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REVIEW ARTICLE

Advances in the Synthesis of Biologically Important 1,2,4-Trioxanes

[1]Subhendu Chakroborty*, [2]Chittaranjan Bhanja, [2]Satyaban Jena

[1]Department of Chemistry, Ravenshaw University, Cuttack-753003, Odisha, India

[2]Department of Chemistry, Utkal University, Bhubaneswar-751004, Odisha, India

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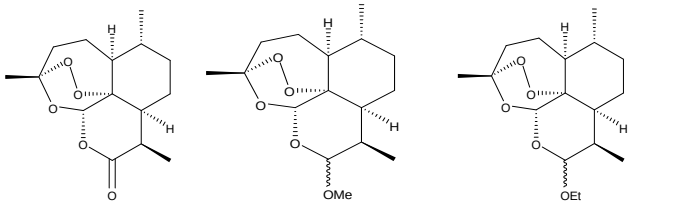
ABSTRACT

Artemisinin and its semisynthetic daughters having 1, 2, 4-trioxane ring system has become the drugs of choice in the treatment of malaria chemotherapy. The incorporation of substituents into the central peroxide ring as well as further ring annulation are efficient approaches for the preparation of other active derivatives and has attracted much attention worldwide for tackling the forthcoming problem of multi-drug resistant malaria. The present review addresses the most significant contemporary status of synthesis for 1, 2, 4-trioxane scaffolds as well as their hybrids as reported in the literature up to middle of 2012

KEYWORDS: *Antimalarial*; *Artemisinin*; *Peroxide; Plasmodium; 1, 2, 4-Trioxanes*.

1. INTRODUCTION

Malaria is one of the world's most devastating infectious diseases, caused by various species of *Plasmodium protozoa*. According to the recently compiled data from World Health Organization (WHO), about 3.3 billion people were at risk of malaria in 2010[1] and each year about 1 to 3 million are dying with this infectious disease due to the increasing resistance of the parasite *Plasmodium falciparum* to the classical drugs. After the discovery of artemisinin Fig. **1a** as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, was a major quantum leap in malaria chemotherapy. Artemisinin exhibits its antimalarial activity due to the presence of 1,2,4-trioxane system and is active against both chloroquinine-sensitive and chloroquinine-resistant malaria. Artemisinin derivatives, e.g. artemether Fig. **1b** and arteether Fig. **1c** are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *Plasmodium falciparum*[2].But artemisinin and its derivatives are associated with several serious problems such as high cost, poor solubility in both oil and water, high rate of recrudescence, limited availability from natural sources and poor bioavailability[3]. Since the discovery of 1,2,4-trioxane as the pharmacophore for the antimalarial activity of Artemisinin, synthetic methodologies allowing the rapid access to synthetic 1,2,4-trioxane system are highly desirable in organic synthesis and chemical biology/medicinal chemistry. As a result, several new methods for their synthesis have been developed in the past years. The aim of this review is to cover the synthetic methodologies developed for the synthesis of biologically important 1,2,4-trioxane system as well as their hybrids as reported in the literature up to mid of 2012.



(a) Artemisinin (b) Artemether (c) Arteether

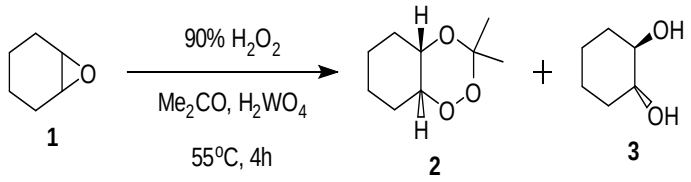
Figure 1

2. SYNTHETIC METHODOLOGIES FOR 1,2,4-TRIOXANES:

A methodology addressing the first synthesis of 1,2,4-trioxanes was reported by Payne and Smith[4] in 1957. The

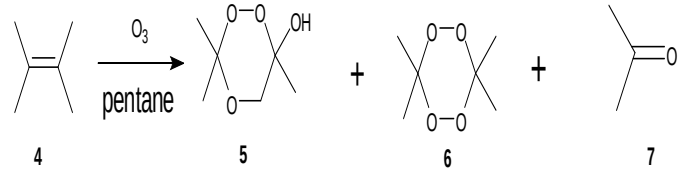
*Corresponding author: Subhendu Chakroborty |Mobile No.:- +917205353853 |Email: subhendu.cy@gmail.com

method involved the oxidation of cyclohexene epoxide **1** with acidified H_2O_2 in acetone that furnished the bicyclic trioxane **2** together with trans diol **3** with good yield Scheme 1.



