Review

Peroxides with Anthelmintic, Antiprotozoal, Fungicidal and Antiviral Bioactivity: Properties, Synthesis and Reactions

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Abstract: The biological activity of organic peroxides is usually associated with the antimalarial properties of artemisinin and its derivatives. However, the analysis of published data indicates that organic peroxides exhibit a variety of biological activity, which is still being given insufficient attention. In the present review, we deal with natural, semi-synthetic and synthetic peroxides exhibiting anthelmintic, antiprotozoal, fungicidal, antiviral and other activities that have not been described in detail earlier. The review is mainly concerned with the development of methods for the synthesis of biologically active natural peroxides, as well as its isolation from natural sources and the modification of natural peroxides. In addition, much attention is paid to the substantially cheaper biologically active synthetic peroxides. The present review summarizes 217 publications mainly from 2000 onwards.

Keywords: peroxides; anthelmintic; antiprotozoal; fungicidal; antiviral

1. Introduction

Peroxides are widely used in various areas of life [1–3]. Traditional and the most developed field is the application of peroxides as radical initiators in industrial processes in the manufacture of polymers from unsaturated monomers: styrenes, butadienes, chlorovinyls, ethylenes, acrylates, as well as in crosslinking of silicone rubbers, acrylonitrile-butadiene rubbers, fluororubbers, polyethylene, ethylene-propylene copolymer, etc. [4–9].

Hydrogen peroxide and peracids are active components of antiseptics and disinfectants [10–14]. Synthesis and mechanism of antiseptic action of hydrogen peroxide and the most common peracids (performic, peracetic, etc.) are elucidated in a few studies [15–17] and are not considered in this review. Antimalarial properties of peroxides are currently intensively studied. Artemisinin (Qinghaosu) (I), a natural peroxide possessing high antimalarial activity, was isolated in 1971 from leaves of annual wormwood (Artemisia annua) in the context of the scientific program “Project 523”, initiated by Chinese government in 1967 [18–20]. The Nobel Prize in Physiology or Medicine 2015 was awarded to Chinese pharmaceutical chemist Tu Youyou “for her discoveries concerning a novel therapy against Malaria” [21–23]. Considering the development of antibiotic resistance of Plasmodium to some traditional drugs, such as quinine, chloroquine, and mefloquine, and other anti-parasitic ones, pharmaceuticals based on artemisinin and its semi-synthetic derivatives—dihydroartemisinin (2), artemether (3) and artesunate (4) (Figure 1)—are currently the most effective drugs against malaria [24–30].
The modern trend in medicinal chemistry of peroxides is the search of effective anticancer drugs. The natural and synthetic peroxides exhibiting a cytotoxic effect on cancer cells already include hundreds of compounds [31–34]. Peroxides possessing antimalarial and cytotoxic activity are the subject of numerous studies [35–42], and are not considered in this review.

In the present review, we deal with natural, semi-synthetic and synthetic peroxides exhibiting anthelmintic, antiprotozoal, fungicidal, antiviral and other activities that have not been described in detail earlier. The review is mainly concerned with the synthesis of such peroxides, as well as its isolation from natural sources and covers literature published between 1912 and 2017.

There are several review articles, where the various kinds of the biological activity of artemisinin [43–45] and artemether [46,47]; the problems of trematode infection therapy with artemisinin, its derivatives and several synthetic ozonides [48]; and antiviral activity of artemisinin and artesunate [49] are discussed. Advances in the development of anti-parasitic peroxides are described in the review of Muraleedharan [50]. A number of reviews are devoted to promising anthelmintic peroxides [51]. Some natural antiviral peroxides are mentioned in the review [52]. However, none of these articles pay sufficient attention to the methods of peroxide synthesis.

Since peroxides with a related structure have different types of activity, the systematization of this review is based on the structure of the peroxide fragment (Figure 2). The first sections consider the preparation of cyclic peroxides in order of increasing cycle and the number of oxygen atoms in it, while the last section deals with peroxides of acyclic structure. The following abbreviations are used in describing the biological activity of peroxides: minimum inhibitory concentration (MIC), minimum lethal concentration (MLC), half maximal inhibitory concentration (IC50), concentration of inhibiting 90% of activity (IC90), half maximal effective concentration (EC50), and median effective dose (ED50) [53,54].

2. 1,2-Dioxolanes

A number of cyclic peroxides, many of which exhibit antibacterial, antifungal and anti-cancer activity, were isolated from the marine organisms, in particular from the sponges Plakinidae [55]. Plakinic acid A (5) effectively inhibits the growth of fungi *Saccharomyces cerevisiae* and *Penicillium atroumenetum* [56];
plakinic acid F (7) and epi-plakinic acid F (8) exhibit moderate antifungal activity against *Candida albicans* and *Aspergillus fumigatus* [57]; 1,2-dioxolane acids 9 and 10 inhibit the growth of *Candida albicans* [58]; and plakortide E (11) show good activity against *Trypanosoma brucei* (Scheme 1) [59].

