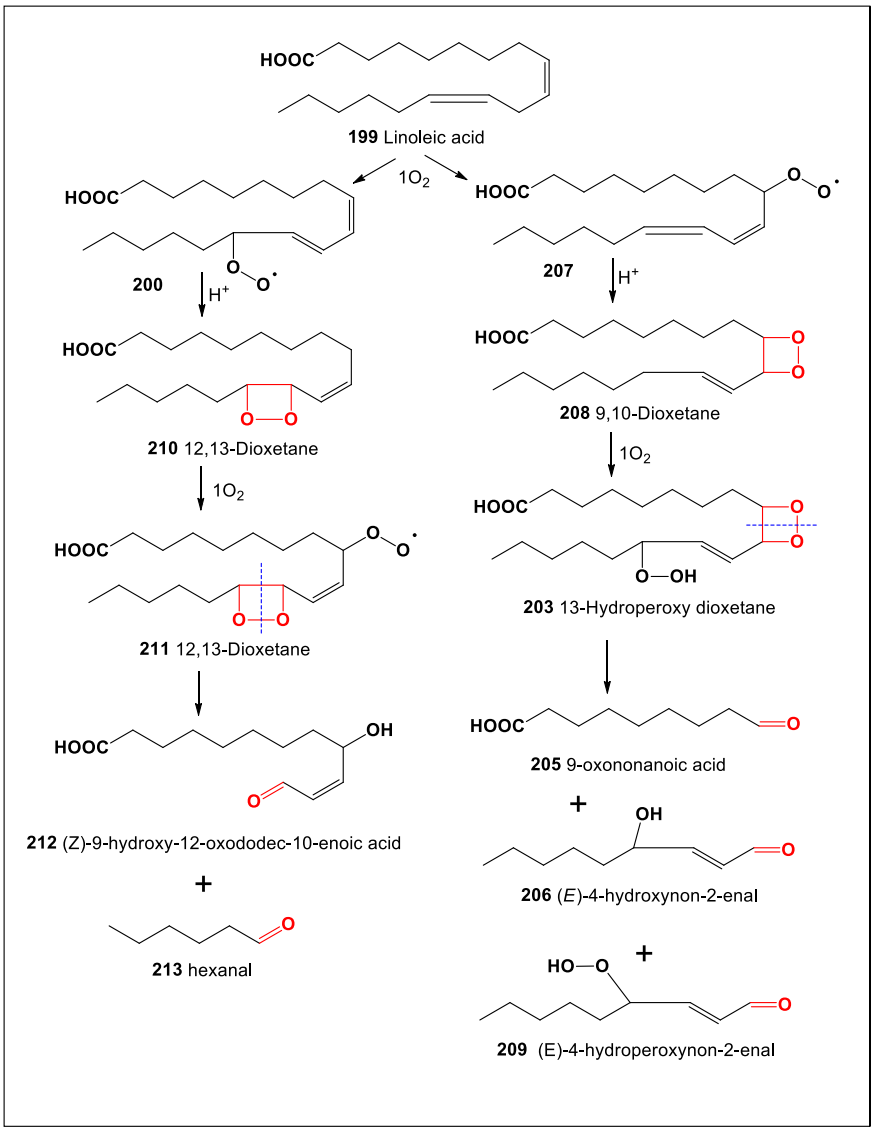
Over 25 years ago, Salomon and co-authors [233] proposed the peroxycyclization-dioxetane fragmentation mechanism. This theory suggests a competitive process between peroxycyclization leading to fragmentation products and the formation of derivatives such as (**205**, **206**, **209**, **212**, and **213**) as depicted in Scheme 14.



Scheme 14. Proposed of peroxycyclization-dioxetane fragmentation mechanism.

According to this scheme 14, linoleic acid (**199**) can undergo two distinct oxidative pathways. During the oxidation process, four dioxetanes (**203**, **208**, **210**, and **211**) are formed. The subsequent decomposition of these dioxetanes results in the production of three different aldehydes (**77**, **80**, and **84**) and two keto acids (**205** and **212**). This detailed mechanism outlines the complexity and diversity of pathways available in the oxidative degradation of linoleic acid, highlighting how various intermediates and end products can arise from the same precursor under oxidative conditions.

5.1.12. Oxidation of Arachidonic Acid with Formation of Dioxetane Unit

Arachidonic acid (**214**, or eicosatetraenoic acid, 20:4) is a 20-carbon chain polyunsaturated fatty acid featuring four double bonds at positions 5, 8, 11, and 14. It is found in various sources including animals [234–240], red [241–247] and brown algae [247–251], and marine invertebrates [249]. In mammals, arachidonic acid is primarily located in the phospholipids of cell membranes, such as phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine, and phosphatidylinositides, with high concentrations in the brain, muscles, liver, and also in fish [252–254]. Arachidonic acid

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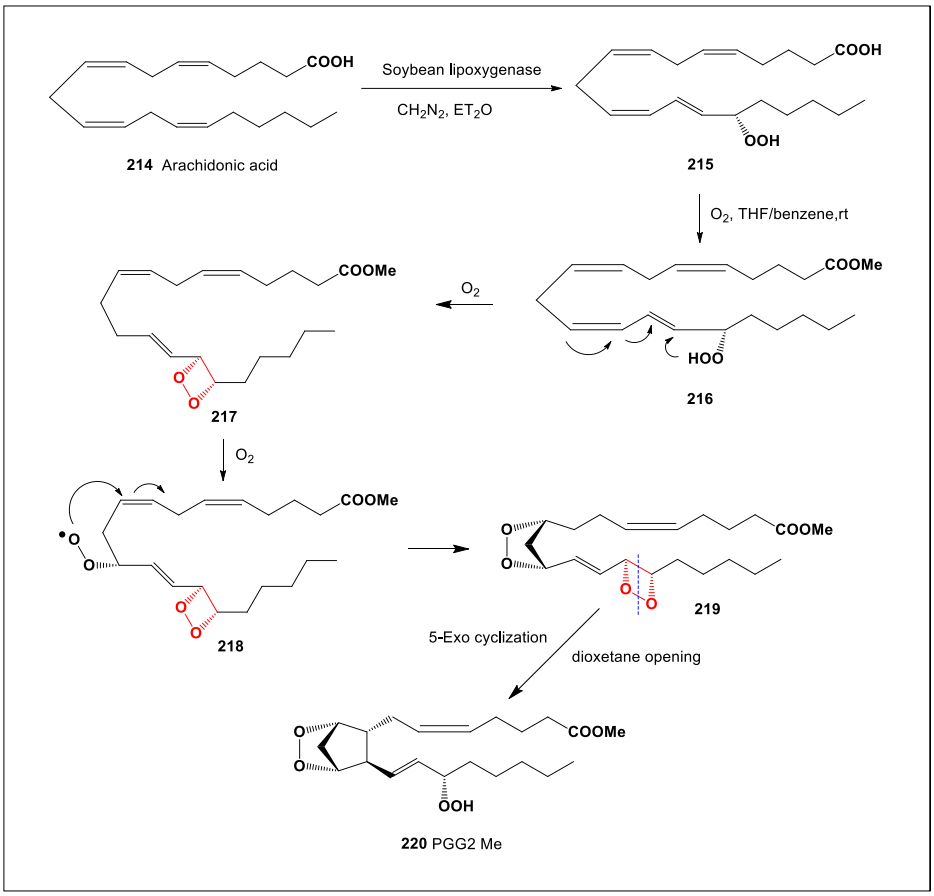
serves as a precursor for the biosynthesis of prostaglandins, isoprostanes, thromboxane, and endoperoxides [255–259].

The oxidation products derived from arachidonic acid are crucial for the normal functioning of various human organs [260–262]. When arachidonic acid is oxidized by cyclooxygenases, it leads to the production of the bicyclic endoperoxide prostaglandin G2, along with other oxidized metabolites such as thromboxane, PGF2, PGD2, PGE2, and prostacyclin [263–268]. In both in vitro and in vivo conditions, the free radical oxidation of arachidonic acid generates numerous isoprostanes, which are stereoisomers of PGF2 resulting from the reduction of bicyclic endoperoxides [269–272].