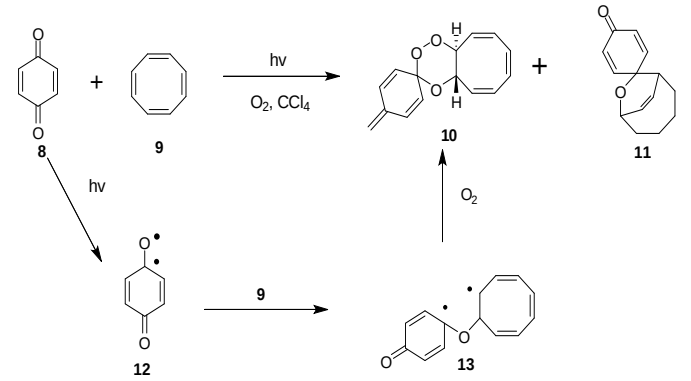
Scheme 1

An ozone-mediated synthesis of a 1,2,4-trioxane along with 1,2,4,5-tetraoxane was first reported by Story and Burgess[5] in 1967. Thus the ozonolysis of tetramethylethylene **4** afforded 1,2,4-trioxane derivative **5** and 1,2,4,5-tetraoxane **6** with appreciable yields Scheme 2.



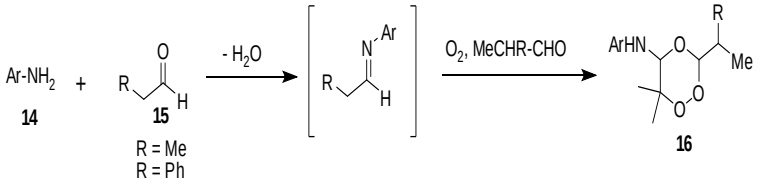
Scheme 2

In 1973, Wilson[6] et al. reported the first ground state molecular oxygen-mediated synthesis of 1,2,4-trioxanes by oxidative photocycloaddition of *p*-benzoquinone **8** and cyclooctatetraene **9**. In their protocol, irradiation of a mixture of **8** and **9** with argon laser in CCl_4 in the presence of oxygen gave trioxane **10** together with the normal anaerobic product **11**. Mechanistically, the triplet diradical **13** formed by reaction of **8** and **9** is trapped by molecular oxygen to give the trioxane **10** Scheme 3**.**



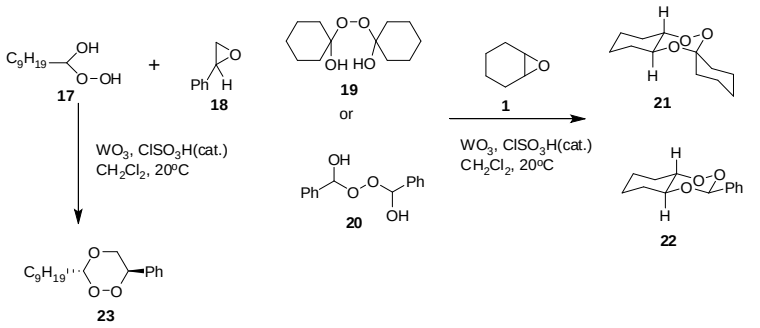
Scheme 3

Synthesis of some arylamino-l,2,4-trioxans was then presented by Yamamoto[7] et.al, in1980. The atmospheric $^1O_2$-mediated reaction of arylamines **14** with aldehydes **15** having an active hydrogen in hexane-ether gave the 5-arylamino-l, 2,4-trioxans **16** Scheme 4.



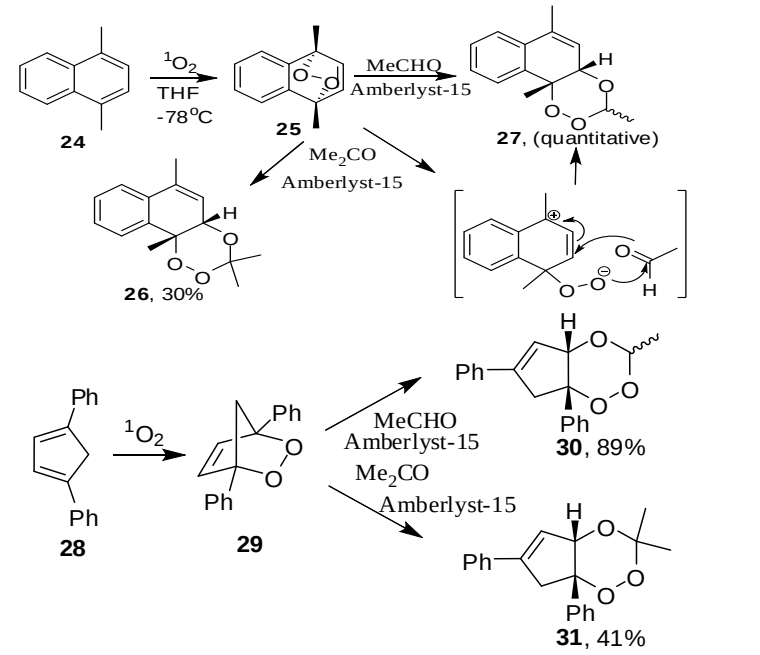
Scheme 4

A new method involving the treatment of α-hydroxy hydroperoxides **16** or their precursors such as **17** & **18** with epoxides **19** (cyclic or acyclic) in presence of tungstic anhydride (WO_3) and $ClSO_3H$ (as catalyst) that furnish 1,2,4-trioxanes **20**, **21** and **22** was reported by Nojima[8] et al.in 1981 Scheme 5.