**Scheme 1.** Antifungal and anti-parasitic activity of 1,2-dioxolanes, isolated from the sponges *Plakinidae*.

The first synthesis of diastereomeric saturated analogs of plakinic acids A, C and D 17 was reported in 1996 by Bloodworth and colleagues [60]. Peroxides 17 were prepared in four steps from ketones 12. In the first step, ketone 12 was condensed with ethyl 3-methylbut-2-enoate with formation of cyclic lactones 13 hydrolysis, which led to acids 14. Peroxymercuration of esters 15 followed by reduction with sodium borohydride afforded 1,2-dioxolanes 16 saponification, which resulted in 1,2-dioxolanes 17 with carboxylic group (Scheme 2).

The synthesis of diastereomeric 1,2-dioxolanes 22 from alkynes was described [61]. Carboalumination of alkyne 18, followed by treatment of the intermediate alkenylaluminum with acetaldehyde, resulted in an allylic alcohol that was oxidized to enone 19. Conjugate addition of H\textsubscript{2}O\textsubscript{2} to 19 in the presence of LiOH followed by acid-catalyzed esterification of diastereomeric dioxinole by 2-methoxyethanol provided alkoxydioxolane 20. Substitution of the methoxymethoxy group in 20 by the action of silyl keteneacetal ethyl thioacetal in the presence of TiCl\textsubscript{4} led to thioether 21 as a 1:1 mixture of two diastereomers. The hardly-separable cis- and trans-diastereomeric peroxides 22 were obtained as a result of hydrolysis with high yield (Scheme 3).
was used for the synthesis of stereomeric acids 39.

The desirable plakinic acids hydrolyzed with formation of plakortide E (11) reported [63,64]. The key intermediate 2-ethyl-1,1,2-cyclopropanetricarboxylate (34) was transformed into alkoxydioxolane 35, and after that into thioester 36. The ring opening with TMSOTf provided easily separable 3-hydroxy hydroperoxides 33 and epi-33; 33 was converted into peroxy ketone 34 by subsequent silylation and oxidation. The ketone 34 was transformed into alkoydioxolane 35, and a similar strategy was used for the synthesis of stereomic acids 39 from 3-hydroxy hydroperoxide epi-33.

As a result of following transformation epoxy alcohol 29a was prepared, which was oxidized into aldehyde; subsequent addition of methylmagnesium bromide resulted in isomeric secondary epoxy alcohols 30a and 30b (Scheme 5). After transformation of minor 30b into 30a, the latter was reduced to diol 31. The treatment of diol 31 with stoichiometric quantity of TsCl and excess of t-BuOK led to oxetane 32. The ring opening with TMSOTf provided easily separable 3-hydroxy hydroperoxides 33 and epi-33; 33 was converted into peroxy ketone 34 by subsequent silylation and oxidation. The ketone 34 was transformed into alkoydioxolane 35, and after that into thioester 36.

The desirable plakinic acids 38 were prepared by hydrolysis of methyl esters 37. A similar strategy was used for the synthesis of stereomic acids 39 from 3-hydroxy hydroperoxide epi-33.

A total synthesis of plakortide E (11) based on radical oxygenation of vinylcyclopropanes was reported [63,64]. The key intermediate 2-ethyl-1,1,2-cyclopropanetricarboxylate (42) prepared from methylene malonate (40) and α-chloro ester 41 was transformed into lactone 43. The treatment of the latter with oxygen, Ph2Se2 and AIBN furnished spiro 1,2-dioxolane 44, followed by lactone ring opening of 44 to form diol 45. The precursor of the plakortide E 49 was synthesized from the iodo-derivative of 1,2-dioxolane 47 and the halogen derivative 48 by Negishi reaction. Desilylation of alcohol 49, subsequent oxidation and Horner-Wadsworth-Emmons olefination provided ester 51 which was hydrolyzed with formation of plakortide E (11) (Scheme 6) [63].
Scheme 4. Construction of asymmetric plakinic acids side chain.

Scheme 5. Asymmetric synthesis of plakinic acids 38 and 39.
A similar strategy based on the radical oxygenation of vinyl cyclopropanes was used for the synthesis of epiplakinic acid F (8) [65]. The vinyl cyclopropane 53 obtained from trans-1,2-cyclopropanedicarboxylate 52, was then converted to 1,2-dioxolane 55 (Scheme 7). After separation of the diastereomeric mixture isomer 55b was used for further transformations.

Enantiomerically pure 55b was reduced by LiBH₄ to alcohol 56, which was transformed to vinylether 57 by subsequent PCC oxidation and Wittig olefination. Oxidation of 57 to methyl ester 58, reductive ozonolysis of 58, and Wittig olefination gave predominantly the Z-isomer of vinyl iodide 59. The Negishi coupling of 59 with the halogen derivative led to the desired product 60. Desilylation of 60 followed by reduction of 61 resulted in saturated alcohol 62. The oxidation of 62 led to an aldehyde, the Wittig olefination of which provided the precursor 63 as a mixture of isomers. The product of photoinduced isomerization of this mixture was the trans-isomer 64. The target epiplakinic acid F (8) was obtained by alkaline hydrolysis of ester 64 (Scheme 8).
Scheme 7. Construction of 1,2-dioxolane fragment for epiplakinic acid F (8).

