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A Review on Antimalarial 1,2,4-Trioxane Derivatives

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ABSTRACT

Malaria in recent years becomes a major health hitch globally due to the surfacing of multidrug-resistant strains of *Plasmodium falciparum* parasite. In recent times, artemisinin (ART)-based drugs and combination therapies become the drugs of preference for the treatment and prophylaxis of resistant *P. falciparum* malaria. Endoperoxide compounds natural, semi-synthetic or synthetic signifying a massive number of antimalarial agents which possess a wide structural miscellany with needed antimalarial effectiveness against resistant *P. falciparum* malaria. The 1,2,4-trioxane ring system deficient the lactone ring which constitutes the most significant endoperoxide structural scaffold which is believed to be the key pharmacophoric moiety and is principally responsible for the pharmacodynamic potential of endoperoxide-based antimalarials. This becomes the main reason for the research related to endoperoxide particularly 1,2,4-trioxane-, 1,2,4-trioxolane- and 1,2,4,5-tetraoxane-based scaffolds gaining the noteworthy interest in recent years for developing antimalarial drugs against resistant malaria. In this paper, a comprehensive endeavour has been made to review the development of different endoperoxide antimalarial agents and structural diversity of endoperoxide molecules derived from 1,2,4-trioxane- based structural scaffolds.

Keywords: Endoperoxide; 1,2,4-trioxane; pharmacophores; artemisinin; antimalarial.

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1. INTRODUCTION

Malaria is the broadest tropical parasitic disease [1] and is brought about by contaminations of protozoan parasites of the variety Plasmodium and transmitted to man by specific types of tainted female Anopheles mosquito [2]. It is one of humankind's oldest and the broadest irresistible diseases on the planet today, exists in more than 100 nations including the United States. Around 40% of the entire population is in danger of malaria contamination, and every year, in excess of 250 million individuals experience malarial ailment and over 1.5 million person's die [3].

1.1. Causative agents

Malaria is brought about by five types of the parasite Plasmodium, to be specific *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* [4] of these, *P. falciparum* is mainly perilous and destructive species that cause serious malaria, for example, cerebral malaria [5] and is conscientious for the majority of deaths from malaria in humans [6-10].

1.2. Signs and symptoms

Malaria infection is usually characterized by the following signs and symptoms such ashigh fever, diarrhoea, anemia, muscle pain, abdominal pain, convulsions, coma, chill, sweating, bloody stools, headache, vomiting, nausea [11].

1.3. Life cycle of malaria parasite

The life cycle of malaria parasites includes two hosts, humans and Anopheles mosquitoes. The disease is conveyed to human by a bite of an infected Anopheles mosquito that introduces the sporozoites of plasmodia (*P. falciparum, P. vivax, P. malariae, P. knowlesi and P. ovale*) into the human's blood [12]. The sporozoites pass through the blood to the liver, where they grown-up, and finally infect the human red blood cells. Intraerythrocytic parasites either continue asexual reproduction to produce more Merozoites, which can attack other erythrocytes or can develop into gametocytes that are capable of infecting the next hungry mosquito. At that point, the parasites enter the stomach of Anopheles mosquito and eventually attack the mosquito salivary organs. When an Anopheles mosquito bites a human, these sporozoites complete and repeat the complicated Plasmodium life cycle [13].