Scheme 5

A new approach for the $^1O_2$-mediated synthesis of structurally simple 1,2,4-trioxanes was reported by Jefford[9] *et al.* in 1983 . The methodology utilised bicyclic endoperoxides and 1,2-dioxetanes as starting materials, which themselves were obtained by photooxygenation of suitable cyclic dienes and enol ethers. Thus endoperoxide **25** obtained from 1,4-dimethylnaphthalene **24** on treatment with acetaldehyde and acetone in presence of catalytic amberlyst-15 gave *cis*-fused bicyclic 1,2,4-trioxanes **26** and **27** respectively. Similarly endoperoxide **29** gave *cis*-fused cyclopenteno trioxanes **30** and **31** Scheme 6.



Scheme 6

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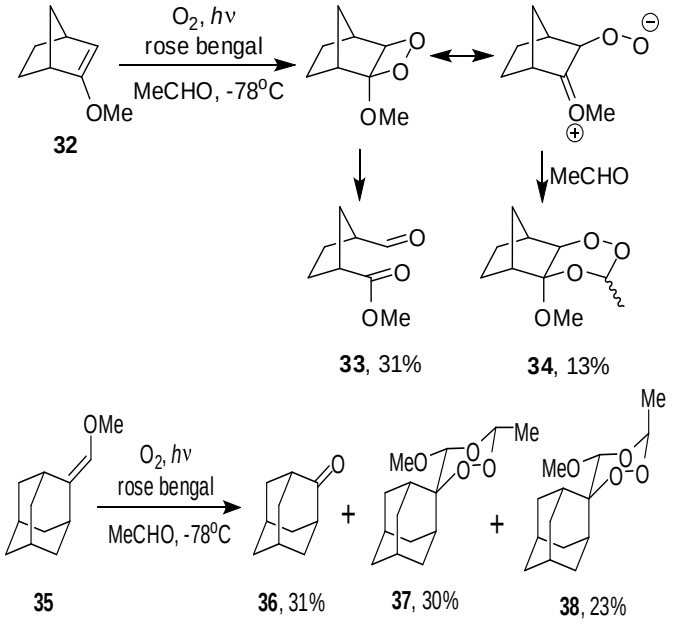
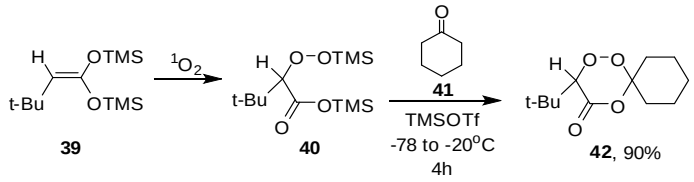
As continuation of the work, photooxygenation of 2-norbornenol-methyl ether **31** at -78°C in acetaldehyde solvent gave aldehyde ester **32** (31% yield) and trioxane **33** (2:3 mixture of stereoisomers; 13% yield). Similarly photooxygenation of 2-(methoxymethylene)-adamantane **34** in acetaldehyde solution at -78°C furnished 2-adamantanone **35** and two isomeric spiro trioxanes **36** & **37** Scheme 7.



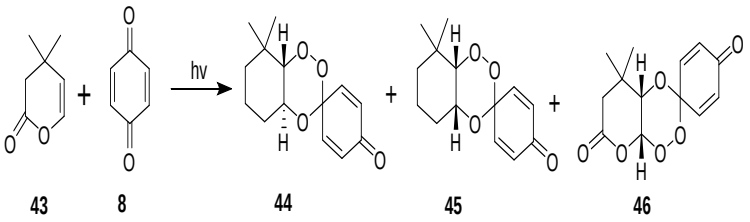
Scheme 7

Continuing their pioneering work, the same group[10] reported the synthesis of 1,2,4-trioxan-5-ones, a new reckon of 1,2,4-trioxanes. The protocol involved photooxygenation of bis(trimethylsilyloxy) ketone acetal **39** that gave trimethylsilyl α-trimethylsilylsilylperoxy ester **40** which underwent facile condensation with cyclohexanone using TMSOTf as catalyst to furnish trioxanone **42** (90% yield), Scheme 8.