The synthesis of prostaglandin PGF2 during the oxidation of arachidonic acid involves the formation of dioxetanes (**217** - **219**), as illustrated in Scheme 15. The synthesis process begins with the 4-exocyclization of the peroxyl radical, leading to an intermediate dioxetane. This mechanism is proposed not only for the biosynthesis of prostaglandins but also for the formation of 4-hydroxynonenal, underscoring the complex pathways involved in the metabolic processing of arachidonic acid.



Scheme 15. Prostaglandin PGF2 (**220**) is synthesized during the oxidation of arachidonic acid (**214**) and the formation of dioxetanes (**217**, **218** and **219**), which are formed from hydroperochids (**216**). The last stage goes through 5-exo cyclization and dioxetane opening.

Isoprostanes, which are prostaglandin-like compounds, can be formed via the dioxetane/endoperoxide mechanism as outlined in Scheme 16 [237,273–275]. This process involves several steps and initiates with molecular oxygen attacking double bonds at specific positions in the arachidonic acid backbone, leading to the formation of various isoprostanes.

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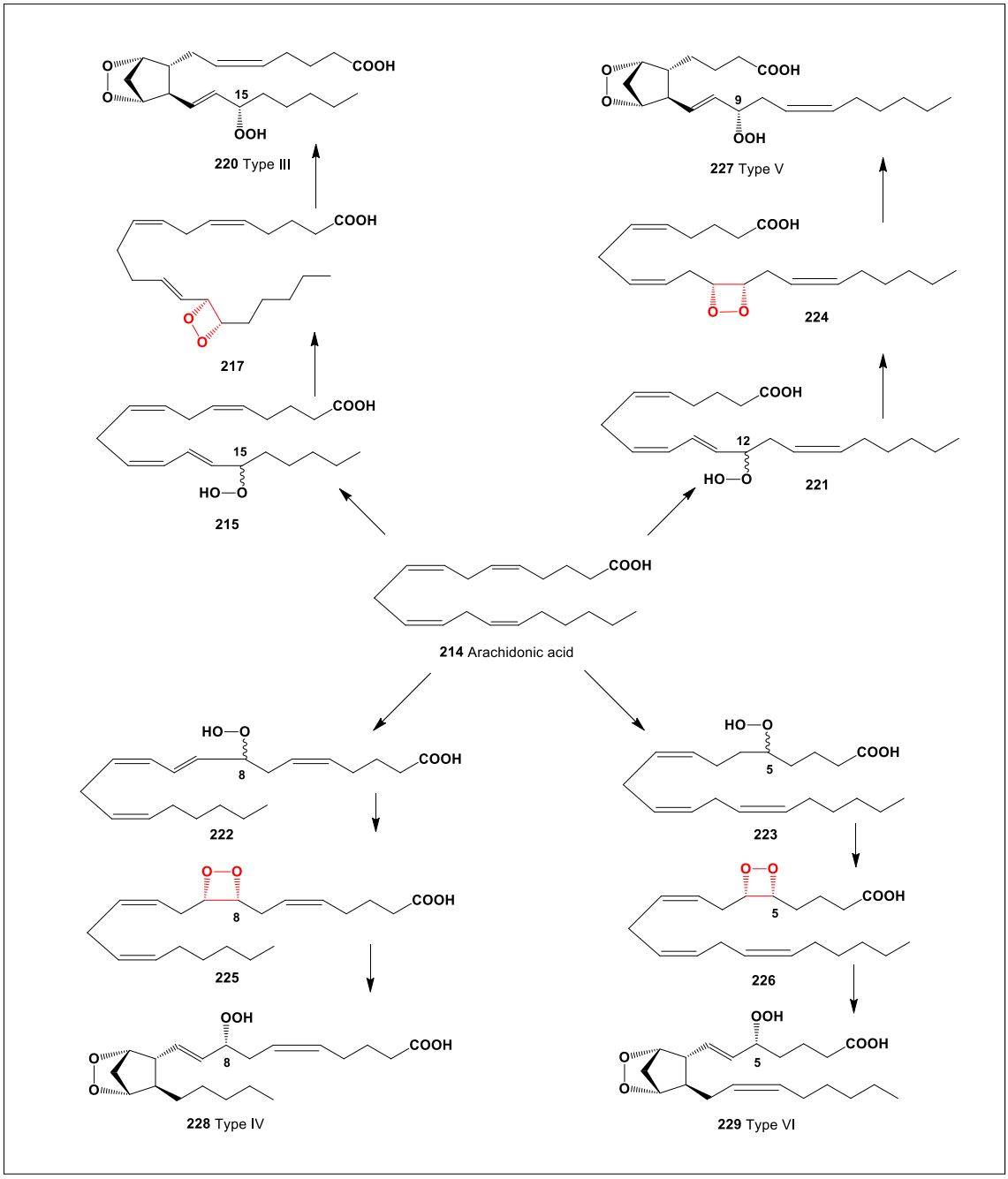

Scheme 16. Proposed dioxetane / endoperoxide mechanism for the formation of various types of isoprostanes.

Initially, oxygen molecules attack the double bonds at positions 15 (type 3, structure **215**), 12 (type 5, structure **221**), 8 (type 4, structure **222**), and 5 (type 6, structure **223**) on the arachidonic acid chain. This attack leads to the formation of corresponding hydroperoxides for each type (**215**, **221**, **222**, and **223**). These hydroperoxides then convert into hydroperoxy radicals.

These radicals undergo further transformations to form corresponding dioxetanes (**217**, **224**, **225**, and **226**). The subsequent cleavage of these dioxetanes results in the formation of different types of isoprostanes, specifically isoprostanes **220**, **227**, **228**, and **229** for each respective original position of the double bond attack. This complex mechanism highlights the intricate biochemical pathways involved in the oxidative stress response and lipid peroxidation processes in the body.

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5.1.13. Formation of Dioxetanilated Phosphatidic Acids and Triacylglycerols

Dioxetanilated phosphatidic acids and triacylglycerols are specialized compounds that involve the incorporation of a dioxetane ring into the molecular structure of phosphatidic acids and triacylglycerols, respectively. The incorporation of a dioxetane ring into phosphatidic acids and triacylglycerols creates dioxetanilated phosphatidic acids and dioxetanilated triacylglycerols. This modification is of particular interest due to the unique chemical and physical properties of dioxetanes, especially their ability to undergo chemiluminescent decomposition. Unique dioxetanilated phosphatidic acids (**230**-**232**, **234**-**237**, **239**-**241**, **243**-**245**, **247**-**249**, **122**-**125**) have been synthesized and identified as potent anticancer agents [276]. These phospholipids, including phosphatidylserine (**239**, **234**, **239**, **243**, **247**, **251**), phosphatidylinositol (**231**, **235**, **240**, **244**, **248**, **252**), and phosphatidylethanolamine (**232**, **237**, **241**, **245**, **249**, **253**) with dioxetane-containing fatty acids, have shown promising anticancer activity against L-1210 tumor cells.

Linoleic acid and its derivatives, specifically trilinolenoylglycerol dioxetanes (TAG, **233**, **238**, **242**, **246**, **250**, and **125**), were prepared through the ozonation of linoleic acid methyl ester at 80°C in acetone (Me_2CO) [277]. These trilinolenoylglycerols with dioxetane groups, as well as the linoleic acid methyl ester dioxetanes, also displayed cytotoxicity against L-1210 leukemia cells [276,277].

The breakdown of fatty acid hydroperoxides from phospholipids can be facilitated by phospholipase A2 [278], including its mitochondrial calcium-dependent isoform triggered by superoxide, or by a calcium-independent isoform. While fatty acid hydroperoxides are transient and non-radical, they are highly reactive and typically degrade into hydroxyl fatty acids through the action of glutathione peroxidase or phospholipid hydroperoxide glutathione peroxidase. They can also decompose into toxic epoxy acids and $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes [279].

The free radical-initiated autoxidation of polyunsaturated fatty acids has been implicated in numerous human diseases, such as atherosclerosis and cancer [275]. The dioxetane group-containing linoleic acid derivatives (**230**-**254**), along with other peroxides, have been extensively studied and identified, underscoring the critical role these compounds play in health and disease [271,276,277,280].