Scheme 8. Asymmetric synthesis of epiplakinic acid F (8).
The method of the preparation of andavadoic acid (76), a natural compound isolated from the sponges of *Plaxortis aff simplex*, based on the Isayama-Mukaiyama reaction and subsequent cyclization was known [66]. The starting substrate was epichlorohydrin (65), which was converted to epoxide 66 by a subsequent the organomagnesium compound addition and cyclization with the help of alkaline. The regioselective opening of the epoxide cycle of 66 by the lithium salt of ethyl propiolate in the presence of BF₃ resulted in the secondary alcohol 67 in almost quantitative yield. Alcohol 67 was converted into lactone 68 by reaction with Me₂CuLi, followed by acidification. Oxidation of lactone 68 to 69, subsequent ring opening, oxidation of hydroxyl to the carbonyl group, and methylation resulted in epoxy ketone 70, which was then converted to epoxy alkene 71. Isayama-Mukaiyama peroxidation, the base-catalyzed cyclization of peroxide 72, leading to a mixture of diastereomeric 1,2-dioxolanes 73/73a followed by separation and thioacylation resulted in a peroxy thioester 74 which was converted into andavadoic acid (76) by subsequent reduction and hydrolysis of ester 75 (Scheme 9).

![Scheme 9. Synthesis of andavadoic acid (76).](image)

The symbiont of beetle of the southern pine (*Dendroctonus frontalis*), actinomycetous bacterium produces mycangimycin peroxide (77) with pronounced fungicidal activity (Scheme 10) [67]. Mycangimycin effectively inhibits growth of *Candida albicans* wild type, *C. albicans* ATCC10231, amphotericin-resistant strain *C. albicans* ATCC 200955, *Saccharomyces cerevisiae* and *Ophiostoma minus* [68].
Two saturated analogs of mycangimycin were synthesized from alkene 78 and ester 79 (Scheme 11) [69]. The Kulinkovich reaction of 78 with 79 resulted in cyclopropane 80, which formed 1,2-dioxolane 81 by a cobalt-catalyzed cleavage in the presence of oxygen. TfOH-catalyzed reduction of the alcohol 81 by silane led to 3,5-disubstituted 1,2-dioxolane 82. The result of desilylation and oxidation of the obtained alcohol 83 is the first saturated analog of mycangimycin, acid 84, which can be converted into ester 85.

The diterpenoid peroxide 86, which has a weak fungicidal activity against C. albicans, was isolated from the liverwort Jungermannia atrobrunnea (Scheme 12) [70]. Dinardokanshone B (87), sesquiterpene peroxide, isolated from the roots and rhizomes of Nardostachys chinensis Batal. (Valerianaceae) showed significant enhancement effects on SERT activity (Scheme 12) [71].
Synthetic 1,2-dioxolanes 88 showed high in vitro activity against helminths *Schistosoma mansoni* (Scheme 13) [72].

5,5-Dimethyl 1,2-dioxolanes 88a were prepared by peroxidation of mesityl oxide (89) in the basic medium, followed by alkylation of the free hydroxyl group of 3-hydroxy-1,2-dioxolanes 90 (Scheme 14) [73]. Synthesis of cyclohexyl derivatives 88b started from oxidation of alcohol 92 to an unsaturated ketone 93, followed by Isayama-Mukaiyama peroxidation with formation of 1,2-dioxolane 94. Further protection of hydroxyl group resulted in derivatives 88b (Scheme 14) [73].

The series of tricyclic monoperoxides 97 with 1,2-dioxolane moiety showed a high anti-schistosomal activity. The maximum activity was observed for compound 97a, which revealed high worm burden reductions by 82.8% in *S. mansoni* mouse model (Scheme 15) [74]. Peroxides 97 can be obtained from β, δ-triketones 96 and hydrogen peroxide with use of either sulfuric acid [75], or boron trifluoride [76] as catalyst and co-solvent (Scheme 15).
were observed with a single oral dose of 1000 mg/kg OZ78 (98)

Antichistosomal activity of OZ78 (98) against S. mansoni cultures was found that the spiroadamantane fragment and the carboxyl group in the OZ78 (98) are necessary for activity against F. hepatica and adult triclabendazole-resistant F. hepatica and adult

The ozonides OZ78 (98) and OZ288 (99) showed low toxicity and high efficiency against helminth cultures Schistosoma mansoni and S. japonicum harboured in mice and hamsters with a single oral dose of 200 mg/kg [82,83]. Antichistosomal activity of OZ78 (98) against S. japonicum was confirmed in

Scheme 15. Synthesis of tricyclic monoperoxides 97 with high anti-schistosomal activity.