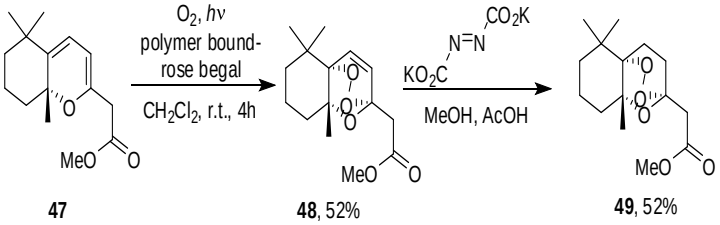
Scheme 8

A synthesis of artemisinin type 1,2,4-trioxanes by molecular oxygen trapping of 1,4-diradicals obtained from 3,4-dihydro-4,4-dimethyl-2H-pyran-2-one **43** and quinones (p-benzoquinone and phenanthroquinone) was reported by Adam[11] et al in 1988 . Thus oxygen mediated irradiation of a mixture of **43** and p-benzoquinone **8** in CCl_4 furnished trioxanes **44**, **45** and **46** in a ratio of 28:9:18 Scheme 9.



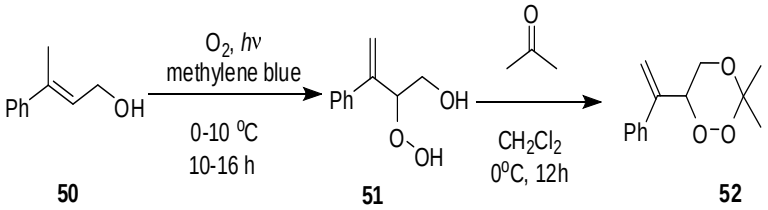
Scheme 9

Subsequently, a straightforward synthesis of 1,2,4-trioxanes was reported by Kepler[12] et al. using photooxygenation of tetrahydrobenzopyrans as the key step. Thus photooxygenation of tetrahydrobenzopyran **47** gave unsaturated 1, 2, 4-trioxane **48** (52% yield), which on diimide reduction furnished saturated trioxane **49** (52% yield) Scheme 10.



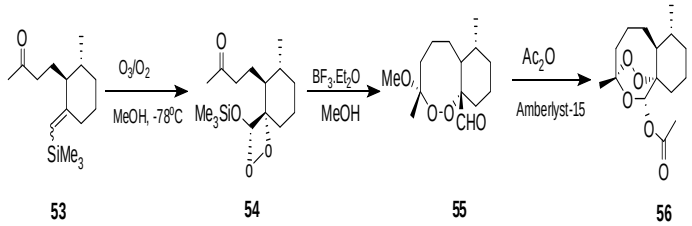
Scheme 10

Singh[13] et.al. in 1990, reported a new $^1O_2$-mediated synthesis of 1,2,4-trioxanes using photooxygenation of 3-aryl-2-butenols. In their methodology, methylene blue sensitized photooxygenation of 3-phenyl-2-butenol **50** at 0-10 °C gave 2-hydroperoxy-3-pheny-3-butenol **51**, which on condensation (ketalisation) with acetone furnished 3,3-dimethyl-6-(1-phenylvinyl)-1,2,4-trioxane **52** Scheme 11.



Scheme 11

Later on, Avery[14] et al. in 1990 reported the synthesis of tricyclic 1,2,4-trioxanes using ozonolysis of vinyl silanes as the key step. Thus alcohol mediated ozonolysis of keto vinyl silane **53** formed an intermediate **54** which on treatment with $BF_3.Et_2O$ gave stable endoperoxide aldehyde **55**. The aldehyde on further treatment with acetic anhydride and Amberlyst-15 gave tricyclic trioxane **56** Scheme 12.



Scheme 12

Bunnelle[15] et al. in 1991 reported another ozone-mediated synthesis of 1,2,4-trioxanes *via* the cationic ring expansion