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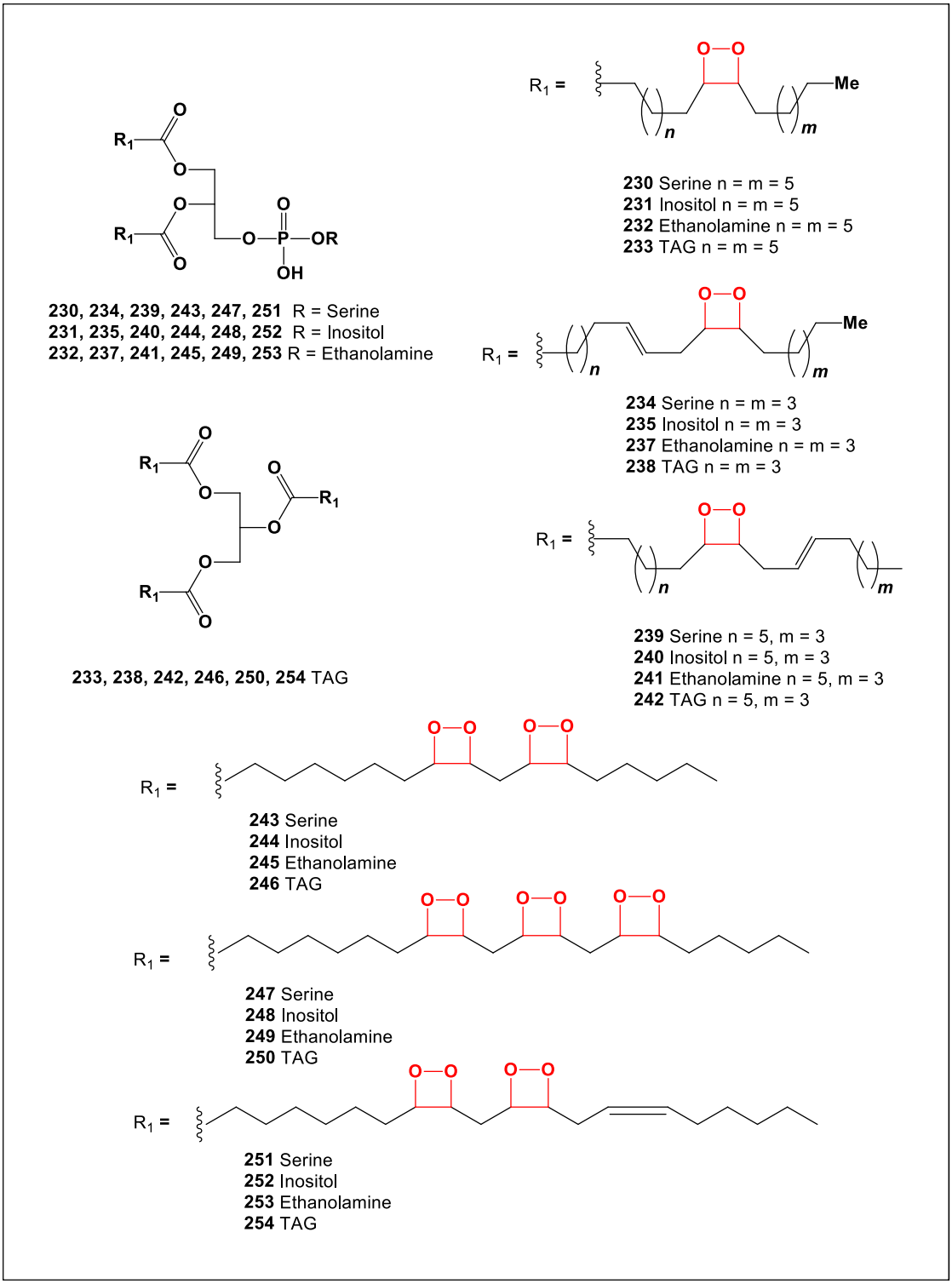

Figure 17. The unique dioxetanilated phosphatidic acids, phospholipids and TAG were detected during oxidation lipids.

5.1.14. Oxidation of Carotenoids and Similar Compounds

Polyene terpenoids, known as carotenoids (C40), are synthesized by bacteria, plants, and algae and can also be found in marine invertebrates and some protozoa. Mammals obtain carotenoids primarily through their diet, predominantly in the forms of β-carotene (provitamin A) and lycopene. To date, over 700 different carotenoids have been identified from various natural sources. Carotenoids are susceptible to oxidative cleavage of their double bonds, resulting in smaller

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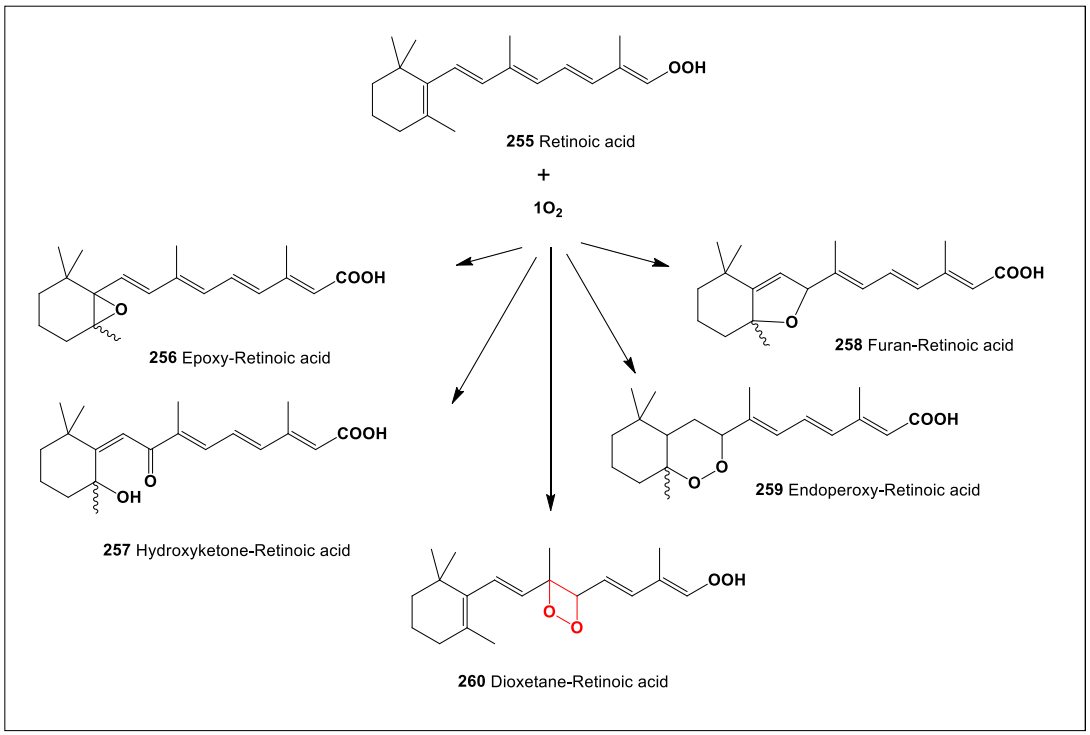
molecules known as apocarotenoids or norisoprenoids [281–283]. This splitting can be specific or nonspecific: nonspecific cleavage typically occurs via photo- or chemical oxidation, while specific cleavage is mediated by enzymes known as carotenoid cleavage dioxygenases, producing fatty aldehydes and other compounds like the phytohormones strigolactone and abscisic acid [284–286].

Currently identified are nine different products from the interaction of retinoic acid (**255**) with singlet oxygen, some of which are illustrated in Scheme 18 [287,288]. These oxidation products include an epoxide (**257**), hydroxyketone (**258**), a furan derivative (**259**, through rearrangement of **256**), endoperoxide (**259**), dioxetane (**260**), and four degradation products with molecular weights lower than that of the parent retinoic acid. Similar oxidation products have been reported for other vitamin A derivatives such as retinal [289–291], retinol [289,292,293], and retinol palmitate [289,293]. In most of these cases, oxidation is often limited to the addition of two oxygen atoms, with 5,8-endoperoxide (similar to **130**) frequently proposed as either the major or sole initial product [294].