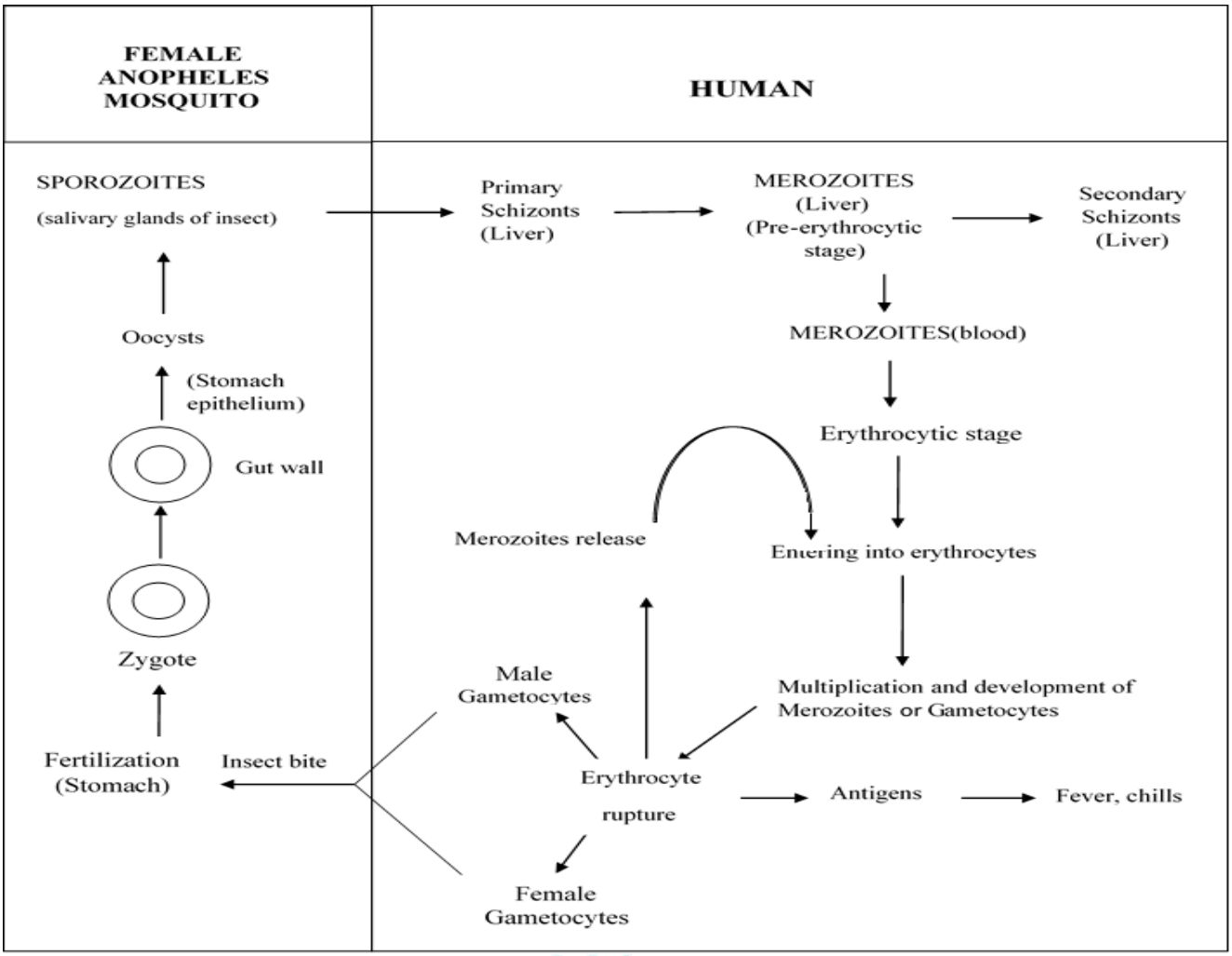


Figure 1: Life cycle of Malaria

1.4. Global disease burden

As per the report of WHO (2018) 219 million instances of malaria were anticipated to occur globally in 2017 compared to 239, 214 and 217 million instances, respectively in 2010, 2015 and 2016. Approximately 20 million fewer instances of malaria were recorded in 2017 than in 2010 and no important improvement was shown in this timeframe in decreasing worldwide instances of malaria. Most cases of malaria were in the African region in 2017 (200 million or 92%), followed by the South-East Asian region (5%), the East Mediterranean region (2%). Including India and 15 countries in sub-Saharan Africa accounted for nearly 80% of the global malaria burden and 274,000 deaths worldwide in 2017 [14]. However; India reported 3 million cases during the period of 2016-2017. *P. falciparum* is the predominant malaria species in the african area, accounting for 99.7% of expected disease case in 2017, as well as in South-East Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%) and also *P. vivax* is America's predominant malaria parasite (74.1 per cent) [15].

1.5. Classification

The antimalarial drugs are classified according to chemical structure [16-20].

Table 1: Classification of antimalarial drugs

Class	Drug
4- Aminoquinolines	Chloroquine, Amodiaquine,Piperaquine
Quinolone-methanol	Mefloquine
Cinchona alkaloid	Quinine, Quinidine
Biguanides	Proguanil (chloroguanide), Chloroguanil
Diaminopyrimidines	Pyrimethamine
8- Aminoquinoline	Primaquine,Bulaquine, Pamaquine, Tafenoquine
Sulfonamides and sulfone	Sulfadoxine,Sulfamethopyrazine,Dapsone
Antibiotics	Tetracycline, Doxycycline, Fluoroquinolones,Azithromycin, Clindamycin
Sesquiterpene lactone	Artesunate, Artemether,Arteether,Artelinic acid
Amino alcohols	Halofantrine,Lumefantrine
Naphthaquinones	Atovaquone
Mannish base	Pyronaridine

1.6. 1,2,4-trioxane as a potent antimalarial agent

1,2,4-Trioxane (Fig. 2) is one of the isomers of trioxane. It has a ring-like structure of six members of three carbon and three oxygen atoms with a molecular formula of $C_3H_6O_3$. A peroxide functional group formed by two adjacent oxygen atoms and the other formed an ether functional group. The peroxide bridge is considered as the most chemically reactive moiety of 1,2,4 trioxanes [21, 22].

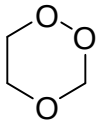


Figure 2: 1,2,4-trioxane

1.7. Artemisinin

Artemisinin is a natural 1,2,4-trioxane sesquiterpene isolated from *Artemisia annua* [23-26] and its byproducts are a powerful class of antimalarial drugs [27]. Chemically, artemisinin is a Sesquiterpene-lactone with an unusual peroxide bridge. The peroxide bridge is considered to be the most chemically reactive moiety responsible for antimalarial activity in artemisinin [28].

Artemisinin and its byproducts share a common structural characteristic called endoperoxide linkage [29]. Artemisinin usually have bad water or oil solubility. However, a more water-soluble derivative of dihydroartemisinin (DHA) can be achieved, which is more active than artemisinin, by decreasing Artemisinin's C-10 carbonyl group. By including methyl or ethyl ether at the same carbonyl group, oil-soluble Artemether and water-soluble sodium artesunate compounds were obtained. These three Artemisinin derivatives become very powerful anti-malarial drugs that are efficient against *P. falciparum* chloroquine-resistant strains [30-33].

1.7.1. Mechanism of action of Artemisinin

Artemisinin mechanism of action is based on haemoglobin digestion leading to iron-containing heme release. In its molecule, the Endoperoxide Bridge appears to interact with the parasite's heme. Iron-mediated bridge cleavage to release an extremely reactive free species of radicals selectively targets *P. falciparum's* sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase, changing calcium stores. The artemisinin actually may form covalent adduct to particular membrane proteins that cause lipid peroxidation, damage endoplasmic reticulum, inhibit protein synthesis and eventually cause malaria parasite death [34,35].

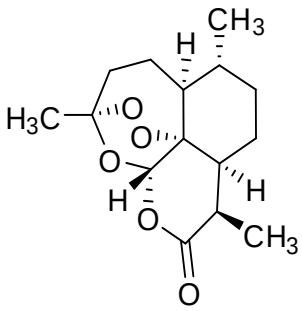
1.7.2. Artemisinin-based combination therapy

Plasmodium falciparum is a most dangerous species of Plasmodium responsible for severe malaria, such as cerebral malaria. ACTs are currently considered the most beneficial treatment for multidrug-resistant *P. falciparum* malaria, according to the World Health Organization. As the *Plasmodium* strains are more resistant to commonly used antimalarial drugs such as chloroquine and sulfadoxine/pyrimethamine.Artemisinin-based combinations therapy include: [35-38]

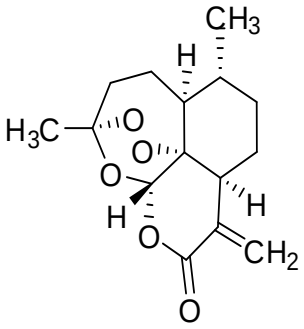
1. Artesunate + Amodiaquine
2. Artemether + Lumefantrine
3. Dihydroartemisinin + Piperaquine
4. Artesunate + Pyronaridine
5. Artesunate + Sulfadoxine + Pyrimethamine
6. Artesunate +Mefloquine

1.7.3. Artemisinin derivatives

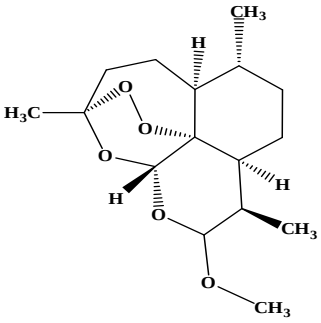
Artemisinin and its derivatives such as artemether, arteether and artesunic acid are well suited for the treatment of cerebral malaria caused by multidrug-resistant *Plasmodium falciparum*.These drugs arehighly active against both chloroquine-sensitive and resistant malaria [39-47].