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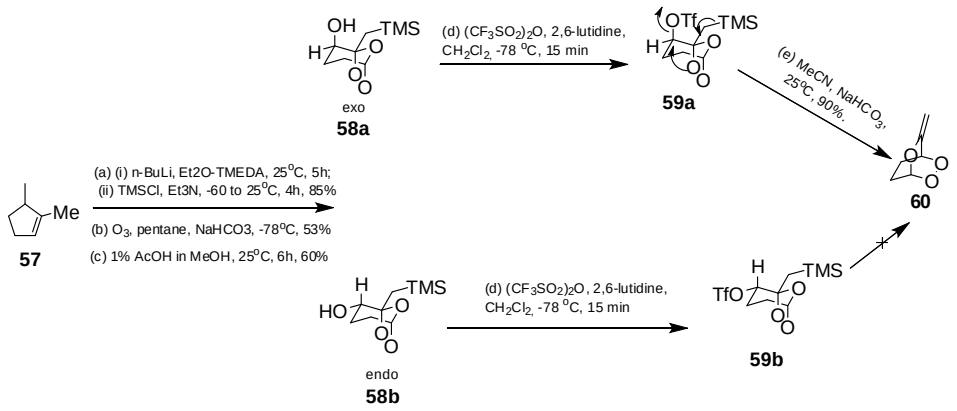
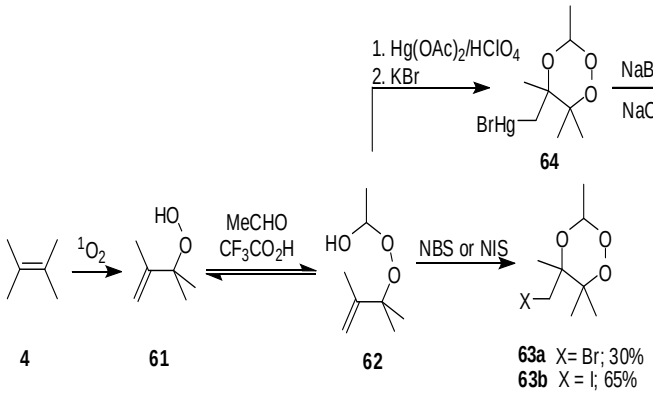
of ozonides as a viable route. The ozonides **58a** and **58b** thus obtained by ozonolysis of **57** were converted to the respective triflates **59a** and **59b** and, of the two triflates only **59a** rearranged to 1,2,4-trioxane Scheme 13.



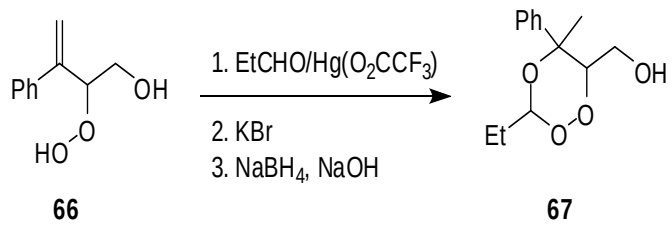
Scheme 13

Utilizing the same photooxygenation strategy, Bloodworth[16] et al. reported a synthesis of 1,2, 4-trioxanes in 1991 and subsequently again in 1993. The method involved photooxygenation of appropriate alkenes **4** to form an intermediate hemiperoxyacetal **62** obtained *in situ* from allylic hydroperoxide **61** and acetaldehyde that cyclized either with N-bromosuccinimide (NBS), N-iodosuccinimide (NIS) or $Hg(OAc)_2$ to furnish trioxanes **63**, **64** or **65** respectively Scheme 14.



Scheme 14

In continuation of their works, Bloodworth[17] et al. in 1994 reported a synthesis of hydroxy-functionalized 1,2,4-trioxanes, **66** using intramolecular oxymercuration of 2-hydroperoxy-3-aryl-3-butenols **67**, as the key step Scheme 15.



Scheme 15

A new synthetic methodology of 1,2,4-trioxanes, *via* cyclization of unsaturated hydroperoxyacetals **69**, obtained from the ozonolysis of appropriate enol ethers in presence of allylic alcohols was presented by Dussault and Davies[18] in 1996 . Thus ozonolysis of enol ether **68** in presence of allyl alcohol gave unsaturated hydroperoxyacetal **69** which underwent facile cyclization on treatment with Hg $(OAc)_2$/ KBr, to furnish 1,2,4-trioxane Scheme 16.

Scheme 16

In 1998, Posner[19] et. al**.** first reported a convergent synthesis of a series of structurally simple and clinically effective sulfide and sulfone 1,2,4-trioxanes as potent antimalarials. Reaction of cyanoethylcyclohexanone **72** with n-butyllithium promoted deprotonated dimethylarylthiomethane phosphonates followed by methyllithum addition to the nitrile group gave methyl ketone vinyl sulfides **73**. Photooxygenation of **73** followed by t-butyldimethylsilyl triflate then gave anomeric sulfide trioxane diastereomers (α and β). Separate oxidation of each of the vinyl sulfide trioxanes (α and β) with m-CPBA gave the corresponding sulfone trioxanes Scheme 17.