Scheme 18. The reaction of retinoic acid with singlet oxygen main breakdown products.

Astaxanthin Oxidation Reaction

Astaxanthin is a keto-carotenoid, belonging to a larger class of chemical compounds known as terpenes. It is a naturally occurring pigment that's part of the carotenoid family, which includes beta-carotene, lutein, and canthaxanthin. Astaxanthin is most notable for its strong antioxidant properties, and it is what gives the pink and red color to many marine organisms including salmon, shrimp, lobster, and some algae [295–297]. Astaxanthin, like other carotenoids, is susceptible to oxidation, particularly when exposed to light, heat, or oxygen. The oxidation of astaxanthin involves complex chemical changes that can affect its color, antioxidant capacity, and biological activity. Understanding these oxidation processes is crucial for the stability and efficacy of astaxanthin in various applications, including dietary supplements and food products. An oxidative mechanism has been observed in the oxidation of astaxanthin and its derivatives, as detailed in Scheme 19 [295–297]. Through the application of liquid chromatography coupled with photodiode array and electrospray ionization mass spectrometry (LC/PDA ESI-MS) and electron spin resonance (ESR) spectrometry, various reaction products of astaxanthin (**261**) and its acetate with reactive oxygen species have been isolated and identified.

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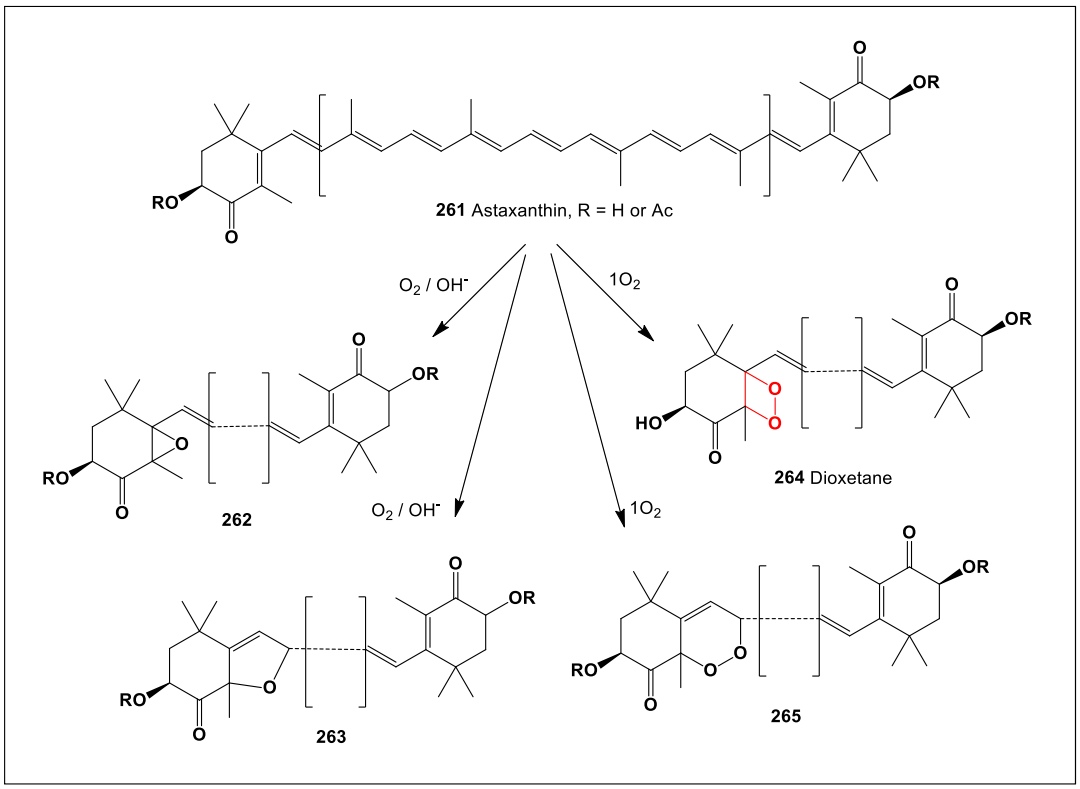

Scheme 19. Astaxanthin oxidation reaction and main oxidation products.

Astaxanthin epoxides (**262** and **263**) emerged as the major reaction products when astaxanthin interacted with superoxide anion radicals and hydroxyl radicals. In contrast, when reacting with singlet oxygen, astaxanthin predominantly formed endoperoxides, including compounds identified as a dioxetane (**264**) and an endoperoxide (**265**). These findings were consistent with the reactions involving astaxanthin acetate, indicating a reproducible pattern of oxidation products across different astaxanthin derivatives [298,299]. This research highlights the sensitivity of astaxanthin to oxidative modifications and provides insight into the chemical behavior of carotenoids under oxidative stress.

β-Carotene Oxidation Reaction

β-Carotene is a type of carotenoid that is widely recognized for its vibrant orange color. It is a provitamin A carotenoid, meaning it can be converted into vitamin A in the body. Beta-carotene is an essential nutrient that offers numerous health benefits, primarily due to its role as a precursor to vitamin A and its antioxidant properties. It is a hydrocarbon molecule, consisting of a long chain with alternating double bonds (a conjugated system). This structure is responsible for its chemical properties and its ability to act as an antioxidant. The molecule is fat-soluble, meaning it is best absorbed when consumed with dietary fats. It is commonly found in fruits and vegetables that are orange, yellow, or deep green in color. Key sources include carrots, sweet potatoes, pumpkins, spinach, kale, and cantaloupe [300–303].

The oxidative reactions of β-carotene are thoroughly studied and detailed in Scheme 20 [300]. This includes the well-documented all-trans-cis isomerization of β-carotene, extensively explored by Doering and colleagues, who evaluated the stabilization energy of semi-rigid conjugated systems with varying numbers of double bonds [301,302]. Scheme 20 illustrates that *trans*-β-carotene (**266**) can convert to 15,15'-cis-β-carotene (**267**). This cis-isomer, upon interaction with singlet oxygen, forms a dioxetane (**268**) through the cleavage at the 15,15' double bonds and also forms a 5,8-endoperoxide (**269**). Additionally, free radical oxidation of 15,15'-cis-β-carotene (**267**) leads to the formation of 5,6-epoxy-β-carotene, which can also arise from the cleavage of the 5,8-endoperoxide (**269**) [302,303].

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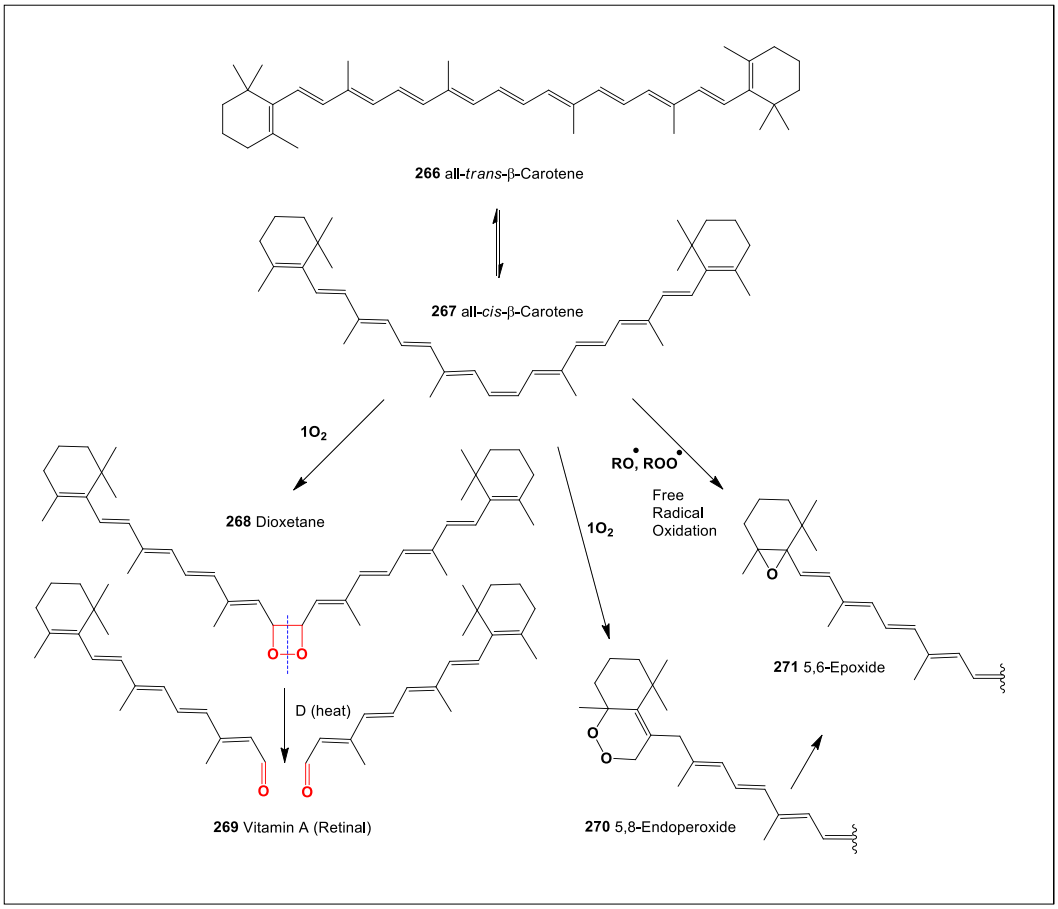