3. 1,2,4-Trioxolanes (Ozonides)

Various tetrasubstituted 1,2,4-trioxolanes (ozonides) have become the breakthrough in the field of biologically active synthetic peroxides. Nowadays ozonides are considered as the most promising candidates in the treatment of helminth diseases (Scheme 16). The 100% worm burden reductions were observed with a single oral dose of 1000 mg/kg OZ78 (98) in Echinostoma caproni-infected mice. A single dose of 100 mg/kg OZ78 (98) resulted in 100% worm burden reductions against juvenile and adult Fasciola hepatica-mouse model [77]. Single oral doses of 100 mg/kg OZ78 (98) is efficient against adult triclabendazole-resistant F. hepatica-infected rats [78]. Later, the efficacy of 1,2,4-trioxolane OZ78 (98) against an experimental infection with Fasciola hepatica in sheep was confirmed [79,80]. It was found that the spiroadamantane fragment and the carboxyl group in the OZ78 (98) are necessary for activity against F. hepatica [81].

Scheme 16. Tetrasubstituted synthetic ozonides with the highest anthelmintic activity.
experiments in mice and rabbits [84]. Later, the promising ozonide OZ418 (100) with high activity against both helminths of S. mansoni and S. haematobium was discovered [85].

Synthesis of tetrasubstituted unsymmetrical ozonides was discovered by Griesbaum and colleagues in 1995 (Scheme 17, top) [86,87]. Later this method was used for the diastereoselective synthesis of tetrasubstituted ozonides 103. Peroxides 103 were prepared by ozonolysis of 2-adamantanone O-methyl oxime (101) in the presence of substituted cyclohexanones 102 (Scheme 17, bottom) [88,89]. 1,2,4-Trioxolane ring in compounds 103 is resistant to the action of a wide range of reagents, which allows to proceed a variety of modifications of the cyclohexane substitut [88].

![Griesbaum co-ozonolysis](image)

Scheme 17. Synthesis of tetrasubstituted unsymmetrical ozonides.

### 4. 1,2-Dioxanes

A number of compounds containing 1,2-dioxane fragment isolated from the Plakinidae sponges showed high fungicidal and anti-trypanosomal activity. Plakinic acid B (104) exhibited good fungicidal activity against Saccharomyces cerevisiae and Penicillium atroneum (Scheme 18) [56]. The acid 105 in vitro inhibits the growth of fungi Aspergillus fumigatus with IC50 = 5.6 μg/mL [58]. Compounds 106 and 107 were weakly active against Staphylococcus aureus [90]. 11,12-Didehydro-13-oxo-plakortide Q (108) was more active against Trypanosoma brucei [91]. Plakortide F acid (PFA) (109) showed high activity against Candida albicans, Cryptococcus neoformans and A. fumigatus [21]. Plakortides 110 and 111 also demonstrated high activity against a number of fungi [92]. Significant fungicidal activity of mixture of peroxyketals acids isolated from sea sponges was also reported [93].

A series of peroxysterpenes was isolated from the sponges Diacarnus bismarckensis, the most active of which, (+)-muqubilone B (112) and sigmosceptrellin B (113) showed high activity against Trypanosoma brucei [94]. (+)-Muqubilone B (112) and muqubilin (114) (isolated from the sponges Prianos [95]) were in vitro effective against herpes virus (HSV-1), muqubilin (114) and (−)-sigmosceptrellin B (113) exhibited in vitro activity against Toxoplasma gondii (Scheme 19) [96]. Muqubilin (114) possesses herbicidal activity against tobacco Nicotiana tabacum [97], as well as epimuqubilin (115) showed NO inhibitory activity [98]. Myperoxide B (116) displays high antiviral activity against vesicular stomatitis virus and herpes simplex virus type-1 (HCV-I) [99].

Several synthetic approaches to plakonic acids and their derivatives containing 1,2-dioxane ring were described. Natural 6-epiplakortolide E (127) was firstly synthesized from available 1-bromo-10-phenyldecane (117) in 10 steps by Diels–Alder reaction with singlet oxygen followed by iodolactonization (Scheme 20) [100]. In the first stage, the addition of the organonitrogen reagent to the unsaturated ketone resulted in enone 118, which was converted to a tertiary alcohol 119. Hydroboration of 119 led to diol 120, protection of hydroxyl group of which provide silyl ether 121. Diels-Alder reaction of diene 122 prepared by dehydration of 121 with singlet oxygen resulted in diastereomeric 1,2-dioxanes 123a and 123b. Deprotected diastereomer 124 was oxidized to acid 125, subsequent iodolactonization of this acid gave bicycle 126. Desirable 6-epiplakortolide E (127) was formed as result of radical reduction of iodine-containing bicycle 126. It was noted that related plakortolide G (128) is active against the protozoa Toxoplasma gondii [101].
Scheme 18. 1,2-Dioxanes isolated from the sponges *Plakinidae*; their antifungal, antibacterial and anti-trypanosomal activity is also shown.