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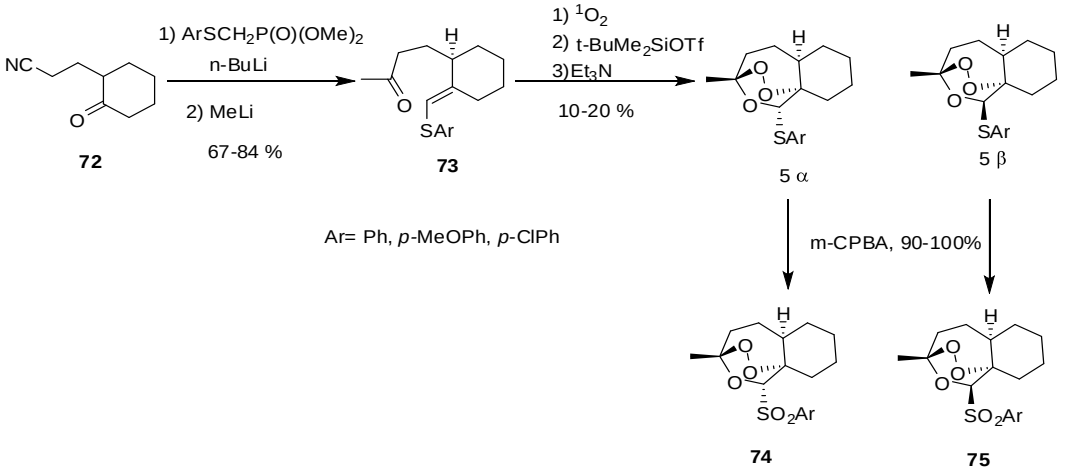
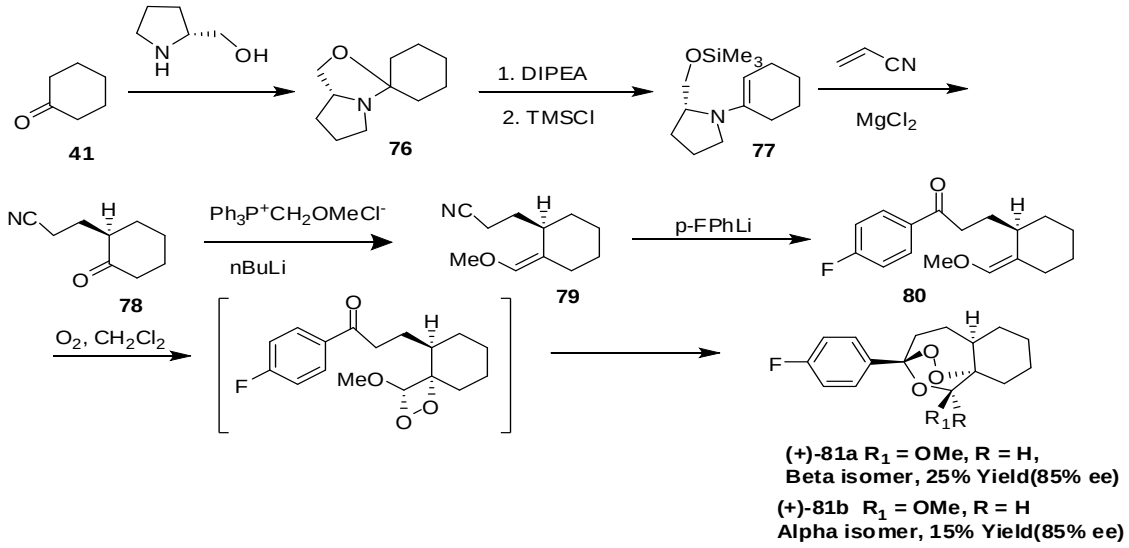


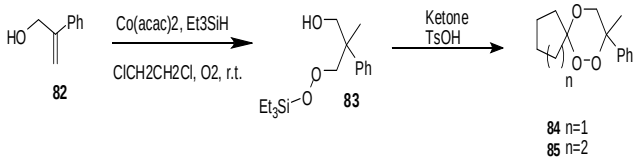
Scheme 17

O'Neill[20] et. al. in 1999 reported an asymmetric synthesis of enantiomeric 3-*p*-fluorophenyl 1, 2, 4-trioxane analogues of the antimalarial Artemisinin. The key step in the preparation of (+)-**81a** involved an asymmetric $MgCl_2$ promoted Michael addition of the (R)-(-)pyrrolidinemethanol-derived enamine **77** to acrylonitrile. This gave the corresponding ketone **78** in 50% yield (>95% ee). Subsequent elaboration of **78** provided the trioxane target (+)-**81a** in greater than 85% ee.



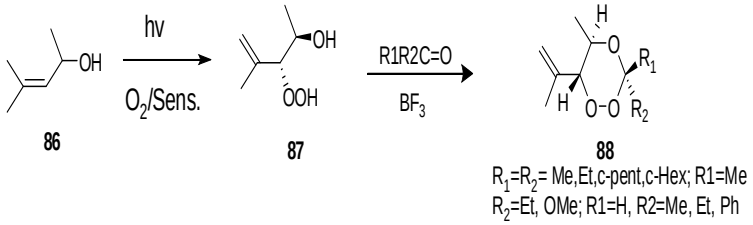
Scheme 18

The same authors[21] in 2001 further reported $Co(acac)_2$-mediated regioselective Mukaiyama-Isayama Peroxysilylation process for the synthesis of 1,2,4-trioxanes. Reaction of 2-phenyl-prop-2-en-1-ol **81** with Et_3SiH, $Co(acac)_2$ and O_2 followed by acid catalyzed condensation of the intermediate triethyl silyl peroxy alcohol **83** with cyclopentanone and cyclohexanone afforded spiro trioxanes **84** and **85** respectively Scheme 19.