Scheme 20. β-Carotene oxidation reaction and main oxidation products.

An alternative pathway, highlighted in Scheme 21, demonstrates the formation of retinal, a precursor to vitamin A, from 15,15'-cis-β-carotene (**270**). This process involves the cleavage of 15,15'-cis-β-carotene (**271**) by carotenoid 15,15'-oxygenases, which are enzymes found in mammals, chickens, fruit flies, zebrafish, and the fungus Fusarium fujikuroi, as well as apo-carotenoid 15,15'-oxygenases found in cyanobacteria. The end product of these cleavage reactions is retinal (**272**) [304–306]. In both Schemes 20 and 21, the transformation of β-carotene to retinal is central, showcasing the importance of these pathways in vitamin A biosynthesis.

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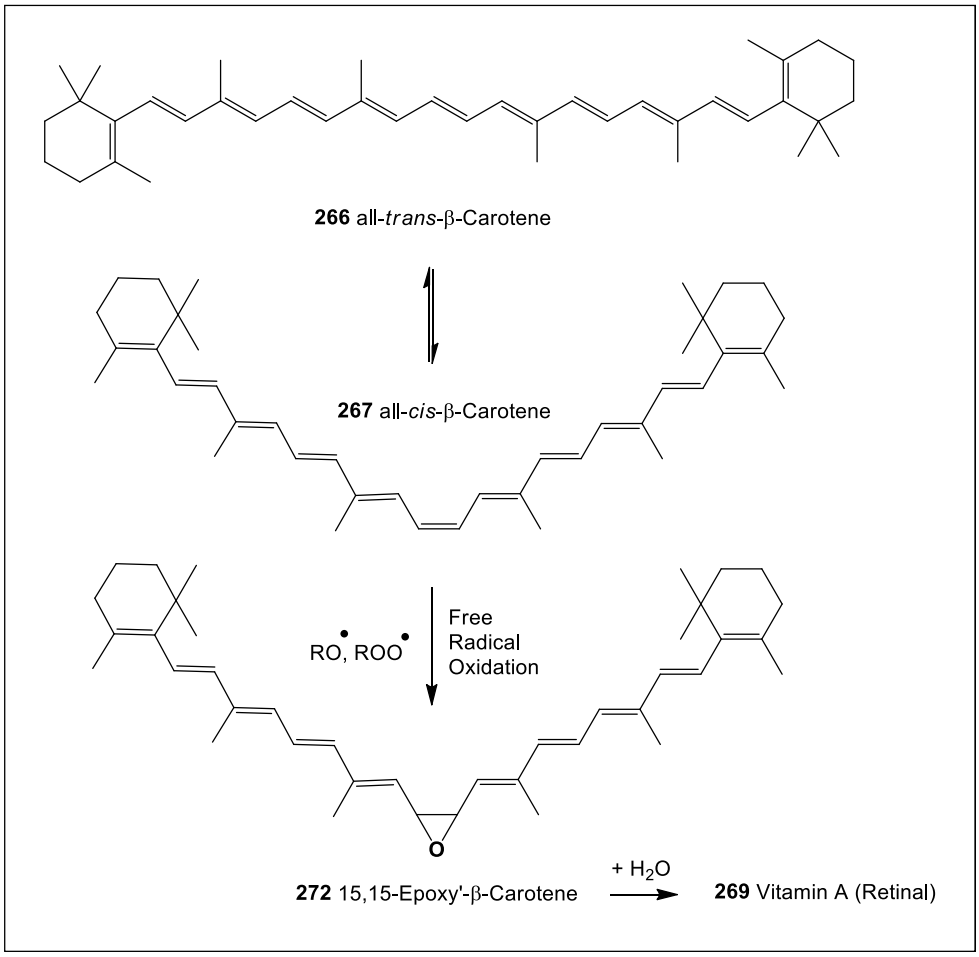

Scheme 21. β-Carotene oxidation reaction and retinal oxidation products.

5.1.15. Synthesis and Biological Activities of Chromones

Chromones are a class of organic compounds characterized by a benzo-gamma-pyrone structure. This structure features a benzene ring fused to a pyrone ring, making chromones a subset of the larger chemical family known as benzopyrones. They are of significant interest in chemistry and pharmacology due to their wide range of biological activities and potential therapeutic applications.The core structure of chromones consists of a 4-chromone backbone. The general formula is $C_9H_6O_2$, where a benzene ring is fused with a four-membered lactone (a cyclic ester) ring [307,308].

Chromones are naturally occurring compounds found in a variety of plants, including species in the Asteraceae and Fabaceae families. They are also identified in certain types of fungi and bacteria. In plants, chromones are often involved in chemical defense mechanisms against pests and diseases [309–311].

Furocoumarins, particularly psoralens, undergo photolysis when exposed to UVA radiation in solution, leading to a variety of products depending on their molecular structure and the specific reaction conditions [312,313]. This photoreaction is significant because it influences the phototherapeutic uses of psoralens in medical treatments. One of the best-known chromones in medical use is cromolyn sodium, a medication used primarily to treat asthma and allergic reactions. It works by preventing the release of substances in the body that cause inflammation, such as histamine and leukotrienes.

Viola and colleagues have specifically investigated the products of furocoumarin photolysis induced by UV irradiation, focusing on their biological impact [314]. Their study on 8-methoxypsoralen (**273**) revealed that its oxidation under UV light produces a dioxetane intermediate (**274**). In a methanol solution, this intermediate transforms into product (**275**) and further decomposes