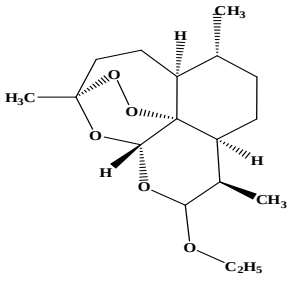
Artemisinin (1)



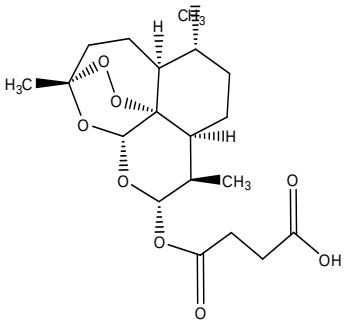
Artemisitene (2)



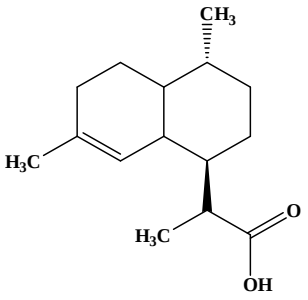
Artemether (3)



Arte-ether (4)



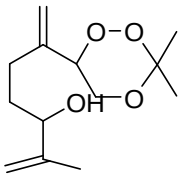
Artesunic acid (5)



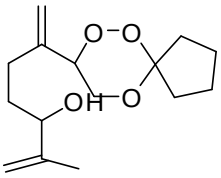
Dihydroartemisinic acid (6)

Novel series of hydroxy-functionalized 1, 2, 4-trioxanes

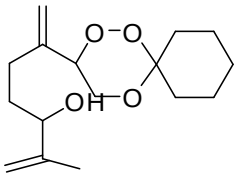
A novel series of hydroxyl-functionalized antimalarial 1,2,4-trioxanes were synthesized for *in-vitroPlasmodium falciparum* (NF-54 strain). The most active are trioxanes with the adamantane moiety (7d and 8d), while those with 3,3-dimethyl substituent (7a and 8a) are the least active. Trioxane (7d) has also been assessed in Swiss mice for its *in-vivo* antimalarial efficacy against multi-drug-resistant *P. yoleii* and demonstrates promising activity. A sequence of novel 1,2,4 trioxanes using an abundant natural product that demonstrates promising antimalarial activity. The novel feature of these trioxanes is the side chain with a hydroxyl bond. This hydroxyl group offers some additional options to make new derivatives of these trioxanes [48].



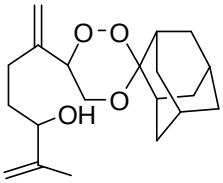
(7a)



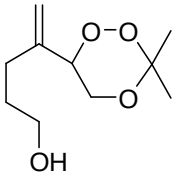
(7b)



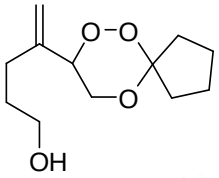
(7c)



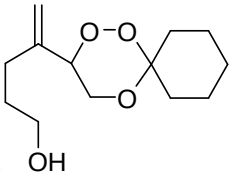
(7d)



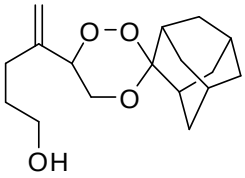
(8a)



(8b)



(8c)



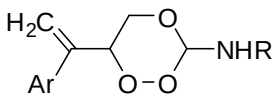
(8d)

Amino functionalised synthetic 1,2,4-trioxanes

A new series of amino functionalised 1,2,4-trioxanes were synthesised (shown in table 2), among these the 9'd compound has very potent action against multidrug resistance *P. yoelii*. The compound was further taken for the in vivo profiling against *P. yoelii* as antimalarial agents, where 9'd compound had shown100% suppression in Swiss mice on the 4th day and all the mice were alive at the end of the testing period.The most potent compound 9d in the series is very close to that of β-arteether [49].

Table 2: Amino functionalised 1,2,4 trioxanes

Compound no.	Ar	R
9a	Phenyl	Phenyl
9b	Phenyl	4- Methoxyphenyl
9c	Phenyl	3,5 dichlorophenyl
9d	Phenyl	4-Acetylaminophenyl
9e	Phenyl	1-Naphthyl
9'a	4-Biphenyl	4-Methoxyphenyl
9'b	4-Biphenyl	4-Acetylaminophenyl
9'c	4-Biphenyl	1-Naphthyl
9'd	4-Biphenyl	Phenyl
9'e	4-Biphenyl	3,5 dichlorophenyl

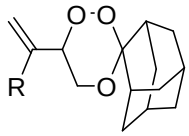


(9)

6-cycloalkylvinyl substituted 1, 2, 4-trioxanes

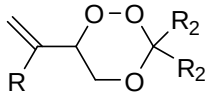
A new series of 6-cycloalkylvinyl substituted 1,2,4-trioxanes were prepared (shown in table 3) by using a photo-oxygenation route and tested in mice against MDR *P.yoleii* by intra-muscular. Trioxane 10a was found the most active compound of the series [50].