Scheme 19

Griesbeck[22] et. al. in 2002, reported the synthesis of a series of monocyclic and spirobicyclic 1,2,4-trioxanes by photooxygenation of the chiral allylic alcohol, 4-methyl-3-penten-2-ol **88** in nonpolar solvents and subsequent Lewis acid-catalyzed peroxyacetalization Scheme-20.



Scheme 20

Meunier[23] et. al. in 2003, reported the synthesis of a new kind polycyclic 1,2,4-trioxane by using hetero Diels-Alder dimer **91** of 2-methylene cyclohexanone **90** and subsequent oxidation reaction with 30% H_2O_2 in acidic-medium Scheme-21.

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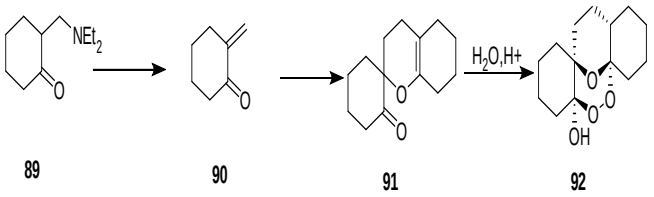
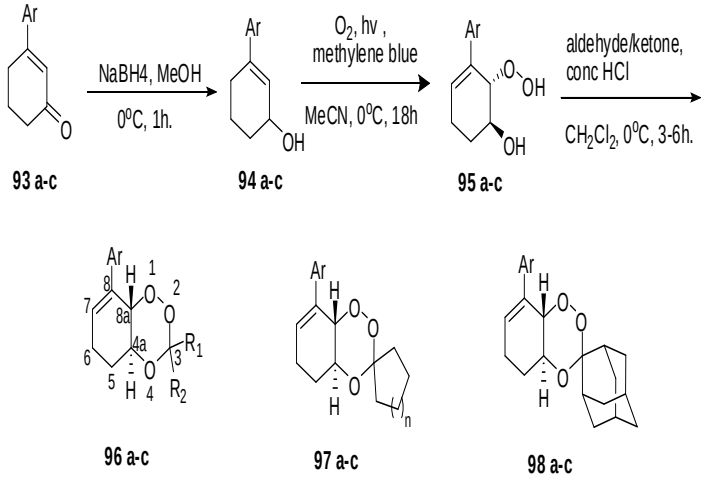


Scheme 21

The synthesis of several bicyclic 1,2,4-trioxanes was then reported by Singh[24] et. al. in 2005 using photooxygenation as the key step. The stereoselective photooxygenation of 3-aryl-2-cyclohexenols **94 a-94c** and acid catalyzed condensation of trans-2-hydroperoxy-3-aryl-3-cyclohexenols **95a-95c** with aldehydes and ketones afforded the trans-fused bicyclic 1, 2, 4-trioxanes Scheme-22



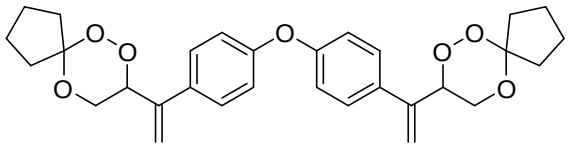
(**a**, Ar=Ph; **b**, Ar=4-ClC_6H_4; **c**, Ar=4-PhC_6H_4)

Scheme 22

1,2,4-TRIOXANES AS ANTIMALARIAL AGENTS:

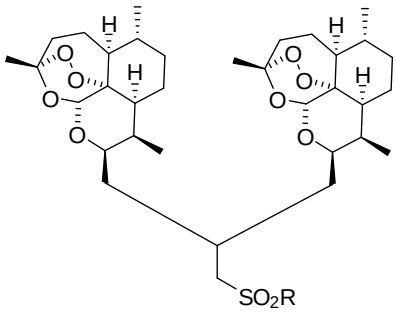
In drug design programmes, the synthesis of molecules which are novel, yet resemble new biologically active molecules by virtue of the presence of critical structural features essential for desired pharmacologic effect, becomes an essential component in search of new leads. In this context, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting biological profiles. Adopting this approach and realising that such hybrid molecules might be considered as a possible response to the recently growing resistance of various malarial parasites to 1,2,4- trioxanes pharmacophores like Artemisinin and its derivatives, efforts are directed towards the synthesis of various structurally diverse hybrid molecules for their antimalarial activity.