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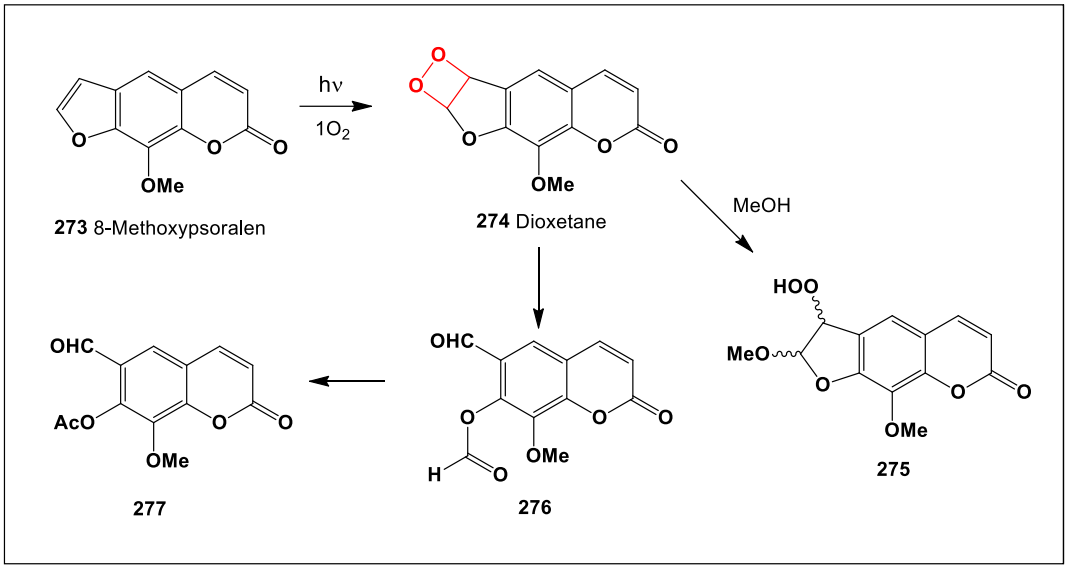
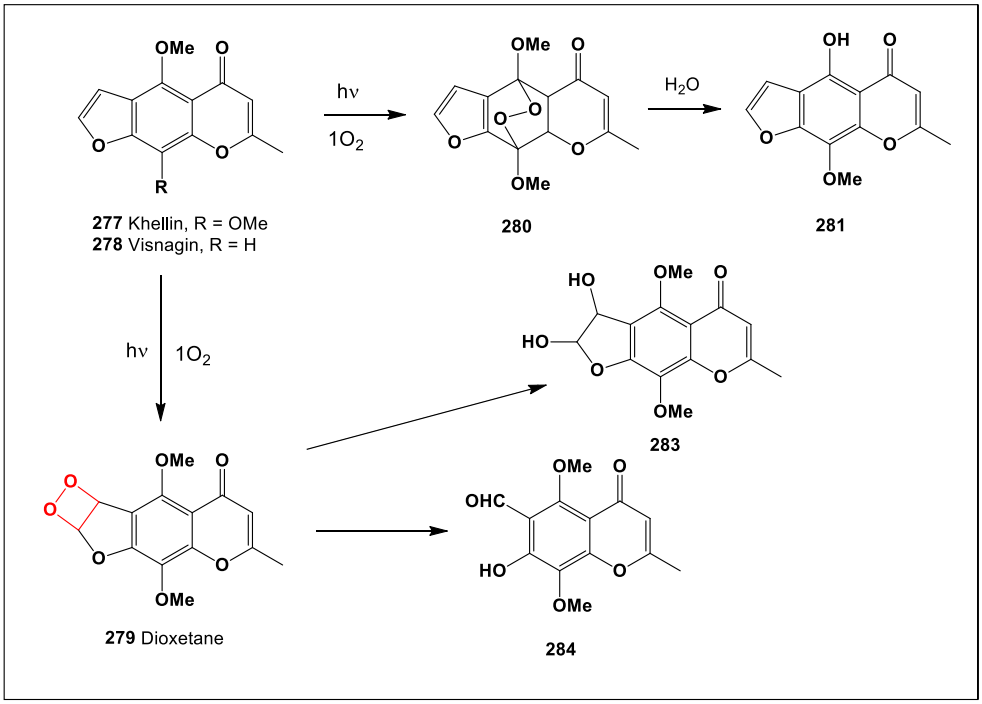
to yield two distinct molecules (**276** and **277**, as shown in Scheme 22). Importantly, the irradiated solution of 8-methoxypsoralen significantly induces erythroid differentiation in K562 cells, a human leukemia cell line, suggesting potential applications in medical research and therapy involving erythroid differentiation. This example highlights the complex chemistry and biological relevance of furocoumarins under specific environmental conditions like UV exposure.



Scheme 22. Photolysis of 8-methoxypsoralen with formation of dioxetane.

Scheme 23 shows the photolysis of furochromones and the formation of endoperoxides (**279**, dioxetane and **280**) during the decomposition of which the products of photolysis are formed (**281**-**284**) [312,313,315].



Scheme 23. Photolysis of khellin with formation of dioxetane.

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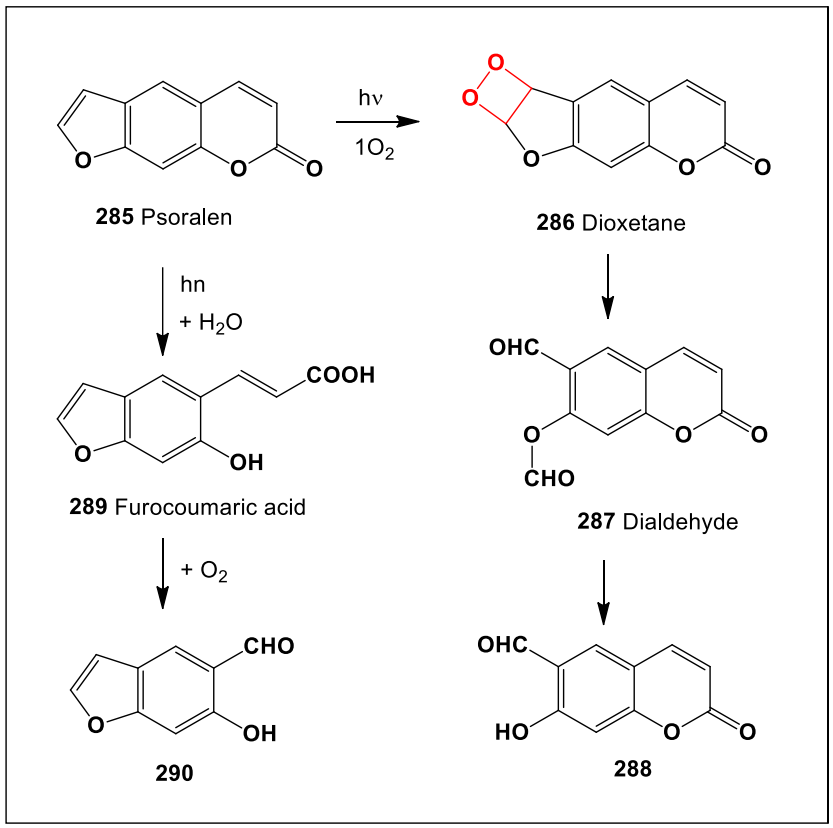
5.1.16. The Photooxidation of Psoralen

Psoralen is a naturally occurring compound that belongs to a group of substances known as furocoumarins. Furocoumarins are a class of organic chemical compounds that are derived from a fusion of a furan ring and a coumarin structure. Psoralens are particularly notable for their photosensitizing properties, which have been utilized in medicine, especially in treating skin disorders. Psoralen itself consists of a coumarin nucleus fused with a furan ring. The basic chemical formula is $C_{11}H_6O_3$. This structure allows psoralen to absorb ultraviolet (UV) light, leading to a photochemical reaction that can form cross-links with DNA, altering its structure [316–319]. Psoralen is found in several plant species, particularly those belonging to the Apiaceae family, such as celery, parsley, and figs. It is also present in the seeds of the Psoralea corylifolia plant, commonly known as Babchi, a plant used in traditional Indian and Chinese medicine [317–320]. The photooxidation of psoralen (**285**) in solutions has been extensively studied, with findings documented across several publications [316–320]. Psoralen, when photooxidized, can lead to products with split pyrone rings through two primary mechanisms:

Mechanism A: Upon absorption of a photon, an electronically excited psoralen molecule may undergo solvolysis with water, leading to the formation of furocoumaric acid (**289**). This initial reaction can be followed by further oxidation of the opened pyrone ring double bond by oxygen dissolved in the water, resulting in the formation of 5-formyl-6-hydroxybenzofuran (**290**), as illustrated in Scheme 24. This pathway emphasizes the role of water as a solvent in facilitating the breakdown of the psoralen structure into more oxidized derivatives.



Scheme 24. Supposed photochemical mechanisms which result in formation of aldehydic POP-products (6-formyl-7-hydroxycoumarin (**288**), 5-formyl-6-hydroxybenzofuran (**290**).