Table 3: 6-cycloalkylvinyl substituted



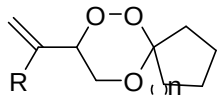
(10)

Compound no.	R
10a	Cyclopropyl
10b	Cyclohexyl
10c	Phenyl



(11)

Compound no.	R	R_1	R_2
11a	Cyclopropyl	H	Phenyl
11b	Cyclopropyl	CH_3	CH_3
11c	Cyclohexyl	CH_3	CH_3



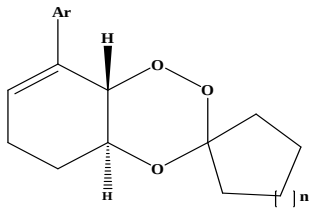
(12)

Compound no.	R	n
12a	Cyclopropyl	1
12b	Cyclopropyl	2
12c	Cyclopropyl	3
12d	Cyclohexyl	1
12e	Cyclohexyl	2

Trans-fused bicyclic 1, 2, 4-trioxanes

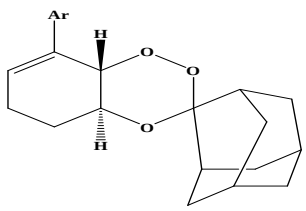
Trans-fused bicyclic 1,2,4-trioxanes (shown in table 4) have been prepared by Photo-oxygenation route. Stereoselective photo-oxygenation of 3-aryl- 2-cyclohexenols and acid catalyzed condensation of trans-2-hydroperoxy-3-aryl-3-cyclohexenols with aldehydes and ketones are the key steps of this method. Trioxanes 13c, 13'c, 13"c & 14b showed more than 95% suppression of parasitaemia at 96 mg/kg/day by oral route. The most energetic compound of the series is trioxane 14c. It shows a complete suppression of parasitaemia on day 4 [51].

Table 4: Trans-fused bicyclic 1, 2, 4-trioxanes



(13)

Compound no.	Ar	n
13a-c	Phenyl, 4- ClC_6H_4, 4- PhC_6H_4	1
13'a-c	Phenyl, 4- ClC_6H_4, 4- PhC_6H_4	2
13"a-c	Phenyl, 4- ClC_6H_4, 4- PhC_6H_4	3



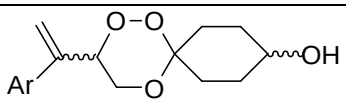
(14)

14a-c	Phenyl, 4- ClC_6H_4, 4- PhC_6H_4

Spiro 1, 2, 4-trioxanes

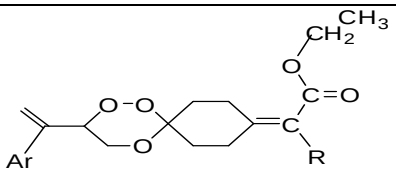
The next generation of orally effective spiro 1,2,4-trioxanes was prepared (as shown in table 5) and evaluated for their *in-vivo* antimalarial action against *p. yoelii* in Swiss mice by the oral and i.m. route. All the synthesised compounds showed potential against *p. yoelii* and Trioxane 16a was the series' most effective compound among them [52].

Table 5: Spiro 1, 2, 4-trioxanes



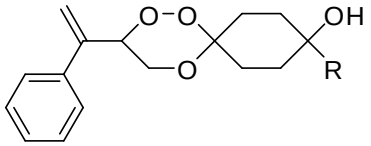
(15)

Compound no.	Ar
15a	4- biphenyl
15b	Phenyl



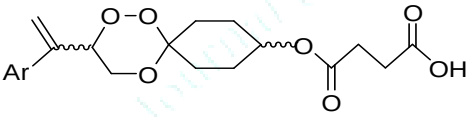
(16)

Compound no.	Ar	R
16a	Phenyl	H
16b	4-biphenyl	H
16c	4-biphenyl	CH_3
16d	Phenyl	CH_3



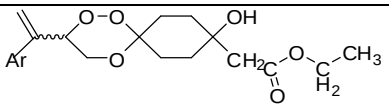
(17)

Compound no.	R
17a	Methyl (higher Rf)
17b	Methyl (lower Rf)
17c	Phenyl (higher Rf)
17d	Phenyl (lower Rf)



(18)

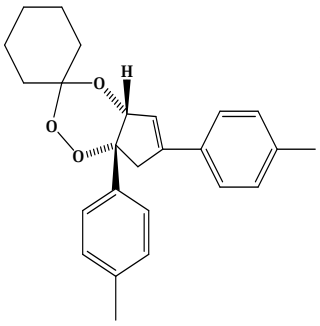
Compound no.	Ar
18a	Phenyl
18b	4-biphenyl



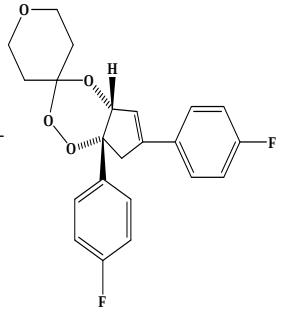
(19)

Compound no.	Ar
19a	Phenyl (higher Rf)
19b	Phenyl (lower Rf)
19c	4-biphenyl (higher Rf)
19d	4-biphenyl (lower Rf)

Cis-fused cyclopentene-1, 2, 4-trioxanes



(20)



(21)

A new series of compounds were synthesised having a blood schizontocidal activity 1,2,4-trioxanes against the MDR of *P. yoelii nigeriensis* strain deadly in Swiss mice. The formulations of these compounds were freshly prepared either in neutral groundnut oil or in Tween-DMSO-water and were evaluated for their antimalarial activity. Only two fenozan derivatives 20 and 21 which were formulated in neutral groundnut oil for oral administration, showed maximum activity with 100% treat rate in MDR *P. yoelii nigeriensis* infected mice while the formulations in Tween-DMSO-water were found inactive [53].