| Compound | Activity | IC50/EC50 | Reference |
|----------|----------|-----------|-----------|
| muqubilone B (112) | *T. brucei* | 2 µg/mL | | | | | |
| | herpes simplex type 1 (HSV-1) | ED50 = 30 µg/mL | | | | | |
| muqubilin (114) | herpes simplex type 1 (HSV-1) | ED50 = 7.5 µg/mL | | | | | |
| | Toxoplasma gondii | >90% inhibition at 0.1 µM | | | | | |
| | Nicotiana tabacum | 66% inhibition at 6.4 µM | | | | | |
| epimuqubilin A (115) | NO inhibitory activity | IC50 = 7.4 µM | | | | | |

Scheme 19. Muqubilin (114) and related natural peroxides.
Asymmetric synthesis of alkoxy-1,2-dioxane 136 related to plakortolides was realized in 8 steps from carbonyl compounds 129 and 130 (Scheme 21) [102]. Enantioselective aldol reaction in first step resulted in aldol 131 which was converted into protected diol 132 in three steps. Diastereomeric 1,2-dioxanes 133a and 133b were formed by selective ozonolysis of double bond of 132. Hydrozirconation of 133a with following treatment by iodine led to the formation of vinyl iodide 134, followed cross-coupling of one resulted in 1,2-dioxane 135. Deprotection of 135 provided desirable peroxide 136.

Natural endoperoxide 9,10-dihydroplakortin (148) and diastereomer 149 were synthesized through Evans’ chiral auxiliary chemistry (Scheme 22) [103]. Alkylation of oxazolidinone 137 and subsequent reduction of 138 led to alcohol 139, which was transformed into acrylic ester 140 (predominantly in E-configuration) by oxidation and Horner-Wadsworth-Emmons olefination. The ester 140 was reduced into corresponding alcohol, which was converted into iodide 141, alkylation of oxazolidinone by which resulted in derivative 142. The cleavage and olefination of 142 provided the ester 143. The reduction of 143 furnished alcohol 144 followed by Sharpless epoxidation and protection of primary hydroxy-group with formation of epoxide 145. Isayama-Mukaiyama peroxidation of epoxide 145 afforded mixture of diastereomeric 1,2-dioxanes 146 and 147 which were independently transformed into 9,10-dihydroplakortin (148) and 6-epi-dihydroplakortin (149).
Scheme 21. Asymmetric synthesis of 1,2-dioxane 136.

Scheme 22. Synthesis of natural endoperoxide 9,10-dihydroplakortin (148) and its diastereomer 149.
In the synthesis of diastereomeric plakortolides 160 and 161, the key steps are construction of protected diol 155 from protected 2-methyl glycidol 154 and vinyl bromide 152, diastereoselective Mukaiyama addition of aldehyde 156 with formation of ester 157 and hydroperoxidation of alkene 158 with subsequent cyclization of 159 (Scheme 23) [104].

![Scheme 23. Synthesis of diastereomeric plakortolides 160 and 161.](image)

Synthesis of analogs of plakinic acids, 1,2-dioxanes 166 with a pronounced anti-trypanosomal activity was proposed from E-hexen-4-ol (162) (Scheme 24) [105]. Swern oxidation of alcohol 162 and subsequent Wittig-olefination led to ester 163. The reaction of unsaturated scaffold 163 with singlet oxygen and following cyclization provided 1,2-dioxane 164, which was hydrolyzed to acid 165. Derivatives 166 were prepared from ester 164 by consistent ozonolysis, reductive cleavage and Wittig reaction. Compounds 166 exhibited high activity against *T. brucei brucei*.

![Scheme 24. Synthesis of 1,2-dioxanes 166 with high anti-trypanosomal activity.](image)

Diastereomeric cyclic peroxides 171, one of which is the methyl ester of the mycaperoxide B (116), were prepared from protected hydroxyperoxide 167 (Scheme 25) [106]. In the first step,
peroxide 167 was oxidized to aldehyde 168, which was converted into unsaturated ester 169 by Wittig reaction. Hydroperoxide 170 synthesized by deprotection of 169 was cyclized into 1,2-dioxane 171 and oxolane 172 by the action of triethylamine.

![Scheme 25. Synthesis of diastereomeric peroxides 171.]

5. 1,2-Dioxenes

The plant *Chenopodium ambrosioides* is used for the production of essential chenopodium oil, which has been used as an anthelmintic agent for a long time [107,108]. The first isolation of the most active component—ascaridole (174), from the *Chenopodium ambrosioides* and the determination of its structure was dated to the beginning of the last century [109–112]. In the 1950s, the ascaridole (174) was completely characterized (Scheme 26) [113,114].

The first laboratory synthesis of ascaridole (174) was performed via photo-induced addition of singlet oxygen to terpene 173 by Schenck in 1944 (Scheme 26) [115]. Later, this reaction was realized in an industrial scale, because ascaridole was of great importance as an anthelmintic agent [116]. The method for the preparation of ascaridole using singlet oxygen generated in situ from sodium molybdate and hydrogen peroxide is known [117].

![Scheme 26. Ascaridole synthesis (174).]