Mechanism B: Another pathway involves the action of singlet oxygen, which is generated during the photooxidation of psoralen in solution. This reactive oxygen species attacks the double bond of the furan ring, leading to the formation of an intermediate dioxetane (**286**). Subsequent simultaneous cleavage of the O–O and C–C bonds within the dioxetane structure results in the production of a dialdehyde (**287**). Further hydrolysis of the ether bond within this compound then yields 6-formyl-7-

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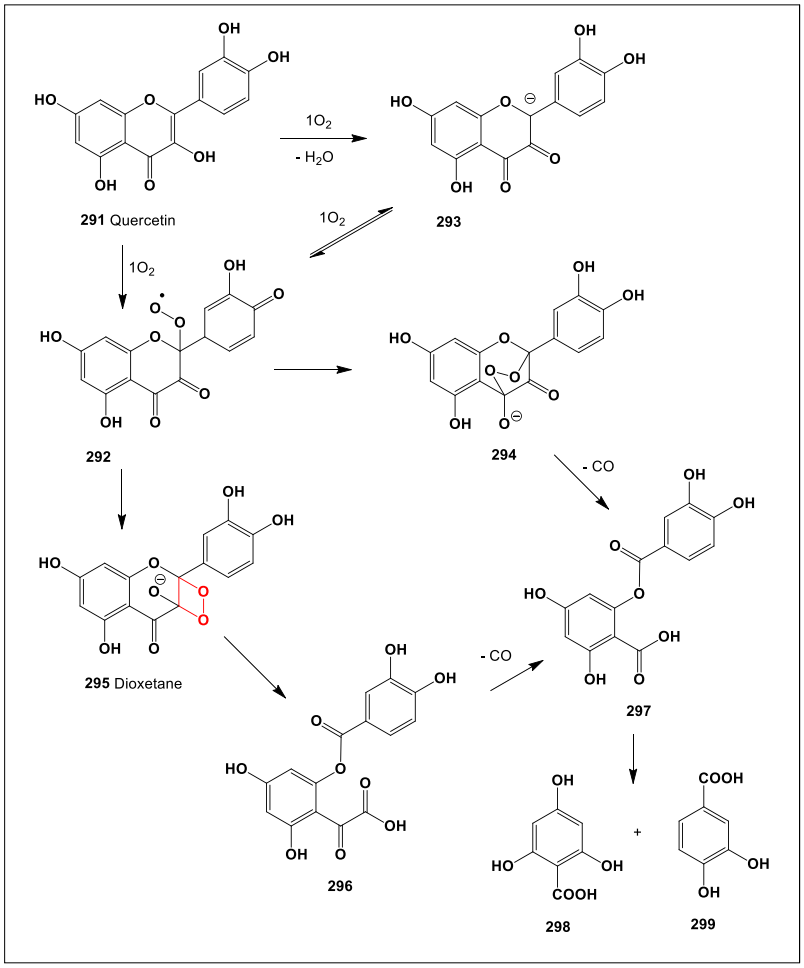
hydroxycoumarin (**288**). This mechanism highlights the role of singlet oxygen in driving the oxidative cleavage that results in significant structural changes to the psoralen molecule.

Both mechanisms demonstrate the complex chemical transformations psoralen can undergo under photooxidative conditions, leading to various products that differ significantly from the original compound. These transformations are not only of interest chemically but could also have implications in biological systems where psoralen and its derivatives are known to have significant effects.

5.1.17. Oxidation of Quercetin

Quercetin is a flavonoid, a type of naturally occurring plant pigment that is part of a larger group of compounds known as polyphenols. It is widely recognized for its potent antioxidant properties and a range of other health benefits. Quercetin is found in many fruits, vegetables, leaves, and grains; it is one of the most abundant antioxidants in the human diet and plays a significant role in fighting free radical damage. Quercetin is commonly found in onions (especially red onions), capres, apples, berries (like blueberries and blackberries), grapes, red wine, green tea, and buckwheat [325–330].

In the oxidative transformation of quercetin (**291**), an intramolecular nucleophilic attack by the peroxide function at either the C3 or C4 position can lead to the formation of unstable intermediates such as a 1,3-endoperoxide (**294**) or a 1,2-dioxetane (**295**), *via* **292** and **293**, as depicted in Scheme 25. These intermediates are inherently unstable and rapidly decompose, leading to further reaction products.



Scheme 25. Proposed mechanism for superoxide anion radical mediated oxidation of quercetin.

The 1,3-endoperoxide (**294**) undergoes ring fission and decarbonylation to directly form compound (297). In the case of the 1,2-dioxetane (**295**), it has been reported to transform into 2-(2-

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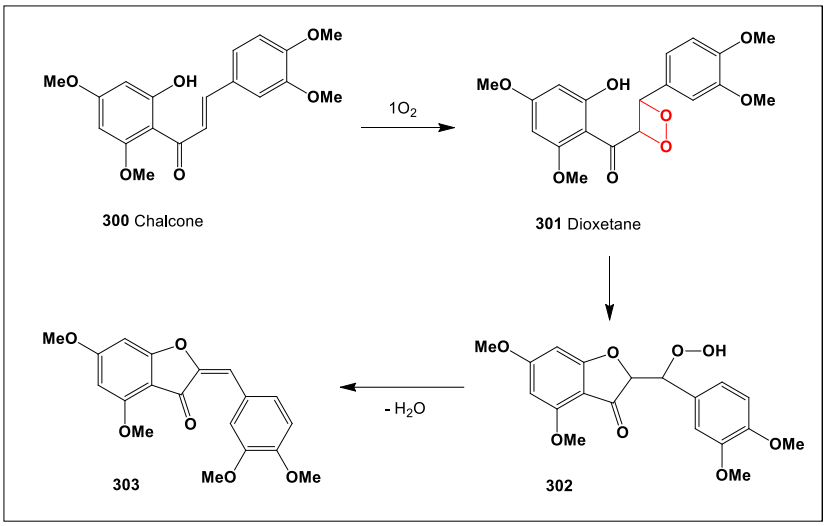
((3,4-dioxocyclohexa-1,5-dienyl)(hydroxyl)methoxy)-4,6-dihydroxy-phenyl)-2-oxoacetic acid (**296**) [325]. Further hydrolysis of compound (**297**) results in the formation of various benzoic acid derivatives. Notably, this includes 2,4,6-trihydroxybenzoic acid (**298**, also known as phloroglucinol carboxylic acid) and 3,4-dihydroxybenzoic acid (**299**, known as protocatechuic acid) [326–330]. These transformation products underline the extensive metabolic pathways of quercetin and similar polyphenols, which contribute significantly to their biological activities and potential health benefits.

5.1.18. Oxidation of Chalcones Derivatives by Peroxidase

Chalcones are aromatic ketones and enones that form the central core of a variety of important biological natural metabolites [331–333]. They are essential precursors for the biosynthesis of flavonoids in plants and exhibit a broad spectrum of biological activities. These include antioxidative, antibacterial, antihelmintic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic, and immunosuppressive effects [334,335].

The oxidative mechanism of methoxy chalcone (**300**) involves the formation of an unstable dioxetane (**301**), which upon hydration of a hydroperoxide intermediate (**302**) leads to the formation of the final product (**303**), as depicted in Scheme 26 [336].



Scheme 26. Mechanism of attack of $^1O_2$ in the chalcone derivative.

Further investigations into chalcone transformations have been conducted using cell-free extracts from garbanzo (*Cicer arietinum*) and soya (*Glycine max*). These extracts have been shown to catalyze the oxidation of 4,2',4'-trihydroxychalcone (**304**, isoliquiritigenin) into dihydroflavonol (**306**) and what is termed "hydrated aurone" (**309**) along with another compound (**310**) [337,338]. Additionally, the dioxetane derivative of 2′,4,4′-trihydroxychalcone (**305**) was previously identified as a product from peroxidase-catalyzed oxidation and detected in dye-sensitized photooxygenation of the same chalcone, indicating it plays a role in the formation of several products.

In contrast, studies utilizing purified enzymes from garbanzo or with horseradish peroxidase revealed that the main isolatable oxidation product of isoliquiritigenin (**304**) under controlled conditions was an unstable compound, later characterized as benzoxepinone-spiro-cyclohexadienone (**307**). This novel compound, isomeric with 7,4′-dihydroxyflavonol (**306**)—also found as a minor product—highlights the complex oxidation pathways of chalcones. Additionally, under specific experimental conditions, the epoxide tautomer of (**308**) was also isolated. Subsequent research uncovered the existence of compounds other than (**307**) as initial products of the enzymatic reaction, revealing various stereochemical modifications of the 4-membered cyclic peroxide (1,2-dioxetane) structure (**305**), which were isolated and characterized in Scheme 27.