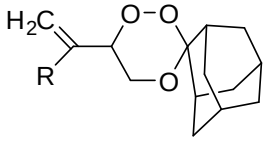
Spiro 1,2,4-trioxanes based on adamantane

A new series of 6-arylvinyl and 6-adamantylvinyl-substituted 1,2,4-trioxanes were synthesised (shown in table 6 and7) and assessed against multi-drug resistance *P. yoelii nigeriensis* in mice through oral and i. m. route for their antimalarial action. The 6-arylvinyl substituted 1,2,4 trioxanes showed promising activity, whereas all 6-adamantyl substituted 1,2,4-trioxanes were found inactive. Trioxane 22f, the most effective compound of the 6- arylvinyl substituted 1,2,4-trioxanes. The most active compound of the series showed antimalarial activity better than that of arteether and artesunic acid by the oral route [54].

a) 6-arylvinyl-substituted 1,2,4-trioxanes

Table 6: 6-arylvinyl-substituted

Compound no.	Substituent (R)
22a	1-naphthyl
22b	2-naphthyl
22c	2-tetrahydronaphthyl
22d	2-phenanthrenyl
22e	3-phenanthrenyl
22f	2-fluorenyl
22g	1-adamantyl

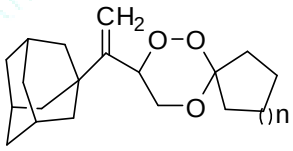


(22)

b) 6-adamantylvinyl-substituted 1,2,4-trioxanes:

Table 7: 6-adamantylvinyl-substituted

Compound no.	Substituent
23a	n=1
23b	n=2



(23)

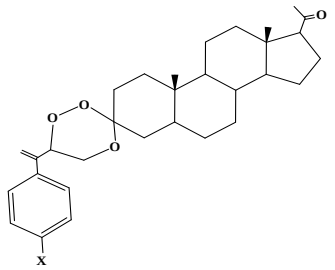
1, 2, 4-trioxane based on steroids

A new series of orally active steroids based 1,2,4-trioxanes were synthesised (shown in table 8, 9 and 10) and evaluated by oral route for antimalarial activity against MDR *Plasmodium yoelii* in Swiss mice. The *in-vivo* antimalarial activity demonstrated that all 1,2,4-trioxanes dependent on pregnane had a substantial effect compared to 1,2,4 trioxanes depending on cholestane and tigogenine. Among the series most active compounds, 1,2,4-trioxanes 24b and 24f are pregnane based. Both trioxanes showed 100 per cent clearance of parasitaemia on day 4 at 96mg / kg/4×day and all treated mice lived after day 28 [55].

Pregnane-based trioxanes

Table 8: Pregnane-based trioxanes

Compound no.	X
24a	H
24b	CH_3OH
24c	CH_3
24d	F
24e	Cl
24f	Br

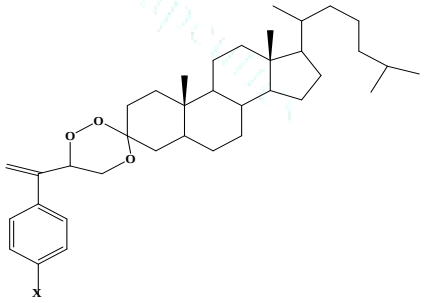


(24)

Cholestane based 1,2,4, trioxanes

Table 9: Cholestane based trioxanes

Compound no.	X
25a	H
25b	CH_3OH
25c	CH_3
25d	F
25e	Cl
25f	Br

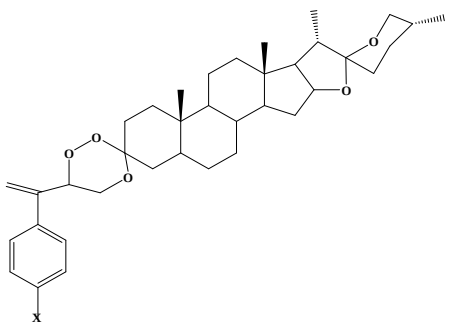


(25)

Tigogenine-based trioxanes:

Table 10: Tigogenine-based trioxanes

Compound no.	X
26a	CH_3OH
26b	CH_3
26c	F
26d	Cl

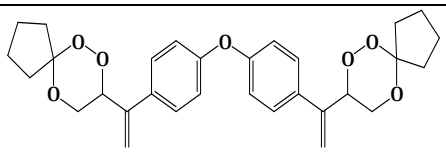
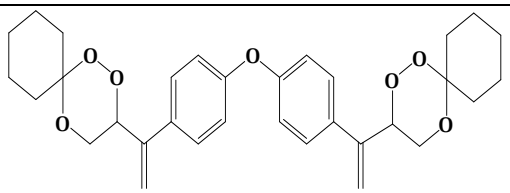
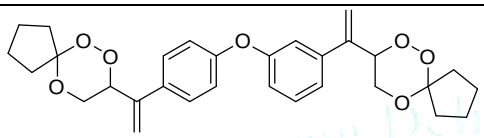
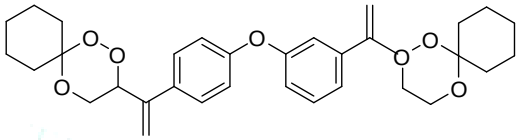
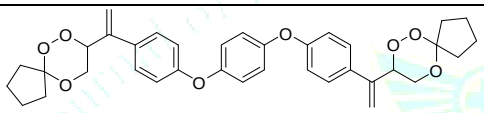
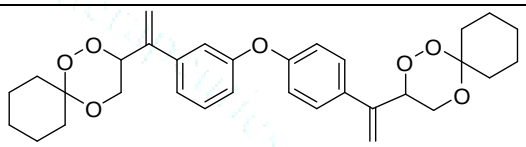
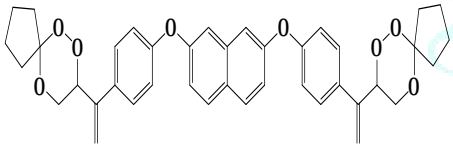
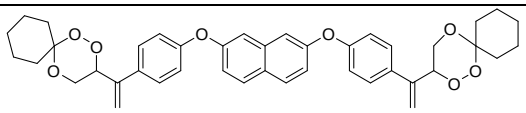
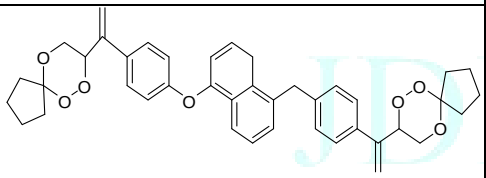
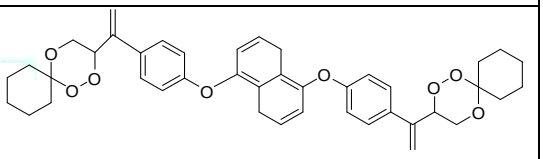
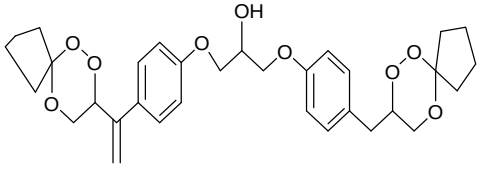
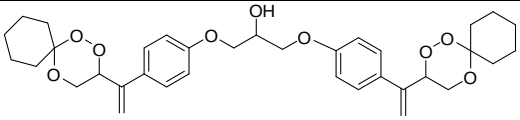
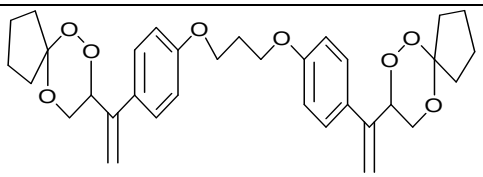
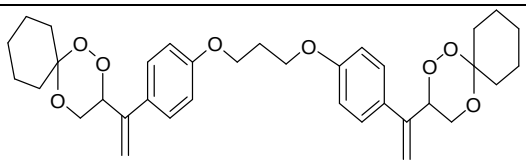
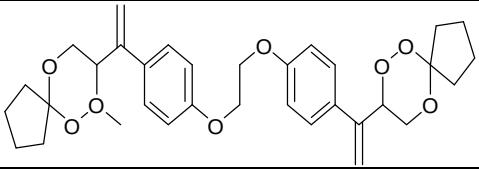
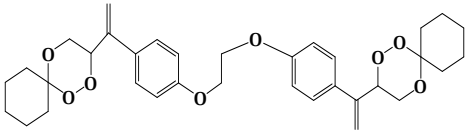