It was shown that ascaridole (174) at concentration 4 mM almost completely inhibits the growth of fungi *Sclerotium rolfsii* [118]. Presently, the side effects of ascaridole on the gastrointestinal tract have been described, and ascaridole is currently not used [119].

In 1990, Gunasekera with colleagues isolated 1,2-dioxenes 175 and 176 from sea sponge *Plakortis angulospiculatus* (Scheme 27) [120]. It was shown that these natural peroxides exhibit antifungal activity against *Candida albicans* (MIC = 1.6 µg/mL).
The total synthesis of stereoisomeric 1,2-dioxenes 185 was performed in 18 steps with a total yield of 2.8% (Scheme 28) [121]. The treatment of hydroxy ester 177 with tert-butylidiphenylsilyl chloride followed by Dibal reduction and replacement of hydroxyl by iodine provided iodide 178, which was converted into aldehyde 179 by subsequent asymmetric alkylation, reduction of prepared amide into alcohol and Swern oxidation. Alkene 180 was synthesized from sulfone derivative of aldehyde 179 to obtain mainly trans-isomer. Deprotection of 180, nucleophilic substitution of hydroxyl by iodine, subsequent substitution of iodine by cyano-group and reduction of cyano-group led to aldehyde 181 which was then transformed into alkyne 182 by PPh3/CBr4 treatment and HBr elimination. The synthesis of enone 183 was performed by addition of ethylcuprate followed by propionyl chloride to alkyne 182. The diene 184 was prepared predominantly in trans-conformation by condensation of enone 183 with lithium salt of propargyl phosphonate with subsequent hydroboration. Ene reaction of diene 184 with singlet oxygen and methylation by diazomethane resulted in 1,2-dioxenes 185a and 185b.  

Scheme 28. Synthesis of stereoisomeric 1,2-dioxenes 185.
The cyclic peroxide shuangkangsu (186) isolated from the buds of Lonicera japonica showed high antiviral activity against respiratory syncytial virus on the cell lines and influenza virus in the chicken embryos (Scheme 29) [122].

![Scheme 29. Peroxide shuangkangsu (186) isolated from Lonicera japonica.](image)

Ergosterol peroxide (187) isolated from different natural sources including the fungi Pycnoporus cinnabarinus demonstrated moderate antiviral activity against Herpes simplex and Polio virus [123], and also antifungal activity against pathogenic fungi Microsporum canis, Trichophyton rubrum and Epidermophyton floccosum (Scheme 30) [124]. Ergosterol peroxide acetate 189 was synthesized with quantitative yield by photo-oxidation of ergosterol acetate 188 in the presence of trityl tetrafluoroborate (Scheme 30) [125].

![Scheme 30. Ergosterol peroxide (187), exhibited antiviral and antifungal activities and synthesis of its derivatives.](image)

Analogs of ergosterol peroxide without multiple bonds in the side chain 194 were obtained by eosin Y catalyzed photooxidation of steroids 191 followed by hydrolysis and oxidation. Peroxides 194 showed significant ability to inhibit the growth of hepatitis B virus (Scheme 31) [126].
Scheme 31. Synthesis of 194, antiviral analogs of ergosterol peroxide.

A number of 1,2-dioxenes 196 with simpler structure were synthesized from 1,3-butadienes 195. Epoxidation of 196 resulted in 1,2-dioxanes 197 and 198. These peroxides exhibit moderate antifungal activity against Candida family (Scheme 32) [127]. Later, a wide range of derivatives 196, 197 and 198 that inhibits Candida albicans was synthesized [128]. 1,2-Dioxene 196a showed high antifungal activity against C. tropicalis and C. krusei [129].

Scheme 32. Synthesis of 1,2-dioxenes 196 and their further modification.

6. 1,2,4-Trioxanes

Among the class of 1,2,4-trioxane, various aspects of the biological activity of artemisinin and its derivatives are studied most extensively. Synthetic strategies for peroxide ring construction in artemisinin were discussed in detail [130]. Compared with other methods the synthesis of artemisinin (1) based on dihydroartemisinic acid seems most preferable [131], as it can satisfy the demand for cheaper production of sufficient quantities of artemisinin. The key stages of the transformation of dihydroartemisinic acid into artemisinin (1) are described in the fundamental studies of Richard K. Haynes [132].
In addition to antimalarial and cytotoxic activity, artemisinin (1) has activity against trypanosomatides Leishmania major [133], Leishmania donovani [134], Trypanosoma brucei rhodesiense and Trypanosoma cruzi [135], as well as parasite Toxoplasma gondii (Scheme 33) [136]. Artemisinin showed a synergistic or additive effect in combination with itraconazole against fungi Aspergillus fumigatus [137], as well as moderate activity against Fusarium oxysporum [138]. Antiviral activity of artemisinin (1) was reported in few studies; inhibition of the human immunodeficiency virus (HIV-1) at 60% in peripheral blood mononuclear cells [139], the hepatitis C virus (HCV) in human liver cells [140], the bovine viral diarrhea virus (BVDV) [141], as well as hepatitis B virus [142] was shown.