Singh et. al.in 2008 synthesised a series of bis and tris-1,2,4-trioxanes which were evaluated against multidrug-resistant *plasmodium yoelii* in Swiss mice by oral route. Among the various synthesized compounds, *bis*-trioxane[25] **99** was screened to be the most active compound of the series, showing 100% and 80% protection at 48 and 24 mg/kg×4 days, respectively. Clinically used drug Arteether showed only 20% protection at 24 mg/kg×4 days.



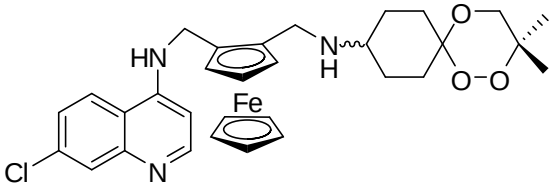
99

Synthesis of a new series of dimeric trioxane sulfones[26] were then reported by Posner et. al.in 2009. Among the synthesised compounds only dimeric trioxane sulfone carbamate **101** was thermally and hydrolytically stable chemical entities and screened to be completely cured malaria-infected mice *via* a single oral dose of 144 mg/kg. Its parent trioxane dimer **100** also shows powerful and selective anticancer activities.



101 R= -Ph-4-CH_2OH
102 R= -Ph-4-$CH_2OC(O)NMe_2$

Robert and co-workers in 2010 reported the synthesis of a series of trioxaferroquines[27], containing a quinoline and a trioxane linked by a ferrocene moiety as potential antimalarial molecules, which were evaluated with *P. vinckei petteri* infected mice. Among the screened compound, only **102**, when given orally at low dose, was able to clear parasitaemia below detectable level.



102

Subsequently, Singh et. al. synthesised a new series of orally active amino-functionalized spiro 1,2,4-trioxanes[28]. All these new trioxanes were assessed for their oral antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in Swiss mice. 2-Naphthalene-based trioxanes **103** and **104**, the most

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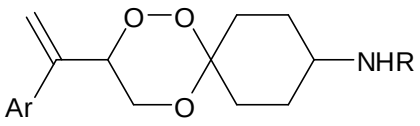
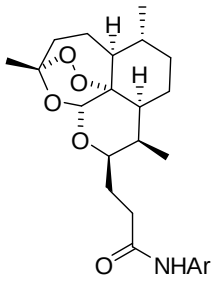
active compounds of the series, provided 100% protection to the malaria-infected mice at 24 mg/kg x 4 days.



Ar = 2-naphthyl **103 R** = 4-chlorophenyl
104 R = 4-trifluoromethyl phenyl

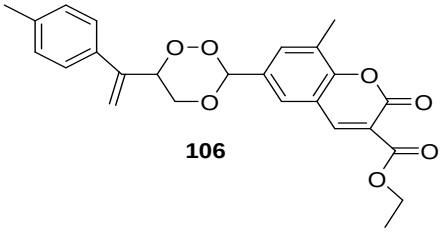
In 2012, Posner et. al. synthesised the new anilide derivatives of the natural trioxane artemisinin from the coupling of Artemisinin carboxylic acid with anilides carrying one or two sulfide, sulfoxide, or sulfone substituents on the anilide aromatic ring and evaluated for their antimalarial efficacy in *Plasmodium berghei* infected mice. Out of the synthesised moleules, only trioxane sulphides[29], **105** fully cured malaria-infected mice using only one 6 mg/kg oral dose combined with 18 mg/kg mefloquine hydrochloride.



105

Ar = 3-arteSanilide

Very recently, Sashidhara[30] and co-workers synthesised the first novel coumarin–trioxane hybrid molecules by the condensation of β-hydroxyhydroperoxides and the appropriate coumarins containing free aldehydes. Among all the synthesised compounds, compound **106** showed an *in vivo* suppression of 41.14% on day 4 against multidrug-resistant *Plasmodium yoelii* in Swiss mice by oral route



106

3. CONCLUSION:

The potentiality of synthetic and semi-synthetic 1, 2, 4-trioxans as antimalarial drug against multidrug-resistant *Plasmodium Falciparum* have been evidented from their pharmacokinetic profiles. Because of low abundance and high cost of Artemisinin and its derivatives that contain natural 1,2,4-trioxan structural motif , efforts have been made for the developments of synthetic methodologies for the rapid access of these structural motives. In this review we have emphasized on various methodologies developed so far for the synthesis of 1, 2, 4-trioxane derivatives and in subsequent we have also highlighted their hybrids having antimalarial activity. The work concludes that in most synthesis photo-oxygenation is the key step to introduce the trioxane group initially or at the end of the reaction sequence, respectively. Despite these advances, there is plenty of room for new contributions and findings, particularly for the developments of new methodologies for rapid, scalable synthesis of this structural motif.

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Conflict of Interest: None Declared

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