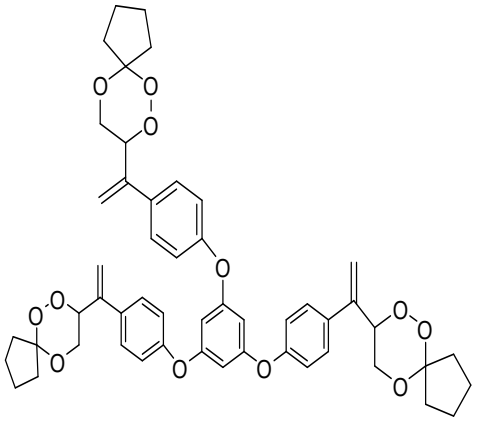
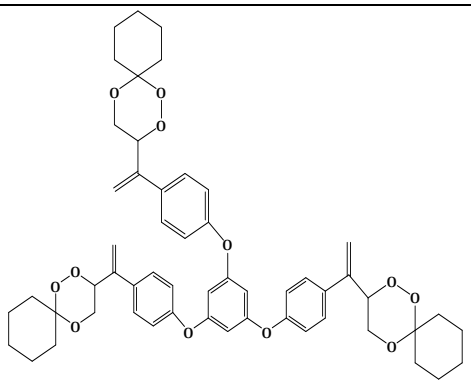
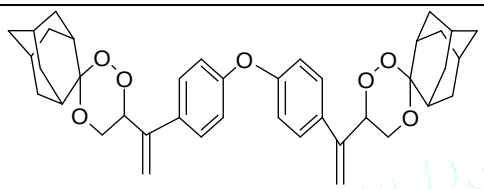
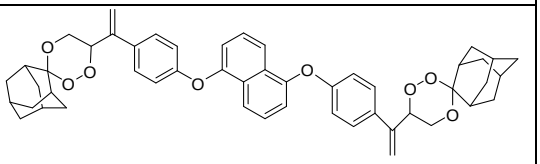
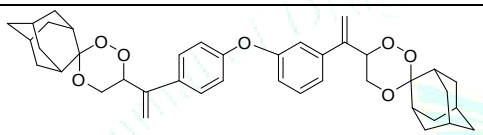
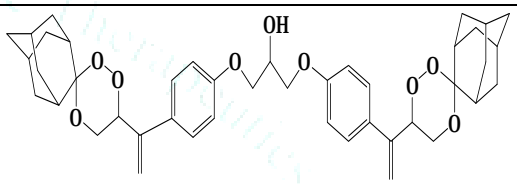
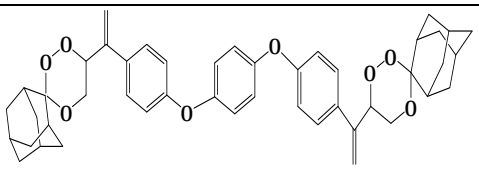
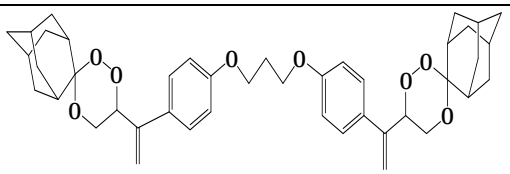
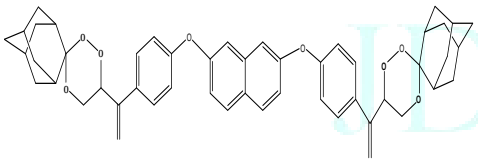
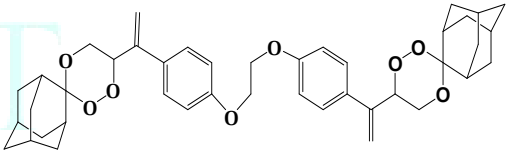
(26)

Novel bis- and tris-1,2,4-trioxanes

A series of bis-1,2,4-trioxanes have been prepared and evaluated against multidrug-resistant *P. yoelii* in mice by the oral route. These bis-trioxanes have been set up by a minor alteration of photo-oxygenation technique. Basically, these bis-trioxanes are two 6-arylvinyl-1,2,4-trioxane moieties joined by a variety of linkers and their antimalarial activity shows a strong dependence on the nature of the linker. A novel sequence of bis and tri-1,2,4 trioxanes were synthesised (shown in table 11) and assessed by oral route against *P. yoelii* MDR in Swiss mice. Trioxanes based on cyclopentane 27a, 27b, 27f-h and cyclohexane 28a, 28f and 28 g showed promising activity. Trioxane (compound 28a) was the most effective compound in the series, offers 100% and 80% safety at 48 and 24 mg/kg within 4 days. The clinically used arteether showed only 20 % at 24mg / kg 4 days [56].