![Scheme 33. Artemisinin and various types of its bioactivity.](image)

Artemisinin derivative, artemether (3), is actively used to treat schistosomiasis, a parasitic disease caused by flat worms of the genus Schistosomiasis [46,47]. A double-blind field trial in the Poyang Lake region (southern China) confirmed that artemether (3) significantly reduces the frequency and intensity of S. japonicum infection and does not cause side effects [143]. Despite the proven pathogenic effects on the reproductive system of Fasciola hepatica [144,145], artemether (3) had practically no effect in the treatment of fascioliasis in humans [146]. Artemether activity against Leishmania major [133], and Toxoplasma gondii [136,147] was detected; it was shown also that artemether is effective in the treatment of experimental rheumatoid arthritis [148,149]. Artemether (3) is obtained by reduction of artemisinin (1) to dihydroartemisinin (2) followed by methylation (Scheme 34) [150,151]. This synthesis can be performed in flow reactor [152,153].

![Scheme 34. Synthesis of artemether (3) and its bioactivity.](image)

Artesunate (4), artemisinin derivative containing free carboxylic group showed high efficiency against S. japonicum [154,155], and also in the therapy of fascioliasis caused by Fasciola hepatica or Fasciola gigantica (Scheme 35) [156]. It was determined that artesunate (4) causes changes in the reproductive system of Fasciola hepatica [144]. Antiviral activity of artesunate is displayed...
against the hepatitis B virus [157] and the hepatitis C virus [158], the herpes virus (HHV) type 4 and type 6 [159,160], human cytomegalovirus (HCMV) [161–163], including therapy-resistant mutants of human cytomegalovirus [164]. Artesunate (4) is prepared by reaction of dihydroartemisinin (2) with succinic anhydride in basic conditions (Scheme 35) [152].

Scheme 35. Synthesis of artemisin (4) and its bioactivity.

The library of 10-deoxo-derivatives of artemisinin 205 showed high activity against parasites Leishmania donovani (Scheme 36). Synthesis of 205 was performed from artemisitene 199 by radical addition of compound 200 followed by reduction of carbonyl group in 202. Dehydration and deprotection resulted in phenol 204, which formed a series of compounds 205 by reaction with derivatives of carboxylic and sulfonic acids [165].

Scheme 36. Antileishmaniasis derivatives of artemisinin 205.
Attempts to synthesize the antitoxoplasma derivatives of artemisinin have been made [147,166], however their in vitro activity did not exceed the activity of artemether (3).

Among artemisinin derivatives tested for fungicidal activity, anhydrodihydroartemisinin (206) and arteether (207) were most active against *Cryptococcus neoformans* [167], their activity surpassed the one of amphotericin B. Both derivatives were obtained [168,169] in one step from dihydroartemisinin (2) (Scheme 37). Later it was found that arteether (207) [170] exhibits moderate antiviral activity against human immunodeficiency virus and anhydrodihydroartemisinin (206) [171] is high active against hepatitis B virus.

![Scheme 37](image)

**Scheme 37.** Antifungal and antiviral artemisinin derivatives— anhydrodihydroartemisinin (206) and arteether (207).

High antiviral activity against human immunodeficiency virus [170] was demonstrated by butyl-derivative of artemisinin 209, prepared via photo-oxidation of alcohol 208 with 12% yield (Scheme 38) [172].

![Scheme 38](image)

**Scheme 38.** Antiviral artemisinin derivative 209.

Combination of dihydroartemisinin (2) with antiviral drug azidothymidine (210) resulted in compound 211 exhibited both antimalarial as antiviral activity (Scheme 39) [173].

A new trend in the medical chemistry of artemisinin derivatives is the synthesis of dimers and trimers. Among a series of artemisinin dimers obtained by condensation of dihydroartemisinin (2) with binucleophile, compounds 212 and 213 showed the highest activity against fungi *Cryptococcus neoformans* and parasites *Leishmania donovani*, respectively (Scheme 40) [174].
Scheme 39. Synthesis of hybrid 211 based on dihydroartemisinin 2 and azidothymidine 210.

Scheme 40. Synthesis of artemisinin dimers 212 and 213 with antifungal and anti-parasitic activity.

Dimers and trimers of artemisinin showed antiviral activity were summarized in Table 1.

Table 1. Dimers and trimers of artemisinin showed antiviral activity.

| No. | Dimer/Trimer Structure | Synthesis | Bioactivity          |
|-----|------------------------|-----------|----------------------|
| 1   | ART ART                | from artemisinin (1) 3 steps, 67% [175] | HCMV EC50 = 0.15 µM [176,177] |
|     | 214                    |           |                      |
| 2   | ART ART                | from 214 3 steps, 42% [176] | HCMV EC50 = 0.06 µM [176] |
|     | 215                    |           |                      |
Table 1. Cont.