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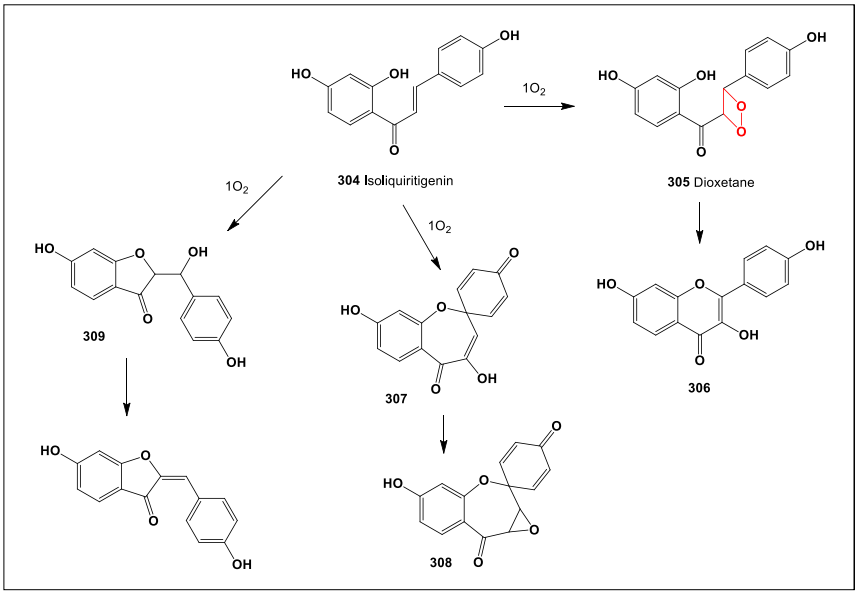

Scheme 27. Stable dioxetane (**305**) was isolated during oxidation of isoliquiritigenin.

5.1.19. Photooxidation Products of Ellagic Acid

Ellagic acid (**310**), the dilactone of hexahydroxydiphenic acid, is recognized as a potent natural phenolic antioxidant and exhibits a wide array of biological activities, notably antiproliferative, antibacterial, and anticancer properties [339–343]. It is predominantly found in various fruits and nuts, with particularly high concentrations in strawberries, raspberries, blackberries, cherries, and walnuts [344–346].

The photoreaction of ellagic acid has been extensively studied, including work by Tokutomi and co-authors [347], who observed a notable color change in the solution from colorless to yellow when ellagic acid was irradiated in aerated tetrahydrofuran (THF). This change corresponds to a new absorption band at 405 nm, indicating significant molecular transformations due to the photoreaction. The crystalline π-structures analysis suggests that the photo-oxidation products of ellagic acid are various peroxides, which result from the interaction of ellagic acid with singlet oxygen followed by subsequent stages of splitting and rearrangements.

This photoreaction of π-molecules with singlet oxygen ($^1O_2$) has been identified to proceed through either [4+2] or [2+2] cyclization reactions, as illustrated in Scheme 28. The most stable singlet oxygen adduct identified for ellagic acid was the reaction intermediate of the [2+2]-1 structure (**312**), which was found to be energetically more favorable by 61.0 and 73.6 kJ/M than the [2+2]-2 (**314**) and [4+2] (**315**) cyclization products, respectively. The high stability of the [2+2]-1 (**312**) adduct is attributed to effective conjugation which imparts relatively high stability, while the destruction of this π-conjugation in the [4+2] (**315**) cyclization process leads to a destabilized intermediate structure. Notably, the photogenerated dioxetane intermediate [2+2]-1 (**313**) is unstable and easily cleaves to form a tricycle intermediate (**314**) featuring a terminal conjugated enol carboxylic acid group. When ellagic acid is directly oxidized under UV light in THF, the reaction typically yields the final product (**312**). This detailed understanding of the photochemical behavior of ellagic acid underlines its complex reactivity and potential pathways leading to biologically active products.

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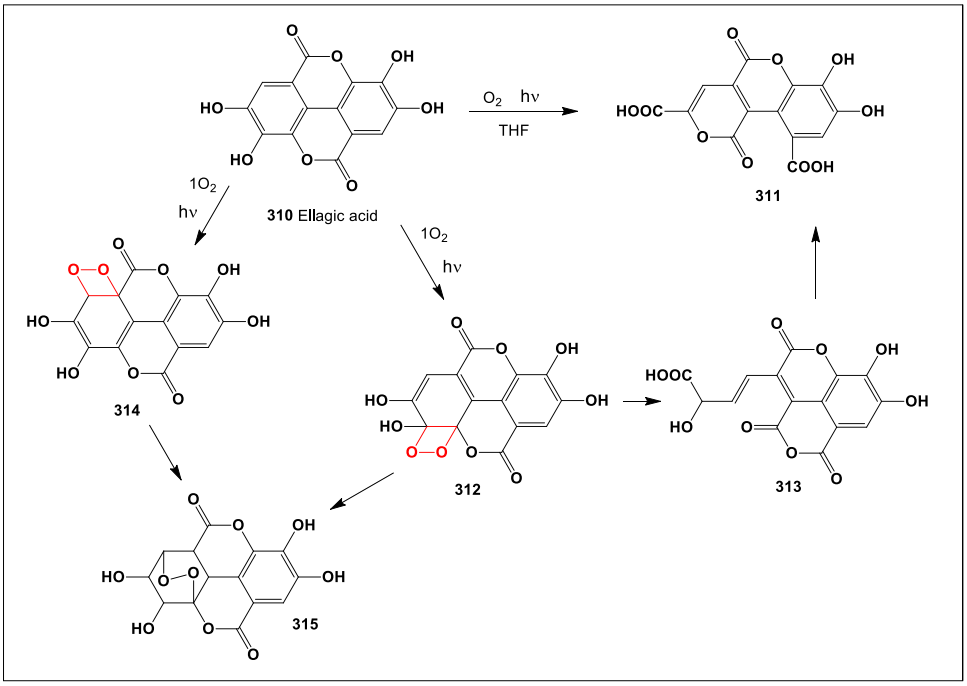

Scheme 28. Photoreaction mechanism of ellagic acid in THF, and relative stability of three possible intermediate ellagic acid/oxygen adducts, including dioxetanes (**312** and **314**).

6. Conclusion

The study of natural products containing oxetane and 1,2-dioxetane rings within the broader scope of highly oxygenated cyclobutane rings offers profound insights into the structural intricacies and biochemical properties that confer distinct biological activities. These compounds, often biosynthesized by an array of microorganisms as well as sourced from plant, fungal, and marine invertebrate extracts, demonstrate a wide range of pharmacological potentials that are essential for innovative drug development.

Our review has highlighted the substantial role that the structural features of oxetane and 1,2-dioxetane rings play in achieving molecular stability and enhancing pharmacological effectiveness. This underscores the importance of these structures in contributing to the molecular diversity seen in natural products, which in turn supports ongoing research into their applications in medicine, particularly in the development of anti-inflammatory and antiprotozoal therapies.

Furthermore, the instability and reactivity of 1,2-dioxetane rings as intermediates in oxidation reactions suggest new areas for chemical research, including the exploration of their breakdown products and their roles in biological processes. This opens up potential pathways for the synthesis of novel compounds with desirable properties.

However, synthesizing these complex ring structures in the lab remains a significant challenge. The intricate nature of their formation in natural biosynthetic pathways often presents difficulties in replicating these conditions synthetically. Addressing these challenges will require innovative approaches in synthetic chemistry, possibly integrating biotechnological methods to mimic natural processes more closely.

Moving forward, research in this field should continue to explore the mechanistic underpinnings of how these oxygenated rings influence the activity of the molecules they are part of. Understanding these mechanisms can lead to more targeted drug design and synthesis strategies that harness the full potential of these fascinating natural structures. Thus, continued interdisciplinary research is essential, bringing together organic chemists, biochemists, and pharmacologists to delve deeper into the secrets of nature's molecular arsenal.

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