Table 11: Bis- and Tris-1,2,4-trioxanes

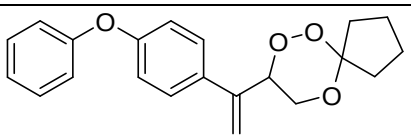
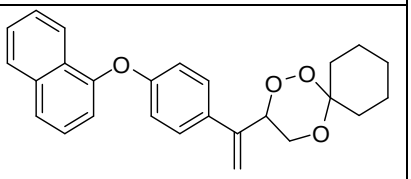
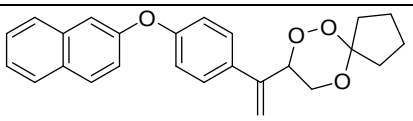
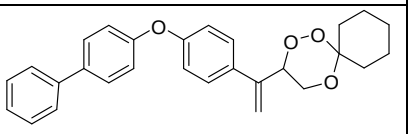
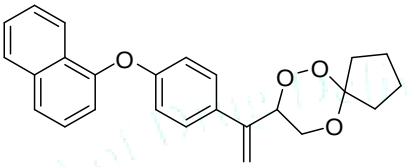
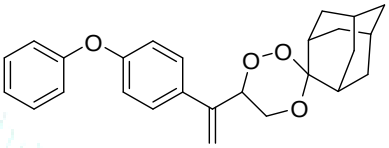
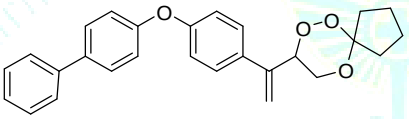
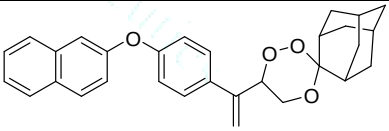
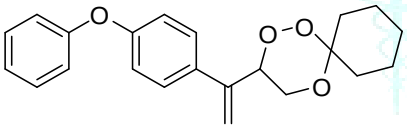
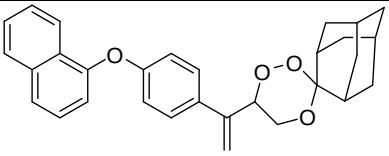
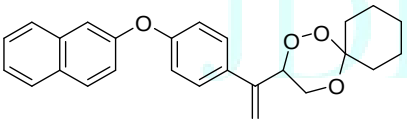
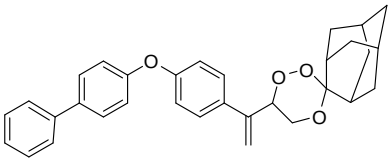
Compound no.	Structure	Compound no.	Structure
27a		28a	
27b		28b	
27c		28c	
27d		28d	
27e		28e	
27f		28f	
27g		28g	
27h		28h	

27i		28i	
29a		29e	
29b		29f	
29c		29g	
29d		29h	

6-(4-aryloxy-phenyl)vinyl-1, 2, 4-trioxanes

A new 6-(4-aryloxy-phenyl)vinyl-1,2,4-trioxanes sequence have been synthesized (shown in table 12) and evaluated for their antimalarial activity against MDR of *P. yoelii* in Swiss mice after oral administration. The most effective compounds of the sequence are Trioxanes 30b and 30c, Protected the mice 100% at 48 mg/kg × 4 days. These two compounds displayed a similar activity as that of β-arteether [57].

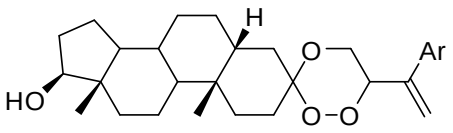
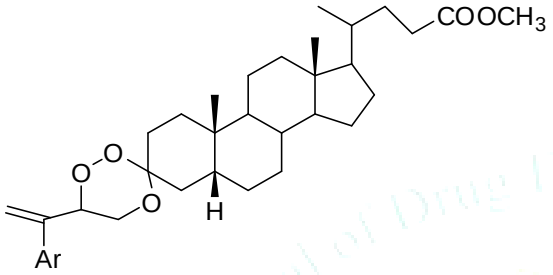
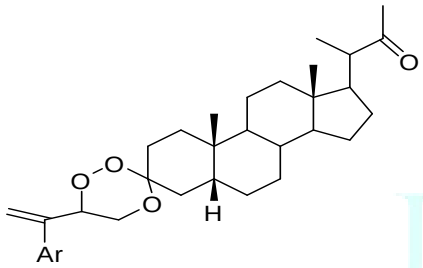
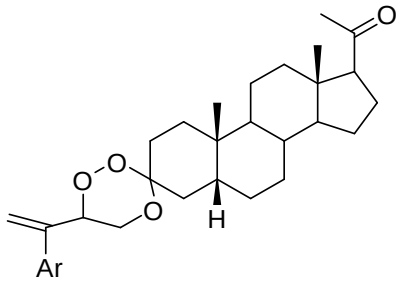
Table 12: 6-(4-Aryloxy-phenyl)vinyl-1, 2, 4-trioxanes

Compound no.	Structure	Compound no.	Structure
30a		31c	
30b		31d	
30c		32a	
30d		32b	
31a		32c	
31b		32d	

1,2,4-trioxane derivatives based on bile acid

A new sequence of bile acid-based 1,2,4-trioxanes have been synthesised (shown in table 13), the antimalarial activity of these trioxanes showed strong dependence both the stereochemistry around trioxanes ring and length of the side chain. Trioxanes is more polar than the less polar one was considerably more active. The more polar trioxane diastereomer 33a, 33b, 33c were the series most effective compounds. All three trioxanes were 100% protected at 24 mg/kg for 4 days and twice active as β-arteether [58].