| No. | Dimer/Trimer Structure | Synthesis | Bioactivity |
|-----|------------------------|-----------|-------------|
| 3   | ![Dimer/Trimer Structure](image) | from 214 1 step, 96% [179] | HCMV EC_{50} = 0.04 µM [180–182] |
| 4   | ![Dimer/Trimer Structure](image) | from 214 1 step, 25% [183] | HCMV EC_{50} = 44 nM [183] |
| 5   | ![Dimer/Trimer Structure](image) | from threo-214 and artesunate (4), 1 step, quantitative yield [184] | HCMV EC_{50} = 0.04 µM [184,185] |
| 6   | ![Dimer/Trimer Structure](image) | from threo-214 1 step, 67% [186] | HCMV EC_{50} = 0.11 µM [186] |
| 7   | ![Dimer/Trimer Structure](image) | not reported | HCV EC_{50} = 3.2 µM [187] |

Synthetic 1,2,4-trioxanes 223 obtained by condensation of hydroxy-hydroperoxide 221 with adamantane followed by hydrolysis of ester 222 showed high in vivo activity against helminths *Fasciola hepatica* in rats (Scheme 41) [188].
7. **1,2,4,5-Tetraoxanes**

Synthetic 1,2,4,5-tetraoxane 226 [189], prepared by condensation of bis-hydroperoxide 224 with adamantananone followed by hydrolysis ester 225, showed high in vivo activity against helminths *Fasciola hepatica* in rats (Scheme 42) [188].

![Scheme 42. Synthesis of 1,2,4,5-tetraoxane 226 with high anthelmintic activity.](image)

Based on related 1,2,4,5-tetraoxanes 227, hybrids 229 with a fragment of an anthelmintic drug praziquantel 228 were obtained (Scheme 43) [190]. Synthesized hybrids 229 exhibit high activity against *Schistosoma japonicum* and *Schistosoma mansoni* [191].

![Scheme 43. Synthesis of hybrids 229 as anti-schistosomal agents.](image)
Bridged 1,2,4,5-tetraoxanes 231 demonstrated high in vitro and in vivo activity against trematodes Schistosoma mansoni [74,192]. The best result was shown for adamantane-substituted tetraoxane 231a which caused 75% worm burden reductions in S. mansoni harbored in mice following the administration of peroxide at single oral dose of 400 mg/kg. Peroxides 231 were synthesized from β-diketones 230 and H₂O₂ with good yields by the action of various acids: sulfuric [193], phosphomolybdic and phosphotungstic acids [194] (Scheme 44).

![Scheme 44. Synthesis of bridged 1,2,4,5-tetraoxanes 231.](image)

8. Acyclic Peroxides

Many acyclic peroxides are applied as oxidants in organic synthesis [195,196]. Benzoyl peroxide (234) is actively used in the food industry as a flour bleach [197–199], and in pharmaceuticals. The first mention about the medical using of benzoyl peroxide dates back to 1929, where Lyon and Reynolds reported effective treatment of burns, wounds and varicose veins by benzoyl peroxide [200]. Subsequently it was found that it has antibacterial [201,202], anti-inflammatory [203], cheratolic [204], and wound-healing [205,206] effects. Presently, benzoyl peroxide is widely used agent for acne treatment because of its efficacy and good tolerability in patients [207,208]. Benzoyl peroxide is a good alternative to monotherapy with antibiotics for the treatment of Acne vulgaris caused antibiotic-resistant strains, for example Propionibacterium acnes [209,210].

Benzoyl peroxide is commercially produced by the reaction of benzoyl chloride (232), sodium hydroxide and hydrogen peroxide (Scheme 45, top) [211,212]. Benzoyl peroxide can also be prepared from benzoic anhydride (233) by the action of an alkali metal perborate in an aqueous solution (Scheme 45, bottom) [213].

![Scheme 45. Benzoyl peroxide (234) production.](image)

Oxanthromicin (235) isolated from bacteria Actinomadura sp. [214] showed high antifungal activity against Trichophyton mentagrophytes, Micosporum canis, M. gypseum, Epidermophyton floccosum, Candida albicans, and Aspergillus niger (Scheme 46) [215].
Hydroperoxide 236 obtained by biotransformation of Artemisia cina metabolites exhibits high in vitro activity against protozoa Trypanosoma brucei (Scheme 47) [216].

Scheme 46. Antifungal natural acyclic peroxide, oxanthromicin (235).

Scheme 47. Anti-trypanosomal hydroperoxide 236.

Four monoterpene hydroperoxides 237a–d were isolated from aerial parts of Chenopodium ambrosioides. Minimum lethal concentration (MLC) in vitro of its peroxides against Trypanosoma cruzi was 1.2, 1.6, 3.1, and 0.8 µM, respectively (Scheme 48) [107].

Scheme 48. Hydroperoxides 237a–d isolated from Chenopodium ambrosioides.

A geminal bis-hydroperoxides 239 synthesized from cyclic ketones 238 show pronounced in vitro antimicrobial and antifungal activity against B. cereus, E. coli, P. aeruginosa, S. aureus, C. albicans, and A. niger comparable with the effect of some antiseptics and, to a lesser extent, antibiotics (Scheme 49) [217].
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