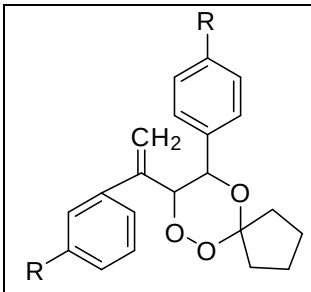
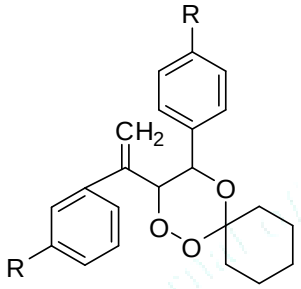
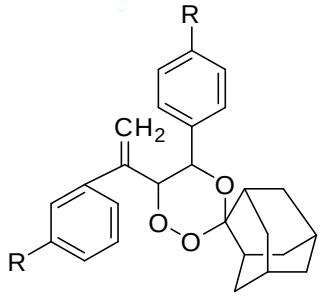
Table 13: Bile acid-based 1,2,4, trioxanes

	Compound no.	Ar
 **(33)**	33a	Phenyl (less polar isomer)
		Phenyl (more polar isomer)
	33b	4-fluorophenyl (less polar isomer)
		4-fluorophenyl (more polar isomer)
	33c	4-bromophenyl (less polar isomer)
		4-bromophenyl (more polar isomer)
 **(34)**	34a	Phenyl (less polar isomer)
		Phenyl (more polar isomer)
	34b	4-fluorophenyl (less polar isomer)
		4-fluorophenyl (more polar isomer)
	34c	4-Chorophenyl (less polar isomer)
		4-Chorophenyl (more polar isomer)
	34d	4-bromophenyl (less polar isomer)
		4-bromophenyl (more polar isomer)
 **(35)**	35a	Phenyl (less polar isomer)
		Phenyl (more polar isomer)
	35b	4-fluorophenyl (less polar isomer)
		4-fluorophenyl (more polar isomer)
	35c	4-Chorophenyl (less polar isomer)
		4-Chorophenyl (more polar isomer)
	35d	4-bromophenyl (less polar isomer)
		4-bromophenyl (more polar isomer)
 **(36)**	36a	Phenyl (less polar isomer)
		Phenyl (more polar isomer)
	36b	4-fluorophenyl (less polar isomer)
		4-fluorophenyl (more polar isomer)
	36c	4-Chorophenyl (less polar isomer)
		4-Chorophenyl (more polar isomer)
	36d	4-bromophenyl (less polar isomer)
		4-bromophenyl (more polar isomer)

3, 3-spiro anellated 5, 6-disubstituted 1, 2, 4-trioxanes

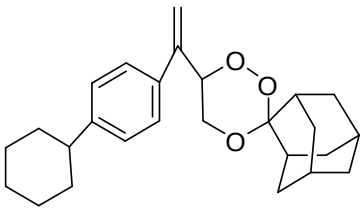
Novel 3,3-Spiro anellated 5,6-Disubstituted 1, 2, 4-Trioxanes (shown in table 14) have been synthesized and evaluated for their *in-vivo* antimalarial activity against multi drugs resistance of *P. yoelii nigeriensis* in Swiss mice by the oral route. The 38b compound of the sequence was most active, protected the mice 100% at 24 mg/kg × 4 days. The other trioxanes 37d, 38c, 38d, 39b also displayed promising activity. The compound 39b showed a similar *in-vitro* pharmacokinetic profile to β-arteether [59].

Table 14: 3, 3-Spiroanellated 5, 6-Disubstituted 1, 2, 4-Trioxane

	Compound no.	R
 **(37)**	37a	H
	37b	Cl
	37c	CH_3
	37d	Br
	37e	F
 **(38)**	38a	H
	38b	Cl
	38c	CH_3
	38d	Br
	38e	F
 **(39)**	39a	H
	39b	Cl
	39c	CH_3
	39d	CH_3OH
	39e	Br
	39f	F

CDRI compound no. 99/411 is a potent 1,2,4-trioxane antimalarial candidate drug

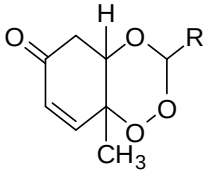
The Central Drug Research Institute, Lucknow, India developed 99/411, a novel antimalarial agent that is a semisynthetic derivative of artemisinin. It is a potent 1,2,4-trioxane antimalarial candidate [60,61].



(40)

New series of derivatives of 1,2,4-trioxane

Three new series of 1,2,4-trioxane derivatives were synthesised and appraised in vitro for their antimalarial activity. Substitutions at the C-3 position of 1,2,4-trioxane ring system with different aliphatic, aromatic and heteroaromatic groups afforded target trioxane derivatives (shown in table 15, 16&17) as antimalarial agents, of which three series of 1,2,4 trioxane derivatives, five compounds (41'd, 41'e, 41"b, 41"c, 41"l) exhibited antimalarial activity well in vitro, with three compounds (41"b, 41"l, 41'd) showing greater activity against *Plasmodium falciparum* (RKL9) than sensitive (3D7) one. 41"l and 41'd were the best compounds from the aryl sequence and the other from the heteroaryl sequence [6].



(41)

Table 15: Alkyl series

Compound no.	R
41a	Ethyl
41b	Propyl
41c	Butyl
41d	Pentyl
41e	1-formyl-but-4-yl

Table 16: Heteroaryl series

Compound no.	R
41'a	Furan-2-yl
41'b	Thiophen-2-yl
41'c	Pyrrole-2-yl
41'd	Indole3-yl
41'e	Pyridine-4-yl

Table 17: Aryl series

Compound	R	Compound	R
41"a	Phenyl	41"h	4-Fluorophenyl
41"b	2-Hydroxyphenyl	41"i	1-Naphthyl
41"c	3-Methoxyphenyl	41"j	4-Dimethylaminophenyl
41"d	4-Chlorophenyl	41"k	4-Cinnamyl
41"e	4-Nitrophenyl	41"l	4-Hydroxy-3-methoxyphenyl
41"f	4-Tolyl	41"m	4-Dimethoxyphenyl
41"g	4-Bromophenyl	41"n	Isophthalyl

CONCLUSION

The present paper concludes that there are different types of 1,2,4-trioxane derivatives that are synthesised by the different methods for the treatment of malaria. Artemisinin derivatives contain a 1,2,4-trioxane ring which is responsible for the antimalarial activity. Many of the different drugs are used to treat malaria but due to MDR against malaria strains, synthesis of new artemisinin derivatives is a good approach to treat malaria caused by the different Plasmodium species.

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